Impact of Gastrointestinal Surgery on Absorption of Oxycodone

Experimental studies in patients with Roux-en-Y gastric bypass and short bowel syndrome

Ladebo, Louise

DOI (link to publication from Publisher):
10.54337/aau432703049

Publication date:
2021

Document Version
Publisher's PDF, also known as Version of record

IMPACT OF GASTROINTESTINAL SURGERY ON ABSORPTION OF OXYCODONE

EXPERIMENTAL STUDIES IN PATIENTS WITH ROUX-EN-Y GASTRIC BYPASS AND SHORT BOWEL SYNDROME

BY
LOUISE LADEBO

DISSERTATION SUBMITTED 2021

AALBORG UNIVERSITY
DENMARK

IMPACT OF GASTROINTESTINAL SURGERY ON ABSORPTION OF OXYCODONE

EXPERIMENTAL STUDIES IN PATIENTS WITH ROUX-EN-Y GASTRIC BYPASS AND SHORT BOWEL SYNDROME

PHD THESIS

by

Louise Ladebo

AALBORG UNIVERSITY
DENMARK

AALBORG UNIVERSITY HOSPITAL

Dissertation submitted 2021

Dissertation submitted: April 2021

PhD supervisor: Prof. Anne Estrup Olesen, PhD, M.Sc. (Pharm)
Aalborg University Hospital
Aalborg University, Denmark

Assistant PhD supervisors: Prof. Asbjørn Mohr Drewes, MD, DM.Sc., PhD
Aalborg University Hospital
Aalborg University, Denmark

Prof.Emer. Lona Louring Christrup, PhD, M.Sc. (Pharm)
University of Copenhagen, Denmark

PhD committee: Professor Karen Dybkær (chairman)
Aalborg University

Clinical Professor Kim Peder Dalhoff
University of Copenhagen

Professor Thorsten Lehr
Saarland University

PhD Series: Faculty of Medicine, Aalborg University

Department: Department of Clinical Medicine

ISSN (online): 2246-1302
ISBN (online): 978-87-7210-927-5

Published by:
Aalborg University Press
Kroghstræde 3
DK – 9220 Aalborg Ø
Phone: +45 99407140
aauf@forlag.aau.dk
forlag.aau.dk

Printed in Denmark by Rosendahls, 2021

CV

Louise Ladebo

Born in 1992, Odense, Denmark

Current position

2020 – now	Academic employee at Steno Diabetes Center Copenhagen
2017 – now	PhD student at Aalborg University, Department of Clinical Medicine and Mech-Sense, Department of Gastroenterology and Hepatology, Aalborg University Hospital.

Education

2017	M.Sc. Pharm at University of Southern Denmark.

Research interests

I strive to define the best treatment guidelines for patients through well-designed clinical trials and computer-based mathematical modelling.

Stay abroad

Location: 3 months at the Australian Centre for Pharmacometrics, University of Southern Australia, Adelaide, Australia.

Purpose: develop a population pharmacokinetic-pharmacodynamic model of oxycodone in healthy participants.

Outcome: data processing and analysis, “R” language, use of the NONMEM software for population analysis.

Publications

1. **Ladebo L**, Pedersen PV, Pacyk GJ, Kroustrup JP, Drewes AM, Brock C, Olesen AE. Gastrointestinal pH, motility patterns and transit times after Roux-En-Y gastric bypass. Obes Surg. 2021: E-pub.

2. **Ladebo L**, Foster DJR, Abuhelwa AY, Upton RN, Kongstad KT, Drewes AM, Christrup LL, Olesen AE. Population pharmacokinetic-pharmacodynamic modelling of immediate and controlled-release formulations of oxycodone in healthy volunteers. Basic Clin Pharmacol Toxicol. 2020: 126(3):263-276.

3. Simoni AH, **Ladebo L**, Christrup LL, Drewes AM, Johnsen SP, AE Olesen. Chronic abdominal pain and persistent opioid use after bariatric surgery. Scand J Pain. 2020: 20(2):239-251.

4. Olesen AE, **Ladebo L**, Drewes AM. Kapitel 39: Smertefysiologi & Analgetika, Basal og Klinisk Farmakologi af Brøsen K, Dalhoff K & Simonsen U. 6. udgave. FADL's Forlag. 2019.

5. Thuesen AD, Finsen SH, **Rasmussen LL**, Andersen DC, Jensen BL, Hansen PBL. Deficiency of T-type Ca2+ channels Cav3.1 and Cav3.2 has no effect on angiotensin II-induced hypertension but differential effect on plasma aldosterone in mice. Am J Physiol Renal Physiol. 2019: 317(2):F254-F263.

6. Stage TB, Graff M, Wong S, **Rasmussen LL**, Nielsen F, Pottegård A, Brøsen K, Kroetz DL, Khojasteh SC, Damkier P. Dicloxacillin induces CYP2C19, CYP2C9 and CYP3A4 in vivo and in vitro. Br J Clin Pharmacol. 2018: 84(3):510-519.

7. **Ladebo L**, Olesen AE. Do genes affect morphine response? Pharmacogenomics. 2017:18(17):1553-1555.

LIST OF PAPERS

This thesis is based on the following papers:

I. **Ladebo L**, Pedersen PV, Pacyk GJ, Kroustrup JP, Drewes AM, Brock C and Olesen AE. Gastrointestinal pH, motility patterns and transit times after Roux-en-Y gastric bypass. Obes Surg. 2021: E-pub.

II. **Ladebo L**, Foster DJR, Abuhelwa AY, Upton RN, Kongstad KT, Drewes AM, Christrup LL, Olesen AE. Population pharmacokinetic-pharmacodynamic modelling of liquid and controlled-release formulations of oxycodone in healthy volunteers. Basic Clin Pharmacol Toxicol. 2020: 126(3):263-276.

III. **Ladebo L**, Abuhelwa AY, Foster DJR, Upton RN, Kongstad KT, Pacyk GJ, Kroustrup JP, Drewes AM, Christrup LL, Olesen AE. Effect of Roux-en-Y gastric bypass on the pharmacokinetic-pharmacodynamic relationships of liquid and controlled-release formulations of oxycodone. *Invited for revision: Basic Clinical Pharmacology Toxicology. 2021.*

IV. **Ladebo L**, Neuhoff S, Steffansen B, Drewes AM, Christrup LL, Olesen AE. A physiological pharmacokinetic model of immediate- and controlled-release oxycodone: Absorption refinement and extended application. *In preparation. 2021*

V. **Ladebo L**, Vinter-Jensen L, Hestvang J, Mikkelsen MS, Christrup LL, Drewes AM and Olesen AE. Oral absorption of opioids in patients with short bowel syndrome. *Submitted: Scandinavian Journal of Gastroenterology. 2021*

ABBREVIATIONS

ADAM Advanced Dissolution, Absorption and Metabolism

BMI Body mass index

CNS Central nervous system

CRF Controlled-release formulation

EC_{50} Half maximal effective concentration

PBPK Physiological-based pharmacokinetic modelling

pK_a acid dissociations constant

PKPD Pharmacokinetic-pharmacodynamic modelling

RYGB Roux-en-Y gastric bypass

SBS Short bowel syndrome

WMC Wireless motility capsule

ENGLISH SUMMARY

Gastrointestinal surgery, associated with resection or bypass, challenges the use of orally administered drugs, as drug absorption may be altered. Approximately, 14 % of gastrointestinal postsurgical patients are chronic opioid users. The consequence that patients may in one end of the spectrum experience inadequate pain relief and in the other end severe side-effects such as respiratory depression and excessive sedation. Oxycodone is one of the most commonly used opioids for treatment of moderate to severe pain. The aim of this PhD thesis was therefore to investigate the impact of gastrointestinal surgery on the pharmacokinetics and pharmacodynamics of different oral oxycodone formulations, as a model for drug absorption in general.

First, to obtain more knowledge of gastrointestinal physiology relating to drug absorption after surgery, 19 patients with Roux-en-Y gastric bypass (RYGB) underwent a standardized assessment using the wireless motility capsule. This capsule can determine the pH, transit time and motility activity of the different gastrointestinal segments. Compared to healthy age- and gender-matched participants, the oro-cecal segment (stomach and small intestine) was characterized by accelerated transit, elevated pH and motility activity, whereas transit time through the colon was longer in patients with RYGB.

Secondly, a randomized, cross-over study was conducted to assess and evaluate the exposure-response relationship of oral solution, lipid-based and water-swellable controlled-release oxycodone formulations administered in 15 healthy participants and 21 patients with RYGB. Pupil diameter was used as a biomarker for the pharmacodynamic profile of oxycodone. A pharmacokinetic-pharmacodynamic model was developed. The model could not demonstrate any pharmacokinetic differences between the two controlled-release formulations in neither of the populations. In comparison to healthy participants, bioavailability of oxycodone was elevated in patients with RYGB.

Thirdly, two full physiological-based pharmacokinetic models (oral solution and controlled-release oxycodone), with absorption predicted using the Advanced Dissolution, Absorption and Metabolism model, were successfully developed and verified against published clinical data. Additionally, simulations in healthy populations of varying age and ethnicity as well as patients with renal and hepatic impairment indicated a need for dose adjustments, which was in reasonable agreement with published data.

Lastly, the absorption profile of oxycodone administered as an oral solution was explored by performing a pharmacokinetic study in six patients with short bowel syndrome. Expectedly, the absorption fraction was significantly reduced in patients with short bowel syndrome compared to reference values obtained in healthy

participants. A positive correlation tended to be present between functional intestinal length and fraction absorbed. Furthermore, maintenance of the colon seemed favorable in regard to higher oxycodone bioavailability (absorption fraction).

In conclusion, gastrointestinal surgery, associated with resection or bypass, impacts the absorption of orally administered oxycodone. In patients with RYGB, the physiochemical properties of a drug may be superior to the formulation design in regard to altered pharmacokinetics. Hence, any of the tested formulations can be prescribed to patients with RYGB, but the increased bioavailability of oxycodone may necessitate dose adjustments to prevent side-effects such as respiratory depression and sedation. This may be further addressed using a combination of pharmacokinetic-pharmacodynamic and physiological-based pharmacokinetic modelling. In patients with short bowel syndrome, lack of functional intestine tended to influence the absorption of oxycodone. Nevertheless, oral solution oxycodone may be used in patients with short bowel syndrome, although drug dosing must be individualized and most patients will presumably require higher doses to obtain therapeutic efficacy. Future studies may apply our results to further develop physiological-based pharmacokinetic models in patients with different gastrointestinal diseases and assist individualization of drug therapy.

DANSK RESUME

Mave-tarm-kanalens blodforsyning, fysiologi og funktion har stor betydning for hvorledes et lægemiddelstof frisættes fra en lægemiddelformulering og optages til blodbanen. Af denne årsag kan lægemiddeldosering til patienter med fysiologiske forandringer i mave-tarm-kanalen, som f.eks. korttarmssyndrom eller gastrisk bypass, være en udfordring. Den forandrede fysiologi kan medføre at patienterne bliver under- eller overdoseret selvom de modtager standarddosis. En del patienter med forandringer i mave-tarm-kanalen har kroniske smerter og har behov for smertestillende medicin. Oxycodon er et af de mest anvendte opioider til behandling af moderate til svære smertetilstande. For at kunne optimere kvaliteten og sikkerheden af fremtidige behandlinger er det således relevant at undersøge, hvorledes kirurgi i mave-tarm-kanalen, i form af resektion eller bypass, påvirker den farmakokinetiske og –dynamiske profil af oxycodon administreret i forskellige lægemiddel-formuleringer.

Transittid, pH og motilitet blev karakteriseret i de forskellige gastrointestinale segmenter hos 19 patienter med Roux-en-Y gastrisk bypass (RYGB) ved brug af en trådløs motilitetskapsel (wireless motility capsule). Sammenlignet med referenceværdier fra raske personer var det oro-cecale segment (mavesæk og tyndtarm) hos patienter med RYGB karakteriseret ved kortere transittid samt øget pH og motilitet, mens transittiden i tyktarmen var længere.

Et randomiseret overkrydsningsstudie, undersøgte dernæst den farmakokinetiske og -dynamiske profil af oxycodon administreret som oral opløsning, lipid-baseret- og kvældbar-depottablet i 15 raske forsøgsdeltagere og 21 patienter med RYGB. Pupildiameteren blev anvendt som biomarkør for den farmakodynamiske profil. Baseret på disse data blev en farmakokinetisk-farmakodynamisk model udviklet. Modellen viste, at der ikke var farmakokinetiske forskelle mellem de to depotformuleringer, hverken hos raske forsøgsdeltagere eller patienter med RYGB. Dog havde oxycodon generelt en højere biotilgængelighed i patienter med RYGB sammenlignet med raske deltagere.

To fysiologisk-baseret farmakokinetiske modeller (oral opløsning og depottablet oxycodon) blev herefter udviklet og verificeret ift. klinisk observerede data. Lægemiddelabsorptionen blev beskrevet vha. den såkaldte Advanced Dissolution, Absorption and Metabolism model, som tillader simulering af absorptionen af oxycodon efter administration af forskellige formuleringer samt at undersøge effekten af forskellige fysiologiske forandringer i mave-tarm-kanalen. De to verificerede modeller blev brugt til at simulere farmakokinetiske parametre i raske populationer med varierende alder og etnicitet såvel som patienter med nedsat nyre- og leverfunktion. Simuleringerne indikerede et behov for dosisjusteringer, hvilket var i rimelig overensstemmelse med tidligere publicerede data.

Sidst, men ikke mindst, blev den farmakokinetiske profil for oxycodon, givet som oral opløsning, bestemt i seks patienter med korttarmsyndrom. I sammenligning med referenceværdier fra raske personer, var absorptionsfraktionen af oxycodon hos patienter med korttarmsyndrom som forventet lavere. Der sås en tendens til en positiv sammenhæng mellem funktionel tarmlængde og biotilgængelighed (absorptionsfraktion). Bevaring af tyktarmen syntes desuden at være en fordel ift. en højere biotilgængelighed (absorptionsfraktion) af oxycodon.

Kirurgi i mave-tarm-kanalen, i form af resektion eller bypass, påvirker absorptionen af oralt administreret oxycodon. Hos patienter med RYGB lader det til, at de fysisk-kemiske egenskaber af et lægemiddel har en større betydning for en eventuel ændret lægemiddelabsorption sammenlignet med selve frisætningsmekanismen af forskellige depottabletter. Generisk substitution af depottabletterne, der indgik i undersøgelsen, er sikker at anvende for patienter med RYGB. Dosisjusteringer bør overvejes pga. den øgede biotilgængelighed hos patienter med RYGB. Mere specifikke anbefalinger kan forudsiges ved en kombination af farmakokinetisk-farmakodynamisk og fysiologisk-baseret farmakokinetiske modellering. Hos patienter med korttarmsyndrom, var der en umiddelbar sammenhæng mellem absorptionen af oxycodon og funktionel tarmlængde. Sidst, men ikke mindst, kan oxycodon, administreret som en oral opløsning, anvendes til patienter med korttarmsyndrom. Lægemiddeldosering skal dog individualiseres, og de fleste patienter vil sandsynligvis, som følge af den lavere biotilgængelighed, kræve højere doser for at opnå terapeutisk virkning.

Resultaterne fra undersøgelserne kan i fremtiden bruges til videreudvikling af fysiologisk-baseret farmakokinetiske modeller for patienter med forskellige gastrointestinale sygdomme. Dette kan på sigt medvirke til en individualisering og forbedring af den medicinske behandling hos disse patienter.

ACKNOWLEDGEMENTS

This thesis would not have materialized without the help and support of a number of people to whom I am immensely thankful.

First and foremost, I would like to express my gratitude to my main supervisor Professor Anne Estrup Olesen for giving me the opportunity to perform this exciting PhD project. You are an inspiration and I have learnt so much from our fruitful discussions, your constructive criticism and excellent supervision. I appreciate your inevitable encouragement and have also enjoyed your company during multiple research trips. Especially, the PBPK work-shop in Krakow was memorable. There is no doubt that you have played an important role in my development as a researcher.

I would also like to thank my co-supervisors Professors Asbjørn Mohr Drewes and Lona Louring Christrup. Asbjørn, I envy your enthusiastic energy and work structure. No matter how busy you are, you also have time for small talk and a piece of cake. Your prompt replies and constructive feedback have been and are still highly appreciated. Lona, you have enlightened me with great knowledge within the research fields of pharmacokinetics and opioids. We have also had many intellectual discussions that have helped improve my work.

I would also like to express my gratitude to David Foster and Richard Upton for welcoming me to their group at University of South Australia, in Adelaide, Australia, and for great supervision and introduction to pharmacokinetic-pharmacodynamic modelling. I also wish to thank Ahmad Abuhelwa for his help, supervision and support during my entire stay. I learnt so much from my stay abroad not only professionally, but also personally.

I would also like to acknowledge Sibylle Neuhoff, who has been my personal PBPK tutor. Our multiple virtual training sessions have been extremely informative and I have gained so much from your criticism and reflective questions.

All co-authors deserve a special recognition: Bente Steffansen, Pernille Pedersen, Lars Vinter-Jensen, Henrik Højgaard Rasmussen, Kenneth Kongstad, Jens Peter Kroustrup, Grzegorz Pacyk, Johanne Hestvang and Maja Mikkelsen for contributing to papers I-V.

Moreover, I would like to thank my colleagues at Mech-Sense for creating a pleasant and stimulating work environment. A special thanks to Anne-Marie Wegeberg, who has been a great friend, support and mentor of the Smartpill device, and to Isabelle Myriam Larsen, who made the countless hours in the laboratory fly by with her endless jokes and stories.

Furthermore, I wish to thank all study participants and our collaborators at the Department of Gastroenterology and Hepatology.

Project funders are also highly appreciated. The work was funded by the Talent Management Programme received from Aalborg University and the Hørslev Foundation. Travel expenses were funded by Aalborg University, the Heinrich Kopps Foundation, Augustinus Foundation and Oticon Foundation.

Lastly, I wish to thank Stig, my husband, best friend and father to our son, as well as my entire family and friends for their endless love and support in all aspects of life.

Louise Ladebo, April 2021

TABLE OF CONTENTS

CHAPTER 1. INTRODUCTION

Oral drug formulations are most widely used for the pharmacological treatment of diseases. However, the release rate and hence its absorption is highly dependent on the gastrointestinal physiology, where factors such as composition of gastrointestinal fluids, motility surface area, transporter expression or simply resection play a major role. Thus, therapeutic failure may appear in patients who have pathophysiological changes of the gastrointestinal tract.

1.1. ROUX-EN-Y GASTRIC BYPASS

The Roux-en-Y gastric bypass (RYGB) is one of the most commonly performed bariatric surgeries in the world due to its effectiveness against morbid obesity and obesity related diseases such as diabetes mellitus type 2, obstructive sleep apnea, hypertension etc. The large, sustainable weight loss is achieved by laparoscopically dividing the stomach into a small upper pouch (approx. 30 mL in size) and a gastric remnant. Approx. 75 cm distal to the Treitz, the jejunum is anastomosed end-to-side to the pouch. Finally, the biliopancreatic limb is anastomosed side-to-side with the alimentary limb approximately 150 cm distal to the pouch (Figure 1). This gastrointestinal reconstruction creates a Y-configuration, hence the name "Roux-en-Y". More importantly, it restricts ingestion of large food quantities and affects nutrient uptake, as large portions of the stomach as well as the entire duodenum and initial parts of the jejunum are bypassed. Furthermore, it causes hormonal changes that induce a feeling of satiety (1). Factors which all favor weight-loss.

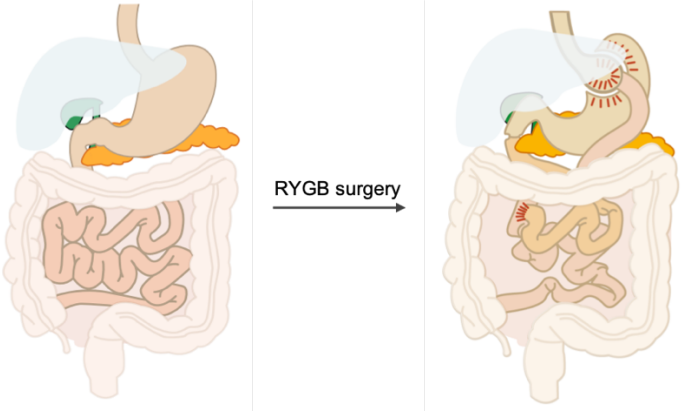

Figure 1. Anatomical differences before (left) and after Roux-en-Y gastric bypass surgery (right).

In the period of 2009-2018 a total of 165.138 RYGB operations were conducted in 51 different countries (2). This number is likely to be increasing, as developing countries become more industrialized and the global obesity epidemic continues(1). Patients with RYGB may constitute a growing health care concern, as postsurgical complications are rather common. Short-term complications may include anastomotic leak, small bowel obstruction, gastrointestinal hemorrhage, dumping syndrome. Long-term complications may include anastomotic stricture, abdominal pain, internal hernias, gall stone formation and nutritional deficiency (3). Hence, other surgery procedures with less complications such as "gastric sleeve" are increasingly in use.

Results from several studies have also demonstrated altered drug pharmacokinetics following RYGB surgery (4,5), which is concerning as many patients are or will be prescribed oral drugs in relation to postsurgical complications, metabolic co-morbidities, psychological conditions or simply age-related diseases. Figure 2 illustrates physiological alterations that may affect the pharmacokinetics of orally administered drugs.

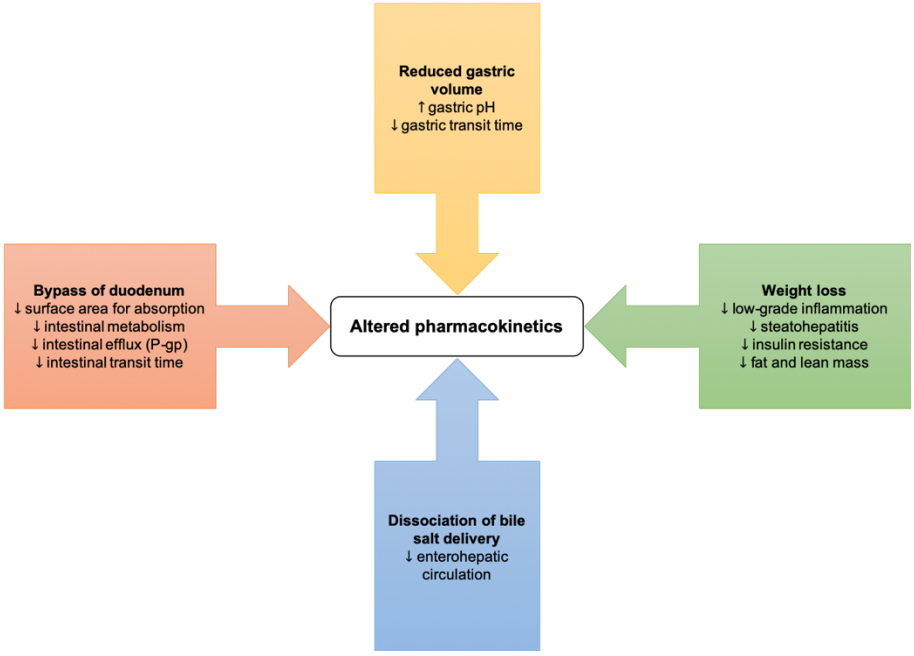

Figure 2. Physiological alterations following RYGB surgery that may affect the pharmacokinetics and subsequent pharmacodynamics of orally administered drugs.

The European Guidelines on Metabolic and Bariatric Surgery recommend substitution of modified-release formulations to immediate-release formulations to minimize risks of reduced drug absorption (6). However, recommendations are not evidence-based.

Additionally, results from a study showed that 75 % of bariatric patients admitted to the hospital were administered modified-release formulations and that only 50 % of these were deprescribed at discharge (7).

Until now, only few studies have addressed the impact of RYGB surgery on drug absorption from modified-release formulations (8–10). In general, the aim of these studies was to determine the effects of surgery-related weight loss on drug pharmacokinetics rather than the surgery itself, as pharmacokinetics was assessed before and shortly after RYGB surgery. Furthermore, the significance of altered pharmacological effects was not assessed. Hence, results were inconclusive with respect to long-term recommendations. Another study addressed the pharmacokinetics of controlled-release oxycodone in patients after total gastrectomy (11). As expected, the absorption of oxycodone was not altered, since the release of oxycodone from the used formulation was not affected by pH. In none of the abovementioned studies the possible impact of altered release from mechanistically different controlled-release formulations (CRF) was investigated. However, bile salt- and fat malabsorption as well as altered gastrointestinal pH and fluid composition could potentially affect drug release and subsequent absorption from lipid-based and water-swellable matrix systems (see section 1.3.2.1). Thus, studies acquiring such information are highly warranted and of outmost clinical importance as results will promote the development of evidence-based treatment algorithms with guidance on appropriate formulation choice. This will be of benefit for patients, society and the pharmaceutical industry.

1.2. SHORT BOWEL SYNDROME

Short bowel syndrome (SBS) is a rare, but lifechanging and burdensome malabsorptive condition associated with several complications, frequent hospitalization, high mortality rates, psychological challenges and poor quality of life (12–17). It is estimated that three patients are newly diagnosed per million per year (18). The prevalence does, however, vary greatly between countries ranging from 0.4 to 30 and 40 cases per million in Poland, United States and Denmark, respectively (14). Furthermore, SBS occurs more frequently among women than men and approx. 15 % of adults undergoing major intestinal resections are consequently diagnosed with SBS (19).

In adults, SBS is defined by a length of functional short bowel less than 200 cm combined with a need of nutritional and fluid supplements (20). The condition is most often a result of congenital intestinal disease or extensive resection necessitated in relation to e.g. Crohn's disease, neoplasms, mesenteric ischemia, radiation enteritis, trauma or different benign conditions (14). The list of possible symptoms and complications is long, some examples include diarrhea, abdominal pain, nutrient and fluid deficiencies, which among other factors may lead to steatorrhea, intestinal

failure-associated liver disease, hyponatremia, renal failure, nephrolithiasis, hypomagnesemia, D-lactic acidosis and osteopenia (21).

Patients with SBS are classified by their anatomy as having a stoma or preserved intestinal continuum with either end-jejunostomy, jejunoileal anastomosis or jejunocolonic anastomosis. The pathophysiology of SBS changes with time and can be categorized into 3 phases: i) acute phase, ii) adaptive phase and iii) maintenance phase (20).

The acute phase occurs the first 3-4 weeks post-resection. It is marked by the significant intestinal loss giving rise to metabolic derangements, hypergastrinemia and gastric hypersecretion as hormone signaling pathways are dysregulated (20,22,23). During this phase close patient monitoring is vital to prevent serious complications such as dehydration and acute kidney failure.

The adaptive phase occurs 1-2 years post-surgery and is characterized by intestinal adaption with elongation and enlargement of the intestinal villi as well as peristalsis deceleration, thus maximizing capacity and time for fluid and nutrient absorption (23,24).

The final phase is the maintenance phase, which deals with management and prevention of SBS complications. Maintenance of a good nutritional status is superior, although often accompanied by pharmacotherapy (20). Oral drug therapy is preferred due to its convenience for patients, however, opposes major challenges for the prescribing physician, which must titrate doses by trial and error with high risks of serious advent events or no clinical effects (25–27).

To date, limited studies investigating the absorption of orally administered drugs have been conducted in patients with SBS and most are case reports or studies with few participants. Nevertheless, in the review by Santamaría *et al.* all studies shows altered drug bioavailability and large inter-individual variation (28). Results and therapy recommendations do, however, deviate greatly between different drugs and formulations. This emphasizes the main drawback of oral formulations, namely absorption variability, which is a result of the interplay between three key elements: i) formulation design, ii) individual characteristics and iii) physiochemical drug properties (Figure 3). To improve drug therapy for this complex patient population additional investigations are needed and should ideally aim at investigating the specific associations between these three elements.

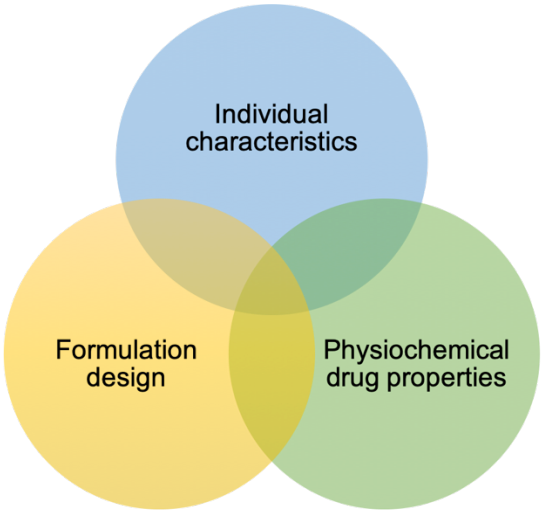

Figure 3. Factors that interact and affect the process and outcome of oral drug absorption.

1.3. FORMULATION DESIGN

Pharmaceutical formulations can have great impact on drug absorption as they can control the time, rate and concentration of drug release. Numerous formulation designs have evolved over the years to ensure plasma concentrations fall within the therapeutic index of a drug and to reduce dosing frequency of drugs with short elimination half-lives.

The following section will focus on the enteral forms: oral liquid dosage forms and oral solid dosage forms, which were applied in the studies of this PhD project.

1.3.1. ORAL LIQUID DOSAGE FORMS

The oral liquid dosage form is a homogenous preparation typically consisting of a solution, an emulsion or a suspension. An oral solution was used in this PhD project. Oral solutions have no dissolution parameter, thus enabling immediate drug absorption resulting with a rapid onset and offset of action. In comparison to controlled-release formulations, the main disadvantages are a shorter duration of action and higher peak concentrations, which may result with increased dosing frequency, additional and/or worse side-effects.

The terms “oral solution”, “oral liquid” and “immediate-release formulation” are used interchangeably throughout this thesis and included papers.

1.3.2. ORAL SOLID DOSAGE FORMS

The oral solid dosage form comes in varies forms such as tablets, capsules, powders and granules. Tablets and capsules can be designed in several ways to affect drug release. Some are designed to have an immediate drug release and are termed "immediate-release" tablets or capsules. Others have a modified drug release and may be categorized as either a prolonged-, extended-, targeted-, biphasic-, delayed-, sustained- or controlled-release formulation, depending on the drug release design.

1.3.2.1 Controlled-release formulations

Over the past decades, the controlled-release formulation has emerged greatly due to its prolonged and stabile drug-release profile and consequently giving a nearly constant absorption rate. Thus, reducing dosing frequency and fluctuations in the plasma concentration, which limits side-effects and increases patient compliance (29). Various designs of controlled-release tablets exist. Each have a specific drug-release mechanism. The following section will describe the differences between controlled-release forms with a lipid and hydrophilic matrix system.

Lipid matrix system

A lipid matrix system consists of waxes or similar materials. Drug release is dependent on tablet erosion by bile acids and lipases found in the digestive fluids of the stomach and small intestine (30). The concept is illustrated in Figure 4.

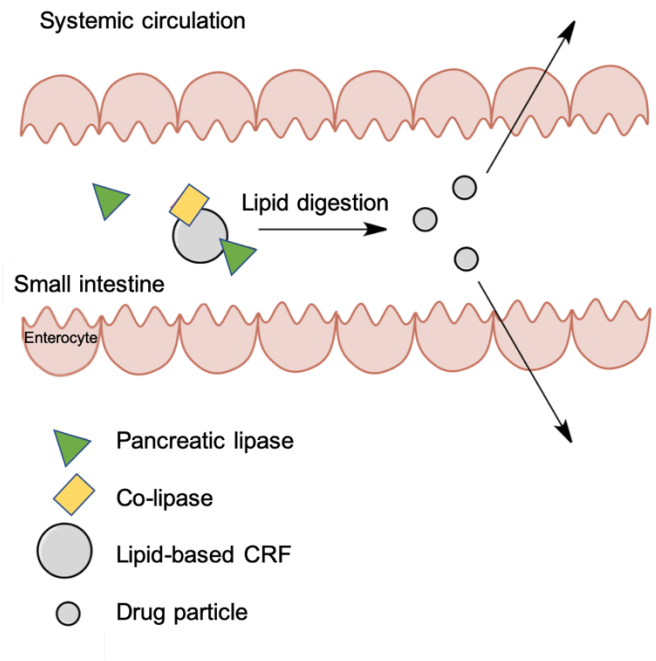

Figure 4. Mechanism of drug release for a controlled-release tablet with a lipid matrix system. CRF: controlled-release formulation.

Hydrophilic matrix system

A hydrophilic matrix system consists of polymers with a gelling property. Drug release is triggered by the contact of fluids, whereby an outer gel layer is formed and the drug can slowly escape through small pores (31) (Figure 5). This matrix system is also called a water-swellable matrix system and will from hereon be referred to as such.

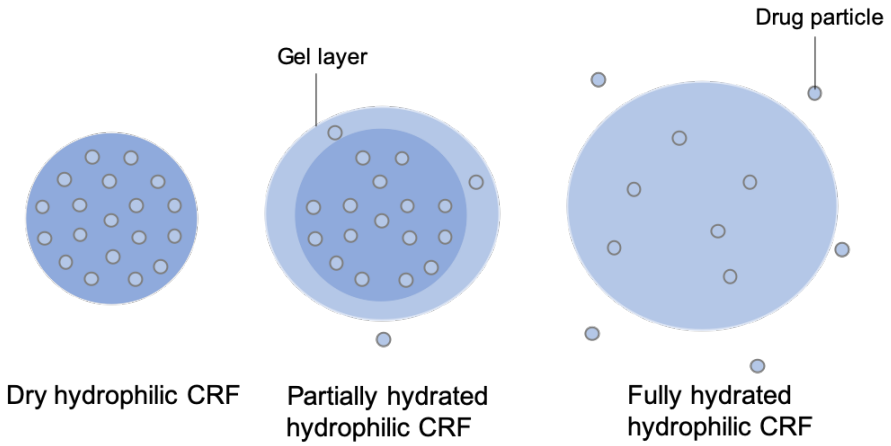

Figure 5. Mechanism of drug release for a controlled-release tablet with a water-swellable matrix system. CRF: controlled-release formulation.

Optimal drug release from lipid-based and water-swellable matrix systems is clearly dependent on specific factors of the gastrointestinal tract. Thus, therapeutic failure may appear in patients who have pathophysiological changes of the gastrointestinal tract.

1.4. OXYCODONE

Oxycodone was used as a model substance in this PhD project for several reasons. First of all, a results from recent epidemiological study revealed that 14.4 % of gastrointestinal postsurgical patients are chronic opioid users and that oxycodone was the most commonly used opioid (32). Secondly, oxycodone has few active metabolites, which was an advantage in regard to the modelling work. Lastly, oxycodone exists in a wide variety of formulations.

Oxycodone is an opioid agonist, which was first synthesized from the opiate alkaloid, thebaine, in 1916 and the following year prescribed for severe to moderate pain on the German market. However, it was not until the launch of a controlled-release formulation in 1995, that the global oxycodone consumption increased dramatically, and in 2000 it exceeded the consumption of morphine (33).

1.4.1. PHARMACOKINETICS

After oral administration the bioavailability of oxycodone varies between 60-87% (34–36). Once in the blood 38-45% is protein-bound, primarily to albumin and to less an extent α1-glycoprotein (5-10%) (37). Maximum plasma concentrations are reached

after approx. 1 hour and 3 hours for oral solution and controlled-release oxycodone, respectively (36,38).

The volume of distribution after intravenous administration has been estimated to 2.6 L/kg, confining the drug to the plasma and reflecting the high degree of plasma protein binding (39). Furthermore, oxycodone penetrates the blood-brain barrier without the need of an active transporter, according to rat and sheep data (40,41). The active metabolite oxymorphone does, however, seem to depend on an unknown active transporter (42).

Oxycodone is primarily metabolized by the cytochrome P450 enzymes CYP3A4/5 to noroxycodone (accounting for 45%) and CYP2D6 to oxymorphone (accounting for 19%)(43,44). Noroxycodone and oxymorphone are further metabolized to noroxymorphone by CYP2D6 and CYP3A4/5, respectively (Figure 6). The biotransformation of oxymorphone to noroxymorphone is, however, considered negligible based on *in vitro* data (44). Other metabolites are formed by reduction and glucuronidation pathways. *In vitro* data has shown that oxycodone undergoes glucuronidation primarily by the UDP-glucuronosyltransferases (UGTs) UGT2B7 and UGT2B4. Elimination of oxycodone through this pathway is, however, minor (45). Oxymorphone is also glucuronidated by UGT2B7, while it remains unknown how noroxycodone undergoes glucuronidation (46,47).

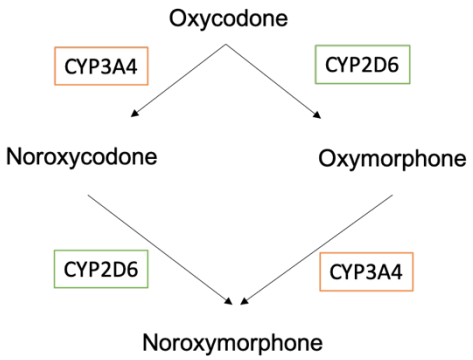

Figure 6. Biotransformation of oxycodone to its three main metabolites.

Elimination of oxycodone and its metabolites occurs predominately through the kidneys (72 %), with 8% unchanged oxycodone and the remaining as metabolites (47% as oxidative metabolites)(43). Plasma clearance has been estimated to 0.8 L/min. The elimination half-life is 4-5 hours for controlled-release oxycodone tablets and 3 hours for oral solution oxycodone (43,48).

1.4.2. PHARMACODYNAMICS

Despite oxycodone being known for more than a century, the mechanism of action has still not been fully identified. What we do know is that oxycodone and its' metabolites bind selectively to the my (μ), delta (δ) and kappa (κ) opioid receptors, with highest affinity for the μ-opioid receptor, and thus triggers a G-protein coupled receptor signaling pathway, whereby the release of nociceptive neurotransmitters (e.g. substance P, glutamate, dopamine, acetylcholine, noradrenaline and gamma-aminobutyric acid) is inhibited, subsequently limiting the transmission of pain. Furthermore, oxycodone blocks N-voltage gated potassium channels, causing hyperpolarization and a dampened neuronal excitability (49,50).

Oxycodone's binding affinity to the μ-opioid receptor is 5-fold less than morphine (43). Noroxycodone binds to the μ-opioid receptor with a 3-fold lower affinity compared to oxycodone (43). In contrast, is the binding affinity to the μ-opioid receptor 10-45-fold higher for oxymorphone and two-to-four-fold higher for noroxymorphone compared to oxycodone (43,51).

The analgesic potency of noroxycodone is 5- to 10- fold less than oxycodone. On the other hand, oxymorphone is 8- to 44-fold more potent and noroxymorphone is 2-3 times as potent as oxycodone (43).

The brain-to-plasma partitioning is much higher for oxycodone compared to its' metabolites, presumable due to differences in lipophilicity, which limits penetration across the blood brain barrier (43). Noroxycodone is recognized as an inactive metabolite and the analgesic contribution of noroxymorphone is also considered negligible due to its limited blood brain barrier penetration (43,52). However, the clinical significance of oxymorphone remains debatable due to inconsistent data on the analgesic effects. The concentration of oxymorphone in the brain is believed to be too low to have a significant analgesic effect (53). However, in CYP2D6 poor metabolizer the analgesic effects after oxycodone were lower, which could suggest that oxymorphone has some clinical significance (54). Findings were based on few participants; thus, additional investigations should be conducted to confirm these results.

CHAPTER 2. AIMS & HYPOTHESES

This PhD thesis is based on the results of two studies and data from an existing research database resulting in five scientific papers (I-V). An overview of conducted studies, papers and corresponding aims is illustrated in Figure 7.

The overall aim of the PhD project was to investigate the impact of gastrointestinal surgery, associated with resection or bypass, on absorption of orally administered oxycodone formulations, and subsequently evaluate the appropriateness of such formulations to patients with RYGB and SBS.

The detailed aims were:

Aims

I. To characterize segmental gastrointestinal pH profiles, motility measures and transit times in patients with RYGB, using the wireless motility capsule (WMC) (paper I).

II. To develop and evaluate a pharmacokinetic-pharmacodynamic (PKPD) model of oral solution and two controlled-release oxycodone formulations in healthy participants (paper II).

III. To develop and evaluate a PKPD model of oral solution and two controlled-release oxycodone formulations in patients with RYGB, using the PKPD model established in healthy participants as a base model. Furthermore, to determine PKPD differences of the three oxycodone formulations between patients with RYGB and healthy participants (paper III).

IV. To develop and verify a physiological-based pharmacokinetic (PBPK) model with extensive absorption characteristics for oral solution and controlled-released oxycodone in a healthy population Furthermore, to apply the developed PBPK models in healthy populations of varying age, ethnicity as well as in patients renal and hepatic impairment (paper IV).

V. To explore the pharmacokinetics of oral solution oxycodone in patients with short bowel syndrome (paper V).

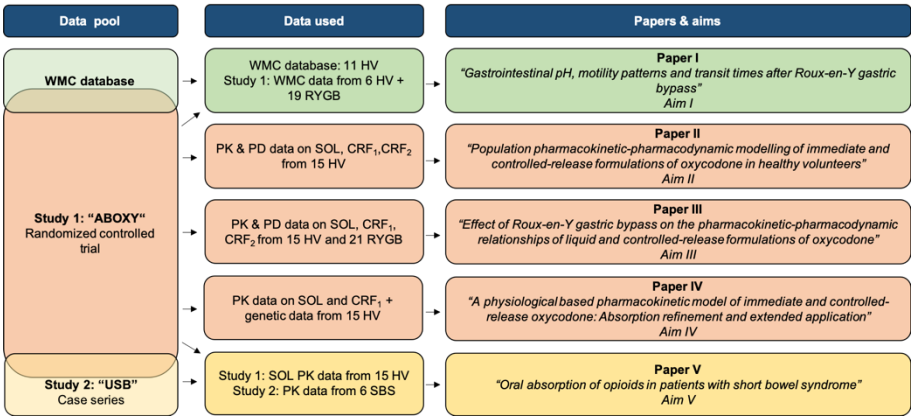

Figure 7. Overview of available data and data flow in regard to the scientific papers. The data pool consisted of a database with WMC traces and two studies referred to as "Study 1: ABOXY" and "Study 2: USB". Abbreviations: WMC: wireless motility capsule, HV: healthy participants, RYGB: patients with Roux-en-Y gastric bypass, SBS: patients with short bowel syndrome, PK: pharmacokinetic, PD: pharmacodynamic, SOL: oral solution, CRF_1: lipid-based controlled-release formulation, CRF_2: water-swellable controlled-release formulation.

To fulfill the five aims the objectives and hypotheses were as follows:

Objective 1 – paper I

The first objective was to determine specific physiological differences of the gastrointestinal tract in patients with RYGB, which could impact and help explain postsurgical symptoms as well as possible absorption alterations. Hence, pH, transit time and motility measures were assessed, using the WMC. It was *hypothesized* that patients with RYGB would have a shorter transit and increased luminal pH of the oro-cecal segment and no differences in the colon as compared to healthy participants.

Objective 2 & 3 – paper II & III

The second objective was to assess and evaluate the exposure-response relationship of oral solution, lipid-based and water-swellable controlled-release oxycodone in healthy participants and patients with RYGB, using a PKPD modelling approach. It was *hypothesized* that the PKPD relationship would deviate between the two mechanistically different controlled-release tablets in patients with RYGB. More specifically, we expected results to reflect a poor drug release from the lipid-based matrix, due to the altered digestive fluid composition. Furthermore, a shorter lag time and lower bioavailability was expected for the controlled-release tablets among patients with RYGB compared to healthy participants, whilst a higher absorption rate and bioavailability was *hypothesized* for the oral solution.

Objective 4 – paper IV

The third objective was to develop and verify PBPK model with extensive absorption characteristics for oral solution and controlled-release oxycodone in a healthy population. This could then be used to predict pharmacokinetic outcomes in special populations.

Objective 5 – paper V

The last objective was to explore the magnitude of varying intestinal lengths on the absorption degree of oral solution oxycodone by performing a pharmacokinetic study in patients with SBS. A correlation was *hypothesized* to be present between intestinal length and the pharmacokinetic measures AUC (area under the concentration-time curve) and C_{max} (maximum plasma concentration).

CHAPTER 3. MATERIALS & METHODS

As mentioned, this thesis is based on data from two studies, referred to as "Study 1: ABOXY" and "Study 2: USB" and an existing WMC database, resulting in paper I-V (Figure 7). As shown in Figure 7, study 1 included data from healthy participants and patients with RYGB. Study 2 included data from patients with SBS and from the WMC database supplied WMC data from healthy participants.

Study 1 was approved by the Danish Medicine Agency (EudraCT number: 2017-00732-34, registered at www.clinicaltrialregister.eu), the North Denmark Region Committee on Health Research Ethics (N-20170039) and registered at the Danish Data Protection Agency. Eligible participants underwent a screening session, where a physician evaluated their medical history to ensure that all inclusion and no exclusion criteria were fulfilled. Oral and written information about the study was given prior to signing the informed consent. If found eligible, the participant was enrolled in the study.

Study 2 was a clinical investigation conducted on the basis of unsatisfactory pain relief reported by the patient. Thus, an approval from the medical authorities was not necessary according to Danish law. Nevertheless, all patients were detailed informed about study procedures before giving their oral consent prior to study entry.

The WMC database has previously been approved by the North Denmark Region Committee on Health Research Ethics (N-2009008) and registered at the Danish Data Protection Agency.

All data was collected at Department of Gastroenterology and Hepatology at Aalborg University Hospital and were conducted in compliance with the Declaration of Helsinki and International Conference on Good Clinical Practice guidelines.

In the following sections a short description of applied materials and methods for each study will be given. For specific details please refer to the corresponding papers.

3.1. STUDY 1: ABOXY

Study 1 was a randomized, controlled, three-armed, semi-double blinded, cross-over study including 15 healthy participants and 22 patients with RYGB, whereof one patient with RYGB was excluded after the first treatment visit due to an adverse event and another withdrew her informed consent after the WMC assessment, thus before starting treatment visits (Figure 8).

Specific in- and exclusion criteria were set to minimize inter-individual variability (e.g. ethnicity), adverse events (e.g. known allergies) and bias of obtained results (e.g. strong inhibitors or inducers of CYP3A4). Furthermore, several ethical considerations had to be taken into consideration, as oxycodone is highly addictive and has several severe side-effects. Hence, all participants had to be mature adults (25-80 years), healthy participants had to be opioid naïve[1] with no present nor previous history of any drug abuse. Additionally, women had to assure a negative pregnancy test prior to each treatment visit and could not be lactating. Furthermore, RYGB surgery of patients had to had occurred at least one year before study inclusion, to allow time for gut adaption and a more stabilized weight. Finally, patients with RYGB were not allowed to consume oxycodone at least 1 week in advance of study inclusion and under the whole period of study conduct. In addition, any new needs or alterations of current medications were evaluated prior to treatment visits and if deemed to impact study results, participants were excluded from further participation.

Figure 8 gives an overview of the study flow. As illustrated, eligible participants underwent a standardized assessment using the WMC assessment and 3 treatment visits – one for each oxycodone formulation. The order of administered oxycodone formulations was completely random. A computer-generated randomization list was generated by personnel, who were not otherwise involved in the study. Participants were assigned chronologically to a randomization number as they were enrolled.

[1] Opioid naïve is defined as a person who is not opioid tolerant (i.e. a higher dose is required to obtain the same amount of pain relief of previous lower doses) and who has not taken opioids in one week or longer. However, in this study we defined opioid naïve as a person who did not have a history of opioid use/addiction. If the opioids were used more than five years before the start of experiment as an analgesic to treat pain post-surgery etc., this person was also considered opioid naïve. Finally, if the person had never used opioids to treat pain but had participated in pain studies where opioids were given more than a year before this study, this person was also considered opioid naïve.

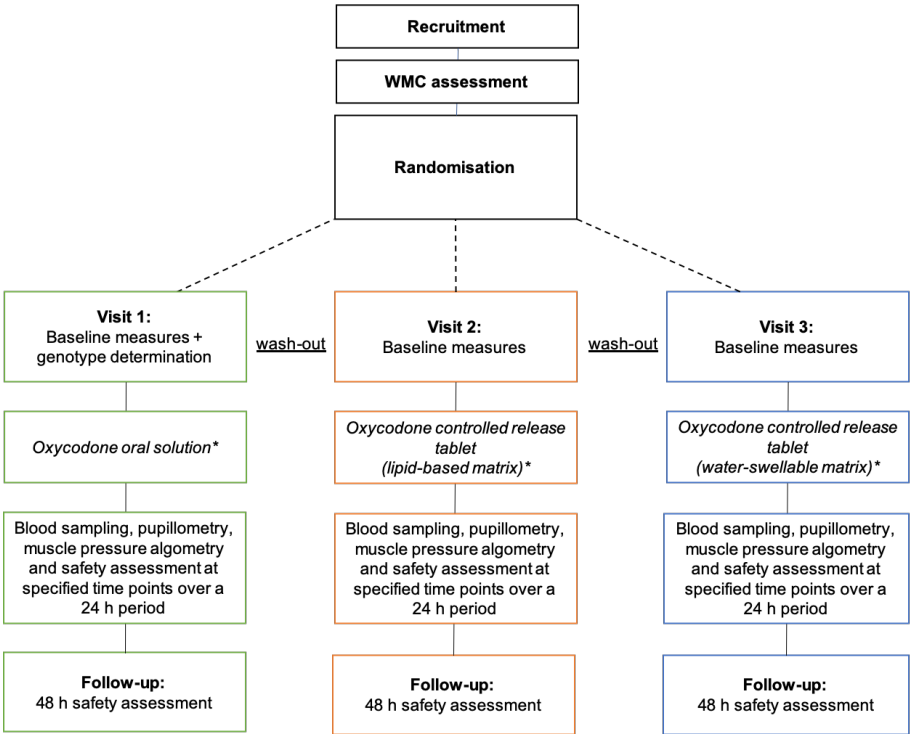

Figure 8. Flow diagram for Study 1. *The order of oxycodone formulations was completely random from one participant to another. h: hour, WMC: wireless motility capsule.

Of note, the WMC has several contraindications e.g. complications. Thus, it was not a requirement to undergo a WMC assessment in order to participate in study 1. This is also the reason why only 19 out of the included 22 patients with RYGB were included in paper I. One patient had gastrointestinal complications related to the RYGB surgery, another was allergic towards the Smartbar® content (see below) and the last had an implanted electro-mechanical medical device.

3.1.1. WIRELESS MOTILITY CAPSULE ASSESSMENT

The WMC (SmartPill®, Medtronic, Minneapolis, USA) was used to assess segmental intraluminal pH, transit time and motilities indices. The technical capsule records body temperature (with an accuracy of 1°C), pH (with an accuracy of 0.5 units) and pressure (with an accuracy of 5mmHg below or 10 mmHg above 1000 mmHg) as it navigates through the gastrointestinal tract. Measurements are instantly transmitted to a portable data receiver worn by the participant. The receiver stores data until it is transferred to a computer and subsequently analyzed.

Prior to study start, participants had fasted overnight and ingested a standardized meal. Shortly after, the SmartPill® was swallowed with 200 mL water and the data receiver was subsequently placed around the participant's neck. Participants were instructed to wear this device until the SmartPill® was expelled from their system (receiver stopped recording) or for at least 5 days. Furthermore, participants were ordered to restrain from foods, beverages the first 6 hours post capsule ingestion and extreme physical activities during the entire test. Finally, participants received a dairy where date and time of specific daily routines (e.g. meals, bowel movements, going to bed and getting up and other relevant comments) could be noted during the test period.

In this study, the analysis software MotilitiGI (version 3.0, Medtronic, Minneapolis, USA) was used. Two segments, oro-cecal and colonic, were distinguished from each other by significant alterations in temperature and pH as described by Sarosiek *et al.* (55). Contraction frequency and amplitude data was used to calculate the motility index, as proposed by Camilleri *et al.* (56). Transit time, pH and motility index was determined for each segment as well as for the first and last hour of each segment. Measurements were compared between the two populations using a linear mixed model. Any indication of a restriction violation was evaluated (e.g. increase in pH after food and liquid ingestions or temperature rise and drop after liquid ingestions) and data was discarded unless the temperature drop was due to limited water intake (e.g. rapid normalization of the temperature). Further details are reported in paper I.

3.1.2. STUDY PROCEDURES RELATED TO TREATMENT VISITS

Treatment visit 1-3: Participants arrived at the research unit after an overnight fast. Baseline measurements were obtained. These includes blood pressure, heart rate, body mass index (BMI), blood sample, pupil diameter and muscle pressure stimulation threshold and judgement of well-known side effects of oxycodone. A blood sample (9 mL) for evaluation of paraclinical values was collected for patients with RYGB. Additionally, a blood sample for genotype determination was collected (only visit 1). After the completion of baseline measurements, participants administered either a) 10 mL oral solution oxycodone, b) 20 mg water-swellable matrix CRF or c) 20 mg lipid based CRF in a randomized order. Formulation a) was administered with 50 mL of water, while formulation b) and c) were administered with 240 mL of water. Blood

samples, pupillary measurements and muscle pressure stimulation threshold was subsequently conducted at specific time points over the next 24 hours. Participants were supplied with standardized meals during treatment visits. Naloxone was available in the laboratory as an antidote/rescue medication for oxycodone. Patients with RYGB noted any drug use in a dairy two days prior to treatment visits and we encouraged to take the same medication at the same time before each visit.

Follow-up: Participants were contacted by telephone approximately 48 hours after each drug administration, in order to register potentially late occurring adverse effects/events and any opioid withdrawal symptoms.

Wash-out: Visit 1-3 were separated by a wash-out period of at least 5 days to minimize the risk of a carry-over effect between treatment visits.

3.1.2.1 Study medication

The study medication consisted of:

a) Oxynorm®, oral liquid mixture 1mg/ml; Norpharma A/S / Mundipharma A/S, Vedbaek, Denmark. 1 mL contains 1 mg oxycodone. Only 10 mL was administered orally.

b) Oxycodone hydrochlorid "Lannacher", controlled-release tablet 20 mg; Lannacher Heilmittel Ges.m.b.H, Lannach, Austria. One tablet contains 20 mg oxycodone. Only 1 tablet was administered orally. Tablet design: controlled-release tablet with water-swellable matrix system.

c) Oxycodone Depot "Sandoz", controlled-release tablet 20 mg; Sandoz A/S, Copenhagen, Denmark. One tablet contains 20 mg oxycodone. Only 1 tablet was administered orally. Tablet design: controlled-release tablet with lipid-based matrix system.

The oral solution was included in the study to better elaborate upon the impact of RYGB on drug release from the two mechanistically different controlled-release tablets, as this formulation has no dissolution parameter.

The dosage of the oral solution was half that of the controlled-release formulations, because its absorption is more rapid resulting with higher peak concentrations, which is associated with a greater risk for side-effects (57,58).

3.1.3. ASSESSMENT OF OXYCODONE PHARMACOKINETICS

To evaluate the pharmacokinetics of the different oxycodone formulations, venous blood samples were collected before and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.33, 2.66, 3, 3.33,

3.66, 4, 5, 6, 8, 12 and 24 h after drug administration. These sampling times were chosen to best capture the pharmacokinetic profile of oxycodone and were based on previously conducted pharmacokinetic studies (11,38,59–69). Plasma concentrations of oxycodone, noroxycodone and oxymorphone were determined using high-performance liquid chromatography.

3.1.4. ASSESSMENT OF OXYCODONE PHARMACODYNAMICS

3.1.4.1 Pupillometry

Pupillometry, measurement of the pupil diameter, is a recognized objective method, to assess the pharmacodynamic effects of opioids (70–74). In the current study, pupillometry measurements were conducted after each blood sampling, using a digital infrared hand-held NeuroOptics VIP 200 pupillometer (NeuroOptics, Irvine, CA, USA). All measurements were performed under consistent light conditions and always on the same eye.

3.1.4.2 Muscle pressure algometry

The subjective analgesic effect of oxycodone was assessed prior to and 1, 2.5, 3, 3.5, 4.5, 6, 12, 24 h post drug administration, using a handheld pressure algometer (Type 2, Somedic production AB, Sweden). Stimulations were conducted on the dorsal forearm 10 cm distal to the elbow. Stimulations ceased once participants reached their pain detection threshold (first time sensation was perceived as painful), corresponding to a score of 5 on the modified visual analogue scale.

Unfortunately, this data was not meaningful in regard to the analysis due to extreme variability. Hence, this data was discarded and is therefore not mentioned in any of the papers.

3.1.4.3 Safety assessment

To evaluate the safety of the different oxycodone formulations, the degree of 12 well-known side-effects were rated as (0) none, (1) slight, (2) moderate, (3) high degree and (4) very high degree and registered prior to and 1.5, 3, 6, 12 and 24 h post drug administration. The 12 side-effects included nausea, dizziness, headache, stomach pain, itchy skin, dry mouth, vomiting, sedation, changes in heart rate, sweating, constipation and difficulties breathing. Any additionally mentioned side-effects were also registered.

3.1.4.4 Pharmacogenomic profiling

Pharmacogenomic tests were performed to determine each participant's genetic make-up in relation to specific drug metabolizing enzymes and receptors, which impacts a

person's exposure and response to oxycodone. Hence, the blood samples which were collected during participants' first treatment visit, were delivered to GeneTelligence Aps (Denmark), who analyzed the participants' pharmacogenetic profile and subsequently provided a detailed Personal Medicine Profile™. The Personal Medicine Profile™ included information on the following genes: CYP1A2, CYP2B6, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, DPYD, IFNL3, OPRM1, SLCO1B1, TPMT, UGT1A1, and VKORC1. Genotypes were translated to phenotypes by the GeneYouIn PillCheck™ "black-box" technology, which uses data from PharmGKB, PharmVar, CPIC, FDA and EMA. The genotyping was performed by the State Serum Institute, Copenhagen, Denmark, using Agena's MassARRAY® system and validated using AgenaBio® ADME assays.

Unfortunately, these results were obtained late during the project period and thus only used in paper IV.

3.1.5. POPULATION PHARMACOKINETIC-PHARMACODYNAMIC MODELLING

The PKPD relationship of oral solution, lipid-based and water-swellable controlled-release oxycodone was determined for healthy participants and patients with RYGB by fitting population data, obtained in study 1, to models using the nonlinear mixed effects modelling tool NONMEM® (version 7.4; ICON Development Solutions, Ellicott City, MD) with the Wings for NONMEM interface (http://wfn.sourceforge.net) and IFort compiler. In addition, the first order conditional estimation with interaction (FOCE-I) method was used.

A PKPD model was first developed in healthy participants (paper II). This model was then used as a base/reference model to further develop a PKPD model in patients with RYGB (paper III). This model could then distinguish PKPD differences among patients with RYGB as well as between healthy- and patient participants.

A general modelling procedure applied for both model developments. As described by Ladebo *et al.* (2020) in paper II, models were developed using a sequential PKPD modelling approach:

"*… whereby the PK component of the model was developed first, with the PD model developed sequentially using the PPP&D (Population PK Parameters and Data) method with the PK model parameters fixed at the previously determined values and the PK data retained during the PD model estimation step* (75). *Processing NONMEM output and generating plots were conducted with the R software* (76) *(Version 3.3.3 or later) using gglot2, plyr, doBy and scales packages and their associated dependencies.*

Selection criteria for the base model were based on mechanistic plausibility, a statistically significant (P < 0.05) improvement of the fit (3.8-unit decrease in the objective function for the addition of a single parameter) and visual inspection of standard goodness-of-fit diagnostic plots. The final model was also required to pass the covariance step. Visual predictive checks (VPC) based on 1000 simulations of the index dataset were used to evaluate the predictive performance of the adequacy of the final model in describing the observed data.

Potential significant covariates were identified by visualizing plots of covariates versus between-subject variability (BSV) of parameter estimates. Physiologically plausible covariates (eg. vomit, sex, age) were evaluated for statistical significance using a stepwise covariate modelling of forward addition and backward elimination (77). *The statistical criteria for retaining a covariate in the model were P < .01 during forward addition and P < .001 for backward elimination."* (78)

For the specific details on the two modelling strategies, please see paper II and III.

3.1.6. PHYSIOLOGICAL-BASED PHARMACOKINETIC MODELLING

The Simcyp Population-based ADME Simulator (version 18.2, Certara UK Ltd., Simcyp Division, Sheffield, UK) was used to develop two oxycodone PBPK models (Model I: oral solution (also termed immediate-release in paper IV) and Model II: controlled-release) in healthy Caucasians.

Detailed information on the modelling approach can be found in paper IV.

In brief, Model I was built first using physiochemical data combined with *in vitro* information on metabolism and permeability. Absorption was described using the "Advanced Dissolution Absorption and Metabolism" (ADAM) model, which is embedded within the Simcyp Simulator. The model was refined by sensitivity analysis of specific parameters and verified against 16 clinical pharmacokinetic studies (8 per oral single dose, 1 per oral multiple dose, 7 drug-drug interaction studies). The model was accepted if the simulated pharmacokinetic parameters (AUC, C_{max}, T_{max}) were within 0.7-1.3-fold error of the corresponding observed values (79). Model II was developed using Model I as baseline. The formulation type was then altered to monolithic controlled-release and dissolution data added. This model was verified against 2 per oral single dose pharmacokinetic studies. Finally, the two verified models were further extended to specific populations: i) healthy >65 years, ii) healthy Japanese, iii) healthy Chinese iv) patients with moderate and severe renal impairment, and v) patients with cirrhosis Child-Pugh class A-C. These populations were all found within the Simcyp default library and have previously been verified. The simulated AUC for the different populations was compared to the simulated AUC of healthy Caucasians.

3.2. STUDY 2: USB

Study 2 was an explorative case series including 6 patients with short bowel syndrome (type III). Each patient was allocated into one of three categories: 1) jejunostomy < 50 cm small intestine, 2) jejunostomy with 50-150 cm preserved small intestine, and 3) jejunocolic anastomosis. All participants underwent a pharmacokinetic assessment of 10 mg oral solution oxycodone. Blood samples were collected at specified time point before and up to 6 hours after drug administration. Oxycodone plasma concentrations were determined by high-performance liquid chromatography and noncompartmental analysis was used to obtain pharmacokinetic parameters. Specific baseline characteristics was collected from the patients' medical records and used to evaluate the pharmacokinetic outcomes both among patients and between patients and reference values. For specific study details please refer to paper V.

CHAPTER 4. KEY RESULTS

The following section summaries the key results in regard to the proposed aims in chapter 2. Detailed results are reported in the papers.

Paper I: "Gastrointestinal pH, motility patterns and transit times after Roux-en-Y gastric bypass"

Aim I

To characterize segmental gastrointestinal pH profiles, motility measures and transit times in patients with RYGB, using the wireless motility capsule.

Key results

- In comparison to healthy, the oro-cecal segment of patients with RYGB was characterized by a more alkaline microenvironment ($P < 0.001$), high motility activity ($P < 0.012$) and short transit ($P < 0.001$).
- In addition, transit of the colon was prolonged in patients with RYGB ($P = 0.048$).

Interpretation

These findings reflect the anatomical changes following RYGB surgery. The findings were not overly surprising; however, it is important to systematically determine differences to help explain possible absorption alterations as well as post-operative complications, which these patients may experience.

Paper II: "Population pharmacokinetic-pharmacodynamic modelling of immediate and controlled-release formulations of oxycodone in healthy volunteers"

Aim II

To develop and evaluate a PKPD model of oral solution and two controlled-release oxycodone formulations in healthy participants.

Key results

- The pharmacokinetics of oxycodone was best described by a two-compartment model with first order absorption.
- No differences in the PKPD relationship were found between the two controlled-release formulations.

- The absorption rate was approx. 80 % lower for controlled-release tablets as compared to the oral solution.
- Tablets had an absorption lag of 23 minutes.
- The pharmacodynamics was best described by a proportional E_{max} model.
- Males had approximately a 40 % lower plasma concentration at EC_{50} (half maximal effective concentration).

Interpretation

Generic substitution of the two controlled-release formulations is safe in persons with a healthy, intact gastrointestinal tract. The pharmacokinetic profile of the oral solution vs. controlled-release tablets was consistent with known release profiles. In addition, the pharmacodynamic model indicated oxycodone to be more potent in males. This PKPD model may serve as reference/base for future patient PKPD models.

Paper III: "Effect of Roux-en-Y gastric bypass on the pharmacokinetic-pharmacodynamic relationships of liquid and controlled-release formulations of oxycodone"

Aim III

To develop and evaluate a PKPD model of oral solution and two controlled-release oxycodone formulations in patients with RYGB, using the PKPD model established in healthy participants as a base model. Furthermore, to determine PKPD differences of the three oxycodone formulations between patients with RYGB and healthy participants.

Key results

- A PKPD model was successfully developed using the PKPD model established in healthy participants.
- No PKPD differences were found between the two controlled-release formulations in patients with RYGB.
- Patients with RYGB had an absorption lag, which was 2.5 minutes shorter than healthy participants ($P < 0.001$).
- Bioavailability was 14.4 % higher in patients compared to healthy controls, regardless of formulation type ($P < 0.001$).

Interpretation

This PKPD model can be used to determine pharmacokinetic and pharmacodynamic differences on two levels: 1) between the two controlled-release tablets in patients with a RYGB and 2) between patients with RYGB and healthy controls. In addition, monophasic lipid-based and water-swellable controlled-release oxycodone tablets

may be generically substituted in patients with RYGB. Finally, the shorter lag time observed for patients with RYGB is not expected to be of clinical significance. However, dose adjustments may be required to prevent serious side-effects, due to the increased oral bioavailability of oxycodone.

Paper IV: "A physiological based pharmacokinetic model of immediate and controlled-release oxycodone: Absorption refinement and extended application"

Aim IV

To develop and verify a PBPK model with extensive absorption characteristics for oral solution and controlled-released oxycodone in a healthy population Furthermore, to apply the developed PBPK models in healthy populations of varying age, ethnicity as well as in patients renal and hepatic impairment.

Key results

- A full PBPK was successfully built and verified for oral solution and controlled-release oxycodone in healthy adults.
- Absorption was described with the ADAM model.
- 90 % of the simulated versus observed pharmacokinetic parameters (AUC, C_{max}, T_{max}) were within 0.7-1.3-fold difference.
- Simulations using the final models indicated that healthy persons > 65 years had 1.5-fold higher AUC, when compared to simulated results in healthy Caucasians.
- Simulations in healthy Japanese and Chinese adults revealed a 1.3- and 1.5-fold increase in AUC, respectively, as compared to simulated data in healthy Caucasians.
- Simulations in patients with moderate and severe renal impairment revealed a 1.6-fold increase in AUC, as compared to simulated data in healthy Caucasians.
- Simulated AUC was 1.5-, 2.5- and 3.2-fold higher in patients with cirrhosis Child-Pugh class A, B and C, respectively, as compared to simulated results in healthy Caucasians.
- Overall, simulation outcomes in the respective populations were in reasonable agreement with observed data.

Interpretation

These models may be used to predict the pharmacokinetics of oxycodone of different drug-drug interaction scenarios, dosing regimens and in populations of varying age, ethnicity and in patients with renal and hepatic impairment. The simulations indicate that dose adjustments of oxycodone are required in patients with renal and hepatic

impairment. In addition, healthy elderly as well as Japanese and Chinese persons may also need dose adjustments.

Paper V: "Oral absorption of opioids in patients with short bowel syndrome"

Aim V

To explore the pharmacokinetics of oral solution oxycodone in patients with short bowel syndrome.

Key results

- All six patients with short bowel syndrome absorbed clinically relevant concentrations of oxycodone.
- The total intestinal length tended to correlate positively with the relative bioavailability of oxycodone.
- Preservation of the colon had a positive effect on the relative bioavailability of oxycodone.

Interpretation

Patients with short bowel syndrome may be treated with oral solution oxycodone, although drug dosing must be individualized according to the patient's functional intestinal length as well as other relevant patient characteristics (e.g. co-medications).

CHAPTER 5. DISCUSSION

Work conducted as part of this thesis investigated aspects of how gastrointestinal surgery, associated with bypass or resection, impacts the absorption of orally administrated oxycodone. In summary the following was characterized:

- specific physiological alterations of the gastrointestinal tract following RYGB (paper I)
- the PKPD-relationship of oral solution, lipid-based and water-swellable controlled-release oxycodone in 15 healthy participants and 21 patients with RYGB (paper II & III)
- a full PBPK model of oxycodone after administration of an oral solution and a controlled-release formulation (paper IV)
- the pharmacokinetic profile of oral solution oxycodone in 6 patients with short bowel syndrome (paper V)

This section will first address the strengths and limitations of the clinical studies (Study 1: ABOXY and Study 2: USB). This is then followed by methodological considerations of the applied techniques. Lastly, the clinical findings and potential implications will be discussed.

5.1. STRENGTHS AND LIMITATIONS OF THE CLINICAL STUDIES

A perfect clinical trial is impossible to construct, as compromises must be made either due to ethical or practical reasons.

5.1.1. STUDY PARTICIPANTS

Selecting in- and exclusion criteria is a balance between obtaining clear scientific answers, producing generalizable results and reflecting clinical reality.

A major limitation of the clinical studies conducted was the co-administration of different medications among patients, which could potentially bias pH and transit measures (paper I) as well as pharmacokinetic and pharmacodynamic parameters (papers III and V). Nonetheless, we wished to reflect the clinical setting and ensure a rapid recruitment, which would otherwise be difficult and perhaps also unethical and irresponsible, if participants had to refrain from their daily medications. In addition, the effects of CNS agents were tested both in paper I and paper III and results indicated that these agents did not affect neither transit time (paper I) nor the PKPD-relationship of oxycodone in patients with RYGB (paper III). Furthermore, patients were

instructed to administer their medications consistently 2 days prior to study visits, which could help minimize intra-individual variation.

An inclusion criterion for patients with RYGB was that their surgery had to be conducted a year in advance of study start, however, there was no maximum limit for how long ago it had taken place. Thus, the number of years since the operation was performed varied widely among participants with RYGB. This could potentially introduce additional inter-individual variability as the effects of enteroplasticity changes over time. Possible effects of enteroplasticity include: 1) morphological alterations of the villi length, crypt depth and/or total number (80), 2) enteroendocrine changes of gastrointestinal peptides such as glucagon-like peptide-1 (81), 3) nervous system adaptions affecting innervation and neuron activity, and 4) nutrient signaling adaptions where the number of nutrient transporters increase (82). These factors may play an important role in drug absorption. Furthermore, enteroplasticity also occurs in patients with SBS (23,24), thus this may also have influenced results in paper V to an unknown degree.

Psychological conditions such as depression and anxiety are common both before and after bariatric surgery (83). Thus, the comprehensiveness of, especially, study 1 may have discouraged some patients from participation. Hence, study participants may compose a selected group. In addition to the long list of in-and exclusion criteria (e.g. North European descent), this may minimize the generalizability of results.

5.1.2. STUDY DESIGN

Study 1 was a randomized, cross-over study with three treatment arms. This type of study is at the top of the hierarchy of clinical evidence. Nevertheless, inclusion of a placebo arm would have been beneficial in order to control for the effects of co-medications on both pharmacokinetic and pharmacodynamic measures. Furthermore, it would allow to control for circadian alterations of the pupil diameter (84). However, this was not a part of the study design, because it would increase the comprehensiveness of the study and potentially make patient recruitment more difficult. In addition, we were primarily interested in determining any differences in drug release and thus absorption between the two controlled-release formulations. The inclusion of the oral solution, as a third treatment arm, was important in regard to this. As previously mentioned, participants were also advised to administer their daily medications consistently two days prior to treatment visits. Thus, we assumed a uniform effect of co-medications on oxycodone pharmacokinetics and pharmacodynamics.

As study 1, was the first study investigating how altered GI-physiology affects release of oxycodone from controlled release formulations, no proper sample size calculation could be provided. Thus, the sample size was based on previous bioequivalence studies, which usually include 12-24 study participants (85) as well as previous

pharmacokinetic studies conducted in patients with RYGB, where the participant number ranged between 5-34 (4,5). We considered 15 healthy participants and 20 patients with RYGB to be sufficient to determine PKPD differences between the different formulations, which was the primary aim.

Study 2 was a case series with information on six patients with SBS. This study design was chosen due to its' simplicity. Patients with SBS are very heterogenous and rather vulnerable patients. Recruitment for larger and more comprehensive studies such as randomized controlled trials can therefore be very difficult. A case series is a weak type of study due to possible selection bias and limited power. Assessment of potential confounders was therefore not possible in paper V. Nevertheless, case series can provide useful information for theoretical hypothesis and thus limit unethical conductance of larger trials.

5.2. METHODOLOGICAL CONSIDERATIONS

5.2.1. WIRELESS MOTILITY CAPSULE

To date, the wireless motility capsule is the only method that can simultaneously determine regional gastrointestinal transit, contractility and pH patterns. In addition, it has several other advantages such as being minimally invasive, time efficient and does not require inpatient care. The method is also highly standardized and data is easy to interpret. Nevertheless, its use in patients with RYGB was challenged (paper I). For instance, it was not possible to distinguish the pouch from the small intestine, as pH changes were not significant. Other techniques such as scintigraphy may therefore be more useful to determine the exact transit between these two regions, although scintigraphy exposes participants to radiation and is rather expensive and time-consuming (86). This technique has previously been applied in patients with RYGB and found accelerated gastric emptying (87–90).

The Smartbar® is an element of the wireless motility capsule system and was used as a standardized meal in paper I. Nonetheless, approx. 60 % of participants with RYGB were unable to ingest the entire Smartbar®, due to nausea and fear of dumping syndrome, which could result from the carbohydrate-rich content (91). This may have biased results, as meal content and volume has shown to impact transit time (88,90). Although, the post-hoc analysis performed in paper I did not find such associations. We still recommend future studies to consider a tailored standardized meal depending on the population of interest. Apart from patients with RYGB, this could also be of relevance for diabetics, who may experience hyperglycemia, which can decelerate gastric emptying (92). Based on the current nutritional recommendations (93), a small, solid but easily chewable, protein-rich meal may have been a more suitable meal for patients included in paper I.

Lifestyle differences (e.g. eating habits, physical activity) between healthy participants and patients with RYGB may also have biased, especially, transit measures to an unknown degree (94). Such confounders could be eliminated if participants were monitored until capsule expulsion. Though, this would make the study extremely comprehensive. Instead, participants were advised to refrain from any foods or liquids (except limited quantities of water) the first 6 hours of the test period. In addition, extreme physical activity was not allowed during the entire test. None of the traces indicated violation of substance ingestion, however performance of physical activity could not be evaluated. Thus, we could only trust that participants would obey the study restrictions.

5.2.2. PHARMACOMETRIC METHODS

Modelling techniques are cost-effective analytical tools, which apply mathematical equations to describe and better understand the interaction between drugs and humans. Such information is useful for drug development, regulatory assessments, optimization of dosing regimens, and designing better clinical trials. The reliability of models is, however, dependent on the quality of existing input data as well as the modelling strategies applied. Simulation outputs must therefore be interpreted and used carefully, as they will not be entirely realistic.

In this PhD project, two pharmacometric methods were applied, namely PKPD and PBPK modelling.

PKPD models describe the exposure-response relationship as a function of time by fitting models to population data. Hence, PKPD modelling greatly replies on empiric data, which also means that a population mean as well as interindividual and residual variability of both pharmacokinetic and pharmacodynamic changes can be characterized (95,96). This is useful for establishing safety margins and optimal dosing regimens for a specific population (97). In contrast, PBPK models describe the pharmacokinetics of drugs by physiological parameterized compartments, representing organs and tissue function, as well as known flow rates of the circulating system, which connects the compartments (98). Models also incorporate data on the physiochemical properties of the drug of interest as well as trial design information. Thus, PBPK models can simulate clinical scenarios (e.g. different dosage regimens and drug-drug interactions) in different populations including healthy persons of varying ages, ethnicity as well as post-surgery or in diseased patients (e.g. patients with gastric bypass or short bowel) etc. This is beneficial in regard to answering very specific questions related to physiological changes as well as guiding dosing regimens for, especially, sensitive populations such as pediatrics, pregnant women and patients subjected to bariatric surgery. Like PBPK models, PKPD models also apply compartments to describe drug pharmacokinetics, however, these are much more simplified and not always physiologically meaningful. PKPD models may incorporate intrinsic (e.g. age, weight) and extrinsic factors (e.g. food, co-medication) that are

considered biological plausible, however the physiological impact will never be as detailed as in PBPK models. Finally, PBPK models are easy to conceptualize, as user friendly software is available (e.g. Simcyp^{TM}, GastroPlus® and PK-Sim®). However, users must be aware of the many assumptions and limitations behind the in vitro-in vivo extrapolations and various sub-models to fully understand and accurately apply model predictions.

In summary, the two modelling approaches can answer different pharmacology questions, thus complementing each other well. Hence, the emerging field of "personalized medicine" may benefit from combining PBPK models with fully mechanistic pharmacodynamic models that also incorporate individual variability, which PBPK currently lack.

In the following two sections specific modelling considerations of paper II-IV will be discussed.

5.2.2.1 PKPD modelling

In paper III, the developed PKPD model from paper II was used as a baseline model to determine the PKPD-relationship of the same formulations in patients with RYGB. This approach may be overruled by analyzing all data in one analysis, which potentially could increase the power of the PKPD study and allow a more systematic evaluation of the influence of formulation, patient group, age etc. Hence, this could be interesting to verify and thus update the current results of paper III.

In paper II and III, oxycodone plasma concentrations and pupil diameter measurements were successfully used to assess the PKPD-relationship of oral solution, lipid-based and water-swellable controlled-release oxycodone in healthy participants and patients with RYGB. Nevertheless, the model could have benefitted from additional pharmacokinetic and pharmacodynamic measures such as metabolite plasma concentrations and muscle pressure stimulation threshold measurements, respectively. Initially, these data were collected, however, it was not possible to determine metabolite concentrations adequately and results of the muscle pressure stimulations were not meaningful due to high variability. In addition, the degree of side-effect scores seemed to follow the dynamics of oxycodone concentrations (paper III), thus it could have been interesting to include these side-effect metrics in the model. Ideally, this would require that the safety assessment be validated as a pharmacodynamic measure. Furthermore, it could have been interesting to investigate the effects of different CYP2D6, CYP3A4 and μ-, δ-and κ-opioid receptor (OPRM1, OPRD1, OPRK1) polymorphisms, as these may have a significant impact on both oxycodone exposure and response (54,99,100). Unfortunately, these data were obtained late in the modelling process and thus not a part of the PKPD models in paper II and III.

5.2.2.2 PBPK modelling

One of the main limitations of the oxycodone PBPK model (Paper IV) is the inconsistent data on physiochemical properties. In addition, some parameters have only been determined in animals (e.g. B/P). This limits the validity of our model and may be improved by determining these values in humans.

Like the PKPD model, metabolites were not incorporated within the model, however this could improve the model, especially, for future drug-drug interaction simulations.

The PBPK models were applied in different populations and simulations were qualitatively compared to observed data of similar populations. In some cases, a quantitative comparison could have been conducted (e.g. healthy Japanese and Chinese) and would have been superior to the qualitative statements of paper IV.

Finally, the absorption was described using the ADAM models, which allows for further exploration of oxycodone pharmacokinetics in patients with different gastrointestinal dysfunctions, once these populations have been validated.

5.3. IMPACT OF GASTROINTESTINAL SURGERY ON DRUG ABSORPTION

5.3.1. PHYSIOLOGICAL ALTERATIONS

The accelerated oro-cecal transit (paper I), shorter absorption lag time for controlled-release tablets (paper III) and overall increased oxycodone bioavailability in patients with RYGB (paper III) could suggest that drugs are more rapidly available for absorption in the jejunum as compared to healthy participants. This seems plausible due to the anatomical changes and is in line with other pharmacokinetic studies finding shorter T_{max} and higher C_{max} and AUC (4).

Paper I revealed that patients with RYGB have a more alkaline intraluminal environment. Drug dissolution, solubility, lipophilicity and permeability is influenced by the degree of ionization, which depends on pH. Thus, depending on the acid dissociation constant, drug absorption may be more or less affected. The higher gastric pH may be of great importance for the bioavailability of oxycodone, which was increased in patients with RYGB (paper III). Results from an animal model demonstrated that bioavailability of sublingual oxycodone spray was 70 % at pH 9 and only 45 % at pH 4 (101). As oxycodone is a weak base (pKa = 8.53), higher pH will increase the amount of unionized oxycodone, which limits water solubility and the fraction available for permeation. On the other hand, unionized oxycodone is more lipophile, which increases the permeation rate. Hence, this indicates that the lipophilicity of oxycodone is more important than its water solubility. Weather this also applies in the intestine, where the surface area for absorption is much larger than

the oral cavity is questionable. The use of physiologically-based pharmacokinetic modelling may help answer this question as well as determine the impact of altered drug absorption and gut wall metabolism caused by physiological alterations of the surgery.

In paper V, preservation of the colon seemed to increase oxycodone bioavailability greatly. This could be due to colonic adaption (24) or increased GLP-1 or GLP-2 secretion from colonic L cells (22), which all favor the process of absorption by increasing the absorptive capacity, slowing motility and enhancing blood flow, respectively (23).

5.3.2. FORMULATION CHOICE – DOES ONE SIZE FIT ALL?

The physiological alterations following gastrointestinal surgery, whether associated with resection or bypass, challenges the use of oral formulations.

Paper III revealed no pharmacokinetic nor pharmacodynamic differences between the two controlled-release formulations and generic substitution was therefore considered safe in patients with RYGB. This was not in agreement with our hypothesis, and suggested drug release between the two controlled-release formulations to be equal and unaffected by the physiological alterations following RYGB surgery. Concurrently, the result was relieving, as an effectuation of new guidelines on formulation choice was not necessary. Nonetheless, the bioavailability of the three tested oxycodone formulations was approximately 14% higher in patients with RYGB compared to healthy participants. Initial dosages may therefore need to be reduced regardless of formulation. Though, the clinical significance still needs to be addressed. Furthermore, the uniform increase in bioavailability among the different formulations could suggests that the that physiochemical drug properties are superior to the formulation design, when it comes to altered pharmacokinetics in patients with RYGB. This would also explain why only some drugs show altered pharmacokinetics, irrespective of the formulation type, in patients with RYGB (4,102). Contradictory, Yska *et al.* demonstrated opposing bioavailability between immediate-release and controlled-release metoprolol before and after RYGB (9). However, the study was not a cross-over study and included few patients with large intra- and interindividual variability, thus questioning the reliability of the results.

The small intestine is the most vital organ for intestinal absorption, thus it was expected and in agreement with previous findings (28), that patients with SBS showed impaired oxycodone absorption (paper V). More importantly, results of paper V indicated a trend between total intestinal length and relative oxycodone bioavailability. Similar trends using oral antibiotics in children have been demonstrated (103), although contradictory findings also exist (104,105). Nevertheless, it could be of outmost relevance to verify this trend by conducting a larger clinical study, that assessed the pharmacokinetics of several medications in

relation to functional intestinal length. A study with more power, would allow to control for potential confounders and covariates, thus giving a more confident result as compared to case studies. Another interesting trend observed in paper V was the positive correlation between total parenteral nutrition and fraction absorbed. This could simultaneously be investigated and has also been suggested previously (106,107).

Overall, patients with RYGB and SBS were able to orally absorb clinically significant amounts of oxycodone, although with some pharmacokinetic variation compared to healthy participants. Based on the current data:

1) Both oral liquid and solid dosages forms may be used in patients with RYGB, however, bioavailability may be altered significantly, thus requiring dose adjustments from general dosing guidelines and close monitoring of especially narrow therapeutic drugs.

2) Oral liquid dosages forms may be used in patients with SBS, however, dosing regimens must be individualized in accordance to the patient's characteristics such as functional intestinal length, renal and hepatic function. Drug prescribing may therefore become a rather extensive task. Thus, parenteral, sublingual, transdermal, rectal or buccal administration forms may be more appropriate and can ensure a better therapeutic effect.

In summary, one formulation does not fit all and should ideally be selected carefully, depending on the patient's characteristics and the physiochemical drug properties. This may not only apply to the investigated populations included in this thesis, but also to other populations, where the gastrointestinal physiology is altered. This could be in patients with inflammatory bowel diseases or irritable bowel syndrome, who have altered gastrointestinal transit, fluid composition, permeability and enzyme expression (108). It could also be of relevance to patients with chronic pancreatitis, who suffer from fat malabsorption, due to loss of exocrine pancreatic enzyme production (109), which may impact drug absorption from lipid-based formulations.

CHAPTER 6. CONCLUSION

This PhD thesis had four objectives divided into five aims. In conclusion, it has demonstrated that:

Aim I (paper I)

- The anatomical alteration following RYGB surgery was suitably reflected by an increased intraluminal pH, shorter transit and increased motility of the oro-cecal segment.
- Transit of the colon was longer in patients with RYGB. This may be explained by gut adaption or confounding factors such as opioid consumption.
- Alterations may impact drug release and absorption of pH-sensitive formulations and/or drugs. In addition, results may be useful for understanding the underlying pathophysiology following RYGB surgery.

Aim II-III (paper II and III)

- A PKPD model of oral solution, lipid-based and water-swellable controlled-release oxycodone was successfully developed in healthy participants and patients with RYGB.
- The model did not find any pharmacokinetic nor pharmacodynamic differences between the two controlled-release formulations for any of the populations, thus generic substitution of these formulations may be considered safe in both populations.
- A higher bioavailability of oxycodone was demonstrated in patients with RYGB, which may imply slightly lower initial doses and monitoring of side-effects.
- Further PKPD and PBPK modelling may help explain the increased bioavailability in patients with RYGB and further guide dose adjustment.

Aim IV (paper IV)

- A full PBPK model for oral solution and controlled-released oxycodone was successfully developed and verified. In addition, the PBPK models were applied in special populations and simulations were in reasonable agreement with observed data.
- The PBPK model may be used to predict different clinical scenarios (e.g. drug-drug interactions, multiple dosing etc.).
- The model may also be used to investigate the impact of bariatric surgery as well as other gastrointestinal diseases on the pharmacokinetics of oxycodone from different formulations, as the ADAM model was applied.

Aim V (paper V)

- Absorption of oxycodone was clearly marked by the reduced functional intestinal length of patients with SBS.
- Preservation of the colon seemed essential for absorption enhancement.
- Individualized drug therapy is needed due to large variability among patients with SBS.
- Functional intestinal length as well as total parenteral nutrition may be useful measures to adjust dosing regimens for patients with SBS.

Overall, our results showed that gastrointestinal surgery, associated with resection or bypass, impacts the absorption of orally administered oxycodone.

In patients with RYGB, the physiochemical properties of a drug may be superior to the formulation design in regard to altered drug pharmacokinetics. Hence, any of the tested formulations may be prescribed to patients with RYGB, however, the increased bioavailability of oxycodone may necessitate dose adjustments to prevent side-effects such as addiction and tolerance. This may be addressed using a combination of PKPD and PBPK modelling.

In patients with SBS, lack of functional intestine tended to deteriorate the absorption of oxycodone. Nevertheless, oral solution oxycodone may be used in patients with SBS, although drug dosing must be individualized and will for most presumably require higher doses to obtain therapeutic efficacy.

CHAPTER 7. FUTURE PERSPECTIVES

As a result of the work conducted, during this PhD project, new research ideas arose and could be of relevance to address in the future.

Firstly, it could be informative to address the physiological reason behind the increased bioavailability observed in patients with RYGB. Thus, we intend to build and verify a RYGB population within the Simcyp Simulator and thus apply the developed oxycodone PBPK models to evaluate this. Concurrently, different clinical scenarios could be investigated.

Secondly, the developed PBPK models in paper IV may be used to further investigate oxycodone pharmacokinetics in populations with different gastrointestinal diseases, specific drug-drug interaction scenarios, effects of multiple dosing as well as other relevant clinical situations. Such information may help optimize current treatment guidelines for the investigated populations.

Thirdly, despite no PKPD differences of the two tested controlled-release formulations in patients with RYGB. This may not apply to other modified-release formulations as well as other populations with gastrointestinal dysfunction. Prior investigations applying suitable dissolution systems, such as the gastrointestinal simulation system (GISS) developed by Yska *et al.* (110), or development of PBPK models is recommended, as such evidence may be able to answer speculations with reasonable probability before conducting time-consuming and costly clinical trials.

Finally, it could be interesting to asses functional intestinal length as well as total parenteral nutrition as predictive measures for both C_{max} and fraction absorbed in patients with SBS. Such information could be used to develop a model, that could guide physicians to ensure safer and more optimal drug usage rather than the current trial and error approach.

LITERATURE LIST

1. Björklund P, Fändriks L. The pros and cons of gastric bypass surgery - The role of the Roux-limb. Best Pract Res Clin Gastroenterol. 2019;40–41:101638.

2. Himpens J, Ramos A, Welbourn R, Dixon J, Frcp F, Kinsman ER, et al. The IFSO global registry report 2018 [Internet]. 2018. Available from: https://www.ifso.com/pdf/4th-ifso-global-registry-report-last-2018.pdf

3. Ma IT, Madura JA. Gastrointestinal Complications After Bariatric Surgery. Gastroenterol Hepatol (N Y). 2015;11:526–35.

4. Hachon L, Declèves X, Faucher P, Carette C, Lloret-Linares C. RYGB and Drug Disposition: How to Do Better? Analysis of Pharmacokinetic Studies and Recommendations for Clinical Practice. Obes Surg. 2017;27:1076–90.

5. Angeles PC, Robertsen I, Seeberg LT, Krogstad V, Skattebu J, Sandbu R, et al. The influence of bariatric surgery on oral drug bioavailability in patients with obesity: A systematic review. Obes Rev. 2019;20:1299–311.

6. Fried M, Yumuk V, Oppert JM, Scopinaro N, Torres A, Weiner R, et al. Interdisciplinary European guidelines on metabolic and bariatric surgery. Obes Surg. 2014;24:42–55.

7. Lizer MH, Papageorgeon H, Glembot TM. Nutritional and pharmacologic challenges in the bariatric surgery patient. Obes Surg. 2010;20:1654–9.

8. Krieger CA, Cunningham JL, Reid JM, Langman LJ, Grothe KB, Clark MM, et al. Comparison of Bioavailability of Single-Dose Extended-Release Venlafaxine Capsules in Obese Patients Before and After Gastric Bypass Surgery. Pharmacother J Hum Pharmacol Drug Ther. 2017;37:1374–82.

9. Yska JP, Wanders JTM, Odigie B, Apers JA, Emous M, Totté ERE, et al. Effect of Roux-en-Y gastric bypass on the bioavailability of metoprolol from immediate and controlled release tablets: a single oral dose study before and after surgery. Eur J Hosp Pharm Sci Pract. 2020;27:e19–24.

10. Gesquiere I, Darwich AS, Van Der Schueren B, De Hoon J, Lannoo M, Matthys C, et al. Drug disposition and modelling before and after gastric bypass: Immediate and controlled-release metoprolol formulations. Br J Clin Pharmacol. 2015;80:1021–30.

11. SzaŁek E, Karbownik A, Murawa D, PoŁom K, Tezyk A, Gracz J, et al. The

pharmacokinetics of oral oxycodone in patients after total gastric resection. Eur Rev Med Pharmacol Sci. 2014;18:3126–33.

12. Siddiqui MT, Al-Yaman W, Singh A, Kirby DF. Short-Bowel Syndrome: Epidemiology, Hospitalization Trends, In-Hospital Mortality, and Healthcare Utilization. JPEN J Parenter Enteral Nutr. 2020;0:jpen.2051.

13. Carroll RE, Benedetti E, Schowalter JP, Buchman AL. Management and Complications of Short Bowel Syndrome: an Updated Review. Curr Gastroenterol Rep. 2016;18:40.

14. Massironi S, Cavalcoli F, Rausa E, Invernizzi P, Braga M, Vecchi M. Understanding short bowel syndrome: Current status and future perspectives. Dig Liver Dis. 2020;52:253–61.

15. Pederiva F, Khalil B, Morabito A, Wood SJ. Impact of Short Bowel Syndrome on Quality of Life and Family: The Patient's Perspective. Eur J Pediatr Surg. 2019;29:196–202.

16. Carlsson E, Bosaeus I, Nordgren S. Quality of life and concerns in patients with short bowel syndrome. Clin Nutr. 2003;22:445–52.

17. Kalaitzakis E, Carlsson E, Josefsson A, Bosaeus I. Quality of life in short-bowel syndrome: Impact of fatigue and gastrointestinal symptoms. Scand J Gastroenterol. 2008;43:1057–65.

18. Aggarwal L, Sattavan S, Lal R, Sharma D, Borgharia S, Shrivastava N, et al. Short Bowel Syndrome: An Uncommon Clinical Entity and a Therapeutic Challenge—Our Experience and Review of Literature. Indian J Surg. 2017;79:349–53.

19. Thompson JS. Comparison of massive vs. repeated resection leading to short bowel syndrome. J Gastrointest Surg. 2000;4:101–4.

20. Pironi L. Definitions of intestinal failure and the short bowel syndrome. Best Pract Res Clin Gastroenterol. 2016;30:173–85.

21. Shakhsheer BA, Warner BW. Short Bowel Syndrome. Curr Treat Options Pediatr. 2019;5:494–505.

22. Jeppesen PB, Hartmann B, Thulesen J, Hansen BS, Holst JJ, Poulsen SS, et al. Elevated plasma glucagon-like peptide 1 and 2 concentrations in ileum resected short bowel patients with a preserved colon. Gut. 2000;47:370–6.

23. Markovic MA, Brubaker PL. The roles of glucagon-like peptide-2 and the intestinal epithelial insulin-like growth factor-1 receptor in regulating microvillus length. Sci Rep. 2019;9:13010.

24. Warner BW. The Pathogenesis of Resection-Associated Intestinal Adaptation. Cell Mol Gastroenterol Hepatol. 2016;2:429–38.

25. Severijnen R, Bayat N, Bakker H, Tolboom J, Bongaerts G. Enteral Drug Absorption in Patients with Short Small Bowel. Clin Pharmacokinet. 2004;43:951–62.

26. Titus R, Kastenmeier A, Otterson MF. Consequences of gastrointestinal surgery on drug absorption. Nutr Clin Pract. 2013;28:429–36.

27. Godoy BZ, Faintuch J, Marin MLM, Nogueira MA, Pinto VB, Pollara WM. Off label pharmacological therapy in patients with short bowel syndrome. Eur Rev Med Pharmacol Sci. 2013;17:3285–90.

28. Santamaría MM, Villafranca JJA, Abilés J, López AF, Rodas LV, Goitia BT, et al. Systematic review of drug bioavailability following gastrointestinal surgery. Eur J Clin Pharmacol. 2018;74:1531–45.

29. Park K. Controlled drug delivery systems: past forward and future back. J Control Release. 2014;190:3–8.

30. Kalepu S, Manthina M, Padavala V. Oral lipid-based drug delivery systems – an overview. Acta Pharm Sin B. 2013;3:361–72.

31. Gazzaniga A, Palugan L, Foppoli A, Sangalli ME. Oral pulsatile delivery systems based on swellable hydrophilic polymers. Eur J Pharm Biopharm. 2008;68:11–8.

32. Jiang X, Orton M, Feng R, Hossain E, Malhotra NR, Zager EL, et al. Chronic Opioid Usage in Surgical Patients in a Large Academic Center. Ann Surg. 2017;265:722–7.

33. Hastie BA, Gilson AM, Maurer MA, Cleary JF. An examination of global and regional opioid consumption trends 1980-2011. J Pain Palliat Care Pharmacother. 2014;28:259–75.

34. Poyhia R, Seppala T, Olkkola K, Kalso E. The pharmacokinetics and metabolism of oxycodone after intramuscular and oral administration to healthy subjects. Br J Clin Pharmacol. 1992;33:617–21.

35. Nieminen TH, Hagelberg NM, Saari TI, Pertovaara A, Neuvonen M, Laine K, et al. Rifampin greatly reduces the plasma concentrations of intravenous and oral oxycodone. Anesthesiology. 2009;110:1371–8.

36. Mandema JW, Kaiko RF, Oshlack B, Reder RF, Stanski DR. Characterization and validation of a pharmacokinetic model for controlled-release oxycodone. Br J Clin Pharmacol. 1996;42:747–56.

37. Pöyhiä R, Seppälä T. Liposolubility and protein binding of oxycodone in vitro. Pharmacol Toxicol. 1994;74:23–7.

38. Kokki M, Välitalo P, Rasanen I, Sirpa Aaltomaa, Ojanperä I, Matti Eskelinen, et al. Absorption of different oral dosage forms of oxycodone in the elderly: a cross-over clinical trial in patients undergoing cystoscopy. Eur J Clin Pharmacol. 2012;68:1357–63.

39. Poyhia R, Olkkola K, Seppala T, Kalso E. The pharmacokinetics of oxycodone after intravenous injection in adults. Br J Clin Pharmacol. 1991;32:516–8.

40. Villesen HH, Foster DJR, Upton RN, Somogyi AA, Martinez A, Grant C. Cerebral kinetics of oxycodone in conscious sheep. J Pharm Sci. 2006;95:1666–76.

41. Boström E, Simonsson USH, Hammarlund-Udenaes M. Oxycodone pharmacokinetics and pharmacodynamics in the rat in the presence of the P-glycoprotein inhibitor PSC833. J Pharm Sci. 2005;94:1060–6.

42. Sadiq MW, Boström E, Keizer R, Björkman S, Hammarlund-Udenaes M. Oxymorphone active uptake at the blood-brain barrier and population modeling of its pharmacokinetic-pharmacodynamic relationship. J Pharm Sci. 2013;102:3320–31.

43. Lalovic B, Kharasch E, Hoffer C, Risler L, Liu-Chen LY, Shen DD. Pharmacokinetics and pharmacodynamics of oral oxycodone in healthy human subjects: role of circulating active metabolites. Clin Pharmacol Ther. 2006;79:461–79.

44. Lalovic B, Phillips B, Risler LL, Howald W, Shen DD. Quantitatlve contribution of CYP2D6 and CYP3A to oxycodone metabolism in human liver and intestinal microsomes. Drug Metab Dispos. 2004;32:447–54.

45. Romand S, Spaggiari D, Marsousi N, Samer C, Desmeules J, Daali Y, et al. Characterization of oxycodone in vitro metabolism by human cytochromes

P450 and UDP-glucuronosyltransferases. J Pharm Biomed Anal. 2017;144:129–37.

46. Coffman BL, King CD, Rios GR, Tephly TR. The glucuronidation of opioids, other xenobiotics, and androgens by human UGT2B7Y(268) and UGT2B7H(268). Drug Metab Dispos. 1998;26:73–7.

47. Cone EJ, Darwin WD, Buchwald WF, Gorodetzky CW. Oxymorphone metabolism and urinary excretion in human, rat, guinea pig, rabbit, and dog. Drug Metab Dispos. 11:446–50.

48. Kinnunen M, Piirainen P, Kokki H, Lammi P, Kokki M. Updated Clinical Pharmacokinetics and Pharmacodynamics of Oxycodone. Clin Pharmacokinet. 2019;58:705–25.

49. Trescot AM, Datta S, Lee M, Hans H. Opioid pharmacology. Pain Physician. 2008;11:133–54.

50. McDonald J, Lambert DG. Opioid receptors. BJA Educ. 2015;15:219–24.

51. Thompson CM, Wojno H, Greiner E, May EL, Rice KC, Selley DE. Activation of G-proteins by morphine and codeine congeners: insights to the relevance of O- and N-demethylated metabolites at mu- and delta-opioid receptors. J Pharmacol Exp Ther. 2004;308:547–54.

52. Kokki M, Välitalo P, Kuusisto M, Ranta VP, Raatikainen K, Hautajärvi H, et al. Central nervous system penetration of oxycodone after intravenous and epidural administration. Br J Anaesth. 2014;112:133–40.

53. Klimas R, Witticke D, El Fallah S, Mikus G. Contribution of oxycodone and its metabolites to the overall analgesic effect after oxycodone administration. Expert Opin Drug Metab Toxicol. 2013;9:517–28.

54. Samer C, Daali Y, Wagner M, Hopfgartner G, Eap C, Rebsamen M, et al. Genetic polymorphisms and drug interactions modulating CYP2D6 and CYP3A activities have a major effect on oxycodone analgesic efficacy and safety. Br J Pharmacol. 2010;160:919–30.

55. Sarosiek I, Selover KH, Katz LA, Semler JR, Wilding GE, Lackner JM, et al. The assessment of regional gut transit times in healthy controls and patients with gastroparesis using wireless motility technology. Aliment Pharmacol Ther. 2010;31:313–22.

56. Camilleri M, Malagelada J-R. Abnormal intestinal motility in diabetics with

the gastroparesis syndrome. Eur J Clin Invest. 1984;14:420–7.

57. Wolfe D, Yazdi F, Kanji S, Burry L, Beck A, Butler C, et al. Incidence, causes, and consequences of preventable adverse drug reactions occurring in inpatients: A systematic review of systematic reviews. PLoS One. 2018;13:e0205426.

58. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA. 1998;279:1200–5.

59. Gosai P, Ducharme MP, Godfrey AR, Freeman JC, Monif T, Kumar KS, et al. Bioequivalence of oxycodone hydrochoride extended release tablets to marketed reference products OxyContin® in Canada and US. Int J Clin Pharmacol Ther. 2013;51:895–907.

60. Devarakonda K, Morton T, Margulis R, Giuliani M, Barrett T. Pharmacokinetics and bioavailability of oxycodone and acetaminophen following single-dose administration of MNK-795, a dual-layer biphasic IR/ER combination formulation, under fed and fasted conditions. Drug Des Devel Ther. 2014;8:1125–34.

61. Komatsu T, Kokubun H, Suzuki A, Takayanagi R, Yamada Y, Matoba M, et al. Population pharmacokinetics of oxycodone in patients with cancer-related pain. J Pain Palliat Care Pharmacother. 2012;26:220–5.

62. Webster LR, Bath B, Medve RA, Marmon T, Stoddard GJ. Randomized, double-blind, placebo-controlled study of the abuse potential of different formulations of oral oxycodone. Pain Med. 2012;13:790–801.

63. Perrino PJ, Colucci S V, Apseloff G, Harris SC. Pharmacokinetics, tolerability, and safety of intranasal administration of reformulated OxyContin(®) tablets compared with original OxyContin (®) tablets in healthy adults. Clin Drug Investig. 2013;33:441–9.

64. Fujiwara Y, Toyoda M, Chayahara N, Kiyota N, Shimada T, Imamura Y, et al. Effects of aprepitant on the pharmacokinetics of controlled-release oral oxycodone in cancer patients. PLoS One. 2014;9:1–7.

65. Press D. Pooled post hoc analysis of population pharmacokinetics of oxycodone and acetaminophen following a single oral dose of biphasic immediate-release / extended-release oxycodone / acetaminophen tablets. 2015;4587–97.

66. Kokubun H, Yoshimoto T, Hojo M, Fukumura K, Matoba M. Pharmacokinetics of Oxycodone After Intravenous and Subcutaneous Administration in Japanese Patients with Cancer Pain. J Pain Palliat Care Pharmacother. 2014;28:338–50.

67. Hao GT, Zhou HY, Gao HZ, Qu HY, Liang YG, Li YY, et al. Pharmacokinetics of oxycodone hydrochloride and three of its metabolites after intravenous administration in Chinese patients with pain. Pharmacol Reports. 2014;66:153–8.

68. Kim J-Y, Lee S-H, Park C-W, Rhee Y-S, Kim D-W, Park J, et al. Design and in vivo evaluation of oxycodone once-a-day controlled-release tablets. Drug Des Devel Ther. 2015;9:695–706.

69. Gudin J, Levy-Cooperman N, Kopecky EA, Fleming AB. Comparing the Effect of Tampering on the Oral Pharmacokinetic Profiles of Two Extended-Release Oxycodone Formulations with Abuse-Deterrent Properties. Pain Med (United States). 2015;16:2142–51.

70. Höfle M, Kenntner-Mabiala R, Pauli P, Alpers GW. You can see pain in the eye: pupillometry as an index of pain intensity under different luminance conditions. Int J Psychophysiol. 2008;70:171–5.

71. Fischer IW, Hansen TM, Lelic D, Brokjær A, Frøkjær JB, Christrup LL, et al. Objective methods for the assessment of the spinal and supraspinal effects of opioids. Scand J Pain. 2017;14:15–24.

72. Brokjær A, Olesen AE, Kreilgaard M, Graversen C, Gram M, Christrup LL, et al. Objective markers of the analgesic response to morphine in experimental pain research. J Pharmacol Toxicol Methods. 2015;73:7–14.

73. Connelly MA, Brown JT, Kearns GL, Anderson RA, St Peter SD, Neville KA. Pupillometry: a non-invasive technique for pain assessment in paediatric patients. Arch Dis Child. 2014;99:1125–31.

74. Barvais L, Engelman E, Eba JM, Coussaert E, Cantraine F, Kenny GN. Effect site concentrations of remifentanil and pupil response to noxious stimulation. Br J Anaesth. 2003;91:347–52.

75. Zhang L, Beal SL, Sheiner LB. Simultaneous vs. sequential analysis for population PK/PD data I: best-case performance. J Pharmacokinet Pharmacodyn. 2003;30:387–404.

76. R Core Team. R: a language and environment for statistical computing. R

Foundation for Statistical Computing, Vienna, Austria. [Internet]. 2014 [cited 2018 Dec 20]. Available from: http://www.r-project.org/

77. Mandema JW, Verotta D, Sheiner LB. Building population pharmacokinetic--pharmacodynamic models. I. Models for covariate effects. J Pharmacokinet Biopharm. 1992;20:511–28.

78. Ladebo L, Foster DJR, Abuhelwa AY, Upton RN, Kongstad KT, Drewes AM, et al. Population pharmacokinetic-pharmacodynamic modelling of liquid and controlled-release formulations of oxycodone in healthy volunteers. Basic Clin Pharmacol Toxicol. 2020;126:263–76.

79. Guest EJ, Aarons L, Houston JB, Rostami-Hodjegan A, Galetin A. Critique of the two-fold measure of prediction success for ratios: application for the assessment of drug-drug interactions. Drug Metab Dispos. 2011;39:170–3.

80. Drozdowski LA, Clandinin MT, Thomson ABR. Morphological, kinetic, membrane biochemical and genetic aspects of intestinal enteroplasticity. World J Gastroenterol. 2009;15:774–87.

81. Peterli R, Steinert RE, Woelnerhanssen B, Peters T, Christoffel-Courtin C, Gass M, et al. Metabolic and hormonal changes after laparoscopic Roux-en-Y gastric bypass and sleeve gastrectomy: a randomized, prospective trial. Obes Surg. 2012;22:740–8.

82. Seeley RJ, Chambers AP, Sandoval DA. The Role of Gut Adaptation in the Potent Effects of Multiple Bariatric Surgeries on Obesity and Diabetes. Cell Metab. 2015;21:369–78.

83. de Zwaan M, Enderle J, Wagner S, Mühlhans B, Ditzen B, Gefeller O, et al. Anxiety and depression in bariatric surgery patients: a prospective, follow-up study using structured clinical interviews. J Affect Disord. 2011;133:61–8.

84. Van Egroo M, Gaggioni G, Cespedes-Ortiz C, Ly JQM, Vandewalle G. Steady-State Pupil Size Varies with Circadian Phase and Sleep Homeostasis in Healthy Young Men. Clocks & Sleep. 2019;1:240–58.

85. Bhupathi C, Vajjha VH. Sample size recommendation for a bioequivalent study. Statistica. 2017;77:65–71.

86. Parkman HP. Scintigraphy for evaluation of patients for GI motility disorders--the referring physician's perspective. Semin Nucl Med. 2012;42:76–8.

87. Dirksen C, Damgaard M, Bojsen-Møller KN, Jørgensen NB, Kielgast U,

Jacobsen SH, et al. Fast pouch emptying, delayed small intestinal transit, and exaggerated gut hormone responses after Roux-en-Y gastric bypass. Neurogastroenterol Motil. 2013;25:346-e255.

88. Nguyen NQ, Debreceni TL, Burgstad CM, Neo M, Bellon M, Wishart JM, et al. Effects of Fat and Protein Preloads on Pouch Emptying, Intestinal Transit, Glycaemia, Gut Hormones, Glucose Absorption, Blood Pressure and Gastrointestinal Symptoms After Roux-en-Y Gastric Bypass. Obes Surg. 2016;26:77–84.

89. Näslund I, Beckman K-W. Gastric Emptying Rate after Gastric Bypass and Gastroplasty. Scand J Gastroenterol. 1987;22:193–201.

90. Nguyen NQ, Debreceni TL, Burgstad CM, Wishart JM, Bellon M, Rayner CK, et al. Effects of Posture and Meal Volume on Gastric Emptying, Intestinal Transit, Oral Glucose Tolerance, Blood Pressure and Gastrointestinal Symptoms After Roux-en-Y Gastric Bypass. Obes Surg. 2015;25:1392–400.

91. van Beek AP, Emous M, Laville M, Tack J. Dumping syndrome after esophageal, gastric or bariatric surgery: pathophysiology, diagnosis, and management. Obes Rev. 2017;18:68–85.

92. Abid S, Rizvi A, Jahan F, Rabbani F, Islam N, Khan MH, et al. Poor glycaemic control is the major factor associated with increased frequency of gastrointestinal symptoms in patients with diabetes mellitus. J Pak Med Assoc. 2007;57:345–9.

93. Sherf Dagan S, Goldenshluger A, Globus I, Schweiger C, Kessler Y, Kowen Sandbank G, et al. Nutritional Recommendations for Adult Bariatric Surgery Patients: Clinical Practice. Adv Nutr. 2017;8:382–94.

94. Peters HPF, De Vries WR, Vanberge-Henegouwen GP, Akkermans LMA. Potential benefits and hazards of physical activity and exercise on the gastrointestinal tract. Gut. 2001;48:435–9.

95. Mould DR, Upton RN. Basic Concepts in Population Modeling, Simulation, and Model-Based Drug Development—Part 2: Introduction to Pharmacokinetic Modeling Methods. CPT Pharmacometrics Syst Pharmacol. 2013;2:e38.

96. Upton RN, Mould DR. Basic concepts in population modeling, simulation, and model-based drug development: Part 3-introduction to pharmacodynamic modeling methods. CPT Pharmacometrics Syst Pharmacol. 2014;3:1–16.

97. Mould DR, Upton RN. Basic Concepts in Population Modeling, Simulation, and Model-Based Drug Development. CPT Pharmacometrics Syst Pharmacol. 2012;1:e6.

98. Jones H, Rowland-Yeo K. Basic Concepts in Physiologically Based Pharmacokinetic Modeling in Drug Discovery and Development. CPT Pharmacometrics Syst Pharmacol. 2013;2:63.

99. Olsen R, Foster DJR, Upton RN, Olesen AE, Ross JR, Droney J, et al. Modelling the PKPD of oxycodone in experimental pain — Impact of opioid receptor polymorphisms. Eur J Pharm Sci. 2016;86:41–9.

100. Olesen AE, Sato H, Nielsen LM, Staahl C, Droney J, Gretton S, et al. The genetic influences on oxycodone response characteristics in human experimental pain. Fundam Clin Pharmacol. 2015;29:417–25.

101. Al-Ghananeem AM, Malkawi AH, Crooks PA. Effect of pH on sublingual absorption of oxycodone hydrochloride. AAPS PharmSciTech. 2006;7:3–7.

102. Gesquiere I, Hens B, Van der Schueren B, Mols R, de Hoon J, Lannoo M, et al. Drug disposition before and after gastric bypass: fenofibrate and posaconazole. Br J Clin Pharmacol. 2016;60:1325–32.

103. Menardi G, Guggenbichler JP. Biovailability of oral antibiotics in children with short-bowel syndrome. J Pediatr Surg. 1984;19:84–6.

104. Faye E, Drouet L, De Raucourt E, Green A, Bal-dit-Sollier C, Boudaoud L, et al. Absorption and Efficacy of Acetylsalicylic Acid in Patients With Short Bowel Syndrome. Ann Pharmacother. 2014;48:705–10.

105. Cheung YW, Barco S, Mathôt RAA, van den Dool E-J, Stroobants AK, Serlie MJ, et al. Pharmacokinetics of dabigatran etexilate and rivaroxaban in patients with short bowel syndrome requiring parenteral nutrition: The PDER PAN study. Thromb Res. 2017;160:76–82.

106. Pironi L, Steiger E, Brandt C, Joly F, Wanten G, Chambrier C, et al. Home parenteral nutrition provision modalities for chronic intestinal failure in adult patients: An international survey. Clin Nutr. 2020;39:585–91.

107. Pironi L, Konrad D, Brandt C, Joly F, Wanten G, Agostini F, et al. Clinical classification of adult patients with chronic intestinal failure due to benign disease: An international multicenter cross-sectional survey. Clin Nutr. 2018;37:728–38.

108. Effinger A, O'Driscoll CM, McAllister M, Fotaki N. Impact of gastrointestinal disease states on oral drug absorption – implications for formulation design – a PEARRL review. J Pharm Pharmacol. 2019;71:674–98.

109. Pezzilli R. Chronic pancreatitis: maldigestion, intestinal ecology and intestinal inflammation. World J Gastroenterol. 2009;15:1673–6.

110. Yska JP, Punter RJ, Woerdenbag HJ, Emous M, Frijlink HW, Wilffert B, et al. A gastrointestinal simulation system for dissolution of oral solid dosage forms before and after Roux-en-Y gastric bypass. Eur J Hosp Pharm Sci Pract. 2019;26:152–6.

ISSN (online): 2246-1302
ISBN (online): 978-87-7210-927-5

AALBORG UNIVERSITY PRESS