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List of original papers

This study is based on the following original publications, which are referred in the text by Roman numerals I-VI:

I. Klepstad P, Kaasa S, Skauge M, Borchgrevink PC. Pain intensity and side effects during titration of morphine to cancer patients using a fixed schedule dose escalation. Acta Anaesthesiol Scand 2000; 44: 656-664.

II. Klepstad P, Borchgrevink PC, Kaasa S. Effects on cancer patients' health-related quality of life after the start of morphine therapy. J Pain Symptom Manage 2000; 20: 19-26.

III. Klepstad P, Kaasa S, Jystad Å, Hval B, Borchgrevink PC. Randomised, double-blind comparison of immediate-release morphine and sustained-release morphine for dose-finding during start of morphine treatment of cancer pain. Submitted for publication.

IV. Klepstad P, Kaasa S, Borchgrevink PC. Start of oral morphine to cancer patients: Effective serum morphine concentrations and contribution from morphine-6-glucuronide to the analgesia produced by morphine. Eur J Clin Pharmacol 2000; 55: 713-719.

V. Klepstad P, Loge JH, Borchgrevink PC, Mendoza T, Cleeland, Kaasa S. The Norwegian Brief Pain Inventory. Translation and validation in cancer patients. Accepted in J Pain Symptom Manage.

VI. Klepstad P, Borchgrevink PC, Dale O, Zahlsen K, Aamo T, Fayers P, Fougner B, Kaasa S. Drug monitoring of serum concentrations of morphine, morphine-3-glucuronide and morphine-6-glucuronide do not predict clinical observations in cancer patients. Submitted for publication.

Abbreviations

AUC	Area Under Curve
BBB	Blood Brain Barrier
BPI	Brief Pain Inventory
CSF	Cerebrospinal Fluid
EAPC	European Association for Palliative Care
EORTC	European Organization for Research and Treatment of Cancer
HPLC	High Pressure Liquid Chromatography
HRQOL	Health Related Quality Of Life
IR	Immediate Release
IV	Intravenous
LC-MS	Liquid Chromatography - Mass Spectrometry
M6G	Morphine-6-Glucuronide
M3G	Morphine-3-Glucuronide
MMS	Mini Mental State Examiniation
NMDA	N-methyl-D-aspartate
NRS	Numeric Rate Scale
NSAID	Non-Steroidal Anti-Inflammatory Drug
PCA	Patient Controlled Analgesia
RIA	Radioimmunoassay
SC	Subcutaneous
SR	Slow Release
VAS	Visual Analogue Scale
VRS	Verbal Rate Scale
WHO	World Health Organization

Study objectives

The objectives of the present study were:

I. To assess the effects from start of morphine treatment to cancer pain patients in respect to time needed for dose-finding, dose needed for pain control and adverse symptoms.

II. To assess the effects from start of morphine treatment to cancer pain patients on health related quality of life.

III. To compare the efficacy of start of morphine treatment with sustained vs. immediate release morphine.

IV. To investigate the relationships between serum concentrations of morphine, M6G and M3G and subjective symptoms during start of therapy and after long-term morphine administration.

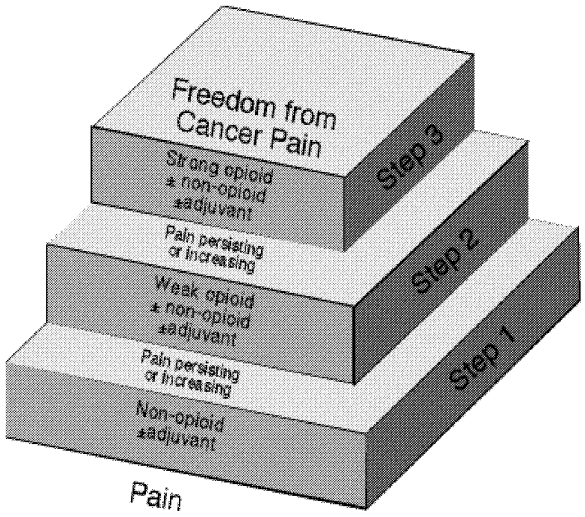
V. To assess the feasibility of a Norwegian translation of the Brief Pain Inventory questionnaire

Introduction

WHO guidelines for pain treatment of cancer patients

The leading principle for pain management of cancer pain today has been stated by the WHO in the pain ladder (fig.1) (World Health Organisation, 1996). The WHO pain ladder is based on a three-step approach for pain treatment.

Fig. 1: WHO Pain Ladder.



Step one is the use of non-opioids such as acetaminophen or NSAIDs. Step two escalates treatment to the use of an opioid for mild to moderate cancer pain combined or not combined with a non-opioid analgesic. In Norway the dominating opioid for mild to moderate cancer pain is codeine with dextropropoxyphene as the other commercial available alternative. Both are marketed in tablets also containing acetaminophen. Thus, the addition of the non-opioid analgesic acetaminophen is nearly obligate in Norway during step two treatment. If pain persists or increases despite administration of a step two opioid the pain treatment is changed to an opioid for moderate to severe cancer pain. Morphine is the most frequently used opioid for moderate to severe cancer pain, but several alternative opioids are in clinical use. These alternatives vary between different countries possibly due to clinical tradition

and marketing related circumstances. In Norway the commercial available alternatives suitable for long-term treatment of cancer pain are IR morphine, SR morphine, IR oxycodone, controlled-release oxycodone, fentanyl patches, IR ketobemidone and controlled-release ketobemidone.

Validation of the WHO guidelines for treatment of cancer pain

The principles in WHO guidelines are supported in the majority of reviews on pain therapy for cancer patients (Levy, 1996; Foley, 1985; Donnelly et al., 2002; Jacox et al., 1994b; Bruera & Neuman, 1999a; Twycross, 1994). In 1993 more than 250.000 copies of the guidelines were distributed throughout the world (Jadad & Browman, 1995). The WHO principles are implemented in most hospital, national and regional guidelines for treatment of cancer pain (Borchgrevink, 2001; Jacox et al., 1994; Hanks et al., 2001).

The validation of the WHO guidelines is based on prospective observational studies. Zech et al. followed 2118 cancer pain patients during a total of 40478 treatment days (Zech et al., 1995). The intensity of pain therapy corresponded to step one of the WHO pain ladder in 11% of treatment days, to step two for 31% of treatment days, while pain treatment was escalated to step three for 49% of the treatment days. Good pain relief was reported by 76% of the patients, satisfactory pain relief by 12% and 12% of the patients reported inadequate pain relief. The study by Zech et al., however, has some limitations in respect to generalizability of the findings to other countries. First, in this German study tramadol, a combined weak opioid agonist and serotonine/noradrenaline reuptake inhibitor, was the most used step two analgesic. In contrast tramadol is not considered a part of the pain ladder for treatment of cancer pain in Norway (Borchgrevink, 2001). Second, the study did not state whether the levels of analgesia were better than those achieved before implementation of the WHO pain ladder. A recent longitudinal observational study published in 2001 surveying 593 cancer patients replicated the findings from the study by Zech et al.. This later study, also originating from the University of Cologne, Germany, demonstrated that the analgesic efficacy from the use of the WHO pain ladder was good for 70%, satisfactory for 16%, and inadequate for 14% of the patients (Meuser et al., 2001).

Regional guidelines for treatment of cancer pain

In Europe the EAPC has published detailed recommendations for the use of opioids for treatment of cancer pain. The guideline was first presented in 1996 with a revised version of the guidelines published in 2001 (Expert Working Group of the European Association for Palliative Care, 1996; Hanks et al., 2001). The recommendations are based upon scientific evidence or if evidence not available upon consensus from an European expert panel. The recommendations are summarized into twenty treatment strategies for the administration of opioids to cancer pain patients (table 1). The 1996 EAPC guidelines described the use of morphine. Recognizing the lack of data from randomized controlled trials comparing the use of opioids for cancer pain the 2001 EAPC guideline was extended to cover the use of alternative opioids. The 2001 guidelines categorized the scientific level of evidence for each specific advice. These evaluations show that much of the treatment for cancer pain is not scientific tested but based upon tradition or expert opinions (table 1). The guidelines published in 2001 represent the prevailing treatment recommendations. The 1996 guidelines are essential for this thesis since these recommendations were valid during the planning and performance of the studies presented in the thesis. None of the recommendations relevant to the issues of this thesis were revised in the latest issues of the EAPC guidelines. Consequently, the findings of the paper I-IV are relevant to the 2001 version of the EAPC guidelines for the use of morphine and alternative opioids in cancer pain.

The US counterpart of the European guidelines for treatment of cancer pain, the Agency for Health Care Policy and Research Guidelines for Cancer Pain Management, follows the same principles for treatment (Jacox et al., 1994a). The US guideline is more comprehensive in respect to other treatments for cancer pain and does not take a stand on the choice of a particular opioid. The value of implementing treatment recommendations for the treatment of cancer pain has been studied by Du Pen et al. who compared the use of the US guidelines with standard care in a randomized study on cancer pain patients (Du Pen et al., 1999). Patients receiving guideline directed treatment had less pain but equal intensity of other symptoms and global quality of life as patients receiving standard care.

Table 1.
Morphine and alternative opioids in cancer pain: The EAPC recommendations

No	Recommendation	Strength of evidence
1	The opioid of first choice for moderate to severe cancer pain is morphine	C
2	The optimal route of administration of morphine is by mouth. Ideally two types of formulation are required. Normal release (for dose titration) and modified release (for maintenance treatment)	C
3	The simplest method of dose titration is with a dose of normal release morphine given every 4 hours and the same dose for breakthrough pain. The rescue dose may be given as often as required (up to hourly) and the total daily dose of morphine should be reviewed daily. The regular dose can then be adjusted to take into account the total amount of rescue morphine.	C
4	If pain returns consistently before the next regular dose is due the regular dose should be increased. In general, normal release morphine does not need to be given more often than every 4 hours and modified release morphine more often than 12 or 24 hours (according to the intended duration of the formulation). Patients stabilized on regular oral morphine require continued access to a rescue dose to treat breakthrough pain	A
5	Several countries do not have a normal release formulation of morphine, though such a formulation is necessary for optimal pain management. A different strategy is needed if treatments started with modified release morphine. Changes to the regular dose should not be med more frequently than every 48 hours, which mean that the dose titration phase will be prolonged.	C
6	For patients receiving normal release morphine every 4 hours, a double dose at bedtime is a simple and effective way of avoiding being woken by pain	C
7	Several modified release formulation are available. There is no evidence that the 12-hourly formulations (tablets, capsules or liquids) are substantially different in their duration of effect and relative analgesic potency. The same is true for the 24-hour formulations though there is less evidence to draw on.	A

Table 1. cont.
Morphine and alternative opioids in cancer pain: The EAPC recommendations

No	Recommendation	Strength of evidence
8	If patients are unable to take morphine orally the preferred alternative route is subcutaneous. There is generally no indication for giving morphine intramuscularly for chronic cancer pain because subcutaneous administration is simpler and less painful	C
9	The average relative potency ratio of oral morphine to subcutaneous morphine is between 1:2 and 1:3 (i.e. 20-30 mg of morphine by mouth is equianalgesic to 10 mg by s.c. injection)	C
10	In patients requiring continuous parenteral morphine, the preferred method of administration is by subcutaneous infusion	C
11	Intravenous infusion may be preferred by patients: a. who already have a in-dwelling intravenous line; b. with generalized oedema; c. who develop erythema, soreness or sterile abscesses with subcutaneous administration; d. with coagulation disorders; e. with poor peripheral circulation	C
12	The average relative potency ratio of oral to intravenous morphine is between 1:2 and 1:3	A
13	The buccal, sublingual and nebulized routes of administration of morphine are not recommended because at present time there is no evidence for clinical advantage over the conventional routes	B
14	Oral transmucosal fentanyl citrate (OFTC) is an effective treatment for breakthrough pain in patients stabilized on regular oral morphine or an alternative step 3 opioid	A
15	Successful pain management with opioids requires that adequate analgesia be achieved without excessive adverse effects. By these criteria the application of the WHO and the EAPC guidelines (using morphine as the preferred step 3 opioid) permit effective control of chronic cancer pain in the majority of patients. In a small minority of patients adequate relief without excessive adverse effects may depend on the use of alternative opioids, spinal administration of analgesics or non-drug methods of pain control	B

Table 1. cont.
Morphine and alternative opioids in cancer pain: The EAPC recommendations

No	Recommendation	Strength of evidence
16	A small proportion of patients develop intolerable adverse effects with oral morphine (in conjunction with a non-opioid and adjuvant analgesics as appropriate) before achieving adequate pain relief. In such patients a change to an alternative opioid or change in the route of administration should be considered	B
17	Hydromorphone or oxycodone, if available in both normal release and modified release formulations for oral administrations, are effective alternatives to oral morphine.	A
18	Methadone is an effective alternative but may be more complicated to use compared with other opioids because of pronounced interindividual differences in its plasma half-life, relative analgesic potency and duration of action. Its use by non-specialist practioneers is not recommended.	C
19	Transdermal fentanyl is an effective alternative to oral morphine but it is best reserved for patients whose opioid requirements are stable. It may have particular advantages for such patients if they are unable to take oral morphine, as an alternative to subcutaneous infusion.	B
20	Spinal (epidural or intrathecal) administration of opioid analgesics in combination with local anaesthetics or clonidine should be considered in patients who derive inadequate analgesia or suffer intolerable adverse effects despite the optimal use of systematic opioids and non-opioids	B

Level of evidence: **A**, requires at least one randomized controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation; **B**, requires the availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation; **C**, requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applied clinical studies (Hanks et al., 2001).

Critical remarks to the WHO guidelines for treatment of cancer pain

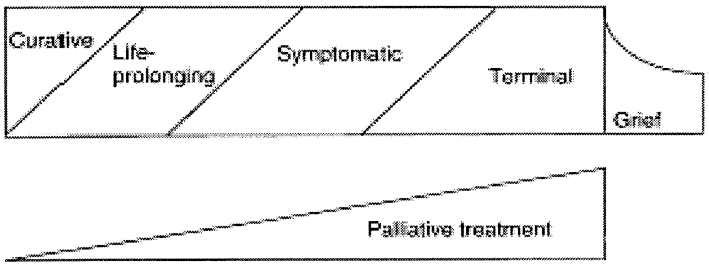
The major objection against the WHO guidelines is the lack of a scientific validation of the treatment principles. The validation of the WHO guidelines is based upon prospective observational studies showing that treatment following the WHO three step pain ladder gives satisfactory pain relief for most (90%) patients (Zech et al., 1995; Meuser et al., 2001). However, the literature does not provide evidence on the effectiveness of the WHO ladder compared to other treatment approaches (Jadad & Browman, 1995). It is important to recognize that the WHO guidelines were developed in order to increase the quality of pain treatment as early as 1986. An important feature was to propose a simple and low cost treatment that could be implemented in undeveloped countries. It is conceivable that 15 years later in countries not restricted by the lack of resources other approaches for pain treatment could give even better results than the use of the WHO three step pain ladder. This view was stated eloquently by Jadad and Bowman in the title of a 1995 JAMA paper; "The WHO analgesic ladder for cancer pain management. Stepping up the quality of its evaluation" (Jadad & Browman, 1995).

Another criticism is that the WHO pain ladder is incomplete. The WHO pain ladder does not illustrate important parts of treatment of cancer pain such as radiotherapy, palliative surgery, palliative cytotoxic treatment, physiotherapy and psychological support. Also, the pain ladder does not illustrate the alternatives in respect to routes, the use of neuroaxial applied local anesthetics or the use of neurolytic blocks (Ahmedzai, 2001; Breivik, 2001). The simplicity of the WHO pain ladder is an important factor for it success, but it is vital to recognize that the WHO pain ladder only represents a skeleton of a minimum standard for cancer pain treatment that must be extended by physicians responsible for delivering palliative care.

It is an evolving understanding underlining the importance to not make a distinction between ongoing anticancer treatment and palliative care. Treatment of cancer patients was traditionally divided in three phases. First, the patient is treated with the sole purpose of cure from cancer. Second, for a period of time treatments are life prolonging. Only after the hope of cure or prolongation of life is abandoned the goals of patient treatment have been directed at palliative care issues. This distinction of treatment is artificial since most patients are in need for symptom control also when the cancer disease is

the main treatment target (fig. 2) (Kjær, 1997; Kaasa & De Conno, 2001). Further, there are no reasons in favor of withholding palliative care since such care will not interfere with the efficacy of anticancer treatment and the risk for complications such as addiction in survivors is neglible (Paice et al., 1998).

Fig. 2: Palliative care as an integrated approach in all stages of cancer patient treatment (from Kaasa & De Conno, 2001)



The last revision of the WHO guidelines was published in 1996. The appropriate shelf time for guidelines is not established, but a general rule of three years between reassessments has been proposed (Shekelle et al., 2001). However, in a paper studying intervals between reassessments of guidelines the 1994 US practice guideline for management of cancer pain was considered to need only minor updates (Jacox et al., 1994a, Shekelle et al., 2001). Also the minor changes between the EAPC guidelines published in 1996 and 2001 indicate that the WHO guidelines is not out-dated (Expert Working Group of the European Association for Palliative Care, 1996; Hanks et al., 2001).

Knowledge of the principles for treatment of cancer pain

Despite the current knowledge and multiple available measures for the treatment of cancer pain, surveys on symptom prevalences amongst cancer patients and surveys on the knowledge of treatment principles for cancer pain consistently show defiances. Cleeland et al. surveyed the intensity of pain in 1308 outpatients with metastatic cancer and observed that 42% of those with

pain were not given adequate analgesic therapy (Cleeland et al., 1994). Melsom and Wist reported that 50 of 52 patients admitted for palliative care experienced pain at admission indicating increased intensity of pain therapy (Melsom & Wist, 2001). A high prevalence of patients with unacceptable pain was also observed in patients on ongoing morphine therapy admitted to our hospital (fig.3)(paper V). These findings may indicate that pain intensity is often higher than normally accepted.

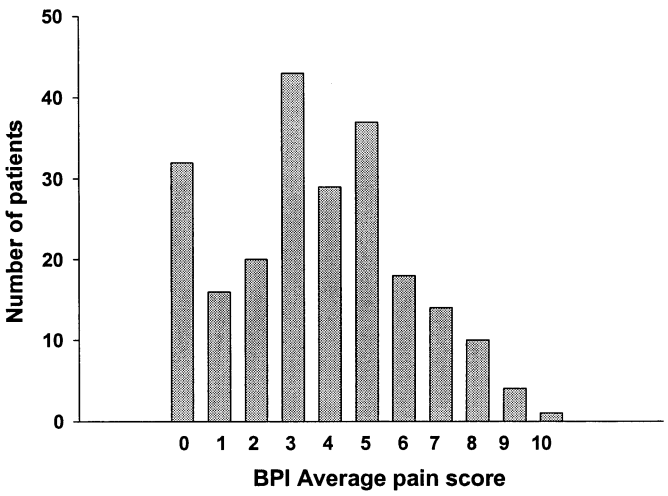


Fig. 3: Distribution of BPI scores on the item "average pain last 24 hours" in patients admitted to hospital receiving morphine. 0 – no pain, 10- pain as bad as you can imagine (paper VI).

Surveys on the physicians' self reported knowledge of cancer pain treatment also show a potential for improvement. In an US 1996 survey 98% of residents prescribed an opioid for cancer pain, but only 18% of the prescriptions were for regular use and 88% did not provide rescue analgesics. Further, only 24% of the residents increased the doses sufficiently in persistent severe pain (Sloan et al., 1996). In a Norwegian survey published in 1994 including 306 physicians treating cancer patients, 86% were willing to prescribe opioids for moderate to severe for cancer pain but in cases were opioids were appropriate 46% of the physicians prescribed to low doses (Warncke et al., 1994). The majority of physicians (72%) believed that their education in treating cancer pain was insufficient. In a survey in our hospital health care workers generally believed that the treatment of cancer pain is highly prioritized, and the health care workers were satisfied with the treatment results in most cases (physicians 94%; nurses 78%)(Skauge et al.,

1996; Skauge et al., 1998). Both physicians and nurses were more often satisfied with pain control in cancer patients with pain than for those having chronic non-malignant pain. These studies did not compare the health care workers perceived results from pain treatments with patients' self-reports of pain. Whether the differences between these two Norwegian surveys in physicians' reports of their understanding of cancer pain treatment are caused by improved knowledge during the years between the surveys, by differences between hospitals or by differences in study design is not known. One shared limitation is that self-evaluations of clinical skills are not necessarily related to the actual level of performance (Cherny & Catane, 2001).

Start of morphine

The three step approach

The WHO pain ladder and the EAPC guidelines recommend that an opioid for moderate to severe cancer pain is not started before the patient experience inferior pain relief from an opioid for weak to moderate pain (World Health Organsation, 1996; Hanks et al., 2001). It has been argued that the opioid included into step two of the WHO pain ladder can be replaced with a low dose of an opioid for moderate to severe pain (Grond & Meuser, 1998). The most used step two opioid codeine is metabolized to morphine in the liver, and some researchers propose that codeine partly can be regarded as a prodrug with morphine as the active substance (Poulsen et al., 1996). Because about 10% of Caucasians lack the CYP2D6 enzyme that catalyze codeine O-demethylation to morphine it can be argued that direct start with a low morphine dose is more effective (Alván et al., 1990). Few studies compare the WHO three step pain ladder with an alternative two step ladder applying a direct escalation of treatment from non-opioids to a low dose of an opioid for moderate to severe cancer pain. Mercadante et al. randomized 32 patients suffering from cancer pain to treatment with SR morphine (20 mg daily) or with dextropropoxyphene (Mercadante et al., 1998b). They found equally pain relief in the two study groups, but morphine resulted in higher intensity of xerostomia, nausea and drowsiness during the first ten days of treatment. Three of the 16 patients randomized to dextropropoxyphene were maintained on the same drug until death. For the majority of patients, however, the time interval where step two opioids are in use is short. De Conno et al. observed that the numbers of patients still benefiting 4 weeks after start of treatment

were for dextropropoxyphene 29/107, for codeine 30/132 and for pentazocine 26/139. The corresponding numbers after 14 weeks were 3/107, 9/132 and 1/139, respectively (De Conno et al., 1991). An increased frequency of adverse effects associated with direct start of an opioid for moderate or strong cancer pain was supported in an open study comparing start of transdermal fentanyl 25 μg/h to patients without any previous use of an opioid (n=14) versus start of transdermal fentanyl 25 μg/h to patients using codeine (n=14) (Vielvoye-Kerkmeer et al., 2000).

The arguments in favor of the continued use of a step two opioid for mild to moderate pain are several. First, the use of opioids for mild to moderate pain serves as an educational tool for physicians and patients making them more familiar with the concept of opioid therapy. Second, opioids for mild to moderate pain are more freely available since prescription of oral opioids for moderate to severe pain is restricted for use by governmental rules or even in some countries not available (Pargeon & Hailey, 1999). Third, to exclude opioids for mild to moderate pain can postpone start of opioids for moderate to severe pain because of patient barriers related to fear from addiction or fear of that early treatment decreases efficacy at a more terminal stage of the cancer disease (Grond & Meuser, 1998; Pargeon & Hailey, 1999; Weiss et al., 2001). Thus, the three step pain ladder, including the use of a step two opioid for mild to moderate pain, is more based upon practical feasibility, availability and health politics than pharmacological reasoning.

The start of an opioid for severe pain is a critical incident

The initiation and titration of an opioid for moderate and severe pain is critical during individual patient treatment. The time to start opioid treatment is most often associated with progressive disease, and most patients receive several other treatments. Also, per definition the pain itself is not controlled. The experience of pain is a direct burden on the patients' total situation and the patients will, often rightly, interpret increased pain as a sign of disease progression.

Findings in patients on long-term morphine treatment are not equal to findings in opioid naive patients. A principle difference between morphine treatment during start and long-term treatment is that tolerance to side effects has yet to

develop at the time of start of opioid administration. Bruera et al. showed that escalations of opioid doses increased cognitive impairment as measured by the MMS (Bruera et al., 1989). The cognitive impairment associated with dose increments disappeared after one week. This effect, however, was not reflected in the patients' self-reports of confusion. Bruera et al. also observed that drowsiness and nausea are increased after morphine dose adjustments (Bruera et al., 1989). The importance of differentiating between chronic and naive opioid users was also shown in a study by Shore et al. applying the risk for hip fracture as a primary end-point (Shore et al., 1992). In this study the relative risk for hip fractures in elderly new users of codeine or dextropropoxyphene was 2.2 compared with non-users, while chronic users of the two opioids had only slightly elevated risk for hip fractures (relative risk 1.3 compared with non-users). The importance of previous opioid use for symptoms associated with start of an opioid was also illustrated in the study by Vielvoye-Kerkmer et al. (Vielvoye-Kerkmeer et al., 2000). They observed that side effects after start of fentanyl patches (25 μg/h) were more frequent in opioid naive patients than in patients previously consuming codeine.

Studies on start of morphine

Despite the frequent and widespread use of morphine few studies have assessed how to optimize treatment start. The time needed for morphine titration in previously morphine naive cancer patients is reported by Vijayaram et al., who observed a mean titration duration of four days until satisfactory pain control (Vijayaram et al., 1990). However, that paper did not describe the procedure for morphine titration or the mean effective morphine dose. In another study, including 28 patients needing escalation of pain treatment from step two to step three in the WHO pain ladder, the patients used for dose finding PCA morphine for 24 hours until switched to SR morphine with additional PCA morphine for breakthrough pain (Radbruch et al., 1999b). At the time the patients needed two or less PCA boluses daily, the PCA was terminated and rescue morphine changed to oral morphine. With this approach stable oral treatment was achieved after a median of four days and three quarter of the patients rated this method as good.

Studies on start of other opioids

In a study on start of oxycodone for cancer pain Salzman et al. reported that dose titration was accomplished as readily with oral controlled release oxycodone as with IR oxycodone. However, the majority of patients included into this study were at the time of inclusion treated with other opioids for moderate to severe pain. Consequently, this study was not designed in order to conclude on the use of SR versus IR formulations during start of opioid therapy. Another limitation with this study was that the treatments were not blinded (Salzman et al., 1999).

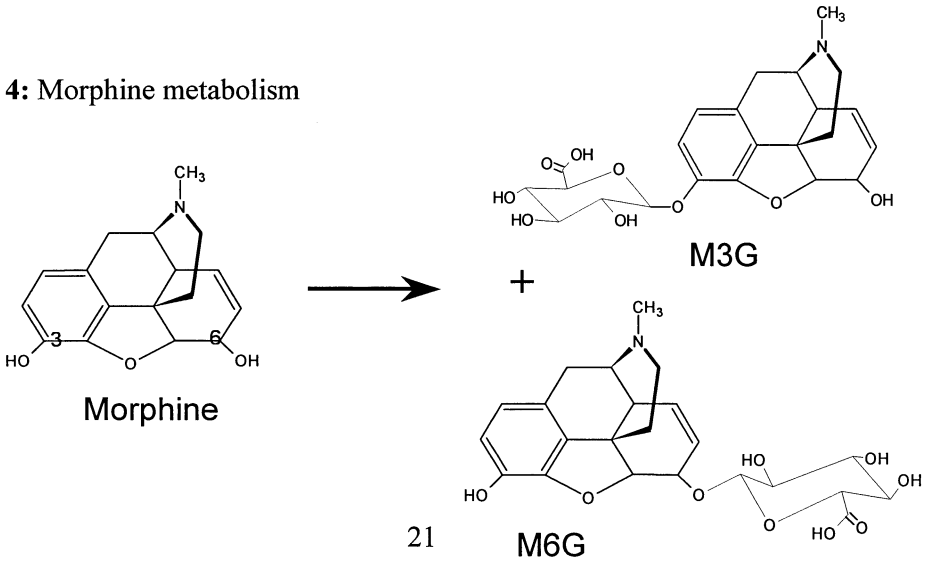
Zech et al. reported the use of PCA dose finding before start of transdermal fentanyl (Zech et al., 1992). The direct start of fentanyl patches have been described by Grond et al. and Korte et al. who reported successful titration of transdermal fentanyl in 50 and 39 cancer patients, respectively (Grond et al., 1997; Korte et al., 1996).

Morphine, M6G and M3G pharmacology

Morphine metabolism

Oral morphine is extensively absorbed from the intestines (Milne et al., 1996). Mazoit et al. showed that there was no concentration gradient between the mesenteric artery and the superior mesenteric vein indicating no gut wall metabolism of morphine (Mazoit et al., 1990). As a result morphine reach the liver in unaltered form. In the liver morphine undergoes an extensive first-pass metabolism by the UGT2B7 enzyme which catalyses morphine at both the 3- and 6-hydroxyposiotions into its two principle metabolites M3G and M6G (fig. 4)(Coffman et al., 1997; Milne et al., 1996).

Fig 4: Morphine metabolism



Morphine is also metabolized at a lower rate by the enzymes UGT1A8 and UGT2A1 (Tukey & Strassburg, 2000). Pharmacokinetic modeling after oral morphine to young healthy volunteers showed that 82% of morphine was absorbed from the gut. Of this 42 % passed untransformed through the liver resulting in an oral bioavailability of 34%. Of the total amount of M6G most (71%) was formed during the first pass metabolism while the rest was formed by metabolism of systemic morphine (Lötsch et al., 1999). Morphine is metabolized in humans to several other metabolites such as normorphine, normorphine-6-glucuronide, morphine-3-sulfate, and morphine-3,6-diglucuronide, but these substances are found in small concentrations compared with M6G and M3G (Milne et al., 1996; McQuay & Moore, 1997). Other sites than the liver have a potential to metabolize morphine as proved by a small production of M3G and M6G during the anhepatic phase of liver transplantation (Bodenham et al., 1989) and by that the total body clearance exceeds hepatic clearance (Mazoit et al., 1990). One of the proposed sites for extrahepatic metabolism is the lung. However, the difference between morphine concentrations in the pulmonary and radial artery is small indicating that pulmonary clearance of morphine is not important (Persson et al., 1986). Renal morphine metabolism to M6G and M3G is demonstrated in animal studies while studies on humans have not supplied clear evidence for a role for the kidneys in morphine metabolism (Milne et al., 1996; McQuay & Moore, 1997). A study by Wahlström et al. demonstrated the formation of morphine from M6G in the brain while Sandouk et al. demonstrated formation of M3G and M6G after intracerebroventricular administration of morphine (Wahlström et al., 1988; Sandouk et al., 1991). The clinical importance of extrahepatic morphine metabolism is not established.

Concentrations of morphine and metabolites in serum

M6G and M3G are consistently found in higher serum concentrations than morphine during chronic morphine therapy. M6G serum concentrations are typically about 6 times higher than morphine serum concentrations and M3G serum concentrations six times higher than the serum concentrations of M6G (McQuay et al., 1990; Wollf et al., 1995; Tiseo et al., 1995; van Dongen et al., 1994). These findings are present after a few days of treatment (paper IV) as in patients on long-term morphine treatment. Patients receiving morphine by a parenteral route have lower ratios of M6G and M3G relative to morphine

because the first-pass metabolism is bypassed (Tiseo et al., 1995; Wollf et al., 1996). The studies consistently show large interindividual variability in serum concentrations. The M6G/morphine and M3G/morphine ratios vary widely between patients while the ratio M3G/M6G is more stable (Faura et al., 1998).

Concentrations of morphine and metabolites in the central nervous system

The results on BBB transport of M6G and M3G from animal studies are conflicting. Poor permeability for M3G and M6G through the BBB is shown in rats by injecting M3G and M6G tracers in the carotid artery (Bickel et al., 1996). Data from arterio-venous gradients in the pig, however, demonstrated rapid uptake of morphine from serum into the brain and high extraction of M6G and M3G into the brain (Bjorkman et al., 1995). M3G and M6G exist in extended and folded forms. The folded forms may mask part of the polar group and consequently enhance transport through BBB (Carrupt et al., 1991).

Several studies on cancer pain patients suggest that M6G and M3G have less ability to penetrate the BBB than morphine. During chronic oral morphine therapy van Dongen et al. observed CSF/plasma ratios for morphine 0.9, for M6G 0.09 and for M3G 0.12 (van Dongen et al., 1994). These findings are close to observations in studies by Portenoy et al. and by Wollf et al. (Portenoy et al., 1991b; Wollf et al., 1995). The effect site concentrations in the brain extracellular fluid are also influenced by the transport of morphine and metabolites into the brain cells. In animal studies Stain-Texier et al. showed that morphine enters the brain cells while M6G is almost exclusively retained in the extracellular fluid (Stain-Texier et al., 1999). It was also a slower diffusion of M6G from extracellular brain fluid into the CSF. As a consequence M6G may be trapped in the extracellular fluid in the brain and thereby more available for interaction with opioid receptors. Pharmacokinetic modeling after oral morphine has proposed that CSF/plasma ratios are not representative for the ratios between effect site concentrations and serum concentrations (Lötsch et al., 1999). In pharmacokinetic simulations the effect site concentrations of M6G reach levels two times higher than for morphine 80-100 hours after oral morphine administration (Lötsch et al., 1999), which is considerable longer than the time needed for equibrillium between CSF and plasma metabolite concentrations after oral morphine (D`Honneur et al., 1994). The delayed increase of brain extracellular fluid

concentrations may explain some of the time delay from t_{max} in serum concentrations to maximal analgesic efficacy. In two studies, measuring concentrations in extracellular brain fluid by the microdialysis sampling technique, transport across the BBB counted for 85% and 50% of the antinociceptive delay in onset after morphine and M6G administration in rats, respectively (Bouw et al., 2000b; Bouw et al., 2001). The long onset time after M6G administration is also demonstrated in humans who have 6.5 hours M6G transfer half-life time from serum to effect site (Lötsch et al., 2001). The complexity of the issues related to effect site concentrations has recently been further illustrated by a report of a patient with head trauma showing higher extracellular fluid morphine concentrations in brain areas near the head trauma than in other parts of the brain (Bouw et al., 2000a). Whether regional differences in extracellular fluid morphine concentrations and possible M6G concentrations are present in patients without intracranial pathology is unknown (Lötsch & Geisslinger, 2001).

What determines morphine, M6G and M3G serum concentrations

Several factors are proposed to influence on serum concentrations of morphine, M6G and M3G. McQuay et al. showed in a survey of 151 cancer patients that dose was the most important factor explaining variation of morphine and metabolites (McQuay et al., 1990). This finding is supported by the results from several smaller studies (Neumann et al., 1982; Wollf et al., 1995; McQuay & Moore, 1997). The influence from other patient and treatment related factors are more disputed. The use of parenteral routes (e.g. SC, IV) results in lower serum concentrations of M6G and M3G relative to morphine because of lack of first-pass metabolism (Peterson et al., 1990; Osborne et al., 1990; Faura et al., 1998). The importance of age related to morphine and metabolite serum concentrations is limited to the extremes of age. A systematic review on metabolite and morphine ratios concluded that neonates have lower ratios compared with older children and adults (Faura et al., 1998). McQuay et al. observed that age greater than 70 years was associated with higher M6G and M3G serum concentrations during oral morphine treatment (McQuay et al., 1990). The effects from age are not equal for morphine and its metabolites. Van Crugten et al. showed that plasma M6G AUC was 1.6 times higher in old rats compared with young rats while the curves after morphine administration were not different (Van Crugten et al.,

1997). No studies have demonstrated gender related differences in morphine pharmacokinetics.

M6G and M3G are primarily subject to renal elimination, and several studies have consistently showed that patients with renal failure accumulate M6G and M3G after morphine or M6G administration (Chauvin et al., 1987; Sear et al., 1989; Wolff et al., 1988; D`Honneur et al., 1994; Hanna et al., 1993). The influence from renal failure is evident when dichotomizing patients in having normal renal function versus having supranormal serum creatinine serum concentrations but without clinical evident renal failure (Faura et al., 1998; McQuay et al., 1990). Detoriating renal function is parallelled by increased M6G/ morphine ratio during progressive renal failure (Portenoy et al., 1991a). The relationship between renal failure and higher levels of M6G and M3G serum concentrations can not automatically be interpreted to the extent that metabolite serum concentrations are influenced by variations in serum creatinine concentrations below the upper limit for normal values. Peterson et al. and Tiseo et al. observed significant correlations between normal range creatinine values and M6G/morphine and M3G/morphine ratios (Peterson et al., 1990; Tiseo et al., 1995). On the other hand Wollf et al. observed that plasma M3G/morphine and M6G/morphine ratios were not related to serum concentrations of creatinine in patients receiving oral morphine (Wollf et al., 1995).

Elimination of morphine is impaired in patients with severe liver cirrhosis (history of encephalopathy) and M3G/morphine ratio was lower than in normal subjects during oral morphine therapy but not during SC morphine therapy (Hasselström et al., 1990). However, this effect is evident only in patients with clinical significant liver failure implying that liver function is not an important factor for morphine metabolism.

The patients' genetic or ethnic predisposition will influence upon opioid pharmacology. The UGT2B7 enzyme exists in two forms; one with histidine at position 268 and one with tyrosine at position 268. Both forms catalyze morphine (Coffman et al., 1998). Consequently, it could be argued that variability or mutations on the genes coding for the UGT2B7 enzyme may cause differences in morphine metabolism. However, in a study by Holthe et al. no significant differences in M6G/morphine and M3G/morphine ratios were observed in cancer patients with the polymorphism UGT2B7, His268Tyr

(Holthe et al., 2001). There are few studies on ethniticity and morphine pharmacogenetics. Cepeda et al. showed that Caucasians have significantly higher M6G levels than native Indians and Latinos after an IV morphine bolus (Cepeda et al., 2001). The results from this study, however, were contradictionary since Caucasians had a more pronounced respiratory depression after IV morphine than Native Indians (Cepeda et al., 2001). It has also been reported that Chinese have greater clearance of morphine because of higher rates of glucuronidation (Zhou et al., 1993)

Clinical effects from M6G and M3G

Effects from M6G

M6G has a 20-fold increased affinity for μ-receptors compared to morphine in animal studies and SC, intracerbroventricular and intrathecal M6G is tenfold more potent than morphine in the rat tail flick test, rat writhing test and as a ventilatory depressant in rats (Pasternak et al., 1987; Stain et al., 2001; Paul et al., 1989; Gong et al., 1991). M6G is more potent than morphine for analgesia in human experimental pain (electrical and cold pain tests) (Buetler et al., 2000; Thompson et al., 1995), but in contrast to the experimental studies on pain Lötsch et al., assessing pupil size changes associated with morphine infusions in human volunteers, calculated a M6G EC_{50} 22 times greater than the corresponding EC_{50} of morphine (Lötsch et al., 2001). Lötsch et al. speculate if this discrepancy is caused by an incomplete transfer of M6G from plasma to effect site or by development of short-term tolerance to M6G.

Lötsch et al. also observed that M6G failed to have clinical effects on human experimental pain after short-term administration (Lötsch et al., 1997). Motamed et al. supported this finding in a study demonstrating lack of effect on postoperative pain after a single dose of 0.1 mg/kg M6G, while Osborne et al. giving higher doses of M6G (0.5 to 4.0 mg/kg iv M6G) achieved analgesia in 17 of 19 patients (Motamed et al., 2000; Osborne et al., 1992). However, the study by Osborne et al. did not observe any relation between serum M6G concentrations and pain relief (Osborne et al., 1992). The use of intrathecal M6G 100 or 125 μg for postoperative pain after hip replacement showed equal efficacy as 500 μg morphine, but all three study groups had unacceptable high incidences of side effects (Grace & Fee, 1996).

Studies on chronic cancer pain support that M6G contributes to the analgesia induced by morphine. Portenoy et al. observed that the M6G/morphine ratio correlated with pain relief in 14 patients with cancer pain and normal creatinine serum concentrations (Portenoy et al., 1992), and Faura et al. found that pain relief in 39 cancer patients was related to the sum of morphine and M6G serum concentrations (Faura et al., 1996a). Other studies have not observed any relationship between morphine or M6G plasma concentrations and pain scores (Somogyi et al., 1993).

The relationships between M6G and adverse effects associated with morphine treatment are not clearly understood. Some patients with renal failure receiving morphine have developed profound sedation caused by accumulation of M6G (Osborne et al., 1986; Bodd et al., 1990). The evidences in favor of an effect from M6G on sedation or cognitive function in patients having normal renal function are not convincing. Wood et al. observed no associations between neuropsychological test and M6G serum concentrations in 18 palliative care unit patients (Wood et al., 1998). Tiseo et al. identified 40 patients with cognitive failure and found that these patients had not different M6G/morphine ratios compared with historical controls (Tiseo et al., 1995). M6G was proposed to give a lesser risk for respiratory depression than morphine in a study comparing the effects from M6G and morphine in doses equipotent for human experimental pain (Thompson et al., 1995). A study by Peat et al. on healthy volunteers comparing the respiratory effects from M6G and morphine gave a more complex answer since morphine but not M6G increased end-tidal CO_2 while the ventilatory response to a CO_2-challenge was blunted by both drugs (Peat et al., 1991). In one convincing case report high levels of M6G was believed to be associated with nausea. This notion was supported by a reduction in nausea when M6G levels declined (Hagen et al., 1991). M6G is also demonstrated to elicit nausea and retches at lower doses than morphine in animal emetic models (Thompson et al., 1992). On the other hand nausea is uncommon in studies using M6G for acute pain in humans (Peat et al., 1991; Osborne et al., 1992).

Effects from M3G

Several reports from animal experimental studies have demonstrated that M3G antagonize M6G or morphine induced effects such as antinociception and ventilatory depression (Gong et al., 1992; Smith et al., 1990; Faura et al.,

1996b; Smith & Smith, 1995; Barjavel et al., 1995). An exception from these positive findings in animal models is a study by Hewett et al. where intrathecal M3G administered to rats had no antagonism to morphine effects (Hewett et al., 1993). A patient with high M3G CSF concentration and not detectable M6G CSF concentration, who reported worsened pain despite escalating intrathecal morphine doses, led Morley to propose the phenomenon of morphine induced paradoxical pain (Morley et al., 1992). Other studies on humans do not support an antianalgesic action from M3G. In a study on human experimental ischemic pain M3G did not inhibit the effect from morphine or M6G (Penson et al., 2000). Also, a study assessing 11 patients with morphine resistant pain found that these patients had similar serum and CSF M3G/M6G ratios as historical controls (Goucke et al., 1994).

M3G has been proposed to elicit excitatory effects associated with high doses of morphine. This effect from M3G is supported by cases where high concentrations of M3G are observed in patients with hyperalgesia, myoclonus or allodynia (Sjøgren et al., 1998). While such cases are convincing for M3G excitatory effects in exceptional patients receiving high morphine doses Wood et al. found no association between neuropsychological test and M3G serum concentrations in palliative care unit patients (Wood et al., 1998).

The mechanisms of M3G effects are not established. M3G do not significantly inhibit the binding of ligands to GABA, NMDA and glycine reseptors in rat brain homogenate (Barlett et al., 1994). An inverse relationship between binding to opioid receptors and excitatory activity of morphine derivatives suggest that the excitatory effects is mediated through receptors distinct from the opioid system (Labella et al., 1979).

Effects from other metabolites

Besides M6G and M3G, normorphine is the only product from morphine metabolism that has been proposed to elicit a clinical effect, namely myoclonus. However, the case for this effect is not very convincing since it has only been presented in two case stories (Glare et al., 1990).

Adverse symptoms in cancer patients

It exists an extensive body of literature describing prevalences and characteristics of symptoms associated with cancer diseases (Lawlor & Bruera, 1998; Cherny et al., 2001). The reviews on symptoms associated with use of opioids generally do not differentiate between effects from the various opioids. This approach was supported by an Expert Working Group of the EAPC who after a search of the literature and discussions amongst experts stated that there is overall very little evidence for that one opioid has a better side effect profile than any other (Cherny et al., 2001).

Nausea

The data on the prevalence of nausea in cancer patients using opioids varies between studies. A 1982 survey from UK by Hanks in 296 palliative care patients showed that 71% of patients received one antiemetic drug and 8% needed two or more antiemetic drugs (Hanks, 1982). This finding was confirmed in a later UK survey showing that 56% of cancer patients required an antiemetic (Hoskin & Hanks, 1988), and by the findings in a Canadian survey by Fainsinger et al. showing that 71 of 100 cancer patients experienced nausea during the last week of life (Fainsinger et al., 1991). However, the intensity of nausea was moderate or low in most of the patients assessed in this survey. Other reports present lower rates for nausea and vomiting. The large WHO validation study by Zech et al. registered that nausea was present in 23% of pain treatment days (Zech et al., 1995). In a longitudinal study replicating the study by Zech et al. Meuser at al. observed that the prevalence of nausea and vomiting did not increase during the course of disease and there were no major difference between step two and three of the WHO pain ladder (Meuser et al., 2001). Campora et al. reported that 16% of cancer patients using morphine experienced moderate or severe nausea and that 30% of the patients had more than two daily emetic episodes (Campora et al., 1991). These prevalences were not different from those observed in patients using codeine or buprenorphine (Campora et al., 1991). Low prevalences of nausea are also found in patients with advanced cancer disease as exemplified by a study by Coyle et al. where only 12% of patients (76% on ongoing opioid treatment) reported nausea 4 weeks before death (Coyle et al., 1990).

Sedation

Self-reported sedation is more frequent and severe during step three than step two treatment in the WHO pain ladder (Meuser et al., 2001). Sedation is especially pronounced during the last week of life (one week before death: alert 72%, drowsy 28%, unresponsive 0%; day of death: alert 2%, drowsy 41%, unresponsive 57%)(Fainsinger et al., 1991).

Cognitive failure

Cognitive functions are influenced by the use of opioids (Bruera & Neuman, 1999b). One-fourth of cancer patients spontaneously report the experience of mental haziness or confusion the last month before death (Coyle et al., 1990; Zech et al., 1995). Such experiences of neuropsychological symptoms are more frequent and severe during step three than step two of the WHO pain ladder for treatment of cancer pain (Meuser et al., 2001). However, all experiences of impaired mental status should not be attributed to the effects from opioids. Leipzig et al. observed 35 cancer patients of which 27 experienced a total of 45 episodes of impaired mental status. The causes for each episode were reviewed and only 15 episodes of impaired mental status were considered related to opioids. The rest of the episodes were caused by other correctable factors such as other drugs or intercurrent diseases (Leipzig et al., 1987). Other studies have shown that the cause of cognitive failure is difficult to establish in a majority of cases (56%) (Bruera et al., 1992). Studies applying objective test for cognitive function have shown higher incidences of impaired cognitive function than the patients' self-reports. Cognitive failure as defined by a MMS score equal or less than 24 was observed in 44% of patients when admitted to a palliative care unit and in 68% when assessed prior to death (Pereira et al., 1997). Wood et al. observed sub-normal results on neuropsychological test in palliative care unit patients despite no clinical evidence of impairment of cognitive function (Wood et al., 1998). The findings on mental impairment caused by opioids are not universally in agreement. Cognitive ability as measured by driving ability was not worse in cancer patients on chronic morphine therapy compared with age matched pain free volunteers without regular analgesics (Vainio et al., 1995). The role of opioids was also doubted in a double-blind, crossover study on 12 volunteers comparing the cognitive and psychomotor effects from oral morphine, lorazepam and placebo, and in a study on ten healthy subjects taking repeated doses of dextropropoxyphene, morphine, lorazepam and placebo (O'Neill et

al., 2000; Hanks et al., 1995). Both studies showed that lorazepam but not morphine caused clinical significant cognitive impairment. In a study on 130 cancer patients by Sjøgren et al. the performances on neuropsychological tests were related to lower performance status and higher pain intensity but not to the use of opioids (Sjøgren et al., 2000). This finding is supported by Lorenz et al., who observed that perceptual cognitive status in patients with chronic non-malignant pain improved after the start of morphine (Lorenz et al., 1997). Lorenz et al. speculated if this finding was caused by lack of pain as a mental stressor.

Constipation

Constipation is present in 23% of treatment days during all three steps of the WHO pain ladder for treatment of cancer pain (Zech et al., 1995; Meuser et al., 2001). In a longitudinal study of 593 cancer patients constipation was more severe during step three than during step two of the WHO pain ladder for treatment of cancer pain despite the use of adequate prophylactics (Meuser et al., 2001). The constipation during step two treatment with codeine is possibly partly caused by morphine as indicated by that bowel transit time is prolonged in extensive metabolizers of codeine (Mikus et al., 1997). The incidence of constipation is higher in patients with more advanced cancer disease as shown by Fallon and Hanks who found that 35 of 50 patients (70%) are constipated on referral to a palliative care team (Fallon & Hanks, 1999). After treatment with laxatives 26% of the patients remained constipated. Persistent constipation was associated with performance level and not with opioid dose. The relation between opioids and constipation is supported by that addition of NSAIDs in order to decrease the morphine dose is shown to correct opioid bowel syndrome in some cases (Joishy & Walsh, 1999). Opioid induced constipation may also be attenuated by the use of oral opioid antagonists such as naloxone or other opioid antagonist substances that do not cross the BBB (Liu & Wittbrodt, 2002; Taguchi et al., 2001).

Respiratory depression

Respiratory depression is a feared complication during treatment of acute pain, but is very infrequent during long-term morphine treatment for cancer pain (McQuay, 1999). The lack of a respiratory depression associated with even high doses of morphine during chronic treatment may be caused by that

the pain experienced by cancer patients counteracts the respiratory depressant action from opioids. This hypothesis is supported by Combes et al. who observed an increase of respiratory influence from morphine when pain is abolished by local anesthetics and by Borgbjerk et al. who demonstrated that experimental pain attenuated opioid induced respiratory depression in human volunteers (Combes et al., 2000; Borgbjerg et al., 1996).

Other adverse effects

Itching is reported in about 6 % of treatment days during all three steps of the WHO pain ladder for treatment of cancer pain. The finding that itching is not more frequent after start of opioids suggests that the itching is only occasionally caused by oral morphine (Meuser et al., 2001).

Morphine given in high doses may elicit excitatory side effects such as hyperalgesia and myoclonus. Gattera et al. have shown that the use of morphine is one of several risk factors for akathisa in terminal cancer patients (odds ratio 5.9 (CI; 1.9-14.2)) and Sjøgren et al. reported several cases where excitatory symptoms resolved after morphine treatment was changed to other opioids (Gattera et al., 1994; Sjøgren et al., 1993; Sjøgren et al., 1994). The excitatory adverse effects from morphine are speculated to be caused by accumulation of M3G (Sjøgren et al., 1998; Mercadante, 1998).

Opioids may also cause vertigo and dizziness. The importance of these adverse effects should not be underrated since vertigo is related to falls. Shore et al. have shown that even the opioids for mild or moderate pain, codeine and dextropropoxyphene, increased the relative risk of hip fracture in elderly patients to 1.6 compared to non-users. Concomitant use of psychotropic drugs enhanced this increased relative risk to 2.6 compared with non-users of opioids (Shore et al., 1992).

Methodological considerations

The methods applied in studies investigating effects from morphine used for cancer pain varies. These variations include different inclusion and exclusion criteria for defining the study populations, different study settings, different study designs, different methods for measuring pain, different methods for measuring adverse effects, different morphine formulations and different previous durations and doses of morphine before entering the studies. Some studies are limited in that details describing the study population or relevant outcomes are not presented or in that results are given without describing the specifics of the methods.

The cancer pain patient population

The cancer pain patient population represents in itself a challenge for doing research. The patients have often several concomitant symptoms as found by Walsh et al. in a survey of 1000 palliative care patients having an average number of 11 (range; 1-27) symptoms (Walsh et al., 2000). In addition to multiple symptoms the patients are exposed to methodological difficulties caused by multisystem affection and polypharmacy (Kaasa & DeConno, 2001; Mazzocato et al., 2001). Such factors are especially important in studies on subjective outcomes, whereas other diseases and medications may mimic opioid induced adverse effects (Cherny et al., 2001).

Several drugs are reported to have a potential to interact with opioids, but the clinical importance of such interactions are less established (Bernard & Bruera, 2000). A complete list of all drugs proposed to interact with morphine is too extensive in order to be presented in this thesis. Ranitidine has been associated with increased morphine serum concentrations (McQuay et al., 1990), but did not significantly influence serum concentrations of morphine, M6G and M3G in a cross-over study in human volunteers (Aasmundstad & Størset, 1998). Addition of nimodipine, a calcium-channel blocking agent, decreased the morphine dose requirement and morphine dose escalation in cancer patients (Santillan et al., 1994). This finding was replicated in a later blinded study on cancer patients (Santillan et al., 1998), while another randomized study on cancer patients did not observe an enhancement of morphine analgesia from nimodipine in cancer patients (Roca et al., 1996).

The combination of an opioid and a NMDA blocking agent may enhance analgesia (Wiesenfeld-Hallin, 1998), and may inhibit the development of tolerance to opioids. Low-dose ketamine may provide profound analgesia in cancer patients with escalating morphine doses and pain (Fine, 1999; Mercadante et al., 2000; Klepstad et al., 2001a). However, a randomized study of cancer patients titrated to the next step of the WHO pain ladder did not show any efficacy from dextromethorphan (Mercadante et al., 1998a). The cholecystokinin antagonist L-364,718 enhanced morphine analgesia in the rat tail flick test (Dourish et al., 1988). In chronic non-cancer pain proglumide is demonstrated to enhance the analgesic efficacy of morphine (McCleane, 1998). This effect is mediated through an antagonistic effect on cholecystokinin.

Pharmacological actions on the opioid receptors may have clinical implications. In animals the co-administration of morphine, a μ-opioid agonist, and oxycodone, a k-agonist, gives a synergistic action in respect to analgesia (Ross et al., 2000). In postoperative pain treatment low-dose naloxone reduced the incidence of side effects without influence pain intensity. It is speculated that the concentration effect curves are different for different opioid effects (Mercadante, 1998).

The WHO pain ladder involves the use of non-opioids such as NSAIDs, which have an analgesic efficacy comparable to opioids for mild to moderate pain. The NSAIDs shows a dose response relationship within the recommended dosage interval, but have not increased efficacy in doses above those recommended for other pains. NSAIDs may decrease the dosage requirements of opioids and by this mean reduce adverse effects. The exact role for NSAIDs in respect to treatment with opioids for moderate to severe pain is not established (Eisenberg et al., 1994; Jenkins & Bruera, 1999). Some interactions between NSAIDs and morphine may be caused by an interaction of NSAIDs with the renal elimination of morphine metabolites (Hobbs, 1997).

Clinical studies on drugs for cancer patients are often performed on patients at an early stage of cancer and in patients younger than the ordinary cancer population. The studies often defines several exclusion criteria selecting patients without any confounding factors and the results are extrapolated to the terminally ill cancer pain population (Kaasa & De Conno, 2001; Mazzocato et al., 2001). The rationales for performing studies at an early

stage of cancer are to avoid confounding factors (e.g. other medications, radiotherapy, other symptoms) and to have an expected survival that outlasts the planned duration of a study. It is important to recognize that clinicians must be aware the limited generalisability for the palliative care population of data collected in studies on more healthy patients (Kaasa & De Conno, 2001). Consequently, clinical trials should be performed in a population that resembles as much as possible the population were the intervention will be used (Mazzocato et al., 2001). The studies presented in this thesis illustrate the presence of multiple factors besides the use of a study drug. Several patients received anti-cancer therapy (radiotherapy 35%, chemotherapy 25%, hormonal therapy 15% and corticosteroids 17% (paper I and II). The patients included into paper I used an extensive list of 40 different non-pain related medications.

The inclusion of patients with advanced cancer disease into a study needs careful planning of the study design. The use of research instruments must be appropriate in respect to the selected study population. Lengthy questionnaires may create little discomfort in patients with local disease but be burdensome for patients with advanced disease. In a validation study on the BPI questionnaire Radbruch et al. found that the number of incomplete questionnaires increased with detoriating performance status (Radbruch et al., 1999a). The limited feasibility of questionnaires in severely ill patients is also demonstrated for HRQOL questionnaires, and few patients are able to return complete questionnaires during the last month before death (Jordhøy et al., 1999). Consequently, studies including patients with advanced cancer disease should use instruments, for measuring pain and other symptoms, which are short and easily understood. Compliance can also be improved if questionnaires are handed directly to and collected directly from the patients.

The information gained by having a long follow-up period must be carefully weighted against the risk for drop-outs caused by death or impairment caused by progressive disease (Kaasa & De Conno, 2001). The number of drop-outs in longitudinal studies on cancer pain is typically more than one third, and some studies have drop-out rates that seriously questions the validity of findings (Bruera et al., 1998). One explanation for the high drop-out rates is that physicians tend to overestimate the duration for life of terminal cancer patients (Vigano et al., 1999). The patients are also exposed to acute episodes of intercurrent diseases such as infections,

acute surgery for a number of causes and psychiatric crises. Consequently in the planning of longitudinal palliative care studies it is important to have realistic expectations for the patients' ability for long-term participation. This is illustrated in paper I and III with twelve of eighty patients excluded during the study period despite a short period for follow-up. However, it is worthwhile to note that no patients included into the studies in this thesis were excluded due to adverse effects from morphine or failure to achieve adequate pain relief.

Patients experiences of pain

Pain is not a uniform sensation. In paper I of the thesis we observed that the patients reported a median number of 4 pain qualities. The observed frequency of pain qualities were aching pain 33/40, burning pain 11/40, deep pain 32/40, dull pain 32/40, lancinating pain 15/40, sharp pain 14/40, superficial pain 8/40 and tearing pain 17/40. As illustrated in table 1 of paper I we observed no apparent systematic combinations of pain qualities. The number of patients did not invite to analysis on subgroups.

Pain is a more complex sensation than nociception and pain can not be assumed to be directly related to the nociceptive stimuli (Fields, 1988). Variability may be caused by physiological mechanism such as differences in pain pathophysiology and in differences in the non-specific (placebo) activation of endogenous opioid system (Fields, 1988; Amanzio et al., 2001). The patients' responses to pain vary. Weiss et al. showed that a large proportion of patients with pain chose to tolerate pain instead of increasing pain therapy (Weiss et al., 2001; Ahmedzai, 2001). After titration of morphine in paper II the study patients EORTC QLQ-C30 pain scores were as high as 41 compared to a score of 24 in the general population (paper II)(Hjermstad et al., 1998). Still, the patients chose to stop escalation and reported satisfactory pain relief. This may be due to a trade-off between the expected adverse effects and expected pain relief associated with increasing opioid dosages. Another possibility is that the patients' expectations of pain relief during malignant disease influences the level of pain intensity perceived as satisfactory. Patients' reluctance to receive appropriate pain therapy may also be caused by fear of addiction or fear of development of tolerance (Weiss et al., 2001; Paice et al., 1998). Paice et al. demonstrated that patients who fear addiction or tolerance experienced more pain than patients not having these concerns (Paice et al.,

1998). In the study by Paice et al. one quarter of the hospitalized patients also were concerned to bother the nurses. These patients experienced more pain than patients not hesitant to call for the nurse (Paice et al., 1998). As for other drugs a potential bias in studies on pain treatment is lack of compliance. Patients adherences to opioid analgesics prescribed around-the-clock-basis are rather good (89%) while use of opioids prescribed on a per needed basis showed a low compliance (25%) of the prescribed doses (Miaskowski et al., 2001). The patients' pain experiences are also influenced by treatments besides conventional therapy. Risberg et al. showed in a Norwegian sample of 642 cancer patients that 20% of the patients used non-proven therapy such as healing by hand, faith healing, herbs, vitamins, and diets (Risberg et al., 1997).

Baseline drift

One important methodological issue in longitudinal studies on effects from morphine in cancer patients is baseline drift (natural fluctuation of symptoms not associated with the intervention). Baseline drift is important both in respect to assessments of symptoms and to the pharmacological actions from morphine. The patients' experiences of subjective symptoms are linked to their expectations of intensity of symptoms. This phenomenon is called response shift. Despite increased intensity patients may report equal or less intensity of a particular symptom. They relate symptom intensity more to what they expect at that stage of disease than to the absolute intensity of a symptom (Carr et al., 2001).

The development of tolerance to the antinociceptive effect from morphine is well established in animals models, and this development of tolerance may be modified by agents interacting with protein kinases, cholecystokinin, nitrogen oxide and NMDA receptor functions (Zeitz et al., 2001; Dourish et al., 1988; Kolesnikov et al., 1995; Ben-Eliyahu et al., 1992; Tiseo et al., 1994; Trujillo & Akil, 1991; Marek et al., 1991; Manning et al., 1996; Mao et al., 1996) The development of tolerance is complex and may share some of the neural mechanisms associated with neuropathic pain (Mao et al., 1995a). Tolerance may be related to properties of opioids such as intrinsic efficacy (Duttaroy & Yoburn, 1995). It has also been proposed that tolerance may be attenuated by alternating between delta and mu-opioid agonist (Russel & Chang, 1989). The efficacy of opioids may also be modulated through G_s-coupled GM1

ganglioside-regulated receptor functions. These receptors are hypotized to mediate opioid induced excitatory effects and consequently display a bimodal effect of opioids. Blocking of this excitatory opioid binding receptors enhances the inhibitory effect of opioids and attenuates tolerance during chronic opioid exposure (Crain & Shen, 1998; Mao et al., 1995b; Elliot et al., 1994).

The clinical implications from opioid tolerance during treatment of cancer pain are not established. In a clinical study escalation of dose was associated with progression of the cancer disease while patients without disease progression had stable doses (Collin et al., 1993). This observation argues against tolerance as a clinical problem. In a recent review by Mercadante and Portenoy it is concluded that tolerance rarely represent a limiting factor during opioid treatment (Mercadante & Portenoy, 2001). Tolerance for some of the adverse effects is believed to develop without a parallel development of tolerance for opioid analgesia. Differential development of tolerance has been shown in a animal study by Ling et al. where tolerance to antinociception and prolactin release developed before tolerance for respiratory depression and effect on gastrointestinal transit time (Ling et al., 1989). A transient impairment in cognitive function after start of opioid therapy or after dose escalation is demonstrated in cancer patients (Bruera et al., 1989). However, this phenomenon, although often described, is not formally studied for other adverse effects (Cherny et al., 2001).

Ethics

Research that involves patients at the end of life creates several ethical challenges. Dying patients are especially vulnerable, adequate informed consent is difficult to obtain, balancing research and clinical roles are difficult, and the risks and benefits of palliative research are difficult to assess (Casarett & Karlawish, 2000; Kaasa & De Conno, 2001). Patients with advanced cancer disease are at risk for several symptoms and imminent death caused by the cancer disease and by necessary therapy. It is important to recognize that the risks associated with research should be the risks above and beyond the risks associated with usual care (Freedman et al., 1992). For instance, the patients studied in this thesis are exposed to some risk for adverse effects from morphine. However, morphine treatment would be

started also during standard care and consequently such risks should not be attributed to the patients participating in a study.

Informed consent is a prerequisite, with rare exceptions, for participation in a clinical study. The value of informed consent as the sole instrument preventing inclusions of patients into studies that may cause harm can be overemphasized. A survey of patients participating in studies on cancer directed treatment showed that 90% of the patients were satisfied with the informed consent process, the consent discussion lasted longer than one hour for 48%, and 84% had relatives or friends present at the consent discussion (Joffe et al., 2001). Despite this thorough consent procedure many patients did not recognize unstandard treatment (74%), the unproven nature of treatment (70%) and that trials are done mainly to the benefit of future patients (25%) (Joffe et al., 2001). The ethics of studies on cancer pain patients relies on the ethics of the researchers, the physicians responsible for treatments and the institutional ethics committees.

Assessment of subjective symptoms

The most widely applied method for measuring subjective symptoms is self-reports. Self-reports can be obtained as single items where the patient chose a number (NRS) or a verbal description (VRS) corresponding to the intensity of a symptom, as a line anchored with verbal description of no and maximal symptom intensities on which the patient can chose a point corresponding to symptom intensity (VAS), or as organized questionnaires with several items giving a sum corresponding to the intensity of a symptom. Whatever method investigators chose in order to measure a symptom there are several methodological issues that should be documented. Some of these methodological issues are:

- **Validity**: Does the instrument measure what it intends to measure?
- **Reliability**: Does the instrument produce the same results when repeated on the same population?
- **Inter observer reliability**: Does the instrument produce the same results when repeated by different investigators?
- **Ability to detect changes**: Does the instrument detect clinically meaningful changes?

- **Translation**: Is the instrument formally validated into the appropriate language?
- **Difference of clinical interest**: Is the difference of clinical interest on the outcome measured by the instrument known?
- **Data on the responses in the general population**: Are the responses of the instrument in the general population known?

It should be clear from this list that the development of a validated instrument for measuring a subjective symptom is a time-consuming process that needs expert capabilities in research methodology issues. It is therefore strongly to advice for researchers doing studies to apply previously validated instruments to measure subjective outcomes. The use of widely recognized, validated instruments is also a prerequisite in order to compare results across different studies and across different patient populations. Validated instruments are available for several symptoms, for performance status and for HRQOL. However, research on cancer pain is still hampered by a lack of clear definitions for cancer entities and important constructs such as breakthrough pain and neuropathic pain (Caraceni, 2001).

Pain assessment

There are several validated methods for measuring pain. Pain can be assessed using numeric rate scales (NRS), verbal rate scales (VRS) (paper I-IV), or visual analogue scales (VAS) (paper I-IV). Several variants of these scales exist using different numbers of numeric responses, different verbal categories in the VRS or different terms anchoring the VAS. These principles for quantifying pain are used as single items or included into questionnaires on pain (e.g. BPI) (paper V, VI) or HRQOL questionnaires (e.g. SF-36, EORTC QLQ-C30) (paper II, V). There are also validated questionnaires that assess pain qualities (McGill Pain questionnaire) or pain interference with functions (BPI, EORTC QLC-C30).

Jensen et al. compared VAS, NRS (101-point), 11-point box scale, 6-point behavioral scale, 4-point VRS and 5-point VRS in chronic pain patients. All scores had similar results in respect to predictive validity and the number of subjects that responds correctly. The authors recommended NRS because this was judged as the most practical of the methods (Jensen et al., 1986). The practical feasibility of NRS was confirmed in comparisons of pain

measurements in old cognitive impaired and in old cognitive normal patients (Chibnall & Tait, 2001). The NRS together with VAS and VRS correlate well with pain relief in cancer patients while more complex concepts of pain such as the McGill and The Integrated pain score (combination of intensity and duration of pain) show less association with changes in pain intensity (De Conno et al., 1994).

The NRS scores correlate well with VRS scores. Serlin et al. found that based on interference with function mild pain corresponds to 1-4 on a 11-point NRS, moderate pain corresponds to 5-6 and severe pain corresponds to 7-10 (Serlin et al., 1995). VRS moderate pain corresponds to a mean VAS score of 49 (85% of patients with VRS moderate pain reported more than 30 on the VAS score) and VRS severe pain corresponds to a mean VAS score of 75 (85% of patients with VRS severe pain reported more than 54 on the VAS score) (Collins et al., 1997). An important concept is the size of changes on a pain scale that are perceived by the patients as a meaningful pain relief. In a large analysis of data from 2724 patients Farrar et al. reported that much improved or very much improved pain corresponded to a 30% decline or a 2-point decline on a 11-point NRS (Farrar et al., 2001). This 2-point reduction of pain intensity on a 11-point NRS was also the reduction of pain sufficient for patients not asking for a second analgesic rescue dose (Farrar et al., 2000). However, as pointed out by Rowbotham it is important to recognize that these data are applied on groups of patients while individuals may vary in their relations between NRS and pain relief (Rowbotham, 2001). It is also important to recognize that pain is not a linear concept, and patients with high intensity of pain (VAS > 6) require a greater absolute change in VAS score in order to achieve clinically significant pain relief (Bird & Dickson, 2001).

The EORTC pain scores showed positive significant correlations with VRS and VAS pain scores and all three pain scores demonstrated sensitivity for change over time after start of morphine treatment (paper II). This indicates that the EORTC pain score measures the same biological effect as the VRS and VAS pain score. However, the observed correlation coefficients between the EORTC pain and VAS / VRS pain scores were in the range of $r = 0.31$ to $r = 0.60$ while the correlations between VRS and VAS pain scores ranged from $r = 0.62$ to $r = 0.82$. The EORTC pain score consists of two questions, one related to pain intensity and one related to how pain influences daily activities. These questions are different expressed than in VAS and VRS items and are present in the

context of other HRQOL questions. Consequently, the EORTC pain score may reflect other aspects of patient experience than pain. In the BPI the items on pain intensity and interference from pain are not calculated into a common pain score, but loads on two different indexes, pain severity index and pain interference index (Daut et al., 1983; Cleeland et al., 1996). Forthcoming recommendations from EAPC expert working group and reviews on pain measurements recommend the use of BPI in order to assess the intensity and the impairment on function caused by pain (Caraceni et al., 2001; Chapman & Dunbar, 1998). The BPI has gained widespread recognition and has been validated in Japanese (Uki et al., 1998), Italian (Caraceni et al., 1996), Chinese (Wang et al., 1996), Hindi (Saxena et al., 1999), Taiwanese (Ger et al., 1999), German (Radbruch et al., 1999a) and Greek (Mystakidou et al., 2001). The BPI has also been demonstrated to detect changes after adjustments of opioid therapy in patients with osteoarthritis (Roth et al., 2000). Despite it's extensive validation there are still several unresolved issues of the BPI. The most important issue in respect to palliative care research is the BPI's ability to gain a high compliance in patients with severely advanced cancer disease. In a study by Radbruch et al. performed on patients admitted to a palliative care unit a BPI pain severity index was obtained in 81 of 123 and a BPI pain interference index was obtained in 67 of 123 patients. The number of missing items correlated with cognitive function and performance status but not with age or opioid dose (Radbruch et al., 2000). Also in studies on out-patients and in general cancer patients a high proportion of patients were not able to complete the BPI (Radbruch et al., 1999a).

Other assessments

An extensive description of available methods used to assess symptoms besides pain is beyond the scope of this thesis. Consequently, this section summarizes the methods applied in the papers included into this thesis.

Nausea

Nausea was assessed using self-reports on VRS (paper I, III, IV) and VAS (paper I). Related measures on nausea were frequency of vomiting and the use of rescue antiemetics (paper I). Nausea was reported in paper II and VI as a symptom score on the EORTC QLQ-C30 nausea and vomiting symptom scale.

Constipation

Constipation was assessed using self reports VRS with the categories "not at all, some", "severe" and "very severe constipation" (paper I, III, IV) and as EORTC QLQ-C30 symptom item scores (paper II, VI).

Sedation

Sedation was assessed using self reports VRS with the categories "not at all", "some", "severe" and "very severe tiredness" (paper I, III, IV). In study VI the EORTC QLQ-C30 four categorical item, "Were you tired" with the response choices "not at all", "a little", "quite a bit" and "very much", was applied in order to assess tiredness. In a study on patients with advanced cancer disease receiving morphine the majority of patients reported to feel tired (Klepstad et al., 2002). This phenomenon, however, was not reflected in objective assessments of sedation (OAA/S score) (Chernic et al., 1990), which showed no or little sedation in all except one patient (Klepstad et al., 2002). Thus, patients experience sedation (tiredness) before they exhibit signs of pharmacologically profound sedation. The term sedation is easily misinterpreted. In some contexts sedation means decreased level of consciousness as a targeted end point for pharmacological interventions while in some contexts it is used for tiredness experienced by patients during chronic disease or drug therapy. Terms clearly distinguishing between sedation for procedural interventions, terminal sedation at the end of life, sedation as an adverse effect from opioids or other drugs, and sedation used as a term describing tiredness related to decreased general health are needed.

Cognitive function

Cognitive self-reports of cognitive function were reported as an EORTC QLQ-C30 cognitive function scale score (paper II-III). This score is calculated from the patients' responses on two items; "Have you had difficulty in concentrating on things, like reading a newspaper or watching television?" and "Have you had difficulty remembering things?". The objective test to measure cognitive function, MMS, was applied in paper V and VI. The MMS score ranges from 0 to 30, with higher scores meaning better cognitive function. This standardized cognitive screening examination has been shown to be valid, reliable and able to document changes in cognitive function (Folstein et al., 1975). The feasibility of MMS has also been demonstrated in studies on patients with terminal cancer (Pereira et al., 1997). Studies in both patients cured from cancer and in patients with terminal

cancer disease shows that self-reported cognitive function and results from objective tests are not directly related (Cull et al., 1996; Klepstad et al., 2002). The dissociation between self-reports and observations have several plausible explanations. First, the objective test may not be sensitive enough to detect small but perceivable alternations of cognitive function. It is conceivable that patients despite being able to perform the tasks included in the MMS, experience a reduced ability in respect to other more intellectual demanding occupations. Second, with increasing detoriated cognitive function as assessed by the MMS the patients may have increasingly lack of insight resulting in a paradoxical lack of relationship between objective scores and self-reports of cognitive function. Third, the patient may experience other symptoms such as tiredness or lack of general health that influences the patients' perception of cognitive function.

Health related quality of life

Several methods are developed to measure HRQOL (Portenoy, 1990; Kaasa, 1992) and the importance of assessments of HRQOL in clinical studies is widely recognized (Wisløff et al., 1996). In the papers (paper II, III, V and VI) reporting data on HRQOL we have applied the EORTC QLQ-C30 HRQOL questionnaire (Aronsen et al., 1993). The questionnaire consists of 30 items, which incorporates five functional scales (physical, role, emotional, cognitive, social), three symptom scales (fatigue, pain, nausea/vomiting), a global health and quality of life scale and six additional single items (dyspnea, appetite loss, sleep disturbance, constipation, diarrhea, financial impact of the disease and treatment). The psychometric properties and validity of the questionnaire have been found to be satisfactory (Aaronson et al., 1993; Kaasa et al., 1995; Wisløff et al., 1996) and the test/retest reliability is optimal (Jensen Hjermstad et al., 1995). In all studies we delivered and collected the questionnaires directly from the patients. This procedure ensured that all questionnaires were returned.

In order to exclude that the lack of observed differences in HRQOL scores before and after start of morphine was caused by lack of assay sensitivity we compared our findings with the expected observations in a general Norwegian population using reference data adjusted for the distribution of age and gender (Jensen Hjermstad et al., 1998; Hjermstad et al., 1998). The patients included into the studies (see table 2, paper II) had severely disturbed functional scores and fatigue, pain, nausea and vomiting, appetite loss, and constipation

symptom scores compared with a normal population confirming the assay sensitivity of the EORTC QLQ-C30.

As for pain an important concept during interpretation of HRQOL results is the clinical difference of interest. Osoba et al. showed that for the EORTC QLQ-C30 a change of 5-10 points corresponded to "little change", a 10-20 change in points corresponds to "moderate change" and more than 20 change in points corresponds to "very much change" (Osoba et al., 1998).

Performance status

Performance status was assessed using Karnofsky performance status in all papers included into the thesis (Karnofsky et al., 1948; Yates et al., 1980).

Pharmacological analyses

Preanalytical factors

Westerling et al. have compared the effects of different preanalytical conditions on the measurements of morphine, M6G and M3G serum concentrations. Comparisons of heparin tubes, gel tubes and EDTA tubes showed equal results in respect to reference values for all M6G and M3G analyses. The results on morphine serum concentrations in EDTA tubes were significantly higher than reference morphine results, but the clinical importance of this difference is limited since EDTA tubes only gave 4.8% higher measurements of morphine serum concentrations than reference samples. Comparisons of incubation of samples at 0° and 20° had no influence on measurements of morphine, M6G and M3G. In accordance with this finding, the use of different centrifugation temperatures (0° versus 20°) had no influence on the results. Incubation at body temperature (37°) resulted in 4.4% higher results on morphine concentrations while M6G and M3G was not affected. The implication of this finding is limited since incubation at body temperature is not common practice. The effect from incubation time, ranging from 15 to 240 minutes, was studied at all three alternative temperatures (0°, 20° and 37°), without any influence on the morphine, M6G and M3G serum concentrations results. Samples were analyzed directly fresh from centrifugation, after being frozen and after being melted and refrozen, without the finding of any significant differences in the morphine, M6G and M3G

serum concentrations (Westerling et al., 1996). Morphine and glucuronides are also demonstrated to be stable when stores in plasma for up to two years (Milne et al., 1991). Thus, analyses of morphine, M6G and M3G are robust to differences in preanalytical handling of samples.

Analytical factors

Serum samples were stored at –20°C until the analyses were performed. In paper III serum concentrations of morphine (morphine base), M3G and M6G were determined by reverse phase HPLC with ultraviolet and electrochemical detection (Svensson et al., 1982). The lower limits of quantification were as follows: morphine 10 nmol/l, M3G 100 nmol/l and M6G 10 nmol/l.

In paper VI the samples were analyzed for serum concentrations of morphine, M6G and M3G applying LC-MS (Bogusz et al., 1997). LC-MS has good sensitivity and shorter analysis time and fewer interfering peaks than HPLC. The limits of detection using the LC-MS in paper V were 0.35 nmol/l for morphine and 2.2 nmol/l for M6G and M3G. The analytical coefficients of variation were 3.0% for morphine, 5.5% for M6G and 7.0% for M3G.

To which degree is an obtained serum concentration representative?

Sample in respect to time of administration

Samples should be taken at defined times in respect to administration of morphine. This is most vital in single dose studies since patients on stable doses shows less fluctuations during a dosage interval. In paper IV we observed only small fluctuation of serum concentrations of morphine, M6G and M3G after IR morphine administration while the serum concentrations fluctuated about 50% after SR morphine administration. The fluctuations of the relations between morphine and M6G and M3G were stable after IR morphine and varied in the same order of magnitude as the absolute serum concentrations after SR morphine administration. (paper IV). The study presented in paper VI did not obtain samples at an exact time in respect to morphine administration. This approach was used in order to assess the feasibility of clinical routine drug monitoring of morphine and metabolites.

Interfering rescue medication

The incidence of breakthrough pain (temporary or incident pain) varies between studies but are typically reported in about half the cancer patients (Portenoy & Hagen, 1990; Petzke et al., 1999; Portenoy et al., 1999). The breakthrough pain is mostly severe and often occurs several times each day (Petzke et al., 1999; Portenoy et al., 1999). The frequency and incidence of breakthrough pain are often underestimated by caregivers (Fine & Busch, 1998). Breakthrough pain necessitate that patients have access to rescue analgesics. In studies that measure serum concentrations of morphine and metabolites, rescue doses taken before blood sampling may cause unrepresentative elevated serum concentrations. Paradoxical, the patients' low compliance for taking analgesic per needed is favorable in regard to this methodological confounding effect on measurements of opioid serum concentrations (Miaskowski et al., 2001).

Chronotropic variability

Gourlay et al. showed that plasma morphine concentrations have chronotropic variability with different plasma concentrations observed during three day-time 4-hourly IR morphine intervals (Gourlay et al., 1995). Consequently, in order to have strict standardization of the time of blood sampling it is necessary to obtain the samples during the same dosage intervals. Pain intensity also vary throughout the day (paper I). Despite this chronotropic variability the existence of a significant diurnal variability in the use of opioids in cancer patients is not established (Klepstad et al., 2001c), and it is not recommended that clinicians should systematically consider chronopharmacological factors in the routine prescription of strong opioids. Still, tailoring of opioid doses in respect to time may be appropriate according to the needs of the individual patient.

Interindividual day-to-day-variation

Vermeire et al. observed that in cancer patients receiving continuous SC morphine infusions serum concentrations fluctuated between samples obtained at different days (Vermeire et al., 1998). We found that compared to SC morphine treatment the day-to-day variations were higher during oral morphine with median relative standard deviations for morphine 55%, for M6G 37%, and for M3G 43% (Hilton et al., 2002). The corresponding median max/min ratios were 2.7, 2.4, and 2.1. These findings are not surprising since factors such as food intake, gastric retention, malabsorption, effects from

other drugs on gastric emptying, vomiting and variability of first-pass metabolism will influence the pharmacokinetic observations during oral administration. Results from blood samples taken in order to assess a patient's pharmacological morphine status must be interpreted with the understanding of that considerable fluctuation of serum concentrations may occur.

Serum samples in respect to effect compartment

The relations between measurements of serum concentrations with the corresponding concentrations of morphine and metabolites in the central nervous system are discussed in the introduction. Several factors may influence on the this relation such as transport of morphine and metabolites through the BBB, transport of morphine and metabolites from the extracellular space into brain cells, endogen production of morphine in the brain, and brain metabolism of morphine to M6G and M3G. Besides interindividual differences such functions may be altered because of intracranial pathology (Bouw et al., 2000a). The uncertainty in the relations between serum concentrations in respect to effect site concentration in the brain extracellular fluid is a shared limitation of all studies, including the results in paper IV and VI.

Statistics

The results are generally presented as means or medians for normal distributed and non-parametric variables, respectively. The distribution of the data are given using standard deviations, confidence intervals or ranges as appropriate for the data and also according to the different journals instructions. Comparisons of data were defined as appropriate for paired comparisons of non-parametric data (Wilcoxin signed ranks test) (paper I, II, IV), paired comparisons of continuous data (paired Student t-test) (paper I, IV), dichotome variables (Mc Nemar test) (paper I), non-parametric comparison of two study groups (Mann Whitney U-test)(paper III, VI) and comparison of continuous data in two study groups (Student –t test).

Correlations were performed with Pearson (paper II) or Spearman's correlation (paper IV, V) as appropriate. Linear regression analyses were used in order to analyze potential factors predicting variability of morphine serum

concentrations (paper III) and variability of pain intensity and the intensity of adverse effects (paper VI).

Construct validity of the BPI was examined using a principal axis factor analysis (paper V), while Chronbach's alphas coefficients were calculated in order to assess the reliability of the items included in the pain severity and pain interference indexes of the BPI (paper V).

The specifics of the sample size estimations are given in each individual paper.

Summary of papers

Paper I

Pain intensity and side effects during titration of morphine to cancer patients using a fixed schedule dose escalation

Considerable dose variations and frequent initial side effects are postulated during start of morphine treatment to patients with pain caused by malignant disease. However, to our knowledge, only one previous study reports effective doses in morphine naive cancer patients and no prospective evaluations have compared symptoms before start of morphine with symptoms after morphine titration. We recruited forty cancer patients with uncontrolled pain despite receiving codeine or dextropropoxyphene. Baseline data were obtained for two days before start of morphine titration using a fixed scheduled escalation of IR morphine. When a stable morphine dose was achieved IR morphine was replaced with SR morphine in equivalent doses. We assessed intensity of pain and side effects daily along with registrations of daily consumption of morphine, rescue analgesics and rescue antiemetics.

We observed that the mean titration time needed to achieve adequate analgesia was 2,3 days (range; 1 - 6) and the mean daily titrated morphine dose was 97 mg (range; 60 - 180). Nausea was unaltered after start with morphine but an increased incidence of vomiting occurred. Transient sedation delayed dose increment in nine of the forty patients but mean sedation scores were not altered. Constipation scores increased while other side symptom scores were unaltered. Eighty-two percent of the patients were satisfied or very satisfied with the introduction of morphine.

The study finds that in cancer patients with uncontrolled pain on opioids for mild to moderate pain, successfully titration of morphine is achieved fast, with a three-fold morphine dose variation and with little increase in side effects.

Paper II

Effects on cancer patients' health-related quality of life after the start of morphine therapy.

In order to investigate the effects from morphine on cancer patients' HRQOL we measured HRQOL by EORTC QLQ-C30 before start of morphine (baseline), after stabilization with IR morphine, and 3 days after start of SR morphine. The study was performed in the same patient population as presented in paper I. EORTC QLQ-C30 pain score decreased from 65 before start of morphine to 43 and 41 after start of IR and SR morphine, respectively. The EORTC QLQ-C30 global health score increased after IR morphine titration (baseline score 40, IR morphine period score 49) but a significant difference from baseline did not persist during the SR morphine period (score 44). The other functional HRQOL scores showed no significant fluctuation. After start of IR morphine two of the HRQOL symptom scores increased, nausea/vomiting and constipation, but also these changes did not persist during the SR morphine period. Intensity of pain was associated with a lower level of function and higher intensity of symptoms but only with relatively small (not higher than 0.44) correlation coefficients. Compared to norm data from the general population physical function, role function, social function and global health were impaired in the study patients. The patients also suffered more fatigue, pain, nausea/vomiting, appetite loss and constipation. In conclusion, in cancer patients with reduced HRQOL, the start of morphine therapy had no major influence on other aspects of HRQOL than pain.

Paper III

Randomised, double-blind comparison of immediate-release morphine and sustained-release morphine for dose-finding during start of morphine treatment of cancer pain.

The EAPC recommendations (recommendation number 3, table 1) includes a titration procedure using IR morphine given four-hourly during start of oral morphine for cancer pain. This procedure is based upon expert opinion, and no controlled study has been performed. We compared the clinical efficacy of

this recommended method with a direct start of oral sustained-release morphine given once daily. Forty patients with malignant disease and pain despite treatment with opioids for mild to moderate pain were included into a randomized, double-blind, double-dummy, parallel-group comparison of titration with IR morphine given 4-hourly plus placebo once daily, and titration with sustained-release morphine given once daily plus placebo 4-hourly. The primary end point was time needed to achieve adequate pain relief. Secondary end points were other symptoms (nausea, tiredness, lack of sleep, vertigo, appetite and constipation), HRQOL (EORTC QLQ-C30) and patient satisfaction.

The mean times needed for titration were 2.1 (95% CI; 1.4-2.7) days using IR morphine and 1.7 (95% CI; 1.1-2.3) days using sustained-release morphine. We observed no differences in side effects or HRQOL function scales. Similar global satisfactions with the morphine treatments were reported. The results in this study suggest that a simplified titration of morphine to cancer pain patients using sustained-release morphine given once daily is equal effective and has not more side effects than titration using IR morphine given four-hourly.

Paper IV

Start of oral morphine to cancer patients: Effective serum morphine concentrations and contribution from morphine-6-glucuronide to the analgesia produced by morphine

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The aim of this study was to investigate the serum concentrations of morphine, M3G and M6G during start of morphine in cancer patients and the relations between the serum concentrations and clinical effects. We included forty patients with malignant disease and intolerable pain on opioids for mild to moderate pain (codeine / dextropropoxyphene). Morphine treatment was started with IR morphine and changed to SR morphine when a stable dose was achieved. Clinical data and serum concentrations of morphine, M3G and M6G were obtained at the end of the IR and SR morphine periods.

The mean trough serum morphine concentration associated with pain relief when disease progression necessitated an increase of intensity of pain therapy

from step two to step three in the WHO pain ladder was 66 nmol/l. The corresponding mean concentrations of M6G and M3G were 257 nmol/l and 1943 nmol/l respectively. Morphine serum trough concentrations showed a 33-fold variation. Seventy percent of the variation was predicted in a model including age, daily morphine dose and M6G/morphine ratio as independent variables. No associations were observed between side effects and serum concentrations of morphine and its metabolites.

Increased ratio of M6G vs. morphine serum concentrations predicted lower effective serum morphine concentrations. This observation support that M6G contributes to the analgesia produced by oral morphine in patients with pain caused by malignant disease.

Paper V

The Norwegian Brief Pain Inventory. Translation and validation in cancer patients.

The EAPC recommends the BPI as a pain assessment tool in clinical studies. After translation into Norwegian we administered BPI to 300 hospitalized cancer patients. Chronbach's alphas were computed to assess reliability, and factor analysis was utilized to ascertain construct validity. The BPI interference and pain severity scales were validated against items on pain intensity and pain influence on daily function in the EORTC QLQ-C30 questionnaire. In total, 235 patients (78%) were able to complete the BPI questionnaire, but 82 (35%) of these questionnaires had one or more missing items. Chronbach's alphas were 0.871 for the pain severity and 0.921 for the interference scales. A factor analysis identified three factors; pain intensity, interference with physical function, and interference with psychological functions/sleep. These three factors explained 82% of the variance. The correlation between BPI pain severity index and the EORTC QLQ-C30 item on pain intensity was 0.695 ($p<0.001$). The correlation between BPI interference index and the EORTC QLQ-C30 item on pain influence on daily living was 0.621 ($p<0.001$). We conclude that BPI has satisfactory psychometric properties, but is not completed by a significant proportion of patients. Further research is needed to establish pain assessment tools for patients unable to answer a comprehensive pain questionnaire, to establish

routines for analysis of missing values, and to investigate if pain interference items also reflect disease-related impairment.

Paper VI

Drug monitoring of serum concentrations of morphine, morphine-3-glucuronide and morphine-6-glucuronide do not predict clinical observations in cancer patients.

The relationships of serum concentrations of morphine, M6G and M3G to clinical effects during chronic morphine therapy are not established. This uncertainty limits the value of serum concentration determinations for clinical decision making. Morphine, M6G and M3G serum concentrations in 300 cancer pain patients on oral or SC morphine were measured. Regression analyses were performed to investigate if serum concentrations of morphine, M3G and M6G or demographic variables predicted pain intensity (BPI), HRQOL variables (EORTC QLQ-C30) and cognitive function (MMS). Serum concentrations and ratios in patients categorized as morphine "treatment successes" with patients classified as "treatment failures" were compared.

The median morphine doses for patients receiving oral morphine (n=263) and sc morphine (n=35) were 80 and 110 mg/24h, respectively. The serum concentrations of morphine, M6G or M3G did not predict pain intensity, cognitive function, nausea or tiredness. "Treatment failures" caused by nausea, tiredness, cognitive failure or constipation were not associated with statistically significant different morphine, M6G and M3G serum concentrations as compared to patients classified as "treatment successes". We observed no differences in M6G/morphine, M3G/morphine and M3G/M6G ratios between treatment successes and failures.

This study demonstrated a lack of serum concentration-effect relationships of morphine, M3G or M6G with pain intensity, nausea, constipation, tiredness or cognitive failure during chronic morphine therapy in cancer patients. These findings suggest that monitoring of serum concentrations of morphine and morphine metabolites during routine morphine treatment is of limited clinical value

Discussion

Effects and adverse effects from start of morphine

Paper I demonstrated that a rapid titration (daily dose increase 33-50 %) using a fixed scheduled dose titration protocol was well tolerated by the patients and gave fast satisfactory analgesia. This finding was confirmed in paper III. The time needed for morphine titration was 2.3 days in paper I and 2.1 and 1.7 days in paper III. In morphine naive cancer patients Vijayaram et al. reported a mean period of 4 days until satisfactory pain control (Vijayaram et al., 1990). However, that paper did not describe the procedure for morphine titration or the mean effective morphine dose. In our study oral IR morphine titration was accomplished at average daily doses of 97 mg (paper I), 94 mg and 82 mg (paper IV).

The pain relief observed in paper I after start of morphine was shown by a decrease in self-reports of pain intensities and a decrease in use of analgesics given per needed. The clinical significance of preintervention pain experienced by the patients was illustrated by the high numbers of patients reporting that pain influenced on physical and social function (paper I).

Several studies report that oral morphine treatment is complicated by constipation, nausea and sedation, while effects on vital functions (e.g. respiration depression and hypotension) are infrequent (Twycross, 1994; Thirlwell et al., 1989; Mignault et al., 1995; Khojasteh et al., 1987; Hanks, 1989; Gourlay et al., 1997). However, these studies evaluate cancer patients receiving long-term treatment with high doses of morphine and their findings may not be relevant for cancer patients previously exposed only to opioids for mild to moderate pain. In addition, these studies are not designed in order to distinguish between opioid induced symptoms and symptoms related to other causes. One obvious approach in order to make this distinction is to compare the patients' symptoms before start of morphine and after start of morphine.

In paper I start of morphine was not associated with an increase in nausea, neither in respect to intensity, in respect to number of patients reporting increased, unchanged or decreased nausea after start of morphine, nor in respect to consumption of antiemetics. The same results appeared in paper

III (unpublished results). Previous studies have reported higher prevalence of opioid induced nausea (Zech et al., 1995; Hanks, 1982; Campora et al., 1991). The findings in our studies demonstrate that observations obtained before start of morphine are valuable in order to differentiate opioid induced nausea from nausea caused by tumor involvement of the gastrointestinal tract, metabolic effects from tumor, chemotherapy, radiotherapy, renal failure or brain metastasis. The lack of change in nausea associated with start of morphine could partly be due to nausea or development of opioid tolerance from codeine or dextropropoxyphene prior to inclusion in the study. The higher prevalences of nausea observed in other studies can also be explained by the inclusion of patients with more advanced cancer disease.

In the combined nausea and vomiting scale of the EORTC QLQ-C30 an increased score were observed after start of morphine (paper II). This finding may at first seem to be in conflict with the lack of differences in nausea VRS and VAS scores (paper I). In paper I, however, the frequency of vomiting increased after start of morphine, and interestingly more than half of the patients who vomited did not report clinical significant nausea. Thus, the finding in paper I of no difference in nausea but increased incidence of vomiting harmonizes with the increased nausea and vomiting scale score observed in paper II. These observations indicate the potential of a dissociation between nausea and vomiting. Both nausea and vomiting can be caused by stimulation of chemosensitive and vestibular structures and by decreased peristaltic activity. Still, the relatively importance of these mechanisms may differ between nausea and vomiting and these two symptoms should not be summarized on the same continuum (Allan, 1993).

Sedation is considered to be a common side effect after initiation or dose escalation of oral morphine therapy (Bruera et al., 1989; Twycross, 1994). However, to our knowledge, no studies have compared sedation before and after initiation of morphine treatment. In paper I and III (unpublished results) the start of morphine did not increase self-reported sedation, although in paper I one quarter of the patients postponed a dose increment because of sedation. This lack of difference in VRS sedation could partly be due to sedation or development of opioid tolerance from opioids for mild to moderate pain prior to inclusion in the study. Excessive tiredness

experienced by cancer patients may also be explained by causes other than opioid therapy such as lack of sleep due to pain, fatigue due to the physical and psychological impact of cancer or sedation induced by concomitant drugs. It could be argued that premorphine tiredness from exhaustion may be partly exchanged with opioid induced sedation thereby veiling an opioid effect. If so, this should be a good trade off for the patients as they are relieved from pain and can expect tolerance for opioid induced tiredness to develop.

Constipation increased after start of morphine (paper I). This increase was significant despite the prestudy use of codeine or dextropropoxyphene, which both are known to cause constipation. This finding supports previous studies on constipation in cancer patients receiving opioids for moderate to severe pain (Meuser et al., 2001; Fallon, 1999).

Effects from starting morphine on HRQOL

In paper I we reported that the majority of patients (82%) were satisfied or very satisfied with pain treatment during titration of morphine. The other 12% were indifferent while no patients were dissatisfied. Also, the majority of patients experienced equal or lower intensity of side effects, and equal or less pain intensity than anticipated before start of morphine (paper I). Results on patient satisfaction with pain treatment were in the same order of magnitude after start of morphine in paper III. However, patient satisfactions with pain treatment or successful pain therapy are not automatically synonymous with improvements in the patients HRQOL. Patient distress is a result a multiple factors such as physical symptoms, psychological symptoms, existential distress and family distress (Cherny et al., 1994; Portenoy, 1990). In fact the number of symptoms may be more appropriate predictor for HRQOL than the intensity of a particular symptom (Portenoy et al., 1994). Previous reviews on the relation between HRQOL and pain in cancer patients have called attention to the lack of data on the influence from pain therapy on HRQOL (Portenoy, 1990). Despite this focus there are, to our knowledge, no previous studies on the effects on HRQOL from start of morphine. It also exits little information about the influence from pain intensity on cancer patients HRQOL. In paper II we report a lack of influence from start of morphine and pain relief on the functional scales

of the EORTC QLQ- C30 (physical, social, role, emotional, cognitive). The patients' global self-report of quality of life showed a statistical significant increase at the end of the IR morphine period compared with the baseline observation. This difference from baseline did not persist during the SR morphine period, and the improvement in scores was lower that the clinical difference of interest proposed by Osoba et al. (Osoba et al., 1998). The lack of changes in EORTC QLQ-C30 HRQOL scores was confirmed in the study comparing titration with IR and sustained-release morphine (paper III)(data not shown in the paper).

The effects from other pain treatments on HRQOL have been reported. Grond et al. observed that an increase in EORTC quality of life sum score and improved global assessment of quality of life were associated with improved pain control after fentanyl titration (Grond et al., 1997). However, this paper did not assess the effects on HRQOL from start of strong opioids for moderate to severe pain since the majority of patients had received long-term therapy with morphine before transdermal fentanyl was started. The interpretation of the findings in this paper is also complicated by that the paper did not report the scores of the different HRQOL scales and did not discuss if the observed differences represented clinical significant improvements. A lack of relationship between pain intensity and quality of life was also the result in a study on cancer patients obtaining pain relief from celiac plexus blocks (Kawamata et al., 1996). The minor association of the HRQOL scores with pain intensity agrees with that the number of symptoms was a more important determinant for quality of life than the intensity of one particular symptom (Portenoy et al., 1994), and is supported by Du Pen et al. who in a randomized study observed that the use of Agency for Health Care Policy and Research Guidelines for Cancer Pain Management resulted in less pain but equal intensity of other symptoms and equal global quality of life as standard care (Du Pen et al., 1999).

The lack of a major influence from start of morphine on HRQOL in paper II could be caused by factors related to design. This study does not answer if a subsequent improvement of the patients HRQOL would have been revealed with a longer follow-up period. However, an improvement of HRQOL scores after the observation periods is not likely given the expected progression of the patients' malignant disease. Following the same line of thought, the natural course of HRQOL during the study period could be a decrease in HRQOL outcomes and consequently the stable course observed in association to start of

morphine treatment represents an improvement compared to the natural course. In order to make a certain conclusion on this hypothesis a study that randomize one treatment arm to postpone start of pain treatment is needed. For obvious reasons this approach is not ethical acceptable.

The HRQOL questionnaires do not take into account which part of life that is important for the well being of the individual patient. More patient centered methods for measuring quality of life such as weighting of the items can be hypotized to be more sensitive to treatments effects important for the individual patients (Carr & Higginson, 2001). Second, HRQOL may also be more related to the gap between expectations of health and the experience of health than to the absolute symptoms intensities. If so the perception of quality of life will vary between individuals and be dynamic within individuals (Carr et al., 2001).

What is the effective method for starting morphine?

The EAPC guideline recommends titration with oral IR morphine given 4-hourly. The dose is increased daily until an optimal balance between analgesia and side effects is achieved (Hanks et al., 2001). The morphine treatment is then changed to a controlled-release opioid for maintenance therapy (Jacox et al., 1994a; Hanks et al., 2001). The arguments in favor of IR morphine titration is to allow for steady state as quickly as possible in order to ease the assessment of adequacy of analgesia during the dose finding period and to make rapid changes in dose (Expert Working Group of the European Association for Palliative Care, 1996). However, in the absence of controlled studies the guidelines for start of morphine treatment are based upon expert opinions (Hanks et al., 2001).

In chronic treatment studies there are no clinical significant differences in pain relief and between IR morphine and controlled release morphine treatment (Thirlwell et al., 1989; Deschamps et al., 1992; Finn et al., 1993; Khojasteh et al., 1987; Hanks et al., 1987; Goughnour et al., 1989). Treatment of cancer pain is a common therapeutic procedure that often involves frail and elderly patients with several physical and psychological symptoms in addition to pain (Cherny et al., 1994). The use of 5-6 daily scheduled morphine doses

is cumbersome and may reduce patient compliance (Ferrel, 1998). A direct start with controlled-release morphine would simplify the treatment, reduce the risk for low compliance and thereby enhance efficacy. A 1997 congress abstract reported that start of SR morphine either as in a fixed dose during the first 4 days of treatment or allowed to escalate daily for the first 3 days with 60 mg/24h dose increments were effective (Boureau et al., 1997). A sustained-release morphine formulation given once daily, Kapanol, has been shown to have equal efficacy as 12-hourly SR morphine or 12-hourly Kapanol (Broomhead et al., 1997; Gourlay et al., 1997). In the study comparing start with controlled-release versus IR morphine (paper III) we chose to use sustained-release morphine in order to test IR morphine against the most extreme of the controlled-release morphine formulations. In this study patients receiving titration with sustained-release morphine did not need more time to achieve stable pain control than patients titrated with IR morphine (IR morphine titration 2.1 (95% CI: 1.4-2.7) days; sustained–release morphine titration 1.7 (95% CI: 1.1-2.3) days). The titrated daily morphine doses in the two study groups were similar, and so were use of rescue analgesics and pain intensity at the end of titration. The study showed no differences in the incidence or intensity of adverse effects between the study groups. Thus, the fear of accumulation during sustained-morphine titration causing severe sedation was not supported. It is important to recognize that this study did not include the number of patients needed to determine the risk for rare adverse effects. A further limitation of this study is that the titration used in this study was not adhering to the EAPC guidelines in all details. First, in order to secure identical conditions during titration the patients entered a two-day baseline period before start of titration. Second, to keep the blinding of the study intact, the upward titration was performed in predefined steps while the EAPC guidelines titration procedure increases the dose each day according to the consumption of rescue opioids the foregoing day. For methodological reasons we chose to have a baseline period securing identical conditions at start of titration and predefined titration steps to keep the blinding of the study intact at the cost of having an exact EAPC guidelines replica. Third, in order to secure blinding all patients had to receive medications (active medications or placebo) four-hourly. As a consequence this study could not reflect a possibly improved patient satisfaction associated with replacing multiple daily doses with morphine given once daily.

To our knowledge, no studies have compared the efficacy of different morphine formulations during start of morphine treatment. Observational studies on start of morphine treatment using oral solution (mean 4 days), IR tablets (mean 2.3 days) (paper I) and intravenous PCA (median 4 days until stable oral dose) report times needed for dose finding similar as or longer than the findings in paper III (Vijayaram et al., 1990; Radbruch et al., 1999b). Comparisons of start with IR and controlled-release formulation of other opioids are also sparse. Salzman et al. reported that dose titration was accomplished as readily with controlled release as with IR oxycodone (Salzman et al., 1999). However, because the majority of patients had been treated with other opioids for moderate to severe pain before inclusion, this study did not claim to assess the start of opioid therapy. The findings in the study by Salzman et al. were supported in a study by Than et al. who observed that titration with IR oxycodone 6-hourly gave equal analgesia and HRQOL scores as controlled release oxycodone 12-hourly (Than et al., 2001). However, this study did not assess the times needed for titration and the specifics of the study are difficult to assess because it is to our knowledge only available as a congress abstract.

The use of controlled-release morphine from day one of morphine treatment has several potential advantages. First, patient perception of overmedication ("taking to much") is associated with decreased compliance (Fincke et al., 1998). With the use of controlled-release morphine during titration the patients are spared from a multiple dose schedule. Besides increased convenience this reduces the potential for decreased patient compliance and confusion concerning medications (Ferrel, 1998). This consideration should be especially important in old, frail patients, namely the typical cancer patient in need of an opioid for achieving pain control (Ferrel, 1998). Second, direct start of controlled-release morphine omits the need for conversion of morphine therapy to a controlled-release preparation after dose finding with IR-release morphine. Consequently, the physician does not need to educate the patients to a new opioid regimen, which reduce both patient and doctor burden, and give less chance of confusion and errors during pain therapy. Furthermore, it is reasonable to assume that the use of controlled-release morphine for scheduled morphine therapy and IR morphine used only as a rescue analgesic will make the distinction between scheduled and rescue morphine therapy more clear-cut.

Effective morphine and M6G serum concentrations during start of morphine

One approach in order to assess interindividual variability not related to the inclusion of patients from various stages of cancer is to measure morphine and metabolites serum concentrations at a defined stage of the disease. In paper IV we include patients defined by the need for escalating pain treatment from step two to step three in the WHO pain ladder for treatment of cancer pain. The patients required a mean daily dose of 97 mg with a three-fold variability of doses (range; 60 - 180 mg). The mean trough serum concentrations after start of morphine were for morphine 66 nmol/l, for M6G 257 nmol/l and for M3G 1943 nmol/l (paper IV). The morphine serum concentration were surprisingly identical to serum concentrations observed in other pain states, such as the minimum effective plasma concentration of 54 nmol/l observed during PCA morphine administration for pain after major abdominal surgery (Dahlström et al., 1982).

The individual morphine trough serum concentrations in our patient population varied from 7 nmol/l to 212 nmol/l and showed a standard deviation about two third of the mean value. This 33-fold interindividual variation was less than observed by Faura et al., Wollf et al. (standard deviations two-fold of the mean) and Ashby et al. (standard deviation equal to the mean morphine serum concentration) (Faura et al., 1996a; Ashby et al., 1997; Wollf et al., 1995). The study by McQuay et al. did not specify a calculated measure of the spread of data, but the observed range of 2 to 3497 suggests a significant variation (McQuay et al., 1990). The lower interindividual variation observed in our study is due to a well defined patient population in respect to pain intensity, a well defined target of pain relief, exact defined times for obtaining blood samples, the use of standardized morphine formula, and a well defined duration of morphine treatment (4 - 7 days). However, despite the somewhat lower interindividual variability in paper IV compared with other studies the interindividual variability in serum concentrations of morphine was still 10-fold higher than the three-fold variability in doses. In a study including 300 cancer patients multivariate analyses patients' characteristics (gender, age, weight, renal function, liver function, dose, route of administration) explained about two thirds of the variability in serum concentration of morphine and morphine metabolites

(Klepstad et al., 2001b). This finding suggests that interindividual variability of morphine serum concentrations is a complex phenomenon not fully explained. In this study the major factor explaining variability was morphine dose, since models omitting the dose explained about 10% of variabilities in serum concentrations of morphine, M6G and M3G.

In paper IV a high concentration of M6G relative to morphine (high M6G/morphine ratio) predicted lower serum concentrations of morphine (table 3, paper IV). This observation supports the putative role for M6G in morphine induced analgesia, because if M6G has an analgesic effect it would be expected that patients who metabolize a larger fraction of morphine to M6G need lower serum morphine concentrations in order to achieve pain relief. However, an argument against the regression analysis in paper IV is the use of M6G/morphine as an independent variable and morphine serum concentration as the dependent variable (Plummer, 2000). To further explore the relationship between ratios and morphine serum concentrations we divided our patients into three groups; 1) patients with serum morphine concentrations less than 50 nmol/l, 2) patients with serum morphine concentrations 50 – 100 nmol/l, 3) patients with serum concentrations higher than 100 nmol/l. The M6G/morphine ratios in these three groups were 8.1 ± 4.1 (mean ± SD), 3,7 ± 2.3 and 3.1 ± 2.0, respectively (1 vs. 2 $p<0.05$, 1 vs. 3 $p<0.01$, 2 vs. 3 ns.; Mann-Whitney-U tests)(Klepstad et al., 2000b). If the patients had received a fixed dose of morphine a high metabolism of morphine would have resulted in low morphine serum concentrations and high M6G serum concentrations, or the opposite in patients with a low metabolism of morphine. In our study we increased the dose of morphine until the patients opioid receptor stimulation resulted in pain relief. We believe that if M6G was an inert substance in respect to analgesic efficacy such a morphine dose titration would result in an interindividual variation in morphine serum concentrations caused by the patients variable need of opioid receptor stimulation, and a M6G/morphine ratio not systematically different between patients with high vs. low morphine serum concentrations.

Others support our observation of a contribution from M6G to the analgesia produced by morphine. Faura et al. observed that level of morphine serum concentrations did not differentiate between patients with optimal versus moderate pain control while a sum of morphine and M6G serum concentrations (405 nmol/l) could delimit patients with optimal pain control

from those achieving moderate pain control. (Faura et al., 1996a). Another support for a contribution from M6G to the analgesic effect produced by morphine is the positive relation between pain relief and M6G/morphine ratio observed in patients receiving intravenous morphine for chronic pain (Portenoy et al., 1992). Several other studies on the effects from M6G are commented in the introduction of this thesis.

Relationship between serum concentrations of morphine, M6G and M3G and clinical observations

Säve et al. did not observe a relation between morphine serum concentration and pain or adverse effects in cancer patients (Säve et al., 1983). Wollf et al. did not observe any significant relations between both serum and CSF concentrations of morphine and metabolites with pain intensity in cancer patients receiving oral morphine (Wollf et al., 1995). Extracellular brain fluid morphine concentration are related to respiratory depression in animal studies (Bhargava et al., 1991) (Barjavel et al., 1995). However, this relationship was not observed in patients treated with morphine for postoperative pain (Rigg, 1978),

The clinical efficacy of M6G is not settled (Lötsch & Geisslinger, 2001). Some investigators, including our study group (paper IV), claim that M6G contributes to the analgesia produced by morphine (Portenoy et al., 1992; Faura et al., 1996a; Osborne et al., 1992; Gourlay et al., 1986), while others have not observed a relationship between pain relief and M6G (Wollf et al., 1995; Lötsch et al., 1997). Accumulation of M6G in association with renal failure may cause sedation, but other relationships between M6G and opioid adverse effects are uncertain (Bodd et al., 1990; Wollf et al., 1995; Tiseo et al., 1995; Tiseo et al., 1995). M3G has in several case series been shown to elicit myoclonus and hyperalgesia (Smith et al., 1990; Faura et al., 1996b; Sjøgren et al., 1998), however consistent results from M3G are not the case (Goucke et al., 1994). The conflicting results in the published studies may be explained by small sample sizes. A recent systematic review on the ratios between morphine and its metabolites showed that only 6 of 49 studies included more than 30 patients (Faura et al., 1998). Furthermore, most of these studies, including the only study with more than 100 patients, did not

explore the relationships between opioid serum concentrations and clinical observations. Other explanations for the lack of a firm conclusion on the relationship between serum concentrations of morphine and metabolites and clinical outcome could be confounding effects from other patient related factors such as metabolic status, hydration, and severity / localization of the cancer disease (Mercadante, 1999). Also, most patients use several non-pain related drugs or are exposed to anti-tumor directed therapy. Because these factors are difficult to control in studies on cancer patients, we believed that a large number of patients are necessary in order to conclude on the relationship between opioid serum concentrations and clinical outcomes.

The results from paper VI demonstrated that serum concentrations of morphine, M6G and M3G did not have a direct concentration-effect relationship with pain intensity, nausea, tiredness, cognitive function or constipation. The lack of concentration-effect relationships between serum concentrations of morphine, M6G and M3G with clinical outcomes suggests that receptor properties or intracellular pharmacodynamic factors are important in order to explain the variability of clinical effects of morphine and M6G. There may be differences in μ-opioid receptor properties, variability of non-specific activation of endogenous opioids, variability of active p-glycoproteine transport of opioids out of the cells, and variability in opioid induced activation of protein kinase A by Gs-coupled gangliosides counteracting opioid inhibitory effects (Thompson et al., 2000; Amanzio et al., 2001; Crain & Shen, 1998). Another possible explanation for the lack of direct serum concentration-effect relationships is that serum concentrations are not necessarily directly related to the concentration at the effect sites. A more direct concentration-effect relationship may exist for opioid concentrations near the effect sites as shown in animal pain models where antinociceptive responses correlate well with morphine and metabolite concentrations measured in cortical extracellular fluid (Barjavel et al., 1995). However, human studies using microdialysis are further complicated by the existence of regional cortical differences in extracellular fluid concentrations (Bouw et al., 2000a). Morphine pharmacodynamics may also display a quantal nature (a profound response when increasing the last little step before response) as shown for alfentanil during treatment of postoperative pain (Tverskoy et al., 1996). We are not aware of data suggesting such a relationship for morphine but recognize that a quantal serum concentration response relationship could obscure a linear regression analysis of the

predictions on clinical outcomes from serum morphine and metabolite concentrations.

An obvious prerequisite for routine use of morphine, M6G and M3G serum concentrations during clinical decision-making is a close relationship between serum estimates and clinical findings. The lack of a concentration-effect relationship seen in the patients included in paper VI combined with the sparse support of a direct relationship between serum concentrations of morphine and morphine metabolites found in previous smaller studies, suggests that therapeutic drug monitoring during morphine treatment has limited value for clinical decision making.

The Norwegian BPI

The Norwegian population differed from previous analysis in other languages in that the factor analysis divided the interference items into two groups; items on interference with physical functions and items on interference with psychological functions. This three-factor model result has previously only been observed in patients speaking Hindi (Saxena et al., 1999). The finding of physical and psychological interference items loading on two different factors may reflect that pain in patients with advanced cancer have a different interference on physical and psychological symptoms. The interference on physical symptoms from pain is probably caused by a direct limiting capacity on physical function. The influence from pain on psychological symptoms could be related to a combination of the physical suffering, and the patients' interpretations of pain in the context of malignant disease. The differences in the factor models between languages may also be caused by alternations in the items conceptual meaning.

Several patients were not able to complete the BPI or returned questionnaires with one or more missing items. The fraction of non-completers observed in our study equalized the findings in German hospitalized patients (Radbruch et al., 2000). In the German study the ability to complete the BPI was related to the patients' cognitive function and performance status. The relation with performance status was replicated in our study, while we observed similar MMS examination scores in BPI completers and non-completers. However,

this study's lack of a difference in cognitive function scores between BPI completers and non-completers may be caused by that the majority of patients not answering the BPI was also not able to answer the MMS examination. Because of the high frequency of non-complete questionnaires we doubt if the BPI is feasible in studies during the last days of life.

The high frequency of missing responses on some of the items also raises the question of face validity. Some patients spontaneously reported that they had difficulties to perform the task of defining to what extent pain did influence on function. This was most evident on questions regarding the interference from pain on relations with others and interference from pain on enjoyment. A potential confounding factor in the evaluation of face validity of the interference items is that these items are placed at the end of the questionnaire, and that patients participating in studies often are administered additional questionnaires. Consequently, the high number of missing items on interference items may simply be a result of exhaustion after complying with other study procedures. A further observation in the Radbruch study was that interference scores were higher in patients with deteriorated functional performance (Radbruch et al., 1999a). This raises the question if the patients are able to report pain influence on function without bias from decreased function caused by other factors.

Despite its limitations we believe that the introduction of the BPI into Norwegian was important for two reasons. First, this is the first Norwegian version of a questionnaire that aims to assess the functional limiting effects caused by pain. Second, in order to participate in multinational trials and to compare study results with other trials it is important to use instruments with widespread international recognition. Further development of the Norwegian BPI should investigate to what extent the BPI provides information for the treating physician beyond what is gained from pain items included in a HRQOL questionnaire, develop routines for handling missing values, generate BPI data from the normal population in order to compare study results with the expected frequency and intensity of symptoms in the general population, and to assess the BPI ability to detect changes. Before BPI is considered implemented into routine pain assessment studies should investigate if the use of this domain specific pain questionnaire improves patient outcome.

Conclusions and clinical significance of the studies

I. Start of morphine following the WHO three-step ladder for treatment of cancer pain gives most patients rapid pain relief without increased intensity of nausea or sedation.

II. Start of morphine does not improve the patients HRQOL.

III. Start and titration with once-daily sustained-release morphine has equal efficacy in respect to time needed for titration and equal incidence of adverse symptoms as the recommended titration using 4-hourly IR morphine.

IV. Serum concentrations of morphine, M3G and M6G were not associated with clinical findings. This finding questions the use of serum concentration determinations as a useful tool for guiding opioid treatment.

V. The translated Norwegian BPI had satisfactory psychometric properties. The BPI is not feasible for routine use in terminal ill patients because many patients are not able to complete the questionnaire.

Issues for further research

Start of opioids

Which opioid?

Randomized controlled trials comparing different opioids in the cancer pain population have not consistently demonstrated the superiority of one particular opioid. Further research should compare different opioids and routes of administrations in blinded, randomized, controlled trials. Evidence from animal research suggests that individuals have different profiles of μ-opioid receptor subgroups and hence may have a variable clinical efficacy from different opioid agents (Pasternak, 2001). Lötsch et al. recently published exciting results demonstrating that polymorphism in genes coding the μ-receptor influenced the efficacy on pupil constriction of one opioid substance (M6G), while the efficacy a second opioid (morphine) was unaffected (Lötsch et al., 2002). A forthcoming research issue is to elucidate if the clinical effect and adverse effect profiles from different opioids are related to the patients opioid receptor profiles.

The feasibility of step II of the WHO pain ladder

The WHO pain ladder is validated through longitudinal observational studies. From a pharmacological point of view the use of opioids for mild or moderate pain (e.g. codeine, dextropropoxyphene) could be replaced with low-dose controlled-release opioids traditionally used as WHO pain ladder step three analgesics. The feasibility of the step two of the WHO pain ladder could be questioned, but this challenge should be directed through a randomized, controlled study comparing the current standard of treatment with an alternative strategy.

Opioid adverse effects

There is a general lack of knowledge on the adverse effects from opioids. In contrast to pain there have been little emphasis on the development of

standardized, practical instruments to measure the intensity of adverse effects. Many studies apply unstandardized or even do not report methods used to measure adverse effects. Second, there is a lack of knowledge on to what extent adverse effects are elicited by opioids or caused by other factors. Third, most treatments directed to decrease the intensity of adverse effects from opioids are based on results from other patient populations or based on anecdotic evidence (Cherny et al., 2001).

Measurement of pain

Is it possible to measure influence on function from pain?

An important feature of the BPI is that it measures the influence from pain on patients' functions. However, it is not established to what extent the patients are able to differentiate between a decrease in a particular function caused by pain and a reduction in the same function caused by the disease itself.

Research methods vs. routine methods

Several of the questionnaires including scales on pain (e.g. BPI, EORTC QLQ-C30) are too lengthy in order to be used on a routine basis or to be repeated frequently during follow-up. On the other hand the sole use of short items (e.g. VAS, VRS, NRS) may cause loss of valuable information. A methodological challenge is to integrate questionnaires developed for research with short items designed for use during clinical routine follow-up consultations. Studies are in progress evaluating new methods for obtaining clinical data such as the use of handheld computers.

Pharmacology of opioids

The observed interindividual responses to opioids are still intriguing. Pharmacogenetic studies on the variability of opioid receptors are in progress in our and other study groups. These studies aim to investigate if genetic

opioid receptor variability predisposes to interindividual responses. Pharmacogenetic variability may also be related to other receptors than the μ-opioid receptors or to membrane functions such as anion-kation transporters. New methodology applying microdialysis techniques may give opioid measurements in the effect site compartments. Important information maybe disclosed when such measurements at effect receptor sites are linked to studies on opioid receptors and membrane functions.

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Paper I

Paper I is not included due to copyright.

Paper II

Original Article

Effects on Cancer Patients' Health-Related Quality of Life After the Start of Morphine Therapy

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Abstract
To investigate the effects of morphine on cancer patients' health-related quality of life (HRQL), we prospectively studied 40 cancer patients with moderate or severe pain despite treatment with "weak" opioids. The patients were titrated to pain relief using immediate-release (IR) morphine and then switched to slow-release (SR) morphine in the same daily dosages. HRQL was measured by the European Organization for Research and Treatment of Cancer core quality-of-life questionnaire (EORTC QLQ-C30) before the start of morphine (baseline), after stabilization with IR-morphine, and 3 days after start of SR-morphine. The mean titrated daily morphine dosage was 97 mg (range, 60–180). The EORTC QLQ-C30 global health score increased after IR morphine titration (baseline score 40, IR morphine period score 49), but a significant difference from baseline did not persist during the SR morphine period (score 44). The other functional HRQL scores showed no significant fluctuations. After start of IR morphine, two of the HRQL symptom scores increased, nausea/vomiting and constipation, but these changes also did not persist during the SR morphine period. Intensity of pain was associated with a lower level of function and higher intensity of symptoms, but only with relatively small (not higher than 0.44) correlation coefficients. Compared to normative data from the general population, physical function, role function, social function, and global health were impaired in the study patients. The patients also suffered more fatigue, pain, nausea/vomiting, appetite loss, and constipation. In conclusion, in cancer patients with reduced HRQL, the start of morphine therapy had no major influence on aspects of HRQL other than pain. J Pain Symptom Manage 2000;20:19–26. *© U.S. Cancer Pain Relief Committee, 2000.*

Key Words
Pain, cancer, morphine, quality of life, EORTC QLQ-C30

Introduction

Most studies on morphine therapy describe the effects of morphine treatment on pain and side effects. However, patient distress also results from other factors that add to suffering, such as anxiety, depression, nightmares, changes in body perception, changes in professional and social function, increased dependency, distress from retrospection, future concerns of separation, fear of death, or spiritual concerns.[1,2] Relationships with health care providers also may lead to difficulties (e.g., com-

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munication, ineffectiveness, and financial expense).[1]

To study the effects of both physical and non-physical influences on patient well-being, an instrument must assess more dimensions than the intensity of pain or other physical symptoms. The most used tool for assessing such subjective experiences, during disease or treatment, is a health-related quality of life (HRQL) questionnaire. One of several validated questionnaires, often used in European studies involving cancer patients, is the European Organization for Research and Treatment of Cancer core quality-of-life questionnaire (EORTC QLQ-C30).[3]

Previous reviews on the relation between quality of life and pain in cancer patients have called attention to the lack of data on the influence from pain therapy on HRQL.[2] The effects of the start of morphine therapy on HRQL have not been reported. There is also little information about the influence of pain intensity on cancer patients HRQL.

HRQL questionnaires typically include a measure of pain. In the EORTC QLQ-C30 questionnaire, a pain scale score is calculated from one question rating pain intensity and one question rating the degree to which pain interferes with daily activities. Whether HRQL questionnaire pain scores correlate with visual analogue scale (VAS) pain scores or verbal rate scale (VRS) pain scores is unknown.

The principal aims of this prospective study were to describe the influence on HRQL of the start of morphine therapy for moderate or severe cancer pain, and to study the relationships between pain intensity and HRQL. In addition, we wanted to compare HRQL with the corresponding scores in the normal population and to describe the correlations of the EORTC QLQ-C30 pain symptom scale with a VAS pain score and a VRS pain score.

Methods

Patients

Forty cancer patients with moderate or severe pain despite treatment with "weak" opioids were included. The exclusion criteria for the study were decreased gastrointestinal uptake of oral medications and reduced cognitive function (e.g., dementia, psychiatric disease).

All patients were receiving codeine-acetaminophen (codeine 60 mg × 4 plus acetaminophen 800 mg × 4) ($n = 34$) or dextropropoxyphene-acetaminophen (dextropropoxyphene 140 mg plus acetaminophen 800 mg × 4) ($n = 6$) combinations. Five patients also used nonsteroidal anti-inflammatory drugs (NSAIDs). The opioids in combination with acetaminophen were stopped at the start of the study. NSAIDs were continued in stable dosages. During the study period, 14 patients received fractionated radiotherapy (bone metastasis 8, lymph nodes 5, lung metastasis 1). Sixteen patients used anticancer drugs, hormone therapy (6 patients), or chemotherapy (10 patients), at study entry. All patients received a bowel regimen of a stimulant laxative, bisacodyl, plus a stool softener, lactulose. No prophylactic antiemetic drugs were administered, but 6 patients used steroids for other reasons than emesis.

Study Design

The study period was divided in three parts as illustrated in Figure 1.

Period 1: Baseline Period. The baseline period lasted two days. In this period, the patients did not obtain any regularly scheduled opioids but were allowed to request "rescue" analgesics.

Period 2: Titration with Immediate-Release (IR) Morphine. After completion of the baseline period, the patients started with oral IR morphine 10 mg every 4 hours. The oral morphine dosages were increased according to a fixed schedule of 33–50% increments each day (schedule: 10 mg × 6, 15 mg × 6, 20 mg × 6, 30 mg × 6, 45 mg × 6, 60 mg × 6) until the patient reported satisfactory pain relief and requested no more than two doses of rescue medication per day. Satisfactory pain relief was defined by dichotomizing the VRS pain score into satisfactory pain relief (no, near unnoticeable, or little pain) and unsatisfactory pain relief (moderate, severe, very severe, or unbearable pain). If necessary, a scheduled dosage increase was postponed for one day due to sedation (the patient choosing a delay of upward titration of morphine dosages due to tiredness). This study period lasted for a minimum of four and a maximum of seven days and included at least two days after the final titrated morphine dosage was achieved.

Study period	Duration	Scheduled analgesics	Rescue analgesics	Daily measurements	Measurements at end of period
Baseline Period	2 Days	None	Ketobemidone 5 mg as needed	Pain VAS, VRS Ketobemidone Use	EORTC QLQ-C30 Karnofsky score
IR Morphine Period	4 - 7 Days	IR Morphine Titration	Ketobemidone 5 mg as needed	Pain VAS, VRS Ketobemidone Use	EORTC QLQ-C30
SR Morphine Period	3 Days	SR Morphine	Ketobemidone 5 mg as neeed	Pain VAS, VRS Ketobemidone Use	EORTC QLQ-C30

Fig. 1. Trial profile.

Period 3: Slow-Release (SR) Morphine. After the completion of Period 2, IR morphine was replaced with SR morphine (Dolcontin®) given three times daily in the same total daily dosages as the final titrated IR morphine dose. SR morphine was administered in unaltered dosage for three days.

"Rescue" Medication

Rescue medication for pain during all study periods was oral ketobemidone (Ketogan®) 5 mg. Ketobemidone is a μ-opioid receptor agonist with a potency comparable to that of morphine. No limits in respect to number of daily dosages or lockout intervals between doses were defined.

Pain Scores

During the study, pain was observed once daily as a global rating for the previous day using a seven point VRS score (1—no pain, 2—near unnoticeable pain, 3—little pain, 4—moderate pain, 5—severe pain, 6—very severe pain, 7—unbearable pain), and a VAS score (10 cm, anchored with 0—no pain and 100—unbearable pain). The daily use of rescue analgesics was also recorded.

Health-Related Quality of Life Score

The European Organization for Research and Treatment of Cancer core quality-of-life questionnaire (EORTC QLQ-C30) version 2.0 questionnaire was used to measure HRQL.[3] The questionnaire consists of 30 items, which incorporates five functional scales (physical, role, emotional, cognitive, social), three symptom scales (fatigue, pain, nausea/vomiting), a global health and quality of life scale, and six additional single items (dyspnea, appetite loss, sleep disturbance, constipation, diarrhea, financial impact of the disease and treatment). The psychometric properties and validity of the questionnaire have been found to be satisfactory[3–5] and the test/retest reliability is optimal.[6]

The EORTC QLQ-C30 questionnaire was administered three times during the study: in the baseline period, at the end of the IR morphine period, and at the end of the SR morphine period. The questionnaires were delivered and collected directly from the patients. This procedure ensured that all questionnaires were returned.

Comparison with Norm Data Material

The EORTC QLQ-C30 HRQL observations were compared with the expected observations in a general Norwegian population using reference data adjusted for the distribution of age and gender in the study patients.[7,8] In the age- and gender-adjusted comparisons of the HRQL data, the exact standard deviations of the norm data could not be generated, but a standard deviation of 25 in the norm material was applied as this represents the typical deviation of the data throughout the different ages and genders.

Ethics

The Regional Ethical Committee, University of Trondheim approved the study, and all patients gave their oral and written informed consent before inclusion into the study.

Statistics

Data are presented as means and 95% confidence intervals if not otherwise specified. Because of non-normal distributions, VRS and VAS pain scores are compared applying the Wilcoxon rank sum test. Consumption of rescue ketobemidone is compared using the Student t-test for paired data.

Scores for each scale on the EORTC QLQ-C30 questionnaire were calculated as suggested by the EORTC Study Group on Quality of Life.[9] Missing items were assumed to be equal to the average of those items for that respondent.[9] All scale and items were linearly transformed so that the scales ranged from 0 to 100. For the five functional and the global health/quality of life scale, higher scores represent higher levels of functioning. For the three symptom scales and the six single items, higher scores represent higher levels of symptoms. Because of non-normal distribution, the EORTC scales scores were compared using the Wilcoxon signed ranks test for paired data. Because a large number of comparisons were performed, a P value of < 0.01 was considered necessary for statistical significance. Pearson correlations were employed for estimating the association between the different pain scoring methods and the association between the pain EORTC symptom score and the other EORTC scores.

The statistical software SPPS for Windows 95 v. 8.0 was used for analysis.

Results

Patient Characteristics

The patients' age, gender, cancer diagnoses and metastases, time from diagnosis, and time from start of uncontrolled pain are shown in Table 1. No patients suffered from neuropathic pain. Thirteen patients reported having incident pain. During the study period, 6 patients were excluded, due to acute relapse of panic disorder (1), acute surgery (1), acute compression of the spinal cord (1), spontaneous remission of pain (1), and death (2) (Fig. 2). No patients were excluded due to morphine side effects.

Table 1
Patient Characteristics

Male/Female	21/19
Age mean (range) years	63 (34–78)
Cancer Diagnosis	
Breast	9
Prostate	7
Gastric	3
Colon	8
Myeloma	3
Bladder	2
Pancreatic	2
Others	6
Metastasis	
Bone	18
Liver	11
Others	5
Time mean (range) months from diagnosis	24 (0–109)
Time mean (range) months from uncontrolled pain start of	4.3 (0.5–18)

The mean daily morphine dosage after titration was 97 mg (95% CI, 82–112; range, 60–180) and the mean time needed for completion of titration was 2.3 days (1.8–2.9; range, 1–6).

Pain Scores and Rescue Medication

The EORTC QLQ-C30 pain symptom score decreased significantly from a mean of 65 (95% CI, 56–71) in the baseline period to 43 (34–53) at the end of the IR morphine period and 41 (32–51) at the end of the SR morphine period. The corresponding values at the same times using the VRS pain score were 3.6 (3.2–4.0), 2.6 (2.2–2.9), and 2.8 (2.5–3.1). The VAS pain scores were 32 (25–39), 16 (11–21) and 18 (14–23). The EORTC pain symptom scores mean decrease after the start of morphine was 22 (95% CI, 14–29). The mean decrease of the VRS pain scores was 1.1 (0.7–1.5) and the mean decrease of VAS pain scores was 16 (10–24).

The daily consumption of rescue ketobemidone (mg/24h) were 29.2 (23.4–35.0), 4.4 (1.5–7.4), and 6.0 (2.7–9.3) in the baseline, IR morphine, and SR morphine periods, respectively.

No differences were observed in pain scores from patients obtaining anticancer treatment (radiotherapy or anticancer drugs) and patients who were not receiving anticancer therapy.

Other EORTC QLQ-C30 Symptom Scores

Compared with the scores obtained before the start of morphine therapy, the patients re-

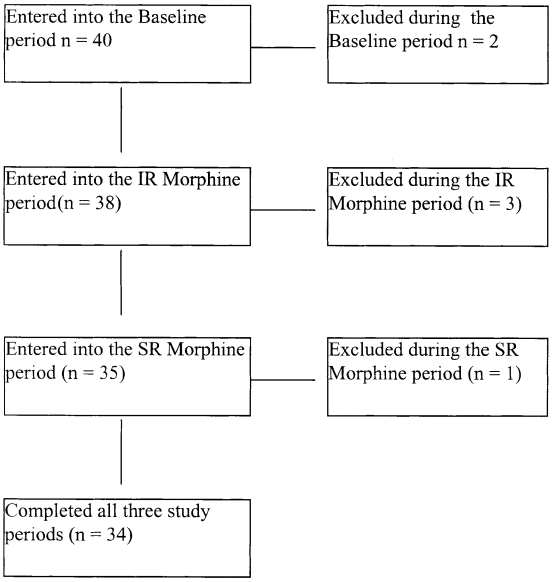

Fig. 2. Patient flow.

ported significantly higher scores for nausea/vomiting and constipation at the end of the IR morphine titration period. These differences had subsided at the end of the SR morphine period. No statistically significant differences were observed in the fatigue, dyspnea, sleep disturbance, appetite loss, and diarrhea symptom scores after start of morphine therapy. No differences in symptom scores were observed between the IR and SR morphine periods (Table 2).

EORTC QLQ-C30 Functional Scores

There was a statistically significant increase in global score of health at the end of the IR morphine period compared with the baseline observation. This difference from baseline did not persist during the SR morphine period. The other functional scales—physical, role, emotional, cognitive and social function—were not changed after start of morphine treatment. No differences in functional scale scores were observed between the IR and SR morphine period (Table 2).

No differences were observed in EORTC QLQ-C30 scores from patients obtaining anticancer treatment (radiotherapy or anticancer drugs) compared to those who were not receiving anticancer therapy.

Relationship Between Pain and Other Functional and Symptom Scores

The relationships between pain and the other scales included in EORTC QLQ-C30 were explored using data from all the completed questionnaires (n = 107). Pain scores were significantly, but not strongly, associated with role function (r = −0.29), social function (r = −0.30), cognitive function (r = −0.29) and global health (r = −0.44). There were no significant associations with physical function (r = −0.18) or emotional function (r = −0.24). Three of the symptom scores, fatigue (r = 0.27), sleep disturbance (r = 0.37), and loss of appetite (r = 0.29), showed significant correlation with pain intensity. The other symptoms scores, nausea/vomiting (r = 0.24), dyspnea (r = 0.14), constipation (r = 0.08), and diarrhea (r = 0.01), were not significantly associated with pain intensity.

EORTC QLQ-C30 Scores: Comparison with Reference Data from the General Population

In all the study periods, patients' HRQL scores were disturbed compared with age-and gender-adjusted expected observations in the normal general population (Table 2). The

Table 2
EORTC QLQ-C30 Scores at Baseline, Immediate-Release, and Slow-Release Morphine Periods

	Baseline mean score (SD)	Immediate-release morphine mean score (SD)	Slow release morphine mean score (SD)	Comparisons between treatment periods (*P*-value)			Reference scores in the general population[a]
				Baseline vs. immediate-release morphine	Baseline vs. slow-release morphine	Immediate vs. slow release morphine	
Function scales (range 1–100, higher score represents higher level of function)							
Physical	31 (27)	33 (27)	35 (30)	0.87	0.87	0.42	83
Role	33 (33)	32 (37)	32 (37)	0.41	0.44	1.00	88
Emotional	85 (19)	83 (21)	87 (19)	0.69	0.31	0.19	84
Cognitive	76 (28)	77 (19)	77 (27)	0.45	0.98	0.37	83
Social	56 (30)	54 (33)	51 (30)	0.59	0.31	0.36	82
Global health	40 (21)	49 (17)	44 (19)	**0.003**	0.05	0.46	73
Symptoms scales/items (range 1–100, higher score represents higher level of symptoms)							
Fatigue	47 (22)	50 (21)	45 (25)	0.26	0.88	0.19	29
Pain	65 (22)	43 (26)	41 (26)	**<0.001**	**<0.001**	0.76	24
Nausea and vomiting	9 (16)	21 (29)	18 (26)	**0.008**	0.03	0.59	4
Dyspnea	20 (30)	18 (22)	20 (27)	0.78	0.76	0.71	19
Sleep disturbance	21 (27)	15 (28)	16 (26)	0.25	0.15	0.95	23
Appetite loss	46 (36)	41 (35)	41 (37)	0.67	0.79	0.81	7
Constipation	29 (35)	51 (33)	42 (33)	**0.005**	0.09	0.18	14
Diarrhea	10 (21)	6 (21)	3 (17)	0.25	0.12	0.58	10
Financial impact	7 (16)	6 (20)	13 (26)	1.00	0.05	0.06	10

[a]Reference scores from general population adjusted for age and sex.[7,8]

physical function, role function, social function, and global health scores were lower than in the general population. Emotional and cognitive function were not different from the general population. The patients also reported higher levels of fatigue, pain, nausea/vomiting, appetite loss, and constipation than the general population. The dyspnea, sleep disturbances, and diarrhea symptoms scores were equal to the scores in the reference data.

Correlations Between EORTC, VRS and VAS Pain Scores

The correlation coefficients between EORTC pain symptom scores and VAS pain scores were r = 0.31 ($P < 0.01$) in the baseline period, r = 0.60 ($P < 0.001$) in the IR morphine period, and r = 0.44 ($P < 0.01$) in the SR morphine period. The corresponding correlation coefficients between EORTC pain symptom scores and VRS pain scores were r = 0.46 ($P < 0.01$), r = 0.60 ($P < 0.001$) and r = 0.41 ($P < 0.01$) and between VAS pain scores and VRS pain scores r = 0.75 ($P < 0.001$), r = 0.82 ($P < 0.001$) and r = 0.74 ($P < 0.001$).

The two items in the EORTC pain score, pain intensity and pain influence on daily living, were also correlated against VAS pain and VRS pain scores separately. The correlation coefficients of the isolated items were in the same magnitude as the correlation coefficients of the EORTC pain score.

Discussion

Although Portenoy[2] in a 1990 review called for studies on the relationship between pain and quality of life, to our knowledge the effect from the start of morphine on HRQL has not been previously reported. One study has investigated the effect from titration of transdermal fentanyl on quality of life.[10] This study observed an increase in EORTC quality of life score sum and improved global assessment of quality of life associated with improved pain control after fentanyl titration. The paper did not assess the effects on HRQL from the start of "strong" opioids because the majority of patients had received long-term therapy with morphine before transdermal fentanyl was

started. This study also did not report the scores of the different HRQL items and did not discuss if the observed differences represented clinical significant improvements.

In our study, the start of morphine therapy did not influence any of the EORTC scales for physical, role, emotional, cognitive, and social function. Global health score increased after the introduction of IR morphine. However the score increase of 9, while statistically significant, may not represent a clinically significant improvement. In the EORTC questionnaire, a score alteration of 10 has been cited to represent a clinically significant difference.[11] Besides pain, we did not observe improvements in symptom scores after start of morphine. Two symptoms, nausea/vomiting and constipation, showed a transient increase after start of morphine.

The lack of clinically significant improvement in HRQL scores in our study must be interpreted with caution. First, this study does not answer if a subsequent improvement of the patients HRQL would have been revealed with a longer follow-up period. However, an improvement of HRQL scores after the observation periods is not likely given the expected progression of the patients' malignant disease. Second, the changes after start of morphine may be partly attenuated by the administration of ketobemidone in the baseline period. Our study can not rule out the possibility that HRQL scores after the start of morphine would have changed more if patients had been totally naive to strong opioids. However, there was a low consumption of rescue analgesics (mean 29 mg ketobemidone daily) in the baseline period compared to the consumption of analgesics in the IR morphine period (mean 97 mg morphine plus an additional 4 mg rescue ketobemidone daily). Also, a study design applying a methodologically ideal analgesic-free baseline period would for obvious reasons be in conflict with ethical obligations.

Intensity of pain was associated with a lower level of function and higher intensity of symptoms but only with relatively small (not higher than 0.44) correlation coefficients. Thus, pain intensity was not closely associated with other symptoms in cancer patients. A lack of relationship between pain intensity and quality of life was also observed in a study of cancer patients who obtained pain relief from celiac plexus blocks. This study observed no significant changes of HRQL for a period of 8 weeks after the procedure.[12] The minor association of the HRQL scores with pain intensity also agrees with a descriptive study of HRQL in cancer patients, which observed that the number of symptoms was a more important determinant for quality of life than the intensity of one particular symptom.[13]

The comparisons with age-and gender-adjusted reference HRQL scores demonstrate that the patients in our study suffered from several physical symptoms other than pain and from psychological distress, which are important for HRQL.[7,8] Examples of experiences that might influence HRQL are fear of death, concern for the future of their families, and spiritual life crises.[2,14] These worries and other sources of suffering are inherent in serious ill patients and it is unrealistic to believe that even successful symptomatic treatment can reinstate a premorbid level of quality of life.

Because pain had to be observed daily in order to guide the titration of morphine, VRS and VAS pain scores were obtained in addition to the EORTC QLQ-C30 pain symptom scale scores. In a study with longer intervals between observations, the sole use of the EORTC questionnaire could obliterate the need for several concomitant pain variables. The EORTC pain scores showed positive significant correlations with VRS and VAS pain scores, and all three pain scores demonstrated sensitivity for change over time after start of morphine treatment. These positive correlations indicate that the EORTC pain score measures the same biological effect as the VRS and VAS pain scores. However, the observed correlation coefficients between the EORTC pain and VAS/VRS pain scores were in the range of $r = 0.31$ to $r = 0.60$, whereas the correlations between VRS and VAS pain scores ranged from $r = 0.62$ to $r = 0.82$. The EORTC pain score consists of two questions, one related to pain intensity and one related to how pain influences daily activities. These questions are different than the VAS and VRS scores, and are present in the context of other HRQL questions. Consequently, the EORTC pain score may reflect other aspects of patient experience than pain VRS or VAS scores, and our results do not support using EORTC pain scores interchangeably with pain VRS or VAS scores. This issue should be addressed in studies including a larger

number of observations before any firm conclusion can be drawn.

In the morphine periods, the study patients' EORTC QLQ-C30 pain scores were 41 and 43, respectively, compared to a score of 24 in the general population. Still, the patients chose to stop escalation and reported satisfactory pain relief. This may be due to a trade-off between the expected side effects and pain relief associated with increasing opioid dosages. Another possibility is that the patients' expectations of pain relief during malignant disease influences the level of pain intensity perceived as satisfactory.

The principal observation of this study is that the start of morphine therapy, with the exception of a transient and probably not clinically significant increased score of general health, did not influence patient function as measured by a validated HRQL questionnaire. With the exception of pain, there were no improvements in the patients symptom scores. These observations were further supported in the low associations between pain intensity and functional or symptom scores in the EORTC QLQ-C30 HRQL questionnaire.

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Paper III

Immediate- or sustained-release morphine for dose-finding during start of morphine to cancer patients: a randomized, double-blind trial

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Summary

A titration procedure using immediate-release morphine given four-hourly is recommended during start of oral morphine for cancer pain. This recommendation is not based on evidence from controlled studies, and many physicians start morphine treatment with controlled-release morphine. We included forty patients with malignant disease and pain despite treatment with opioids for mild to moderate pain in a randomized, double-blind, double-dummy, parallel-group study comparing titration with immediate-release morphine given 4-hourly with titration with sustained-release morphine given once daily. The primary end point was time needed to achieve adequate pain relief. Secondary end points were other symptoms (nausea, tiredness, lack of sleep, vertigo, appetite and constipation), health related quality of life and patient satisfaction. The mean times needed for titration were 2.1 (95%CI; 1.4-2.7) days using immediate-release morphine and 1.7 (95%CI; 1.1-2.3) days using sustained-release morphine. Patients titrated with immediate-release reported statistical significant more tiredness at the end of titration. We observed no other differences in adverse effects or health related quality of life function between the two treatments. Similar global satisfactions with the morphine treatments were reported. In conclusion, a simplified titration using sustained-release morphine once daily is equally effective as immediate-release morphine given 4-hourly.

Key words

Pain, cancer, morphine, start, sustained-release morphine, immediate-release morphine

Introduction

The morphine dose adequate to relieve pain varies between the individual cancer patients and the correct dose in each patient is not predictable before start of treatment (Hanks et al. 2001). Consequently, morphine administration should be titrated in each individual patient to a dose sufficient to ensure analgesia without causing overdosing (Hanks et al. 2001). Start of morphine is recommended when opioids for mild to moderate pain (e.g. codeine), corresponding to step II of the WHO pain ladder, fails to give satisfactory analgesia (Jacox et al. 1994, Hanks et al. 2001). The European Association for Palliative Care (EAPC) guidelines and the US Agency for Health Care Policy and Research guidelines for Management of Cancer Pain recommend that titration is performed using oral immediate-release morphine given 4-hourly. The dose is increased daily until an optimal balance between analgesia and side effects is achieved. The morphine treatment is then changed to a controlled-release opioid for maintenance therapy (Jacox et al. 1994, Hanks et al. 2001). The EAPC guidelines arguments in favor of immediate-release morphine titration are to allow for steady state as quickly as possible in order to ease the assessment of analgesia during the dose finding period and to make rapid changes in dose (Expert Working Group of the European Association for Palliative Care 1996). However, in the absence of controlled studies the guidelines for start of morphine treatment are based upon expert opinions (Hanks et al. 2001).

Treatment of cancer pain is a common therapeutic procedure that often involves frail and elderly patients with several physical and psychological symptoms in addition to pain (Cherny et al. 1994). The use of 5-6 daily scheduled morphine doses is cumbersome and may reduce patient compliance (Ferrel 1998). A direct start with controlled-release morphine would simplify the treatment, reduce the risk for low compliance and thereby enhance efficacy.

In order to compare the efficacy of oral immediate-release morphine titration and sustained-release morphine titration a randomized, double-blind controlled study was conducted with an expectation of sustained-release morphine having similar pain relief as immediate-release morphine.

Methods

Patient selection

Forty adult, hospitalized patients with documented malignant disease and pain despite ongoing treatment with opioids for weak to mild pain (codeine n=35, dextropropoxyphene n=5) were recruited. The attending physicians referred patients to the study. Referred patients with the following characteristics were not included; weak opioids not titrated to maximal recommended dose (n=3), suspected morphine intolerance (n=2), decreased gastrointestinal uptake of oral medications (n=3), lack of ability to communicate (n=2), scheduled transfer from hospital the next day (n=1) or lack of consent (n=1).

The Regional ethical committee of the Health Region IV, Norway, approved the study and all patients gave informed written consent before study entry.

Treatments

A randomized, double-blind, double-dummy, parallel group design was applied. The hospital pharmacy performed a computerized randomization, and delivered coded drug containers for each patient. None of the pharmacists assigning study drugs were involved in other parts of the study. The pharmaceutical companies manufacturing the active tablets supplied placebo tablets identical in appearance and taste. During the study the assignment code was stored in a sealed, non-transparent envelope and the code was not broken until all patients had completed the study.

The patients were randomized to one of the treatment groups at study entry. Treatment with opioids for weak to moderate pain was stopped, while NSAIDs (n=6) were continued. The patients received 5 mg oral ketobemidone (Ketogan, Searle AS), a μ-opioid agonist which potency comparable to morphine, as rescue analgesic. If 5 mg had inferior effect an increased dose of 10 mg was administered. All patients received an anticonstipation regimen of lactulosis and bisakodyl. No patients received prophylactic antiemetic treatment.

After inclusion the patients entered a two-day baseline period where all patients received the same pain treatments (ketobemidone per needed) in order to have identical conditions in the two study groups at start of morphine titration. The immediate-release study group was titrated with immediate-release morphine (Morfin, NycomedPharma AS) four-hourly plus placebo once daily. The sustained-release study group was titrated with sustained-release morphine (Kapanol, GlaxoWellcome AS) once daily and placebo four-hourly. In accordance to standard practice a double bedtime dose of immediate-release morphine or placebo was given to avoid waking the patients during night (Hanks et al. 2001). The total daily dose of morphine at start of treatment was 60 mg in both study groups and was increased each study day according to a fixed titration schedule (60 - 90 – 120 - 180 – 270 – 360 mg morphine daily) until acceptable pain relief was achieved. To exemplify, a patient titrated to a daily dose of 120 mg morphine randomized to sustained-release morphine received sustained-release morphine 120 mg once daily plus placebo every four hour. If randomized to immediate-release morphine the same patient would receive immediate-release morphine 20 mg every four hour plus placebo once daily. Acceptable pain relief was defined as a maximum of 3 on a 7-point pain verbal rate scale (VRS) (1 - no pain, 2 - near unnoticeable pain, 3-little pain, 4 - moderate pain, 5 - severe pain, 6 - very severe pain, 7 - unbearable pain) and not more than two daily requests for rescue analgesics (Klepstad et al. 2000a). The study period terminated two days after the morphine dose was stabilized.

Assessments

Patients reported daily average pain for the previous 24 hours using a visual analogue scale (VAS) (anchored 0 mm - no pain, 100 mm - unbearable pain) and a 7-point VRS (Klepstad et al. 2000a). The daily use of rescue medication was recorded.

Nausea, loss of sleep, tiredness, loss of appetite, constipation and vertigo were reported on a VRS (1 - not at all, 2 - some, 3 - severe, 4 - very severe). Additional variables obtained at inclusion were Karnofsky performance status and health related quality of life (HRQOL) assessed by the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire (version 2.0) (Schag et al. 1984,

Aaronsen et al. 1993). The HRQOL scores were calculated according to standardized guidelines (Fayers et al. 1995). At the end of the study HRQOL assessments were repeated and the patients reported global satisfaction with the pain treatment on a 5-point VRS.

Statistical analysis

The sample size calculation was based on the primary outcome measure specified as time needed to achieve pain relief. The clinical relevant difference was defined as 1.5 days, and a standard deviation of 1.47 days observed in a previous descriptive study on start of morphine treatment was applied (Klepstad et al. 2000a). A one-tail test with power of 0.90 and a level of significance 0.05, required 34 patients (Campbell et al. 1995).

All data are given as absolute numbers or as means and 95% confidence intervals. In the comparisons between the two study groups student-t test was applied for continuous variables while Mann Whitney-U test was applied for the non-continuous variables. Significance was defined as p-value 0.05 or less.

Results

Patients

The two study groups had similar patients' characteristics at inclusion (table 1 and 2). Six patients did not complete the study because of impairment due to progressive disease (n=1), sepsis (n=1), unstable angina pectoris (n=1), spontaneous remission of pain (n=1), acute spinal cord compression (n=1) or refusal to participate further in the study (n=1)(fig.1). No patients dropped out of the study because of failure to achieve pain relief or because of morphine related adverse effects. Of the patients assessed for efficacy, 15 received immediate-release morphine and 19 received sustained-release morphine (fig.1).

Treatment effects on pain relief

Patients receiving titration with sustained-release morphine did not need more time to achieve stable pain control than patients titrated with immediate-release morphine. Acceptable pain relief was achieved after 2.1 (1.4-2.7) days in the immediate-release morphine group and after 1.7 (1.1-2.3) days in the sustained-release morphine group. The titrated daily morphine doses in the two study groups were 94 (71-117) mg for immediate-release morphine and 82 (68-96) mg for sustained-release morphine. The VRS pain scores, use of rescue medication and fraction of patients stabilized on morphine dose during the titration procedure were similar for both groups (fig. 2). VRS pain intensity scores at completion of titration were 2.9 (2.2-3.5) for patients treated with immediate-release morphine and 2.7 (2.3-3.1) for patients treated with sustained-release morphine. The corresponding VAS pain scores were 26 (17-36) and 22 (14-29), respectively.

Side effects and health-related quality of life

Patients receiving sustained-release morphine reported statistically significant less tiredness than patients receiving immediate-release morphine. No other differences in intensity of symptoms were associated with the use of sustained-release morphine titration compared with immediate-release morphine (table 2).

None of the HRQOL scores were influenced by the choice of immediate versus sustained-release morphine for titration (table 3).

Global satisfaction with pain treatment

Most patients in both treatment groups rated their global satisfaction with the pain treatment as "satisfied" or "very satisfied" (immediate-release morphine 13/16, sustained-release morphine 10/13)(table 4).

Discussion

The EAPC guidelines and the US guidelines for management of cancer pain published by the U.S. Agency for of Health and Human Service recommend that titration of morphine is performed with immediate-release morphine (Jacox et al. 1994, Hanks et al. 2001). The argument stated in favor of immediate-release morphine is that a short action of duration allows steady state to be achieved as quickly as possible (Expert Working Group of the European Association for Palliative Care 1996). These recommendations based upon expert opinion were not supported by this randomized, double-blinded study comparing the use of immediate-release and sustained-release morphine for dose finding during start of morphine treatment. The use of sustained-release morphine did not increase the time needed to find the correct dose, nor the intensity of opioid induced adverse effects.

Several studies have observed equal efficacy and risk of adverse effects from immediate-release and controlled-release morphine during chronic morphine therapy (Thirlwell et al. 1989, Deschamps et al. 1992, Broomhead et al. 1997, Gourlay et al 1997). However, to our knowledge, no studies have compared the efficacy of different morphine formulations during start of morphine treatment. Observational studies on start of morphine treatment using oral morphine solution, immediate-release morphine and intravenous morphine patient controlled analgesia report times needed for dose finding similar as or longer than the titration times observed in this study (Vijayaram et al. 1990, Radbruch et al. 1999, Klepstad et al. 2000a). These findings supports that the titration procedure applied in this study is not inferior to other titration protocols. Comparisons of start with immediate–release and controlled-release formulations of other opioids are also sparse. Salzman et al. reported that

dose titration was accomplished as readily with controlled-release as with immediate-release oxycodone (Salzman et al. 1999). However, because the majority of patients were treated with other opioids for moderate to strong pain at inclusion, this study did not assess the start of opioid therapy.

The use of controlled-release morphine from day one of morphine treatment has several potential advantages. First, the patients are spared from a multiple dose schedule. Besides increased convenience this reduces the potential for decreased patient compliance and confusion concerning medications (Ferrel 1998). This consideration should be especially important in old or frail patients, namely the typical cancer patient in need of an opioid for achieving pain control (Ferrel 1995, Klepstad et al. 2000b). Second, direct start of controlled-release morphine omits the need for conversion of morphine therapy to a controlled-release preparation after dose finding with immediate-release morphine. Consequently, the physician does not need to educate the patients to a new opioid regimen, which reduce both patient and doctor burden, and give less chance of confusion and errors during pain therapy. Furthermore it is reasonable to assume that the use of controlled-release morphine for scheduled morphine therapy and immediate-release morphine used only as rescue analgesic, will make the distinction between scheduled and rescue morphine therapy more clear-cut.

Our result is based on a strict design following recommendations for randomized controlled trials. In order to secure blinding all patients had to receive medications four-hourly. As a consequence this study could not reflect the possible improved patient satisfaction associated with replacing multiple daily doses with morphine given once daily. Another possible limitation of the study is that anticancer treatment was allowed during the study period. It could be argued that studies on cancer pain therapy should exclude patients receiving anticancer treatment since such treatment can influence on symptoms. However, the aim of our study was to observe clinical relevant changes associated with start of morphine therapy. Palliative and anticancer therapies are often administered concomitantly and to exclude patients who receive anticancer treatment limits a study generalizability into daily clinical practice.

The titration used in this study was not adhering to the EAPC guidelines in all details. First, in order to secure identical conditions during titration the patients entered a two-day baseline period before start of titration. Second, to keep the blinding of the study intact, the upward titration was performed in predefined steps while the EAPC guidelines titration procedure increases the dose each day according to the consumption of rescue opioids the foregoing day. For methodological reasons we chose to have a baseline period securing identical conditions at start of titration and predefined titration steps to keep the blinding of the study intact at the cost of having an exact EAPC guidelines replica. We believe that the comparisons between the study groups are valid because the same approach for dose increments and rescue medications were used in both study groups.

In conclusion sustained-release morphine given once daily is equal effective and has no more side effects than titration with immediate-release morphine given four-hourly. Given that the clinical efficacy is equal we suggest that the more convenient method using sustained-release morphine is to be recommended.

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Legends

Figure 1.

Flow of patients through trial

Figure 2.

Pain VRS score (panel A), consumption of rescue pain medication (ketobemidone mg/24h)(panel B) and percentage of patients completed morphine titration (panel C) during baseline and morphine titration for immediate-release morphine (squares) and sustained-release morphine (circles). VRS pan scores and rescue medications consumption are given as mean and 95% confidence intervals (confidence intervals are shown in one direction for the purpose of clarity).

Table 1

Characteristics of patients		**Treatment group**	
		Immediate-release morphine (n=19)	**Sustained-release morphine (n=21)**
Age (years)		66 (61-71)	62 (57-66)
Men / women		13/6	9/12
Karnofsky performance status		60 (53-67)	64 (59-70)
Cancer diagnosis	Breast	2	3
	Prostate	7	2
	Gastrointestinal	3	3
	Pulmonary	2	5
	Others	5	7
Clinical chemistry analyses	Haemoglobin serum concentration (g/dl)	12.2 (10.0-13.7)	12.3 (10.9-13.7)
	Creatinine serum concentration (μmol/l)	91 (78-103)	84 (73-95)
	ALAT activity	33 (22-44)	67 (8-127)
	Albumine serum concentration (g/l)	37 (33-39)	38 (35-40)
Intensity of pain at inclusion	Pain VAS score	62 (49-75)	55 (44-66)
	Pain VRS score	5.2 (4.7-5.7)	4.5 (4.1-4.8)
Concomitant treatments	NSAID	3	3
	Radiotherapy	1	4
	Antihormonal treatment	2	3
	Cytotoxic treatment	0	1

All numbers given as frequencies or as mean and 95% confidence intervals

Table 2

Intensity of symptoms before and after titration with immediate-release and sustained-release morphine

	Inclusion		After titration	
	Immediate release morphine	Sustained release morphine	Immediate release morphine	Sustained release morphine
Nausea	1.6 (1.2-1.9)	1.9 (1.4-2.4)	1.6 (1.3-2.0)	1.6 (1.3-1.9)
Tiredness	2.6 (2.2-3.0)	2.5 (2.2-2.9)	2.4 (2.0-2.8)*	1.9 (1.5-2.2)
Constipation	1.7 (1.2-2.2)	2.1 (1.5-2.6)	1.7 (1.2-2.2)	1.9 (1.4-2.4)
Appetite	2.4 (1.8-3.0)	2.6 (2.0-3.1)	2.4 (1.9-2.9)	2.3 (1.8-2.7)
Vertigo	1.4 (1.0-1.8)	1.3 (1.0-1.5)	1.5 (1.1-1.8)	1.4 (1.1-1.7)
Lack of sleep	2.0 (1.4-2.6)	2.2 (1.6-2.8)	1.3 (1.0-1.5)	1.6 (1.1-2.0)

All symptoms reported at a 4-point verbal rate scale. * $p<0.05$ for tiredness after titration with immediate versus sustained release morphine (Mann Whitney U test)

Table 3

Health related quality of life function scores (EORTC QLQ-C30) before and after titration with immediate and sustained release morphine

	Inclusion		After titration	
	Immediate release morphine	Sustained release morphine	Immediate release morphine	Sustained release morphine
Physical function	35 (22-48)	48 (34-63)	35 (22-49)	46 (29-62)
Role function	17 (5-28)	33 (19-47)*	15 (.3-30)	30 (13-46)
Emotional function	78 (69-87)	70 (61-79)	73 (62-85)	67 (57-77)
Cognitive function	70 (58-81)	59 (45-74)	68 (53-82)	74 (62-87)
Social function	49 (33-65)	43 (27-60)	46 (25-66)	44 (28-61)
Quality of life	44 (34-55)	37 (25-50)	42 (34-50)	44 (35-53)

All data presented as mean and 95% confidence intervals. Scores ranges from 0 to 100, higher scores means higher level of function. * $p<0.05$ for role function score in the two study groups at inclusion (t test)

Table 4

Global satisfaction with titration of morphine treatment

	Very dissatisfied	Dissatisfied	Indifferent	Satisfied	Very satisfied
Immediate release morphine	0	1	2	3	7
Sustained release morphine	1	0	3	5	8

Fig. 1

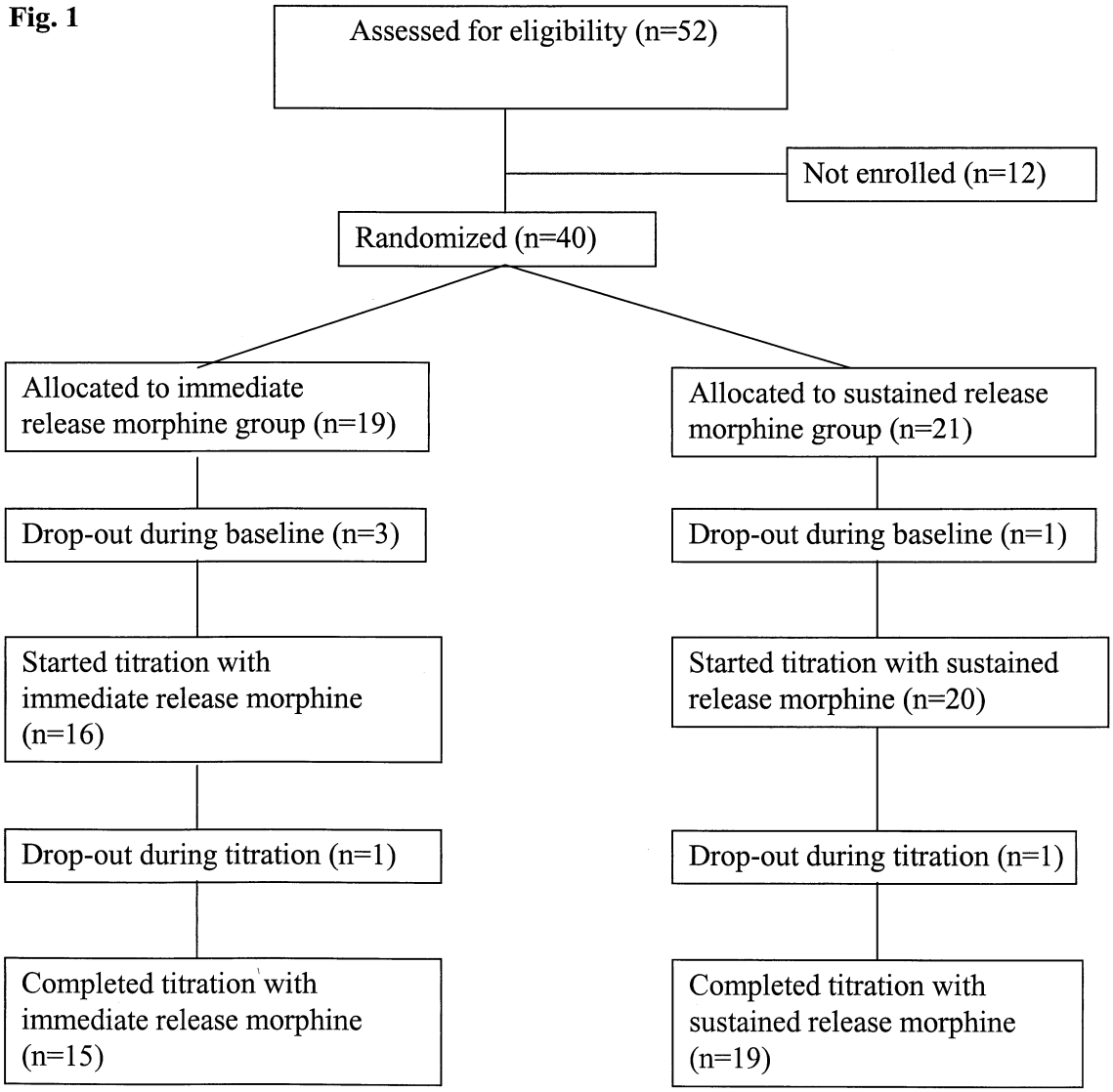
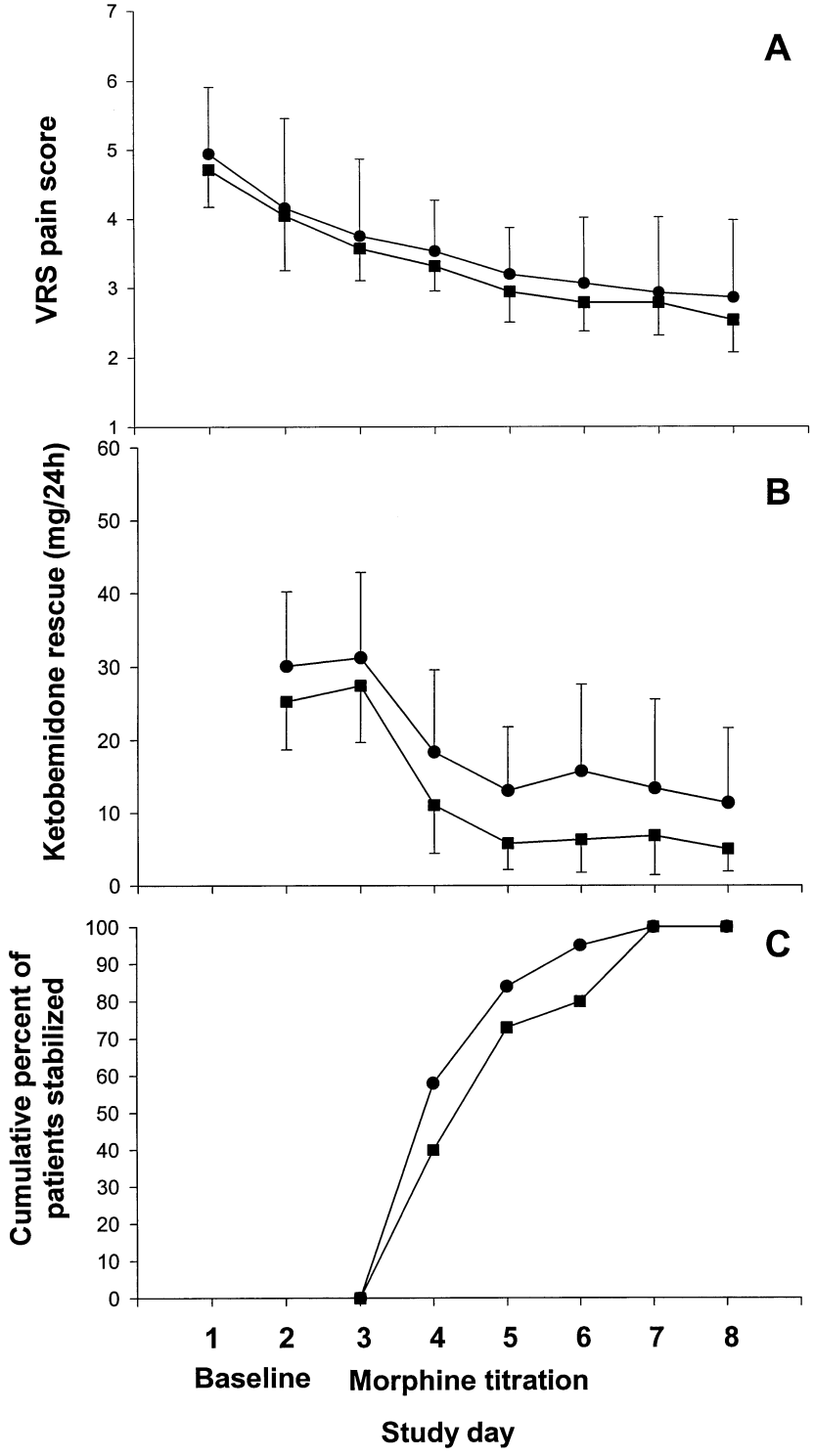

Assessed for eligibility (n=52)
Not enrolled (n=12)
Randomized (n=40)
Allocated to immediate release morphine group (n=19)
Allocated to sustained release morphine group (n=21)
Drop-out during baseline (n=3)
Drop-out during baseline (n=1)
Started titration with immediate release morphine (n=16)
Started titration with sustained release morphine (n=20)
Drop-out during titration (n=1)
Drop-out during titration (n=1)
Completed titration with immediate release morphine (n=15)
Completed titration with sustained release morphine (n=19)

Fig. 2


A
VRS pain score
7
6
5
4
3
2
1
B
Ketobemidone rescue (mg/24h)
60
50
40
30
20
10
0
C
Cumulative percent of patients stabilized
100
90
80
70
60
50
40
30
20
10
0
1
2
3
4
5
6
7
8
Baseline
Morphine titration
Study day

Paper IV

Paper IV is not included due to copyright.

Paper V

The Norwegian Brief Pain Inventory questionnaire: Translation and validation in cancer pain patients

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Running title: Norwegian Brief Pain Inventory

Abstract

The European Association of Palliative Care recommends the Brief Pain Inventory questionnaire (BPI) as a pain assessment tool in clinical studies. After translation into Norwegian we administered BPI to 300 hospitalized cancer patients. Chronbach's alphas were computed to assess reliability, and factor analysis was utilized to ascertain construct validity. The BPI interference and pain severity scales were validated against items on pain intensity and pain influence on daily function in the EORTC QLQ-C30 questionnaire. In total, 235 patients (78%) were able to complete the BPI questionnaire, but 82 (35%) of these questionnaires had one or more missing items. Chronbach alphas were 0.871 for the pain severity and 0.921 for the interference scales. A factor analysis identified three factors; pain intensity, interference with physical function, and interference with psychological functions/sleep. These three factors explained 82% of the variance. The correlation between BPI pain severity index and the EORTC QLQ-C30 item on pain intensity was 0.70 ($p<0.001$). The correlation between BPI interference index and the EORTC QLQ-C30 item on pain influence on daily living was 0.62 ($p<0.001$). We conclude that BPI has satisfactory psychometric properties, but is not completed by a significant proportion of patients. Further research is needed to establish pain assessment tools for patients unable to answer a comprehensive pain questionnaire, to establish routines for analysis of missing values, and to investigate if pain interference items also reflect disease-related impairment.

Keywords: cancer, pain, pain measurement

Introduction

Pain is a subjective experience and pain measurements must rely on the patients' self-report. Several methods for scoring pain severity or/and pain quality are developed and extensively used in clinical studies [1-2]. The methods traditionally used to assess pain (e.g. visual analogue scales, numeric rate scales or verbal rating scales) give reliable results for pain intensity, but tell little about the influence from of pain on the patients' functional capacity. Quality of life questionnaires such as EORTC QLQ-C30 and SF-36 measure function but do not differentiate between function reduced by pain or reduced by other factors such as fatigue or nausea[3-4]. Given that pain is the a causal factor contributing to reduced function interventions directed at pain should both relieve the suffering from pain and improve function. An example illustrating that pain relief is not always associated with improved function, is intense pain treated with high doses of intrathecal local anesthetics, resulting in both pain relief and decreased function due to motoric paralysis.

Recognizing that impairment of function is central to comprehensive pain assessment, Cleeland and colleagues[5] developed the Brief Pain Inventory (BPI). The BPI is designed in order to measure two targets; the subjective intensity of pain and the impairment caused by pain. The BPI have been validated across cultures and languages[6-12], is sensitive to changes in pain[13], and is so simple that most patients are able to complete the questionnaire[14]. The BPI has consequently reached increased popularity and is recommended as a pain measurement tool by the Expert Working Group of the European Association of Palliative Care[15].

The purposes of this study were to identify difficulties during translation to Norwegian, to assess the completeness of data in cancer pain patients, and to validate the Norwegian BPI with respect to construct validity, criteria validity and internal consistency.

Methods

Translation procedure

The first step of the translation involved forward translation of the original American BPI into Norwegian by two native Norwegians who spoke English fluently. After producing the individual translations, the translators met to agree on a common pilot version. The quality of the translation of this pilot version was then evaluated by two other native Norwegians both fluent in English, who evaluated the quality of the translation. These two translators proposed alternative translations if they deemed the original translated items or response choices unacceptable. The alternative translations were returned to the principal investigator who in collaboration with the other first translator modified problematic items and response choices to a preliminary forward Norwegian version. The preliminary forward translated version was subsequently given to a translator, native speaker of English, who translated the questionnaire back into English. The back-translation was compared with the original BPI by the first author of this paper. For the items or response choices where the back-translated and the original did not agree, the choice of words was discussed between the Norwegian and English translator until a final version was reconciled.

The translators rated the difficulty of translating each item and response choice using a rating scale from 0 (not at all difficult) to 10 (extremely difficult).

Patients and study design

The study prospectively included 300 patients with malignant disease admitted to the University Hospital of Trondheim. All patients admitted to the hospital with a diagnosis of malignant disease, aged 18 years or more, and who used regularly scheduled morphine treatment, were asked to participate in the study. Patients refusing to participate in the study (n=3), not able to give an informed consent (n=11) or not capable of the Norwegian language (n=3) were not included in the study. Demographic data were collected from the patient's records. The patients completed the BPI, the European Organisation for Research and Treatment of Cancer health related quality of life questionnaire (EORTC QLQ-C30) and the Mini Mental State Examination (MMS) and the investigator Karnofsky Performance Status at the time of

inclusion. All questionnaires were administered by one of the investigators to the patients. We also collected the questionnaires directly from the patients. This practical approach ensured that all completed questionnaires were returned. The questionnaires were not reviewed for completeness once returned by the participants.

Symptom assessments

The patients were asked to respond to the Norwegian version of the BPI. The BPI consists of four questions related to pain severity and seven questions related to pain interference on function. The pain severity items are presented as numeric rating scales, with 0 = no pain and 10 =pain as bad as you can imagine. The BPI asks the patients to rate their pain at the time of responding to the questionnaire (pain now) and pain at its worst, least and average for the last 24 hours. A pain severity index is calculated by adding the scores on the pain severity items[7]. The seven items of pain interference on patient function are also presented as numeric rating scales, with 0 = does not interfere and 10 = interfere completely. The interference items ask how pain interferes with general activity, mood, walking, work, relations with others, sleep, and enjoyment of life. A function interference index is calculated by adding the scores on the interference items[7].

We compared the results of the Norwegian BPI with the two items in the pain symptom scale of EORTC QLQ-C30 v.3.0 (" Have you had pain?" and "Did pain interfere with your daily activities?"). Both items are scored on a 4-point categorical scale (not at all to very much). The EORTC QLQ-C30 was chosen because the Norwegian version of the instrument is extensively validated and the common use of the instrument in subjective assessment of symptom assessment in cancer patients[3].

Ethics

The Regional Committee for Medical Research Ethics, Health region IV, Norway approved the study, and all patients gave their oral and written informed consent before inclusion into the study.

Statistical analysis

To examine the factor structure of the Norwegian BPI, we fitted a two-factor model as reported in the Taiwanese, German, Japanese, Italian, Greek and Chinese language versions of the BPI[6-10]. We also fitted a three-factor model as described in the development of a Hindi version of the BPI[12] and in a report published by Cleeland et al.[16]. We used principal axis factor analysis with oblimin rotation to perform construct validation[17]. The number of factors was determined by examining the eigenvalues through the scree plot, and evaluating whether or not it was possible to interpret the factors. The ability of the factors to represent the data was expressed by the percentage of explained variance. Loading of the items with the factor was also examined.

To assess the reliability of the Norwegian version of the BPI, alpha coefficients were computed for the seven interference items, for the four severity items and for subscales identified in the factor analysis. Alpha coefficients were also calculated if single items were deleted.

The criterion validity of the interference and severity indexes in the Norwegian BPI were further validated against pain items from the EORTC QLQ-C30. Spearman correlations were performed between the BPI severity index and the item of pain intensity in the EORTC QLQ-C30, and between the BPI interference index and the item of pain influence on daily function in the EORTC QLQ-C30.

Results

Translation

The translators rating of difficulty to translate ranged from 0 to 4 for the items and from 0 to1 for the response choices (median items 1, median response choices 0).

Patient characteristics

The patients included 166 males and 134 females. Median age was 63 (range; 29 - 89) years. The primary tumor locations were breast (n=61), gastrointestinal (n=35), prostate (n=61), hematological (n=26), bladder (n=21), pancreatic (n=5), lung (n=54), unknown origin (n=13) and other sites (n=24). Confirmed metastatic disease was diagnosed in 235 patients. Median MMS score was 27 (range; 10 – 30) and median Karnofsky score was 70 (range; 10 – 90). The median time from the diagnosis of cancer was 19 (range; 0,5 - 216) months.

Completeness of data and descriptive statistics

Sixty-five of the 300 patients (22%) included in the study were not able to answer to the BPI compared to 53 patients for the EORTC QLQ-C30 and 68 patients for the MMS. The reasons for not answering were either that the patients were not able to communicate at the time the questionnaires were administered or that the patients felt too exhausted. One or more items were missing in 82 (35 %) of the completed BPIs. The number of patients with a missing value within each item ranged from 1 (average pain item) to 40 (interference with work and interference with relations to others items) (table I). The number of patients with a missing item was higher for the pain interference items (range; 23-40) than for the pain severity items (range; 1-12). Consequently, the pain severity index could be calculated for 219 patients while the pain interference index could be calculated for 161 patients. Age, gender distribution, cognitive function (MMS score), Karnofsky performance status and total morphine dose did not differ between responders with complete questionnaires and non-completers / patient with missing items (age in years: all items 65 (SD 12), non-completers/missing items 61 (SD13); gender: all items male:female=80:74, non-completers/missing items male:female=86:60; MMS score: all items 26.0 (SD 3.5), non-

completers/missing items 25.5 (SD 4.1); Karnofsky performance status: all items 68 (SD 12), non-completers/ missing items 63 (SD 15)). However, the non-completers had lower performance scores than patients completing all or parts of the BPI (Karnofsky performance score: completers 68 (SD 12), non-completers 57 (SD 16))

The distributions of each BPI item score are given in table I. The distributions of scores are generally skewed to the left meaning that most of the cancer patients experienced little or moderate pain severity (table I). The descriptive statistics for each item and for the sums of the severity and interference items are given in table II. The percentage of patients reporting a minimum item score (%floor) ranged from 14% (pain worst) to 38% (pain least). The percentage of patients reporting a maximum item score (%ceiling) ranged from 0% (pain least and pain now) to 26% (interference with work).

Construct validity

One of our two working theories was that pain is a latent construct that can be represented using two factors, pain severity (sensory) and pain interference (reactive). The other theory was that a three factor solution best represent pain. These are pain severity, activity-related interference and mood-related interference. In the two-factor model above, we observed that the severity items and the activity-related items loaded together under one common factor, which is neither severity nor interference. This makes the two factor solution uninterpretable, and the model was dropped for further consideration. In the three factor model the items on pain intensity loaded on a factor, the interference items describing pain influence on physical functions (general activity, walking ability and normal work) loaded on another factor while items describing pain influence on psychological related functions (mood, relations with other people and enjoyment of life) and sleep loaded on a third factor (table 3). The eigenvalues of the three factors were 6.9, 1.1 an 0.99. The third factor with eigenvalue of .99 was retained, in contrast to the usual guideline of adopting factors with an associated eigenvalue of at least unity, because of the interpretability of the three-factor model. These three factors explained 82% of the variance.

In order to test the adequacy of the three-factor solution, we examined the differences between the reproduced correlations based on the three-factor

pattern solution and the observed correlations. The adequacy was then judged by examining the size and distribution of these residual correlations. According to Harman[18], a solution is considered adequate if the standard deviation of the residuals is slightly less than or approximately equal to the standard error of a correlation coefficient which is the reciprocal of the square root of the sample size. The standard deviation of the residuals is .021 which is smaller than 0.08, the reciprocal of the square root of our sample size (n=154) indicating that we have an acceptable fit with our three factor solution.

Reliability

To assess the reliability of the BPI, separate alpha coefficients were calculated for the severity scale (four pain severity items) and the interference scale (7 interference items). The alpha coefficients were 0.87 for the pain severity and 0.92 for the interference scales, respectively. The alpha values for the two subscales of the interference subscales identified in the factor analysis were 0.92 and 0.90 for the physical and psychological subscales, respectively. All alpha values are above the threshold defined by Altman for demonstrating good internal consistency[19]. The alpha values for the scales if an item was deleted were comparable to the overall alpha coefficient for the scales (table 4). This observation indicates that each of the items contributes similarly to the underlying construct it is meant to measure.

Criterion validity

The correlation between the BPI pain severity index and the pain intensity item in the EORTC QLQ-C30 was 0.70 ($p<0.001$). The correlation between the BPI interference factor and the influence from pain on daily function item in the EORTC QLQ-C30 was 0.62 ($p<0.001$).

Discussion

The introduction of the BPI to Norwegian is important for two reasons. First, this is the first Norwegian version of a questionnaire that aims to assess the functional limiting effects caused by pain. Second, in order to participate in multinational trials and to compare study results with other trials it is important to use instruments with widespread international recognition.

Factor analyses, using similar statistical techniques, of the BPI in several languages have identified a two-factor model with pain intensity items and interference items loading on the two factors[7-9,11-12]. The Norwegian population differed from previous analysis in other languages as the factor analysis divided the interference items on interference with physical function and items on interference with psychological function. This three-factor model result has previously only been observed in patients speaking Hindi [12]. The differences in the factor models between languages may be caused by alternations in the items conceptual meaning during the translation. However, multidimensional scaling, eliminating the effect of a general response bias (a general tendency for a particular individual to respond to a series of questions in a systematic manner) on pain ratings standardized within countries was able to discern similar physical and psychological dimensions of the BPI in different languages [16].

The finding of physical and psychological interference items loading on two different factors may reflect that pain in patients with advanced cancer have a different interference on physical and psychological functions. The interference on physical symptoms from pain is probably caused by a direct limiting capacity on physical function. The influence from pain on psychological symptoms could be related to a combination of the physical suffering, and the patients' interpretations of pain in the context of malignant disease.

Criterion validity of the BPI was assessed using correlations with items from an established health related quality of life questionnaire (EORTC QLQ-C30). This questionnaire was chosen because it contains items on both pain intensity and pain influence on daily living. The correlations observed in this study showed agreement between the BPI and the EORTC QLQ-C30 items. The BPI should also be compared with other methods for pain measurement

since different pain measurements such as EORTC pain items, visual analogue scales and verbal rate scales are not linearly related[20].

An important issue is if BPI provides information for the treating physician beyond what is gained from pain items included in a quality of life questionnaire. The BPI supplements the EORTC QLQ-C30 in assessing pain at a more differentiated scale and in assessing pain intensity both at present and as the average, worst and least pain for the foregoing day. The BPI further supplements the EORTC QLQ-C30 in assessing pain influence on several aspects of function. However, it is not established if a detailed data collection such as in the BPI improves routine pain assessment. This question must be addressed in a comparative study with patient outcome as the endpoint.

Several patients were not able to complete the BPI or returned questionnaires with one or more missing items. The patient's ability to complete the BPI differs between studies[11,16]. These differences may partly be explained by variations in study populations. Cleeland et al reported that 3.6% of out-patients were unable to complete the BPI. The higher fraction of non-completers amongst the hospitalized patients observed in our study equalized findings in German hospitalized patients[14,21]. In the German study the ability to complete the BPI was related to the patients' cognitive function and performance status. The relation with performance status was replicated in our study and is also in concordance with studies on other questionnaires showing that compliances decline in the last month before death[22]. We observed a similar MMS score in BPI completers and non-completers. However, this study's lack of a difference in cognitive function scores between BPI completers and non-completers may be caused by that the majority of patients not answering the BPI was also not able to answer the MMS examination. Consequently, we doubt if the BPI is feasible in studies on patient populations with severely advanced malignant disease in where patients that are not able to complete questionnaires or patients with cognitive failure are encountered frequently.

The high frequency of missing responses on some of the items also raises the question of face validity. In our study some patients spontaneously reported that they had difficulties to perform the task of defining to what extent pain did influence on function. This was special evident on questions regarding the

interference from pain on relations with others and on enjoyment as reflected by the high number of missing responses on these items. Radbruch et al[7] reported that the maximum percentage of patient reporting difficulties with a BPI item was 6,8% (relations with others). However, in the Radbruch et al study 34 of 151 questionnaires had missing items and it was not reported to what extent missing items were coincidental with items rated to be difficult to score. A potential confounding factor in the evaluation of face validity of the interference items is that these items are placed at the end of the questionnaire. Consequently, the high number of missing items on interference items may simply be a result of exhaustion after complying with other study procedures.

A further observation in the Radbruch study[7] was that the interference score was higher in patients with deteriorated functional performance. This raises the question if the patients are able to report the pain influence on function without bias from decreased function caused by other factors.

The translators rated the translation procedure as relatively easy. This is in agreement with former translations of the BPI. The BPI translation is facilitated by the fact that the items and response choices relevant to pain are all relatively universal and the conceptual meaning are equal throughout the American English and Norwegian language.

A limitation with the BPI is the lack of a formal procedure for handling missing values. Some studies using the BPI exclude questionnaires with missing items from the calculation of pain severity and pain interference indexes[7]. Other studies, which use the BPI, do not specify the routine for handling missing items[9,11-12]. Other questionnaires have developed standardized procedures for the handling of missing values (e.g. the EORTC QLQ-C30 assumes that the missing value is equal to the individual's average score on the other items in the same scale) [23]. Further research should address and validate routines for the handling of missing items in the BPI.

In our study the patients did not repeatedly complete the BPI. Consequently, we have no data that validates the BPI ability to detect changes in pain severity or interference with function. One study on pain during acute herpes zoster has reported the sequential use of BPI[13]. However, this study used the item "worst pain", but reported not the other BPI items. A study investigating

the results from repeated assessment of all items and scales is needed to validate the BPI's ability to detect changes.

Another limitation of the BPI is the lack of data from a normal population. Subjective symptoms including pain are present in the general population[24]. In order to define a study population it is important to compare study results with the expected frequency and intensity of symptoms in the general population. Such normal data should also be possible to adjust for gender and age distribution in the study population[25].

In conclusion, the Norwegian BPI showed satisfactory psychometric properties, but was different from other translations with regard to the factor analysis that differentiated between interference items addressing physical and psychological functions. Furthermore, the low compliance questions the use of BPI in patients with severely advanced malignant disease. The BPI can be especially suited if the functional impairment caused by pain is considered an important outcome, but further research is needed to clarify whether the interference items reflect pain induced or disease related impairment of function.

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Table I: Distribution of responses and missing data for each item (n=235)

	Patient score											
Item	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Missing**
Worst pain	33	11	11	20	29	24	24	34	27	11	11	1
Pain least	86	40	43	29	16	10	2	1	2	0	0	7
Pain average	32	16	20	43	29	37	18	14	10	4	1	12
Pain now	71	31	36	42	15	13	12	6	7	1	0	2
General activity	43	5	16	13	10	25	4	19	36	13	27	25
Mood	59	18	24	23	12	18	9	13	17	7	9	27
Walking	52	14	13	15	9	16	10	20	28	11	23	25
Work	39	6	10	7	10	17	2	23	20	11	51	40
Relations with others	67	14	22	17	10	16	12	11	14	7	6	40
Sleep	78	21	25	13	6	20	11	10	13	5	11	23
Enjoy	54	14	18	25	10	21	8	10	18	10	8	39

A higher score indicates more severe pain or more interference on function caused by pain

Table II: Descriptive statistics for each item (n=235)

Item	Mean	Std.dev.	CI[a]	Median	Range	% Floor[b]	%Ceiling[c]
Pain worst	4.8	3.0	4.1-5.1	5	0-10	14	5
Pain least	1.6	1.7	1.3-1.8	1	0-8	38	0
Pain average	3.7	2.4	3.1-3.9	4	0-10	14	0.4
Pain now	2.3	2.2	1.8-2.5	2	0-9	30	0
General activity	4.8	3.6	4.3-5.4	5	0-10	20	13
Mood	3.1	3.0	2.6-3.5	2	0-10	28	4
Walking	4.2	3.6	3.6-4.7	4	0-10	25	11
Work	5.4	3.8	4.8-6.0	6.5	0-10	20	26
Relations to others	2.9	3.1	2.4-3.4	2	0-10	34	3
Sleep	2.9	3.2	2.4-3.4	2	0-10	37	5
Enjoy	3.3	3.2	2.8-3.8	2.5	0-10	28	4
Sum of severity scores[d,f]	11.9	8.4	10.5-13.2	12	0-37	12	0
Sum of interference scores[e,f]	26.5	19.4	23.4-29.5	25	14-66	0	0

[a]95% confidence interval, [b]percentage of scores with lowest possible score, [c]percentage of scores with highest possible score, [d]highest possible sum 40, [e]highest possible sum 70, [f]the severity (n=219) and interference (n=161) sums were only calculated for the patients with no missing values

Table III: Factor loading for the Norwegian version of the Brief Pain Inventory

	Factor I Activity interference	**Factor II Mood and sleep interference**	**Factor III Pain severity**
Pain worst	0.417	-0.128	**0.631**
Pain least	-0.107	0.128	**0.854**
Pain average	0.373	0.011	**0.614**
Pain now	-0.033	0.165	**0.753**
General activity	**0.794**	0.147	0.060
Walking	**0.791**	-0.010	0.070
Work	**0.879**	0.186	-0.102
Mood	0.045	**0.767**	0.115
Relations to others	0.042	**0.798**	0.029
Enjoy	0.025	**0.980**	-0.066
Sleep	0.125	**0.496**	0.227

Factor analysis with a principal factor solution with a direct oblimin solution. Bold numbers highlight the factor to which the item belong.

Table IV: Reliability analysis and α-values if item deleted

Pain severity items (α= 0.87)		**Pain interference items** (α= 0.921)		**Physical interference items** (α=0.92)	**Psychological interference items** (α=0.91)
Pain worst	0.84	General activity	0.90	0.87	
Pain least	0.85	Mood	0.91		0.83
Pain average	0.80	Walking	0.921	0.89	
Pain now	0.85	Work	0.910	0.87	
		Relations to others	0.91		0.88
		Sleep	0.92		0.91
		Enjoy	0.91		0.85

The subgroups of physical and psychological interference items were identified in the factor analysis.

Paper VI

Drug monitoring of serum concentrations of morphine, morphine-3-glucuronide and morphine-6-glucuronide do not predict clinical observations in cancer patients

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Running head: Drug monitoring of morphine, M3G and M6G

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Abstract

The feasibility of drug monitoring of serum concentrations of morphine, morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G) during chronic morphine therapy is not established. We measured morphine, M6G and M3G serum concentrations in cancer pain patients receiving oral (n=263, median dose 80 mg/24h) or subcutaneous (sc) (n=35, median dose 110 mg/24h) morphine. Regression analyses were performed to investigate if serum concentrations of morphine, M3G and M6G or demographic variables predicted pain intensity (Brief Pain Inventory), health related quality of life variables (EORTC QLQ-C30) and cognitive function (Mini Mental Score). Serum concentrations were also compared in patients categorized as morphine "treatment successes" and as "treatment failures". We found that serum concentrations of morphine, M6G or M3G did not predict pain intensity, cognitive function, nausea or tiredness. "Treatment failures" caused by nausea, tiredness, cognitive failure or constipation were not associated with statistically significant different morphine, M6G and M3G serum concentrations as compared to patients classified as "treatment successes". In conclusion, this study demonstrated a lack of serum concentration-effect relationships of morphine, M3G or M6G with pain intensity, nausea, constipation, tiredness or cognitive failure during routine clinical drug monitoring of morphine and morphine metabolites in cancer patients.

Key words:

Morphine, morphine-6-glucuronide, morphine-3-glucuronide, cancer, drug monitoring

Implication statement

The feasibility of drug monitoring of serum concentrations of morphine, M6G and M3G during chronic morphine therapy was studied in 300 cancer patients. Pain intensity, cognitive function, nausea, tiredness and constipation were not related to serum concentrations of morphine, M3G and M6G. This finding suggests that therapeutic drug monitoring as a routine tool during morphine treatment has limited value for clinical decision making.

1.0 Introduction

Morphine-3-glucuronid (M3G) and morphine-6-glucuronide (M6G) are found in higher serum concentrations than their parental drug, morphine, during chronic oral morphine treatment in humans (1,2). M6G has higher affinity to the opioid μ-receptor than morphine and possess higher analgesic potency in animal models (3). However, the clinical efficacy of M6G is not settled. Some investigators claim that M6G contributes to the analgesia produced by morphine (4-6), while others do not observe a relationship between pain relief and M6G (2). Accumulation of M6G in association with renal failure may cause sedation, but other relationships between M6G and opioid induced adverse effects are uncertain (2,6-8). M3G has in several case series been shown to elicit myoclonus and hyperalgesia (9-10), however consistent results regarding M3G effects are not the case (11).

The conflicting results in previous studies may be explained by small sample sizes. A recent systematic review on the ratios between morphine and its metabolites showed that only 6 of 49 studies included more than 30 patients (12). Furthermore, most of these studies, including the only study with more than 100 patients, did not explore the relationships between opioid serum concentrations and clinical observations.

One prerequisite for routine use of morphine, M6G and M3G serum concentrations during clinical decision-making is a close relationship between serum estimates and clinical findings. Based upon these considerations a prospective study including a large sample of cancer patients receiving chronic morphine treatment was performed in order to investigate the association of morphine, M6G and M3G serum concentrations to clinical symptoms.

2.0 Methods

2.1 Ethics

The study was done in accordance to the principles of the Helsinki declaration. The Regional Committee for Medical Research Ethics, Health Region IV, Norway, approved the study, and all patients gave their oral and written informed consent before inclusion in the study.

2.2 Patients

Three hundred patients admitted because of a malignant disease to the Trondheim University Hospital, a 900-bed tertiary hospital, and who received chronic treatment with morphine were prospectively included in the study. Patients below 18 years of age or unable to speak Norwegian were not included.

The following information was collected from the hospital records for each patient: Cancer diagnosis, time since diagnosis, presence of metastases and time since start of morphine. The scheduled morphine doses, use of rescue morphine for the last 24 hours, and route of administration were collected from the patients' ward charts. The patients were assessed after admission in order to obtain assessments before adequate changes in pain therapies were performed. This approach ensured that the study included a mix of patients with adequate and non-adequate symptom management.

2.3. Assessments

The European Organization for Research and Treatment of Cancer core quality-of-life questionnaire (EORTC QLQ-C30) version 3.0 was used to assess the patients' self-reported symptoms (13). This questionnaire includes scales or items for nausea/vomiting, constipation, fatigue and tiredness. The psychometric properties and validity of the questionnaire is good (13). All scales and single items are linearly transformed giving a score range from 0 to 100, higher scores represent higher levels of symptoms (14).

Pain was measured using the item of "average pain" during the last 24 hours in the Brief Pain Inventory questionnaire (BPI). The BPI asks the patient to rate pain on a numeric scale, where 0 represents "no pain" and 10 represents "pain as bad as you can imagine". The BPI is developed for the use in cancer pain patients, is validated in several different languages, and is recommended by the European Association of Palliative Care as a pain assessment tool in clinical studies (15-16).

Cognitive function was assessed by the Mini Mental State (MMS) examination. The MMS score ranges from 0 to 30, with higher scores meaning better cognitive function. This standardized cognitive screening examination has been shown to be valid, reliable and able to document changes in cognitive function (17). The feasibility of MMS has also been demonstrated in studies on patients with terminal cancer (18).

The patients' functional status was assessed using the Karnofsky performance status score (19).

2.4. Blood samples and analyses

All blood samples for determination of serum concentrations of morphine, M6G and M3G were obtained during the routine morning round for collecting blood samples, 1-2 hours after the morning dose of slow-release morphine. The blood samples were placed in EDTA tubes, separated by centrifugation (3000 r.p.m, ten minutes) and stored at -85^0 C. All samples were analysed for serum concentrations of morphine, M6G and M3G applying liquid chromatography mass spectrometry (20). The limits of detection were 0.35 nmol/l for morphine and 2.2 nmol/l for M6G and M3G. The analytical coefficients of variation were 3.0% for morphine, 5.5% for M6G and 7.0% for M3G.

Serum values of creatinine concentrations (reference interval; male < 100, female <120 µmol/l), aspartate aminotransferase activities (ASAT) (reference interval; <50 U/l) and albumine concentrations (reference interval; 37-48 g/l) were determined using standard analytical methods.

2.5.Statistics

Results are given in medians and ranges. The relationships between the pharmacokinetic observations and clinical assessments were analyzed applying two different approaches.

The first approach was to analyze potential factors predicting variability of pain intensity (BPI average pain), cognitive function (MMS score), nausea (EORTC QLQ-C30 nausea and vomiting symptom scale) and tiredness (EORTC QLQ-C30 "Were you tired" item) using linear regression analyses. Independent variables were those, which were considered to have the potential to influence the dependent variable. Age, gender, Karnofsky performance score, cancer diagnosis and serum concentrations of morphine, M6G and M3G were included as independent variables in all regressions. Because of skewed distributions we transformed the observed serum concentrations results into plots as square roots, inverse values and $\log_{10}$ transformation in order to explore if a transformation of data resulted into a normal distribution. Log_{10} transformed serum concentrations were normally distributed and were used in the regression analyses. Additional independent factors in the analyses of pain intensity were cognitive function (MMS), fatigue (EORTC QLQ-C30 fatigue scale) and nausea (EORTC QLQ-C30 nausea and vomiting scale). The additional independent factors in the analysis of cognitive function were fatigue and pain intensity (BPI average pain). In the analysis of nausea, fatigue and pain intensity were included as independent factors. For the analysis of tiredness, cognitive function and pain intensity were additional independent factors.

The second approach used to explore the relationships between the serum concentrations observations and clinical assessments was to compare treatment successes and failures. The patients were considered pain-relieved if the average pain item on the 11-point NRS in the BPI was 3 or less, while higher scores were categorized as unacceptable pain. The self-reports of side effects were dichotomized into complainers and non-complainers. The cut off point for categorizing a patients as complainer was 50 or more on the EORTC QLQ-C30 nausea/vomiting scale and the constipation scale. For tiredness, patients reporting a Likert score of three or more on the EORTC QLQ-C30 item "Were you tired" were considered as complainers (21). Cognitive function was dichotomized using a score of 23 or less on the MMS

examination to indicate the presence of cognitive failure (18). After dichotomizing patients as pain-relieved vs. not pain-relieved and side effects complainers vs. non-complainers the patients could be categorized into 4 groups; 1) Pain relieved and side effect non-complainers – treatment success, 2) Pain relieved and side effect complainers – morphine dose too high, 3) Pain not relieved and side effects non-complainers – morphine dose too low, 4) Pain not relieved and side effect complainers – treatment failure (fig. 1). The serum concentrations in the treatment success groups and the treatment failure groups were compared using the Mann-Whitney U test. Bonferroni corrections were performed to adjust for multiple comparisons.

A formal exact sample size calculation is difficult in a study on prognostic factors. Reviews on sample size estimations advise against studies that include less than 25 patients per prognostic factor (22). We decided to include 300 patients in order to have a sample size beyond this proposed limit.

The statistical software SPPS for Windows v. 10.07 was used for the all analysis except regressions, which were performed with the statistical software Stata v. 6.

3.0 Results

3.1. Patient demographics

We included 166 males and 134 females. Forty-eight eligible patients were not included because of refusal to consent (32), unable to give consent (n=13) or unable to speak Norwegian (3). All patients were Caucasian. Median age was 63 (range; 29 - 84) years. The patient median weight was 69 (range; 39-110) kg. The primary tumor locations were breast 61, prostate 61, lung 54, gastro-intestinal 35, hematological 26, bladder 21, pancreas 5, others 24 and unknown origin 13. For patients with confirmed metastatic sites the most important metastatic manifestation were bone 123, lymph nodes 33, lung 29, peritoneal seed 10, liver 10, skin 3, brain 3 and other sites 25. The median time from establishing the diagnosis of cancer was 19 (range; 0,5 - 216) months. The median time from start of morphine therapy was 1 (range 0.4-50) month. Median Karnofsky performance status score was 70 (range; 10 - 80).

The patients' median serum creatinine concentrations was 77 (range; 39 - 485) μmol/l, median ASAT was 31 (range 7 - 1002) U/l, and median serum albumine was 32 (range 17- 44) g/l. Twelve patients (3,7%) had serum creatinine concentrations more than 150 μmol/l, while 11 (3,4%) of the patients had ASAT above 200 IU/l. No patients were dependent on renal dialysis or had clinically overt hepatic failure.

3.2. Morphine administration and pharmacological observations

The scheduled morphine therapy was administered as slow-release oral morphine to 263 patients and as subcutaneous (sc) continuously infusion to 35 patients. Two patients received combinations of two routes; oral plus sc and oral plus rectal, respectively. Ninety-one patients received additional rescue morphine for breakthrough pain. Rescue morphine was given orally (immediate-release morphine)(n=70), sc (n=14), iv (n=4) or rectal (n=5). The median morphine dose for the patients receiving oral morphine was 80 (range; 20-1700) mg/24h. The median morphine dose for the patients receiving sc morphine was 110 (range; 10-1200) mg/24h.

The median serum concentrations of morphine, M6G and M3G for patients receiving oral morphine were 60 (range; 1-2560), 320 (range; 10-9180) and 2020 (range; 110-32134) nmol/l, respectively. The corresponding median serum concentrations for patients receiving sc morphine were 179 (range; 3-1680), 394 (range; 30-14210) and 3323 (range; 160-62130) nmol/l. The median ratios of M6G/morphine, M3G/morphine and M3G/M6G for patients receiving oral treatment were 6.0 (range; 0.5-83), 36 (range; 6-486) and 6.1 (range; 3-43), respectively. The corresponding median ratios for patients receiving s.c. treatment were 2.3 (range; 1-23), 15 (range; 4-111) and 5.7 (range; 3-15).

3.3. Clinical outcomes

The patients' median score for BPI average pain was 4 (range; 0-10). The distribution of pain scores is shown in figure 2. The median MMS score representing the patients' cognitive function was 27 (range; 10-30). Median EORTC QLQ-C30 score for nausea and vomiting and constipation were 16.7 (range; 0–100). The distributions of the MMS scores and the EORTC CLC-C30 nausea and vomiting scores are shown in figure 3 and 4. The distribution of the responses on the EORTC QLQ-C30 item "Were you tired" was "not at all" 5%, "a little" 29%, "quite a bit" 36% and "very much" 30%. The distribution of the EORTC QLQ-C30 constipation item responses was "not at all" 24%, "a little" 21%, "quite a bit" 29% and "very much" 27%.

3.4. Relations between clinical outcomes and pharmacological observations

3.4.1.Regression analyses

In linear regression analysis none of the clinical factors age, gender, performance status, cancer diagnosis, cognitive function, fatigue, nausea or serum concentrations of morphine, M6G and M3G significantly predicted pain intensity. In the regression analysis examining cognitive function, age and Karnofsky performance score were significant predictors, whereas gender, cancer diagnosis, fatigue, BPI average pain and serum concentrations of morphine, M6G and M3G were not. The regressions analyses on tiredness and nausea each had only one significant predictor, Karnofsky performance

status predicting tiredness and fatigue predicting nausea. As shown in table I none of the models explained a major part of the variability in symptom intensity.

3.4.2. Treatment success vs. treatment failures

Patients categorized as treatment failures because of nausea, tiredness, cognitive failure or constipation did not have statistically significant different serum concentrations of morphine, M6G or M3G (table II). Furthermore, no statistically significant differences were observed in M6G/morphine, M3G/ morphine and M3G/M6G ratios between treatment successes and failures (table II).

4.0. Discussion

This study demonstrates that serum concentrations of morphine, M6G and M3G obtained during clinical routine drug monitoring do not have a direct concentration-effect relationship with pain intensity, nausea, tiredness, cognitive function or constipation. M6G is shown to contribute to the analgesic effect during chronic morphine treatment (4,6). Still, except from a study by Faura et al. (5), which reported a 400 nmol/L threshold of the summed M6G and morphine serum concentrations for achieving pain relief in hospitalized cancer patient, studies have not observed a direct relationship between pain intensity and serum concentrations (23-24). Also, studies examining concentrations and ratios of morphine, M3G and M6G in cerebrospinal fluid did not observe concentration-effect relationships with pain (2,25). M3G has been proposed to exert an anti-analgesic action implying that patients with high serum concentrations of M3G may not be expected to achieve adequate pain relief (26). Our finding of no significant associations between M3G and pain intensity agrees with previous studies (2,5,25) including the finding by Goucke et al. (11) where patients with morphine resistant pain had similar M3G concentrations as patients with well-controlled pain.

The dispute about direct concentration-effect relationships also relates to adverse effects. Hagen et al. (27) reported a patient with renal failure who developed nausea that resolved parallel to a decline in serum concentrations of M6G. Furthermore, Ashby et al. (28) observed higher dose adjusted M6G and M3G serum concentrations in patients suffering from nausea and vomiting. However, these patients also had renal failure, suggesting that nausea and elevated metabolite concentrations might both be caused by renal failure. The findings in patients with normal renal function presented in this paper and in a previous study from our hospital argue against a concentration-effect relationship between nausea and serum concentrations of morphine, M6G or M3G (6).

Ashby et al. (28) also observed that serum concentrations of M3G and M6G in patients with confusion were higher than for patients without this adverse effect. However, another study performed by the same research group observed no correlation between serum concentrations and neuropsychological tests in cancer patients receiving morphine (29). Tiseo et

al. (8) identified cancer patients as confusion cases and confusion non-cases and found no significant difference in morphine, M6G concentrations between the two groups. These findings are supported by the lack of relationship between the patients' cognitive function and serum concentrations observations in the present study. Also, our study did not find a significant association between serum concentrations and ratios of morphine and metabolites and the patient self-reports of tiredness. The observation on tiredness replicated the findings in a previous study performed by our group (6).

The inconclusive results on the concentration-effect relationships of morphine and morphine metabolites from previous studies could be explained by the small numbers of patients causing variability of events due to random chance alone (30). Another explanation may be confounding effects from other patient related factors such as anti-tumor treatments, metabolic status, hydration, and severity / localization of the cancer disease (24). Because these factors are difficult to control in studies on cancer patients, we believe that a large number of patients is necessary in order to conclude on the relationship between opioid serum concentrations and clinical outcomes.

The lack of concentration-effect relationships between serum concentrations of morphine, M6G and M3G with clinical outcomes suggests that receptor properties or intracellular pharmacodynamic factors are important in order to explain the variability of clinical effects of morphine. There may be differences in μ-opioid receptor properties, variability of non-specific activation of endogenous opioids, variability of active p-glycoprotein transport of opioids out of the cells, and variability in opioid induced activation of protein kinase A by Gs-coupled gangliosides counteracting opioid inhibition (31-33). Another possible explanation for the lack of direct serum concentration-effect relationships is that serum concentrations are not necessarily directly related to the concentration at the effect sites. A more direct concentration-effect relationship may exist for opioid concentrations near the effect sites as shown in animals where antinocioceptive responses correlate with morphine and metabolite cortical extracellular fluid concentrations (34).

We recognize some limitations in this study. First, the cut-off value for dichotomizing data is open for discussion. We chose to use the same cut-off

values as applied in previous studies (18,21). However, to our knowledge, these cut-off values are not formally validated. Second, we do not know if the adverse effects classifying patients as complainers are equal to dose limiting adverse effects. On the other hand many patients chose to decline additional pain treatment despite having moderate or severe pain (35). Consequently, we decided to use the intensity of pain and side effects when dichotomizing into treatment failures or successes, since applying success or failure to titrate to adequate pain relief is prone to bias by variable requests for increase in pain management and by differences in acceptability of adverse effects. Third, the serum samples were obtained at a routine laboratory round, and symptoms were measured as a daily average. This study design was chosen in order to assess the association between serum concentrations and clinical symptoms under conditions corresponding to routine drug monitoring of morphine treatment. Fourth, we did not exclude patients using other drugs or recently having received anti-tumor treatment. This approach was most appropriate since we wanted to study the concentration-effect relationships in a population that resembled the population in which physicians would consider serum concentrations determination potentially helpful for decision making (36).

In conclusion, this study demonstrated a lack of direct relationships of serum concentrations and ratios of morphine, M3G and M6G obtained during routine clinical drug monitoring with pain intensity or opioid induced adverse effects such as nausea, constipation, sedation and cognitive failure during chronic morphine therapy in cancer patients. The lack of a concentration-effect relationship found in this study combined with the sparse support of a direct relationship between serum concentrations of morphine and morphine metabolites found in previous smaller studies, suggests that therapeutic drug monitoring as a routine tool during morphine treatment has limited value for clinical decision making.

Acknowledgements

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Table I: Linear regression model of factors predictive clinical outcome variables

Outcome	Factors contributing to outcome	Estimates for individual factors within model			Estimates for models
		Coef.	SE	p-value	R-square
Pain intensity (BPI average pain)	None				
Cognitive function (MMS score)	Age	-0.12	0.02	<0.001	0.31
	Physical performance (Karnofsky score)	0.05	0.02	<0.01	
Tiredness (EORTC QLQ-C30 item "Were you tired")	Physical performance (Karnofsky score)	-0.02	0.01	<0.05	0.10
Nausea (EORTC QLQ-C30 nausea and vomiting scale)	Fatigue (EORTC QLQ-C30 fatigue scale)	0.53	0.09	<0.001	0.22

Age, gender, Karnofsky physical performance score, cancer diagnosis, $\log_{10}$ transformed serum concentrations of morphine, M6G and M3G were included as independent variables in all regression analyses. Additional independent factors in the analyses were as follows: for pain intensity: cognitive function, fatigue and nausea; for cognitive function: pain intensity and fatigue; for tiredness: cognitive function and pain intensity; for nausea: pain intensity and fatigue.

Table II: Serum concentrations in treatment successes and failures caused by nausea, tiredness, cognitive failure or constipation

		Morphine (nmol/l)	M6G (nmol/l)	M3G (nmol/l)	M6G/morphine ratio	M3G/morphine Ratio	M3G/M6G Ratio
Nausea and vomiting	Success (n=87)	60 (30-112)	260 (90-513)	1540 (864-3449)	4.7 (2.7-7.7)	30.8 (16.8-43.4)	6.0 (5.1-7.6)
	Failure (n=37)	62 (32-160)	330 (179-9269)	2372 (1297-3687)	5.5 (3.0-8.1)	35.4 (18.8-60.0)	5.8 (4.6-7.6)
Tiredness	Success (n= 42)	36 (20-100)	210 (70-361)	1490 (470-2864)	4.8 (2.4-8.0)	29.9 (13.9-54.0)	6.1 (5.6-8.1)
	Failure (n=72)	60 (30-170)	325 (168-901)	2250 (1340-4011)	5.6 (3.3-9.6)	33.0 (19.9-64.0)	5.8 (4.6-7.5)
Cognitive Failure	Success (n=83)	50 (28-127)	260 (80-645)	1610 (809-3680)	5.0 (2.7-8.7)	32.9 (17.8-50.6)	5.9 (5.0-7.7)
	Failure (n=18)	40.0 (11-168)	273 (130-518)	2020 (1023-2967)	7.0 (4.0-11.9)	39.5 (23.8-64.1)	6.1 (5.0-8.2)
Constipation	Success (n=60)	45 (27-100)	265 (83-595)	1592 (675-3456)	5.1 (2.8-8.7)	30.1 (16.8-52.0)	5.9 (5.0-7.0)
	Failure (n= 72)	60 (30-148)	330 (172-669)	2250 (1303-3799)	5.5 (3.0-8.8)	30.4 (20.9-55.0)	5.9 (4.7-7.6)

Treatment success: Acceptable pain (BPI average pain score ≤ 3) and side effect non-complainer. Treatment failure: Unacceptable pain and side effect complainer. Cut-off points for defining complainers; EORTC QLQ-C30 Nausea and vomiting scale and constipation symptom score ≥50; EORTC-QLQ-C30 item "Were you tired" score ≥3; MMS (cognitive function) score <24. All numbers are given as median (25% – 75% per-centiles). No statistically significant differences were observed between treatment successes and failures.

Legends

Fig. 1

Criteria used to categorize patients as treatment successes versus treatment failures

Fig. 2

Distribution of Brief Pain Inventory average pain score responses (0 represents "no pain", 10 represents "pain as bad as you can imagine".

Fig. 3

Distribution of Mini Mental State examination score responses

Fig. 4

Distribution of EORTC QLQ-C30 health related quality of life questionnaire "Nausea and vomiting" score responses

Fig. 1

		Side effects	
		Complainers	Non-complainers
Pain	Acceptable	Morphine dose too high	Treatment success
	Unacceptable	Treatment failure	Morphine dose too low

Fig. 2

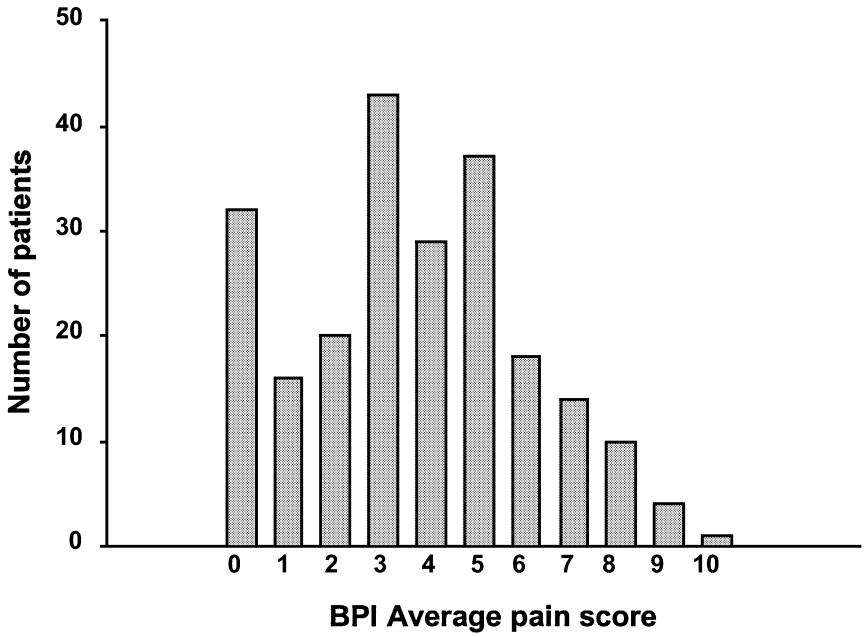

50
40
30
20
10
0
Number of patients
0 1 2 3 4 5 6 7 8 9 10
BPI Average pain score

Fig. 3

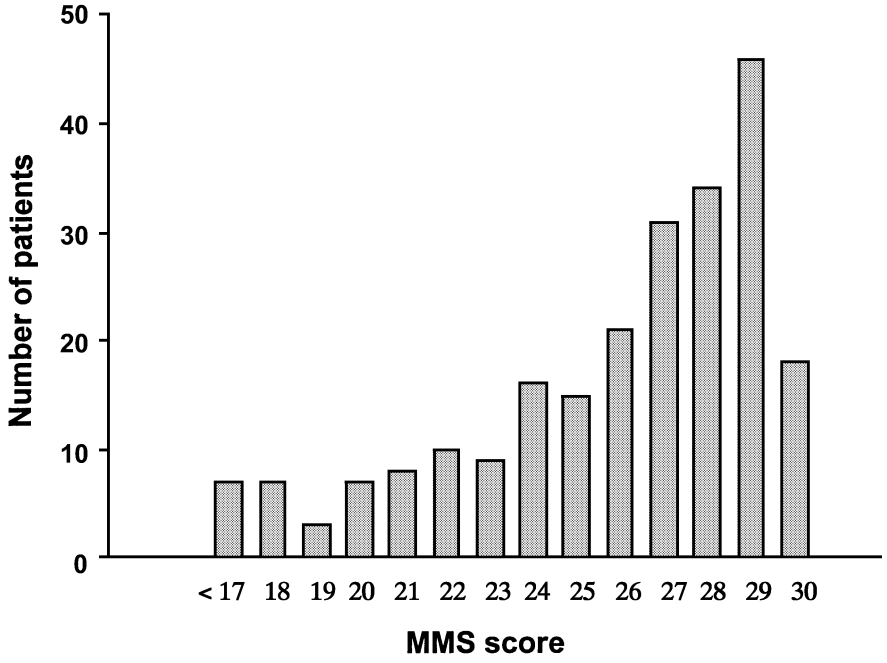
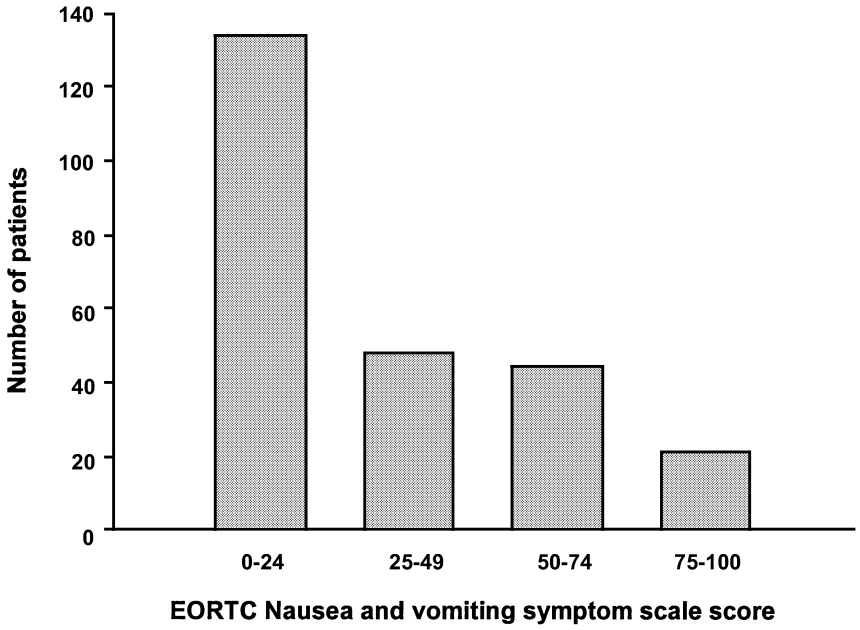

50
40
30
20
10
0
Number of patients
< 17
18
19
20
21
22
23
24
25
26
27
28
29
30
MMS score

Fig. 4


140
120
100
80
60
40
20
0
Number of patients
0-24
25-49
50-74
75-100
EORTC Nausea and vomiting symptom scale score

Dissertations at the Faculty of Medicine, NTNU

1977
1. Knut Joachim Berg: EFFECT OF ACETYLSALICYLIC ACID ON RENAL FUNCTION
2. Karl Erik Viken and Arne Ødegaard: STUDIES ON HUMAN MONOCYTES CULTURED *IN VITRO*

1978
3. Karel Bjørn Cyvin: CONGENITAL DISLOCATION OF THE HIP JOINT.
4. Alf O. Brubakk: METHODS FOR STUDYING FLOW DYNAMICS IN THE LEFT VENTRICLE AND THE AORTA IN MAN.

1979
5. Geirmund Unsgaard: CYTOSTATIC AND IMMUNOREGULATORY ABILITIES OF HUMAN BLOOD MONOCYTES CULTURED IN VITRO

1980
6. Størker Jørstad: URAEMIC TOXINS
7. Arne Olav Jenssen: SOME RHEOLOGICAL, CHEMICAL AND STRUCTURAL PROPERTIES OF MUCOID SPUTUM FROM PATIENTS WITH CHRONIC OBSTRUCTIVE BRONCHITIS

1981
8. Jens Hammerstrøm: CYTOSTATIC AND CYTOLYTIC ACTIVITY OF HUMAN MONOCYTES AND EFFUSION MACROPHAGES AGAINST TUMOR CELLS *IN VITRO*

1983
9. Tore Syversen: EFFECTS OF METHYLMERCURY ON RAT BRAIN PROTEIN.
10. Torbjørn Iversen: SQUAMOUS CELL CARCINOMA OF THE VULVA.

1984
11. Tor-Erik Widerøe: ASPECTS OF CONTINUOUS AMBULATORY PERITONEAL DIALYSIS.
12. Anton Hole: ALTERATIONS OF MONOCYTE AND LYMPHOCYTE FUNCTIONS IN REALTION TO SURGERY UNDER EPIDURAL OR GENERAL ANAESTHESIA.
13. Terje Terjesen: FRACTURE HEALING AN STRESS-PROTECTION AFTER METAL PLATE FIXATION AND EXTERNAL FIXATION.
14. Carsten Saunte: CLUSTER HEADACHE SYNDROME.
15. Inggard Lereim: TRAFFIC ACCIDENTS AND THEIR CONSEQUENCES.
16. Bjørn Magne Eggen: STUDIES IN CYTOTOXICITY IN HUMAN ADHERENT MONONUCLEAR BLOOD CELLS.
17. Trond Haug: FACTORS REGULATING BEHAVIORAL EFFECTS OG DRUGS.

1985
18. Sven Erik Gisvold: RESUSCITATION AFTER COMPLETE GLOBAL BRAIN ISCHEMIA.
19. Terje Espevik: THE CYTOSKELETON OF HUMAN MONOCYTES.
20. Lars Bevanger: STUDIES OF THE Ibc (c) PROTEIN ANTIGENS OF GROUP B STREPTOCOCCI.
21. Ole-Jan Iversen: RETROVIRUS-LIKE PARTICLES IN THE PATHOGENESIS OF PSORIASIS.
22. Lasse Eriksen: EVALUATION AND TREATMENT OF ALCOHOL DEPENDENT BEHAVIOUR.
23. Per I. Lundmo: ANDROGEN METABOLISM IN THE PROSTATE.

1986
24. Dagfinn Berntzen: ANALYSIS AND MANAGEMENT OF EXPERIMENTAL AND CLINICAL PAIN.
25. Odd Arnold Kildahl-Andersen: PRODUCTION AND CHARACTERIZATION OF MONOCYTE-DERIVED CYTOTOXIN AND ITS ROLE IN MONOCYTE-MEDIATED CYTOTOXICITY.
26. Ola Dale: VOLATILE ANAESTHETICS.

1987
27. Per Martin Kleveland: STUDIES ON GASTRIN.
28. Audun N. Øksendal: THE CALCIUM PARADOX AND THE HEART.
29. Vilhjalmur R. Finsen: HIP FRACTURES

1988
30. Rigmor Austgulen: TUMOR NECROSIS FACTOR: A MONOCYTE-DERIVED REGULATOR OF CELLULAR GROWTH.
31. Tom-Harald Edna: HEAD INJURIES ADMITTED TO HOSPITAL.
32. Joseph D. Borsi: NEW ASPECTS OF THE CLINICAL PHARMACOKINETICS OF METHOTREXATE.
33. Olav F. M. Sellevold: GLUCOCORTICOIDS IN MYOCARDIAL PROTECTION.
34. Terje Skjærpe: NONINVASIVE QUANTITATION OF GLOBAL PARAMETERS ON LEFT VENTRICULAR FUNCTION: THE SYSTOLIC PULMONARY ARTERY PRESSURE AND CARDIAC OUTPUT.
35. Eyvind Rødahl: STUDIES OF IMMUNE COMPLEXES AND RETROVIRUS-LIKE ANTIGENS IN PATIENTS WITH ANKYLOSING SPONDYLITIS.

36. Ketil Thorstensen: STUDIES ON THE MECHANISMS OF CELLULAR UPTAKE OF IRON FROM TRANSFERRIN.
37. Anna Midelfart: STUDIES OF THE MECHANISMS OF ION AND FLUID TRANSPORT IN THE BOVINE CORNEA.
38. Eirik Helseth: GROWTH AND PLASMINOGEN ACTIVATOR ACTIVITY OF HUMAN GLIOMAS AND BRAIN METASTASES - WITH SPECIAL REFERENCE TO TRANSFORMING GROWTH FACTOR BETA AND THE EPIDERMAL GROWTH FACTOR RECEPTOR.
39. Petter C. Borchgrevink: MAGNESIUM AND THE ISCHEMIC HEART.
40. Kjell-Arne Rein: THE EFFECT OF EXTRACORPOREAL CIRCULATION ON SUBCUTANEOUS TRANSCAPILLARY FLUID BALANCE.
41. Arne Kristian Sandvik: RAT GASTRIC HISTAMINE.
42. Carl Bredo Dahl: ANIMAL MODELS IN PSYCHIATRY.

1989

43. Torbjørn A. Fredriksen: CERVICOGENIC HEADACHE.
44. Rolf A. Walstad: CEFTAZIDIME.
45. Rolf Salvesen: THE PUPIL IN CLUSTER HEADACHE.
46. Nils Petter Jørgensen: DRUG EXPOSURE IN EARLY PREGNANCY.
47. Johan C. Ræder: PREMEDICATION AND GENERAL ANAESTHESIA IN OUTPATIENT GYNECOLOGICAL SURGERY.
48. M. R. Shalaby: IMMUNOREGULATORY PROPERTIES OF TNF-α AND THE RELATED CYTOKINES.
49. Anders Waage: THE COMPLEX PATTERN OF CYTOKINES IN SEPTIC SHOCK.
50. Bjarne Christian Eriksen: ELECTROSTIMULATION OF THE PELVIC FLOOR IN FEMALE URINARY INCONTINENCE.
51. Tore B. Halvorsen: PROGNOSTIC FACTORS IN COLORECTAL CANCER.

1990

52. Asbjørn Nordby: CELLULAR TOXICITY OF ROENTGEN CONTRAST MEDIA.
53. Kåre E. Tvedt: X-RAY MICROANALYSIS OF BIOLOGICAL MATERIAL.
54. Tore C. Stiles: COGNITIVE VULNERABILITY FACTORS IN THE DEVELOPMENT AND MAINTENANCE OF DEPRESSION.
55. Eva Hofsli: TUMOR NECROSIS FACTOR AND MULTIDRUG RESISTANCE.
56. Helge S. Haarstad: TROPHIC EFFECTS OF CHOLECYSTOKININ AND SECRETIN ON THE RAT PANCREAS.
57. Lars Engebretsen: TREATMENT OF ACUTE ANTERIOR CRUCIATE LIGAMENT INJURIES.
58. Tarjei Rygnestad: DELIBERATE SELF-POISONING IN TRONDHEIM.
59. Arne Z. Henriksen: STUDIES ON CONSERVED ANTIGENIC DOMAINS ON MAJOR OUTER MEMBRANE PROTEINS FROM ENTEROBACTERIA.
60. Steinar Westin: UNEMPLOYMENT AND HEALTH: Medical and social consequences of a factory closure in a ten-year controlled follow-up study.
61. Ylva Sahlin: INJURY REGISTRATION, a tool for accident preventive work.
62. Helge Bjørnstad Pettersen: BIOSYNTHESIS OF COMPLEMENT BY HUMAN ALVEOLAR MACROPHAGES WITH SPECIAL REFERENCE TO SARCOIDOSIS.
63. Berit Schei: TRAPPED IN PAINFUL LOVE.
64. Lars J. Vatten: PROSPECTIVE STUDIES OF THE RISK OF BREAST CANCER IN A COHORT OF NORWEGIAN WOMAN.

1991

65. Kåre Bergh: APPLICATIONS OF ANTI-C5a SPECIFIC MONOCLONAL ANTIBODIES FOR THE ASSESSMENT OF COMPLEMENT ACTIVATION.
66. Svein Svenningsen: THE CLINICAL SIGNIFICANCE OF INCREASED FEMORAL ANTEVERSION.
67. Olbjørn Klepp: NONSEMINOMATOUS GERM CELL TESTIS CANCER: THERAPEUTIC OUTCOME AND PROGNOSTIC FACTORS.
68. Trond Sand: THE EFFECTS OF CLICK POLARITY ON BRAINSTEM AUDITORY EVOKED POTENTIALS AMPLITUDE, DISPERSION, AND LATENCY VARIABLES.
69. Kjetil B. Åsbakk: STUDIES OF A PROTEIN FROM PSORIATIC SCALE, PSO P27, WITH RESPECT TO ITS POTENTIAL ROLE IN IMMUNE REACTIONS IN PSORIASIS.
70. Arnulf Hestnes: STUDIES ON DOWN´S SYNDROME.
71. Randi Nygaard: LONG-TERM SURVIVAL IN CHILDHOOD LEUKEMIA.
72. Bjørn Hagen: THIO-TEPA.
73. Svein Anda: EVALUATION OF THE HIP JOINT BY COMPUTED TOMOGRAMPHY AND ULTRASONOGRAPHY.

1992

74. Martin Svartberg: AN INVESTIGATION OF PROCESS AND OUTCOME OF SHORT-TERM PSYCHODYNAMIC PSYCHOTHERAPY.
75. Stig Arild Slørdahl: AORTIC REGURGITATION.
76. Harold C Sexton: STUDIES RELATING TO THE TREATMENT OF SYMPTOMATIC NON-PSYCHOTIC PATIENTS.
77. Maurice B. Vincent: VASOACTIVE PEPTIDES IN THE OCULAR/FOREHEAD AREA.
78. Terje Johannessen: CONTROLLED TRIALS IN SINGLE SUBJECTS.
79. Turid Nilsen: PYROPHOSPHATE IN HEPATOCYTE IRON METABOLISM.
80. Olav Haraldseth: NMR SPECTROSCOPY OF CEREBRAL ISCHEMIA AND REPERFUSION IN RAT.
81. Eiliv Brenna: REGULATION OF FUNCTION AND GROWTH OF THE OXYNTIC MUCOSA.

1993

82. Gunnar Bovim: CERVICOGENIC HEADACHE.
83. Jarl Arne Kahn: ASSISTED PROCREATION.
84. Bjørn Naume: IMMUNOREGULATORY EFFECTS OF CYTOKINES ON NK CELLS.
85. Rune Wiseth: AORTIC VALVE REPLACEMENT.
86. Jie Ming Shen: BLOOD FLOW VELOCITY AND RESPIRATORY STUDIES.
87. Piotr Kruszewski: SUNCT SYNDROME WITH SPECIAL REFERENCE TO THE AUTONOMIC NERVOUS SYSTEM.
88. Mette Haase Moen: ENDOMETRIOSIS.
89. Anne Vik: VASCULAR GAS EMBOLISM DURING AIR INFUSION AND AFTER DECOMPRESSION IN PIGS.
90. Lars Jacob Stovner: THE CHIARI TYPE I MALFORMATION.
91. Kjell Å. Salvesen: ROUTINE ULTRASONOGRAPHY IN UTERO AND DEVELOPMENT IN CHILDHOOD.

1994

92. Nina-Beate Liabakk: DEVELOPMENT OF IMMUNOASSAYS FOR TNF AND ITS SOLUBLE RECEPTORS.
93. Sverre Helge Torp: *erb*B ONCOGENES IN HUMAN GLIOMAS AND MENINGIOMAS.
94. Olav M. Linaker: MENTAL RETARDATION AND PSYCHIATRY. Past and present.
95. Per Oscar Feet: INCREASED ANTIDEPRESSANT AND ANTIPANIC EFFECT IN COMBINED TREATMENT WITH DIXYRAZINE AND TRICYCLIC ANTIDEPRESSANTS.
96. Stein Olav Samstad: CROSS SECTIONAL FLOW VELOCITY PROFILES FROM TWO-DIMENSIONAL DOPPLER ULTRASOUND: Studies on early mitral blood flow.
97. Bjørn Backe: STUDIES IN ANTENATAL CARE.
98. Gerd Inger Ringdal: QUALITY OF LIFE IN CANCER PATIENTS.
99. Torvid Kiserud: THE DUCTUS VENOSUS IN THE HUMAN FETUS.
100. Hans E. Fjøsne: HORMONAL REGULATION OF PROSTATIC METABOLISM.
101. Eylert Brodtkorb: CLINICAL ASPECTS OF EPILEPSY IN THE MENTALLY RETARDED.
102. Roar Juul: PEPTIDERGIC MECHANISMS IN HUMAN SUBARACHNOID HEMORRHAGE.
103. Unni Syversen: CHROMOGRANIN A. Phsysiological and Clinical Role.

1995

104. Odd Gunnar Brakstad: THERMOSTABLE NUCLEASE AND THE *nuc* GENE IN THE DIAGNOSIS OF *Staphylococcus aureus* INFECTIONS.
105. Terje Engan: NUCLEAR MAGNETIC RESONANCE (NMR) SPECTROSCOPY OF PLASMA IN MALIGNANT DISEASE.
106. Kirsten Rasmussen: VIOLENCE IN THE MENTALLY DISORDERED.
107. Finn Egil Skjeldestad: INDUCED ABORTION: Timetrends and Determinants.
108. Roar Stenseth: THORACIC EPIDURAL ANALGESIA IN AORTOCORONARY BYPASS SURGERY.
109. Arild Faxvaag: STUDIES OF IMMUNE CELL FUNCTION *in mice infected with* MURINE RETROVIRUS.

1996

110. Svend Aakhus: NONINVASIVE COMPUTERIZED ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND SYSTEMIC ARTERIAL PROPERTIES. Methodology and some clinical applications.
111. Klaus-Dieter Bolz: INTRAVASCULAR ULTRASONOGRAPHY.
112. Petter Aadahl: CARDIOVASCULAR EFFECTS OF THORACIC AORTIC CROSS-CLAMPING.
113. Sigurd Steinshamn: CYTOKINE MEDIATORS DURING GRANULOCYTOPENIC INFECTIONS.
114. Hans Stifoss-Hanssen: SEEKING MEANING OR HAPPINESS?
115. Anne Kvikstad: LIFE CHANGE EVENTS AND MARITAL STATUS IN RELATION TO RISK AND PROGNOSIS OF CANSER.

116. Torbjørn Grøntvedt: TREATMENT OF ACUTE AND CHRONIC ANTERIOR CRUCIATE LIGAMENT INJURIES. A clinical and biomechanical study.
117. Sigrid Hørven Wigers: CLINICAL STUDIES OF FIBROMYALGIA WITH FOCUS ON ETIOLOGY, TREATMENT AND OUTCOME.
118. Jan Schjøtt: MYOCARDIAL PROTECTION: Functional and Metabolic Characteristics of Two Endogenous Protective Principles.
119. Marit Martinussen: STUDIES OF INTESTINAL BLOOD FLOW AND ITS RELATION TO TRANSITIONAL CIRCULATORY ADAPATION IN NEWBORN INFANTS.
120. Tomm B. Müller: MAGNETIC RESONANCE IMAGING IN FOCAL CEREBRAL ISCHEMIA.
121. Rune Haaverstad: OEDEMA FORMATION OF THE LOWER EXTREMITIES.
122. Magne Børset: THE ROLE OF CYTOKINES IN MULTIPLE MYELOMA, WITH SPECIAL REFERENCE TO HEPATOCYTE GROWTH FACTOR.
123. Geir Smedslund: A THEORETICAL AND EMPIRICAL INVESTIGATION OF SMOKING, STRESS AND DISEASE: RESULTS FROM A POPULATION SURVEY.

1997

124. Torstein Vik: GROWTH, MORBIDITY, AND PSYCHOMOTOR DEVELOPMENT IN INFANTS WHO WERE GROWTH RETARDED *IN UTERO*.
125. Siri Forsmo: ASPECTS AND CONSEQUENCES OF OPPORTUNISTIC SCREENING FOR CERVICAL CANCER. Results based on data from three Norwegian counties.
126. Jon S. Skranes: CEREBRAL MRI AND NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN. A follow-up study of a geographically based year cohort of VLBW children at ages one and six years.
127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUTION OF CORONARY ARTERY DISEASE.
128. Grethe Elisabeth Borchgrevink: DIAGNOSIS AND TREATMENT OF WHIPLASH/NECK SPRAIN INJURIES CAUSED BY CAR ACCIDENTS.
129. Tor Elsås: NEUROPEPTIDES AND NITRIC OXIDE SYNTHASE IN OCULAR AUTONOMIC AND SENSORY NERVES.
130. Rolf W. Gråwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs.

1998

132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.
133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.
134. Egil Lien: SOLUBLE RECEPTORS FOR **TNF** AND **LPS**: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.
135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.
139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

1999

141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.
142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.

145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153. Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

2000

158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING
159. CLINICAL AND EXPERIMENTAL STUDIES
160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.
162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.
163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.
164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.
168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

2001

178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT
192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS
193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM
198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

2002

201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS

208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN