Pål Gjerden

The use of anticholinergic antiparkinson agents in Norway

Epidemiology, toxicology and clinical implications

Thesis for the degree of Doctor Philosophiae

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Norwegian University of Science and Technology
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Bruk av antikolinerge antiparkinsonmedikamenter i Norge.
Epidemiologi, toksikologi og kliniske konsekvenser.

Pål Gjerden

På slutten av 1990-tallet oppdaget vi at legemidlet orfenadrin, markedsført i Norge under navnet Disipal©, foruroligende ofte forårsaket forgiftningsdødsfall. Orfenadrin tilhører en gammel og lite påaktet gruppe medikamenter, antikolinerge antiparkinsonmedikamenter, som opprinnelig ble brukt i behandling av Parkinsons sykdom. I to artikler i Tidsskrift for den norske legeforening advarte vi mot bruken av dette medikamentet. Etter advarselen gikk salget ned i Norge. Det var ingen tilsvarende reduksjon i Sverige og Danmark, noe som kan tyde på at advarselen i fagtidsskriftet hadde effekt på legers forskrivningspraksis. Orfenadrin ble trukket fra det skandinaviske markedet i 2005, men er fortsatt tilgjengelig i store deler av verden.

Ved hjelp av data fra Reseptregisteret har vi i ettertid vist at antikolinerge antiparkinsonmedikamenter nå i all hovedsak brukes sammen med antipsykotiske legemidler, og at bruken av antikolinerge midler kan indikere forekomst av en spesiell type alvorlige bivirkninger forårsaket av slike antipsykotiske medisiner. Vi brukte denne sammenhengen for å undersøke hvilke spesifikke antipsykotiske medisiner som var tryggest å bruke. Denne tilnærmingsmåten for å vurdere legemiddelsikkerhet er på mange måter ny. Det er blitt påstått at nyere antipsykotika gir færre bivirkninger enn eldre. Vi fant stor variasjon mellom de ulike antipsykotika, men ingen systematiske forskjeller mellom eldre og yngre midler mht. sambruk med antikolinerge antiparkinsonmidler. Påstanden om at nyere antipsykotika har en generelt bedret bivirkningsprofil synes primært å dreie seg om markedsføring.

Vi ønsket også å vurdere risiko for bivirkninger ved å se på hvilke medikamenter som ble foretrukket over tid. Vi antok at langtidsbruk av medisiner betyr at pasientene er fornøyde, enten fordi de opplever god virkning eller lite bivirkninger eller begge deler. Klozapin (Leponex©) og zuclopentixol (Cisordinol©) var de antipsykotiske medisinene som var hyppigst i kontinuerlig bruk over tre år. Vi fant en høy grad av sambruk av zuclopentixol og antikolinerge medikamenter. En forklaring kan være at effekten av zuclopentixol ble oppfattet som så god at det veide opp for bivirkningene. En slik måte å vurdere medikamenteffekt på har heller ikke vært gjort tidligere. Et overraskende og bekymringsfullt bifunn var at bruk av haloperidol (Haldol©) var assosiert med betydelig overdødelighet.

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1. Overview

1.1 Summary

This thesis is based on two fundamental questions: Which patients are currently using anticholinergic antiparkinson drugs? Does it matter which anticholinergic antiparkinson drug they are using? These questions were further investigated, using a variety of methods, as follows:

Are anticholinergic antiparkinson agents predominantly used to treat Parkinson's disease or antipsychotic induced extrapyramidal side-effects (EPS)?

Is there a high risk of abuse of anticholinergic antiparkinson agents?

Can alleged differences in receptor binding profiles of typical first- (FGA) and atypical second (SGA) -generation antipsychotic agents predict concomitant use of anticholinergic agents?

Can long-term co-prescription of anticholinergic antiparkinson agents shed some light on the efficacy of antipsychotic agents?

Does the literature indicate differences in toxicity and fatality rates of anticholinergic antiparkinson agents? Does an autopsy material indicate differences between anticholinergic agents regarding toxicity and fatality risk?

Are warnings in a medical journal against the use of the most toxic anticholinergic agent enough to reduce its use?

Can patients stop using anticholinergic agents without further remedies?

The thesis has the following conclusions:

The overwhelming majority of anticholinergic users were patients concomitantly using antipsychotic agents, presumably for the alleviation of antipsychotic induced EPS. The use of anticholinergics was not particularly skewed and we could not find any other indication of abuse, indicating that concomitant use of anticholinergics can be a proxy for the liability of specific antipsychotic agents to cause EPS.

For patients using only one antipsychotic agent, the concurrent use of anticholinergics varied between 0.4% and 26.0%, but largely independently of the distinction between typical and atypical antipsychotics. High D_2-receptor antagonism and a high 5-HT_{2A}/D_2-receptor-affinity ratio coincided with the use of anticholinergics.

Clozapine and zuclopentixol demonstrated the highest level of prescription persistence in a three-year period. The high prevalence of concomitant use of anticholinergics and zuclopentixol may indicate that the latter was considered efficacious enough to outweigh its probable side-effects. Haloperidol was associated with a mortality three times that of any other antipsychotic agent in the study.

Orphenadrine is by far the most toxic anticholinergic antiparkinson agent with a high mortality risk. Warnings in a medical journal against the use of a toxic drug can have an impact on prescription patterns.

At least one-third of the patients using anticholinergic antiparkinson agents do not need them.

1.2 List of papers

Paper 1:
Gjerden P, Bramness JG, Slørdal L: The use and potential abuse of anticholinergic antiparkinson drugs in Norway. A pharmacoepidemiological study. British Journal of Clinical Pharmacology, 2008; 67(2), 228-233.

Paper 2:
Gjerden P, Slørdal L, Bramness JG: Association between the use of anticholinergic antiparkinson drugs and safety and receptor drug-binding profiles of antipsychotic agents. European Journal of Clinical Pharmacology, 2009; 65(12): 1229-1235.

Paper 3:
Gjerden P, Slørdal L, Bramness JG: Prescription persistence and safety of antipsychotic medication: a national registry-based three-year follow-up. European Journal of Clinical Pharmacology, 2010; 66: 911-917.

Paper 4:
Gjerden P, Slørdal L: Antikolinerge antiparkinsonmedikamenters kliniske farmakologi. En oversikt med vekt på akutt toksisitet. Tidsskrift for Den norske lægeforening, 1998; 118: 53-55.

Paper 5:
Gjerden P, Engelstad KS, Pettersen G, Slørdal L: Dødsfall forårsaket av antikolinerge antiparkinsonmedikamenter. Analysefunn i et nasjonalt 11-årsmateriale. Tidsskrift for Den norske lægeforening, 1998; 118: 42-44.

Paper 6:
Gjerden P, Bramness JG, Slørdal L: Effect of warnings in a medical journal on the use of orphenadrine. Journal of Evaluation in Clinical Practice, 2008; 14: 615-617.

Paper 7:
Gjerden P, Slørdal L, Bramness JG: The use of antipsychotic and anticholinergic antiparkinson drugs in Norway after the withdrawal of orphenadrine. British Journal of Clinical Pharmacology, 2009; 68(2): 238-242.

1.3 Acknowledgements

This thesis is the conclusion of a task that started an evening 13 years ago when Lars Slørdal and I was discussing anticholinergic antiparkinson agents while nurturing a beer at Oslo Mikrobryggeri. Before this evening I was under the assumption that all anticholinergic antiparkinson agents were equal and of no particular concern, neither to psychiatrists nor their patients. Lars, at that time working at the National Institute of Forensic Toxicology in Oslo, had made a note of some drug-related deaths involving orphenadrine. This triggered our interest in this group of drugs, eventually resulting in this thesis. Without the scientific curiosity and ongoing interest displayed by Lars, this work would never have been done. Thank you, Lars, you are my brother!

Jørgen G. Bramness had read our first articles and found the topic interesting. He was at that time working with the Norwegian Prescription Database at the Norwegian Institute of Public Health in Oslo and saw some interesting possibilities in the use of this database. Thank you, Jørgen, for your enthusiasm, creativity and effectiveness!

I would like to thank Telemark Hospital, Department of Psychiatry, for granting me the time and the facilities I needed to write this thesis. The librarian at Telemark Hospital, Mirjam Håndlykken, has been very helpful. I would also like to thank the staff at ward 1A, in particular Inger T. Asheim, who has been very patient and managed without me for extended periods of time. Finally I thank my wife, Torbjørg Straand, for support and encouragement. Without her, this work would not be worthwhile!

2 General introduction

2.1 Anticholinergic agents

Acetylcholine acts at two different classes of cholinergic receptors, nicotinic ligand-gated ion channels and G-protein-coupled muscarinic receptors. Both confer a wide range of effects in the periphery as well as the central nervous system (1). Acetylcholinesterase inhibitors, used in the treatment of Alzheimer's disease, are the best known modulators of nicotinic receptor function. The class of drugs called anticholinergic agents acts as competitive antagonists at muscarinic receptors only and should more precisely be named antimuscarinic agents. However, the term anticholinergic agents is the term used in the official nomenclature of World Health Organization (WHO) and is thus adopted throughout this thesis (2).

Anticholinergic agents have been known in many cultures for thousands of years. The prototype of the muscarinic antagonists, atropine, is naturally occurring in *Atropa belladonna* and several other members of the *Solanaceae* genus of plants (1). These naturally occurring anticholinergic agents have been used for a variety of reasons through history. The term *belladonna* refers to the beautiful women of Italy who considered the mydriatic effect aesthetically desirable.

The first man-made anticholinergic agents were introduced in 1946, trihexyphenidyl/benzhexol and biperiden followed by procyclidine, benztropine and, lastly, orphenadrine in 1951 (3-10). The effect conferred by these agents on Parkinson's disease and neuroleptic-induced parkinsonism is assumed to be mediated by reducing the imbalance between cholinergic and dopaminergic activity in nigrostriatal neurons. Orphenadrine confers a wide range of effects in addition to muscarinic blockade (11).

2.2 Parkinson's disease

James Parkinson published "An essay on the shaking palsy" in 1817. Although incomplete, this was the first description of a clinical condition that Jean-Martin Charcot half a century later named "maladie de Parkinson". The medically correct term *paralysis agitans* has never been as popular in clinical use as *Parkinson's disease*. First thought to be a nosological entity, its heterogeneity makes it more correct to use the term Parkinson's syndrome instead of Parkinson's disease. The classic symptoms tremor, rigidity and bradykinesia are assumed to find their primary neurological substrate in the loss of dopaminergic neurons in the nigrostriatal pathway, although the pathogenetic process behind this deficiency may vary (12-14).

The first medicinal intervention was the administration of extract from *Atropa belladonna* in 1867. From the late 1940s onwards synthesized anticholinergic agents came into extensive use. Until the development of L-dopa in the early 1960s, they were the mainstay of Parkinson's disease treatment (12). The medical treatment of Parkinsons' disease has made further progress since then (15).

2.3. Parkinsonism

Before antipsychotic agents came into use the terms Parkinson's disease and parkinsonism were used synonymously. Following the introduction of chlorpromazine in 1952, the propensity of antipsychotic agents to induce parkinsonian symptoms was recognized and eventually named parkinsonism (drug-induced parkinsonism), as a entity different from, but mimicking, Parkinson's disease (idiopathic parkinsonism). At first it was regarded as a clinical manifestation of the desirable pharmacological action and it took many years before it was considered an undesirable

adverse effect. Sedation, anticholinergic effects and hypotension were the acknowledged side-effects of the early low-potency agents and it was not until the introduction of the more potent and specific D_2 receptor antagonists, culminating with the synthesis of haloperidol in 1958, that parkinsonian adverse effects were recognized as a major problem. Eventually, drug-induced parkinsonism came to be considered the most serious hindrance for the use of antipsychotic agents and a diminished liability to promote parkinsonism became the main argument in the endeavour to define a new generation of antipsychotics (16).

The first - some would say the only - atypical antipsychotic agent was clozapine, demonstrating virtually no parkinsonian side-effects. Clozapine was marketed from the early 1970s, withdrawn because of its significant haematological toxicity and reintroduced in the 1990s because of its unique efficacy. In a quest to replicate the efficacy and lack of abnormal motor symptoms demonstrated by clozapine, avoiding its haematological side-effects, a number of novel atypical antipsychotic agents have been synthesized in the last decade (17).

Abnormal motor symptoms caused by antipsychotic agents are usually named extrapyramidal side-effects (EPS) and most often sub-divided into acute dystonia, parkinsonism and akathisia, thus defining tardive dyskinesia as an entity of its own. Some authors, however, include tardive dyskinesia as an EPS. In clinical practice, the terms EPS and parkinsonism are often used as synonyms, while akathisia and tardive dyskinesa are described as separate entities. Acute dystonia, being an acute condition, is mostly confined to hospitalized patients and should have little bearing on any of the papers that constitute this thesis.

2.4 Efficacy and effectiveness

The terms efficacy and effectiveness are frequently used in the medical literature. Seemingly similar in meaning, they express different concepts. The term efficacy refers to the question if a treatment works under ideal condition, the randomized controlled trial (RCT) being the archetypal example. The term effectiveness refers to the question if the treatment works in everyday life. If the treatment does more harm than good to the patient, possibly because of bothersome side-effects, the treatment might be rejected and is thus ineffective although it may be efficacious (18). There has been a growing difficulty in translating the results of RCTs into clinical practice concerning the clinical usefulness of old and newer antipsychotic agents (19).

3 Introduction to the present study

3.1. Epidemiology

The use of anticholinergic agents in Parkinson's disease has been in decline, at least in the industrialized countries of the world, but its use is not altogether obsolete (20). The low cost incurred by its use is probably the reason for the not insignificant use of these drugs against Parkinson's disease worldwide. In Norway, the use of anticholinergic agents was assumed to be largely confined to treating antipsychotic induced side-effects. This assumption had, however, not been formally investigated. Paper 1 delineates the prevalence and indication of use of anticholinergic antiparkinson drugs in Norway and investigates possible abuse of these drugs. The users of anticholinergic antiparkinson drugs are further scrutinized in Paper 2, assessing the concomitant use of anticholinergic and antipsychotic agents.

3.1.1. Clinical implications

The prevalence of antipsychotic induced EPS has been much debated. Second-generation antipsychotic agents (SGAs) have been claimed to confer a much lower risk of inducing EPS than first-generation antipsychotics (FGAs). This notion has been challenged in the last few years, in the wake of two large clinical studies that failed to demonstrate any difference between FGAs and SGAs in this respect (21, 22). A confounding factor is that almost all studies of drug-induced EPS have been carried out with schizophrenic patients, a group of patients with an inherent tendency of developing both parkinsonism and tardive dyskinesias even in the absence of antipsychotic agents.

We found that the overwhelming majority of anticholinergic antiparkinson drugs were used concomitantly with antipsychotic agents,

presumably for the amelioration of antipsychotic induced EPS. We could not find indications of a skewed use of anticholinergic drugs. Consequently we assumed that concomitant use of anticholinergics might reflect perceived EPS and that concomitant use of anticholinergics could be used as a proxy for antipsychotic induced EPS. In particular we investigated potential differences between FGAs and SGAs. Paper 2 focuses on differences in the liability of antipsychotic agents to cause EPS and explores some pharmacodynamic differences between FGAs and SGAs.

If doctors and patients stick to a single antipsychotic agent for years, one might assume that both efficacy and lack of side-effects is considered satisfactory and that the drug has demonstrated effectiveness. In addition to assessing prescription persistence as a proxy for the real-life effectiveness of antipsychotic agents, Paper 3 compares concomitant prescription of anticholinergic antiparkinson agents and mortality as indicators of safety of antipsychotic agents. In addition, long-term concomitant prescription of antipsychotic and anticholinergic agents is used in an indirect evaluation of the efficacy of some of the antipsychotic agents in the study.

3.2. Toxicology

Anticholinergic antiparkinson agents constitute a very old class of drugs. They were introduced at a time when preclinical trials were less comprehensive than today and pharmacokinetics and metabolism were scantily described before marketing. This is still the case. Scattered case-reports have been published but, to our knowledge, no review that deals comprehensively with the toxicology of anticholinergic antiparkinson drugs. Standard psychiatric textbooks do not differentiate between the various anticholinergics. Paper 4 is a review of the clinical pharmacology of the three anticholinergic antiparkinson drugs marketed in Norway at the time of the study, with emphasis on acute toxicity. Paper 5 is a study

of a series of fatalities caused by anticholinergic antiparkinson drugs in Norway in an 11-year period.

3.2.1. Clinical implications

The toxicology of anticholinergic antiparkinson agents is not the same. The results from Papers 4 and 5 indicate that orphenadrine stands out from the rest, being responsible for a disproportionately large number of overdose deaths. Consequently, in Paper 5 we warned against the use of orphenadrine. Journal reading is probably the most popular form of continuous medical education but it is difficult to demonstrate an effect on doctors' professional behaviour (23, 24). Studies reporting positive effect of passive educational initiatives are very scarce (25). Paper 6 examines whether warnings in a medical journal against the use of orphenadrine had any effect on the sales of this compound in Norway.

Eventually, orphenadrine was withdrawn from the Scandinavian market. Paper 7 focuses on the consequences for the patients when they stopped using orphenadrine, regarding the use of anticholinergic and antipsychotic agents.

4 Research questions

This work elaborates on two basic questions: Which patients are presently using anticholinergic antiparkinson drugs? Does it matter which anticholinergic antiparkinson drug they are using?

The respective answers to these questions consequently led to the following research questions that this thesis aims to answer:

1. It is assumed that the use of anticholinergic antiparkinson agents today is mainly confined to the alleviation of antipsychotic induced EPS. Is this assumption correct? This question is dealt with in Paper 1.
2. The reported risk of abuse of anticholinergic antiparkinson agents varies considerably in the literature. Is there a high risk of abuse of these drugs? This question is also dealt with in Paper 1.
3. The reported prevalence of antipsychotic induced EPS differs significantly in the literature. In particular, newer studies have questioned the alleged diminished liability of the atypical second-generation antipsychotics to induce EPS. Is the prevalence of drug-induced EPS the same for all antipsychotic agents? Is there a difference between FGAs and SGAs in this aspect? Can alleged differences in receptor binding profiles of FGAs and SGAs predict concomitant use of anticholinergic agents? Paper 2 deals with these questions.
4. Paper 3 deals with prescription persistence and safety, including mortality, associated with antipsychotic medication. Are there any differences between the various antipsychotics? Can concomitant use of anticholinergic agents help differentiate efficacy from perceived side-effects as possible reasons for long-term prescription persistence of antipsychotic agents?

5. What does the literature tell us about the toxicity and fatality risk of anticholinergic antiparkinson drugs? Do these drugs differ from each other in this aspect? Paper 4 deals with this question.
6. Are there differences in toxicity between anticholinergic antiparkinson agents in a Norwegian autopsy material? This question is dealt with in Paper 5.
7. Papers 4 and 5 delineate orphenadrine as a drug quite different from the rest of the anticholinergic antiparkinson agents, carrying a significantly higher risk of death than any other anticholinergic agent. Will a warning against the use of orphenadrine result in a decline of the use of this drug? Paper 6 deals with this question.
8. Can patients stop using orphenadrine or other anticholinergic antiparkinson drugs when they have to, without reducing antipsychotic dosage, switching antipsychotic agent or replacing one anticholinergic agent with another? Paper 7 deals with these questions.

5 Material and methods

5.1 Design

Papers 1, 2, 3 and 7 are pharmacoepidemiological studies. Paper 4 is a literature review while Paper 5 is a retrospective study of a series of autopsy cases. Paper 6 is a naturalistic study with case-control elements.

5.2 Material

Papers 1, 2, 3 and 7 are based on the Norwegian Prescription Database (NorPD) which covers sales of drugs to the entire Norwegian outpatient population from 2004. Paper 4 is based on an extensive literature search in various databases. The basis for Paper 5 is autopsy samples received at the National Institute of Forensic Toxicology during the years 1986 – 1996. Paper 6 compares drug sales to the entire Norwegian, Swedish and Danish outpatient population as reported to the national health authorities.

5.3 Methods

Papers 1, 2, 3 and 7 uses one-year prevalence as the basic measure and collects standard pharmacoepidemiological data from NorPD for this period of time. In addition to standard epidemiological calculations, we also found Lorenz curves and Gini coefficients useful in the evaluation of possible drug abuse in Paper 1. Paper 2 extracts antipsychotic receptor profiles from a previously published external source. Paper 6 uses standard epidemiological data and calculations.

5.4 Statistics

The main statistical methods used in the present analyses are simple frequency analyses performed in SPSS 15.0 using Pearson's chi-square (χ^2) test for the assessment of significance. In addition, Spearman's rank correlation coefficient (σ) was used in Paper 2 and binary logistic regression analyses with odds ratios were performed in Paper 3.

6 Results

6.1 Paper 1.

The use and potential abuse of anticholinergic antiparkinson drugs in Norway. A pharmacoepidemiological study.

Pål Gjerden, Jørgen G. Bramness, Lars Slørdal

British Journal of Clinical Pharmacology 2008; 67(2): 228-233

The use of anticholinergic antiparkinson drugs is assumed to have shifted from the therapy of Parkinson's disease to the amelioration of extrapyramidal adverse effects induced by antipsychotic drugs. There is a considerably body of data suggesting that anticholinergic antiparkinson drugs have a potential for abuse. The aim was to investigate the use and potential abuse of this class of drugs in Norway.

Data were drawn from the Norwegian Prescription Database on sales to a total of 73 964 patients in 2004 of biperiden and orphenadrine, and use in patients with Parkinson's disease or in patients who were also prescribed antipsychotic agents. Possible abuse of these drugs was assessed by the level of use, skewedness of use, indications of drug-seeking behaviour and concomitant use of benzodiazepine tranquillizers, a group of drugs with a recognized potential for abuse.

Patients using antipsychotic medication accounted for 94% of the use of anticholinergics, compared with 4.3% with Parkinsons'disease. We found indications of abuse of benzodiazepine tranquillizers among patients using antipsychotics, but there were no clear indications of abuse of anticholinergics, even among patients who were strongly suspected of abuse of bezodiazepines.

Anticholinergic antiparkinson drugs were primarily used by patients with psychotic illnesses. These patients have a very high prevalence of legal and illegal drug abuse, but the risk of abuse of anticholinergic antiparkinson drugs seemed small.

6.2 Paper 2

Association between the use of anticholinergic antiparkinson drugs and safety and receptor drug-binding profiles of antipsychotic agents

Pål Gjerden, Lars Slørdal, Jørgen G. Bramness

European Journal of Clinical Pharmacology 2009; 65(12): 1229-1235

The use of anticholinergic antiparkinson drugs is almost exclusively confined to treating antipsychotic-induced extrapyramidal side-effects (EPS). We investigated the prevalence of concomitant prescription of anticholinergics as a proxy for antipsychotic-induced EPS and compared variance in prevalence with differences in the assumed mechanisms of action of antipsychotics on central nervous system (CNS) transmitter systems (i.e., receptor drug-binding profiles). We paid special attention to potential differences between typical and atypical antipsychotics.

Data were drawn from the Norwegian Prescription Database on sales of antipsychotic and anticholinergic antiparkinson drugs to a total of 57 130 outpatients in 2004. We assessed concomitant dispensations of antipsychotic and anticholinergic drugs and correlated the prevalence of concomitantly prescribed anticholinergics to previously assessed receptor-binding profiles of antipsychotics.

The concurrent use of anticholinergics varied between 0.4% and 26.0% for patients using a single antipsychotic agent. The prevalence of anticholinergic comedication was more than twice as high in patients using two or more antipsychotic drugs. Four typical antipsychotics (fluphenazine, zuclopentixol, haloperidol and perphenazine) were associated with higher concomitant use of anticholinergics than the rest. For the remaining 14 antipsychotic agents, the difference between typical and atypical antipsychotics was neither pronounced nor systematic. A

high degree of D_2-receptor antagonism and a high 5-HT_{2A}/D_2-receptor-affinity ratio coincided with the use of anticholinergics.

The liability of antipsychotic drugs to cause EPS seemed to vary considerably and largely independently of the distinction between typical and atypical antipsychotics.

6.3 Paper 3.

Prescription persistence and safety of antipsychotic medication: a national registry-based three-year follow-up

Pål Gjerden, Lars Slørdal, Jørgen G. Bramness

European Journal of Clinical Pharmacology 2010; 66: 911-917

Long-term persistence of use, lack of co-prescribed anticholinergic antiparkinson drugs and low mortality may indicate effectiveness and safety of antipsychotic drugs. We aimed to assess three-year prescription persistence, concomitant use of anticholinergic antiparkinson agents and mortality related to the use of all antipsychotic agents available in Norway.

Data were drawn from the Norwegian Prescription Database on the sales of antipsychotic and anticholinergic antiparkinson agents in 2004 to a total of 52 427 patients. The primary study group was a subgroup of 34 494 patients who were prescribed only one antipsychotic agent in 2004. The patients were re-investigated in 2007. For each of the 13 antipsychotic agents studied, assumed prescription persistence was assessed in light of use of anticholinergic antiparkinson agents in 2004 and casualty rates were noted.

The highest persistence was demonstrated by zuclopenthixol (69.8%) and clozapine (88.4%). Zuclopenthixol was often co-prescribed with anticholinergics (22.2%), in contrast to clozapine (3.6%). Ziprasidone was associated with a low mortality (OR=0.08), while chlorprotixene and haloperidol were associated with a high mortality (OR=1.34 and 3.97, respectively) compared to levomepromazine.

Clozapine demonstrated a high degree of continuity of prescription and a low level of concomitant use of anticholinergics. Zuclopenthixol also demonstrated a high degree of continuity of prescription, despite a considerable degree of co-prescribed anticholinergics. We did not find that any other antipsychotic than ziprasidone was associated with a low mortality. The use of haloperidol seemed to confer a mortality risk three times that of any of the other antipsychotic agents included.

6.4 Paper 4.

The clinical pharmacology of anticholinergic antiparkinson drugs: a review with emphasis on acute toxicity

Pål Gjerden, Lars Slørdal

Tidsskrift for Den norske lægeforening 1998; 118: 53-55

Anticholinergic antiparkinson drugs are primarily used to ameliorate extrapyramidal side-effects induced by neuroleptic agents. In 1998 orphenadrine dominated quantitatively among these drugs in Norway, presumably because it was assumed to carry a lower risk of abuse.

There are numerous reports of deaths following orphenadrine overdoses. Orphenadrine has complex pharmacokinetic properties and a narrow therapeutic index. After an overdose, it confers toxic effects of rapid onset to several organ systems. No specific and effective therapy for orphenadrine intoxications has been established. For the two other drugs in this class which were marketed in Norway at this time, biperiden and benztropine, toxicity is mainly connected to their anticholinergic properties. Notably, no reports of lethalities after overdoses of biperiden seem to be available. A small number of accounts of deaths following benztropine intoxications have been published. Neither of these two agents, and benztropine in particular, has been subjected to comprehensive pharmacokinetic evaluations.

The relatively extensive use of orphenadrine should be discouraged.

6.5 Paper 5.

Fatalities caused by anticholinergic antiparkinson drugs: a retrospective study of a series of Norwegian cases

Pål Gjerden, Karen Sofie Engelstad, Grete Pettersen, Lars Slørdal

Tidsskrift for Den norske lægeforening 1998; 118: 42-44

All autopsy samples received at the National Institute of Forensic Toxicology during the years 1986-1996 which contained anticholinergic antiparkinson drugs were reviewed. Of a total of 69 cases, orphenadrine was present in 57 (83%), biperiden in 8 (12%), procyclidine in 3 (4%) and trihexyphenidyl/benzhexol in 1 (1%) of the subjects. The measured concentrations were assessed in light of previously published data. Of 21 cases where causality between drug ingestion and death was classified as either highly probable (18/21) or possible (3/21), all subjects tested positive for orphenadrine. In the autopsy samples from these patients, orphenadrine concentrations in the 4.5 – 600 μmol/l range (mean 62.5 μmol/l, SD 126.5 μmol/l) were determined. Because of a low national autopsy rate, there is reason to believe that the actual numbers of drug-related deaths in this period may have been significantly higher.

It is concluded that orphenadrine is responsible for a disproportionately high number of overdose deaths.

6.6 Paper 6.

Effect of warnings in a medical journal on the use of orphenadrine

Pål Gjerden, Jørgen G. Bramness, Lars Slørdal

Journal of Evaluation in Clinical Practice 2008; 14: 615-617

The effect of journal reading on doctors' professional behaviour has not been extensively studied. We have tried to assess the impact of a warning against the use of orphenadrine published in an extensively circulated Norwegian medical journal.

Based on evidence of excessive toxicity we published a warning against the use of orphenadrine in the Journal of the Norwegian Medical Association in 1998. There were no such initiatives in neighbouring Scandinavian countries. Yearly sales data for orphenadrine in Norway were compared to sales data from Sweden and Denmark before and after this warning.

Sales data showed a steeper decline in the prescription of orphenadrine in Norway compared to Sweden and Denmark from the time of intervention in 1998 until the drug was withdrawn from the Scandinavian market in 2005.

The results of the media alert support the assumption that professional initiatives in a medical journal may alter established prescription practice.

6.7 Paper 7.

The use of antipsychotic and anticholinergic antiparkinson drugs in Norway after the withdrawal of orphenadrine

Pål Gjerden, Lars Slørdal, Jørgen G. Bramness

British Journal of Clinical Pharmacology 2009; 68(2): 238-242

Extrapyramidal side-effects induced by antipsychotic drugs are treated with dose reduction or substitution with another antipsychotic drug or by the addition of anticholinergic antiparkinson agents. The withdrawal of orphenadrine from the Norwegian market provided a possibility to investigate to what degree these alternative measures were taken in clinical practice.

Data were drawn from the Norwegian Prescription Database on the sales of antipsychotics and one of the two anticholinergic antiparkinson agents marketed in 2004, orphenadrine and biperiden, to a total of 39 758 outpatients. These patients were reinvestigated in 2007. The consequences of the withdrawal of orphenadrine from the Norwegian market in 2005 regarding dosing, switching and cessation of antipsychotics and use of anticholinergics were assessed for orphenadrine users compared with biperiden users.

Of the patients originally using orphenadrine, 28.4% stopped using the drug without reducing the antipsychotic dose or replacing orphenadrine with another anticholinergic agent. The corresponding number for biperiden users was 19.3%. Only 11.8% of patients switched to another antipsychotic drug, but they used significantly lower antipsychotic doses than those who stayed on the same drug.

The use of anticholinergic antiparkinson agents could be seen as superfluous for at least one-third of the patients.

7 Discussion

7.1 Methodology

This thesis employs a variety of scientific methods. Four of the papers are pharmacoepidemiological studies. Pharmacoepidemiology is the study of the use of and the effects of drugs in large numbers of people (26). It is a relatively new applied field and from the beginning has primarily concerned itself with the study of adverse drug effects, in particular drug effects that are uncommon, not dose-related and unpredictable. Preclinical toxicity testing has been mandatory for medicinal drugs since the 1938 Food, Drug, and Cosmetic Act was passed in the US. Drug surveillance programs were developed in the 1950s but it was the "Thalidomide disaster" of the early 1960s that demonstrated that epidemiological methods could make significant contributions to the study of drug effects in humans. The teratogenicity of thalidomide was only revealed a number of years after the compound had been introduced as a harmless drug for treating insomnia and morning sickness in pregnant women.

Premarketing studies of drug effects are limited in size and time, usually include homogenous groups of subjects, exclude important subgroups and are most often compared to placebo instead of the best available drugs for the same indication. Postmarketing pharmacoepidemiological studies are much larger, include patients not studied prior to marketing, include patients using other drugs, can discover uncommon or delayed effects and can assess much larger numbers of drugs.

The Norwegian Prescription Database contains information on all drugs filled by individual patients living outside institutions in

Norway from 1 January 2004, covering the entire population of 4.6 million inhabitants. The magnitude and completeness of this database makes it rather unique.

The remaining three studies employ other methods. The literature review of orphenadrine in Paper 4 seems to be the first of its kind since 1982 (27). Several highly relevant papers dealing with orphenadrine have been published in non-indexed, non-English journals, including Dutch periodicals. This may partly explain why orphenadrine has been on the market world-wide for so long, and still is.

7.2 Main results

This thesis reports on the use as well as the qualities of anticholinergic agents. In some aspects it also transcends anticholinergic agents by evaluating antipsychotic agents, both as a class and as individual drugs.

The thesis reports a number of strictly epidemiological findings concerning the users of anticholinergic antiparkinson agents and the selection of anticholinergic agents following warnings in a medical journal and restrictions in availability. It argues that at least one third of the use of anticholinergics is superfluous.

In addition, the thesis seems to allow drawing certain conclusions regarding the innate qualities of anticholinergic agents: The risk of abuse of anticholinergics is low. Toxicity and mortality differs significantly within this class of drugs and orphenadrine stands out as a particularly toxic drug.

The most original contributions made by this thesis are the results that transcend anticholinergic agents: The liability of specific

antipsychotic agents to cause EPS can be compared by the concomitant use of anticholinergics. The concurrent use of anticholinergics demonstrates that the classification of antipsychotic agents as typical first-generation or atypical second-generation does not correspond with the alleged criteria for this classification. Concomitant use of anticholinergics in long-term antipsychotic medication may even be a contributory factor for the evaluation of the efficacy of specific antipsychotic agents, not only their effectiveness.

The disproportionately high mortality confined to long-term prescription of haloperidol must be considered an important but chance finding, a finding supported by other studies but not explained.

7 Conclusions

In Norway in 2004 an overwhelming majority of the anticholinergic users were patients concomitantly using antipsychotic agents. We assumed that the reason for this use was EPS induced by antipsychotic drugs and the presumed alleviation of these symptoms by anticholinergic drugs.

We also found that the use of anticholinergic agents was not very skewed and we did not find any other indications of abuse of anticholinergic agents.

The lack of skewedness, together with the narrow indication for the use of these drugs, instigated the possibility of using the prevalence of concomitantly prescribed anticholinergics as a proxy for the prevalence of the respective antipsychotic agents' liability to cause EPS. The exact prevalence could not be estimated, but the relative risk of each antipsychotic drug to cause EPS compared to the corresponding risk of other antipsychotics should be fairly accurately assessed.

The prevalence of drug-induced parkinsonism varied significantly, but largely independently of the classification of an antipsychotic drug as either FGA or SGA.

Long-term prescription persistence of a specific antipsychotic agent can be a proxy for its effectiveness. Concomitant use of anticholinergic antiparkinson drugs can be a proxy for antipsychotic induced EPS. Comparing long-term use of both antipsychotic and anticholinergic agents may indirectly be used in the evaluation of the efficacy of antipsychotic agents.

The literature clearly demonstrates a difference between the various anticholinergics regarding toxicity and mortality. When we retrospectively studied a series of fatality cases the finding was the same, namely that orphenadrine had been causing a disproportionately high number of deaths compared to the other anticholinergic agents.

When we warned against the use of orphenadrine in Norway, the use declined significantly compared to Sweden and Denmark.

When orphenadrine was withdrawn from the market and the patients had to stop using this drug, one third of them managed to do so without reducing antipsychotic dosage, switching antipsychotic agent or using another anticholinergic agent. At least one third of the patients using anticholinergic agents probably did not need them.

A surprise finding was that every fourth patient being prescribed haloperidol was dead in three years. Haloperidol was associated with a mortality three times that of any of the other antipsychotic agents included in the study.

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10 Appendices

Paper I

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Paper II

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Paper III

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Paper IV

Særtrykk av Tidsskrift for Den norske lægeforening nr. 1/1998

Antikolinerge antiparkinsonmedikamenters kliniske farmakologi

En oversikt med vekt på akutt toksisitet

Antikolinerge antiparkinsonmidler brukes i dag primært for å behandle neuroleptikainduserte ekstrapyramidale bivirkninger. Orfenadrin dominerer dette markedet i Norge. En mulig årsak kan være at medikamentet er blitt antatt å ha mindre misbrukspotensial enn de andre medikamentene i denne gruppen.

Det finnes mange rapporter om dødsfall knyttet til overdoser av orfenadrin i litteraturen. Medikamentets terapeutiske indeks er relativt lav. Overdoser affiserer flere organsystemer, og symptomene utvikler seg raskt. Det finnes ingen spesifikk og effektiv behandling for orfenadrinintoksikasjoner. Orfenadrin har i tillegg farmakokinetiske egenskaper som må antas å kunne komplisere den kliniske bruken ytterligere.

For de to andre medikamentene i denne gruppen, biperiden og benztropin, er toksisiteten knyttet til deres antikolinerge egenskaper. Vi har ikke funnet beskrivelser av dødsfall knyttet til overdoser av biperiden i tilgjengelig litteratur. Det finnes et lite antall beskrivelser av dødsfall etter overdoser av benztropin. Verken biperiden eller benztropin synes å ha vært gjenstand for farmakokinetiske studier, og særlig benztropin er mangelfullt beskrevet.

Den relativt omfattende bruken av orfenadrin bør begrenses.

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The clinical pharmacology of anticholinergic antiparkinsonian drugs: a review with emphasis on acute toxicity

Tidsskr Nor Lægeforen 1998; 118: 53–5

Today, anticholinergic antiparkinsonian drugs are primarily used to ameliorate extrapyramidal side-effects induced by neuroleptic agents. Orphenadrine dominates quantitatively among these drugs in Norway, presumably because it is assumed to carry a lower risk of abuse.

There are numerous reports of deaths following orphenadrine overdoses. Orphenadrine has complex pharmacokinetic properties and a narrow therapeutic index. After an overdose, it confers toxic effects of rapid onset to several organ systems. No specific and effective therapy for orphenadrine intoxication has been established. For the two other drugs in this class which are marketed in Norway, biperiden and benztropine, toxicity is mainly connected to their anticholinergic properties. Notably, no reports of lethalities after overdoses of biperiden seem to be available. A small number of accounts of deaths following benztropine intoxication have been published. Neither of these two agents, and benztropine in particular, has been subjected to comprehensive pharmacokinetic evaluations.

The relatively extensive use of orphenadrine should be discouraged.

Antiparkinsonmidler av antikolinerg type er gamle medikamenter som i dag nesten ikke brukes i behandling av Parkinsons sykdom. Det er imidlertid fremdeles en betydelig bruk av disse medikamentene ved neuroleptikaindusert parkinsonisme.

Her i landet er tre slike medikamenter registrert: orfenadrin, biperiden og benztropin. To tilsvarende stoffer, triheksylfenidyl/benzhexol og procyklidin, ble avregistrert etter fabrikantenes ønsker i henholdsvis 1995 og 1996. Blant de gjenværende preparatene er orfenadrin det klart mest brukte i Norge. Forskrivningen av de tre gjenværende preparatene er på ca. 0,5 (orfenadrin), 0,3 (biperiden) og 0,1 (benztropin) definerte døgndoser (DDD)/1 000 innbyggere/døgn. Orfenadrin og benztropin har hatt en viss tilbakegang i salget de siste ti år, mens bruken av biperiden har økt litt i denne perioden.

Orfenadrin har også vært brukt som analgetikum ved tilstander med muskel- og skjelettsmerter (1). Et kombinasjonspreparat som inneholdt orfenadrin og paracetamol, var registrert i Norge under navnet Norgesic frem til 1996.

Denne gruppen antikolinerge medikamenter er ikke blitt underkastet kritiske farmakologiske evalueringer, og synes dessuten å være gjenstand for en noe stemoderlig behandling i farmakologiundervisningen ved våre medisinske læresteder. Stoffgruppen er etter vår mening også ufullstendig omtalt i sentrale håndbøker som Felleskatalogen og Norsk legemiddelhåndbok. I det følgende gis en kortfattet omtale av de registrerte preparatenes kliniske farmakologi, med hovedvekt på stoffenes akutte toksisitet.

Orfenadrin

DDD er 200 mg, men doser opptil 300 mg er ikke uvanlig. Medikamentet er formulert som tabletter inneholdende 50 eller 100 mg orfenadrin. Absorpsjonen etter inntak gjennom munnen er rask og fullstendig. Ca. 30 % av en peroralt inntatt dose er gjenstand for presystemisk metabolisme (first pass effect). Den vesentlige delen av orfenadrins biotransformasjon skjer i leveren. Anslagsvis halvparten av en inntatt dose utskilles i urin som metabolitter, ca. 8 % gjenfinnes umetabolisert i urin, mens resten elimineres via galle og feces. Halveringstiden i plasma/serum etter et enkeltinntak varierer fra 13 til 20 timer (2, 3). Kontinuerlig daglig inntak kan resultere i blodkonsentrasjoner 2–3 ganger høyere enn det man ville predikere ut fra enkeltdoser, og kontinuerlig bruk ledsages av en forlengelse av orfenadrinets halveringstid opp mot 30–40 timer. Det er blitt spekulert i om dette skyldes at orfenadrinmetabolitten N-desmetyl-orfenadrin konkurrerer med morsubstansen om biotransformasjonsenzym(er), slik at orfenadrinets biotransformasjon er gjenstand for såkalt produktinhibering (4). Orfenadrin er et substrat for P450-isoenzymet CYP3A (5), og farmakokinetiske interaksjoner med andre substrater for CYP3A – som blant annet inkluderer noen antiarytmika, anxiolytika, hormoner og cytostatika – er ikke usannsynlig. Orfenadrin er dessuten en inhibitor av P450-enzymet CYP2B6 (6), som blant annet er ansvarlig for biotransformasjonen av nikotin og cellegiften cyklofosfamid. Medikamentet kan i teorien derfor gi opphav til en lang, uforutsigbar og kompleks rekke av farmakologiske interaksjoner.

Doseavhengige bivirkninger av orfenadrin er knyttet til den antikolinerge effekten. Utilsiktede effekter knyttet til antagonistisk virkning på perifere kolinerge re-

septorer inkluderer munntørrhet, mydriasis, akkomodasjonsparese og – særlig ved prostatisme – vannlatingsplager. Ubehandlet trangvinkelglaukom utgjør en absolutt kontraindikasjon mot orfenadrinbehandling. Orfenadrin reduserer tarmmotiliteten, kan forverre pylorusstenose og gi obstipasjon og – i ekstreme tilfeller – paralytisk ileus. Sentralnervøse antikolinerge bivirkninger omfatter konfusjon og hallusinose, som særlig kan ramme eldre pasienter. Antikolinerge medikamenter kan gi en viss ruseffekt, og det er blitt påstått at orfenadrin har mindre misbrukspotensial enn de andre antikolinerge antiparkinsonmidlene (7). Doseuavhengige bivirkninger synes ikke å være rapportert.

Ved litteraturgjennomgang har vi funnet rapporter om mer enn 60 dødsfall knyttet til overdoser med orfenadrin (3, 8–16). Ytterligere 21 dødsfall beskrives i et norsk materiale (17). Letal dose ved akutt forgiftning er anslått til 2–3 g (13). Andre forfattere oppgir 22 mg/kg for voksne og 72 mg/kg for barn som potensielt dødelige doser (11). Regulær terapeutisk bruk av orfenadrin er assosiert med plasmakonsentrasjoner i størrelsesorden 0,3–0,7 µmol/l (17). Orfenadrinindusert toksisitet er angitt å inntre ved blodkonsentrasjoner rundt 7 µmol/l (8, 18). Rettstoksikologiske analyser har påvist orfenadrin i konsentrasjoner fra 0,37 til 296 µmol/l i blodprøver tatt ved obduksjon av individer antatt døde av orfenadrinoverdoser (14, 15). Det kan imidlertid reises spørsmål ved den analytiske nøyaktighet som ligger til grunn for noen av disse rapportene (15). I oversiktsarbeider er nedre grense for letale blodkonsentrasjoner anført å være 13,4 µmol/l (19) og 14,8 µmol/l (8, 18).

Ved analyser av i alt 18 tilfeller hvor dødsårsaken skyldtes overdoser av enten orfenadrin alene (ti individer) eller i kombinasjon med alkohol eller andre medikamenter, fant Robinson og medarbeidere (14) intracerebrale orfenadrinkonsentrasjoner på ca. 10 % av nivået i fullblod. En vesentlig økning i sentralnervøse orfenadrinnivåer utover disse 10 % kan muligvis indusere intoksikasjonssymptomer i situasjoner hvor blodkonsentrasjonene av medikamentet ikke synes foruroligende høye. Det er imidlertid ikke kjent hvorvidt for eksempel lesjoner i blod-hjerne-barrieren kan endre orfenadrins terapeutiske indeks (20).

Et annet usikkerhetsmoment ligger i muligheten for postmortal redistribusjon av medikamentet. I begrepet ligger at medikamentkonsentrasjoner i blod og andre kroppsvæsker kan endres vesentlig etter at døden er inntrådt, noe som kan vanskeliggjøre tolking av analysefunn i forbindelse med dødsfall. Vi kjenner ikke til at slike fenomener er blitt gjenstand for studier når det dreier seg om dette medikamentet. Målinger av til dels store forskjeller i blodnivåer, avhengig av hvor prøven er tatt, samt forskjeller i orfenadrinkonsentrasjoner mellom høyre og venstre nyre i obduksjonsmateriale, kan gi mistanke om at medikamentet er gjenstand for en signifikant redistribusjon etter døden (14).

Ved lettere overdoser med orfenadrin dominerer de antikolinerge symptomene. Ved mer alvorlige forgiftninger kjennetegnes det kliniske bildet av en generell intoksikasjon med koma, kramper, apné, hjerterytmeforstyrrelser (initialt takykardier, etter hvert bradyarytmier) og sjokk. Til tross for behandling som inkluderer assistert ventilasjon og adekvat krampebehandling, kan utgangen likevel være fatal. I slike tilfeller dør pasienten oftest på grunn av den kardiotoksiske effekten av orfenadrin; enten av rytmeforstyrrelsene eller etter hvert som resultat av hjertets svekkede kontraktilitet og et deraf følgende kardiovaskulært kollaps (2, 13).

Overdoser kan ha fatal utgang få timer etter inntak, vanligvis i løpet av 2–5 timer, men bevisstløshet og død er rapportert etter henholdsvis 30 og 90 minutter (14). Obduksjonsfunn inkluderer hjerneødem, lungeødem, levernekrose og nyrestuvning (11, 14).

Behandlingen av overdosetilfeller er symptomatisk. Fysostigmin kan brukes som antidot ved antikolinerge syndromer. Dette medikamentet, som krysser blod-hjerne-barrieren, frarådes imidlertid brukt ved alvorlige orfenadrinforgiftninger (2, 13).

Biperiden

DDD er 10 mg, vanlig maksimaldosering er 12 mg, men opptil 16 mg daglig kan anvendes klinisk. Medikamentet finnes som tabletter som inneholder 2 mg, og som injeksjonsvæske, inneholdende 5 mg/ml biperiden. Absorpsjonen er rask og fullstendig etter oralt inntak. En omfattende presystemisk metabolisme er ansvarlig for at kun ca. 30 % av den inntatte dose når den systemiske sirkulasjonen. Tilsynelatende distribusjonsvolum er svært stort. Biperiden metaboliseres i leveren, og metabolittene utskilles primært i urin. Ikke-metabolisert morsubstans er ikke påvist i urin. Halveringstiden i plasma/serum etter peroralt inntak av subterapeutiske enkeltdoser er målt til 18–24 timer. Biperiden er høygradig proteinbundet, og muligheten for fortrengningsinteraksjoner bør overveies ved samtidig bruk av andre medikamenter med proteinbindingsgrad overstigende 90 %. Eldre pasienter kan eliminere medikamentet langsommere enn yngre (2).

Doseavhengige bivirkninger er knyttet til den antikolinerge effekten, som nevnt for orfenadrin. I tillegg kan noen pasienter oppleve tretthet og letargi. Doseuavhengige bivirkninger synes ikke å være rapportert. Det er heller ikke rapportert dødsfall knyttet til overdosering av biperiden. Dette bekreftes av Romano & DiBono (21). Systematiske farmakokinetiske studier med pasienter på kontinuerlig biperidenterapi forefinnes så vidt vites ikke, men det synes som om vanlig terapeutisk bruk av medikamentet er assosiert med blodkonsentrasjoner i størrelsesorden inntil 300 nmol/l (18). Det foreligger en rapport om to intoksikasjoner etter minsteinntak av 200 mg og 60 mg biperiden (22). Pasientene hadde blodkonsentrasjoner ved innkomst i sykehus på henholdsvis 890 nmol/l (12 timer etter inntak) og 250 nmol/l (fire timer etter inntak). Begge pasienter utviklet et akutt antikolinergt syndrom og ble behandlet med fysostigmin. Tilstanden normaliserte seg i løpet av 36–48 timer. Grunnen til den mulige diskrepansen mellom angitt terapiområde (18) og den noe lavere konsentrasjonen som ble målt i ett av overdosetilfellene (22), kan være at antikolinerg påvirkning i mindre grad tolereres når utfordringen er akutt og adaptasjon altså ikke har kunnet finne sted.

Assistert ventilasjon kan bli nødvendig ved større overdoser, og arytmier kan også komplisere tilstanden. Biperiden forsinker ventrikkeltømmingen, slik at mageskylling anbefales gjort, selv i tilfelle hvor tidsintervallet etter inntak er i størrelsesorden åtte timer (2).

Benztropin

DDD er 2 mg og maksimaldosering 6 mg. Medikamentet er formulert som tabletter som hver inneholder 2 mg av virkestoffet. Vi har ikke funnet arbeider som beskriver benztropins farmakokinetikk eller metabolisme.

Doseavhengige bivirkninger er knyttet til medikamentgruppens antikolinerge effekter, som beskrevet ovenfor. Det er rapportert ett dødsfall etter paralytisk ileus (23) og ett dødsfall som følge av heteslag hos en pasient som brukte benztropin under en hetebølge (24). Dødsmekanismen i det siste tilfellet ble antatt å være en benztropinindusert hemning av svettesekresjonen og samtidig forstyrret hypotalamisk varmeregulering grunnet bruk av klorpromazin. Catterson & Martin (25) refererer et dødsfall etter en sannsynlig overdose av benztropin. Pasienten ble feildiagnostisert som rammet av et malignt neuroleptikasyndrom, og initiert fysostigminbehandling ble avsluttet. Han hadde tatt en ukjent mengde benztropin, og medikamentkonsentrasjonen i fullblod 24 timer etter døden var 124 nmol/l. Forfatterne anslår at terapeutisk bruk av benztropin er assosiert med blodkonsentrasjoner i størrelsesorden inntil ca. 80 nmol/l (25). del Villar & Liddy har rapportert to dødsfall etter inntak av ukjente mengder benztropin (26).

Misbruk av benztropin er rapportert. Vi har ikke funnet doseuavhengige bivirkninger omtalt.

Konklusjon

Neuroleptikainduserte ekstrapyramidale bivirkninger kan være meget plagsomme, men er i seg selv ikke farlige. Bivirkningene kan til en viss grad minimaliseres ved å trappe opp neuroleptikadoseringen gradvis og be-

nytte moderate doser. Antikolinerge antiparkinsonmidler brukes i det alt vesentlige for å lindre disse bivirkningene. I Norge er orfenadrin det klart mest brukte medikamentet innen denne gruppen.

Orfenadrin er et toksisk medikament. Ved relativt moderate overdoser kan dødsfall inntre raskt. Intoksikasjoner er vanskelige å behandle. Kontinuerlig bruk kan føre til endret farmakokinetikk, med uforholdsmessig høye blodkonsentrasjoner og større risiko for doserelaterte bivirkninger som følge.

Biperiden og benztropin er betydelig mindre farlige. De toksiske effektene ved overdosering er knyttet til deres antikolinerge egenskaper, og bør i de fleste tilfeller kunne behandles med godt resultat i sykehus. Benztropin er påfallende mangelfullt beskrevet i litteraturen.

Antikolinerge antiparkinsonmidler har betydelige bivirkninger, også i terapeutiske doser. De bør derfor brukes restriktivt. Hvis en velger å forskrive et slikt medikament, bør biperiden være førstevalg. I lys av medikamentets uttalte akutte toksisitet synes en innskrenkning av indikasjonene for bruk av orfenadrin å være berettiget.

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○

Paper V

Særtrykk av Tidsskrift for Den norske lægeforening nr. 1/1998

Dødsfall forårsaket av antikolinerge antiparkinsonmedikamenter

Analysefunn i et nasjonalt 11-årsmateriale

Vi har gjennomgått samtlige obduksjonssaker mottatt ved Statens rettstoksikologiske institutt i 11-årsperioden 1986–96 hvor det ble påvist et antikolinergt antiparkinsonmiddel i innsendt blodprøve. Det dreier seg om 69 saker. Av disse ble det funnet orfenadrin hos 57 (83 %), biperiden hos åtte (12 %), procyklidin hos tre (4 %) og triheksylfenidyl/benzhexol hos en (1 %). Av 21 tilfeller hvor dødsårsaken ble vurdert å stå i overveiende sannsynlig (18/21) eller mulig (3/21) sammenheng med inntak av medikamenter tilhørende denne gruppen, hadde alle tatt orfenadrin. Hos disse 21 pasientene ble det ved obduksjon påvist orfenadrinnivåer i størrelsesorden 4,5–600 µmol/l (gjennomsnitt 62,5 µmol/l, SD 126,5 µmol/l). Materialet er ikke representativt, og betydelige mørketall må påregnes. Vi konkluderer likevel med at bruk av orfenadrin synes å generere langt flere overdosedødsfall enn andre medikamenter i denne gruppen, også når det justeres for en relativ markedsdominans.

Tre antiparkinsonmidler av antikolinerg type er registrert i Norge: orfenadrin, biperiden og benztropin. To tilsvarende medikamenter, triheksylfenidyl/benzhexol og procyklidin, ble avregistrert i henholdsvis 1995 og 1996. Orfenadrin er det klart mest brukte av disse stoffene i Norge. Siden det foreligger en rekke rapporter om letale intoksikasjoner etter bruk av orfenadrin i internasjonal litteratur (1), ønsket vi å undersøke den relative forekomsten av overdosedødsfall med medikamenter som tilhører denne gruppen. Slike sammenliknende studier er, så vidt vi kjenner til, tidligere ikke gjennomført for disse stoffene.

Materiale og metode

Alle obduksjonssaker registrert ved Statens rettstoksikologiske institutt i årene 1986–96 hvor blodprøver var positive på antikolinerge antiparkinsonmedikamenter, ble gjennomgått. Det dreier seg om til sammen 69 dødsfall hos 24 kvinner og 45 menn, med en gjennomsnittsalder på 44 år (16–80 år).

I hvert tilfelle ble det vurdert om dødsårsaken overveiende sannsynlig hadde sammenheng med en overdose av et antikolinergt medikament («sannsynlig»), om årsaken muligens hadde sammenheng med overdose av et antikolinergt medikament («mulig»), eller om det var lite sannsynlig/usannsynlig at et av de aktuelle medikamentene hadde spilt en rolle ved dødsfallet. Det presiseres at denne vurderingen er gjort på basis av resultatene av analyser foretatt ved instituttet og opplysninger fra obdusent, slik hos disse fremgår av rekvisisjonsskjema. Alle tilfeller med opplysninger om andre dødsårsaker er ekskludert. Vi har ikke hatt tilgang til de endelige obduksjonsrapportene i sakene.

Obduksjonsmaterialet er sammenholdt med salgstall for de forskjellige medikamentene, slik dette er oppgitt i definerte døgndoser (DDD)/1 000 individer/døgn fra Norsk Medisinaldepot.

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Fatalities caused by anticholinergic antiparkinsonian drugs: a retrospective study of a series of Norwegian cases

Tidsskr Nor Lægeforen 1998; 118: 42–4

All autopsy samples received at the National Institute of Forensic Toxicology during the years 1986–1996 which contained anticholinergic antiparkinsonian drugs were reviewed. Of a total of 69 cases, orphenadrine was present in 57 (83 %), biperiden in 8 (12 %), procyclidine in 3 (4 %), and trihexyphenidyl/benzhexol in 1 (1 %) of the subjects. The measured concentrations were assessed in light of previously published data. Of 21 cases where causality between drug ingestion and death was classified as either highly probable (18/21) or possible (3/21), all subjects tested positive for orphenadrine. In the autopsy samples from these patients, orphenadrine concentrations in the 4.5–600 µmol/l range (mean 62.5 µmol/l, SD 126.5 µmol/l) were determined. Because of a low national autopsy rate, there is reason to believe that the actual numbers of drug-related deaths in this period may have been significantly higher. It is concluded that orphenadrine is responsible for a disproportionally high number of overdose deaths.

Resultater

Totalt ble det funnet 69 enkeltsaker hvor blodprøve inneholdt et antikolinergt antiparkinsonmedikament. Av disse inneholdt 57 (83 %) prøver orfenadrin, mens de øvrige 12 (17 %) fordelte seg med åtte biperidenpositive prøver, tre prosyklidinpositive prøver og en prøve som var positiv på triheksylfenidyl/benzhexol. De som hadde tatt orfenadrin, var i gjennomsnitt 44 år (16–80 år) da de døde, mens de tilsvarende tall for de andre 12 individene var 42 år (20–69 år) .

Figur 1 viser de årlige salgstallene for antikolinerge antiparkinsonmidler i Norge i den aktuelle perioden, oppgitt av Norsk Medisinaldepot.

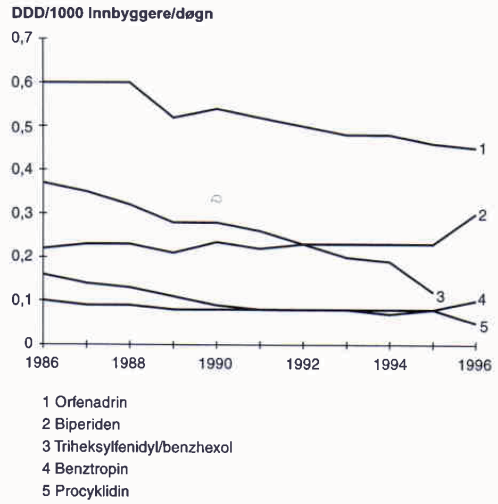
Tabell 1 oppgir «sannsynlige» og «mulige» medikamentforårsakede dødsfall for de ulike medikamentene, sammenholdt med gjennomsnittlig salg i 11-årsperioden. For triheksylfenidyl/benzhexol er gjennomsnittet regnet ut over ti år.

Summen av de «sannsynlige» og «mulige» intoksikasjonsdødsfallene utgjør for orfenadrins vedkommende totalt 21 individer, med alder fra 16 til 66 år rundt et gjennomsnitt på 36,3 år; ni kvinner og 12 menn. Andre legemidler/rusmidler ble påvist hos 16 (76 %) av disse 21. I seks (29 %) av analyserekvisisjonene forelå det opplysninger om sannsynlig suicid. Hos de 21 individene ble det påvist orfenadrinkonsentrasjoner på 4,5–600 µmol/l (gjennomsnitt 62,5 µmol/l, SD 126,5 µmol/l).

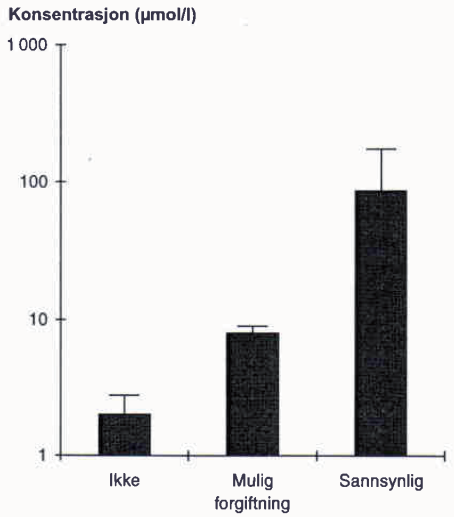
Av disse 21 sakene omfatter de «mulige» orfenadrindødsfallene tre pasienter. En av disse pasientene hadde en orfenadrinkonsentrasjon på 7 µmol/l i tillegg til en klorpromazinkonsentrasjon på 5 µmol/l; et toksisk, men ikke sikkert letalt nivå (2). De to andre tilfellene hadde blodkonsentrasjoner av orfenadrin på henholdsvis 4,5 og 6 µmol/l, og det forelå ikke opplysninger om annen mulig dødsårsak.

De påviste orfenadrinkonsentrasjonene hos de tre gruppene som totalt omfatter alle de 57 orfenadrinpositive individene fremgår av figur 2.

Blant de 69 pasientene som utgjør dette materialet, ble det i blodprøve tatt ved obduksjon påvist neuroleptika hos 42 %. Hos 44 % av de 18 pasientene hvor døden med



Figur 1 Salgstall (definerte døgndoser/1 000 innbyggere/døgn) for fem antikolinerge antiparkinsonmedikamenter for perioden 1986–96. Triheksylfenidyl/benzhexol og procyklidin ble avregistrert henholdsvis i 1995 og 1996



Figur 2 Blodkonsentrasjoner (gjennomsnitt + ett standardavvik) av orfenadrin i til sammen 57 enkeltsaker hvor medikamentet ble påvist i obduksjonsprøver. Sakene er klassifisert i tre grupper; hvor orfenadrin neppe har forårsaket dødsfallet (blodkonsentrasjon < 4,5 µmol/l, n = 36), hvor det foreligger en mulig sammenheng mellom legemiddelinntaket og dødsfallet (blodkonsentrasjon 4,5–13 µmol/l, n = 3) og hvor det er overveiende sannsynlig at orfenadrin har forårsaket døden (blodkonsentrasjon > 13 µmol/l, n = 18). Klassifiseringen er skjønnsmessig

overveiende sannsynlighet ble antatt å være forårsaket av orfenadrin, ble det påvist neuroleptika i blodet.

Diskusjon

Vi har forsøkt å kategorisere dødsfallene som overveiende sannsynlig, muligens eller ikke forårsaket av inntak av et antikolinergt antiparkinsonmiddel. Grensene mellom disse kategoriene må nødvendigvis bli skjønnsmessige og til en viss grad uklare. Blant annet bør det i vurderinger av denne type inngå omfattende viten om de forskjellige medikamentenes farmakokinetiske og farmakodynamiske egenskaper, potensielle interaksjoner i de tilfellene der pasienten har brukt flere medikamenter, og vedkommende pasients generelle helsetilstand. Slik informasjon foreligger bare i beskjeden grad. Grunnlaget for inndelingen er målte medikamentkonsentrasjoner i fullblod, sammenholdt med konsentrasjon-effekt-forhold for letale intoksikasjoner slik dette fremgår av den internasjonale litteraturen på området. Der dette har foreligget, har opplysninger om annen sikker eller mulig dødsårsak i hvert enkelt tilfelle vært til hjelp.

I oversiktsarbeider varierer angivelser for nedre grense av letale konsentrasjoner for orfenadrin i blod fra 13,4 µmol/l (2) til 14,8 µmol/l (3). Det finnes imidlertid flere rapporter om betydelig lavere blodkonsentrasjoner hos individer antatt døde av orfenadrinoverdose (4, 5). Vi har valgt å definere 13 µmol/l som nedre grense for å konkludere med at orfenadrin alene og med overveiende sannsynlighet har ført til døden, men har også vurdert muligheten for at blodkonsentrasjoner ned mot 4 µmol/l kan være dødelige. Disse grensene er, slik vi oppfatter litteraturen på området, restriktive i forhold til kriterier som andre har benyttet (4, 5).

Det finnes ingen rapporterte dødsfall knyttet til overdose av biperiden i litteraturen (6), og informasjon om mulige sammenhenger mellom biperidenkonsentrasjoner og dødsfall er ikke tilgjengelig. Det er også ukjent hvilke konsentrasjoner av benztropin som kan være potensielt letale.

Vi har funnet fem dødsfall knyttet til overdose med benztropin beskrevet i litteraturen, men ingen av tilfellene gir grunnlag for å estimere en mulig nedre grense for letal blodkonsentrasjon (7–10).

Det finnes heller ingen rapporter om dødsfall etter overdose av triheksylfenidyl/benzhexol (11), og informasjon om eventuelle toksiske konsentrasjoner for procyklidin er ikke tilgjengelig.

I de prøvene hvor vi registrerte andre antikolinerge medikamenter enn orfenadrin, var de aktuelle konsentrasjonene – så langt dette kunne vurderes – lavere enn hva som er satt i forbindelse med livstruende intoksikasjoner med disse stoffene.

Tabell 1 Obduksjonssaker sendt til Statens rettstoksikologiske institutt i tiden 1986–96 hvor det ble påvist et antikolinergt antiparkinsonmedikament i blodprøve

	Positiv blodprøve	Overdose sannsynlig dødsårsak	Overdose mulig dødsårsak	Gjennomsnittlig årlig salg (DDD/1 000 innb/døgn)	Gjennomsnittlig markeds-andel (%)
Orfenadrin	57	18	3	0,53	44,5
Biperiden	8	0	0	0,23	19,3
Benztropin	0	0	0	0,09	7,6
Triheksylfenidyl/benzhexol	1	0	0	0,26	21,9
Procyklidin	3	0	0	0,08	6,7
Totalt	69	18	3	1,19	100

De antikolinerge antiparkinsonmedikamentene som er registrert i Norge, har – med unntak for biperiden – vært gjenstand for en reduksjon i salget i den 11-årsperioden som denne undersøkelsen strekker seg over (fig 1). Orfenadrin er det mest solgte i denne medikamentgruppen, med en gjennomsnittlig årlig markedsandel i perioden 1986–96 på 44,5 %. Med bruk av våre estimater for letale blodkonsentrasjoner fremkommer det at alle de 18 dødsfallene som med sikkerhet kan knyttes til overdose med antikolinerge antiparkinsonmidler i materialet, er forårsaket av orfenadrin (tab 1). De tre tilfellene med orfenadrinkonsentrasjoner mellom 4,5 og 13 µmol/l som finnes i materialet, er alle klassifisert som «mulige» orfenadrininduserte dødsfall. Vi anser sannsynligheten for at disse tre dødsfallene reelt sett er forårsaket av orfenadrinoverdoser som stor. Våre data omfatter ingen dødsfall som kausalt kan knyttes til noen av de andre medikamentene i denne gruppen. Disse funnene viser etter vår oppfatning klart at orfenadrin er i en særklasse blant antikolinerge antiparkinsonmidler når det gjelder akutt toksisitet, noe som for øvrig samsvarer godt med den litteraturen som finnes på området (1).

Selv om tendensen synes klar, må det understrekes at dette materialet i beste fall kun uttrykker relative sammenhenger. Obduksjonsfrekvensen i Norge er lav og variabel. Rundt 1990 var det en topp i den rettsmedisinske obduksjonsraten på ca. 7 %, i 1994 var den falt til 4,4 % (12). Vårt materiale er åpenbart mangelfullt, og det synes ikke urimelig å anta at det kan finnes betydelige mørketall hva angår orfenadrininduserte forgiftninger. Detaljert informasjon om de enkelte tilfellenes forhistorie og om obduksjonsresultatene kan også forrykke bildet.

Orfenadrin er i påfallende grad overrepresentert i totalmaterialet; i 83 % av de tilfellene som fylte inklusjonskriteriene forelå det en positiv blodprøve som viste tilstedeværelse av orfenadrin. Dette er dobbelt så mye som salgstallene for dette medikamentet skulle tilsi, noe som i utgangspunktet er vanskelig å forklare. Liten variabilitet i gjennomsnittsalderen til dem som døde med orfenadrin eller andre antikolinergika i blodet, gir ikke grunnlag for å anta at skjevfordelingen skyldes at orfenadrin gis til eldre pasienter. Siden påvisningsgrensen for alle disse stoffene i rettstoksikologisk sammenheng i denne tidsperioden har vært 200 nmol/l, og noen av medikamentene (som for eksempel benztropin og biperiden) er farmakologisk aktive i betydelig lavere konsentrasjoner, kan det imidlertid ikke utelukkes at analytiske forhold i seg selv kan ha dreid praksis bort fra rekvirering av noen av disse stoffene. Når det gjelder benztropin, har det interessant nok ikke vært en eneste forespørsel fra obdusent om analyser med henblikk på dette stoffet i den samlede 11-årsperioden. Dette reflekterer sannsynligvis at medikamentet har en lav akutt toksisitet, men kan også ha bidratt til å gi våre data betydelig metodologisk slagside.

Den overveiende del av bruken av disse medikamentene knyttes til behandling av neuroleptikaindusert parkinsonisme. Et annet påfallende funn i dette materialet er at godt over halvparten av de 69 pasientene ikke hadde målbare neuroleptikamengder i blodet. Dette kan gi grunn til mistanke om at pasienter tar forskrevne neuroleptika i mindre omfang enn antatt. Alternativt kan det heller ikke utelukkes at antikolinerge medikamenter forskrives til andre enn pasienter med neuroleptikainduserte bivirkninger.

Konklusjon

Overdoser med orfenadrin har forårsaket en rekke dødsfall i Norge de siste 11 år. Ingen av de andre antikolinerge antiparkinsonmidlene som har vært i salg i denne perioden, kan med sikkerhet knyttes til overdosedødsfall. Til tross for at materialet er ufullstendig, tyder våre data på at orfenadrin er det klart mest toksiske av disse medikamentene, mens risikoen for suicid eller aksidentell død etter overdose er langt mindre for brukere av de andre medikamentene i denne gruppen.

Vi takker Marianne Saugestad, Norsk Medisinaldepot, for å ha fremskaffet salgstallene for antikolinerge antiparkinsonmidler i den aktuelle tidsperioden.

Litteratur

1. Gjerden P, Slørdal L. Antikolinerge antiparkinsonmedikamenters kliniske farmakologi. En oversikt med vekt på akutt toksisitet. Tidsskr Nor Lægeforen 1998; 118: 53–5.
2. Schultz M, Schmoldt A. Zusammenstellung therapeutischer und toxischer plasmakonzentrationsbereiche von artzneistoffen. Anaesthesist 1994; 43: 835–44.
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Paper VI

Is not included due to copyright

Paper VII

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Errata

Paper 6

The lower panel in Figure 1 in Paper 6 (Effect of warnings in a medical journal on the use of orphenadrine), does not differentiate Denmark from Sweden. The curve for Denmark starts slightly below the curve for Sweden and ends higher.

Paper 3

In the published version of Paper 3 (Prescription persistence and safety of antipsychotic medication: a national registry-based 3-year follow-up) the following changes have been made compared to the original manuscript (the original version in square brackets):

Table 2: ”Risk of death by the end of 2007 for patients using antipsychotic drugs in 2004, expressed as odds ratio (OR) and 95% confidence interval (CI)…” [Odds ratio (OR) for patients using antipsychotic drugs in 2004 of having died at the end of 2007.]

Table 3: ”Likelihood that patients using antipsychotic drugs in 2004 would remain with the same antipsychotic drug in 2007, expressed as odds ratio (OR) and 95% confidence interval (CI)…” [Odds ratio (OR) for patients using antipsychotic drugs in 2004 of staying with the same antipsychotic drug in 2007.]

Introduction: ”…, all antipsychotic agents would be evaluated in the same way.” […, this would require that all antipsychotic agents were evaluated in the same way.]

Material and methods: ”…, use of a drug primarily in institutions might indicate that psychiatrists prefer it as treatment for the most severely…” […, drugs which were primarily used in institutions might indicate which drugs the psychiatrists preferred as treatment for the most severely…]

”comprised patients” [was constituted by patients]

Results: ”the group using chlorprotixene” [the chlorprotixene using group]

”…, use of anticholinergics and use of specific antipsychotics ” […, if the patient used anticholinergics and the use of specific antipsychotics]

Discussion: ”prior to” [preceeding]

A few misspellings have been corrected.

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

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

1990

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

1991

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

1992

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

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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.
86. Jie Ming Shen: BLOOD FLOW VELOCITY AND RESPIRATORY STUDIES.
87. Piotr Kruszewski: SUNCT SYNDROME WITH SPECIAL REFERENCE TO THE AUTONOMIC NERVOUS SYSTEM.
88. Mette Haase Moen: ENDOMETRIOSIS.
89. Anne Vik: VASCULAR GAS EMBOLISM DURING AIR INFUSION AND AFTER DECOMPRESSION IN PIGS.
90. Lars Jacob Stovner: THE CHIARI TYPE I MALFORMATION.
91. Kjell Å. Salvesen: ROUTINE ULTRASONOGRAPHY IN UTERO AND DEVELOPMENT IN CHILDHOOD.

1994

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

1995

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

1996

110. Svend Aakhus: NONINVASIVE COMPUTERIZED ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND SYSTEMIC ARTERIAL PROPERTIES. Methodology and some clinical applications.
111. Klaus-Dieter Bolz: INTRAVASCULAR ULTRASONOGRAPHY.
112. Petter Aadahl: CARDIOVASCULAR EFFECTS OF THORACIC AORTIC CROSS-CLAMPING.
113. Sigurd Steinshamn: CYTOKINE MEDIATORS DURING GRANULOCYTOPENIC INFECTIONS.
114. Hans Stifoss-Hanssen: SEEKING MEANING OR HAPPINESS?
115. Anne Kvikstad: LIFE CHANGE EVENTS AND MARITAL STATUS IN RELATION TO RISK AND PROGNOSIS OF 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.
135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.
139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

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141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.
142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153. Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

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158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
159. xxxxxxxxx (blind number)
160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.
162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.
163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.

164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.
168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

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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
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT
192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS
193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS

195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM
198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

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201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
215. Astrid Rydning: BLOOD FLOW AS A PROTECTIVE FACTOR FOR THE STOMACH MUCOSA. AN EXPERIMENTAL STUDY ON THE ROLE OF MAST CELLS AND SENSORY AFFERENT NEURONS

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216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.
217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.

220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
222. Tom Christian Martinsen: HYPERGASTRINEMIA AND HYPOACIDITY IN RODENTS – CAUSES AND CONSEQUENCES
223. Solveig Tingulstad: CENTRALIZATION OF PRIMARY SURGERY FOR OVARAIN CANCER. FEASIBILITY AND IMPACT ON SURVIVAL
224. Haytham Eloqayli: METABOLIC CHANGES IN THE BRAIN CAUSED BY EPILEPTIC SEIZURES
225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
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