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Farmakokinetiske, farmakodynamiske og farmakogenetiske aspekter ved oksykodon i behandling av kreftsmerter

Kroniske smerter ved kreftsykdom er et utfordrende problem. Selv om sterke smertelindrende medikamenter som morfin eller oksykodon (opioider) er i utstrakt bruk, er det mange kreftpasienter som ikke oppnår tilstrekkelig smertelinding eller plages av bivirkninger. En grunn til at man ikke får god nok virkning hos alle, er at opioider virker svært forskjellig fra individ til individ. For å kunne bedre smertebehandlingen av kreftpasienter er det viktig å finne ut mer om hvorfor det er slike forskjeller.

Denne studien er en del av et EU-prosjekt som har inkludert 2294 kreftpasienter. Av disse var det 461 som benyttet opioidet oksykodon mot sine kreftsmerter. Det er lite kunnskap om hvilke faktorer som påvirker virkningen av oksykodon hos kreftpasienter. Målet med denne studien var derfor å undersøke om alminnelige kliniske opplysninger sammen med målinger av serum konsentrasjoner av oksykodon og nedbrytningsprodukter (metabolitter) av oksykodon eller gener for nedbrytningsenzymer, kan forklare forskjeller mellom individer. Kliniske opplysninger som ble inkludert, var pasientens alder, kjønn, kroppsmasseindeks (BMI), daglig oksykodon dose, opplysninger om tilleggsmedikamenter, hvor lenge pasientene har brukt opioider, hvor mange timer siden forrige dose, fysisk funksjonsstatus, samt indikatorer for lever- og nyre funksjon.

Oksykodon brytes ned i leveren hovedsakelig av CYP3A4 og CYP2D6 enzymer. Disse enzymenes aktivitet kan bli påvirket av andre medikamenter pasienten bruker. I tillegg eksisterer det flere varianter av *CYP2D6*-genet som påvirker dannelsen av det smertestillende nedbrytingsproduktet oksymorfon. Tilleggsmedikamenter og genvarianter av *CYP2D6* kan derfor være med å bestemme den enkelte pasient sitt nivå av oksykodon og metabolitter i blodet, og dermed kanskje den nødvendige doseringen av oksykodon.

Studien har vist at daglige dose oksykodon var den faktoren som forklarte den observerte variasjonen i blodnivået best, mens kjønn og bruk av medikamenter som påvirker nedbrytingen av oksykodon via CYP3A4 enzymene, gav den største effekten på

nivået av oksykodon i blodet og forholdet metabolitt/oksykodon. Bruk av medikamenter som hemmer CYP2D6 enzymene hadde ingen betydning for nivået av oksykodon eller metabolitt/oksykodon forholdet i blodet.

Det var ingen sammenheng mellom nivået av oksykodon eller metabolittene noroksykodon og noroksymorfon i blodet og smerteintensitet, og bivirkninger (kvalme, trøtthet og kognitiv funksjon). Likevel var bruk av CYP3A4 hemmeren flukonazol assosiert med mindre smerte, mens økt mengde av metabolitten oksymorfon pardoksalt nok var assosiert med en økning i smerte i denne gruppen av pasienter. Dette er vanskelig å forklare, men vi observerte også at pasienter som hadde "smerter og bivirkninger", generelt hadde høyere nivåer i blodet av oksykodon og metabolittene enn de som var "godt smertelindret og uten bivirkninger". Spesielt gjaldt dette for bivirkningen "trøtthet", hvor andelen pasienter med "smerte og trøtthet" var mye større enn andelen "godt smertebehandlet og ikke trøtt". Disse resultatene antyder at mange pasienter er relativt overdosert, og kanskje burde vært tilbudt et annet medikament enn oksykodon.

Studien viste også at *CYP2D6* gen varianten påvirker nivået av okymorfon og noroksymorfon i blodet, men dette hadde ingen betydning for virkningen av oksykodonbehandlingen.

At de subjektive utfallssymptomene smerteintensitet, tretthet, kvalme og kognitiv funksjon ikke bare skyldes oksykodonbehandlingen, men også selve kreftsykdommen, gir utfordringer i tolkningen av resultatene.

Oppsummert indikerer denne studien at verken rutinemessig serumkonsentrasjonsmåling eller genotyping av *CYP2D6* er indisert ved bruk av oksykodon. Ved kronisk administrering er oksykodon det vesentlige, aktive virkestoffet. Trøtthet er et hyppig symptom hos de som ikke er godt smertebehandlet og kan indikere behov for å bytte opioid. Pasienter som skal starte eller stoppe med CYP3A4 medikamenter bør følges tett etterpå.

Cand. Scient Trine Naalsund Andreassen

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Summary

Chronic pain during cancer is a challenging problem. Even though strong drugs for pain relief such as morphine or oxycodone (opioids) are extensively used, many cancer patients are inadequately pain relived or suffering from side effects. The large inter-individual variability in the response to opioids is one reason why all patients are not adequately pain relieved. To be able to ensure a better treatment to cancer patients it is important to understand why there is such variation in the response to opioids.

This study is part of a larger EU-project that included 2294 cancer patients. Of these, 461 were scheduled with the opioid oxycodone for their cancer pain. There is little knowledge about which factors that influences the efficacy of oxycodone in cancer patients. Thus, the aim of this study was to examine if clinical information together with measurements of serum concentrations of oxycodone and its metabolites or genes of the metabolizing enzymes, may explain differences between individuals. Clinical information included was the patient's age, sex, body mass index, oxycodone daily dosage, information on co-medication, how long the patient has been using opioids, number of hours since last dose, physical functioning, and indicators for hepatic- and kidney function.

Oxycodone is mainly metabolized in the liver by CYP3A4 and CYP2D6 enzymes. The activity of these enzymes may be affected by other drugs used by the patient. In addition, the *CYP2D6* gene exists in several forms that affect the production of the analgesic metabolite oxymorphone. Co-medication and *CYP2D6* genetic variants can therefore affect the level of oxycodone and its metabolites in the individual patient's blood. This can have implications for the required dose of oxycodone.

The study has shown that the variable "daily dose of oxycodone" best explained the variation in blood level, while sex and use of co-medications that affects the metabolism of oxycodone via CYP3A4 enzymes, had the largest effect on the level of oxycodone in the blood and the ratio metabolite/oxycodone. Use of drugs that inhibit CYP2D6 enzymes had no effect on the level of oxycodone or the metabolite/oxycodone ratio in the blood.

No relationship was found between level of oxycodone or the metabolites noroxycodone and noroxymorphone in the blood and pain intensity, and side effects (nausea, tiredness

and cognitive function). Still, the use of the CYP3A4 inhibitor fluconazole was associated with less pain, while an increase of the metabolite oxymorphone, paradoxically, was associated with increasing pain in this group of patients. This is difficult to explain, but we also observed that patients who had “poor pain control and side effects”, generally had the highest serum concentrations of both oxycodone and metabolites compared to those who were “pain relieved and without side effects”. This was especially true for the side effect “tiredness”, where the portion of patients with “pain and tiredness” was much higher than the portion of patients being “pain relieved and not tired”. This suggests that many patients are overdosed, and that these patients should have been offered a different drug than oxycodone.

This study also showed that the *CYP2D6* genotype influences the level of oxymorphone and noroxymorphone. This, however, does not have any consequence for the effect of the oxycodone treatment between the genotypes.

Subjective outcomes such as pain intensity, tiredness, nausea and cognitive function may also be caused by the cancer disease itself. This makes the results challenging to interpret.

In conclusion, this study implies that neither routine serum concentration measurements nor *CYP2D6* genotyping are indicated during oxycodone administration. During chronic administration, the analgesic effect is mainly mediated by oxycodone itself. Tiredness is a prevalent symptom among those who have poor pain control, and this may indicate a need for a switch to another opioid. Patients who are going to start on- or discontinue drugs that affect the CYP3A4 enzyme system should be monitored closely.

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Acknowledgements

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Trondheim, March 2011

Trine Naalsund Andreassen

List of papers

I. Trine Naalsund Andreassen, Pål Klepstad, Andrew Davies, Kristin Bjordal, Staffan Lundström, Stein Kaasa, Ola Dale. **Influences on the pharmacokinetics of oxycodone – A multicentre cross-sectional study in 439 adult cancer patients.** *European Journal of Clinical Pharmacology, 2011, 67, 5, 493-506. http://dx.doi.org/10.1007/s00228-010-0948-5*

II. Trine Naalsund Andreassen, Pål Klepstad, Andrew Davies, Kristin Bjordal, Staffan Lundström, Stein Kaasa, Ola Dale. **Is oxycodone efficacy reflected in serum concentrations? – A multicentre cross-sectional study in 456 adult cancer patients.** *Accepted for publication in Journal of Pain and Symptom Management*

III. Trine Naalsund Andreassen, Ingrid Eftedal, Pål Klepstad, Andrew Davies, Kristin Bjordal, Staffan Lundström, Stein Kaasa, Ola Dale. **Do the CYP2D6 genotypes reflect oxycodone requirements in cancer pain patients? - A cross-sectional multicentre study.** *Submitted to European Journal of Clinical Pharmacology*

Abbreviations

μ	mu
∞	Infinitely
ANCOVA	Analysis of co-variance
ANOVA	Analysis of variance
AUC	Area under the curve
BBB	Blood-brain barrier
BMI	Body mass index
BPI	Brief Pain Inventory
CI	Confidence interval
C_{max}	The peak plasma concentration of a drug after oral administration
CNS	Central nervous system
CR	Controlled release
CSF	Cerebrospinal fluid
CYP2D6	Cytochrome P450 2D6
CYP3A4	Cytochrome P450 3A4
EM	Extensive metabolizer
EORTC	European Organization for Research and Treatment of Cancer
EPOS	European pharmacogenetic opioid study
h	hour
IASP	International Association for the Study of Pain
IR	Immediate release
M6G	Morphine-6-glucuronide
MMS	Mini mental state
NRS	Numerical rating scale
OR	Odds ratio
PM	Poor metabolizer
QLQ-C30	EORTC's 30 items quality of life questionnaire
R^2	Coefficient of determination
r_s	Spearman rank correlations
SNP	Single nucleotide polymorphism
T_{max}	Time when the peak plasma concentration of a drug after oral administration is reached
UGT2B7	Uridine diphosphate glucuronosyltransferase 2B7
URM	Ultra rapid metabolizer
WHO	World Health Organisation
δ	delta
κ	kappa

Glossary

Agonist	Is a chemical or drug that binds to a receptor of a cell and triggers a response by that cell
Allele	Is one of two or more forms of the DNA sequence of a particular gene
Antagonist	Is a chemical or drug that has affinity for the receptor but does not provoke a biological response itself upon binding to a receptor
Antinociceptive effect	To be able to reduce sensitivity to painful stimuli
Bioavailability	Is the fraction of the dose that is absorbed and escapes the first pass metabolism. It is being calculated: $AUC_{oral}/AUC_{intravenous}$
Blood plasma	Is the yellow liquid component of blood in which the blood cells are removed
Blood serum	Is the component of blood in which the blood cells and fibrinogen or the other clotting factors (i.e., whole blood minus both the cells and the clotting factors) have been removed
Ceiling effect	The phenomenon in which a drug reaches a maximum effect, so that increasing the drug dosage does not increase its effectiveness
Clearance, CL	The volume of plasma cleared of the drug per unit time. CL = rate of elimination / concentration
Conjugation	In metabolism conjugation is a reaction in which two compounds are reacting and merged together to a new more hydrophilic compound
Efficacy	Is the relationship between receptor occupancy and the ability to initiate a response at the molecular, cellular, tissue or system level

Elimination half time	Is the period of time it takes for a substance to be eliminated to the half
First order kinetics	Is when a constant fraction of the drug is eliminated per unit time, as opposed to zero-order kinetics where a constant amount of the drug is eliminated per unit time
First pass metabolism	Is the drug metabolism in the gut wall and liver whereby the concentration of a drug is greatly reduced before it reaches the systemic circulation. After a drug is swallowed, it is absorbed by the digestive system and enters the hepatic portal system. It is carried through the portal vein into the liver before it reaches the rest of the body. This metabolism before it reaches the systemic circulation is called the first pass metabolism
Genotype	Is defined as the combination of alleles on two chromosomes. To equal alleles are said to be a homozygous genotype group, while two unequal alleles are heterozygous
Glomerular filtration rate; GFR ($mlmin^{-1}/1.73\ m^2$)	Is an indication of the state of the kidney, and describes the flow rate of filtered fluid through the kidney. In this thesis GFR was expressed as: calculated glomerular filtration rate x body surface / 1.73 m^2 where glomerular filtration rate was calculated: $175 \times (\text{creatinine}/88.4)^{-1.154} \times \text{age (years)}^{-0.203} \times 0.742$ if women. Body surface was calculated: $0.20247 \times \text{height (m)}^{0.725} \times \text{weight (kg)} \times 1.23 \times 0.85$ if woman. Normal function: GFR ≥ 90 ml/min Dysfunction: GFR < 60 ml/min
Hardy Weinberg equilibrium	States that both allele and genotype frequencies in a population remain constant. A random genetic sample has a distribution of homozygous and heterozygous carriers that correspond to the Hardy-Weinberg equilibrium. p is the frequency of one allele, q of the other allele. p^2 is the frequency of one homozygous group, $2pq$ is the frequency of the heterozygous individuals and q^2 the frequency of the

	other homozygous group. The Hardy-Weinberg equilibrium states that $p^2+2pq+q^2=1$
Hyperalgesia	Is an increased sensitivity to pain
Odds	Number of times an event happens / number of times an event does not happen
Odds ratio	Odds in the group being exposed / odds in group not being exposed
Pathophysiology	Is the study of the changes of normal mechanical, physical and biochemical functions
Pharmacodynamic	Is simply defined as the study of what the drug does to the body, and includes the relationship between drug concentration and effect
Pharmacogenomics	The study of how genes influence the way a patient responds to drug therapy
Pharmacogentic	Is generally regarded as the study or clinical testing of genetic variation that gives rise to differing response to drugs
Pharmacokinetic	Is simply defined as what the body does to the drug. It includes the extent and rate of absorption, distribution, metabolism and excretion
Phenotype	Is an observable attribute of an organism
R^2	An estimate of the amount of the variation in the data that is being explained by a regression model. Equal in linear regression to the square of Pearson's product-moment correlation coefficient
Statistical power	Is the probability that the study will detect a statistical significant difference
Steady-state serum concentration	In steady-state the drug elimination equals drug availability. When a drug is administered every 12 h the serum concentrations of the drug rises and falls. In steady-state this cycle is repeated identically in each administration interval. The steady-state serum concentration then describes the

	average drug concentration during an inter-dose interval
Sublingual administration	Pharmacological route of administration by which drugs diffuse into the blood through tissues under the tongue
Systemic circulation	Is the part of the cardiovascular system which carries oxygenated blood away from the heart to the body, and returns deoxygenated blood back to the heart
Therapeutic window	It is the dosage range of a drug where we get the wanted effect and this exceeds the unwanted adverse effects
Trough blood sample	A blood sample taken at when the concentration of a drug is at a minimum after its administration and just prior to the administration of a subsequent dose in a multiple dosing study
Volume of distribution	The apparent volume in which a drug is distributed immediately after it has been injected intravenously and equilibrated between plasma and the surrounding tissues

Introduction

Cancer patients

Mutation of a single cell, caused by defects in the genes associated with the cell cycle and the cell signaling pathways, which control cell replication and cell death, may be the beginning of a cancer disease. Defects in genes can be inherited, occur by chance, be caused by exposure to certain viruses or by exposure to carcinogens. Age is an important risk factor, as the cellular repair mechanisms tend to be less effective as a person grows older and because risk factors are accumulating. Common characteristics of cancer cells are the ability to avoid apoptosis (programmed cell death), resistance to the normal ageing process, uncontrolled replication, production of chemicals which are harmful to surrounding connective tissue, stimulation of a micro vascular blood supply (angiogenesis), invasion and dissemination to other parts of the body (metastatic spread) and the ability to overcome or paralyze the immune system (McIllmurray, 2010). Cancer can occur at any time and in any part of the body. The stage of disease can vary from being a local tumor to metastatic spread. The cancer symptom burden may be high, often increasing with disease progression. These factors contribute to the heterogeneity of the cancer patients.

In 2004, 7.4 million people died of cancer, making cancer the leading cause of death worldwide. More than 70% of these cancer deaths occurred in low- and middle-income countries (World Health Organization, 2011a) .

In 2008 the cancer incidence in Norway was 26121 (14000 males and 12121 females). Prostate, female breast, colon and lung cancer are the most common types and comprise almost half of the total. 90 % of the Norwegian males and 85 % of the females are diagnosed after the age of 50, and more than half of the incidences are persons above the age of 70. Five years relative survival rates have increased from 48 % (1994-98) to 64 % (2004-08) for males, and from 57 % (1994-98) to 67 % (2004-08) for females (Cancer Registry of Norway, 2009).

Pain

Pain is defined by the International Association for the Study of Pain (IASP[1]) to be "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Further, IASP states pain to always be subjective and that pain is that experience we associate with actual or potential tissue damage (International Association for the Study of Pain, http://www.iasp-pain.org//AM/Template.cfm?Section=Home).

Pain is often multi-dimensional and if there is lack of knowledge about the type of pain; acute or chronic, cancer related or not, nociceptive or neuropathic and so on, this can make the pain difficult to manage. Also, pain is influenced by psychological, social and physiological factors that will vary in intensity and strength, making the management even further complicated. Unfortunately, there is no international consensus in how to classify cancer pain (Knudsen et al., 2009, Kaasa and Borchgrevink, 2007).

Cancer Pain

Cancer patients report pain to be one of the most common and most feared symptom they experience. Pain has a prevalence of 33-64 % in cancer patients, and is not associated with specific types of cancer. Of the patients with pain one-third rates their pain to be moderate to severe (van den Beuken-van Everdingen et al., 2007).

Cancer pain can be chronic or acute, or both at the same time. Chronic cancer pain is defined to be persistent pain with intensity above 3 on the 11-points Numerical Rating Scale (NRS). This pain will vary in intensity over time, and the treatment target is to reduce the pain to below 3. In the beginning of a cancer disease, acute pain occurs, while patients with incurable disease often have chronic pain with episodes of breakthrough pain. The chronic pain may occur because of disease progression, side effects from treatment, or both. Breakthrough pain is an acute pain that is sudden and instant, and that appears on top of the "baseline" pain. Breakthrough pain is measured between six

[1] URL http://www.iasp-pain.org

and nine on a 0-10 numerical rating scale. The duration is short, often 5-10 minutes, and it can be associated with movements of the patient, food intake or during emptying of the bladder. Breakthrough pain can also occur without any obvious reason. The challenge with this intense and unpredictable type of pain is to give an appropriate drug for pain relief. The drugs acquired have to be fast acting and have a relativelly short duration of action due to the high pain intensity and short duration of this type of pain. Knowledge about the diagnosis, the stage of the disease, how the disease will progress and what type of pain to expect is very important when it comes to treatment strategies. Whenever possible, eliminating the cause of pain should be the treatment target. If the chronic pain is caused by the disease progression, it might be impossible to remove the cause of the pain, thus the intention of the treatment may change from "totally pain relieved" to "an acceptable pain level". The most common cause of cancer pain is skeletal metastases. Tumor growth in the peripheral nerve cells or the CNS is the most common cause of neuropathic pain in cancer patients (Kaasa and Borchgrevink, 2007, Kaasa, 2007).

The intensity of the pain is the strategy-guide when the WHO's analgesic ladder is used.

WHO's three-step "ladder" for cancer pain relief

The World Health Organization has developed a three-step analgesic ladder with recommendations on how to treat cancer pain (World Health Organization, 2010). Patients with mild pain should first be treated with a non-opioid analgesic (e.g. paracetamol or aspirin) (step 1). If the pain persists or the patient has moderate pain, a weak opioid should be used (codeine, combination drugs with an opioid- and a non-opioid part) (step 2). If this does not work, or the patient has severe pain strong opioids are recommended (morphine, oxycodone, fentanyl and methadone) (step 3). Adjuvant medication can be used in addition on all steps. To remain pain free drugs should be given every 3-6 hours, rather than "on demand". According to the WHO 80-90 % of the patients should be effectively treated if the right drug and dose is used.

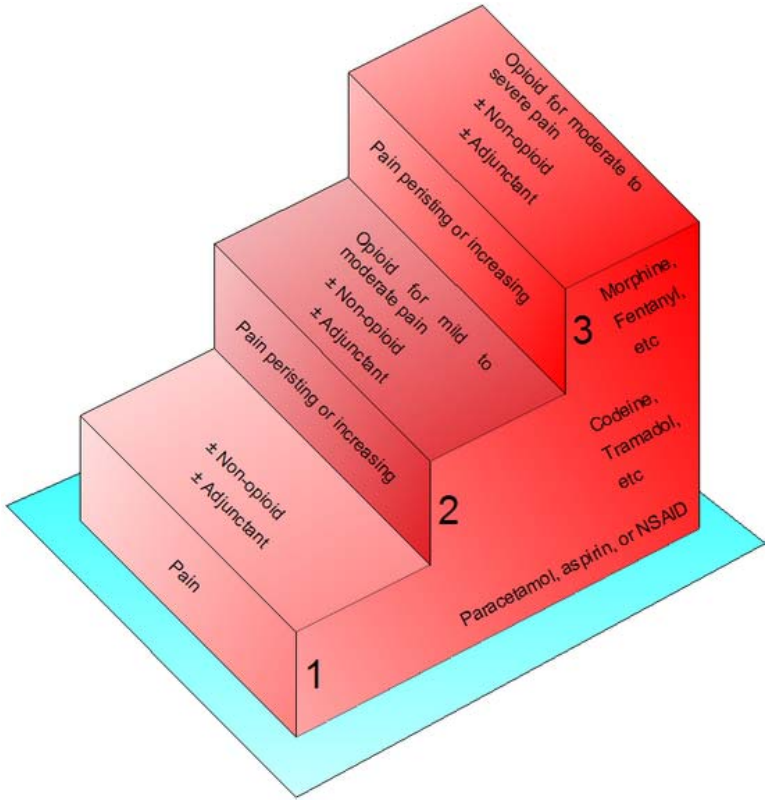


Figure 1 WHO's analgesic ladder

According to the WHO (World Health Organization, 2010) and an expert group working for the European Association for Palliative Care (Hanks et al., 2001), morphine is the opioid of first choice in the treatment of severe cancer pain, of which the others are compared.

However, not all patients benefit from the use of morphine. In one study 26 % of the cancer patients did not respond to morphine. After rotation to oxycodone, 79 % of these non-responders responded to oxycodone (Riley et al., 2006). Also other studies have shown that rotation from morphine to oxycodone might be beneficial when morphine does not give the desired effect (Narabayashi et al., 2008). Further, a low dose

administration of oxycodone and morphine simultaneously seem to be more effective and with fewer side effects, than morphine alone (Lauretti et al., 2003).

Opioid mechanism of action

The effects of most drugs results from their interaction with the macromolecular components of the organism. The interactions cause a change in the macromolecular function, which thereby initiate the biochemical and physiological changes that are characteristic of the response to the drug. The site or macromolecule where a drug binds and initiates its effect is called a receptor. Opioids bind to at type of physiological receptors that are called opioid receptors, and are coupled to a family of trans-membrane G-proteins. These receptors are specialized to recognize and respond to individual signal molecules with great selectivity. Drugs that act on such physiological receptors are therefore often very selective. If a drug binds to a physiological receptor and mimics its endogenous signalling, the drug is called an agonist. Drugs that bind to the receptors without any regulatory effect are called antagonists. The chemical structure of the drug is important for the affinity of the drug for the receptor and also the pharmacological properties of the drug. A small change in chemical structure can cause a huge change in both the pharmacological effect and the receptor affinity. The effect of the drug depends on what type of receptor the drug binds to and also where this receptor is localized in the body. If the drug acts on a receptor that has a function in most cells, the drugs effect will be widespread, while if the drug act on receptors that are unique to only some types of differentiated cells, its effects are more specific (Ross and Kenakin, 2001, Fallon et al., 2010).

The endogenous peptides enkephalin, dynorphins and endorphins are naturally occurring ligands for opioid receptors. Through receptor binding studies and cloning the three main opioid receptors, μ, δ and κ has been characterized, and in 1994 a fourth receptor, the nociceptin/orphanin FQ (N/OFQ) was cloned. This latter receptor has a high structural resemblance with the other three, but does not bind to the conventional opioid ligands. The μ, δ and κ receptor types have been extensively studied and their distribution in the brain, spinal cord and the periphery are known. Studies have shown

that the drugs used in the clinic are relatively selective for the μ-opioid receptor. However, a receptor specific drug will become less receptor specific when administered in large enough doses. μ-opioid receptor effects are analgesia, respiratory depression, alteration of the cardiovascular, gastrointestinal and neuroendocrine functions, affection on the mood and rewarding behaviour. Activation of the μ, δ and κ-receptors cause inhibition of the adenylyl cyclase activity, activates the receptor-operated K^+ currents and suppresses the Ca^{2+} currents in the endogenous neurons. Activation of K^+ currents and suppresses the Ca^{2+} currents is speculated to be the way opioids blocks the neurotransmitter release and pain transmission in the different neuronal pathways (Gutstein and Huda, 2001).

Opioids have an analgesic effect on pathological pain, but are also effective in depression of the natural responses to pain (fear, anxiety, panic and suffering). The depression of these emotional responses to pain increases the individuals' tolerance to the pain. Pain relief and comfort is how a patient with pain experiences the analgesia from therapeutic dose of morphine or a similar drug. However, giving the same morphine dose to a person without pain might cause nausea and vomiting, drowsiness and lessened physical activity. Increased dose, gives increased analgesia, but also increased toxicity and side effects (Gutstein and Huda, 2001).

Blood-Brain Barrier

The major sites of action for opioids are in the central nervous system (CNS). Between the bloodstream and the CNS there is a boundary, the blood-brain barrier, which is a permeability barrier to the passive diffusion of substances from the bloodstream into the various regions of the CNS. Because of this boundary the drug concentration in the bloodstream after oral or parenteral administration differs substantially from the CNS drug concentration. The existence of the boundary varies in the different parts of the brain, and there seem to be little evidence of a barrier between the circulation and the peripheral nervous system. Diffusion of macromolecules is limited through the barrier, but small charged molecules such as neurotransmitters, their precursors and metabolites, and some drugs diffuse or are transported actively. The extent of this

transport depends on the molecular charge, weight and its lipophilicity. Drugs that do not enter the CNS from the bloodstream may do so if they are injected directly into the cerebrospinal fluid (Bloom, 2001).

Inter-individual variability in response to an opioid

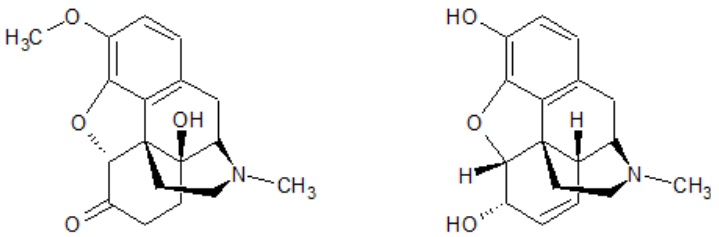
Studies show that there is a large inter-individual variability as to how patients respond to opioids (Kaiko et al., 1983). Some patients get totally pain-relieved, some are partly relieved and some discontinue their opioid treatment due to intolerable side effects. A patient's response to an opioid depends on multiple factors, involving the pharmacokinetics and pharmacodynamics of the drug, and pharmacogenetics of the patient. Inter-individual variability in the pharmacokinetics of a drug may include differences in absorption, distribution, metabolism, and elimination. Pharmacodynamic factors affecting the inter-individual variability are drug concentration at the effect site, and binding- and activation ability at the opioid receptor. Some of these factors may be attributed to pharmacogenetic differences (Klepstad et al., 2004). On top of this, age, gender, cancer diagnosis, pain- intensity, tolerance and pathophysiology will also contribute to the variability in pharmacokinetics and pharmacodynamics of a drug. Because of differences in pharmacokinetics and pharmacodynamics between opioids and because of differences in pharmacogentics between patients, an individual response to an opioid is expected for the individual patient (Vadalouca et al., 2008).

Adverse effects

While analgesia is the wanted effect, adverse effects such as sedation, nausea, vomiting and constipation are commonly reported in relation to opioid treatment (Portenoy et al., 2007, Yu, 2008). Other, less prevalent adverse effects are confusion, hallucinations, nightmares, urinary retention, dizziness and hyperalgesia. Some patients may experience adverse events when they start on an opioid, some after dose escalation, and some experience it spontaneously. Also, this pattern can change over time. The predictive factors for adverse effects are not well understood. This is because studies

comparing adverse effects of one opioid with another are lacking. Also, there is a lack of controlled studies that have looked at adverse events from one opioid given by various routes of administration. From existing literature the adverse effect profiles seem to be similar between different opioids, and there is very little evidence to suggest differences in adverse effects due to route of administration. The inter-individual variability to adverse effects is large, and it is believed that genetic variation plays an important role. Further, the risks for adverse effects from opioids are influenced by age, disease progression, organ dysfunction, co-administration with other medications and previous history of opioid use. The CNS adverse effects sedation, cognitive impairment, hallucinations, myoclonus and respiratory depression are dose-dependent. The dose-response relationship between opioids and gastrointestinal adverse effects is weak, and constipation is not dose-dependent, nor tolerance evolving. The inter-individual differences in this relationship among the patients are large, and some patients develop tolerance towards these adverse effects while others do not (Fallon et al., 2010).

Oxycodone versus morphine



Oxycodone Morphine

Figure 2 Chemical structures of oxycodone and morphine

Morphine and oxycodone have about the same lipophilicity and their plasma protein binding is 38 % and 45 %, respectively. A methoxy-group in the molecular structure of oxycodone is believed to protect oxycodone from being extensively metabolized in the

first pass metabolism partly causing the oral bioavailability of 60-87 % (Leow et al., 1992, Poyhia et al., 1992), which is higher than morphine (20-30 %). Further, oxycodone has an affinity for the μ-opioid receptor that is 1/10-1/40 of morphine (Kalso et al., 1990, Chen et al., 1991), and the ability to activate the opioid receptors is 3-8 times lower than morphine. Unlike morphine, oxycodone is not a substrate for P-glycoprotein (is not being transported via active efflux). Research in rats has shown that oxycodone seems to be actively transported through the blood-brain barrier (BBB) (active influx) causing the brain-to -plasma concentrations of oxycodone to be about six times higher than the brain-to-plasma concentrations of morphine, which does not seem to be actively transported through the BBB (Bostrom et al., 2006, Letrent et al., 1998). Oral oxycodone is about 1.5-2 times more potent as oral morphine, but parenteral oxycodone has a potency of 0.75 compared to parenteral morphine. The difference in their metabolism might explain these differences. Morphine is metabolized via uridine diphosphate glucuronosyltransferase 2B7 (UGT2B7), which yields the active metabolite morphine-6-glucuroide (M6G). M6G contributes to the efficacy of morphine (Murthy et al., 2002). There are very few reports on drug-drug interactions involving morphine. Oxycodone is potentially vulnerable to drug-drug interactions due to its CYP2D6 and CYP3A4 metabolism. Oxycodone also has an active metabolite, oxymorphone; however its contribution to the efficacy of oxycodone is uncertain. Oxycodone and morphine are both effective in cancer- and post-operative pain, and shows similar adverse effects (Mucci-LoRusso et al., 1998, Heiskanen and Kalso, 1997, Curtis et al., 1999). Based on current knowledge, there is no clinical evidence for one being better than the other. Morphine seem to be the first choice due to availability, habits and costs (Fredheim et al., 2010).

Oxycodone

Oxycodone was first used in clinical practice in Germany in 1917 (Falk, 1917) after being synthesized from thebaine in 1916 (Lenz et al., 1986). Indications for oxycodone have historically differed between countries: it has been used as a combination drug in USA, Canada and Australia for moderate pain, while in Europe it has been mainly used

for acute pain (Kalso, 2005). In Norway strong opioids have traditionally been indicated for the treatment of severe pain in diseases with short life prognosis such as cancer or other serious illnesses. Oxycodone was launched in Norway in 2001 and sales have increased gradually since then (Berg et al., 2010).

Controlled-release (CR) versus immediate-release (IR) oxycodone

Oxycodone is mainly used as controlled-release (CR) tablets for chronic pain, while the immediate-release (IR) formulations are used for acute pain, breakthrough pain and dose titration (Citron et al., 1998). Studies comparing efficacy and safety of CR and IR oxycodone in cancer pain have shown both release types to be equally effective (Stambaugh et al., 2001, Salzman et al., 1999). Both formulas commence its effect within one hour after administration. CR has a biphasic delivery system. In the first delivery phase 38 % of the dose is released, and in the second phase the remaining 62 % is released, making CR oxycodone last for 12 h. On the other hand, IR oxycodone has a mono phase release and has to be taken every 4-6 h (Hale et al., 1999, Reder et al., 1996, Kaplan et al., 1998). Oxycodone exhibits the same side effects as other opioids, and does not have any ceiling effect. Nausea (12-24 %), vomiting (7-20 %) and constipation (15-22 %) seem to be the most common adverse events (Yu, 2008, Portenoy et al., 2007, Parris et al., 1998). IR oxycodone has been associated with more adverse events than CR oxycodone (Kaplan et al., 1998), and women seem to suffer more from nausea and vomiting than men (Salzman et al., 1999, Glare and Walsh, 1993). Long-term administration of CR oxycodone has shown that the dose may be increased and that adverse effects diminish over time (Portenoy et al., 2007, Citron et al., 1998).

Oxycodone has also been administered intravenously, intramuscularly, intra-nasally, subcutaneously, rectally and spinally in humans. However, the oral formulations are the most used and the most studied.

Clinical indications

In the clinical use, oxycodone has been applied to acute post-operative pain (Reuben et al., 1999, Cheville et al., 2001, Kaufmann et al., 2004, de Beer et al., 2005, Kalso et al., 1991, Curtis et al., 1999, Sunshine et al., 1996), back pain (Hale et al., 1999, Gammaitoni et al., 2003) and as an alternative to morphine in the treatment of cancer pain (Mucci-LoRusso et al., 1998, Reid et al., 2006, Riley et al., 2006, Bruera et al., 1998, Heiskanen and Kalso, 1997, Hagen and Babul, 1997, Lauretti et al., 2003, Kaplan et al., 1998, Salzman et al., 1999, Stambaugh et al., 2001, Citron et al., 1998, Koizumi et al., 2004, Kalso and Vainio, 1990, Gabrail et al., 2004, Heiskanen et al., 2000). Oxycodone has also shown to be effective in non-malignant chronic neuropathic -, somatic-, and visceral pain (Liguori et al., 2010, Watson and Babul, 1998, Gimbel et al., 2003, Watson et al., 2003, Staahl et al., 2007), and in treatment of pain caused by osteoarthritis (Roth et al., 2000, Ytterberg et al., 1998, Caldwell et al., 1999, Markenson et al., 2005, Zautra and Smith, 2005, Afilalo et al., 2010).

Metabolism and pharmacokinetics

Oxycodone is extensively metabolised in the liver mainly via CYP3A4 to the inactive metabolite noroxycodone (47 % of dose), by 6-keto-reduction to what are most likely inactive metabolites, α- and β-oxycodol (8 % of dose), and via CYP2D6 to the active metabolite oxymorphone (11 % of dose), which is mainly found in conjugated form in plasma. A third, possibly active metabolite noroxymorphone (14 % of dose), is formed from noroxycodone via CYP2D6, but also to a lesser degree from oxymorphone via CYP3A4 (Figure 3) (Lalovic et al., 2004, Moore et al., 2003, Lalovic et al., 2006). Oxycodone and its metabolites are mainly excreted through the kidneys, and the excretion is dependent on kidney and liver function (Kaiko et al., 1996a, Kirvela et al., 1996, Tallgren et al., 1997, Kaiko, 1997). Oxycodone (8 %) and noroxycodone (22 %) are mainly excreted in free form, oxymorphone (11 %) mostly in conjugated form, as oxymorphone-3-glucuronide, and noroxymorphone (14 %) in both free and conjugated form (Lalovic et al., 2006). Up to 91 % of the administered oxycodone dose has been recovered as oxycodone or metabolites in urine (Lalovic et al., 2006). Oxycodone has a

short elimination half time that is dependent on dose and route of administration (4.5 h for CR and 3.2 h for IR). Steady-state plasma concentrations are achieved within 24-36 h after initial administration (Salzman et al., 1999).

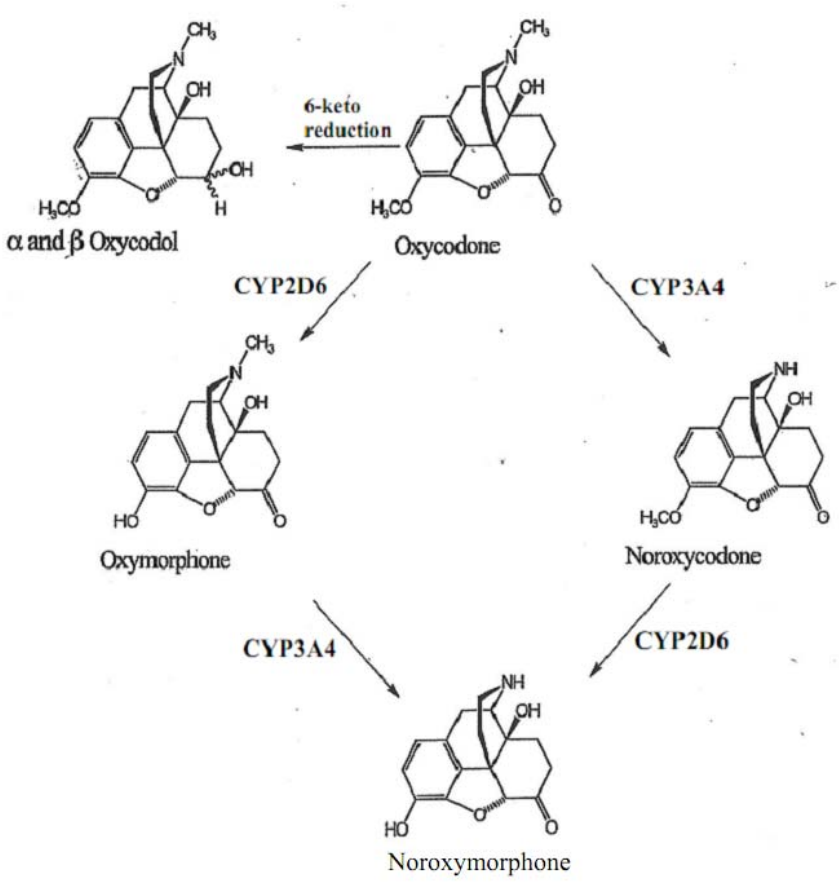


Figure 3 Oxycodone metabolism (modified from Lalovic et al. (Lalovic et al., 2006))

Oxycodone is a pure agonist with known affinity for the μ-opioid receptor in humans (Lalovic et al., 2006, Yoburn et al., 1995, Lemberg et al., 2006), however some animal studies have indicated affinity for the κ-opioid receptor (Nielsen et al., 2007, Ross and Smith, 1997, Khotib et al., 2004).

Most of the opioid analgesia is mediated through affinity and activation of opioid receptors in the CNS. It was first believed that oxymorphone, which is a very potent analgesic, was the principal analgesic when oxycodone was administered. However, inhibition of oxymorphone formation by quinine showed no difference in the analgesic effect of oxycodone in rats (Cleary et al., 1994), and did not attenuate opioid side effects in healthy volunteers (Heiskanen et al., 1998, Kaiko et al., 1996b). Based on the circulating concentrations, affinity and efficacy at the opioid receptors and the accessibility to enter the central nervous system Lalovic et al. (Lalovic et al., 2006) assessed the probability of oxycodone and its metabolites to mediate the analgesic effect. The study showed that even though oxymorphone had a more than 40-fold higher affinity for the μ-opioid receptor and a higher ability to activate the receptor compared to oxycodone, the low concentration of oxymorphone in circulation combined with much lower brain-to-plasma concentrations ratios than oxycodone (0.23 vs. 2.00, respectively) led to the conclusion that it is very unlikely that oxymorphone contribute to the efficacy of oxycodone. They also concluded that noroxycodone, the most abundant metabolite, did not contribute to the effect of oxycodone because of low affinity and activation of the opioid receptors and low brain-to-plasma ratios of 0.1, which corresponded to the weak antinociceptive effect found in rats earlier (Leow and Smith, 1994). According to Lalovic et al., noroxymorphone, was the metabolite with the highest potential of being an active metabolite being the second most abundant species in circulation (about 50 % of the oxycodone or noroxycodone concentration) and with a receptor affinity 3-fold higher than oxycodone. However, it had the lowest brain-to-plasma concentration ratios (0.008). The secondary metabolite α- and β-oxycodol showed low receptor binding and activation and had brain-to-plasma ratios similar to oxymorphone. A model connecting the pharmacokinetic to the pharmacodynamic effect of oxycodone did not include noroxymorphone nor any of the other metabolites, only oxycodone itself.

The CYP3A4 metabolic pathway

The major metabolic pathway of oxycodone goes via CYP3A4 enzymes which belong to the cytochrome P450 system, the principal enzyme system for phase I metabolism. This system is present in virtually all tissues, but is most abundant in the liver and the small intestine (Parkinson and Klaassen, 2001). The *CYP3A4* gene has many known polymorphisms, but no clinically important differences between genotypes have been observed (Ball et al., 1999, Wandel et al., 2000). CYP3A4 may, however, be either inhibited or induced by other drugs (Flockhart, 2007) or dietary elements such as grapefruit juice (Mertens-Talcott et al., 2006). This can change the metabolism of oxycodone and may potentially have clinical consequences (Gronlund et al., 2010a, Nieminen et al., 2010a, Nieminen et al., 2009, Saari et al., 2010, Nieminen et al., 2010b, Nieminen et al., 2010c, Hagelberg et al., 2009).

The CYP2D6 metabolic pathway

About 10 % of oxycodone is metabolized via CYP2D6 enzymes. The CYP2D6 metabolic pathway is prone to both drugs that inhibit this enzyme (Flockhart, 2007) and to the several known *CYP2D6* polymorphisms that influence drug metabolism. Studies where CYP2D6 enzymes have been inhibited by other drugs have shown pharmacokinetic changes in the oxycodone metabolism. However, the pharmacodynamic consequence of such inhibition seem to be minimal (Lemberg et al., 2010, Heiskanen et al., 1998, Gronlund et al., 2010b, Kummer et al., 2010).

CYP2D6 pharmacogenetics

The *CYP2D6* genetic polymorphisms divide the Caucasian population in three clinically relevant genotypes: Poor metabolizers (PM, 5-10 %), extensive metabolizers (EM, 80-95 %) and ultra rapid metabolizers (URM, 1-3 %). Because poor metabolizers are unable to metabolize *CYP2D6* substrates, a drug administered at normal dose may lead to too high and toxic levels of the drug (Foster et al., 2007, Jannetto and Bratanow, 2009). On the other hand, an ultra rapid metabolizer may experience reduced or no effect when given

a drug which is a *CYP2D6* substrate, or adverse drug reactions (Goryachkina et al., 2008, de Leon et al., 2003). If the drug is a pro-drug that needs CYP2D6 bioactivation, like codeine or tramadol, it may have no or only slight therapeutic effect in CYP2D6 poor metabolizers (Poulsen et al., 1996, Stamer et al., 2007), while URMs might experience adverse effects at commonly used doses (Kirchheiner et al., 2007). The *CYP2D6* genotype may therefore be of clinical importance for drugs that are metabolized by CYP2D6 enzymes, not least in the combination with drugs known to alter the CYP2D6- or CYP3A4 enzymes.

The CYP2D6-genotype influence on the pharmacokinetics and pharmacodynamics of oxycodone

In 1998 the first study addressing pharmacogenetic aspects of *CYP2D6* in the metabolism and efficacy of oxycodone was published (Heiskanen et al., 1998). In this study 10 healthy volunteers were genotyped as EM with respect to *CYP2D6*, and the CYP2D6 metabolic pathway was blocked by quinidine. Although, noroxycodone and oxymorphone serum concentrations differed before and after blocking, differences in oxycodone serum concentrations were none-significant, and the reduction of oxymorphone did not cause changes in the subjective drug effect or psychomotor function. Despite not having assessed the analgesia of oxycodone, the investigators concluded that oxymorphone might not be important to the pharmacodynamics of oxycodone. Since then several papers on oxycodone have included pharmacogenetic aspects into their studies (Zwisler et al., 2009, Gronlund et al., 2010b, Gronlund et al., 2010a, Samer et al., 2010a, Samer et al., 2010b, Kummer et al., 2010, Lemberg et al., 2010, Zwisler et al., 2010). Some have assessed pharmacokinetic and/or pharmacodynamic aspects by either blocking the CYP2D6- or the CYP3A4 metabolic pathways, or both. Others have assessed the efficacy of oxycodone between PM, EM and URM.

Two studies have been performed in a clinical setting. -Zwisler et al. (Zwisler et al., 2010) showed that there is no difference in oxycodone requirements for postoperative pain patients between 24 PMs and 246 EMs, and the study of Lemberg et al. (Lemberg et

al., 2010) including 20 chronic pain patients showed that inhibition of the CYP2D6 metabolic pathway did cause pharmacokinetic effects. However, these effects were not statistically different between EMs (n = 18) and URMs (n=2). Further, the pharmacokinetic changes did not cause any change of pharmacodynamic effect of oxycodone for EM and URM.

Assessment of symptoms

Every hospital has a mission; to make the patient feel well. This includes elimination of disease, mitigate disease, and maximize quality of life (QoL). The disease experience is inextricably linked to the symptoms the patients have, and the symptoms present both diagnostic clues and therapeutic challenges. The assessment of symptoms is therefore a very important aspect of clinical care, especially when patients suffer from incurable illnesses and the primary aim of the care is to give the patient comfort and the best quality of life (Ingham et al., 2010).

Assessment of subjective symptoms can be difficult because of absence of specific definition of the symptom and the range of implications associated with the use of them. Also, symptoms changes as the disease progress and treatments are given. Further, different diagnostic groups will experience symptoms in different ways. Symptom assessment aims to quantify aspects of the subjective symptom in a reliable and valid way. Because of this formal validation of the assessment tool intended to use is needed (Ingham et al., 2010).

When considering an assessment tool the researcher have to consider the following methodological issues of the tool:

- Validity
  - Does the instrument measure what it intends to measure?

- Reliability
  - Do repeated measurements in the same population produce the same result?

- Is the same result obtained when repeated by a different investigator (inter observer reliability)?

- Sensitivity
  - Does the instrument detect clinically meaningful changes?

- Language
  - Is the instrument formally validated into the appropriate language?

- Reference data
  - Are there known data (reference data) on the responses of the instrument from the general population?

In cancer research, and especially in cancer palliative care, it is also important that the assessment tools are short and easy to complete, as these patients often suffers from reduced physical and mental status due to their disease and its subsequent indications.

Several studies have demonstrated that the correlation between patient and clinician scoring is low when the patient's subjective symptoms are assessed. Therefore, self-reports are warranted when assessing subjective symptoms (Ingham et al., 2010). In this thesis pain and quality of life were assessed with self-report, while cognitive function and performance status were assessed by the investigators. All assessment tools used in this thesis are widely recognized and validated and they are described in under "Methods" in this thesis.

Rationale for this thesis

Not all cancer patients are adequately pain relieved. Studies have shown that there is a high inter-individual variability in administered dose, serum concentrations and efficacy of oxycodone and because of this un-predictive variability dose-titration may take time, and this causes suffering for the patients.

Drug monitoring can be used to confirm toxicity, or explain why some patients don't have any effect of the drug. It can also be used to make sure the patient is taking his

medication. Further, drug monitoring might be a valuable tool if the therapeutic window is narrow, or if there are certain patients who are more at risk for toxicity or drug-drug interactions. In this study serum concentrations of oxycodone and metabolites were assessed together with patient characteristics to see if this could add any valuable information regarding the variability in serum concentration from patient to patient.

Genotyping is important if the drug is only metabolized via one enzyme system, and this system is a polymorph one, as shown for many antidepressants (Kirchheiner et al., 2004). Genotyping is also important if the drug is a pro-drug that needs metabolite formation to exert its effect, like codeine and tramadol. If the patient reacts in an unexpected and sub-optimal way to the treatment, then genotyping may explain this reaction and might serve as guide to the right choice of drug and treatment. In this study patients were *CYP2D6* genotyped because we wanted to assess if oxycodone efficacy is dependent on the *CYP2D6*-genotype poor-, extensive- or ultra rapid metabolizer.

When this thesis was planned there was an on-going discussion about whether or not active metabolites, of oxycodone existed, and if so, whether or not the active metabolite oxymorphone contributes to the analgesic effect. Except from the one study (Heiskanen et al., 1998) which aimed to address oxymorphone's contribution to the analgesic effect of oxycodone in extensive metabolizers (EM), no information concerning pharmacogenetic aspects in relation to oxycodone existed. In 2009 and 2010 several studies addressed the pharmacokinetic and pharmacodynamic consequences of altering the metabolic pathways of oxycodone. Alteration of the metabolic pathways was performed with inducer/inhibitor drugs known to alter the CYP3A4 metabolic pathway and drugs known to inhibit the CYP2D6 metabolic pathway. Also, some studies assessed how the pharmacokinetics and pharmacodynamics of oxycodone are influenced by *CYP2D6* genotypes. An important limitation in most of these studies has been that they are single dose studies in healthy volunteers. Two clinical studies have been conducted; one with post-operative patients (Zwisler et al., 2010) and the other with chronic pain patients (Lemberg et al., 2010). However, so far no one else has studied the effect of the *CYP2D6* genotype on the pharmacodynamics of oxycodone in a clinical setting of patients with cancer pain and chronic opioid administration.

Whether oxymorphone contributes to the effect of oxycodone is still an ongoing discussion.

Knowledge about pharmacokinetic-, pharmacodynamic- and genetic variables may help us understand which factors are important to the variation in response to opioids. It is only when these factors are acknowledged it is possible to target treatment in a beneficial way.

The aim of this study is to obtain a better understanding on how patient characteristics and genetic differences affect the metabolic pathways of oxycodone, and in turn how this affects oxycodone efficacy. Eventually this would give us extended knowledge on how to target pain treatment in cancer patients.

Study objectives

The overall objectives in this thesis were to assess whether serum concentration measurements of oxycodone and *CYP2D6* genotyping have any role when treating cancer patients with oxycodone for their cancer pain.

Three specific research questions address the overall objectives:

1. Can commonly recorded patient characteristics predict serum concentrations of oxycodone or oxycodone metabolism by CYP2D6 and CYP3A4 enzymes as indicated by the metabolic ratios?

2. Is there an association between the serum concentration of the parent substance oxycodone, or the potentially active metabolites and the clinical outcomes pain intensity, tiredness, nausea and cognitive function?

3. Do the *CYP2D6* genotypes poor metabolizer (PM), extensive metabolizer (EM) and ultra rapid metabolizer (URM) explain variability in the pharmacokinetics and pharmacodynamics of oxycodone?

A cross-sectional multicentre study including 461 cancer pain patients chronically administered with oxycodone was utilized for the purpose of answering these questions.

Material and methods

Patient cohort

The patients included in this thesis is a subgroup of the patients who participated in the European Pharamacogenetic Opioid Study, EPOS, a large cross-sectional study designed for exploring hypotheses generated by genetic findings related to the pharmacogenetics of opioid analgesic and the genetics of pain.

The European Pharmacogenetic Opioid Study, EPOS

EPOS was organized through the EAPC (European Association for Palliative Care) research network (http://www.eapcnet.eu). Eleven European countries and 17 centers were involved in the data collection (2003-2008), and a subgroup of 461 patients was treated with oxycodone.

EPOS was conducted because previous studies on the effects from opioids used for cancer pain lacked the ability to generalize due to small sample sizes, often recruited from a single centre. Single centre studies may be biased by selection bias, i.e. by genetic homogeneity. Thus this multinational study aimed at expanding the research field by inclusion of a large number of patients, by studying other opioids than morphine and by including patients with different ethnicity.

Patients attending EPOS were at least age 18 years, verified with malignant disease, able to deliver a blood sample, were regularly scheduled oral, subcutaneous, transdermal or intravenous opioid treatment (morphine, methadone, fentanyl, hydromorphone, buprenorphine, ketobemidone or oxycodone) for their cancer pain with duration of treatment no less than three days. Patients did not have any known contraindications. The study collected data on pain (Brief Pain Inventory: BPI); health related quality of life (EORTC QLC-C30) and cognitive function (Mini mental Mental Status Examination, MMSE) and Karnofsky performance status score. Additional clinical information collected from each patient was: cancer diagnosis, time since diagnosis, presence of metastasis and time since start of opioids, the scheduled opioid treatment for the last 24

hours and break through-pain, use of non-opioids medications, presence of other diseases and routine clinical laboratory data for assessment of kidney and liver functions and hematological status. Exclusions criteria were not consenting to participate, and not capable of understanding the language used at the study centre. The study included 2294 patients. Data management, pharmacological- and pharmacogenetic analyses were performed in Norway at the Trondheim study centre.

This thesis investigates those of the cancer patients who were scheduled oxycodone daily for their cancer pain, a total of 461 patients; however, some had to be excluded due to lack of data, incomplete analyses or questionable compliance (outlined below). Still without the excluded patients, the group of patients included into this thesis is rather large. A large cohort gives higher statistical power, and the ability to detect small significant differences. However, when interpreting the results it is important to remember that a statistical difference not necessarily is a clinically important one.

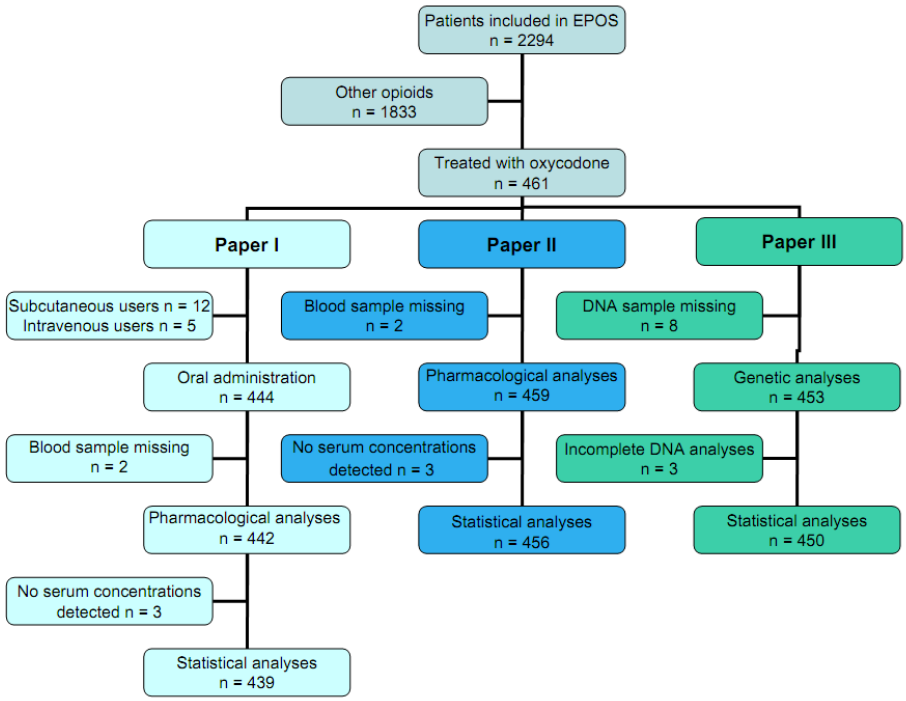


Figure 4 Patient flowcharts of the included EPOS patients used in this thesis

In **paper I** we wanted to explore the association between patients' characteristics and serum concentration level of oxycodone and the metabolic ratio oxymorphone/oxycodone and noroxycodone/oxycodone. Patients scheduled intravenous (n = 5) or subcutaneous (n = 12) oxycodone were excluded because these patients omit the first pass effect and have continuous delivery of oxycodone, thus their serum concentration levels will be very different from those scheduled oxycodone orally every 12 h and having their blood sample taken at trough. After the pharmacological analyses three more patients were excluded because neither oxycodone, noroxycodone, oxymorphone nor noroxymorphone could be detected in their serum. Their compliance was questionable and since this study's aim was to identify variables that influence the serum concentrations of oxycodone and its metabolites we excluded these patients. Four patients lacked a noroxycodone/oxycodone ratio, due to undetectable levels of oxycodone and noroxycodone (n = 2), oxycodone (n = 1) and noroxycodone (n = 1). Fifteen patients had oxymorphone/oxycodone ratio of zero, twelve because oxymorphone was not detected, and three because oxycodone was not detected. Lack of serum concentrations can be caused by metabolic factors, i.e. a patient being a slow or ultra rapid metabolizer. Since serum concentrations and ratios had to be $\log_{10}$-transformed to yield normally distributed residuals, these patients were given a fictive low serum concentration value (assay detection limit x 0.5), and were included into the analyses. Thus 439 patients are included in this study.

In **paper II** we assessed the relationship between serum concentration levels and the clinical outcomes; pain intensity, nausea, tiredness and cognitive function. Two patients were excluded because blood samples from these were not available, and three were excluded because of their compliance could be questionable because neither oxycodone nor its metabolites could be detected in the serum samples. Thus the cohort in this study consisted of 456 patients.

Paper III focused on how genetic polymorphisms of the *CYP2D6* gene influenced serum concentrations of oxycodone and metabolites, and the clinical outcomes; pain intensity,

nausea, tiredness and cognitive function. Of the 461 eligible patients, eight were excluded because lack of DNA sample, and another three because the DNA-analyses were incomplete. Four-hundred and fifty patients were included into the cohort of study three.

Of these patients three lacked serum concentrations of oxycodone and the metabolites. Their compliance may be questioned, but since this paper focused on *CYP2D6* gene polymorphisms, they were not excluded from the analyzed cohort. They are, however, not included in the analyses where we explore the relationships between serum concentrations and the three genetic groups. Also, three patients lacked oxycodone, three lacked noroxycodone, thirteen lacked oxymorphone and twelve lacked noroxymorphone serum concentrations. The lack of serum concentrations in these patients are probably due to genetic or other pharmacokinetic factors, so these patients are important to include into the analyses. Before analyses, serum concentrations were $\log_{10}$ transformed to yield normally distributed residuals in the analyses. Zero is a number that cannot be $\log_{10}$ transformed. Therefore have patients with undetectable serum concentration levels been given fictive low serum concentration values (assay detection limit x 0.5), so that they could be included into the statistical analyses.

Serum concentration analyses by liquid chromatography - tandem mass spectrometry

Serum analyses of oxycodone, noroxycodone, oxymorphone and noroxymorphone were carried out using a liquid chromatography - tandem mass spectrometry (LC-MS/MS) system. Details on sample preparations, the liquid chromatography- and tandem mass spectrometry conditions, together with data on validity and limits of detections are described in detail in paper I.

Liquid chromatography- tandem mass spectrometry is a commonly used analytical technique when quantifying drugs in biological samples. The liquid chromatography system has the capability of physically separate compounds in a complex matrix, and the mass spectrometry act as a very specific and sensitive detector by measuring the mass-

to-charge ratio of charged particles. Thus this system has the ability to separate and quantify compounds with a high specificity and sensitivity.

The liquid chromatography system consists of a pump, a sample injector and a column. In this work reverse phase chromatography was applied. This means that the column which contains the stationary phase consisted of hydrophobic silica material, while the mobile phase was hydrophilic (water/acetonitrile). The physical separation of the drugs in the matrix is dependent on its polarity. The pump constantly pumps mobile phase through the column. After injection of the sample matrix into the mobile phase, the sample is being "pushed" through the column by the mobile phase. Compounds that are hydrophobic will be retained in the column and will slowly go through it, while the more polar compounds will be carried easily through by the hydrophilic mobile phase. This way the compounds elute from the column at different times. After eluting from the column the compounds are transferred to a detector, which in this work was a tandem mass spectrometer; a triple quadrupole mass spectrometer.

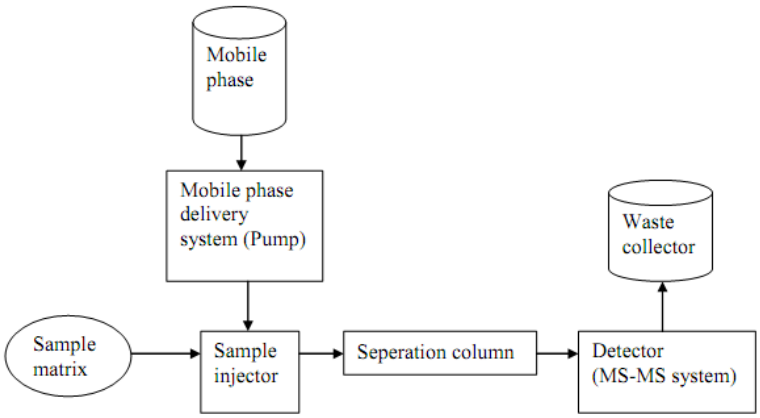


Figure 5 Schematic overview of the LC-MS/MS process

The compounds leave the column as liquids and are immediately evaporated to charged molecules (M+) when entering the mass spectrometer. A triple quadrupole mass

spectrometer consists of two quadrupole mass spectrometers in series. In this way we have two mass-filters in series. In the first quadrupole the molecular ions (M+) of the compound of interest are filtered from the complex matrix (e.g. serum, plasma, urine). In the second quadrupole these M+ ions collide with inert gas e.g. N_2. This collision is controlled in such a way that your M+ ions are fragmented to pre-specified fragment ions. The most abundant of these fragment ions are selected for detection in third quadrupole, while all other ions go to waste. This type of analysis is called multiple-ions-monitoring (MRM) and was used in the serum concentration analyses of oxycodone and metabolites. This feature makes the tandem mass spectrometry analyzer to be highly sensitive and specific tool for quantifying compounds.

Determination of the CYP2D6- genotypes

The gene coding for the cytochrome 450 2D6 (CYP2D6) enzyme is located on chromosome 22. This gene has more than 80 known allelic variants[2], and CYP2D6 enzyme activity varies from non-functional to ultra rapid metabolism. The allelic variants divide a population into four genetic groups; poor metabolizers (PM) with two non-functional alleles, intermediate metabolizers (IM) with one none-functional and one functional allele or two alleles with decreased function, extensive metabolizers (EM) with to functional alleles (wild type) and ultra rapid metabolizers (URM) with more than two copies of functional alleles. The allele frequencies differ substantially between different ethnic groups (Zanger et al., 2004, Scordo et al., 2004). In the Caucasian population about are 5-10 % poor metabolizers, 10-15 % intermediate metabolizers, 72-84 % extensive metabolizers and 1-3 % are ultra rapid metabolizers (Zanger et al., 2004, Spigset, 2001).

The CYP2D6 functional polymorphisms can be distinguished either by genotyping or phenotyping methods. A phenotype is an observational characteristic and can be determined by calculating the mother substance to metabolite ratios (Zanger et al., 2004). E.g. dextromethorphan can be used to determine the CYP2D6 phenotypes by

[2] according to the Human Cytochrome P450 (CYP) Allele Nomenclature Committee (www.cypalleles.ki.se)

measuring the dextromethorphane/dextrorphan ratio in urine (Samer et al., 2010a). This method is however not recommended in patients with for instance renal impairment, or if the patient is using drugs that interfere with the expression of CYP2D6 enzymes. Such interactions may potentially change a patient with an extensive metabolizer genotype appear as an intermediate- or poor metabolizer phenotype.

In this large cross-sectional study with the complexity of the patient population included, genotyping was the only procedure that from a practical point of view allowed for grouping the subjects as of poor-, intermediate-, extensive- and ultra rapid metabolizers. With more than 80 known allelic variants of the *CYP2D6* gene, it was necessary to make a selection which to study. The Department of Pathology and Medical Genetics, St. Olav University Hospital, routinely screens for relevant CYP2D6 allelic variants to determine PM, IM, EM and URM. They have chosen a panel of variants that show clinically significant alteration of enzyme activity, omitting those that have no verified or insignificant effect on drug metabolism *in vivo* or that are extremely rare. We chose to analyze for these routine allelic variants as the aim was to make judgments closely related to everyday clinical and laboratory practice. Their methods were adopted and the work was carried out in their laboratory and with their instrumentation. The methods and details on the genotyping are described in detail in Paper III. The allelic variants detected was CYP2D6*2x2 (duplication), CYP2D6*5 (deletion) and *3, *4, *6, *7 and *8 (SNP mutations). Samples that were negative for all mutations in the test panel were for practical purposes categorized as CYP2D6*1 (functional) variant.

Accordingly the four major mutated allele variants *3, *4, *5 and *6 accounts for 90-99 % of the PM allele variation in Caucasian population (Sachse et al., 1997, Scordo et al., 2004). In addition to the CYP2D6*2x2 duplication (frequency 1.34 %), Sachse et al.'s study showed that duplications of the alleles *1x2 was present in the Caucasian population with a frequency of 0.51 %. Duplications of *1x2 was not included into our duplication analyses, thus it is possible that we have missed about 2 ultra rapid metabolizers as a result of these alleles lacking in the analyses.

Brief pain inventory (BPI)

Pain severity in study II and III was assessed using the item "Pain on average last 24 hours" from the Brief Pain Inventory (BPI[3]). The Pain Research Group at MD Anderson Cancer Centre has developed the Brief Pain Inventory to assess the severity of pain and the impact of pain on daily functions in patient with cancer pain or patients with other chronic diseases that causes pain. The assessment can be done by self-report, interview or via an Interactive Voice Response System (IVR). The questionnaire assess the severity of pain, impact of pain on daily function, location of pain, pain medications, and amount of pain relief in the past 24 hours or the past week. The BPI uses numeric rating scales (NRS) from 0 to10. On the BPI, mild pain is defined as a worst pain score of 1 - 4, moderate pain is defined as a worst pain score of 5 - 6, and severe pain is defined as a worst pain score of 7 – 10 (Serlin et al., 1995). The BPI has been translated into seventeen languages, and is validated in at least 7 languages (Caraceni et al., 1996, Radbruch et al., 1999, Larue et al., 1995, Saxena et al., 1999, Uki et al., 1998, Cleeland et al., 1988).

European Organisation for Research and Treatment of Cancer core quality-of-life questionnaire (EORTC QLQ-C30)

The European Organisation for Research and Treatment of Cancer was founded in 1962 with the aims to conduct, develop, coordinate and stimulate cancer research in Europe. Through their Central Office Data Center more than 80,000 patients have been entered into clinical trials since 1974. In the need of a coherent policy on Quality of Life (QoL) research, the Quality of Life Group (QLG) was created in 1980. This group initiated a research program aimed at developing an integrated, modular approach for evaluating the quality of life of patients participating in cancer trials. This led to the development of the EORTC QLQ-C30[4], a quality of life instrument for cancer patients. The EORTC QLQ-C30 started out as a 36-item questionnaire (EORTC QLQ-C36) in 1987. After several

[3] URL http://www3.mdanderson.org/depts/prg/bpi.htm

[4] URL http://groups.eortc.be/qol/questionnaires_qlqc30.htm

validations and some adjustments the EORTC QLQ C-30 version 3.0 is now the standard version of the QLQ-C30.

The EORTC QLQ C-30 was used to assess the patient's symptoms; tiredness, nausea, constipation and depression.

The EORTC QLQ C-30 has been translated and validated into 81 languages and is used in more than 3,000 studies worldwide. The questionnaire contains five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health and a quality-of-life scale, which assess additional symptoms commonly reported by cancer patients (dyspnoea, insomnia, appetite loss, constipation, diarrhea and financial difficulties).

The questionnaire has a global health status part (global health status/QoL), functional scales part (physical, role, emotional, cognitive and social) and symptom scales / item part (fatigue, nausea and vomiting, pain, and financial difficulties). For the functional scales and the global quality-of-life scale, item responses are recorded so that a higher score represents a better level of functioning. A high symptom score represents a higher level of symptoms.

Scoring of the symptom scales / items is done by a linear transformation to a 0 to 100 scale in the following way:

$$Score = \{(RS - 1)/\, range\ \} \times 100$$

RS = Raw Score = the mean of the component items: $RawScore = (\mathrm{I}_1 + \mathrm{I}_2 + \mathrm{I}_3 + ... + \mathrm{I}_n)/n$ and *range* = is the difference between the possible maximum and the minimum response to individual items. Items who take values from 1 to 4 have a range of 3.

A score of 0-24 on these symptom scales corresponds to "not at all", 25-49 corresponds to "a little", 50-74 to "quite a bit" and 75-100 to "very much". Tiredness was assessed using the item "Were you tired?" with response alternatives "not at all", "a little", "quite a bit" and "very much" (Aaronson et al., 1993, Fayers et al., 2001).

Mini-Mental State (MMS)

The Mini-Mental State was first presented by Folstein and co-workers in 1975 as a tool for grading the cognitive state of patients with delirium or dementia syndromes. It is "mini" because it concentrates only on the cognitive aspects of mental functions, and excludes questions concerning mood, abnormal mental experiences and the form of thinking.

The MMS score range from 0 to 30. Higher score means better cognitive function. The MMS consists of two sections. The first one covers orientation, memory and attention and can give a maximum score of 21. The other section tests the ability to name, follow verbal and written commands, write a sentence spontaneously, and copy a polygon figure. This part gives a maximum score of nine. The MMS has shown to be a reliable and valid tool for cognitive assessment also in palliative cancer patients (Folstein et al., 1975). In this thesis, indication of cognitive failure (cut off) has been defined as having a total MMS of 23 or less. To identify cognitive impairment and delirium in the elderly, using scores from selected items or using the totally score is equally valid (Fayers et al., 2005, Braekhus et al., 1992) .

Karnofsky performance status

The patients' functional status was assessed by the Karnofsky performance status (Karnofsky et al., 1948). Karnofsky performance status has, since it was introduced in 1948, been extensively used by clinicians to rate physical performance and is associated with survival (Bauchet et al., 2010, Hauser et al., 2006, Vigano et al., 2000). The Karnofsky performance status has a linear scoring from 0-100 %. The score is based upon how well a patient is able to carry out normal activities and work, and his or her ability to care for themself. A score of 100 % describes a person with no complaints and who shows no evidence of disease. A score of 0 % is equivalent to the total opposite, namely being dead (Karnofsky et al., 1948).

Statistical methods

Pre-study formal sample size calculations were not performed prior to any of the analyses in this thesis since the patient data were originally included into a larger study (EPOS) designed for exploring hypotheses related to the pharmacogenetics of opioid analgesic and to the genetics of pain. However, the sample size in study I and II is larger than Green's recommendations (104 + k independent variables) (Green, 1991), and large enough to detect a medium effect according to Miles and Shevlin (Miles and Shevlin, 2001).

Many of the demographic group data showed skewed distributions, so descriptive group data in all papers are presented as median (min-max) values. Also, serum concentrations of oxycodone, its metabolites and ratios of oxymorphone/oxycodone and noroxycodone/oxycodone were $\log_{10}$-transformed to yield normally distributed residuals when included into the statistical analyses. Because of skewed distributions of the data, Spearman rank correlations and the non-parametric Mann Whitney U-test were chosen when appropriate. The Statistical Package for Social Science (SPSS) version 16.0 was used for all statistical analyses in the three papers.

A short summery of the statistical methods used is given below. Detailed descriptions of the statistical methods are outlined in the presented papers.

Spearman rank correlations

Used in **paper I** to assess the relationships between

1. Total daily dose of oxycodone and serum concentrations of oxycodone, its metabolites and metabolite/oxycodone ratios.

2. Serum concentrations of oxycodone and its metabolites.

3. Serum concentrations of oxycodone and the ratios noroxycodone/oxycodone and oxymorphone/oxycodone and the patients demographics.

Bivariate linear regressions

- To explore the associations between the continuous outcomes; pain and cognitive function, and serum concentrations of oxycodone and metabolites and the other variables that potentially might influence pain and cognitive function (**Paper II**).

Bivariate logistic regressions

- To explore the associations between the categorical outcomes; nausea and tiredness, and serum concentrations of oxycodone and metabolites and the other variables that potentially might influence nausea and tiredness (**Paper II**).

Multiple linear regressions analyses were used to assess

- The effect of patient variables on $\log_{10}$-transformed serum concentrations of oxycodone and oxymorphone/oxycodone and noroxycodone/oxycodone ratios. The analyses were performed in a manually backward stepwise manner because data covering all variables for all patients were not available. The criterion for removal of a variable was set to $p > 0.1$, and two-sided p-values ≤ 0.05 were considered statistically significant in the final models (**Paper I**).

- The relationship between pain and cognitive function, and serum concentrations of oxycodone and metabolites together with the variables that had passed the $p \leq 0.1$ criteria from the bivariate regressions. The analyses were performed in a manually backward stepwise manner, in the same way and with the same criteria for statistical significant levels as described for paper I (**Paper II**).

Analyses of variance (One-way-ANOVA)

- To compare continuous demographics and characteristics between the *CYP2D6* genetic groups (**Paper III**).

- To compare continuous data (serum concentrations of oxycodone, metabolites, pain intensity and cognitive function) between the three genetic groups. If the overall F-test was significant ($p \leq 0.05$), the Games-Howell procedure was used for post hoc comparisons between the groups. The Games-Howell procedure was chosen because of unequal variance and differences in group sizes (**Paper III**).

Analyses of covariance (ANCOVA)

- To compare the continuous data and to control for variables, shown in paper I and II to affect the outcomes, between the three genetic groups. ANCOVA post hoc comparisons were performed with Sidak correction (**Paper III**).

Ordinal logistic regressions

- To assess the relationships between the categorical outcomes; nausea and tiredness, and serum concentrations of oxycodone and metabolites and variables which had passed the $p \leq 0.1$ criteria from the bivariate logistic regressions. The analyses were performed in a manually backward stepwise manner, in the same way and with the same criteria for statistical significant level as described for paper I (**Paper II**).

- To compare categorical demographics and characteristics between the genetic groups. Two-sided p-values $p \leq 0.05$ were considered statistical significant (**Paper III**).

- To assess the relationships between the categorical outcomes; nausea and tiredness, and the genetic groups with and without covariates. Two-sided p-values $p \leq 0.05$ were considered statistical significant (**Paper III**).

Mann Whitney U-tests

- To compare oxycodone total daily dose between men and women. Two-sided p-values ≤ 0.05 were considered statistical significant (**Paper I**).
- To compare serum concentrations of oxycodone and oxymorphone, and oxymorphone/oxycodone ratio between users and non-users of CYP2D6 inhibitors. Two-sided p-values ≤ 0.05 were considered statistical significant (**Paper I**).
- To compare serum concentrations between "treatment success" and "treatment failure" groups. From these analyses both un-corrected and Benjamini-Hochberg corrected p-values were reported. Benjamini-Hochberg corrected p-values ≤ 0.05 were considered statistically significant (**Paper II**).

Ethics

The European Pharmacogenetic Opioid Study (EPOS) was a multicentre study performed according to the guidelines of the Helsinki-declaration.

The patients were informed by the nature of the study and of that anonymous blood samples was going to be stored for further analyses. Genetic analyses were restricted to analyses related to pain and analgesic drugs.

To minimize the burden of participating in the study, only a limited number of questionnaires were presented at one single occasion and one blood sample was collected, whenever possible, at the same time as the questionnaires.

Before entering the study, participating patients had to give their written informed consent. The procedure of informed consent was performed according to the ethical guidelines in each country, and each participating centre was responsible for approval by the relevant Research Ethics Committee of each study centre.

Financial support

Organization of the European Pharmacogenetic Opioid Study (EPOS) was done by contribution from the European Association for Palliative Care Research Network (EAPC-RN) with grants from the Norwegian Research Council and the EU 6th framework.

The studies and work of this thesis have been supported by the Norwegian Cancer Society, Helse Midt-Norge RHF and by the Pain and palliation research group.

There were no conflicts of interests in this work.

Summary of papers

Paper I Influences on the pharmacokinetics of oxycodone – A multicentre cross-sectional study in 439 adult cancer patients

Many patients with advanced cancer suffer from pain that requires treatment with opioids.

Oxycodone and morphine are widely used opioids for the treatment of cancer pain. The pharmacokinetics of morphine and its metabolites have been much studied, and the results from these studies shows that serum concentrations of morphine and metabolites are dependent on administered dose and route of administration, and that there are large inter-individual variation in serum concentrations of morphine and metabolites. Even though oxycodone is a widely prescribed opioid for cancer pain patients, little is known about the pharmacokinetics of oxycodone in these patients.

The aim of this study was to explore the relationships between ordinary patient characteristics and serum concentrations of oxycodone and the ratios noroxycodone or oxymorphone/oxycodone in cancer patients.

439 patients, aged 18 or older and using oral oxycodone for their cancer pain were included from 9 European centers. The patients' characteristics (sex, age, body mass index (BMI), Karnofsky performance status, "time since starting opioids", "oxycodone total daily dose", "time from last oxycodone dose", use of CYP3A4 inducer/inhibitor, "use of systemic steroids", "number of medications taken last 24 h", glomerular filtration rate (GFR) and albumin serum concentrations) influence on oxycodone serum concentrations or metabolite/oxycodone ratios were explored by multiple regression analyses.

Serum concentrations of oxycodone and metabolites showed large inter-individual variation, even after dose-correction. Total daily dose was highly correlated (r_s = 0.71) with and the variable which best explained the variability of oxycodone serum concentrations. The correlations between oxycodone and metabolites were higher for

females (r_s = 0.64-0.79) than for men (r_s = 0.59-0.76). Females were estimated to have lower serum oxycodone concentrations than men. At a given level of oxycodone serum concentrations, females have higher serum levels of the corresponding metabolite. Also, males are predicted to have 31 % lower noroxycodone/oxycodone ratio than females.

Use of CYP2D6 inhibitors did not influence oxymorphone to oxycodone ratio. Concomitant medication with CYP3A4 inhibitors reduced the noroxycodone/oxycodone ratio and increased oxycodone concentrations. The use of CYP3A4 inducers influenced all three examined outcomes; decreased oxycodone serum concentrations, increased oxymorphone/oxycodone and noroxycodone/oxycodone ratios.

Other variables that predicted serum concentrations and/or ratios were "time from last oxycodone dose", "number of medications taken in last 24 h, "time from last dose to blood sample", albumin, steroids, BMI and GFR. The regression analyses explained 5-35 % of the variability in oxycodone serum concentrations and the ratios oxymorphone/oxycodone and noroxycodone/oxycodone.

Sex differences related to opioids and metabolism may also be true in a cancer population. Drug-drug interactions related to CYP2D6 is probably of little clinical significance; however use of CYP3A4 inducers or inhibitors should be carefully monitored as these might significantly influence the serum concentrations which may possibly change the effects of oxycodone. Other characteristics explained only minor parts of the variability of the outcomes.

Finally, the variables including daily dose explained 1/3 of the variability of oxycodone serum concentrations and only minor parts of the variability of the ratios in this population.

Paper II Is oxycodone efficacy reflected in serum concentrations? –A multicentre cross-sectional study in 456 adult cancer patients

The aim of this study was to assess whether there is a relationship between oxycodone concentrations and pain intensity, cognitive functioning, nausea or tiredness in cancer patients. Also, oxymorphone and noroxymorphone contributions to analgesia and the adverse effects of oxycodone were assessed.

456 cancer patients receiving oxycodone for their cancer pain was included in this study. Pain was assessed using the Brief Pain Inventory (BPI). The EORTC QLQ-C30 was used to assess the symptoms of tiredness, nausea, constipation and depression. Cognitive function was assessed by the Mini Mental State (MMS) examination. Associations between the clinical outcomes and potentially variables were examined by multiple linear- or ordinal logistic regressions. A second approach was to assess whether patients classified as "treatment success" or "treatment failure" had different serum concentrations of oxycodone or metabolites. This was assessed using Mann-Whitney U-tests.

This study shows that there are few concentration-effect relationships between the major subjective symptoms related to treatment with oxycodone and its metabolites, even in this fairly large sample.

Several factors may have contributed to the lack of concentration-effect relationships: The subjective symptoms and the assessment tools used were not specific for the opioid treatment. Further, there is inter-individual variation in pain thresholds and sensitivity to the opioid treatment. Also, genetic differences on the receptor level and the fact that serum concentrations not necessarily reflect the drug concentration at the effect sites in the central nervous system may have influenced the results.

Pain intensity increased with oxymorphone serum concentrations ($p = 0.002$). This is difficult to explain. However, it seem to be in line with what was observed in the sub-group analyses of "success" and "failures" where patients with poor pain control and side effects overall had higher serum concentrations of oxycodone and all the

metabolites, compared to the patients who were pain relieved and without side effects. This trend was also observed in a similar cohort of cancer patients treated with morphine. A finding in both studies was that the number of successes was low and the number of failures high in those who suffered from tiredness. Thus, tiredness seems to be a frequent symptom hindering a needed opioid dose increase in cancer patients with pain. The finding of higher serum concentrations in patients not successfully treated with oxycodone due to adverse effects suggests that an opioid switch should be considered earlier in these patients.

In conclusion, no relationships between oxycodone or noroxymorphone concentrations and pain intensity, tiredness, nausea or cognitive function were found in this cross-sectional cohort of cancer patients.

Paper III Do CYP2D6 genotypes reflect oxycodone requirements for cancer patients treated for cancer pain? - A cross-sectional multicentre study

Oxycodone is extensively metabolized in the liver by CYP3A4 enzymes and also by the variably expressed CYP2D6 enzymes. The aim of this study was to assess the relationship between oxycodone pharmacokinetics, pharmacodynamics and *CYP2D6* genotypes poor metabolizer (PM, n = 27), extensive metabolizer (EM, n = 413) and ultra rapid metabolizer (URM, n = 10) in 450 cancer patients chronically administered with oxycodone for their cancer pain.

The pharmacokinetics was assessed by comparing serum concentrations of oxycodone and metabolites between the three genotype groups. Pharmacodynamics was assessed by comparisons of pain intensity, tiredness, nausea and cognitive function between the three genotype groups. Pain was assessed using the Brief Pain Inventory (BPI). The EORTC QLQ-C30 was used to assess the symptoms of tiredness and nausea. And

cognitive function was assessed by the Mini Mental State (MMS) examination. Associations were examined by analyses of variance (ANOVA) and covariance (ANCOVA), or ordinal logistic regressions without and with covariates.

Our results demonstrate that genetic differences in the *CYP2D6* gene influence the CYP2D6 metabolic pathways. There were no statistical differences between the three genetic groups with respect to oxycodone and noroxycodone serum concentrations ($p = 0.96$ and 0.09, respectively). PMs had lower serum concentrations of oxymorphone and noroxymorphone, than EMs and URMs, while there was no difference between EMs and URMs in serum concentrations of these metabolites.

Although serum concentrations of oxymorphone and noroxymorphone were statistically different, there were no differences in pain intensity-, or adverse effects between the genetic groups. Thus, in this cohort with chronic cancer pain, oxymorphone does not seem to contribute to the analgesic effect of oxycodone. The reason for lack of pharmacodynamic effect of the potent compound oxymorphone could potentially be the very low level of this metabolite in circulation relative to oxycodone.

A difference in pain intensity or adverse events between PM and URM would be expected if noroxymorphone was an active metabolite, maybe also between PM and EM, due to the relatively large difference between the genotypes of circulating noroxymorphone concentrations relative to oxycodone. This was not the case; there was no difference between PM, EM and URM with regard to effect or adverse events, thus it seems very unlikely that noroxymorphone is an important active metabolite of oxycodone.

Patients categorized as PMs of oxycodone have statistical significant lower serum concentrations of oxymorphone and noroxymorphone than EMs and URMs. However, no difference was found between PMs, EMs and URMs when comparisons of their pain intensities, nausea, tiredness and cognitive function were made. The *CYP2D6* genotype does not reflect oxycodone requirements and it is not, associated with common adverse effects in this study of patients with cancer pain.

Discussion

Methodological considerations

Studying cancer patients

Cancer patients are a heterogenic group. This causes several methodological challenges when planning a study. Finding relationships might be difficult in a heterogenic group of patients, thus requiring the group under study to be large. If either a case control or a longitudinal study design is chosen, it may be difficult to include a sufficiently large number of patients in order to compensate for this heterogeneity. Thus, in many clinical studies the patients included have been carefully selected e. g. by a specific cancer diagnosis or a disease stage, or those that have the best prognosis or those with lower age to make the patient group more homogeneous. Also, the study time span is important. A longitudinal study may suffer from many drop-outs if the cancer patients are close to death or the disease progresses. It is also important to consider the amount of data to be recorded on each patient. If the burden of data collection becomes too high, many cancer patients may choose to drop out of the study.

The cancer patients in this study are selected from a rather large cross-sectional multi-centre study that aimed to achieve a representative sample of cancer patient using opioids and being above the age of 18 (Klepstad et al., 2011). Thus, the inclusion criteria in this study were wide. The cross-sectional design ensures high compliance due to its short duration. However, the data missing rates for the self-reported questionnaires (EORTC QLQ C30 and BPI) in this study were about 8-10 %, while when it came to the Karnofsky score, administered by the investigators, it was complete.

The cross-sectional design

A study with a cross-sectional design is an observational study in which the data from the study subjects are collected at one single occasion or within a short period of time. This design gives a "snapshot" picture and is well suited for providing prevalence, describing variables and showing distribution patterns. Associations can also be

assessed with the cross-sectional design, however it might be difficult to decide which variable is the predictor and which one is the outcome. There are also advantages with the cross-sectional design: because there is only one measurement, the burden to the study subjects and the investigators are low allowing many participants to be included. Further, there is no loss to follow up, it is inexpensive compared to other clinical trials, the duration is short and there is no waiting for the outcomes. The data yields prevalence of multiple predictors and outcomes. The data collected define demographics and clinical characteristics of the study group. There are also some weaknesses to consider when choosing this design: One cannot establish causal relationships from this design, rare diseases are impractical to study in a sample from the general population because too many subject would have to be included and no incidence can be obtained (Newman et al., 2007).

Blood sampling and assessments of subjective symptoms

In this study only one blood sample from each patient was taken. Most of the participants were in-patients and their blood sample was taken at trough, while the out-patients gave their blood sample at the same time as their assessments. When the patient is at steady-state, as most of these chronic pain patients on controlled release oxycodone were, then the drug serum concentration and their tissue ratios will remain relatively constant during the 12 h administration periods. A more significant impact on this ratio occurs when immediately release rescue doses are taken, which occurred in about 44 % of our patients. Thus in study I the time since scheduled dose or rescue dose was calculated (= “time since last dose”) and the “total daily dose” (= sum of scheduled dose + break trough dose) was used, and were variables included in the analyses.

As described further below, symptoms were as the average over either the last 24 h or the last week. In a steady state condition with blood samples drawn at trough, it is likely that these symptoms and serum concentrations measured in the single sample, would not vary much if samples were drawn any day at trough. Therefore we can consider this a representative sample for the periods used for symptom average ratings.

Deciding what to assess, when and how to do it is crucial for validity of the outcomes of the study. In study II we wanted to assess if clinical outcomes were associated with steady-state serum concentrations of oxycodone and the metabolites. The primary outcome measure chosen was pain intensity on average last 24 h on a 0-10 NRS. We were interested in the average pain experienced by these patients since they have chronic pain. Pain usually varies during the day and some have episodes of breakthrough pain several times each day. Thus assessing pain right now would have caused an inaccurate measure of the overall pain intensity of the patient.

Also, we were interested in the general well-being of the patient with regards to side effects. As with pain, side effects also vary throughout the day. Since the EPOS study included the EORTC QLQ-C30 version 3.0, elements from this self-reported questionnaire were used for these assessments. Also, here we focused on the average symptom burden, and recall of tiredness and nausea for the last week was chosen. A problem with using these measurements is that what you measure not necessarily reflects the opioid treatment (the measurement does not say anything about the cause), but these are symptoms that opioids are known to cause.

Cognitive impairment is often seen in cancer patients (Pereira et al., 1997, Stromgren et al., 2002) due to the fact that many cancer patients are old, to the disease itself, pain, metastases, the cancer therapy, concomitant medication, anxiety or fatigue. For the advanced cancer patients, cognitive dysfunction usually occurs in the form of delirium. The Mini Mental State Examination is one of the most common interview-based instruments to assess cognitive function (Kaasa and Loge, 2010) and was applied in our study. In healthy volunteer studies opioid administration has caused significantly cognitive impairment and dose-impairment relationship have been shown (Ersek et al., 2004). In cancer patients, opioid use has shown to effect cognitive function in some studies, while not in others (Ersek et al., 2004). There is some evidence that cognitive impairment in cancer patients is related to initial dosing, dose increase or when it is given as rescue, and that tolerance develops during treatment with stable dose (Bruera et al., 1989, Kamboj et al., 2005). Cognitive function is associated with factors such as age (Schor et al., 1992, Elie et al., 1998), Karnofsky status (Klepstad et al., 2003a), disease, pain, metastases, concomitant medication and anxiety (Pereira et al., 1997,

Stromgren et al., 2002, Sjogren et al., 2000). We have adjusted for these factors when analysing for cognitive function and its relation to serum concentrations. As for the other subjective symptoms, tolerance possibly resulting from chronic treatment may dilute these concentration-effect relationships.

It is not clear whether our choice of assessment tools is responsible for our results in paper II or whether such concentration-effect relationships in cancer pain patients just does not exist because they have too many other factors that also affect the outcomes. A lack of relationship could be caused by too small sample sizes in previous studies. However, Klepstad et al. (Klepstad et al., 2003a) included 300 patients on morphine and our study included 456 patients, but still no concentration-effect relationships were found. These facts argue for a non-existence of such a relationship for patients in steady-state.

Statistical considerations

The cancer patients in this study had many confounders that might interfere with our outcomes. Our large sample size made it possible for us to adjust for many of the known confounders by including them into the regression analyses. This was done without exceeding Green's recommendation (Green, 1991) of sample size > 104 + *k* independent variables. The large sample size makes it possible to find many statistically significant relationships, thus it is important to consider whether these relationships are clinically relevant.

In the study where we compared "treatment success" against "treatment failures" we did four multiple comparisons between the groups (nausea, tiredness, cognitive function and constipation). Multiple comparisons increase the risk of making a type I error. A type I error is to reject the null hypothesis (H_0), even though H_0 actually is true. Usually, we set the risk of type I error to 5 % ($p = 0.05$), but by increasing the number of comparisons to four, the risk of type I error increases to 20 % ($0.05 \times 4 = 0.20$). The way to omit this error rate is to lower the significant level. Several methods are available for this purpose. The Bonferroni correction does this simply by setting the significant level

β, by $\beta = \alpha/n$ where $\alpha = 0.05$, and n = number of comparisons. A drawback with this very conservative method, is that it decreases the statistical power. We chose to use a less conservative method in the comparisons of "treatment success" and "treatment failure" groups, namely the Hochberg correction method (Benjamini and Hochberg, 1995). This method gives a greater statistical power, by allowing for a lesser strict control of the error I rate. This method is also designed to cope with situations in which sample sizes are very different (Field, 2009b).

Multiple comparisons tests were also used after significant ANOVA results (F-test) had suggested to rejecting the global null hypothesis H_0 in the comparisons of variables between the three genetic groups; PM, EM and URM (paper III). Multiple comparison procedures (post-hoc tests) were then used to determine which of the groups had different variable-means. The Games-Howell procedure (Games and Howell, 1976) was used for post-hoc tests after ANOVA analyses. This procedure was chosen because it is a good method when the groups you are comparing have unequal sample size and when the variances of the variables compared are unequal (Field, 2009b). This was the case with our analyses.

Post-hoc tests are not designed for situations where covariates are included, so the Games Howell procedure could not be used as ANCOVA post-hoc test. In this situation we chose to use post-hoc Sidàk corrections (Šidàk, 1967). This correction is similar to the Bonferroni correction, but is less conservative (Field, 2009a).

Result discussion

The overall objective of this thesis was to assess whether serum concentration measurements of oxycodone and *CYP2D6* genotyping have any role when treating cancer patients with oxycodone for their cancer pain.

Three specific research questions address the overall objectives and will be discussed separately:

I. Can commonly recorded patient characteristics predict serum concentrations of oxycodone itself or the metabolic pathways, CYP2D6 and CYP3A4 as indicated by the metabolic ratios?

Large inter-individual variations in dose requirements is a well acknowledged phenomenon when administering opioids (Faura et al., 1998, Dale et al., 2009) and oxycodone is no exception (Leow et al., 1995, Pan et al., 2007). Also, large inter-individual variability is seen in the serum concentrations (Klepstad et al., 2003a) and also in the response to opioids (Kaiko et al., 1983). This makes it difficult to predict an effective dose for the patients. Kinetic studies of oxycodone have established the absorption, distribution, metabolism and excretion of this drug and its metabolites. These factors may be affected by patient characteristics. Little is known about how patients' characteristics contribute to the inter-individual variability in serum concentrations of oxycodone. However, Kaiko et al. (Kaiko et al., 1996a)and Kirvela et al. (Kirvela et al., 1996) showed that patients with renal impairment have increased oxycodone and noroxycodone serum concentrations and prolonged elimination. Further, patients with hepatic impairment also have increased oxycodone serum concentrations and prolonged elimination (Kaiko, 1997, Tallgren et al., 1997). One single dose study in healthy volunteers has assessed the relationships between pharmacokinetics of oxycodone and age and gender (Kaiko et al., 1996b). Further, Liukas et al. (Liukas et al., 2008) assessed the influence of age after a single dose of oxycodone in forty post-orthopedic surgery patients. Liukas et al. showed that patients above age of 70 had slower clearance, longer $t_{1/2}$ and more than twofold higher mean plasma oxycodone concentrations than those less than 41 years of age. However, in Kaiko et al.'s study no statistical difference between age and gender in $AUC_{0\text{-}48h}$ for oxycodone and noroxycodone was found, but men had statistical higher $AUC_{0\text{-}48h}$ for oxymorphone. This study also showed that the women who had the highest oxycodone serum concentrations, also had the strongest drug effects and compared with men also had more adverse events.

The first part of this thesis aimed at identifying factors that might contribute to the large variability observed in serum concentrations of oxycodone, and also explore which factors affect the CYP3A4 and CYP2D6 metabolic pathways by exploring associations

between factors and noroxycodone/oxycodone and oxymorphone/oxycodone ratios. This type of approach has previously been addressed for morphine in 300 cancer patients (Klepstad et al., 2003b). In that study patient characteristics such as age, gender, weight, creatinine and liver function together with daily dose and route of administration were assessed. The multivariate analyses showed age, renal function, dose and route of administration explained 35-42 % of the variability in serum concentration of morphine and morphine metabolites. Of the variables, expectedly daily dose was the most prominent factor explaining 30-39 % of the variability. Oxycodone's oral bioavailability is about twice as high as oral morphine. It is claimed that oxycodone serum concentration are less variable and correlations between dose-serum concentrations are higher for oxycodone (Heiskanen et al., 2000, Mucci-LoRusso et al., 1998).

The results from the multivariate analyses showed that oxycodone serum concentrations were associated with total daily dose, sex, the time from last oxycodone dose to blood sample and medication known to inhibit or induce the CYP3A4 metabolic pathway. These factors together explained 35 % of the total inter-individual variability, and expectedly total daily dose was the most prominent factor explaining 17 % of the total of 35 %.

Variability in the CYP2D6 metabolic pathway, which is polymorphic regulated, as represented by the oxymorphone/oxycodone ratio was associated with total daily dose, number of medications (except opioids) taken last 24 h and the use of CYP3A4 inducer medications. Only 5 % of the variability in the oxymorphone/oxycodone ratio was explained, with equal contributions made from each variable. However, only 10 % of the dose is metabolized through this pathway.

The noroxycodone/oxycodone ratio, which represented the CYP3A4 metabolic pathway, was associated with several variables which explained a total of 19 % of its variability. Associated variables were total daily dose, time from last dose to blood sample, albumin, sex, CYP3A4 inhibitor/inducer medications, use of systemic steroids, BMI and glomerular filtration rate. Of these about 3 % were explained by total daily dose, and this was the most prominent of the variables.

The present study has shown that variability in serum concentrations is complex and far from a completely understood phenomenon. Most of the known variables contributing to variation in serum concentrations and ratios were factors which we can control such as "time from last oxycodone dose to blood sample" and use of- and the number of other medications such as CYP3A4 inhibitors/inducers and systemic steroids. In the last years several studies have assessed how oxycodone pharmacokinetics is affected by CYP3A4 inducer and inhibitors and CYP2D6 inhibitors. The results from these studies show that they can cause a significant change in serum concentrations oxycodone and metabolites (Gronlund et al., 2010b, Gronlund et al., 2010a, Samer et al., 2010a, Samer et al., 2010b, Kummer et al., 2010, Lemberg et al., 2010).

In the present study the use of CYP3A4 inhibitors predicted an increase of the serum concentrations of oxycodone by 60 %. This is a significant increase; however, the clinical implication of this is uncertain. Use of a CYP3A4 inducer is predicted to decrease the oxycodone serum concentration by 84 %. This is a dramatic change in serum concentration and a reduction in the efficacy of oxycodone would be expected. A 50 % decrease in oxycodone AUC concentrations by the use of St. John's wort, decreased the self-reported drug effect of oxycodone significantly in healthy volunteers after single dose administration (Nieminen et al., 2010a).

Since patients are titrated to effect, the use of CYP3A4 inhibitors and inducers may not be a problem. However, the potential of these drugs to affect serum concentrations may be important if the CYP3A4 drug is instituted or discontinued in patients already on a successful dose of oxycodone. Withdrawal of a CYP3A4 inhibitor will cause a decrease in serum concentrations of oxycodone, potentially causing a need for an increase in oxycodone dose. The opposite will be true if a CYP3A4 inducer drug is withdrawn. Thus clinicians should be aware of drugs that inhibit or induce the CYP3A4 pathway, so that they can monitor their patients closely for any needs for a change of oxycodone dosage. This is also the case with the synthetic opioid methadone, primarily metabolized via CYP3A4 (Iribarne et al., 1996), but also via CYP2D6 (Eap et al., 2001) and CYP2B6 (Kharasch et al., 2004). Morphine, on the other hand, is mainly metabolized by the

diphosphate glucuronosyltransferase 2B7 (UGT2B7) enzyme. This enzyme does not seem to be inhibited or induced by drugs, thus drug-drug interactions affecting the pharmacokinetics of morphine do not seem to be a concern.

Of the patient characteristics explored only a few seem to affect the level of oxycodone serum concentrations and ratios. Oxycodone serum concentrations were associated with sex. Males were predicted to have higher serum concentrations of oxycodone than women. This is not in line with Kaiko et al.'s (Kaiko et al., 1996b) study in healthy volunteers administered a single dose of 20 mg oxycodone. The $AUC_{0\text{-}48h}$ measurements did not differ between men and women for oxycodone and noroxycodone serum concentrations. However, men had higher oxymorphone concentrations than women. Our study was based on cancer patients while Kaiko et al.'s study was in healthy volunteers. The difference in population studied could by itself cause the observed difference in whether or not there is a difference in serum concentration of oxycodone between the sexes. Disease affects serum concentrations as seen by the more variable serum concentrations in patients than in healthy volunteers (Collins et al., 1998). There is also other methodological differences between our and Kaiko et al.'s study. While Kaiko et al. measured area under the curve (AUC) from 0-48 h after administration, we only have a single blood sample at trough (approximately 12 h after previous dose). Another difference is also that our patients were at steady state conditions, while the healthy volunteers were given a single dose, thus the two studies are not directly comparable. Our patients were titrated to effect and the higher serum concentrations found in men in our study, may reflect that men are less sensitive than women to opioids, and therefore may require higher doses, as has previously been shown in the requirements of morphine (Pleym et al., 2003).

Of the two ratios explored, the noroxycodone/oxycodone ratio was affected by many characteristics, and total daily dose explained most of the variability in serum concentrations (17 %). However, CYP3A4 inducers and inhibitors were predicted to cause the highest effect on the noroxycodone/oxycodone ratio. Patients using CYP3A4 inducers were predicted to have a ratio four times higher than those not using inducers.

And use of CYP3A4 inhibitors was predicted to decrease the ratio by about 50 % compared to the non-users. As already discussed for the oxycodone serum concentrations, cautions should be taken when CYP3A4 inducer or inhibitor drugs is being used.

Men were predicted to have a 22 % lower noroxycodone/oxycodone ratio than women. Formation of noroxycodone by CYP3A4 is the major elimination pathway of oxycodone (Lalovic et al., 2006). The predicted lower noroxycodone/oxycodone ratio for men may fit with a higher CYP3A4 activity in females. Thus the higher serum concentrations in men may be explained by a lower activity of CYP3A4 compared to women. This is supported by a number of *in vitro* studies (Hunt et al., 1992, Schmidt et al., 2001, Wolbold et al., 2003, Schirmer et al., 2007). Also *in vivo* studies have shown that women seem to exhibit faster clearance of CYP3A4-metabolizing drugs (Chen et al., 2006, Harris et al., 1995, Cotreau et al., 2005), although some studies have failed to detect this clearance difference (George et al., 1995, Williams et al., 2004).

The noroxycodone/oxycodone ratio is predicted to increase slightly with decreasing GFR (predicted a 4% increase in ratio when going from a GFR of 60 ml min^{-1} 1.73 m^{-2} to 40 ml min^{-1} 1.73 m^{-2}). Further, the noroxycodone/oxycodone ratio is predicted to decrease slightly with decreasing serum albumin levels (about 13 % when going from 33 g l^{-1} to 23 g l^{-1}).

The polymorph CYP2D6 regulated pathway showed the lowest explained variability, and was only associated with a few of the characteristics explored. Total daily dose, CYP3A4 inducers and number of medications except opioids taken last 24 h contributed about equally to the low explained variability of 5 %. However, use of CYP3A4 inducers predicted the highest effect on this ratio, with users of such inducers were predicted to have a four times higher oxymorphone/oxycodone ratio than non-users. Also, going from using one to using six co-medications other than opioids is predicted to reduce the oxymorphone/oxycodone ratio by 24 %.

The correlation between the *CYP2D6* genotypes and the oxymorphone/oxycodone ratio was not explored in paper I. The low explained variability may be an indication that the well known *CYP2D6* genotypes "poor metabolizer" (PM), "extensive metabolizer" (EM) and "ultra rapid metabolizer" (URM) are important factors that possibly contribute to the explained variability in serum concentrations. This was confirmed in a post-publication analysis, where the *CYP2D6* genotype was included into the regression analyses of oxymorphone/oxycodone ratios and the explained variability increased from 5 % to 18 %. Also, the low explained variability in this ratio could indicate the presence of unknown drug-drug interactions of importance to these ratios as the oxymorphone/oxycodone ratio is predicted to decrease as the number of co-administered drugs increase.

The present study showed that total daily dose explained most of the known variability in serum concentrations of oxycodone and ratios. However, sex and the use of CYP3A4 inducers and inhibitors were predicted to cause the largest effect on oxycodone serum concentrations and the metabolite/oxycodone ratios. Further, several other variables contribute but most of the variability seen is still unaccounted for.

II. Is there an association between the serum concentration of the parent substance oxycodone, or the potentially active metabolites and the clinical outcomes pain intensity, tiredness, nausea and cognitive function?

The results from study I showed that predicting serum concentrations is difficult. However, the releaved correlations between total daily dose and serum concentrations of oxycodone (r_s = 0.7), noroxycodone (r_s = 0.8) and noroxymorphone (r_s = 0.7) were high, and the correlation with oxymorphone was good (r_s = 0.6). However, from a clinical point of view it may be more interesting to examine if the efficacy of oxycodone

could be predicted from the serum concentrations measured. If so, this information might be helpful in the treatment of the individual patient.

Concentration-effect relationships have previously been observed by Kaiko et al (Kaiko et al., 1996b) who studied the pharmacokinetics and pharmacodynamics in 28 healthy volunteers after a 20 mg administration of CR oxycodone. The pharmacodynamic effects were assessed with a drug effect questionnaire, and by assessing mood, pupil size changes and respiratory rate. $AUC_{0\text{-}48h}$ for time versus concentration- and time versus effect were generated. The time course of changes in the variables recorded was in accordance with changes in oxycodone concentrations, and a significant correlation between pupil size and oxycodone plasma concentration (r = - 0.53), but no significant correlation with oxymorphone were found. The strongest correlation was found between oxycodone concentrations and "drug effect" (r = 0.57). The study also showed that those with the highest "drug effect" also had the highest incidents of opioid-related side effects and the highest oxycodone plasma concentrations.

Further, Benziger et al. (Benziger et al., 1997) studied the pharmacokinetics and pharmacodynamics in 22 healthy males after 20 mg CR oxycodone. Plasma samples were collected 0-48 h after dosing and C_{max}, T_{max} and $AUC_{0\text{-}48h,\ 0\text{-}\infty}$ was calculated. Pharmacodynamics assessed were the same as those in Kaiko et al.'s (Kaiko et al., 1996b) study; drug effect questionnaire, mood, sedation, pupil size and respiration. A linear relationship was found between oxycodone plasma concentrations and pupil size, respiratory rate, sedation and most of the items from the drug effect questionnaire. The correlation was strongest between concentrations of oxycodone and pupil size (r = - 0.53), and for "drug effect" (r = 0.53). Variability in plasma concentrations accounted for more than 25 % of the observed changes in pupil size and also 25 % of the changes in "drug effect". The plasma oxycodone concentration versus time curve generally paralleled the pharmacodynamics assessed. Changes in dynamic effects were measurable from baseline at 0.5-12 h after administration. The magnitude of the observed changes in dynamic effect differed considerably among the variables assessed, and all parameters returned to baseline between 12-24 h after dosing.

In the present study no association between serum concentrations of oxycodone and pain intensity, nausea, tiredness or cognitive function for the cancer patients was found. However, increased oxymorphone concentrations were associated with increased pain intensity.

The lack of a relationship is supported by Heiskanen et al. (Heiskanen et al., 2000) who did not find any association between pain intensity, subjective drug effect or adverse effects and plasma concentration of oxycodone, noroxycodone and oxymorphone, nor morphine and its metabolites, at any of the four time points assessed in cancer patients administered with CR oxycodone or CR morphine every 12 h. Pain intensity was assessed, and blood were sampled at trough, and 1, 3 and 5 h after oxycodone administration. In the study by Heiskanen et al. many patients withdrew from the study, thus only 28 were included into analyses. This might be the reason why they did not find any associations.

Whether oxycodone has metabolites adding to the efficacy is not unequivocally settled. However, active metabolites make it more difficult to find a concentration-effect relationship, because the full effect is not only mediated by the mother substance but also by one or more of its metabolites. Wolff et al.'s (Wolff et al., 1995) did not find a concentration-effect relationships for morphine. The reason for this lack of pharmacokinetic-pharmacodynamic relationship could be the high concentration of the active metabolite M6G.

Another reason for not finding a concentration - effect relationship may be that the concentrations measured were in plasma or serum and not at the site of action. Concentrations measured in the CSF are certainly closer to the site of action than serum measurements for opioids. It is shown that there is a significant inter-individual variability in the CSF/plasma ratio for morphine which may obscure plasma concentration – effect relationships (Wolff et al., 1995). However, Samuelsson et al. (Samuelsson and Hedner, 1991) did not find any relationship between pain relief and steady-state CSF concentrations of morphine or its metabolites in cancer patients following epidural administration. In this study there was a wide range in CSF/plasma ratios. Whether similar inter-individual variability exists for oxycodone is not known,

but if it does it could be an additional reason for the lack of concentration-effect relationships.

Microdialysis, a technique that makes it possible to measure real-time unbound drug in both the extracellular fluid of the brain and blood, of rats has shown that the oxycodone concentration in brain in steady state was three times higher than the concentration measured in the blood (Bostrom et al., 2006), and compared to morphine the brain concentration was six fold higher (Bostrom et al., 2008). These studies indicate that oxycodone is actively transported over the blood-brain barrier. Still unproven, it is possible that oxycodone is actively transported into the brain also in humans. This process may be subject to genetic variability (Schwab et al., 2003), and may therefore contribute to impair the relationship between serum concentrations and effects.

Inter-individual differences in sensitivity to opioids cannot be adjusted for and may be another reason we do not find a relationship between oxycodone concentrations and the outcomes. Intra- and inter-individual differences among the patients in pain intensity, pain characteristics and tolerance could have affected the results. In our study we adjusted for factors which potentially could influence pain intensity by including covariates, e.g. pain category, breakthrough pain and constipation status, into the analyses of pain intensity. Thus many factors that were different between the patients and potentially could affect the outcome were eliminated. The same procedure was used for the other outcomes as well. Still no relationships were found.

One factor that we could not adjust for was the fact that these cancer patients were very different in their "baseline" pain, which we had no data on. Adjustment for this difference was therefore not possible. Also, pain is a very subjective experience influenced by genetic and environmental factors, which were not possible to control for, but are expected to vary widely between the patients. Although, polymorphisms causing differences in the μ-opioid receptor have shown to be associated with morphine requirements and efficacy (Rakvag et al., 2005, Klepstad et al., 2004), the evidence that genetic variants are important for opioid efficacy is weak (Lotsch and Geisslinger, 2006).

The assessment tools used to measure pain intensity, nausea, tiredness, cognitive function and quality of life are well acknowledged and validated tools for studies in

cancer patients. These tools are not specific for the opioid treatment; rather they give an overall picture of the patients' subjective symptoms and their well being. Nevertheless, these tools may not have the discriminative power required for establishing concentration- effect relationships. This relates especially to the fact that the symptoms are not specific for the opioid treatment, but may also be caused by the disease itself, or an additional cancer treatment given.

It is also worth mentioning that the studies where a relationship between blood concentrations and effects of oxycodone has been found have been single dose studies with healthy volunteers. In these studies the groups of participants are much more homogenous than in studies with patients, and especially unselected cancer patients. In Kaiko's and Benziger's studies time-plasma concentrations curves and time-effect curves were compared while in our study we did not have the ability to follow the concentration over time, also we did not have baseline measurements of any of the outcomes. Also, the outcomes between the healthy volunteer studies, and the patients' studies were different, and only in the patients' studies assessed the pain-concentration relationship. The only comparable assessments are the subjective drug effect questionnaire used in both studies with healthy volunteers and in Heiskanen's study with cancer patients. In Heiskanen's study no association was found, while the studies with healthy volunteers showed associations. These studies had all about the same number of participants (n = 20-28) so this does not explain the results, however the difference in the participants (healthy versus cancer) could also be a reason for the different results.

An unexpected finding was the proportional association between the serum concentration of the potent μ-agonist oxymorphone (Mayyas et al., 2010, Sloan, 2008) and pain intensity. The increase may be clinically relevant as a patient with 1.0 nM oxymorphone was predicted to have an average pain intensity of 4.1 NRS on the BPI, while patients with 1.5 nM oxymorphone were predicted to have an average pain of 8.3 NRS. This is difficult to explain, but this result was also reflected in the sub-group analyses where serum concentration of oxycodone and metabolites in patients who were pain relieved and without side effects (treatment success) were compared to those who had poor pain control and side effects (treatment failures). These analyses showed

that overall the "treatment failure "patients had the highest serum concentrations of both oxycodone and metabolites. This trend was also observed in a similar cohort of cancer patients treated with morphine (Klepstad et al., 2003a). Several of the comparisons in our study did not reach a statistical significant difference, and none in the analyses of Klepstad et al. did. This might be because the concentration ranges were very wide. However, the serum concentrations of oxycodone, oxymorphone, noroxycodone and noroxymorphone were statistically significant different between the "success" and "failure" groups for tiredness, and in the analyses of tiredness the number of "successes" were low. Thus, tiredness in combination with poor pain control seems to be the most common reason for being unsuccessfully treated. The "failures" also had the highest oxycodone doses. This suggests that these patients are overdosed and that oxycodone is not the choice of drug to these patients.

The lack of relationship between serum concentrations and pain intensity and adverse events once again states the complexity in the mechanism of actions of opioids and also shows how different the cancer patients are. From this study it seems like the "effective serum concentration range" does not exist.

III. Do the CYP2D6 genotypes poor metabolizer (PM), extensive metabolizer (EM) and ultra rapid metabolizer (URM) explain variability in the pharmacokinetics and pharmacodynamics of oxycodone?

In paper III we showed that *CYP2D6* genotypes explain variability in pharmacokinetics of oxycodone. In this cancer cohort PMs had lower serum concentrations of oxymorphone and noroxymorphone, than EMs and URMs, while there were no difference between EMs and URMs in serum concentrations of these metabolites. Further, no difference in oxycodone serum concentrations between the *CYP2D6* genotypes was found. Our findings are supported by the two other studies in humans; Zwisler et al. (Zwisler et al., 2010) compared the oxycodone requirements between PM

and EM in 270 post-operative patients and Samer et al. (Samer et al., 2010a) assessed the effect of *CYP2D6* genotypes as well as CYP2D6 and CYP3A4 drug-drug interactions on the pharmacokinetics of oxycodone in healthy volunteers. Thus current research agrees that the *CYP2D6* genotype affects the pharmacokinetics of oxycodone as predicted in man.

In the present study we did not find any difference in the pharmacodynamics assessed (pain intensity, tiredness, nausea, cognitive function) between the *CYP2D6* genotypes. How the *CYP2D6* genotype affects the pharmacodynamics of oxycodone was recently assessed by others. Assessments of experimental pain in healthy volunteers after a single dose of oxycodone, argues for a difference in the pharmacodynamics between PM, EM and URM (Zwisler et al., 2009, Samer et al., 2010b). The studies involving patients have, however, not been able to confirm differences in pharmacodynamics between *CYP2D6* genotypes (Zwisler et al., 2010, Lemberg et al., 2010).

Zwisler et al. (Zwisler et al., 2009) compared the efficacy of oxycodone after 20 mg administration between 16 EM and 17 PM healthy volunteers. Their study included assessments of nociceptive tests (electrical sural nerve stimulation and cold pressor test) which were assessed several times from 0-4 hours after administration, and side effects (e.g. tiredness, nausea and ability to concentrate) which were continuously reported. The results from the study showed that EMs experienced a better analgesic effect from the drug than the PMs did, and that this difference was largest 1-2 hours after administration. There was no difference in side effects between PM and EM, which is in accordance with the findings in our study. In both studies side effects were assessed utilizing similar five point NRS. Zwisler et al. concluded that oxycodone gives less effects in PMs and that the lower oxymorphone/oxycodone ratio of PMs is causing this difference. Further they suggest that oxymorphone probably contributes in the analgesic effect of oxycodone. Zwisler et al.'s and our study differ in time points for the measurements, some of the assessments differ and the cohort is different. Administration of oxycodone is also performed differently. Our samples and assessments were performed under steady-state conditions, while those of Zwisler et al. were done 0-4 hours after a single dose. Possibly oxymorphone contributes to the efficacy of oxycodone only shortly after administration, as shown in the Zwisler et al.

study, but during chronic administration oxymorphone has little effect. However, it may be more likely that a possible contribution of oxymorphone was diluted by the fact that our sample is heterogeneous and also not opioid naïve. It could also be that oxymorphone exhibits effect when it has reached its C_{max} 1-2 hours after administration, before oxycodone concentrations reach their C_{max} (about 3 h after oral CR) (Heiskanen and Kalso, 1997).

Samer et al. (Samer et al., 2010b) assessed antinociception and psychomotor function by using the same test as Zwisler et al. (Zwisler et al., 2009), and they measured pupil size and recorded adverse events. Two PM, 6 EM and 2 URM were assessed after given an oral dose of 0.2 mg/kg body weight. Blood samples and assessments were done at 0 (before drug administration), 0.5, 1, 1.5, 2, 3 and 6 hours. Based on the time-effect curves generated from 0-90 min. PM had less pharmacodynamic effect than EMs and EM had lower effect than URMs. Further, pupil size was unaffected in PMs, while in EM and URM pupil size decreased after oxycodone administration. Finally, the two URMs and the single EM had side effects, while the two PMs did not report any side effects. The pharmacodynamic differences in effects observed were correlated with oxymorphone and noroxymorphone concentrations, and pupil size was correlated with oxycodone. Based on these correlations Samer et al. suggest that oxymorphone is a major contributor to the efficacy of oxycodone.

Lemberg et al. (Lemberg et al., 2010) used paroxetine to block the CYP2D6 metabolic pathway in 18 EM and 2 URM with chronic pain regularly scheduled oxycodone. Paroxetine increased the plasma concentrations of oxycodone and noroxycodone and decreased oxymorphone and noroxymorphone. Paroxetine did not change the pharmacodynamics of oxycodone. Further, the changes in serum concentrations were not associated with CYP2D6 genotypes and neither was analgesic effect. The authors comment that this probably is due to the small sample size. Adverse effects in this study were associated with paroxetine.

In summary, the experimental pain tests and continuous monitoring of oxycodone and metabolites show that during single administration in healthy volunteers, oxymorphone seems to contribute to the analgesic effect of oxycodone (Zwisler et al., 2009). PMs seem

to have the least effect, and the differences in analgesic effect between genotypes are highest after 1-2 h post-oxycodone administration (Samer et al., 2010b). EM and URM tend to have more adverse events than PM. Differences in drug requirements to relieve pain have not been assessed.

During short-term, repeated patient controlled administration of oxycodone for post operative pain, *CYP2D6* genotypes all had the same consumption of oxycodone. This is in line with our study that also found no difference in pain intensity or the side effects nausea, tiredness and cognitive function among the *CYP2D6* genotype groups. These patient related studies suggest that *CYP2D6* genotype do not show any clinical implication during short-term administration for post-operative pain-, or during chronic administration for chronic pain- and cancer patients. The kinetic difference observed among the *CYP2D6* genotypes, do not cause pharmacodynamic differences in any of the clinical settings studied.

Study implications and future prospective

The evidence so far does not support that metabolites of oxycodone contributes to the efficacy during clinical samples, thus this drug may be a better choice than morphine for cancer pain patients with hepatic- or kidney failure, due to accumulation of morphine's active metabolite, M6G. Hepatic and renal failure may cause changes in the pharmacokinetics of oxycodone, as shown with elevated noroxycodone and oxycodone serum concentrations and prolonged elimination in renal impaired patients, and also increased concentrations and prolonged elimination of oxycodone in patients with hepatic failure (Kaiko et al., 1996a, Tallgren et al., 1997, Kirvela et al., 1996). From the little clinical evidence that exists this does not seem to have any pharmacodynamic consequence during short-time administration. Our results suggests that this may also be true during chronic administration; 58 % of the patients had albumin levels below normal range (< 35 g/L) and 13 % were suffering from renal disease/dysfunction (GFR < 60 ml min^{-1} 1.73 m^{-2}), and these indicators of hepatic and renal impairment had no influence on serum concentrations of oxycodone, and no clinical relevance to the noroxycodone/oxycodone ratio. This should, however, be confirmed and we suggest to

study oxycodone pharmacokinetics during chronic treatment in cohorts of patients with hepatic- or kidney failure, especially in those with kidney failure since these had low prevalence in our study.

Our study showed that noroxycodone/oxycodone ratio was negatively associated with body mass index. The prevalence of obese (BMI > 30 kg/m^2) people in the world is increasing, and epidemiological studies has shown that obesity is associated with diseases as coronary artery disease, diabetes, hypertension and cancer among others (Haslam and James, 2005). WHO estimates that by 2015, approximately 2.3 billion adults will be overweight and more than 700 million will be obese (World Health Organization, 2011b). Thus, an increase in obese patients is expected. However, pharmacokinetic drug studies mainly include non-obese subjects, thus knowledge of drug disposition in obese subjects is currently lacking (Hanley et al., 2010). Obese people have increased adipose tissue, increased total body water, reduced tissue blood flow and increased glomerular filtration rate, which may affect pharmacokinetics and pharmacodynamics of a given drug. For instance, prolonged $t_{1/2}$ is observed in obese with lipophilic drugs (Casati and Putzu, 2005) and nausea and vomiting was more frequent in obese than lean patients after surgery (Lee et al., 2007). As far as we know, no one has assessed how weight affects oxycodone pharmacokinetics and pharmacodynamics, thus we suggest that studies in both obese healthy volunteers and patients should be conducted.

Two studies in healthy volunteers (Kaiko et al., 1996b, Benziger et al., 1997) have found concentration-effect relationships for oxycodone, while in our and Heiskanen et al.'s (Heiskanen et al., 2000) clinical setting no relationship was found. The methods used and the patient cohorts were different in these two settings. Because of this, we do not know if the discrepancy is caused by methodological differences or cohort differences. A study that aims to answer why we observe this discrepancy is warranted. One way of doing such a study could be to include cancer patients with pain into a pharmacokinetic and pharmacodynamic single 20 mg CR oxycodone study where Kaiko et al.'s (Kaiko et al., 1996b) assessment tools (serum concentrations measurements, drug effect questionnaire (ten of the items used by Preston et al. (Preston et al., 1991)), mood, and –pupil size changes and respiratory rate) and assessment intervals (0, ½, 1, 1 ½, 2, 2 ½,

3, 3 ½, 4, 5, 6, 8, 10, 12, 18 (blood only), 24, 30 (blood only), 36, and 48 hours after dosing) are used. In addition pain intensity could be assessed at the same interval as the other assessments.

Studies have shown that drugs inhibiting or inducing the CYP3A4 metabolic pathway may change the pharmacokinetics of oxycodone dramatically. Drugs used in studies to inhibit or induce this pathway have been itraconazole (Saari et al., 2010), telithromycin (Gronlund et al., 2010a, Gronlund et al., 2010b), voriconazole (Hagelberg et al., 2009), ketoconazole (Samer et al., 2010a, Kummer et al., 2010), ritonavir or lopinavir/ritonavir (Nieminen et al., 2010c) and rifampin (Nieminen et al., 2009). Some of these have shown to give a pharmacodynamic consequence, while others have not when tested out in healthy volunteers, after single dose administration. Our study shows that use of the CYP3A4 inhibitor fluconazole is associated with a 1.6 units decrease in pain intensity. This effect shown on a group level may be even more pronounced in the individual patient. Thus, an interesting study would be to monitor the serum concentrations of oxycodone and pain intensity in a patient population who are starting on fluconazole, and continue to monitor this until fluconazole is being discontinued.

Use of the CYP3A4 inducer rifampin (Lee et al., 2006, Nieminen et al., 2009) has shown to reduce the oxycodone exposure and reduce the pharmacodynamic effects, and use of St John's wort (Nieminen 2010) caused reduced oxycodone serum concentrations and reduction in self reported drug effect. Our cohort represents a typical European cancer population and about 50 % used systemic steroids that according to Flockhart (Flockhart, 2007) are drugs that induce CYP3A4. We divided the CYP3A4 inducers into two groups; steroids and other CYP3A4 inducers. In our study steroids were not associated with serum concentrations or ratios, thus it is reasonable to believe that the association with nausea is caused by the effect of the steroid and not as a consequence of CYP3A4 induction. Studies exploring how systemic steroids or groups of steroids may affect pharmacokinetics and pharmacodynamics of oxycodone in cancer patients would still be interesting do due to the fact that so many of the cancer patients are using steroids. Only four patients were categorized into the CYP3A4 inducer group. Of these, three used carbamazepine and one phenobarbital. The CYP3A4 inducer group predicted significantly changes in the pharmacokinetics of oxycodone and both ratios in our study.

We were not able to find any association between CYP3A4 inducers and pharmacodynamic effects in our cross-sectional study; however, similar studies as the one proposed for fluconazole could add valuable information regarding potential drug-drug interactions with carbamazepine and phenobarbital.

In steady state oxymorphone does not seem to contribute to the analgesic effect of oxycodone and oxycodone levels seem to be unaffected of the *CYP2D6* genotype, thus precautions due to the *CYP2D6* genotype do not seem to be necessary. However, information on how the *CYP2D6* genotype is affected during oxycodone administration when there are co-administrations with drugs potentially affecting the hepatic metabolism is lacking and is warranted. The Samer et al. (Samer et al., 2010b) study suggests that URM's may experience overdose and toxic effects if the CYP3A4 metabolic pathway is being blocked. However, Samer et al.'s study only had 2 URM and a total sample size of 10. We suggests that Samer et al.'s finding of URM's being more exposed to toxic effects should be confirmed in a larger cohort.

Conclusions

The overall findings of this thesis are that neither routine serum concentration measurements nor *CYP2D6* genotyping are indicated during oxycodone administration. During chronic administration, the analgesic effect is mainly mediated by oxycodone itself. Tiredness is a prevalent symptom among those who have poor pain control, and this may indicate a need for a switch to another opioid. Patients who are going to start on- or discontinue drugs that affect the CYP3A4 enzyme system should be monitored closely.

The conclusion of the specific research questions are as follows:

1. *Can commonly recorded patient characteristics predict serum concentrations of (A) oxycodone or oxycodone metabolism by (B) CYP2D6 and (C) CYP3A4 enzymes as indicated by the metabolic ratios?*

    - The characteristics explained about 1/3 of the variability of oxycodone serum concentrations and only minor parts of the variability of the ratios in this cancer population.

    A: Sex, total daily dose, CYP3A4 inducers/inhibitors, and "time from last oxycodone dose" were predictors explaining 35 % of the variability in oxycodone concentrations.

    B: Total daily dose, CYP3A4 inducers and "number of medications taken in last 24 h" explained 5 % of the variability in the oxymorphone/oxycodone ratio.

    C: Total daily dose, "time from last dose to blood sample", albumin, sex, CYP3A4 inducers/inhibitors, steroids, BMI and GFR explained 19 % of the variability in noroxycodone/oxycodone ratio.

2. *Is there an association between the serum concentration of the parent substance (A) oxycodone, or the potentially (B) active metabolites and the clinical outcomes pain intensity, tiredness, nausea and cognitive function?*

   - There were few concentration-effect relationships between these subjective symptoms and oxycodone and metabolites.
   - Sub-group analyses of patients classified as "treatment success" and "treatment failures" showed that "treatment failures" generally had the highest concentrations of oxycodone and metabolites.

   A: Serum concentrations of oxycodone were not associated with pain intensity, tiredness, nausea and cognitive function.

   B: Oxymorphone serum concentrations were positively associated with increased pain intensity, but not with tiredness, nausea and cognitive function. Noroxycodone and noroxymorphone were not associated with these subjective outcomes.

3. *Do the CYP2D6 genotypes poor metabolizer (PM), extensive metabolizer (EM) and ultra rapid metabolizer (URM) explain variability in the (A) pharmacokinetics and (B) pharmacodynamics of oxycodone?*

   - The *CYP2D6* genotype explains variability in the pharmacokinetics of oxycodone.
   - The pharmacokinetic variability did not cause any pharmacodynamic consequence.

   A: Poor metabolizers have lower oxymorphone and noroxycodone serum concentrations than both extensive metabolizers and ultra rapid metabolizers. The oxycodone serum concentration is independent of the *CYP2D6* genotype.

B: The *CYP2D6* genotypes PM, EM and URMs were not associated with variability in pain intensity, tiredness, nausea and cognitive function in this sample of cancer pain patients.

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Paper I

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Paper II

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Paper III

Do *CYP2D6* genotypes reflect oxycodone requirements for cancer patients treated for cancer pain? A cross-sectional multicentre study

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Abstract

Objective: Opioids are recommended by the World Health Organization for moderate to severe cancer pain. Oxycodone is one of the most commonly used opioids and is metabolized in the liver by CYP3A4 and CYP2D6 enzymes. The aim of this study was to assess the relationship between oxycodone pharmacokinetics, pharmacodynamics and the CYP2D6 genotypes “poor metabolizer” (PM), “extensive metabolizer” (EM) and “ultra rapid metabolizer” (URM) in a cohort of patients with cancer pain.

Methods: The patients were genotyped for the most common CYP2D6 variants and serum concentrations of oxycodone and metabolites were determined. Pain was assessed using the Brief Pain Inventory (BPI). The EORTC QLQ-C30 was used to assess the symptoms of tiredness and nausea. Cognitive function was assessed by the Mini Mental State (MMS) examination. Associations were examined by analyses of variance (ANOVA) and covariance (ANCOVA), or ordinal logistic regressions with and without covariates.

Results: The sample consisted of 27 PM, 413 EM and 10 URM. PMs had lower oxymorphone and noroxymorphone serum concentrations than EM and URM. No differences between PMs, EMs and URMs in pain intensity, nausea, tiredness or cognitive function was found.

Conclusion: Pharmacokinetic differences due to different *CYP2D6* genotypes were observed, but had no pharmacodynamic consequence. *CYP2D6* genotypes did not influence pain control, the adverse symptoms nausea and sedation or the risk for cognitive failure in this study of patients treated with oxycodone for cancer pain.

Keywords

Oxycodone, metabolites, *CYP2D6* genotypes, pharmacokinetic, pharmacodynamic, cancer pain

Introduction

The World Health Organization (WHO) recommends opioids for the relief of moderate to severe cancer pain[1] . Oxycodone is one of most commonly used opioids [2-4]. Oxycodone is metabolized in the liver mainly by CYP3A4 to noroxycodone, but also by CYP2D6 to oxymorphone, and via 6-keto reduction to α- and β-oxycodol. Noroxycodone and oxymorphone are further metabolized to noroxymorphone by CYP2D6 and CYP3A4, respectively [5]. CYP3A4 and CYP2D6 belong to the cytochrome P450 system, the principal enzyme system for phase I metabolism. This system is present in virtually all tissues, but is most abundant in the liver and in the small intestine [6]. The *CYP3A4* gene has many known polymorphisms, but no clinically important differences between genotypes have been observed [7,8]. *CYP2D6* has several known polymorphisms that influence drug metabolism. Inactivating polymorphisms cause gene mutations and deletion(s) which result in a non-functional enzyme, whereas gene duplication(s) cause over-expression of active enzyme. Individuals with two non-functional alleles of *CYP2D6* are genotyped “poor metabolizers” (PMs, 5-10 % of Caucasians), whilst individuals with one decreased functional allele and one non-functional allele or two decreased functional alleles are “intermediate metabolizers” (IMs, 10-15 % of Caucasians). Persons having two wild type alleles (*CYP2D6*1*), or one functional and one non-functional allele, are referred to as “extensive metabolizers” (EMs, 72-84 % of Caucasians). Individuals with duplicate(s) of the *CYP2D6* gene are “ultra rapid metabolizers” (URMs, 1-3 % of Caucasians) [9,10]. Because poor metabolizers are unable to metabolise *CYP2D6* substrates, a drug administered at normal dose may lead to high or toxic levels of the drug [11,12]. On the other hand, an ultra rapid metabolizer may experience reduced or no effect when given a drug which is a *CYP2D6* substrate, or may experience adverse drug reactions [13,14]. The *CYP2D6* genotype may therefore be of clinical importance for drugs that are metabolized by CYP2D6 enzymes.

The effect of the CYP2D6 genotype on the pharmacodynamics of oxycodone in a clinical setting of patients with cancer pain receiving chronic opioid administration has

not previously been studied. This led us to the following research questions: (1) Do the *CYP2D6* genotypes predict oxycodone and metabolite serum concentrations in patients treated for cancer pain? (2) Is the *CYP2D6* genotype associated with pain intensity-, or the intensity of nausea, tiredness or cognitive function in cancer patients receiving oxycodone?

Materials and methods

Ethics

This multicentre study was performed according to the guidelines of the Helsinki Declaration and was approved by relevant Research Ethics Committee of each study centre. Before entering the study, all participating patients gave their informed written consent.

Patients

We analysed 450 patients receiving oxycodone for cancer pain. The patients were included from 2004 to 2008 in a multicentre cross sectional study (The European Pharmacogenetic Opioid Study-, (EPOS) [15]) designed to explore hypotheses related to the pharmacogenetics of opioid analgesics. The EPOS study included a total number of 2294 patients. Patients included in the present analysis were aged 18 years or more, had a verified malignant disease, and received scheduled oral, subcutaneous, or intravenous oxycodone treatment with a duration of treatment no less than three days. Patients who were not capable of speaking the language used at the study centre were excluded.

Assessments

At the time of inclusion the following information was collected from each patient: Age, gender, weight, height, ethnicity, medications and dosages, the time interval between last opioid administration and blood sampling, time since opioid treatment started, breakthrough pain, cancer diagnosis and time since diagnosis. Pain severity

was assessed using the item “Pain on the average” from the Brief Pain Inventory (BPI), which has a numeric rating scale (NRS) from 0 (“No pain”) to 10 (“Pain as bad as you can imagine”) [16]. The mini mental state (MMS) examination was used to assess cognitive function [17]. Cognitive failure was defined as having a total MMS of 23 or less [18,19]. Functional status was assessed by the Karnofsky performance status [20]. The Karnofsky performance status has a linear scoring from 0-100 %, with higher scores meaning better function. The European Organisation for Research and Treatment of Cancer’s health-related quality-of-life (QoL) questionnaire (EORTC QLQ-C30) version 3.0 was used to assess the patient’s self reported QoL for the symptoms tiredness, nausea, constipation and depression. Tiredness was assessed using the item “Were you tired?” and depression was assessed using the item “Did you feel depressed?” with alternatives “not at all”, “a little”, “quite a bit” and “very much” for both items. Nausea and constipation were assessed using the symptom scale for nausea and vomiting, and constipation, respectively. Scoring of the symptom scales were done by a linear transformation to a 0 to 100 scale. A score of 0-24 on these symptom scales corresponds to “not at all”, 25-49 corresponds to “a little”, 50-74 to “quite a bit” and 75-100 to “very much” [21,22]. Standard analytical methods applied at each centre were used for haemoglobin, creatinine and albumin measurements. Body mass index (BMI) was calculated using the international system of units, BMI = weight (kg) / height^2 (m^2). Renal function was expressed as calculated glomerular filtration rate (GFR)/ 1.73 m^2 body surface [23,24].
Blood samples were obtained shortly prior to drug administration of the patients’ scheduled oral opioid medication (trough value). For practical reasons blood samples from out-patients (n = 68) were taken at the time of examination. Blood samples for opioid analyses in serum were collected in tubes with no additives and left at ambient temperature for 30-60 min. before centrifugation at 2500xg (approx. 3000 rpm) for 10 min. Serum was then aliquoted and stored at -80°C prior to analysis.

Serum concentration analyses

Details on handling of blood samples, analytical technique and instrumentation for serum concentration analyses of oxycodone, and the metabolites oxymorphone, noroxycodone and noroxymorphone have been described previously [25]. Pharmacological analyses were carried using a LC-MS/MS system. Correlation

coefficients were r > 0.998 for all standard curves. Coefficients of variation (intra- and inter-day) for each analyte were 16.5 and 8.3 % for oxycodone, 10.8 and 6.7 % for noroxycodone, 10.0 and 7.5 % for oxymorphone and 14.8 and 7.7 % for noroxymorphone. The limits of quantification were oxycodone; 0.32 nM (0.1 ng/ml), oxymorphone 0.07 nM (0.02 ng/ml), noroxycodone and noroxymorphone 0.17 nM (0.05 ng/ml).

Genetic analyses

Blood samples for genetic analysis were collected at the time of inclusion in vacutainers containing EDTA (K2-EDTA, 5.4 mg/3 ml blood). The blood was aliquoted into cryotubes and frozen (-80ºC) until isolation of DNA. DNA was isolated by a modified salting-out precipitation method for purification (Gentra Puregene Blood Kit, Gentra Systems Inc., MN, USA). Purified DNA was stored at -20°C prior to analysis.

CYP2D6 genotyping

CYP2D6*2x2 (duplication) was detected according to the method of Lovlie et al. [26], with some modifications. PCR was performed using the Gene Amp XL PCR kit (Roche/Applied Biosystems, Foster City, New Jersey, USA) in 50 µl reaction volumes with a hot start. The lower reaction mix layer contained 4.5 µl dH_2O, 6 µl 3.3 XL Buffer II, 2.5 µl $Mg(OAc)_2$ (25 mM), 4 µl dNTP Mix (10 mM), and 1.5 µl of each primer (10 mM)(Table 1). To separate the lower and upper reaction mix layer, wax was melted on top of the lower reaction mix (80 °C, 3-4 min.), and then cooled to room temperature. Then the upper reaction mix containing 18.5 µl dH_2O, 9 µl 3.3 XL Buffer II, 1 µl r*Tth* DNA polymerase (2 U/µl) and 2.5 µl genomic DNA (5-10 ng/µl) was added.

Long-PCR was carried out on a Techne TC-512 (Barloworld Scientific Ltd, Staffordshire, United Kingdom) with the following conditions: an initial denaturing step of 95°C for 1 min., followed by 35 cycles of 94°C for 1 min., 65°C for 30 s and 68°C for 2 min. (+18 s increase for every new cycle), and a final elongation step of 72 °C for 10 min.

The resulting long-PCR products were separated and detected by electrophoresis (30 mA, 40 min.) with 1.2 % agarose gels containing ethidium bromide and tris-acetate buffer (Invitrogen, Carlsbad, California, USA).

Detection of **CYP2D6*5** (deletion) was done in accordance with the method of Steen et al. [27] and Hersberger et al. [28], with some modifications. PCR was performed using the Gene Amp XL PCR kit (Roche/Applied Biosystems, Foster City, New Jersey, USA) in 50 µl reaction volumes with a hot start. To separate lower and upper reaction mix, heated wax was used (as described for detection of CYP2D6*2x2). The lower reaction mix contained 1.95 µl dH_2O, 6 µl 3.3 XL Buffer II, 2.05 µl $Mg(OAc)_2$ (25 mM), 4 µl dNTP Mix (10 mM) and 1.5 µl of each primer (10 mM) (Table 1). The upper reaction mix was as described for detection of CYP2D6*2x2. The PCR conditions, and identification of the amplification products, were done in the same way as described for CYP2D6*2x2.

Long distance and multiplex PCR techniques were combined for the simultaneous detection of the 5 allele groups ***3, *4, *6, *7 and *8** in genomic DNA. Patients who lacked these mutations were categorized as having the **CYP2D6*1** (functional) allele. With some modifications, these reactions were done in accordance with the method of Stüven et al. [29].
First CYP2D6 was specifically amplified as a 4.7 kb fragment by a pre-multiplex long PCR with a hot start. To separate lower and upper reaction mix, heated wax was used (as described for detection of CYP2D6*2x2). PCR was performed using the Gene Amp XL PCR kit (Roche/Applied Biosystems, Foster City, New Jersey, USA) in 50 µl reaction volumes. The lower reaction mix contained 4.5 µl dH_2O, 6 µl 3.3 XL Buffer II, 2.5 µl $Mg(OAc)_2$ (25 mM), 4 µl dNTP Mix (10 mM) and 1.5 µl of each primer (10 mM) (Table 1). The upper reaction mix was as described for detection of CYP2D6*2x2. The pre-multiplex long PCR conditions, and identification of the 4.7 kb PCR product, were done in the same way as for CYP2D6*2x2.
The CYP2D6-specific 4.7 kb pre-amplification product was then used as a template for two separate PCR reactions with primers complementary to either the specific inactivating variant or the corresponding normal (wild type) allele at each potential mutation site (Table 1). Reactions (25 µl) contained 0.8 µl dH_2O, 2.5 µl 10x PCR Gold Buffer, 1.5 µl $MgCl_2$ (25 mM), 0.7 µl dNTP Mix (10 mM), 0.5 µl AmpliTaq Gold

Polymerase (5 U/µl) (all reagents from Applied Biosystems, Foster City, New Jersey, USA), 0.2 µl of the CYP2D6-specific 4.7 kb pre-amplification product and 3.76 µl of each of the following primers in the normal reaction; M (1.06 µM), A1 (0.10 µM), B1 (0.11 µM), E3 (0.12 µM) and T1 (0.64 µM), and for the mutation reaction; 3.13 µl of each primer M (1.06 µM), A2 (0.10 µM), B2 (1.06 µM), E4 (0.10 µM), G2 (0.50 µM) and T2 (0.05 µM) was used.
PCR was carried out on a Techne TC-512 (Barloworld Scientific Ltd, Staffordshire, United Kingdom) with the following conditions: an initial denaturing step of 95°C for 5 min., followed by 14 cycles of 94°C for 1 min., 55°C for 30 s and 72°C for 2 min. 20 s, and a final elongation step of 72 °C for 5 min.
The resulting long-PCR products were separated and detected by electrophoresis (25 mA, 45 min.) with 4.0 % agarose gels containing ethidium bromide and tris-acetate buffer (Invitrogen, Carlsbad, California, USA).

The patients were grouped into three genotype groups:
PM; Patients with two non-functional alleles.
EM; Those categorized as having the wild type allele (*CYP2D6*1*), and in addition patients with one decreased functional allele and one non-functional allele, or two alleles encoding protein with decreased function.
URM; Patients with duplicate(s) of the *CYP2D6* gene.

Statistics

Descriptive group data are given as median (min-max) values. Comparisons between the genetic groups for the continuous descriptive data were explored with analyses of variance (one-way-ANOVA). For the descriptive categorical data the comparisons were explored with logistic regression analyses. Median oxycodone and metabolite serum concentrations were calculated from all 450 patients independent of time since last dose to blood sample and opioid used as rescue medication.

Multiple testing increases the risk of doing a type 1 error. To minimize this risk, we chose to merge the genotype intermediate metabolizers (IM, n = 170) with the extensive metabolizers (EM, n = 243). For practical reasons we have named this

pooled group (n = 413) extensive metabolizers (EM) in all statistical analyses and throughout this paper.

Comparisons between the three genetic groups for the continuous variables (serum concentrations of oxycodone, noroxycodone, oxymorphone and noroxymorphone, pain intensity and cognitive function) were explored with analysis of variance (one-way-ANOVA) and tested for homogeneity. For the variables where the overall F-test showed to be significant ($p \leq 0.05$), the Games-Howell procedure [30] was chosen for the post-hoc tests. The analyses were then repeated with non-genetic covariates previously found to influence the outcomes [25](Andreassen et al. submitted). For serum concentrations of oxycodone and the metabolites these were: Oxycodone total daily dose, use of CYP3A4 inhibitors or inducers, sex, time since last oxycodone dose, the number of medications other than opioids used last 24 h, albumin serum concentrations, use of steroids, BMI and glomerular filtration rate. Covariates in the analyses of pain intensity were oxymorphone serum concentrations, mixed pain, break through pain, paracetamol medication, depression status, constipation status, female reproductive organ cancer and use of fluconazole. Covariates in the analyses of cognitive function were: age, Karnofsky and depression status, use of CYP2D6 inhibitors, steroid medication and breast cancer. Post hoc ANCOVA comparisons between genetic groups were performed with Sidak [31] corrected p-values.

Comparisons between the three genetic groups and categorical data (nausea and tiredness) were explored by ordinal logistic regression without covariates. The analyses where then repeated with inclusion of non-genetic covariates previously known to influence the outcomes [25](Andreassen et al. submitted). For nausea these covariates were sex, depression status, prostate cancer or diagnosis of unknown origin, constipation status, use of antiemetics and steroids. In the analysis of tiredness depression status, breast cancer, Karnofsky status and albumin status were included covariates. The statistical software SPSS for Windows v. 16.0 was used for all statistical analyses.

Results

Patients

Two thousand two hundred and ninety four patients from 17 centres in 11 European countries were included in EPOS, with 461 patients (98 % Caucasians) treated with oxycodone. Eleven patients were excluded; eight because of lack of DNA samples, and three because of incomplete CYP2D6 genotype analyses. Thus, 450 were included in the final analyses.

Six percent (n = 27) were genotyped as poor metabolizers (PM), about 92 percent (n = 413) were extensive metabolizers (EM), while about 2 percent (n = 10) were genotyped as ultra rapid metabolizers (URM).

Descriptive data are shown in table 1 and given as median (min-max) if not stated otherwise. Most of the demographic data were similar in the three genetic groups. However, the median Karnofsky performance status was 70 percent for EM and 50 and 55 percent for PM and URM, respectively ($p = 0.0004$). Also, use of CYP3A4 inducer medications were statistically significantly different in PM (n = 0) compared to the other to genetic groups (n = 2 for both groups) ($p < 0.05$).

Table 1 Patient demographics for poor metabolizers (PM), extensive metabolizers (EM) and ultra rapid metabolizers (URM)

	PM (n = 27)	EM (n = 413)	URM (n = 10)
Gender: female / male (%)	16 / 11 (59 / 41)	180 / 233 (44 / 56)	2 / 8 (20 / 80)
Age (years)*	62 (19-84)	62 (18-91)	63 (44-81)
Karnofsky performance status (%)*¤	50 (20-90)	70 (20-90)	55 (30-70)
Body mass index (kg/m^2)*	23 (14-30)	23 (14-41)	23 (19-28)
Glomerular filtration rate (ml/min/1.73m^2)*	77 (27-239)	96 (24-261)	115 (42-194)
Albumin serum (g/L)*	31 (10-49)	33 (11-91)	29 (22-36)
Time since diagnosis (months)*	31 (0-155)	16 (0-286)	31 (0-79)
Time since opioid treatment started (months)*	1 (0-42)	1 (0-97)	2 (0-21)
Time since last dose (hours)*	11 (1-13)	10 (0.1-17)	11 (0.8-12)
Number of medication ex. opioids*	7 (3-14)	6 (0-17)	9 (3-12)
CYP2D6 inhibitor medication$	2	35	1
CYP3A4 inhibitor medication$	2	21	1
CYP3A4 inducer medication$¤	0	2	2
Breakthrough pain: yes / no (%)	18 / 9 (67 / 33)	256 /156 (62 / 38)	8 /2 (80 / 20)
Cancer diagnosis:			
Gastrointestinal (inclusive pancreas, liver)#	2	87	3
Lung (inclusive mesothelioma)#	6	70	1
Prostate#	4	70	3
Other urological#	0	26	1
Breast#¤	8	56	0
Female reproductive organs#	1	33	0
Haematological#	1	29	0
Head and neck#	1	10	0
Sarcoma#	1	8	1
Skin#	1	8	0
Other#	2	23	1
Unknown origin#	1	12	0
More than one diagnosis#	1	17	0

* median (min-max)

number

$ Number of users

¤ $p < 0.05$

Genetic analyses

The distribution of the CYP2D6 genotypes is shown in Table 2. None of the patients had the *7 and *8 allelic variants. Ten patients were URM due to gene duplication(s). The allelic distributions followed the Hardy-Weinberg equation.

Table 2 Distribution of the CYP2D6 alleles and the corresponding genotype for the genetic groups: extensive metabolizers (EM), poor metabolizers (PM) and ultra rapid metabolizers (URM) for the 450 patients with cancer pain.

Genotype	n	%[#]
EM	**413**	**91.7**
*1/*1 (wild type)	243	54.0
*1/*5 (deletion)	23	5.1
*1/*3	12	2.7
*1/*4	124	27.6
*1/*6	11	2.4
PM	**27**	**6.0**
*3/*4	2	0.4
*4/*4	22	4.9
*4/*6	3	0.7
URM	**10**	**2.2**
*2/*2 (duplication)	10	2.2

None of the patients had the *1/*7 and *1/*8 allele variants

[#] % of total study population

Serum concentrations

Oxycodone total daily dose and serum concentrations for the three genetic groups are given in Table 3 as median (min-max). Median oxycodone total daily dose were 80, 75 and 70 mg/24 h for the PM, EM, and URM, respectively. There were no statistical differences between the three genetic groups with respect to oxycodone and noroxycodone serum concentrations ($p = 0.96$ and 0.09, respectively). There was a significant increase in serum concentrations of oxymorphone and noroxymorphone from PM to EM, –and from PM to URM (all $p < 0.001$). Serum concentrations of oxymorphone were not statistically significant different between EM and URM ($p = 0.16$). Noroxymorphone serum concentrations were statistical

significant lower (p = 0.05) in EM compared to URM, although the result was non-significant after analyses with covariates (p = 0.57) (table 4).
Except from the noroxymorphone serum concentrations, repeating all analyses with inclusion of covariates (ANCOVA analyses) gave similar results with respect to statistical significance (data not shown).

Table 3 Oxycodone total daily dose (mg/24 h) and serum concentrations (nMolar) given as median (min-max) for the three genetic groups poor metabolizers (PM), extensive metabolizers (EM) and ultra rapid metabolizers (URM)

	PM (n = 27)	EM (n = 413)	URM (n = 10)
Total n = 450	6.0%	91.8%	2.2%
Oxycodone total daily dose (mg/24h)	80 (10-960)	75 (10-1600)	70 (25-840)
Oxycodone (nMolar)	110 (0-1408)	107 (0-3551)	74 (23-771)
Noroxycodone (nMolar)	196 (.3-3360)	101 (0-4858)	118 (27-1084)
Oxymorphone (nMolar)	0.2 (0-15)*	1.6 (0-27)	2.3 (1.0-17)
Noroxymorphone (nMolar)	2.5 (0-116)*	18.0 (0-509)	34 (9.4-194)

* Statistically significantly different (p < 0.001) from EM and URM

Table 4 Post hoc analyses of variance (ANOVA) between the three genetic groups; poor metabolizers (PM), extensive metabolizers (EM) and ultra rapid metabolizers (URM), for the outcomes that showed an overall statistical difference (F-test, both p = 0.000).
The statistical significantly different groups are shown with **bold** letters.

Dependent variable[$]	Groups compared	Mean difference between groups (MD)	Std. Error MD	P-value*	95 % CI for MD
Oxymorphone	**PM vs. EM**	**-.84**	**.15**	**.000**	**-1.21 -.47**
	PM vs. URM	**-1.12**	**.20**	**.000**	**-1.62 -.62**
	EM vs. URM	-	-	.16	-
Noroxymorphone	**PM vs. EM**	**-1.04**	**.18**	**.000**	**-1.50 -.58**
	PM vs. URM	**-1.38**	**.22**	**.000**	**-1.91 -.84**
	EM vs. URM	**-.34**	**.12**	**.05[#]**	**-.68 -.0005**

[$] = Log 10 serum concentrations

*The Games-Howell corrected p-values

[#] No statistical difference (p = 0.57) in noroxymorphone between EM and URM in the analyses of covariance (ANCOVA)

Clinical outcomes

Median pain intensity was 4 on the NRS for PM and URM, and 3 for EM. The difference in pain intensity was non-significant between the groups (p = 0.8).
There were no difference between the groups in tiredness (p = 0.7) and nausea (p = 0.6). All three genetic groups had a median score of 67 and 17, respectively, for the EORTC QLQ-C30 on tiredness and nausea.
There were no difference in cognitive function between groups (p = 0.8). PM and URM had a median cognitive function score on the Mini Mental State of 29, compared to a median of 28 for EMs.
PMs had a median of 33, EMs had median 67 and URMs had a median of 50 on the EORTC QLQ-C30 constipation scale. All three genetic groups had a median score of 2 in depression (table 5).

Seven EMs and two URMs used another regular opioid. The exclusion of these patients did not change the results (data not shown).

Table 5 Patients symptoms for the three genetic groups given as median (min-max). Pain intensity from Brief pain inventory, tiredness, nausea, constipation and depression score from EORTC-QLQ-C30 and Cognitive function from Mini Mental Examine Score.

	Poor Metabolizers	Extensive Metabolizers	Ultra Rapid Metabolizers
Pain intensity	4 (0-6)	3 (0-10)	4 (0-6)
Tiredness	67 (0-100)	67 (0-100)	67 (0-100)
Nausea	17 (0-83.33)	17 (0-100)	17 (0-50)
Constipation	33 (0-100)	67 (0-100)	50 (0-100)
Depression	2 (1-3)	2 (1-4)	2 (1-2)
Cognitive function	29 (20-30)	28 (14-30)	29 (20-30)

Discussion

This is the first study to explore the relationships between oxycodone pharmacokinetics, pharmacodynamics and the three *CYP2D6* genotypes (-PM, EM and URM) in patients with cancer pain. In this clinically relevant cohort of patients we observed that oxycodone metabolism, but not oxycodone efficacy, was influenced by *CYP2D6* genotypes.

CYP2D6 activity may have an impact on oxycodone efficacy because oxymorphone in relevant doses is an active analgesic [32], and because noroxymorphone may exhibit analgesic effect due to its abundance in serum and its μ-opioid receptor affinity [33].

Changes in CYP2D6 activity may alter the metabolism of oxycodone. In this study PMs had lower oxymorphone and noroxymorphone serum concentrations than EM and URMs, but no differences were found in oxycodone serum concentrations between the three genetic groups. Correcting for non-genetic covariates, previously shown to influence the serum concentrations of oxycodone and oxycodone/metabolite ratios [25], did not change the results. This means that PMs have lower serum concentrations of oxymorphone and noroxymorphone independent of clinical factors known to alter the oxycodone metabolism. The observed difference in noroxymorphone concentrations between EM and URM was not observed in the analyses corrected for covariates, suggesting the difference in noroxymorphone between EM and URM was not related to *CYP2D6* genotypes, but caused by other factors.

Significant differences in oxymorphone serum concentration levels for PM compared to EM, was also demonstrated in a fairly large (n = 270) study in patients with post-operative pain [34]. Moreover, Samer et al.'s [35] study in healthy volunteers showed that PMs had very low oxymorphone and noroxymorphone levels compared to EMs and URMs. Thus all studies performed in humans consistently shows that CYP2D6 genotypes alter the pharmacokinetics of oxycodone.

Despite the clear effects of *CYP2D6* genotypes on the pharmacokinetics of oxycodone, no difference was found between PMs, EMs and URMs in comparing pain intensities, nausea, tiredness and cognitive function. Thus, this study suggests that *CYP2D6* genotyping and monitoring of oxycodone serum concentrations and its metabolites do not have any value in clinical routine practice. This is in accordance with the clinical study by Zwisler et al. [34] who were unable to confirm an analgesic effect of oxymorphone, or a difference in the efficacy of oxycodone between PMs and EMs, in 270 patients with post-operative pain treated with oxycodone. Further, no difference was found in the analgesic effect and adverse events between EM and URM patients with chronic non-malignant and malignant pain administered oxycodone [36].

In contrasts, experimental pain studies in healthy volunteers [37,38] observed differences between the three *CYP2D6* genotypes. In Zwisler et al.'s [37] study there

was a difference between EM and PM in analgesic effect of oxycodone on pain detection threshold, tolerance threshold and the cold pressor test. Samer et al. [38] showed differences in pain tolerance- and subjective pain thresholds (URM > EM > PM) and differences between URM and EM in psychomotor tests ($p < 0.05$). However, an important shared limitation is that these two studies were single dose oxycodone studies performed in healthy volunteers.

Our study suggests that oxymorphone and noroxymorphone do not contribute to the efficacy of oxycodone in a clinical setting with cancer patients. The reason for lack of pharmacodynamic effect of the potent compound oxymorphone could potentially be the very low level of this metabolite relative to oxycodone [33]. The median oxymorphone serum concentrations in this study were 0.2, 1.5 and 3.1 percent of the median oxycodone serum concentrations in the PM, EM and URMs, respectively.

Median noroxymorphone serum concentrations constitute 2.3, 16.8 and 46 percent of the median oxycodone serum concentrations in the PM, EM and URMs, respectively. A difference in pain intensity or adverse events between PM and URM would be expected if noroxymorphone was an active metabolite, maybe also between PM and EM, due to the relatively large difference between the genotypes of noroxymorphone concentrations relative to oxycodone. This was not the case; there was no difference between PM, EM and URM with regard to effect or adverse events, thus it seems unlikely that noroxymorphone is an important active metabolite of oxycodone.

CYP2D6 inhibitor medication usage was included in the covariate analyses of the efficacy of oxycodone. No association was found suggesting that CYP2D6 inhibition does not affect the efficacy of oxycodone. The prevalence of co-medication with a CYP2D6 inhibitor was only about eight percent and, therefore, a relevant difference could be undisclosed. However, this lack of impact from the use of CYP2D6 inhibitors is in accordance with other studies where inhibition of the CYP2D6 metabolic pathway with paroxetine or quinidine did not influence the efficacy of oxycodone in healthy volunteers [39,40,38,41], or patients with chronic pain [36].

The patients included in this study are heterogenic with regard to characteristics that may affect pain intensity and other symptoms. In studies on healthy volunteer pain

mechanisms is equal for all participants, and the participants are more homogeneous. However, experimental pain has little relevance in clinical practice, while our results reflect the clinical setting. Thus, in this cohort with chronic cancer pain, oxymorphone does not seem to contribute to the analgesic effect of oxycodone.

Conclusion

Patients categorised as PMs of oxycodone have statistical significant lower serum concentrations of oxymorphone and noroxymorphone than EMs and URMs. However, no difference was found between PMs, EMs and URMs when comparisons of their pain intensities, nausea, tiredness and cognitive function were made. The *CYP2D6* genotype does not reflect oxycodone requirements and it is not-, associated with common adverse effects in this study of patients with cancer pain.

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Appendix

Brief pain Inventory

EORTC QLQ C30

Minimental state (MMS)

Karnofsky performance status

40857

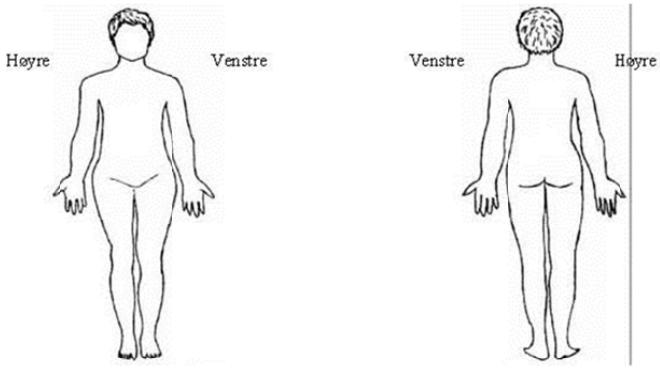
Brief Pain Inventory

Pasientnr. Dato

1. Gjennom livet har de fleste av oss hatt smerter (som lett hodepine, forstuelser eller tannpine). Har du i dag smerter av et annet slag enn slike dagligdagse smerter.

☐ Ja ☐ Nei

2. Vil du skravere de områdene på kroppen hvor du har smerter. Marker med et kryss der du har mest vondt.



3. Vennligst sett ring rundt det tallet som best beskriver de sterkeste smertene du har hatt i løpet av de siste 24 timer.

0 1 **2** **3** **4** **5** **6** **7** **8** **9** **10**

Ingen smerter — Verst tenkelige smerter

4. Vennligst sett ring rundt det tallet som best beskriver de svakeste smertene du har hatt i løpet av de siste 24 timer.

0 1 **2** **3** **4** **5** **6** **7** **8** **9** **10**

Ingen smerter — Verst tenkelige smerter

5. Vennligst sett ring rundt det tallet som best angir hvor sterke smerter du har i gjennomsnitt.

0 1 **2** **3** **4** **5** **6** **7** **8** **9** **10**

Ingen smerter — Verst tenkelige smerter

6. Vennligst sett ring rundt det tallet som best angir hvor sterke smerter du har akkurat nå.

0 **1** **2** **3** **4** 5 **6** **7** **8** **9** **10**

Ingen smerter — Verst tenkelige smerter

Vennligst snu arket

40857

7. Hvilken behandling eller medisiner får du for å lindre smertene dine?

8. I hvor stor grad har behandling eller medisiner lindret smertene dine de siste 24 timene?
Vennligst sett en ring rundt det prosenttallet som viser hvor stor smertelindring du har fått.

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% **100%**
Ingen lindring **Fullstendig lindring**

Sett en ring rundt det tallet som for de siste 24 timene best beskriver hvor mye smertene har virket inn på :

9. Daglig aktivitet

0 1 2 3 4 5 6 7 8 9 **10**
Ikke påvirket **Fullstendig påvirket**

10. Humør

0 1 2 3 4 5 6 7 8 9 **10**
Ikke påvirket **Fullstendig påvirket**

11. Evne til å gå

0 1 2 3 4 5 6 7 8 9 **10**
Ikke påvirket **Fullstendig påvirket**

12. Vanlig arbeid (gjelder både arbeid utenfor hjemmet og husarbeid)

0 1 2 3 4 5 6 7 8 9 **10**
Ikke påvirket **Fullstendig påvirket**

13. Forhold til andre mennesker

0 1 2 3 4 5 6 7 8 9 **10**
Ikke påvirket **Fullstendig påvirket**

14. Søvn

0 1 2 3 4 5 6 7 8 9 **10**
Ikke påvirket **Fullstendig påvirket**

15. Livsglede

0 1 2 3 4 5 6 7 8 9 **10**
Ikke påvirket **Fullstendig påvirket**

Tusen takk for hjelpen!

Morfinbehandling
og morfinmetabolitter

EORTC QLQ-C30

(Versjon 3.0)

Pasient nr. ☐☐☐

Dato ☐☐.☐☐.☐☐☐☐

Vi er interessert i forhold vedrørende deg og din helse. Vær så vennlig å besvare hvert spørsmål ved å sette et kryss x i den bokser som best beskriver din tilstand. Det er ingen «riktige» eller «gale» svar. Alle opplysningene vil bli behandlet konfidensielt.

	Ikke i det hele tatt	Litt	En del	Svært mye
1. Har du vanskeligheter med å utføre anstrengende aktiviteter, slik som å bære en tung handlekurv eller en koffert?	☐	☐	☐	☐
2. Har du vanskeligheter med å gå en lang tur?	☐	☐	☐	☐
3. Har du vanskeligheter med å gå en kort tur utendørs?	☐	☐	☐	☐
4. Er du nødt til å ligge til sengs eller sitte i en stol i løpet av dagen?	☐	☐	☐	☐
5. Trenger du hjelp til å spise, kle på deg, vaske deg eller gå på toalettet?	☐	☐	☐	☐

I løpet av den siste uka:	Ikke i det hele tatt	Litt	En del	Svært mye
6. Har du hatt redusert evne til å arbeide eller utføre andre daglige aktiviteter?	☐	☐	☐	☐
7. Har du hatt redusert evne til å utføre dine hobbyer eller andre fritidsaktiviteter?	☐	☐	☐	☐
8. Har du vært tung i pusten?	☐	☐	☐	☐
9. Har du hatt smerter?	☐	☐	☐	☐
10. Har du hatt behov for å hvile?	☐	☐	☐	☐
11. Har du hatt søvnproblemer?	☐	☐	☐	☐
12. Har du følt deg slapp?	☐	☐	☐	☐
13. Har du hatt dårlig matlyst?	☐	☐	☐	☐
14. Har du vært kvalm?	☐	☐	☐	☐

Bla om til neste side

I løpet av den siste uka:	Ikke i det hele tatt	Litt	En del	Svært mye
15. Har du kastet opp?	☐	☐	☐	☐
16. Har du hatt treg mage?	☐	☐	☐	☐
17. Har du hatt løs mage?	☐	☐	☐	☐
18. Har du følt deg trett?	☐	☐	☐	☐
19. Har smerter påvirket dine daglige aktiviteter?	☐	☐	☐	☐
20. Har du hatt problemer med å konsentrere deg, f.eks. med å lese en avis eller se på TV?	☐	☐	☐	☐
21. Har du følt deg anspent?	☐	☐	☐	☐
22. Har du vært engstelig?	☐	☐	☐	☐
23. Har du følt deg irritabel?	☐	☐	☐	☐
24. Har du følt deg deprimert?	☐	☐	☐	☐
25. Har du hatt problemer med å huske ting?	☐	☐	☐	☐
26. Har din fysiske tilstand eller medisinske behandling påvirket ditt familieliv?	☐	☐	☐	☐
27. Har din fysiske tilstand eller medisinske behandling påvirket dine sosiale aktiviteter?	☐	☐	☐	☐
28. Har din fysiske tilstand eller medisinske behandling gitt deg økonomiske problemer?	☐	☐	☐	☐

Som svar på de neste spørsmålene, sett et kryss i den boksen fra 1 til 7 som best beskriver din tilstand.

29. Hvordan har din helse vært i løpet av den siste uka?

☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

Svært dårlig — Helt utmerket

30. Hvordan har livskvaliteten din vært i løpet av den siste uka?

☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

Svært dårlig — Helt utmerket

51610

Minimental status

Morfinbehandling og morfinmetabolitter

Pasient nr. ☐☐☐

Dato ☐☐.☐☐.☐☐☐☐

1. ORIENTERING	Skår	Maksimal skår
Hvilket år er det?	☐	1
Hvilken måned er det?	☐	1
Hvilken årstid er det?	☐	1
Hvilken dato er det i dag?	☐	1
Hvilken dag er det idag?	☐	1
I hvilket land er vi nå?	☐	1
I hvilken landsdel er vi nå?	☐	1
I hvilken by er vi nå?	☐	1
I hvilket sykehus er vi nå? (Hva er din hjemmeadresse?)	☐	1
I hvilken avdeling er vi nå? (Hvilket postnummer har du?)	☐	1
2. LÆRING Si 3 ord. Bruk 1 sekund til å uttale hvert ord. OST - SYKKEL - BOK. Be pasienten gjenta alle 3 ordene Gjenta ordene, inntil pasienten har lært dem, og kan huske dem Noter antall forsøk ☐	☐	3
3. ABSTRAKT TENKNING Stav ordet SVERD baklengs. Ett poeng for hver riktig bokstav sagt i den rette rekkefølge. Alternativt: Start med tallet 100. Trekk fra 7, rekk fra 7 igjen, og fortsett subtraksjonen i alt 5 ganger.	☐	5
4.KORTTIDHUKOMMELSE Kan du si meg de ordene du skulle huske for litt siden? (OST - SYKKEL - BOK)	☐	3
5. HØYERE KORTIKALE FUNKSJONER		
Vis fram en blyant. Hva er dette?	☐	1
Vis fram en klokke. Hva er dette?	☐	1
Gjenta følgende setning: "Aldri annet enn om og men."	☐	1
Ta et stykke papir med din høyre hånd. Brett det over på midten og legg det på gulvet.	☐	3
Les og utfør: "Lukk øynene dine."	☐	1
Skriv en setning.	☐	1
Kopier denne tegningen.	☐	1
Total skår	☐☐	30

KARNOFSKY INDEX

Kriterier for aktivitesstatus ved skjelettmetastatisk kreftsykdom

Utfører normal aktivitet, trenger ikke spesielt stell	100%	Normal. Ingen plager eller subjektive tegn på sykdom.
	90%	Klarer normal aktivitet, sykdommen gir lite symptomer.
	80%	Klarer med nød normal aktivitet. Sykdommen gir en del symptomer.
Ute av stand til å arbeide. Klarer seg hjemme, greier personlig stell. Trenger varierende grad av hjelp.	70%	Klarer seg selv, ute av stand til normal aktivitet aller aktivt arbeid.
	60%	Trenger noe hjelp, men klarer stort sett å tilfredstille egne behov.
	50%	Trenger betydelig hjelp og stadig medisinsk omsorg.
Ute av stand til å greie seg selv. Avhengig av pleie. Sykdommen i progresjon.	40%	Ufør, trenger spesiell hjelp og omsorg.
	30%	Helt ufør, hospitalisering nødvendig, men fare for død er ikke overhengende.
	20%	Svært syk, hospitalisering og understøttende behandling nødvendig.
	10%	Moribund, dødsprosessen er i rask fremmarsj.
	0%	Død

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 AND 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.
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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.
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40. Kjell-Arne Rein: THE EFFECT OF EXTRACORPOREAL CIRCULATION ON SUBCUTANEOUS TRANSCAPILLARY FLUID BALANCE.
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42. Carl Bredo Dahl: ANIMAL MODELS IN PSYCHIATRY.

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44. Rolf A. Walstad: CEFTAZIDIME.
45. Rolf Salvesen: THE PUPIL IN CLUSTER HEADACHE.
46. Nils Petter Jørgensen: DRUG EXPOSURE IN EARLY PREGNANCY.
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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.

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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.
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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.

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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.

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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.
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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.

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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.
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87. Piotr Kruszewski: SUNCT SYNDROME WITH SPECIAL REFERENCE TO THE AUTONOMIC NERVOUS SYSTEM.
88. Mette Haase Moen: ENDOMETRIOSIS.
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90. Lars Jacob Stovner: THE CHIARI TYPE I MALFORMATION.
91. Kjell Å. Salvesen: ROUTINE ULTRASONOGRAPHY IN UTERO AND DEVELOPMENT IN CHILDHOOD.

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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.
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103. Unni Syversen: CHROMOGRANIN A. Phsysiological and Clinical Role.

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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.

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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 CANCER.
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.

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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.

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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.
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138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.
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140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

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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.
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150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
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156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

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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.

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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
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183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
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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
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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

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201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
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