Pharmacokinetic, pharmacodynamic and pharmacogenetic aspects of oxycodone treatment in cancer pain

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Doctoral Thesis

NTNU
Norwegian University of Science and Technology
Thesis for the degree of philosophiae doctor
Faculty of Medicine
Department of Circulation and Medical Imaging
Pharmacokinetic, pharmacodynamic and pharmacogenetic aspects of oxycodone treatment in cancer pain

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Norwegian University of Science and Technology
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Farmakokinetiske, farmakodynamiske og farmakogenetiske aspekter ved oksydons behandling av kreftmerter

Kroniske smeter ved kreftsykdom er et utfordrende problem. Selv om sterke smertelindrende middelamnter som morfin eller oksydon (epi) er i utstrakt bruk, er det mange kreftpasienter som ikke oppnår tilstrekkelig smertelindring eller plages av bivirkninger. Et grunn til at man ikke får god nok virking hos alle, er at opioider virker svært forskjellig fra individ til individ. For å kunne bedre smertehandleingen av kreftpasienter er det viktig å finne ut om hvorfra det er slike forskjeller.

Denne studien er en del av et EU-prosjekt som har inkludert 2249 kreftpasienter. Av disse var det 461 som benyttet oksydon mot sine kreftmerter. Det er lite kunnskap om hvilke faktorer som påvirker virkningen av oksydon hos kreftpasienter. Målet med denne studien var derfor å undersøke om alminnelige kliniske opplysninger sammen med målinger av serum koncentrasjoner av oksydon og nedbrytningsprodukter (metabolitter) av oksydon eller gener for nedbrytningszymyner, kan forklare forskjeller mellom indi-vider. Kliniske opplysninger som ble inkludert, var pasientens alder, kjønn, kroppsmasseindekk (BMI), daglig oksydon doser, opplysninger om tilleggsmedikamenter, hvor lange passientene har brukt opioider, hvor mange timer siden for tid tidligere, fysisk funksjonstatus, samt indikatorer for lever- og nyrer funksjon.

Oksydon brytes ned i leveren hovedsakelig av CYP2D6 og CYP2D6 enzym. Disse enzymenes aktivitet kan bli påvirket av andre medicin-ner pasienten bruker. I tillegg eksisterer det flere varianter av CYP2D6-gjenet som påvirker dannelsen av det smertelindrende nedbrytningspro-dukatet oksytemor. Tilleggsmedikamenter og genvarianter av CYP2D6 kan derfor være med å bestemme den enkelte pasient sitt stiv av oksydon og metabolitter i blodet, og dermed känne den nødvendige doseringen av oksydon.

Studien har vist at daglige oksydon var den faktoren som forklarte den observerte variasjonen i blodnivået best, mens kjønn og bruk av medikamenter som påvirket nedbrytningen av oksydon via CYP2D4 enzymene, gav den største effekten på

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Det var ingen sammenheng mellom nåvået av oksyhydroks eller metabolittene oksyhydroksog oksyhydroksen i blodet og smerteintensiteten, og brekkeringer (kvalm, trøttet, og kognitive funksjon). Likevel var bruk av CYP3A4 hemmeren fksom bli assosiert med mindre smerte, mens et økt mengde av metabolitt oksyhydroksen blekskutt nok var assosiert med en økning i smerte i denne gruppen av pasienter. Dette er vanskelig å forklare, men vi observerte at pasienter som hadde "smert og brekkeringer", generell hadde høyere nivåer i blodet av oksyhydroksen og metabolittene enn de som var "godt smertelindet og uten brekkeringer". Spesielt galt dette for brekkeringen "trøttet", hvor andelen patienter med "smerte og trøttet" var mye større enn andelen "godt smertelindet og ikke trøtt". Disse resultatene antyder at mange patienter er relativt overdosert, og kanskje burde være tilbudd et annet medikament enn oksyhydroksen.

Studien viste også at CYP2D6 gen varianter påvirket nåvået av oksyhydroksen og oksyhydroksen i blodet, men dette hevdte ingen betydning for virkningen av oksyhydroksenbehandlingen.

At de subjektive uflisymptomene smerteintensitet, trøttet, kvalm og kognitive funksjon ikke bare skyldes oksyhydroksenbehandlingen, men også selv krevhsukommen, gir utfordringer i tolkningen av resultatene.

Oppsommert indikerer denne studien at verken rutesnes og serokonsekvensromologi eller genotyping av CYP2D6 er indirert ved bruk av oksyhydroksen. Ved kronisk administrering er oksyhydroksen det vesentlige, aktive virkestoffet. Trøttet er et hyppig symptom hos de som ikke er godt smertebehandlet og kan indikere behov for å bytte opioid. Patienter som skal starte eller stoppe med CYP3A4 medikamenter bør følges tett etterpå.

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Hovedveileder: Professor Ola Dale
Biveiledere: Professor Pål Klepstad, Professor Stein Kaasa og Ph.D. Ingrid Eftedal

Overvånte avhandling er funnet verdig til å forvare offentlig for graden Ph.D. i klinisk medisin.
Disputasen finner sted i MTA, Auditorium, Medisinsk teknisk forskningsenter, torsdag 23. juni 2011, klokken 12.15
Summary

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

This study is part of a larger EU-project that included 2294 cancer patients. Of these, 461 were scheduled with the opioid oxycodone for their cancer pain. There is little knowledge about which factors influences the efficacy of oxycodone in cancer patients. Thus, the aim of this study was to examine clinical information together with measurements of serum concentrations of oxycodone and its metabolites or genes of the metabolizing enzymes in order to explain differences between individuals.

Clinical information included was the patient’s age, sex, body mass index, oxycodone daily dosage, information on co-medication, how long the patient has been using opioids, number of hours since last dose, physical functioning, and indicators for hepatic- and kidney function.

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

No relationship was found between level of oxycodone or the metabolites normoxycodone and normormorphine in the blood and pain intensity, and side effects (nausea, tiredness).

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No relationship was found between level of oxycodone or the metabolites normoxycodone and normormorphine in the blood and pain intensity, and side effects (nausea, tiredness).
and cognitive function). Still, the use of the CYP3A4 inhibitor fluvastatin was associated with less pain, while an increase of the metabolite oxymorphone, paradoxically, was associated with increasing pain in this group of patients. This is difficult to explain, but we also observed that patients who had "poor pain control and side effects", generally had the highest serum concentrations of both oxycodone and metabolites compared to those who were "pain relieved and without side effects". This was especially true for the side effect "tiredness", where the portion of patients with "pain and tiredness" was much higher than the portion of patients being "pain relieved and not tired". This suggests that many patients are overused, and that these patients should have been offered a different drug than oxycodone.

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

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

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

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I would like to thank the co-authors, Kristin Bjørdal, Staffan Lundström and Andrew Davies, for good and supportive comments and suggestions during the process of writing the articles, and for always responding to my requests. Thank you for the good collaboration!

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I want to express my gratitude to all my colleagues in the Pain and palliation research group. Special thanks to Gro, Guro, Elisabeth, Line and Morten for their friendship during my work with this thesis. This work would not have been the same without our morning tea-breaks filled with inspiring discussions, joyful conversations and your endless support!

I am most grateful to my parents, Kristen and Randi, and to my parents-in-law, Karsten and Vílfríð, for their support and for always being there when we needed some help taking care of the children.

I also want to express my gratitude to my dear children, Marius, Filip and Helle. You make me remember what is most important in life! I want to thank you for the patience you have shown during the months I have hardly been home. I hope you can forgive me, and I promise I will never do it again. You are my pride and joy and I love you all so much.

This thesis would never have been started without encouragement and support from my best friend and beloved husband, Einar. During the writing of this thesis, you took full responsibility of everything concerning the household and the kids, and you never complained. After 10 years of marriage I must say you still impress me! Through good and difficult days; you are always there for me and I love you. It is truly your credit that I finished on time, and I will never forget the evening you surprisingly showed up at work to cheer me up with a dessert, after a rather frustrating working day. Thank you!
List of papers


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

III. Trine Naasland-Andreasen, Ingrid Eihol, Pål Klepetad, Andrew Davies, Kristin Bjordal, Staffan Lundström, Stein Kaasa, Ola Dale. Do the CYP2D6 genotypes reflect oxycodone requirements in cancer pain patients? - A cross-sectional multicentre study. Submitted to European Journal of Clinical Pharmacology
<table>
<thead>
<tr>
<th>Abbreviations</th>
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<tbody>
<tr>
<td>μ m</td>
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<tr>
<td>w</td>
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<tr>
<td>ANCOVA</td>
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<tr>
<td>Analysis of co-variance</td>
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<tr>
<td>ANOVA</td>
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<tr>
<td>Analysis of variance</td>
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<tr>
<td>AUC</td>
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<tr>
<td>Area under the curve</td>
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<tr>
<td>BBB</td>
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<tr>
<td>Blood-brain barrier</td>
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<tr>
<td>BMI</td>
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<tr>
<td>Body mass index</td>
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<tr>
<td>BPI</td>
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<tr>
<td>Brief Pain Inventory</td>
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<tr>
<td>CI</td>
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<tr>
<td>Confidence interval</td>
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<tr>
<td>Cmax</td>
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<tr>
<td>The peak plasma concentration of a drug after oral administration</td>
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<tr>
<td>CNS</td>
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<tr>
<td>Central nervous system</td>
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<tr>
<td>CR</td>
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<tr>
<td>Controlled release</td>
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<tr>
<td>CSF</td>
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<tr>
<td>Cerebrospinal fluid</td>
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<td>CYP2D6</td>
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<td>Cytochrome P450 2D6</td>
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<td>CYP2J4</td>
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<tr>
<td>Cytochrome P450 2J4</td>
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<tr>
<td>EM</td>
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<tr>
<td>Extensive metabolizer</td>
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<td>EORTC</td>
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<tr>
<td>European Organization for Research and Treatment of Cancer</td>
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<td>EPOS</td>
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<td>European pharmacogenomic opioid study</td>
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<td>h</td>
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<td>hour</td>
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<td>IASP</td>
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<td>International Association for the Study of Pain</td>
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<td>IR</td>
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<tr>
<td>Immediate release</td>
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<td>M6G</td>
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<td>Morphine-6-glucuronide</td>
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<td>MNS</td>
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<td>Mini mental state</td>
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<td>NRS</td>
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<td>Numerical rating scale</td>
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<td>OR</td>
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<td>Odds ratio</td>
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<tr>
<td>PM</td>
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<td>Poor metabolizer</td>
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<td>QLQ-C30</td>
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<tr>
<td>EORTC’s 30 items quality of life questionnaire</td>
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<td>Rp</td>
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<tr>
<td>Coefficient of determination</td>
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<td>SNP</td>
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<td>Single nucleotide polymorphism</td>
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<td>Tmax</td>
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<td>Time when the peak plasma concentration of a drug after oral administration is reached</td>
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<td>UGT2B7</td>
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<td>Uridine diphasate glucuronosyltransferase 2B7</td>
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<td>Ultra rapid metaboliser</td>
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<td>Glossary</td>
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<td>Agonist</td>
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<td>Allele</td>
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<td>Antagonist</td>
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<td>Antinociceptive effect</td>
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<td>Bioavailability</td>
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<td>Blood plasma</td>
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<td>Clearance, CL</td>
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<td>Conjugation</td>
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<td>Efficacy</td>
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7

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7
Elimination half time

- The period of time it takes for a substance to be eliminated to the half

First order kinetics

- Is when a constant fraction of the drug is eliminated per unit time, as opposed to zero-order kinetics where a constant amount of the drug is eliminated per unit time

First pass metabolism

- Is the drug metabolism in the gut wall and liver whereby the concentration of a drug is greatly reduced before it reaches the systemic circulation. After a drug is swallowed, it is absorbed by the digestive system and enters the hepatic portal system. It is carried through the portal vein into the liver before it reaches the rest of the body. This metabolism before it reaches the systemic circulation is called the first pass metabolism

Genotype

- Is defined as the combination of alleles on two chromosomes. To equal alleles are said to be a homozygous genotype group, while two unequal alleles are heterozygous

Glomerular filtration rate: GFR

- Is an indication of the state of the kidney, and describes the flow rate of filtered fluid through the kidney. In this thesis GFR was expressed as:

  \[ q = \frac{\text{GFR} \times 90 \text{ ml/min}}{\text{Body surface (m²)}} \]  

- calculated glomerular filtration rate a body surface / 1.73 m² where glomerular filtration rate was calculated:

  \[ 175 \times \text{[creatinine]/(88.4) 1.174 \times \text{[age (years)}]} \times 0.254 \times 0.742 \text{ if women.} \]  

  Body surface was calculated:

  \[ 0.2047 \times \text{height (m)} \times \text{weight (kg)} \times 1.23 \times 0.85 \text{ if woman.} \]  

  Normal function: GFR > 90 ml/min  

  Dysfunction: GFR < 60 ml/min

Hardy Weinberg equilibrium

- States that both allele and genotype frequencies in a population remain constant. A random genetic sample has a distribution of homogenous and heterogenous carriers that correspond to the Hardy-Weinberg equilibrium. \( p \) is the frequency of one allele, \( q \) of the other allele, \( p^2 \) is the frequency of one homozygous group, \( 2pq \) is the frequency of the heterozygous individuals and of the frequency of the
other homozygous group. The Hardy-Weinberg equilibrium states that \( p^2+2pq+q^2=1 \)

**Hyposalgia**

- An increased sensitivity to pain

**Odds**

- Number of times an event happens / number of times an event does not happen

**Odds ratio**

- Odds in the group being exposed / odds in group not being exposed

**Pathophysiology**

- The study of the changes of normal mechanical, physical and biochemical functions

**Pharmacokinetic**

- Is simply defined as the study of what the drug does to the body, and includes the relationship between drug concentration and effect

**Pharmacogenomics**

- The study of how genes influence the way a patient responds to drug therapy

**Pharmacogenetic**

- Is generally regarded as the study of clinical testing of genetic variation that gives rise to differing response to drugs

**Pharmacokinetic**

- Is simply defined as what the body does to the drug. It includes the extent and rate of absorption, distribution, metabolism and excretion

**Phenotype**

- Is an observable attribute of an organism

**\( R^2 \)**

- An estimate of the amount of the variation in the data that is being explained by a regression model. Equal in linear regression to the square of Pearson's product-moment correlation coefficient

**Statistical power**

- Is the probability that the study will detect a statistical significant difference

**Steady-state serum concentration**

- In steady-state the drug elimination equals drug availability. When a drug is administered every 12 h the serum concentrations of the drug rise and falls. In steady-state this cycle is repeated identical in each administration interval. The steady-state serum concentration then describes the

other homozygous group. The Hardy-Weinberg equilibrium states that \( p^2+2pq+q^2=1 \)

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average drug concentration during an inter-dose interval

Sublingual administration
Pharmacological route of administration by which drugs diffuse into the blood through tissues under the tongue

Systemic circulation
It is the part of the cardiovascular system which carries oxygenated blood away from the heart to the body, and returns deoxygenated blood back to the heart

Therapeutic window
It is the dosage range of a drug where we get the wanted effect and this exceeds the unwanted adverse effects

Trough blood sample
A blood sample taken at when the concentration of a drug is at a minimum after its administration and just prior to the administration of a subsequent dose in a multiple dosing study

Volume of distribution
The apparent volume in which a drug is distributed immediately after it has been injected intravenously and equilibrated between plasma and the surrounding tissues

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Introduction

Cancer patients

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

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

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

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**Pain**

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

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

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

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**Cancer Pain**

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

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

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WHO’s three-step ‘ladder’ for cancer pain relief

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

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The intensity of the pain is the strategy-guide when the WHO’s analogic ladder is used.
According to the WHO (World Health Organization, 2010) and an expert group working for the European Association for Palliative Care (Hanks et al., 2001), morphine is the opioid of first choice in the treatment of severe cancer pain, of which the others are compared. However, not all patients benefit from the use of morphine. In one study 26% of the cancer patients did not respond to morphine. After rotation to oxycodone, 79% of these non-responders responded to oxycodone (Riley et al., 2006). Also other studies have shown that rotation from morphine to oxycodone might be beneficial when morphine does not give the desired effect (Kurabayashi et al., 2008). Further, a low dose can be used.
Opioid mechanism of action

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

The endogenous peptides enkephalin, dynorphins and endorphins are naturally occurring ligands for opioid receptors. Through receptor binding studies and cloning the three main opioid receptors, μ, δ and σ has been characterized, and in 1994 a fourth receptor, the nociceptin/orphanin FQ (N/OFQ) was cloned. This latter receptor has a high structural resemblance with the other three, but does not bind to the conventional opioid ligands. The μ, δ and σ receptor types have been extensively studied and their distribution in the brain, spinal cord and the periphery are known. Studies have shown administration of opioids and morphine simultaneously seem to be more effective and with fewer side effects, than morphine alone (Lauretti et al., 2003).

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that the drugs used in the clinic are relatively selective for the µ-opioid receptor. However, a receptor-specific drug will become less receptor-specific when administered in large enough doses. µ-opioid receptor effects are analgesia, respiratory depression, alteration of the cardiovascular, gastrointestinal and neuroendocrine functions, affection on the mood and rewarding behaviour. Activation of the µ, δ and κ receptors cause inhibition of the adenyl cyclase activity, activates the receptor-operated K+ currents and suppresses the Ca2+ currents in the endogenous neurons. Activation of K+ currents and suppresses the Ca2+ currents is speculated to be the way opioids block the neurotransmitter release and pain transmission in the different neuronal pathways (Gutstein and Huda, 2001).

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

Blood-Brain Barrier

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

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

Inter-individual variability in response to an opioid

Studies show that there is a large inter-individual variability as to how patients respond to opioids (Kakko et al., 1983). Some patients get totally pain-relieved, some are partly relieved and some do not relieve their opioid treatment due to intolerable side effects. A patient’s response to an opioid depends on multiple factors, involving the pharmacokinetics and pharmacodynamics of the drug, and pharmacogenetics of the patient. Inter-individual variability in the pharmacokinetics of a drug may include differences in absorption, distribution, metabolism, and elimination. Pharmacodynamic factors affecting the inter-individual variability are drug concentration at the effect site, and binding- and activation ability at the opioid receptor. Some of these factors may be attributed to pharmacogenetic differences (Klepstad et al., 2004). On top of this, age, gender, cancer diagnosis, pain-intensity, tolerance and pathophysiology will also contribute to the variability in pharmacokinetics and pharmacodynamics of a drug. Because of differences in pharmacokinetics and pharmacodynamics between opioids and because of differences in pharmacogenetics between patients, an individual response to an opioid is expected for the individual patient (Yaalauksi et al., 2008).

Adverse effects

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

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comparing adverse effects of one opioid with another are lacking. Also, there is a lack of controlled studies that have looked at adverse events from one opioid given by various routes of administration. From existing literature the adverse effect profiles seem to be similar between different opioids, and there is very little evidence to suggest differences in adverse effects due to route of administration. The inter-individual variability to adverse effects is large, and it is believed that genetic variation plays an important role.

Further, the risks for adverse effects from opioids are influenced by age, disease progression, organ dysfunction, co-administration with other medications and previous history of opioid use. The CNS adverse effects sedation, cognitive impairment, hallucinations, myeloschisis and respiratory depression are dose-dependent. The dose-response relationship between opioids and gastrointestinal adverse effects is weak, and constipation is not dose-dependent, nor tolerance evolving. The inter-individual differences in this relationship among the patients are large, and some patients develop tolerance towards these adverse effects while others do not (Fallon et al., 2010).

**Oxycodone versus morphine**

![Chemical structures of oxycodone and morphine](image)

Morphine and oxycodone have about the same lipophilicity and their plasma protein binding is 38% and 45%, respectively. A methoxy-group in the molecular structure of oxycodone is believed to protect oxycodone from being extensively metabolized in the liver. Oxycodone may be more active than morphine due to greater interaction with the mu-opioid receptor. Oxycodone’s long-acting metabolite, noroxycodone, is responsible for its extended duration of action and duration of euphoria. Oxycodone’s short-acting metabolite, 3-methyloxycodone, is responsible for the rapid onset of action. Oxycodone is associated with nausea/vomiting, constipation, ileus, respiratory suppression, and sedation. Oxycodone is metabolized in the liver to noroxycodone and 3-methyloxycodone.

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first pass metabolism partly causing the oral bioavailability of 60-87 % (Leow et al., 1992, Poyhia et al., 1992), which is higher than morphine (20-30 %). Further, oxycodone has an affinity for the μ-opioid receptor that is 1/10-1/40 of morphine (Kalu et al., 1990, Chen et al., 1991), and the ability to activate the opioid receptors is 3-8 times lower than morphine. Unlike morphine, oxycodone is not a substrate for P-glycoprotein (is not being transported via active efflux). Research in rats has shown that oxycodone seems to be actively transported through the blood-brain barrier (BBB) (active influx) causing the brain-to-plasma concentrations of oxycodone to be about six times higher than the brain-to-plasma concentrations of morphine, which does not seem to be actively transported through the BBB (Bostrom et al., 2006, Letrent et al., 1998). Oral oxycodone is about 1.5-2 times more potent as oral morphine, but parenteral oxycodone has a potency of 0.75 compared to parenteral morphine. The difference in their metabolism might explain these differences. Morphine is metabolised via uridine diphosphate glucuronosyltransferase 2B7 (UGT2B7), which yields the active metabolite morphine-6-glucoside (M6G). M6G contributes to the efficacy of morphine (Murthy et al., 2002). There are very few reports on drug-drug interactions involving morphine. Oxycodone is potentially vulnerable to drug-drug interactions due to its CYP2B6 and CYP3A4 metabolism. Oxycodone also has an active metabolite, oxymorphine; however its contribution to the efficacy of oxycodone is uncertain. Oxycodone and morphine are both effective in cancer- and post-operative pain, and shows similar adverse effects (Mucci-Lellauss et al., 1998, Heitskem and Kalus, 1997, Curtis et al., 1999). Based on current knowledge, there is no clinical evidence for one being better than the other. Morphine seem to be the first choice due to availability, habits and costs (Fredheim et al., 2010).

Oxycodone

Oxycodone was first used in clinical practice in Germany in 1917 (Falk, 1917) after being synthesized from thebaine in 1916 (Lene et al., 1986). Indications for oxycodone have historically differed between countries: it has been used as a combination drug in USA, Canada and Australia for moderate pain, while in Europe it has been mainly used for first pass metabolism partly causing the oral bioavailability of 60-87 % (Leow et al., 1992, Poyhia et al., 1992), which is higher than morphine (20-30 %). Further, oxycodone has an affinity for the μ-opioid receptor that is 1/10-1/40 of morphine (Kalu et al., 1990, Chen et al., 1991), and the ability to activate the opioid receptors is 3-8 times lower than morphine. Unlike morphine, oxycodone is not a substrate for P-glycoprotein (is not being transported via active efflux). Research in rats has shown that oxycodone seems to be actively transported through the blood-brain barrier (BBB) (active influx) causing the brain-to-plasma concentrations of oxycodone to be about six times higher than the brain-to-plasma concentrations of morphine, which does not seem to be actively transported through the BBB (Bostrom et al., 2006, Letrent et al., 1998). Oral oxycodone is about 1.5-2 times more potent as oral morphine, but parenteral oxycodone has a potency of 0.75 compared to parenteral morphine. The difference in their metabolism might explain these differences. Morphine is metabolised via uridine diphosphate glucuronosyltransferase 2B7 (UGT2B7), which yields the active metabolite morphine-6-glucoside (M6G). M6G contributes to the efficacy of morphine (Murthy et al., 2002). There are very few reports on drug-drug interactions involving morphine. Oxycodone is potentially vulnerable to drug-drug interactions due to its CYP2B6 and CYP3A4 metabolism. Oxycodone also has an active metabolite, oxymorphine; however its contribution to the efficacy of oxycodone is uncertain. Oxycodone and morphine are both effective in cancer- and post-operative pain, and shows similar adverse effects (Mucci-Lellauss et al., 1998, Heitskem and Kalus, 1997, Curtis et al., 1999). Based on current knowledge, there is no clinical evidence for one being better than the other. Morphine seem to be the first choice due to availability, habits and costs (Fredheim et al., 2010).

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

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

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Clinical indications

Metabolism and pharmacokinetics
Oxycodone is extensively metabolised in the liver mainly via CYP344 to the inactive metabolite noroxycodone (47 % of dose), by 6-keto-reduction to what are most likely inactive metabolites, α- and β-(4-hydroxy) (8 % of dose), and via CYP2D6 to the active metabolite oxymorphone (11 % of dose), which is mainly found in conjugated form in plasma. A third, possibly active metabolite noroxymorphone (14 % of dose), is formed from noroxycodone via CYP2D6, but also to a lesser degree from oxymorphone via CYP344 (Figure 3) (Lacovic et al., 2004, Moore et al., 2003, Laetic et al., 2006). Oxycodone and its metabolites are mainly excreted through the kidneys, and the excretion is dependent on kidney and liver function (Kalso et al., 1996, Kivela et al., 1996, Talgorn et al., 1997, Kalso, 1997). Oxycodone (8 %) and noroxycodone (22 %) are mainly excreted in free form, oxymorphone (31 %) mostly in conjugated form, as oxymorphone-3-glucuronide, and noroxymorphone (14 %) in both free and conjugated form (Lacovic et al., 2008). Up to 91 % of the administered oxycodone dose has been recovered as oxycodone or metabolites in urine (Lacovic et al., 2006). Oxycodone has a

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

![Figure 3 Oxycodeone metabolism (modified from Lalovic et al. (Lalovic et al., 2006))](image)

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

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Most of the opioid analgesia is mediated through affinity and activation of opioid receptors in the CNS. It was first believed that omeprazole, which is a very potent analgesic, was the principal analgesic when opioids were administered. However, inhibition of omeprazole formation by quinidine showed no difference in the analgesic effect of omeprazole in rats (Clancy et al., 1994), and did not attenuate opioid side effects in healthy volunteers (Henikman et al., 1990; Kalüte et al., 1996b). Based on the circulating concentrations, affinity and efficacy at the opioid receptors and the accessibility to enter the central nervous system Lalovic et al. (Lalovic et al., 2006) assessed the probability of omeprazole and its metabolites to mediate the analgesic effect. The study showed that even though omeprazole had a more than 40-fold higher affinity for the μ-opioid receptor and a higher ability to activate the receptor compared to oxycodone, the low concentration of omeprazole in circulation combined with much lower brain-to-plasma concentrations ratios than oxycodone (0.25 vs. 2.0), respectively led to the conclusion that it is very unlikely that oxycodone contribute to the efficacy of oxycodone. They also concluded that oxycodone, the most abundant metabolite, did not contribute to the effect of oxycodone because of low affinity and activation of the opioid receptors and low brain-to-plasma ratios of 0.1, which corresponded to the weak antinociceptive effect found in rats earlier (Lalovic and Smith, 1994). According to Lalovic et al., omeprazole, was the metabolite with the highest potential of being an active metabolite being the second most abundant species in circulation (about 50 % of the oxycodone or noroxycodone concentration) and with a receptor affinity 3-fold higher than oxycodone. However, it had the lowest brain-to-plasma concentration ratios (0.008). The secondary metabolite α- and β-oxycodone showed low receptor binding and activation and had brain-to-plasma ratios similar to oxycodone. A model connecting the pharmacokinetic to the pharmacodynamic effect of oxycodone did not include noroxycodone nor any of the other metabolites, only oxycodone itself.

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

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

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

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a drug which is a CYP2D substrate, or adverse drug reactions (Goryshchina et al., 2009, de Leon et al., 2003). If the drug is a pro-drug that needs CYP2D bioactivation, like codeine or tramadol, it may have no or only slight therapeutic effect in CYP2D6 poor metabolizers (Poulsen et al., 1996, Stamler et al., 2007), while URM might experience adverse effects at commonly used doses (Kirkbride et al., 2007). The CYP2D6 genotype may therefore be of clinical importance for drugs that are metabolized by CYP2D6 enzymes, not least in the combination with drugs known to alter the CYP2D6- or CYP3A4 enzymes.

The CYP2D6-genotype influence on the pharmacokinetics and pharmacodynamics of oxycodone
In 1998 the first study addressing pharmacogenetic aspects of CYP2D6 in the metabolism and efficacy of oxycodone was published (Høinshagen et al., 1998). In this study 10 healthy volunteers were genotyped as EM with respect to CYP2D6, and the CYP2D6 metabolic pathway was blocked by quinidine. Although, nonoxycodone and oxymorphine serum concentrations differed before and after blocking, differences in oxycodone serum concentrations were non-significant, and the reduction of oxymorphine did not cause changes in the subjective drug effect or psychomotor function. Despite not having assessed the analysis of oxycodone, the investigators concluded that oxymorphine might not be important to the pharmacodynamics of oxycodone. Since then several papers on oxycodone have included pharmacogenetic aspects into their studies (Zwisler et al., 2009, Grenland et al., 2010b, Grenlund et al., 2010a, Sønder et al., 2010a, Sønder et al., 2010b, Kummer et al., 2010, Lemberg et al., 2010, Zwisler et al., 2010). Some have assessed pharmacokinetic and/or pharmacodynamic aspects by either blocking the CYP2D6- or the CYP3A4 metabolic pathways, or both. Others have assessed the efficacy of oxycodone between PM, EM and URM.

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

Every hospital has a mission; to make the patient feel well. This includes elimination of disease, mitigate disease, and maximize quality of life (QoL). The disease experience is intrinsically linked to the symptoms the patients have, and the symptoms present both diagnostic clues and therapeutic challenges. The assessment of symptoms is therefore a very important aspect of clinical care, especially when patients suffer from intractable illnesses and the primary aim of the care is to give the patient comfort and the best quality of life (Ingham et al., 2010). Assessment of subjective symptoms can be difficult because of absence of specific definition of the symptom and the range of implications associated with the use of them. Also, symptoms changes as the disease progress and treatments are given. Further, different diagnostic groups will experience symptoms in different ways. Symptom assessment aims to quantify aspects of the subjective symptom in a reliable and valid way. Because of this formal validation of the assessment tool intended to use is needed (Ingham et al., 2010).

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

- **Validity**: Does the instrument measure what it intends to measure?
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- Is the same result obtained when repeated by a different investigator (inter observer reliability)?
  - Sensitivity
    - Does the instrument detect clinically meaningful changes?
  - Language
    - Is the instrument formally validated into the appropriate language?
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    - Are there known data (reference data) on the responses of the instrument from the general population?

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

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

**Rationale for this thesis**

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

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Drug monitoring can be used to confirm toxicity, or explain why some patients don’t have any effect of the drug. It can also be used to make sure the patient is taking his
medication. Further, drug monitoring might be a valuable tool if the therapeutic window is narrow, or if there are certain patients who are more at risk for toxicity or drug-drug interactions. In this study serum concentrations of oxycodone and metabolites were assessed together with patient characteristics to see if this could add any valuable information regarding the variability in serum concentration from patient to patient.

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

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

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

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

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

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

Three specific research questions address the overall objectives:

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

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

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

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

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Material and methods

**Patient cohort**

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

The European Pharmacogenomic Opioid Study, EPOS

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

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

Patients attending EPOS were at least age 18 years, verified with malignant disease, able to deliver a blood sample, were regularly scheduled oral, subcutaneous, transdermal or intravenous opioid treatment (morphine, methadone, fentanyl, hydromorphone, bupemorphine, ketobemidone or oxycodone) for their cancer pain with duration of treatment no less than three days. Patients did not have any known contraindications.

The study collected data on pain (Brief Pain Inventory: BPI); health related quality of life (EORTC QL-C30) and cognitive function (Mini mental Status Examination, MMSE) and Karnofsky performance status score. Additional clinical information collected from each patient was: cancer diagnosis, time since diagnosis, presence of metastasis and time since start of opioids, the scheduled opioid treatment for the last 24 hours.
hours and break through-pain, use of non-opioids medications, presence of other diseases and routine clinical laboratory data for assessment of kidney and liver functions and hematological status. Exclusions criteria were not consenting to participate, and not capable of understanding the language used at the study centre. The study included 2294 patients. Data management, pharmacological- and pharmacogenetic analyses were performed in Norway at the Trondheim study centre.

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

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

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

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

Paper III focused on how genetic polymorphisms of the CYP2D6 gene influenced serum concentrations of oxycodone and metabolites, and the clinical outcomes; pain intensity, nausea, tiredness and cognitive function. Two patients were excluded because blood samples from these were not available, and three were excluded because of their compliance could be questionable because neither oxycodone nor its metabolites could be detected in the serum samples. Thus the cohort in this study consisted of 456 patients.

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

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

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

Serum concentration analyses by liquid chromatography - tandem mass spectrometry

Serum analyses of oxycodone, norexycodone, oxymorphone and norexynormorphine were carried out using a liquid chromatography - tandem mass spectrometry (LC-MS/MS) system. Details on sample preparations, the liquid chromatography- and tandem mass spectrometry conditions, together with data on validity and limits of detections are described in detail in paper 1.

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

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

The compounds leave the column as liquids and are immediately evaporated to charged molecules (M+) when entering the mass spectrometer. A triple quadrupole mass spectrometer is used to charge ratio of charged particles. Thus this system has the ability to separate and quantify compounds with a high specificity and sensitivity.

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spectrometer consists of two quadrupole mass spectrometers in series. In this way we have two mass-filters in series. In the first quadrupole the molecular ions (M+) of the compound of interest are filtered from the complex matrix (e.g. serum, plasma, urine). In the second quadrupole these M+ ions collide with inert gas e.g. N2. This collision is controlled in such a way that your M+ ions are fragmented to pre-specified fragment ions. The most abundant of these fragment ions are selected for detection in third quadrupole, while all other ions go to waste. This type of analysis is called multiple-ions-monitoring (MRM) and was used in the serum concentration analyses of opyrnolone and metabolites. This feature makes the tandem mass spectrometry analyzer to be highly sensitive and specific tool for quantifying compounds.

### Determination of the CYP2D6 genotypes

The gene coding for the cytochrome 450 2D6 (CYP2D6) enzyme is located on chromosome 22. This gene has more than 80 known allelic variants, and CYP2D6 enzyme activity varies from non-functional to ultra rapid metabolism. The allelic variants divide a population into four genetic groups; poor metabolizers (PM) with two non-functional alleles, intermediate metabolizers (IM) with one non-functional and one functional allele or two alleles with decreased function, extensive metabolizers (EM) with to functional alleles (wild type) and ultra rapid metabolizers (URM) with more than two copies of functional alleles. The allele frequencies differ substantially between different ethnic groups (Zanger et al., 2004, Scrofano et al., 2004). In the Caucasian population about are 5-10% poor metabolizers, 10-15% intermediate metabolizers, 72-84% extensive metabolizers and 1-3% are ultra rapid metabolizers (Zanger et al., 2004, Spigset, 2001). The CYP2D6 functional polymorphisms can be distinguished either by genotyping or phenotyping methods. A phenotype is an observational characteristic and can be determined by calculating the mother substance to metabolite ratios (Zanger et al., 2004). Eg. debrnemorpharpy can be used to determine the CYP2D6 phenotypes by

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

In this large cross-sectional study with the complexity of the patient population included, genotyping was the only procedure that from a practical point of view allowed for grouping the subjects as of poor-, intermediate-, extensive- and ultra rapid metabolizers. With more than 80 known allelic variants of the CYP2D6 gene, it was necessary to make a selection which to study. The Department of Pathology and Medical Genetics, St. Olav University Hospital, routinely screens for relevant CYP2D6 allelic variants to determine PM, IM, EM and UBM. They have chosen a panel of variants that show clinically significant alteration of enzyme activity, omitting those that have no verified or insignificant effect on drug metabolism in vivo or that are extremely rare. We chose to analyze these routine allelic variants as the aim was to make judgments closely related to everyday clinical and laboratory practice. Their methods were adopted and the work was carried out in their laboratory and with their instrumentation. The methods and details on the genotyping are described in detail in Paper III. The allelic variants detected was CYP2D6*2c2 (duplication), CYP2D6*5 (deletion) and *3, *4, *6, *7 and *8 (SNP mutations). Samples that were negative for all mutations in the test panel were for practical purposes categorized as CYP2D6*1 (functional) variant.

Accordingly the four major mutated allele variants *2, *4, *5 and *6 accounts for 90-99 % of the PM allelic variation in Caucasian population (Sachse et al., 1997, Scordo et al., 2004). In addition to the CYP2D6*2c2 duplication (frequency 1.34 %), Sachse et al.’s study showed that duplications of the alleles *1c2 was present in the Caucasian population with a frequency of 0.51 %. Duplications of *1c2 was not included into our duplication analyses, thus it is possible that we have missed about 2 ultra rapid metabolizers as a result of these alleles lacking in the analyses.

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Brief pain inventory (BPI) Pain severity in study II and III was assessed using the item “Pain on average last 24 hours” from the Brief Pain Inventory (BPI). The Pain Research Group at MD Anderson Cancer Centre has developed the Brief Pain Inventory to assess the severity of pain and the impact of pain on daily functions in patient with cancer pain or patients with other chronic diseases that causes pain. The assessment can be done by self-report, interview or via an Interactive Voice Response System (IVR). The questionnaire assess the severity of pain, impact of pain on daily function, location of pain, pain medications, and amount of pain relief in the past 24 hours or the past week. The BPI uses numeric rating scales (NRS) from 0 to 10. On the BPI, mild pain is defined as a worst pain score of 1 - 4, moderate pain is defined as a worst pain score of 5 - 6, and severe pain is defined as a worst pain score of 7 – 10 (Serlin et al., 1995). The BPI has been translated into seventeen languages, and is validated in at least 7 languages (Caraceni et al., 1996, Rainbird et al., 1999, Larue et al., 1995, Semaan et al., 1999, Uli et al., 1998, Cleeland et al., 1989).

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

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

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

The EORTC QLQ-C30 has been translated and validated into 11 languages and is used in more than 3,000 studies worldwide. The questionnaire contains five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health and a quality-of-life scale, which assess additional symptoms commonly reported by cancer patients (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties).

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

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

\[ Score = \frac{RS - \text{range}}{range} \times 100 \]

RS = Raw Score = the mean of the component items: RawScore = \{I, I + 1, I + 1, ..., I\} / n and range = is the difference between the possible maximum and the minimum response to individual items. Items which take values from 2 to 4 have a range of 3.

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

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

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

**Karnofsky performance status**

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

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

**Karnofsky performance status**

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

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Statistical methods

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

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

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

Spearman rank correlations

Used in paper I to assess the relationships between

1. Total daily dose of oxycodone and serum concentrations of oxycodone, its metabolites and metabolite/oxycodone ratios.
2. Serum concentrations of oxycodone and its metabolites.
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- To explore the associations between the continuous outcomes; pain and cognitive function, and serum concentrations of oxycodone and metabolites and the other variables that potentially might influence pain and cognitive function (Paper II).

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

**Multiple linear regressions** analyses were used to assess
- The effect of patient variables on log-transformed serum concentrations of oxycodone and oxymorphone/oxycodone ratios. The analyses were performed in a manually backward stepwise manner because data covering all variables for all patients were not available. The criterion for removal of a variable was set to \( p > 0.1 \), and two-sided \( p \)-values \( \leq 0.05 \) were considered statistically significant in the final model (Paper I).
- The relationship between pain and cognitive function, and serum concentrations of oxycodone and metabolites together with the variables that had passed the \( p \leq 0.1 \) criteria from the bivariate regressions. The analyses were performed in a manually backward stepwise manner, in the same way and with the same criteria for statistical significant levels as described for paper I (Paper II).

**Analyses of variance (One-way-ANOVA)**
- To compare continuous demographics and characteristics between the CYP2D6 genetic groups (Paper III).

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Analyses of covariance (ANCOVA) and logistic regressions

The categorical demographic and characteristic data used in the logistic regression analysis were treated using ANCOVA. For the logistic regression, the dependent variable was log odds ratios of the categorical demographic characteristics, with the independent variable being the categorical characteristic. The covariates used in the logistic regression analysis were the categorical demographic characteristics and characteristics, and the covariates used in the logistic regression analysis were the categorical demographic characteristics and characteristics.

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- To compare serum concentrations of oxycodone and oxymorphone, and oxymorphone/oxycodone ratio between users and non-users of CYP2D6 inhibitors. Two-sided p-values ≤ 0.05 were considered statistical significant (Paper I).

- To compare serum concentrations between "treatment success" and "treatment failure" groups. From these analyses both un-corrected and Benjamin-Hochberg corrected p-values were reported. Benjamin-Hochberg corrected p-values ≤ 0.05 were considered statistically significant (Paper II).

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

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

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

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

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

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Summary of papers

Paper 1 Influences on the pharmacokinetics of oxycodone – A multicentre cross-sectional study in 439 adult cancer patients

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

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

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

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

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

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

Use of CP226 inhibitors did not influence oxymorphone to oxycodone ratio. Concomitant medication with CPY344 inhibitors reduced the normoxycodone/oxycodone ratio and increased oxycodone concentrations. The use of CPY344 inducers influenced all three examined outcomes; decreased oxycodone serum concentrations, increased oxymorphone/oxycodone and normoxycodone/oxycodone ratios.

Other variables that predicted serum concentrations and/or ratios were “time from last oxycodone dose”, number of medications taken in last 24 h, “time from last dose to blood sample”, albumin, ceruloplasmin, BMI and GFR. The regression analyses explained 5.35 % of the variability in oxycodone serum concentrations and the ratios oxymorphone/oxycodone and normoxycodone/oxycodone.

Sex differences related to opioids and metabolism may also be true in a cancer population. Drug–drug interactions related to CP226 is probably of little clinical significance; however use of CPY344 inducers or inhibitors should be carefully monitored as these might significantly influence the serum concentrations which may possibly change the effects of oxycodone. Other characteristics explained only minor parts of the variability of the outcomes.

Finally, the variables including daily dose explained 1/3 of the variability of oxycodone serum concentrations and only minor parts of the variability of the ratios in this population.
The aim of this study was to assess whether there is a relationship between oxycodone concentrations and pain intensity, cognitive functioning, nausea or tiredness in cancer patients. Also, oxymorphone and oxycodone contributions to analgesia and the adverse effects of oxycodone were assessed.

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

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

Several factors may have contributed to the lack of concentration-effect relationships:

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

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

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

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

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

Oxycodone is extensively metabolized in the liver by CYP3A4 enzymes and also by the variably expressed CYP2D6 enzymes. The aim of this study was to assess the relationship between oxycodone pharmacokinetics, pharmacodynamics and CYP2D6 genotypes for metabolizer (PM, n = 27), extensive metabolizer (EM, n = 413) and ultra rapid metabolizer (URM, n = 19) in 450 cancer patients chronically administered with oxycodone for their cancer pain.

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

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

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

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

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

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

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Discussion

Methodological considerations

Studying cancer patients

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

The cancer patients in this study are selected from a rather large cross-sectional multi-centre study that aimed to achieve a representative sample of cancer patient using opioids and being above the age of 18 (Klepstad et al., 2011). Thus, the inclusion criteria in this study were wide. The cross-sectional design ensures high compliance due to its short duration. However, the data missing rates for the self-reported questionnaires (EORTC QC30 and BPI) in this study were about 8-10 %, while when it came to the Karnofsky score, administered by the investigator, it was complete.

The cross-sectional design

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

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

Blood sampling and assessments of subjective symptoms
In this study only one blood sample from each patient was taken. Most of the participants were in-patients and their blood sample was taken at trough, while the out-patients gave their blood sample at the same time as their assessments. When the patient is at steady-state, as most of these chronic pain patients on controlled release oxycodone were, then the drug serum concentration and their tissue ratios will remain relatively constant during the 12 h administration periods. A more significant impact on this ratio occurs when immediately release rescue doses are taken, which occurred in about 44 % of our patients. Thus in study 1 the time since scheduled dose or rescue dose was calculated (= “time since last dose”) and the “total daily dose” (= sum of scheduled dose + break trough dose) was used, and were variables included in the analyses.

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

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

Also, we were interested in the general well-being of the patient with regards to side effects. As with pain, side effects also vary throughout the day. Since the EPOS study included the EQ-5D (1990 version 3.0), elements from this self-reported questionnaire were used for these assessments. Also, here we focused on the average symptom burden, and recall of tiredness and nausea for the last week was chosen. A problem with using these measurements is that what you measure not necessarily reflects the opioid treatment (the measurement does not say anything about the cause), but those are symptoms that opioids are known to cause.

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

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

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

Statistical considerations

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

In the study where we compared "treatment success" against "treatment failures" we did four multiple comparisons between the groups (causes, tiredness, cognitive function and compassion). Multiple comparisons increase the risk of making a type I error. We therefore used the Bonferroni correction. This means that if we have n comparisons and if all the comparisons are independent, the probability of obtaining a significant result by chance alone is decreased by a factor of n. This is done by dividing the desired level of significance (usually 0.05) by the number of comparisons. The resulting level of significance is then used to determine the significance of the individual comparisons.
by $P = \alpha^2$ where $\alpha = 0.05$, and $n =$ number of comparisons. A draweeck with this very conservative method, is that it decreases the statistical power. We chose to use a less conservative method in the comparisons of “treatment success” and “treatment failure” groups, namely the Hochberg correction method (Benjamini and Hochberg, 1995). This method gives a greater statistical power, by allowing for a lesser strict control of the error rate. This method is also designed to cope with situations in which sample sizes are very different (Field, 2009b).

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

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

**Result discussion**

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

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

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Three specific research questions address the overall objectives and will be discussed separately:
Can commonly recorded patient characteristics predict serum concentrations of oxycodone itself or the metabolic pathways, CYP260 and CYP344 as indicated by the metabolic ratios? 

Large inter-individual variations in dose requirements is a well-acknowledged phenomenon when administering opioids (Faura et al., 1998; Dale et al., 2009) and oxycodone is no exception (Leow et al., 1995, Pan et al., 2007). Also, large inter-individual variation is seen in the serum concentrations (Klepstad et al., 2003a) and also in the response to opioids (Kaiio et al., 1983). This makes it difficult to predict an effective dose for the patients. Kinetic studies of oxycodone have established the absorption, distribution, metabolism and excretion of this drug and its metabolites. These factors may be affected by patient characteristics. Little is known about how patients' characteristics contribute to the inter-individual variability in serum concentrations of oxycodone. However, Kaiio et al. (Kaiio et al., 1996) and Kirvela et al. (Kivela et al., 1996) showed that patients with renal impairment have increased oxycodone and noroxycodone serum concentrations and prolonged elimination. Further, patients with hepatic impairment also have increased oxycodone serum concentrations and prolonged elimination (Kaiio, 1997, Tallback et al., 1997). One single dose study in healthy volunteers has assessed the relationships between pharmacokinetics of oxycodone and age and gender (Kaiio et al., 1996b). Further, Liukas et al. (Liukas et al., 2000) assessed the influence of age after a single dose of oxycodone in forty post-orthopedic surgery patients. Liukas et al. showed that patients above age of 70 had slower clearance, longer t1/2 and more than twofold higher mean plasma oxycodone concentrations than those less than 41 years of age. However, in Kaiio et al.'s study no statistical difference between age and gender in AUC0-∞ for oxycodone and noroxycodone was found, but men had statistical higher AUC0-∞ for oxymorphine. This study also showed that the women who had the highest oxycodone serum concentrations, also had the strongest drug effects and compared with men also had more adverse events.

The first part of this thesis aimed at identifying factors that might contribute to the large variability observed in serum concentrations of oxycodone, and also explore which factors affect the CYP3A4 and CYP260 metabolic pathways by exploring associations

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

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

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

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

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

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

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diphenhydramine (2S)-2-[2-(cyclohexylmethyl)cyclohexyl]ethylamine hydrochloride (HCl) and theophylline (Theo-2000) as positive controls. The results are expressed as the mean ± standard deviation (SD) of three independent experiments.

The plasma concentration of theophylline was measured by high-performance liquid chromatography (HPLC) with a reversed-phase column and a UV detector. The plasma concentration of diphenhydramine was measured by HPLC with a reversed-phase column and a UV detector. The plasma concentration of diphenhydramine was measured by HPLC with a reversed-phase column and a UV detector.

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

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

The oxycodone/oxycodone ratio is predicted to increase slightly with decreasing GFR (predicted a 4% increase in ratio when going from a GFR of 60 ml min⁻¹ 1.73 m² to 40 ml min⁻¹ 1.73 m²). Further, the oxycodone/oxycodone ratio is predicted to decrease slightly with decreasing serum albumin levels (about 13% when going from 33 g l⁻¹ to 23 g l⁻¹).

The polymorph CP226 regulated pathway showed the lowest explained variability, and was only associated with a few of the characteristics explored. Total daily dose, CYP3A4 inducers and number of medications except opioids taken last 24 h contributed about equally to the low explained variability of 5%. However, use of CYP3A4 inducers predicted the highest effect on this ratio, with users of such inducers were predicted to have a four times higher oxymorphine/oxycodone ratio than non-users. Also, going from using one to using six co-medications other than opioids is predicted to reduce the oxymorphine/oxycodone ratio by 24%.

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

The results from study I showed that predicting serum concentrations is difficult. However, the released correlations between total daily dose and serum concentrations of oxycodone (r = 0.7), noroxycodone (r = 0.8) and noroxynormorphine (r = 0.7) were high, and the correlation with oxymorphine was good (r = 0.6). However, from a clinical point of view it may be more interesting to examine if the efficacy of oxycodone metabolites/oxycodone ratios. Further, several other variables contribute but most of the variability seen is still unaccounted for.

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

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

Further, Beninger et al. (Beninger et al., 1997) studied the pharmacokinetics and pharmacodynamics in 22 healthy males after 20 mg CR oxycodone. Plasma samples were collected 0-48 h after dosing and C050, T600 and AlCo-os s=s was calculated. Pharmacodynamics assessed were the same as those in Kakei et al.'s (Kakei et al., 1996b) study; drug effect questionnaire, mood, sedation, pupil size and respiration. A linear relationship was found between oxycodone plasma concentrations and pupil size, respiratory rate, sedation and most of the items from the drug effect questionnaire. The correlation was strongest between concentrations of oxycodone and pupil size (r = -0.53); no significant correlation between pupil size and oxycodone plasma concentration (r = -0.53); no significant correlation with oxymorphone were found. The strongest correlation was found between oxycodone concentrations and "drug effect" (r = 0.57). The study also showed that those with the highest "drug effect" also had the highest incidents of opioid-related side effects and the highest oxycodone plasma concentrations.

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

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

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

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

Microdialysis, a technique that makes it possible to measure real-time unbound drug in both the extracellular fluid of the brain and blood, of rats has shown that the oxcycloidine concentration in brain in steady state was three times higher than the concentration measured in the blood (Bostrom et al., 2006), and compared to morphine the brain concentration was six fold higher (Bostrom et al., 2008). These studies indicate that oxcycloidine is actively transported over the blood-brain barrier. Still unproven, it is possible that oxcycloidine is actively transported into the brain also in humans. This process may be subject to genetic variability (Schewch et al., 2005), and may therefore contribute to impair the relationship between serum concentrations and effects.

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

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

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

It is also worth mentioning that the studies where a relationship between blood concentrations and effects of oxycodone have been found have been single-dose studies with healthy volunteers. In these studies the groups of participants are much more homogeneous than in studies with patients, and especially untreated cancer patients. In Kalie's and Benziger's studies time-plasma concentrations curves and time-effect curves were compared while in our study we did not have the ability to follow the concentration over time, also we did not have baseline measurements of any of the outcomes. Also, the outcomes between the healthy volunteer studies, and the patients' studies were different, and only in the patients' studies assessed the pain-concentration relationship. The only comparable assessments are the subjective drug effect questionnaire used in both studies with healthy volunteers and in Heiskanen's study with cancer patients. In Heiskanen's study no association was found, while the studies with healthy volunteers showed associations. These studies had all about the same number of participants (n = 20-25) so this does not explain the results, however the difference in the patients (healthy versus cancer) could also be a reason for the different results.

As unexpected finding was the proportional association between the serum concentration of the potent µ-agonist oxymorphone (Mayoys et al., 2010, Sloan, 2008) and pain intensity. The increase may be clinically relevant as a patient with 1.0 ml oxymorphone was predicted to have an average pain intensity of 4.1 NRS on the BPI, while patients with 1.5 ml oxymorphone were predicted to have an average pain of 3.8 NRS. This is difficult to explain, but this result was also reflected in the sub-group analyses where serum concentration of oxycodone and metabolites in patients who were pain relieved and without side effects (treatment success) were compared to those who had poor pain control and side effects (treatment failures). These analyses showed cancer patients. These tools are not specific for the opioid treatment; rather they give an overall picture of the patients' subjective symptoms and their well being. Nevertheless, these tools may not provide the specific power required for establishing concentration-effect relationships. This relates especially to the fact that the symptoms are not specific for the opioid treatment, but may also be caused by the disease itself, or an additional cancer treatment given.

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

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

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

In paper III we showed that CYP2D6 genotypes explain variability in pharmacokinetics of oxycodone. In this cancer cohort PMs had lower serum concentrations of oxymorphone and norexymorphone, than EMs and URM, while there were no difference between EMs and URM in serum concentrations of these metabolites. Further, no difference in oxycodone serum concentrations between the CYP2D6 genotypes was found. Our findings are supported by the two other studies in humans; Zwisler et al. (Zwisler et al., 2010) compared the oxycodone requirements between PM and EM metabolizers. In the analyses of Klepstad et al. did. This might be because the concentration ranges were very wide. However, the serum concentrations of oxycodone, oxymorphone, noroxycodone and noroxymorphone were statistically significant different between the "success" and "failure" groups for tiredness, and in the analysis of tiredness the number of "successes" were low. Thus, tiredness in combination with poor pain control seems to be the most common reason for being unsuccessfully treated. The "failures" also had the highest oxycodone doses. This suggests that these patients are overdosed and that oxycodone is not the choice of drug to these patients.

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In the present study we did not find any difference in the pharmacodynamics assessed (pain intensity, tiredness, nausea, cognitive function) between the CYP2D6 genotypes. How the CYP2D6 genotype affects the pharmacodynamics of oxycodone was recently assessed by others. Assessments of experimental pain in healthy volunteers after a single dose of oxycodone, argues for a difference in the pharmacodynamics between PM, EM and UBM (Zwierler et al., 2009, Samer et al., 2010b). The studies involving patients have, however, not been able to confirm differences in pharmacodynamics between CYP2D6 genotypes (Zwierler et al., 2010, Lemberg et al., 2010). Zwierler et al. (Zwierler et al., 2009) compared the efficacy of oxycodone after 20 mg administration between 16 EM and 17 PM healthy volunteers. Their study included assessments of noceboic tests (electrical sural nerve stimulation and cold pressor test) which were assessed several times from 0-4 hours after administration, and side effects (e.g., tiredness, nausea and ability to concentrate) which were continuously reported. The results from the study showed that EMs experienced a better analgesic effect from the drug than the PMs did, and that this difference was largest 1-2 hours after administration. There was no difference in side effects between PM and EM, which is in accordance with the findings in our study. In both studies side effects were assessed utilizing similar five point NRS. Zwierler et al. concluded that oxycodone gives less effects in PMs and that the lower oxymporphine/oxycodone ratio of PMs is causing this difference. Further they suggest that oxymporphine probably contributes in the analgesic effect of oxycodone. Zwierler et al.’s and our study differ in time points for the measurements, some of the assessments differ and the cohort is different. Administration of oxycodone is also performed differently. Our samples and assessments were performed under steady-state conditions, while those of Zwierler et al. were done 0-4 hours after a single dose. Possibly oxymorphine contributes to the efficacy of oxycodone only shortly after administration, as shown in the Zwierler et al.

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

Samir et al. (Samir et al., 2018b) assessed antinociception and psychomotor function by using the same test as Zwieter et al. (Zwieter et al., 2009), and they measured pupill size and recorded adverse events. Two PM, 6 EM and 2 URM were assessed after given an oral dose of 0.2 mg/kg body weight. Blood samples and assessments were done at 0 (before drug administration), 0.5, 1, 1.5, 2, 3, and 6 hours. Based on the time-effect curves generated from 0-90 min, PM had less pharmacodynamic effect than EMs and EM had lower effect than URBs. Further, pupill size was unaffected in PMs, while in EM and URM pupill size decreased after oxycodone administration. Finally, the two URBs and the single EM had side effects, while the two PMs did not report any side effects. The pharmacodynamic differences in effects observed were correlated with oxycodone and noroxycodone concentrations, and pupill size was correlated with oxycodone.

Based on these correlations Samer et al. suggest that oxycodone is a major contributor to the efficacy of oxycodone.

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

In summary, the experimental pain tests and continuous monitoring of oxycodone and metabolites show that during single administration in healthy volunteers, oxymorphone seems to contribute to the analgesic effect of oxycodone (Zwieter et al., 2009). PMs seem to be more likely that a possible contribution of oxymorphone was diluted by the fact that our sample is heterogeneous and also not opioid naïve. It could also be that oxymorphone exhibits effect when it has reached its $t_{max}$ 1-2 hours after administration, before oxycodone concentrations reach their $C_{max}$ (about 3 h after oral CR) (Heikkinen and Kalso, 1997).

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

Study implications and future prospective

The evidence so far does not support that metabolites of oxycodeone contributes to the efficacy during clinical samples, thus this drug may be a better choice than morphine for cancer pain patients with hepatic- or kidney failure, due to accumulation of morphine’s active metabolite, 86G. Hepatic and renal failure may cause changes in the pharmacokinetics of oxycodeone, as shown with elevated noreoxycodeone and oxycodeone serum concentrations and prolonged elimination in renal impaired patients, and also increased concentrations and prolonged elimination of oxycodeone in patients with hepatic failure (Kaiko et al., 1996a, Talpeyn et al., 1997, Kivela et al., 1996). From the little clinical evidence that exists this does not seem to have any pharmacodynamic consequence during short-time administration. Our results suggests that this may also be true during chronic administration; 58 % of the patients had albumin levels below normal range (= 35 g/L) and 13 % were suffering from renal disease/dysfunction (GFR = 60 ml min−1 1.73 m−2), and those indicators of hepatic and renal impairment had no influence on serum concentrations of oxycodeone, and no clinical relevance to the noreoxycodeone/oxycodeone ratio. This should, however, be confirmed and we suggest to

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

Our study showed that oxycodone (oxycodone ratio) was negatively associated with body mass index. The prevalence of obese (BMI > 30 kg/m²) people in the world is increasing, and epidemiological studies have shown that obesity is associated with diseases as coronary artery disease, diabetes, hypertension and cancer among others (Hulman and James, 2005). WHO estimates that by 2050, approximately 2.3 billion adults will be overweight and more than 700 million will be obese (World Health Organization, 2016). Thus, an increase in obese patients is expected. However, pharmacokinetic drug studies mainly include non-obese subjects, thus knowledge of drug disposition in obese subjects is currently lacking (Hanley et al., 2010). Obese people have increased adipose tissue, increased total body water, reduced tissue blood flow and increased glomerular filtration rate, which may affect pharmacokinetics and pharmacodynamics of a given drug. For instance, prolonged (\( t_{1/2} \)) is observed in obese with lipophilic drugs (Caetani and Potze, 2005) and nausea and vomiting was more frequent in obese than lean patients after surgery (Lee et al., 2007). As far as we know, no one has assessed how weight affects oxycodone pharmacokinetics and pharmacodynamics, thus we suggest that studies in both obese healthy volunteers and patients should be conducted. The study of oxycodone pharmacokinetics in obese patients is expected.

Two studies in healthy volunteers (Kaiho et al., 1996b, Bengtzer et al., 1997) have found concentration-effect relationships for oxycodone, while in our and Hiskinnen et al.’s (Hiskinnen et al., 2009) clinical setting no relationship was found. The methods used and the patient cohorts were different in these two settings. Because of this, we do not know if the discrepancy is caused by methodological differences or cohort differences. A study that aims to answer why we observe this discrepancy is warranted.

One way of doing such a study could be to include cancer patients with pain into a pharmacokinetic and pharmacodynamic single 20 mg CR oxycodone study where Kaiho et al.’s (Kaiho et al., 1996a) assessment tools (serum concentrations measurements, drug effect questionnaire [ten of the items used by Preston et al., (Preston et al., 1993)], mood, and –pupil size changes and respiratory rate) and assessment intervals (0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 hours) is used. The study of oxycodone pharmacokinetics during chronic treatment in cohorts of patients with hepatic- or kidney failure, especially in those with kidney failure since these had low prevalence in our study.

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

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

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

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Conclusions

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

The conclusion of the specific research questions are as follows:

1. Can commonly recorded patient characteristics predict serum concentrations of (A) oxycodone or oxycodone metabolism by (B) CYP2D6 and (C) CYP3A4 enzymes as indicated by the metabolic ratios?
   - The characteristics explained about 1/3 of the variability of oxycodone serum concentrations and only minor parts of the variability of the ratios in this cancer population.
   - A: Sex, total daily dose, CYP3A4 inducers/inhibitors, and “time from last oxycodone dose” were predictors explaining 35% of the variability in oxycodone concentrations.
   - B: Total daily dose, CYP3A4 inducers and “number of medications taken in last 24 h” explained 5% of the variability in the oxymorphone/oxycodone ratio.
   - C: Total daily dose, “time from last dose to blood sample”, albumin, sex, CYP3A4 inducers/inhibitors, steroids, BMI and GFR explained 19% of the variability in noroxycodone/oxycodone ratio.

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

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

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

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

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

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

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

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Abstract

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

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

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

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

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Introduction

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

The effect of the CYP2D6 genotype on the pharmacodynamics of oxycodone in a clinical setting of patients with cancer pain receiving chronic opioid administration has been observed [7,8]. CYP2D6 has several known polymorphisms that influence drug metabolism. Inactivating polymorphisms cause gene mutations and deletion(s) which result in a non-functional enzyme, whereas gene duplication(s) cause over-expression of active enzyme. Individuals with two non-functional alleles of CYP2D6 are genotyped "poor metabolizers" (PMs, 5-10 % of Caucasians), whilst individuals with one decreased functional allele and one non-functional allele or two decreased functional alleles are "intermediate metabolizers" (IMs, 10-15 % of Caucasians). Persons having two wild type alleles (CYP2D6*1), or one functional and one non-functional allele, are referred to as "extensive metabolizers" (EMs, 72-84 % of Caucasians). Individuals with duplicate(s) of the CYP2D6 gene are "ultra rapid metabolizers" (URMs, 1-3 % of Caucasians). Because poor metabolizers are unable to metabolise CYP2D6 substrates, a drug administered at normal dose may lead to high or toxic levels of the drug [11,12]. On the other hand, an ultra rapid metabolizer may experience reduced or no effect when given a drug which is a CYP2D6 substrate, or may experience adverse drug reactions [13,14]. The CYP2D6 genotype may therefore be of clinical importance for drugs that are metabolized by CYP2D6 enzymes.
not previously been studied. This led us to the following research questions: (1) Do the CYP2D6 genotypes predict oxycodone and metabolite serum concentrations in patients treated for cancer pain? (2) Is the CYP2D6 genotype associated with pain intensity, or the intensity of nausea, tiredness or cognitive function in cancer patients receiving oxycodone?

Materials and methods

Ethics

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

Patients

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

Assessments

At the time of inclusion the following information was collected from each patient: Age, gender, weight, height, ethnicity, medications and dosages, the time interval between last opioid administration and blood sampling, time since opioid treatment started, breakthrough pain, cancer diagnosis and time since diagnosis. Pain severity not previously been studied. This led us to the following research questions: (1) Do the CYP2D6 genotypes predict oxycodone and metabolite serum concentrations in patients treated for cancer pain? (2) Is the CYP2D6 genotype associated with pain intensity, or the intensity of nausea, tiredness or cognitive function in cancer patients receiving oxycodone?

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Serum concentration analyses

Details on handling of blood samples, analytical technique and instrumentation for serum concentration analyses of oxycodone, and the metabolites oxymorphone, noroxycodone and noroxymorphone have been described previously [25]. Pharmacological analyses were carried using a LC-MS/MS system. Correlation was assessed using the item “Pain on the average” from the Brief Pain Inventory (BPI), which has a numeric rating scale (NRS) from 0 (“No pain”) to 10 (“Pain as bad as you can imagine”). The mini mental state (MMS) examination was used to assess cognitive function [17]. Cognitive failure was defined as having a total MMS of 23 or less [18,19]. Functional status was assessed by the Karnofsky performance status [20]. The Karnofsky performance status has a linear scoring from 0-100 %, with higher scores meaning better function. The European Organisation for Research and Treatment of Cancer’s health-related quality-of-life (QoL) questionnaire (EORTC QLQ-C30) version 3.0 was used to assess the patient’s self reported QoL, for the symptoms tiredness, nausea, constipation and depression. Tiredness was assessed using the item “Did you feel depressed?” with alternatives “not at all”, “a little”, “quite a bit” and “very much” for both items. Nausea and constipation were assessed using the symptom scale for nausea and vomiting, and constipation, respectively. Scoring of the symptoms scales were done by a linear transformation to a 0 to 100 scale. A score of 0-24 on these symptom scales corresponds to “not at all”, 25-49 corresponds to “a little”, 50-74 to “quite a bit” and 75-100 to “very much”. Functional methods applied at each centre were used for haemoglobin, creatinine and albumin measurements. Body mass index (BMI) was calculated using the international system of units, BMI = weight (kg) / height² (m²). Renal function was expressed as calculated glomerular filtration rate (GFR) 1.73 m² body surface [23,24]. Blood samples were obtained shortly prior to drug administration of the patients’ scheduled oral opioid medication (trough value). For practical reasons blood samples from out-patients (n = 68) were taken at the time of examination. Blood samples for opioid analyses in serum were collected in tubes with no additives and left at ambient temperature for 30-60 min. before centrifugation at 25000g (approx. 3000 rpm) for 10 min. Serum was then aliquoted and stored at -80°C prior to analysis.

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

CYP2D6 genotyping
CYP2D6*2x2 (duplication) was detected according to the method of Lovlie et al. [26], with some modifications. PCR was performed using the Gene Amp XL PCR kit (Roche/Applied Biosystems, Foster City, New Jersey, USA) in 50 µl reaction volumes with a hot start. The lower reaction mix layer contained 4.5 µl dH2O, 6 µl 3.3 XL Buffer II, 2.5 µl Mg(OAc)2 (25 mM), 4 µl dNTP Mix (10 mM), and 1.5 µl of each primer (10 mM)(Table 1). To separate the lower and upper reaction mix layer, wax was melted on top of the lower reaction mix (80 °C, 3-4 min.), and then cooled to room temperature. Then the upper reaction mix containing 18.5 µl dH2O, 9 µl 3.3 XL Buffer II, 1 µl r 7th DNA polymerase (2 U/µl) and 2.5 µl genomic DNA (5-10 ng/µl) was added.

Long-PCR was carried out on a Techne TC-512 (Bartowond Scientific Ltd, Staffordshire, United Kingdom) with the following conditions: an initial denaturing step of 90°C for 1 min., followed by 35 cycles of 94°C for 1 min., 60°C for 30 s and 68°C for 2 min. (+18 s increase for every new cycle), and a final elongation step of 72 °C for 10 min.

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Long distance and multiplex PCR techniques were combined for the simultaneous detection of the 5 allele groups *3, *4, *6, *7 and *8 in genomic DNA. Patients who lacked these mutations were categorized as having the CYP2D6*1 (functional) allele. With some modifications, these reactions were done in accordance with the method of Stützen et al. [29].

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

Statistics

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

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

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

Multiple testing increases the risk of doing a type 1 error. To minimize this risk, we chose to merge the genotype intermediate metabolizers (IM, n = 170) with the extensive metabolizers (EM, n = 243). For practical reasons we have named this
Analyses were then repeated with inclusion of non-genetic covariates previously found to influence the outcomes [25](Andreasen et al. submitted). For serum concentrations of oxycodone and the metabolites these were: Oxycodone total daily dose, use of CYP3A4 inhibitors or inducers, sex, time since last oxycodone dose, the number of medications other than opioids used last 24 h, albumin serum concentrations, use of steroids, BMI and glomerular filtration rate. Covariates in the analyses of pain intensity were oxycodone serum concentrations, mixed pain, break through pain, paracetamol medication, depression status, constipation status, female reproductive organ cancer and use of fluconazole. Covariates in the analyses of cognitive function were: age, Karnofsky and depression status, use of CYP2D6 inhibitors, steroid medication and breast cancer. Post hoc ANCOVA comparisons between genetic groups were performed with Sidak [31] corrected p-values.

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

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Results

Patients

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

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

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

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<td>Gender: female / male (%)</td>
<td>16 / 11 (59 / 41)</td>
<td>180 / 233 (44 / 56)</td>
<td>2 / 8 (20 / 80)</td>
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</tr>
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<td>Karnofsky performance status (%)</td>
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<td>Body mass index (kg/m²)</td>
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Glomerular filtration rate (ml/min/1.73m²)

- URM (n = 10)
  - 77 (27-239)
  - 96 (24-261)
  - 115 (42-194)

- EM (n = 413)
  - 31 (10-49)
  - 31 (11-91)
  - 29 (22-35)

- PM (n = 27)
  - 31 (0-155)
  - 16 (0-285)
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### Cancer diagnosis:
- Gastrointestinal (inclusive pancreas, liver)
- Lung (inclusive mesothelioma)
- Prostate
- Other urological
- Female reproductive organs
- Haematological
- Head and neck
- Sarcoma
- Skin
- Other
- Unknown origin[^12]

[^12]: number
[^12]: number of users
[^p < 0.05]: p < 0.05
Serum concentrations

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

Genetic analyses

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

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significant lower (p = 0.05) in EM compared to URM, although the result was non-significant after analyses with covariates (p = 0.57) (table 4).

Except from the noroxymorphone serum concentrations, repeating all analyses with inclusion of covariates (ANCOVA analyses) gave similar results with respect to statistical significance (data not shown).

### Table 3

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

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<td>2.3 (1-17)</td>
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<tr>
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<td>2.5 (0-116)*</td>
<td>18.0 (0-500)</td>
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* Statistically significantly different (p < 0.001) from EM and URM

### Table 3

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

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<td>2.5 (0-116)*</td>
<td>18.0 (0-500)</td>
<td>34 (9-194)</td>
</tr>
</tbody>
</table>

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

Median pain intensity was 4 on the NRS for PM and URM, and 3 for EM. The difference in pain intensity was non-significant between the groups (p = 0.8).

There were no difference between the groups in tiredness (p = 0.7) and nausea (p = 0.6). All three genetic groups had a median score of 67 and 17, respectively, for the EORTC QLQ-C30 constipation scale. All three genetic groups had a median score of 28 for EMs, compared to a median of 28 for EMs.

EMs had a median of 33, EMs had median 67 and URMs had a median of 50 on the EORTC QLQ-C30 constipation scale. All three genetic groups had a median score of 2 in depression (table 5).

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Table 4 Post hoc analyses of variance (ANOVA) between the three genetic groups: poor metabolizers (PM), extensive metabolizers (EM) and ultra rapid metabolizers (URM), for the outcomes that showed an overall statistical difference (F-test, both p < 0.005).

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Groups compared</th>
<th>Mean difference between groups (MD)</th>
<th>Std. Error MD</th>
<th>P-value*</th>
<th>95 % CI for MD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deyoxynorphine</td>
<td>PM vs. EM</td>
<td>-1.12</td>
<td>.000</td>
<td>-.12</td>
<td>-.12-.000</td>
</tr>
<tr>
<td>PM vs. URM</td>
<td></td>
<td>-1.12</td>
<td>.000</td>
<td>-.12</td>
<td>-.12-.000</td>
</tr>
<tr>
<td>EM vs. URM</td>
<td></td>
<td>-1.04</td>
<td>.000</td>
<td>-.12</td>
<td>-.12-.000</td>
</tr>
</tbody>
</table>

* The Games-Howell corrected p-values

* No statistical difference (p > 0.05) in noroxynorphine between EM and URM in the analyses of covariance (ANCOVA)
Seven EMs and two URM s used another regular opioid. The exclusion of these patients did not change the results (data not shown).

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

<table>
<thead>
<tr>
<th></th>
<th>Poor Metabolizers</th>
<th>Extensive Metabolizers</th>
<th>Ultra Rapid Metabolizers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain intensity</strong></td>
<td>4 (0-6)</td>
<td>3 (0-10)</td>
<td>4 (0-6)</td>
</tr>
<tr>
<td><strong>Tiredness</strong></td>
<td>67 (0-100)</td>
<td>67 (0-100)</td>
<td>67 (0-100)</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>17 (0-83.33)</td>
<td>17 (0-100)</td>
<td>17 (0-50)</td>
</tr>
<tr>
<td><strong>Constipation</strong></td>
<td>33 (0-100)</td>
<td>67 (0-100)</td>
<td>50 (0-100)</td>
</tr>
<tr>
<td><strong>Depression</strong></td>
<td>2 (1-3)</td>
<td>2 (1-4)</td>
<td>2 (1-2)</td>
</tr>
<tr>
<td><strong>Cognitive function</strong></td>
<td>29 (20-30)</td>
<td>28 (14-30)</td>
<td>29 (20-30)</td>
</tr>
</tbody>
</table>

**Discussion**

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

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

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

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

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

In contrasts, experimental pain studies in healthy volunteers [37,38] observed differences between the three CYP2D6 genotypes. In Zwisl er et al.’s [37] study there were significant differences in oxymorphone serum concentration levels for PM compared to EM, was also demonstrated in a fairly large (n = 270) study in patients with post-operative pain [37,38]. Moreover, Sømer et al.’s [35] study in healthy volunteers showed that PMs had very low oxymorphone and noroxymorphone levels compared to EMs and URM. Thus all studies performed in humans consistently show that CYP2D6 genotypes alter the pharmacokinetics of oxycodone.

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

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

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

The patients included in this study are heterogenic with regard to characteristics that may affect pain intensity and other symptoms. In studies on healthy volunteer pain was a difference between EM and PM in analgesic effect of oxycodone on pain detection threshold, tolerance threshold and the cold pressor test. Samer et al. [38] showed differences in pain tolerance- and subjective pain thresholds (URM > EM + PM) and differences between URM and EM in psychomotor tests (p < 0.05). However, an important shared limitation is that these two studies were single dose oxycodone studies performed in healthy volunteers.

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18
Conclusion

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21. Games PA, Howell JF (1976) Pairwise Multiple Comparison Procedures with Unequal
Appendix

Brief pain Inventory
EORTC QLQ C30
Minimental state (MMS)
Karnofsky performance status

Appendix

Brief pain Inventory
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Minimental state (MMS)
Karnofsky performance status
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<thead>
<tr>
<th>Spørsmål</th>
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**Abstract:**

**AOPPORTUNITETSVÆRN**

*Tilføjelse af eleven i den øvrige klasserum med sikkert bade bryst: 15 sletter*  
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### Karnofsky Index

#### Kriterier for aktivitetsnivå og kjemoterapiisk behov

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<tr>
<th>Aktivitetsnivå</th>
<th>Nivå</th>
<th>Mobiliseringsnivå</th>
<th>Dødsfall</th>
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<tr>
<td>Uført normal aktivitet, kompetanseforløsner stall</td>
<td>100%</td>
<td>Nøyaktig plagsam med subjektiv taper i stjærhod.</td>
<td>Dødegang</td>
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<td>Uført normal aktivitet, kompetanseforløsner stall</td>
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<td>Uført normal aktivitet, kompetanseforløsner stall</td>
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<td>Nøyaktig plagsam</td>
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Dissertations at the Faculty of Medicine, NTNU

1986

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

1985


1984

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

1983


1982

8. Jon Hannum: CYTOSTATIC AND CYTOTOXIC ACTIVITY OF HUMAN MONOCYTES AND EFFUSION MACROPHAGES AGAINST TUMOR CELLS IN VITRO

1981


1980

11. Tor-Erik Waldman: ASPECTS OF CONTINUOUS AMBULATORY PERITONEAL DIALYSIS.

1979


1978


1977

16. Tor-Erik Widerøe: ASPECTS OF CONTINUOUS AMBULATORY PERITONEAL DIALYSIS.  17. Lars Bevanger: STUDIES OF THE Ibc (c) PROTEIN ANTIGENS OF GROUP B STREPTOCOCCI.

1976

18. Arne-Olve Jønsson: SOME BIOCHEMICAL, CHEMICAL AND STRUCTURAL PROPERTIES OF MONOCYTE-DERIVED CYTOKINES FROM PATIENTS WITH CHRONIC OBSTRUCTIVE BRONCHITIS

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28. Ola Dale: VOLATILE ANAESTHETICS.

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30. Ola Dale: VOLATILE ANAESTHETICS.

Dissertations at the Faculty of Medicine, NTNU

1986

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

1985


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

1983


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8. Jon Hannum: CYTOSTATIC AND CYTOTOXIC ACTIVITY OF HUMAN MONOCYTES AND EFFUSION MACROPHAGES AGAINST TUMOR CELLS IN VITRO

1981


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11. Tor-Erik Waldman: ASPECTS OF CONTINUOUS AMBULATORY PERITONEAL DIALYSIS.

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Torbjørn A. Fredriksen: CERVICOGENIC HEADACHE.

Anders Waage: THE COMPLEX PATTERN OF CYTOKINES IN URINARY INCONTINENCE.
Bjørn Christian Eidnes: ELECTROSTIMULATION OF THE PELVIC FLOOR IN FEMALE URINARY INCONTINENCE.

Tore B. Halvorsen: PROGNOSTIC FACTORS IN COLORECTAL CANCER.

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