PUBLICATIONS OF
THE UNIVERSITY OF EASTERN FINLAND

Dissertations in Health Sciences

ANTTI VALTOLA

Clinical insights into the pharmacokinetic aspects of fentanyl, metoprolol and oxycodone dosing after cardiac surgery

CLINICAL INSIGHTS INTO THE PHARMACOKINETIC ASPECTS OF FENTANYL, METOPROLOL AND OXYCODONE DOSING AFTER CARDIAC SURGERY

Antti Valtola

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To be presented by permission of the Faculty of Health Sciences,
University of Eastern Finland for public examination in Large Auditorium,
Kuopio University Hospital
on August 13th, 2021, at 12 o'clock noon

Publications of the University of Eastern Finland
Dissertations in Health Sciences
No 633

Department / School of Medicine
University of Eastern Finland, Kuopio
2021

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University of Eastern Finland

Kuopio Campus Library

P.O. Box 1627

FI-70211 Kuopio, Finland

www.uef.fi/kirjasto

PunaMusta Oy

Joensuu, 2021

ISBN: 978-952-61-4260-9 (nid.)

ISBN: 978-952-61-4261-6 (PDF)

ISSNL: 1798-5706

ISSN: 1798-5706

ISSN: 1798-5714 (PDF)

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Clinical insights into the pharmacokinetic aspects of fentanyl, metoprolol and oxycodone dosing after cardiac surgery
Kuopio: University of Eastern Finland
Publications of the University of Eastern Finland
Dissertations in Health Sciences 633. 2021, 174 p.
ISBN: 978-952-61-4260-9 (nid.)
ISBN: 978-952-61-4261-6 (PDF)
ISSNL: 1798-5706
ISSN: 1798-5706
ISSN: 1798-5714 (PDF)

ABSTRACT

Postoperative drug administration is essential to help cardiac surgery patients recover without undesired events and reap long-term benefits from the surgical procedure. Oral drug administration is preferred due to its convenience for both patients and staff. However, in the early postoperative period, the bioavailability of perorally administered drugs is altered; thus, parenteral routes are preferred until gastrointestinal function has recovered.

After cardiac surgery, atrial fibrillation is the most common arrhythmia likely to develop. It is a serious complication as it causes prolonged hospitalization, may lead to a deterioration of circulatory function, predisposing patients to stroke, and leading to increased treatment costs. Postoperative therapy with ß-blockers has a significant role in preventing postoperative atrial fibrillation.

After cardiac surgery, severe pain is a common outcome, and the effective treatment of postoperative pain is crucial to ensure the patient's smooth recovery. Severe pain predisposes patients to poor pulmonary ventilation and delayed mobilization, both of which may lead to serious complications such as pneumonia. Patients with moderate and severe postoperative pain have an increased risk of suffering persistent postoperative pain.

This doctoral thesis aims to assess the bioavailability of orally administered metoprolol and oxycodone, and intranasally administered fentanyl in the

early postoperative period after coronary artery bypass grafting (CABG). It was hypothesized that better knowledge on the pharmacokinetic properties of these drugs would enhance the prevention and treatment of postoperative atrial fibrillation and pain, and therefore improve patient outcome.

The bioavailability of orally administered metoprolol was evaluated in 12 consecutive male patients undergoing CABG surgery with cardiopulmonary bypass (CPB). Pharmacokinetic analysis followed a non-compartmental model. Compared to the preoperative day, metoprolol bioavailability was markedly reduced on the first postoperative day. On the third postoperative day, the bioavailability returned to preoperative levels.

The bioavailability of peroral oxycodone during the first four postoperative days was evaluated in 24 patients, who were prospectively randomized to CABG surgery either with or without CPB. The pharmacokinetic analysis utilized a 2-compartmental model. On the first postoperative day, oxycodone's peroral bioavailability markedly declined in both groups. On the second postoperative day, it returned to or even rose above the preoperative values. This phenomenon was due to delayed postoperative absorption and it led to drug accumulation.

The bioavailability of intranasal fentanyl was evaluated in 16 consecutive patients undergoing CABG surgery. Each patient received a single dose of 100 µg or 200 µg of medication two days apart in random order before incidental breakthrough pain. Population pharmacokinetic methods were used in the evaluation. The bioavailability of intranasal fentanyl was high and comparable to that reported in healthy adults. Chest tube removal or physiotherapy failed to exacerbate pain in the fentanyl treated subjects.

In summary, in the early postoperative period, the bioavailability of orally administered metoprolol markedly diminishes, necessitating parenteral administration during the first few postoperative days. The absorption of peroral oxycodone is comparably delayed after CABG with or without CPB. In either case, oral administration of oxycodone should be avoided during the first 24 postoperative hours to avoid accumulation. As intranasal fentanyl proved to be a rapid, efficient, and well-tolerated drug, its use in the management of incidental postoperative breakthrough pain in cardiac surgical patients is encouraged.

National Library of Medicine Classification: QV 38, QV 89, QV 132, WG 169, WO 184

Medical Subject Headings: Administration, Oral; Biological Availability; Cardiac Surgical Procedures; Cardiopulmonary Bypass; Coronary Artery Bypass; Fentanyl; Metoprolol; Oxycodone; Pain, Postoperative; Postoperative Period

Valtola, Antti
Kliinisiä havaintoja fentanyylin, metoprololin, ja oksikodonin farmakokinetiikasta sydänleikkauksen jälkeen
Kuopio: Itä-Suomen yliopisto
Publications of the University of Eastern Finland
Dissertations in Health Sciences 633. 2021, 174 s.
ISBN: 978-952-61-4260-9 (nid.)
ISBN: 978-952-61-4261-6 (PDF)
ISSNL: 1798-5706
ISSN: 1798-5706
ISSN: 1798-5714 (PDF)

TIIVISTELMÄ

Sydänleikkauksen jälkeinen lääkitys on keskeisessä asemassa, jotta leikkauksesta toipuminen olisi sujuvaa ilman haittatapahtumia ja että leikkauksesta saatava pitkäaikaishyöty varmistetaan. Suun kautta tapahtuva lääkkeiden annostelu on toivottua johtuen annostelun yksinkertaisuudesta sekä potilaalle että henkilökunnalle. Varhaisessa leikkauksen jälkeisessä vaiheessa suun kautta annosteltujen lääkkeiden hyötyosuus voi kuitenkin jäädä pieneksi. Tämän vuoksi käytetään suonensisäisiä annostelureittejä kunnes mahasuolikanava on toipunut leikkauksesta.

Eteisvärinä on yleisin sydämen rytmihäiriö sydänleikkauksen jälkeen. Se luo potilaalle epämukavuutta, saattaa aiheuttaa verenkierron häiriöitä ja altistaa aivoverenkierron häiriöille. Eteisvärinän on lisäksi osoitettu lisäävän sairaalahoidon kestoa ja hoitokustannuksia. Leikkauksen jälkeinen beetasalpaajalääkitys on merkittävässä roolissa leikkauksen jälkeisen eteisvärinän ehkäisyssä.

Sydänleikkauksen jälkeen kipu on usein kovaa. Tehokas kivunhoito on tärkeää sujuvan toipumisen edistämiseksi. Kova kipu voi haitata esimerkiksi hengitystä ja viivästyttää liikkeellelähtöä. Nämä puolestaan altistavat potilaan haittatapahtumille kuten keuhkokuumeelle. Kova leikkauksen jälkeisen kipu lisää riskiä kivun kroonistumiselle.

Tämän väitöskirjatyön tavoitteena on selvittää suun kautta annetun metoprololin ja oksikodonin sekä nenäsumutteena annetun fentanyylin hyötyosuutta varhaisessa sydänleikkauksen jälkeisessä vaiheessa. Hypoteesi on, että parempi ymmärtämys näiden lääkkeiden farmakokineettisistä ominaisuuksista parantaa leikkauksen jälkeisen eteisvärinän ehkäisyä ja kivunhoitoa kohentaen siten hoitotulosta.

Metoprololin hyötyosuutta selvitettiin 12 perättäisellä miespotilaalla, joille tehtiin sydämen ohitusleikkaus sydänkeuhkokonetta käyttäen. Farmakokineettinen analyysi suoritettiin tilamallitonta menetelmää käyttäen. Metoprololin hyötyosuus laski merkittävästi ensimmäisenä leikkauksen jälkeisenä päivänä verrattuna leikkausta edeltävään päivään. Kolmantena leikkauksen jälkeisenä päivänä hyötyosuus palasi leikkausta edeltävälle tasolle.

Oksikodonin hyötyosuutta selvitettiin neljänä leikkauksen jälkeisenä päivänä 24 potilaalla, jotka etenevästi satunnaistettiin ohitusleikkaukseen sydänkeuhkokonetta käyttäen tai ilman sitä. Farmakokineettinen analyysi suoritettiin 2-tilamallia käyttäen. Ensimmäisenä leikkauksen jälkeisenä päivänä oksikodonin hyötyosuus oli laskenut merkittävästi molemmissa ryhmissä. Toisena leikkauksen jälkeisenä päivänä hyötyosuus oli palautunut ennalleen tai jopa paremmaksi. Ilmiö johtui viivästyneestä imeytymisestä ja se johti oksikodonin kertymiseen.

Nenäsuihkeena annetun fentanyylin hyötyosuutta selvitettiin 16 potilaalla, joille tehtiin sydänleikkaus. Potilaat satunnaistettiin saamaan fentanyyliä joko 100 tai 200 µg kahden päivän välein ennen läpilyöntikipua. Farmakokineettinen analyysi suoritettiin populaatiofarmakokineettista mallia käyttäen. Hyötyosuus todettiin korkeaksi ja vastaavan aiemmin terveillä aikuisilla julkaistuja tuloksia. Fysioterapia tai laskuputkien poisto eivät lisänneet kipua fentanyylin annostelun jälkeen.

Yhteenvetona voidaan todeta, että varhaisessa leikkauksen jälkeisessä vaiheessa suun kautta annetun metoprololin hyötyosuus on merkittävästi laskenut ja siksi metoprololin annostelun tulisi tapahtua suonensisäisesti varhaisessa leikkauksen jälkeisessä vaiheessa. Oksikodonin imeytyminen on hidastunut ohitusleikkauksen jälkeen riippumatta siitä, onko leikkaus tehty sydänkeuhkokoneen kanssa vai ilman sitä. Ensimmäisen 24 tunnin aikana suun kautta annettua oksikodonia tulee välttää kertymisvaaran vuoksi.

Nenäsumutteena annostellun fentanyylin todettiin olevan nopea, tehokas ja hyvin siedetty lääke sydänleikkauksen jälkeisen läpilyöntikivun hoidossa.

Luokitus: QV 38, QV 89, QV 132, WG 169, WO 184

Yleinen suomalainen ontologia: annostelu; kipulääkkeet; kivunhoito; leikkaushoito; lääkehoito; ohitusleikkaukset; opioidit; potilaat; sydänkirurgia; toipuminen

Acknowledgement

This study was carried out in the Department of Cardiothoracic Surgery in the Kuopio University Hospital.

The principal idea for starting to undertake a doctoral thesis came my mind on a return flight from a diving trip in Malta in 2006. The idea was immediately accepted and encouraged by Docent Hannu Kokki. Through his enthusiasm for pharmacological research, the preliminary research plan was ready in the next few weeks after the diving trip. The project started smoothly leading to the first publication in the next year. My late colleague Docent Tapio Hakala was also an important supporter during first steps of this project.

My interest in clinical work with its countless on-calls, however, led to a situation in which scientific work had to remain on the back burner for several years. At the same time, the legislation regulating clinical drug research has developed to become quite complex, changes which have diminished the overall clinical drug research activity. Nevertheless, Docent Hannu Kokki patiently encouraged me to finish the thesis. I warmly thank Docent Merja Kokki for helping me with the paperwork related to these trials.

My warm appreciation goes to Docent Tiina Erkinaro and Docent Ari Mennander for reviewing my thesis. Thank you very much for the encouraging remarks on my thesis.

My warm thanks go to Docent Jari Halonen who has provided me with continuous support in finishing this project.

This thesis was financially supported by the EVO and VTR-grants from the Kuopio University Hospital, and by the legacy of Oiva Vaittinen.

I am grateful to the previous Heads of the Department of Cardiothoracic Surgery in the Kuopio University Hospital; Docent Mikko Hippeläinen and Docent Pekka Jaakkola. They made it possible for me to undertake this project along with my daily clinical duties.

This thesis is a good example of collaboration between experts in different fields of expertise. My sincere thanks to all parties for ensuring that this thesis now sees the light of day.

I am grateful to Professor Ilkka Ojanperä and Merja Gergov Ph.D. in the Department of Forensic Medicine in the University of Helsinki for the analyses of the blood samples in my first study. Dr Valtteri Rinne and Heidi Hautajärvi represent Admescope Ltd and were responsible for the analyses of the blood samples in subsequent studies. Veli-Pekka Ranta Ph.D. and Pyry Välitalo Ph.D. provided a remarkable input to this thesis by sharing their vast knowledge of pharmacokinetics.

I thank Docent Pasi Lahtinen, Pawel Florkiewicz M.D. and Tadeusz Musialowicz Ph.D. for their help in various phases of this thesis. Henriikka Hakomäki M.Sc., Petri Toroi R.N. and Maisa Laakso B.M. provided wonderful help during these studies, thank you.

I am grateful to Ewen MacDonald Ph.D. for reviewing the English language of my thesis.

My very special thanks go to the opposite side of the world, Professor Brian Anderson and James Morse Ph.D. from the University of Auckland in New Zealand and their Departments of Anaesthesia, Pharmacology and Clinical Pharmacology. They made a major contribution to the last two articles by sharing their expertise in population pharmacokinetic modelling and helped with the interpretation of the results.

I want to express my gratitude to my colleagues in the Department of Cardiothoracic Surgery. We constitute a good, strong team. Let the morning conversations in Kaari Hospital's cafeteria continue!

Throughout these years my beloved daughters Veera, Emma and Hilla have grown up to become extremely attractive and often very demanding young ladies. They constantly remind me of the meaning of life. I am so proud of them. Veera has together with her spouse Mikko made me a grandfather by introducing into this world the most charming young lady, Rosa – "Bebeliini".

Finally, my greatest thanks go to my dear wife Kati, who has always been with me in both the good and the not-so-good days. Your patience and support are out of this world. I do have to apologize for my absence from our daily life because of this project. I promise you that I will provide double compensation when you are facing this very same chaos.

Roinila 8.7.2021
Antti Valtola

LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications:

I Valtola, A., Kokki, H., Gergov, M., Ojanpera, I., Ranta, V. P., Hakala, T. (2007). Does coronary artery bypass surgery affect metoprolol bioavailability. Eur J Clin Pharmacol, 63(5), 471-478. doi:10.1007/s00228-007-0276-6

II Valtola, A., Morse, J. D., Florkiewicz, P., Hautajärvi, H., Lahtinen, P., Musialowicz, T., Anderson, B., Ranta, V. P., Kokki, H. (2020). Bioavailability of oxycodone by mouth in coronary artery bypass surgery patients - a randomized trial. J Drug Assess, 9(1), 117-128. doi:10.1080/21556660.2020.1797753

III Valtola, A., Laakso, M., Hakomäki, H., Anderson, B. J., Kokki, H., Ranta, V. P., Rinne, V., Kokki, M. (2021). Intranasal fentanyl for intervention associated breakthrough pain after cardiac surgery. Clin Pharmacokinet. 2021 Jul;60(7):907–919. doi: 10.1007/s40262-021-01002-4.Epub 2021 Mar 9.

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ABBREVATIONS

ACE	Angiotensin converting enzyme
ACS	Acute coronary syndrome
ADME	Absorption, distribution, excretion, extraction
AF	Atrial fibrillation
AKI	Acute kidney injury
ARB	Angiotensin receptor II blocker
ASA	Acetylsalicylic acid
AUC	Area under curve
AVR	Aortic valve replacement
BMS	Bare metal stent
BOV	Between-object variability
BSV	Between-subject variability
CABG	Coronary artery bypass grafting
CBP	Cardiopulmonary bypass
CCB	Calcium channel blocker
CECC	Conventional extracorporeal circulation
CL	Clearance
C_{max}	Maximal plasma concentration
COPD	Chronic obstructive pulmonary disease
COX	Cyclo-oxygenase
CR	Controlled release
CVD	Cardiovascular disease
DAPT	Dual antiplatelet therapy
DES	Drug eluting stent
ECG	Electrocardiogram
EF	Ejection fraction
ERAS	Enhanced recovery after surgery
$ETCO_2$	End-tidal CO_2
GI	Gastrointestinal
HbA1c	Glycated hemoglobin
ICU	Intensive care unit
LAD	Left anterior descending artery

LDL	Low-density lipoprotein
LIMA	Left internal mammary artery
LMWH	Low molecular weight heparin
MEC	Minimal effective concentration
MECC	Miniaturized extracorporeal circulation
MVR	Mitral valve replacement
NCA	Non-compartmental analysis
NOAC	New oral anticoagulant
OPCAB	Off-pump bypass graft surgery
PCA	Patient-controlled analgesia
PCI	Percutaneous coronary intervention
PCSK	Proprotein convertase subtilisin/kexin type 9
PD	Pharmacodynamic
PK	Pharmacokinetics
POAF	Postoperative atrial fibrillation
POBA	Plain old balloon angioplasty
POD	Postoperative day
POP	Postoperative pain
PPP	Persistent postoperative pain
PPS	Postpericardiotomy syndrome
RAAS	Renin-angiotensin-aldosterone system
RBBB	Right bundle branch block
SPID	Sum of pain intensity difference
SpO_2	Peripheral capillary oxygen saturation
t½	Time half concentration
TAVI	Transcatheter aortic valve implantation
t_{max}	Time to reach C_{max}
TR	Tricuspid insufficiency
UFH	Unfractionated heparin
V_d	Volume of distribution

1 INTRODUCTION

The global burden of cardiovascular diseases (CVD) has steadily increased during the last decades. The prevalence of CVD has almost doubled from 1990 to 2019; the number of CVD deaths has increased by more than 50 % during the same time frame (Roth et al., 2020). The main contributing factor to increasing numbers is the increasing numbers of aged individuals in the population. However, prevalent cases of CVD and deaths due to CVD per 100 000 have decreased during the last decades. This can be interpreted as a consequence of successful preventive measures against CVD and the development of CVD treatment.

Despite the improvements in many fields of CVD prevention and care, for decades ischaemic heart disease has been a leading cause of death all over the world (Hartley et al., 2016; Nowbar et al., 2019). Ischaemic heart disease accounted for almost half of global CVD deaths in 2019 (Roth et al., 2020).

The prevalence of calcified aortic valve and degenerative mitral valve diseases have roughly doubled during the last decades due to the expansion of aged individuals in the population (Yadgir et al., 2020). The prevalence and mortality related to valve disease are highest in high-income countries. There has been no significant change in age-adjusted mortality due to calcified aortic valve disease, but it has declined in degenerative mitral valve disease.

A minority of patients with CVD needs invasive treatment. In the era of catheter-based interventions, cardiac surgery does still have an important role in the armament of therapies. Even if percutaneous interventions (PCI) in cardiac revascularization therapy have exceeded surgery in terms of numbers of procedures, surgical revascularization still has a strong recommendation in contemporary guidelines (Neumann et al., 2019). Cardiac surgery is considered as a golden standard in the invasive treatment of valvular heart disease against which developing catheter-based therapies are compared.

Current trends of deaths due to ischaemic heart disease, increase of elderly population and mode of revascularization therapy in Finland are presented in Figure 1.

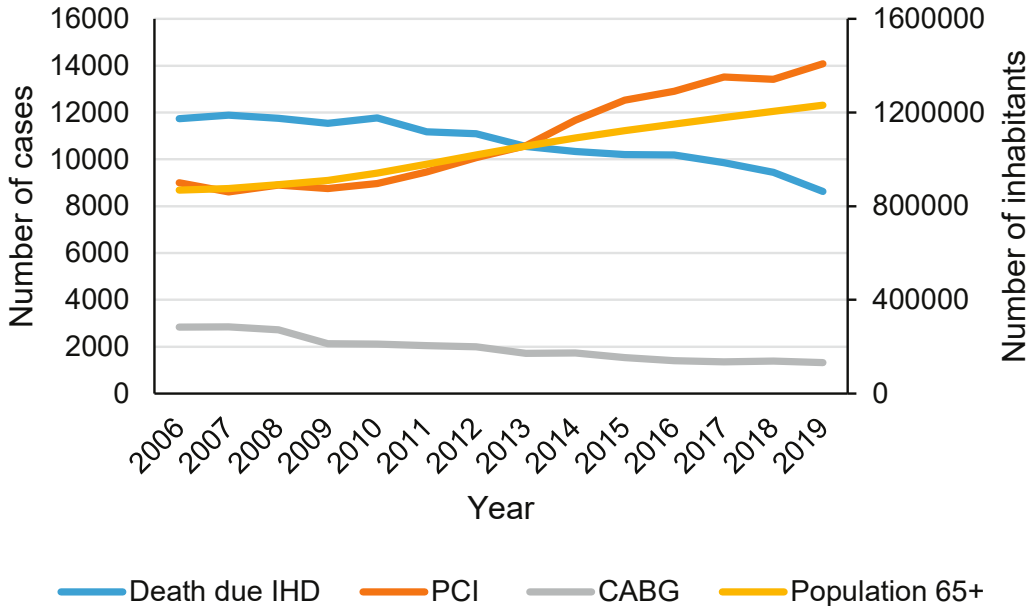


Figure 1. Current trends of mortality due to ischaemic heart disease, aging of population (right side Y-axis) and mode of revascularization therapy (left side Y-axis) in Finland. Data source: The Finnish Society of Cardiology.

Postoperative drug use is essential for cardiac surgery patients to recover without undesired events and reap long-term benefit. Oral drug administration is preferred due to its ease for both patients and staff. However, in the early postoperative period, the bioavailability of peroral medication is altered and thus parenteral routes should be considered until gastrointestinal function has recovered.

After cardiac surgery, the most common arrhythmia is atrial fibrillation. It causes prolonged hospitalization, may lead to circulatory deterioration, predisposes patients to stroke, and leads to increased treatment costs. Postoperative therapy with ß-blockers has a substantial role in prevention of a new postoperative atrial fibrillation.

A severe pain is a common outcome after cardiac surgery. The effective treatment of postoperative pain is crucial for smooth recovery. Severe pain predisposes patients to poor pulmonary ventilation and delayed mobilization, both of which may lead to complications such as pneumonia. Patients with

moderate and severe postoperative pain have an increased risk for persistent postoperative pain.

The rationale of this thesis was to study the absorption, bioavailability, and subsequent pharmacokinetics (PK) of orally administered metoprolol and oxycodone, and intranasally administered fentanyl. Metoprolol is commonly used to prevent and treat atrial fibrillation, whereas opioids play an essential role in the multimodal management of postoperative pain. The new knowledge on the PKs of these drugs may facilitate and enhance the results of cardiac surgical outcome.

2 REVIEW OF THE LITERATURE

2.1 THE EVOLUTION OF CARDIAC SURGERY IN HEART DISEASE

2.1.1 Ischemic heart disease

It was long presumed that atherosclerosis is a rather new phenomenon related to the modern era and contemporary lifestyles. However, some recent studies have shown that atherosclerosis existed 4000 years ago (Thompson et al., 2013). These findings have led scientists to hypothesize that human beings have an inherent susceptibility to atherosclerosis. The speed and severity of its development are secondary to some known and some potentially unknown factors.

As a clinical phenomenon, angina pectoris was first described by ancient Egyptians as in the Ebers Papyrus 3000 BC. In the Arabic literature, angina pectoris was described in the 7th century (Hajar, 2017). Human body dissections were prohibited in ancient Rome, and autopsies were rare until the Renaissance. Leonardo da Vinci was one of the first to describe atherosclerosis, stating that "vessels in the elderly restrict the transit of blood through thickening of the tunics". William Heberden introduced the term ischaemic heart disease; he described 20 cases of ischaemic coronary heart disease at the Royal College of Physicians in London in 1768 (van Tellingen, 2010). John Warren described angina pectoris in 1812, in the first article in the first issue of The New England Journal of Medicine. However, the correlation between anatomical findings and clinical symptoms emerged only in the late 19th and early 20th centuries. In 1879, an American pathologist, Ludvig Hektoen, became the first to conclude that myocardial infarction is caused by coronary thrombosis "secondary to sclerotic changes in the coronaries" (Nabel et al., 2012).

The medical community's understanding of cardiovascular disease was very limited until the mid-20th century. It is believed that the cardiovascular sickness, poor treatment attempts, and the early death of the US wartime President Franklin D. Roosevelt launched the Framingham Heart Study in

1948 (Mahmood et al., 2014). The study revealed several risk factors of cardiovascular disease: hypertension, diabetes, high cholesterol levels, obesity, and smoking; some factors which had been earlier suspected were scientifically confirmed. Clinical findings from the 1950s supported the obvious hereditary nature of coronary artery disease (Gertler et al., 1951). To date, some 60 genes have been linked to an increased risk for coronary artery disease (Khera et al., 2017).

Modern treatment of acute myocardial infarctions started in the 1960s. Cardiac care units were established, the treatment of acute arrhythmias developed along with cardiac monitoring and pacemakers and defibrillators were invented. At the end of the 1980s, the role of thrombolytic agents emerged, and transcatheter interventions in acute myocardial infarctions were initiated. The importance of primary and secondary preventions was widely accepted in the medical community. Simultaneous developments in pharmacology made these conservative measures more effective. On the invasive side, extensive collaboration between surgeons, cardiologists, anaesthesiologists, haematologists, and engineers rapidly helped to develop technology, making possible various rather invasive treatments.

2.1.1.1 Bypass surgery

Coronary artery bypass grafting (CABG) is one of the most widely performed major surgical operations nowadays. In 2013, CABG was performed in Europe, on average, at a rate of 44 per 100 000 individuals (OECD, 2015). CABG outcomes have improved over time despite higher risk patient profiles. Developments in operative techniques have significantly reduced peri- and post-operative mortality and complications. The five-year survival rate is 85 to 95%; the ten-year rate is 75 % (Head et al., 2017).

Principles and techniques were developed almost simultaneously by many surgeons worldwide in the 1950s and 1960s. Many of them were credited “firsts” in the field of cardiac surgery. The first attempt at coronary artery revascularization was as early as 1910, using a carotid artery segment as a graft. Animal experiments increased in the 1950s, encouraging surgeons to conduct human experiments. In 1960, Robert Goetz performed the first clinically successful bypass operation. This operation was performed through

mid-sternotomy on a beating heart, by using a tantalum ring in a suture-less anastomosis. The right internal mammary artery was anastomosed to the right coronary artery. Robert Sabiston conducted the first bypass operation using a saphenous vein graft in 1962, Vladimir Kolesov published the first successful left internal mammary artery (LIMA) to left anterior descending artery (LAD) bypass operation in 1964. The global medical community was rather reluctant to accept this new method of treatment, even at the end of the 1960s. Despite this initial suspicious attitude to coronary artery bypass surgery, the true potential of CABG was recognized in the 1970s.

Rene Favaloro is widely credited for popularizing the CABG technique and for especially understanding the importance of myocardial preservation leading to better CABG outcomes (Favaloro, 1998). Better myocardial preservation techniques were the first step in a series of developments. Another step was understanding the superiority of LIMA-LAD anastomosis over venous graft to the same territory. A third step was the use of other arterial grafts such as radial artery as a second bypass graft. Two other steps were the improved technology in beating heart surgery, and measures taken to diminish the risk of ischaemic brain damage during surgery. These measures include the use of perioperative epi-aortic ultrasound to detect severe ascending aortic atherosclerosis and computed tomography or ultrasound to identify occluding carotid artery disease. Apart from the technical aspects of the CABG itself, a better understanding of the importance of the secondary prevention after surgery has played a key-role in long-term favourable results.

Contemporary indications for CABG are well established. In the current European guidelines, CABG as an invasive method of treatment has a class I recommendation with level A evidence for almost all the manifestations of ischaemic coronary artery disease (Neumann et al., 2019). Exceptions are one- and two-vessel disease without proximal LAD stenosis (Class IIb, level C) and two-vessel disease with proximal LAD stenosis (Class I, level B). Contemporary American guidelines display no substantial differences from their European counterparts (Patel et al., 2017).

2.1.1.2 Transcatheter treatment

The coronary arteriogram did revolutionize the diagnosis and understanding of coronary artery disease. The selective procedure was invented accidentally in 1958 in the Cleveland Clinic (Ryan, 2002). A patient was scheduled for ventriculography, but the catheter accidentally slipped into the right coronary artery during the administration of contrast media, which made visible the right coronary artery. As cineangiography permitted a dynamic visualization of coronary anatomy, it provided a stimulus to develop aorto-coronary bypass surgery as well as catheter-based interventions a few years later. The first reported balloon angioplasty was performed in 1979 (Grüntzig et al., 1979). In the same year, the first successful recanalization of an occluded coronary artery thrombus with simultaneous streptokinase-infusion to the recanalized artery was reported. The technique, in which only a dilatating balloon was used, was named as plain old balloon angioplasty (POBA).

Although balloon angioplasty revolutionized the treatment of coronary artery disease, it was soon realized that the results were suboptimal due to the tendency of coronary arteries to become stenosed again (Bauters et al., 1996). Arteries tended to re-stenose because of local arterial wall dissection, elastic recoiling and late vascular remodelling and neointimal proliferation (Iqbal et al., 2013). The developments of coronary stents have tackled these issues. The 1st generation stents were called bare metal stents (BMS). The first of these stents was implanted into a human coronary artery in 1986 (Sigwart et al., 1987). Bare metal stents were made from stainless steel with a mesh-like structure. Their structure was bulky with a high metallic density. These features caused difficulties in their deployment and early complications. Numerous models were on the market in the 1990s. Two landmark studies demonstrated superiority of BMS over POBA in 1994 (Serruys et al., 1994) (Fischman et al., 1994). These two studies led to an exponential increase in the use of coronary stents in the late 1990s. However, it was soon realized that BMSs had a suboptimal performance in follow-up. In-stent restenosis (ISR) occurred in 20 - 30% of patients in the mid-term or longer follow-up. The aetiology behind ISR was proliferation and migration of vascular smooth muscle cell within the stents (Chen et al., 2006).

Drug-eluting stents (DES) were developed to resolve the disadvantages of bare metal stents (Borhani et al., 2018). The fundamental philosophy in their design is to build a structure able to elute drug for a long period of time, thus preventing smooth cell proliferation and thrombosis causing restenosis. The drugs used were paclitaxel and sirolimus. They were also expected to have enough radial force to prevent re-narrowing of a treated vessel. The first DES came on the market in 2002. The first generation DESs had a stainless-steel platform with multiple layers of polymers for a controlled drug release. However, the biocompatibility of polymers and technical challenges in their structures led to adverse pathological effects even though the performance of the 1st generation DESs was much better than the BMSs. The 2nd generation DESs have thinner struts (cobalt-chromium) and their polymer coating is designed to be more biocompatible than the in-1st generation DESs. The drugs used in the 2nd generation DESs are everolimus and zotarolimus. Coronary stents with fully bioabsorbable struts are called 3rd generation coronary stents and they are currently undergoing further development (Valdes et al., 2020).

In recent years, there have been numerous studies comparing POBA with stents and CABG. The fairness of randomization in these studies is essential. An angiographic tool, Syntax Score (SS) was developed to describe the complexity of the coronary artery disease (Sianos et al., 2005). SS divides the complexity of coronary artery disease into three group: low (SS < 22), intermediate (SS 23-31) and high (SS > 32).

In the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial, PCI with the 1st generation DES was compared to CABG. In a 10-year follow-up, 28 % of patients had died in the PCI-group and 24 % in the CABG-group. With respect to patients with three-vessel disease, 28 % had died in the PCI-group and 21 % in the CABG-group. In patients with left main disease, the proportions of deaths were 27 % vs. 28 % respectively. In that study, diabetes status did not affect long-term results. The benefit of surgery was seen in all groups irrespective of the complexity of coronary artery disease (Thuijs et al., 2019).

In the Nordic-Baltic-British Left Main Revascularization (NOBLE) study, patients were randomized either to PCI or CABG. The PCI procedure was

performed with contemporary stents (73 patients with the 1st generation DES and the rest with the 2nd generation umirolimus DES). After 5 years, the primary endpoint of a major cardiac or cerebrovascular event (MACCE) occurred in 28 % of the PCI-group and in 19 % of the CABG-group. All-cause mortality was similar between groups, 9 %. Secondary endpoints (non-procedural myocardial infarction and repeat revascularization) favoured CABG. Stroke rates were 3.8 % in the PCI-group and 2.2 % in the CABG-group. The conclusion from this study was that PCI was associated with an inferior clinical outcome at 5 years as compared to CABG (Holm et al., 2020).

In the Evaluation of Xience versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial, patients with a low or intermediate anatomical complexity were recruited. The latest generation everolimus DES was used in the PCI procedures. The composite outcome of death, stroke and myocardial infarction was estimated at 5 years. The secondary composite outcome was the primary composite outcome added with ischemia driven revascularization. The primary composite endpoint occurred in 22 % in the PCI-group and 19 % in the CABG-group. The secondary outcome occurred in 31 % in the PCI-group and 25 % in the CABG-group. Authors concluded that there was no significant difference between treatments with respect to the rate of the primary composite outcome (Stone et al., 2019) although some criticisms have been raised concerning the study protocol itself and the interpretation of results. (Brophy, 2020).

2.1.2 Valvular heart disease

Leonardo DaVinci described the functional anatomy of human heart valves in his drawings at the beginning of the 15th century. These superb drawings seemed to have been forgotten as it was not until the end of the 18th century that valvular heart disease was recognized properly although some sporadic descriptions of aortic valve disease were written in the 16th and 17th centuries (Harrington, 2017a, 2017b; Vaslef et al., 1993). The stethoscope was invented in the early 19th century, and this helped physicians to listen to and interpret heart murmurs and subsequently some valvular diseases like mitral stenosis could be diagnosed. Some experimental animal tests to find a suitable

technique to treat these disorders were made and published at the end of the 19th century.

The first operation on a sick human being took place in 1913 in Paris. The patient had aortic stenosis and a dilatation by finger insertion was performed. The patient survived for four and a half years. The first mitral operation was done in the US in 1923 (Cutler et al., 1923). Before the era of the heart-lung machine, most cardiac valve interventions were performed on the mitral valve. Commissurotomies were done either in a transatrial or transventricular way using a finger or special dilatator as an instrument but the results were not satisfactory. Numerous commissurotomies were complicated by mitral insufficiency which was not well tolerated. In one textbook of heart diseases written in 1947, it was stated that "there is no specific treatment for mitral valve disease" and "there is no treatment for aortic valve disease" (PD, 1947; White, 1947).

The invention of the heart lung machine in the middle of the 20th century, made it possible to treat valvular diseases successfully by surgery. The original approach was to reconstruct the patient's own valve with different types of reconstructions and to strengthen the structures with foreign materials if needed. It soon appeared that the results with these kinds of reconstructions were unsatisfactory and this led to the development of valvular prostheses (Effler et al., 1965).

2.1.2.1 Aortic valve

The first successful valvular prosthesis implantation in a human being was performed in 1952 by Charles Hufnagel. He implanted a valve prosthesis into the descending aorta in a 30-year-old female. A few years later, the first open commissurotomy was performed. In 1960, the first implantation of a valvular prosthesis in the aortic position was described (Vaslef et al., 1993).

First generation mechanical prostheses were called caged ball valves. In these valves, an acrylic or silicone ball was housed inside a cage. Blood flow pushed the ball against the cage thus letting blood flow while during the diastolic phase, the ball dropped back to the base of the valve, forming a seal. Caged ball valves were commercially available until 2007. The next generation

of heart valves were developed to improve the hemodynamic performance of these devices.

Tilting disc valves represented the second generation of mechanical heart valves. They were designed to reduce thrombogenicity, have a better hemodynamic performance and cause less haemolysis as compared to caged ball valves (Björk et al., 1970). The first models became available at the end of the 1960s and they were used throughout the 1970s. At the end of 1970s, a third generation of mechanical valves was developed i.e., the tilting disc was replaced by two semilunar discs; this type of valve is called a bi-leaflet valve. Bi-leaflet valves have proved to be very durable and have a good hemodynamic performance. Their thrombogenicity and level of haemolysis is low. The mechanical design has not been altered to any significant extent during the last few decades. Some patients may also be disturbed by the closing sound of the valve.

The greatest disadvantage of mechanical heart valves is their need for life-long anticoagulation to prevent thromboembolic complications and anticoagulation therapy predisposes patients to bleeding complications. The only anticoagulant drug approved by the authorities is warfarin, a vitamin K antagonist. In one large Italian retrospective study, anticoagulation therapy was in the therapeutic range in 71.5 % of time in patients whose INR (International Normalized Ratio) target was 2.0 – 3.0. The higher the INR target, the less time that the INR was in the target range. Thromboembolic events occurred in 0.67/100 patient-years and major bleedings in 1/100 patient years. However, a low level of time in the therapeutic range was not associated with the risk of thromboembolic events (Poli et al., 2018). In a Swedish study, the rate of thromboembolic events was 1.8/100 patient-years in the aortic valve replacement (AVR) group and 2.2/100 patient-years in the mitral valve replacement (MVR) group. Bleeding complications occurred in 4.4 % and 4.6 % respectively (Labaf et al., 2014). The suitability of the oral factor Xa-inhibitor apixaban as an anticoagulation therapy for use in patients with mechanical valves is currently under investigation (ClinicalTrials.gov; NCT04142658). The benefits of the direct thrombin inhibitor dabigatran were investigated in the RE-ALIGN trial. That trial had to be terminated prematurely because of an excess of thromboembolic complications in the dabigatran

group (5 % vs. 0 %) and bleeding complications (4 % vs. 2 %)(Eikelboom et al., 2013).

The history of tissue valves started in 1962 when the first cadaveric homograft was implanted in the aortic position (Ross, 1962). It was noticed that their hemodynamic performance was above the level of contemporary mechanical prostheses and there was no need for permanent anticoagulation due to the valve itself. Nonetheless, availability, collection and preservation were difficult with the homograft and it was appreciated that xenografts would be more readily available. The first xenografts were porcine valves. Later bovine pericardium became another promising xenograft material. The invention of a proper anti-calcification method increased their durability. Initially, tissue valves tended to be preserved with formalin, but this treatment destroyed the collagen structure thus leading to suboptimal durability. The introduction of the glutaraldehyde treatment resolved the preservation and durability problem of tissue valves by preserving the collagen structure and making the tissue immunologically inactive due to antigen modification (Carpentier et al., 1969).

The indications for aortic valve procedures are valve insufficiency, stenosis and congenital anomalies that cause a valvular dysfunction.

2.1.2.2 Mitral valve

The first surgical operation on the mitral valve was performed in 1923 (Cutler et al., 1923). The patient was a young female with a severe rheumatic mitral stenosis. A severe stenosis in comatose patient was relieved by a transapically performed commissurotomy with a scalpel. The patient was discharged a few days later in good condition. In the following years, the same surgeon performed commissurotomies with a specially designed instrument, but all patients succumbed, and these operations were discontinued. In 1964, a twelve-year follow-up of a series of 1571 patients with closed valvuloplasty was published (Ellis et al., 1964).

An open repair for the mitral insufficiency was performed for the first time in 1957 (Lillehei et al., 1957). In general, open repairs under direct vision of the lesion were made possible only after the introduction of the heart-lung machine. The first reports of valvular apparatus repairs were published at

the beginning of the 1960s (Kay et al., 1963). At the same time, the evolution of valvular prostheses was rapid, and the first commercially available mitral prostheses came onto the market. The results of tissue and mechanical valves were rather good but they were associated with many problems such as their durability and thromboembolic events (Cohn et al., 2015). This led to the common consensus that the mitral valve should be repaired whenever possible. The correlation between a preserved subvalvular mitral apparatus and good left ventricular function after the operation was demonstrated in the 1970s (David et al., 1983; Hansen et al., 1986). The basis for the modern era of mitral repair, called "The French Correction", was published in 1983 (Carpentier, 1983). This paper described the basic pathophysiological classification of mitral lesions and has provided a systematic toolbox for the correction of this pathology in a reproducible manner for decades.

Nowadays, an insufficiency of the mitral valve due to a degenerative disease is the main indication for mitral valve surgery. Mitral stenosis as an indication is rare in the Western world. Certain pre- and peri-operative findings in echocardiography indicate the implantation of a valvular prosthesis without a repair attempt. These findings include the restricted motion of mitral leaflets, severely calcified annulus, or leaflets, severely infected and destroyed valvular apparatus, re-operative mitral valve surgery and the mitral insufficiency in patients with ischemic heart disease when severe alterations in the left ventricle geometry are detectable. Whether it is useful to include a mitral valve operation to CABG in patients with ischemic mitral insufficiency is a matter of debate. Meta-analyses have concluded that a mitral procedure in patients with moderate mitral insufficiency does not have any positive impact on the long-term survival or functional class, but a mitral operation enhances left ventricular remodelling after the operation and reduces grade of mitral regurgitation in follow-up echocardiography (Salmasi et al., 2018; Zhang et al., 2015). According to a recent meta-analysis, the repair of a mitral valve in infective endocarditis seems to be a feasible alternative to its replacement if there is sufficient valve tissue left after the removal of all infected tissue (Harky et al., 2018).

The main goal in mitral valve repair is to produce a good coaptation between the leaflets. The key elements for a successful repair are high-quality

intraoperative echocardiography, resection of posterior leaflet prolapse, use of artificial neochords and annuloplasty with a ring. Sparing leaflet tissue by pulling the prolapsed part of the posterior leaflet with neochords seems produce comparable results as resection (Tourmousoglou et al., 2014). Instead of the resection, the anterior leaflet prolapse is principally cured by neochords. An annuloplasty ring is virtually always needed in a mitral valve repair. The recurrence rate of mitral leakage is high without a ring (Cohn et al., 1994).

In most patients, mitral valve surgery is performed through median sternotomy. This incision provides an almost unlimited visualization of the mitral valve and allows concomitant procedures if indicated. A mitral valve repair can also be performed using a minimally invasive technique either with a robot or a video-assisted thoracoscopy. Although, the minimally invasive technique is more demanding, nevertheless, it does seem to be a suitable method also for complex valvular pathologies (Borger et al., 2014; Moscarelli et al., 2020). Furthermore, it has been demonstrated that a minimally invasive mitral repair is an equally safe and effective operation as a conventional repair (Grant et al., 2019).

The durability of mitral valve repair has proved to be good in terms of freedom from reoperation. In some series, long-term durability is even better than after a mitral valve replacement (McNeely et al., 2015). According to one systematic review, freedom from re-operation was 89 – 98 % in repaired patients and 85 – 92 % in replacement patients (McNeely et al., 2015).

2.1.2.3 Tricuspid valve

Tricuspid stenosis is a very rare phenomenon, and it is encountered almost solely in bioprosthesis with structural deterioration or after chest radiation. Tricuspid insufficiency (TR) that needs surgical intervention is divided into primary and secondary categories according to the underlying aetiology. Primary TR accounts for approximately 25 % of cases. The main aetiological factors for primary insufficiency are iatrogenic trauma, infective endocarditis, and congenital anomalies such as Ebstein's anomaly. Secondary TR is mainly a consequence of the left-sided valvular or the left ventricle pathology that leads to pulmonary hypertension, pulmonary hypertension (idiopathic,

thromboembolic, or arteriovenous shunt) or right ventricular pathology (myopathy or ischemic lesion). It has been reported that moderate or severe TR is found in up to 40 % of patients with mitral disease and in up to 35 % of patients with an aortic valve disease (Cao et al., 2020).

Clinically the most important question and a topic of debate is whether to repair mild or severe TR during left-sided valve surgery (Cao et al., 2020; Chikwe et al., 2015; Navia et al., 2017). The frequency of concomitant tricuspid valve surgery with mitral valve surgery varies remarkably throughout the world (Dion, 2015). The most aggressive strategy postulates that the tricuspid valve repair is always needed if a moderate insufficiency is present and/or a tricuspid annular dilatation (>40 mm) is present (Chikwe et al., 2015). The optimal method of tricuspid repair has been evaluated. The valve repair seems to offer slightly better long-term results compared to valve replacement (Jang et al., 2017; Wang et al., 2020). Acceptable results with tricuspid valvectomy in drug users with infective endocarditis instead of its repair or replacement have been reported (Luc et al., 2019).

2.1.2.4 Pulmonary valve

Pulmonary valve disorders which need surgical treatment have a congenital origin almost without exception. Most of these patients are operated during childhood, but some cases with mild symptoms and some cases due to a delayed diagnosis are operated when these individuals reach adulthood. The main reason for surgical intervention is stenosis or regurgitation in the valve itself or in its subvalvular structures. In some patients, the common pulmonary trunk may also be stenosed. The technique of repair includes valve replacement with a tissue valve together with the enlargement of both the infundibular part of the right ventricular outflow tract and the main pulmonary artery with patch material (Matsuo et al., 2018).

2.1.2.5 Catheter-based valve therapy

A new era in the treatment of valvular heart disease started in the 21st century when catheter-based technology was introduced. The first human procedure took place in 2000 when congenital pulmonary valve stenosis was relieved by the implantation of a transcatheter valve (Bonhoeffer et al., 2000). In 2002,

the first transcatheter aortic valve prosthesis (TAVI) was implanted (Cribier et al., 2002). Since the introduction of this new technology, the number of implantations has increased rapidly, superseding surgical aortic valve replacement as the primary invasive treatment of aortic stenosis, especially in the elderly and patients with co-morbidities. In addition, it has been estimated that more than 30 % of symptomatic aortic stenosis patients are not considered as candidates for any invasive treatment due to severe co-morbidities (Iung et al., 2003; Nkomo et al., 2006). This is the population that very likely could most benefit from these less invasive procedures. In general, the population is aging, and it is noteworthy that the prevalence of valvular diseases increases steeply after the age of 55. For example, the prevalence of aortic stenosis is almost doubled after the age of 75 as compared to a 10 years younger population (Nkomo et al., 2006).

It has been estimated that almost half of patients with severe mitral regurgitation are not treated with open mitral valve surgery because of advanced age, poor left ventricular function, or other co-morbidities or contraindications to surgery (Zamorano et al., 2011). Mitral-Clip® device with edge-to-edge repair by a clip has proved to provide acceptable results in this patient group (Maisano et al., 2013; Takagi et al., 2017). The concept of edge-to-edge repair has also been used successfully in the treatment of tricuspid regurgitation. Transcatheter mitral valve prostheses are under currently rapid development (Goode et al., 2020).

2.2 CARDIAC ANESTHESIA AND PERFUSION

2.2.1 General principles

General anaesthesia is the most common form of anaesthesia applied in major surgical procedures. In the literature, numerous techniques have been published. Many of them display institutional and personal preferences. The superiority of one technique over another has never been clearly established (Alexander, 2015). The preoperative evaluation of the eligibility for general anaesthesia is made principally by the same rules as any other

patient requiring general anaesthesia. Complex cases are best evaluated by multidisciplinary cardiac surgical teams.

One of the most critical phases during the cardiac surgical anaesthetic procedure is the induction of anaesthesia. Fluctuations in arterial blood pressure and heart rate mainly due to changes in peripheral resistance in the vasculature together with the underlying heart disease may lead to myocardial ischemia thus deteriorating the cardiovascular hemodynamic status. Frequently short acting vasoconstrictors are needed to counteract the peripheral vasodilatation. The main induction agents in use are propofol, etomidate and thiopentone. The induction dose is commonly reduced by the administration of an opioid before the anaesthetic agent; the commonly used opioids are alfentanil, fentanyl, and remifentanil (Kokki et al., 2018).

Muscle relaxants are commonly used in general anaesthesia for open heart procedures. Pancuronium is widely used due to its long duration of action. It has also sympathomimetic and vagolytic actions which might cause tachycardia that may lead to undesirable effects in patients with aortic stenosis and/or severe coronary artery disease. Other commonly used relaxants are vecuronium and rocuronium; these agents cause less tachycardia but may need repeated dosing because of their shorter duration of action.

Maintaining anaesthesia during cardiac procedures can be divided into three phases: pre-bypass, bypass, and post-bypass phases. Both volatile agents and intravenous agents have been used successfully in all phases. The use of volatile agents during the bypass may lead to a suboptimal level of anaesthesia when the agent is delivered via the bypass circuit oxygenator. Due to these actions, the method of maintaining anaesthesia can be changed during the operation. A total intravenous anaesthesia is considered to provide a more stable cardiovascular stability and a more constant plasma concentration of anaesthetic drugs. Another advantage of using opioids in the induction and maintenance of anaesthesia is their ability to provide sufficient analgesia throughout the operation.

Numerous clinical factors influence PK alterations of anaesthetic drugs during CPB. Among contributing factors are haemodilution and hypothermia. Hypothermia increases the blood/gas partition coefficient making volatile agents more ineffective the deeper hypothermia is used. Haemodilution

leads to decreased plasma concentration of binding proteins in which anaesthetic drugs are bound. These effects are less prominent nowadays when the majority of cardiac surgical operations are performed with CPB circuits that need smaller priming volumes and lower degree of hypothermia (Kunst et al., 2019).

Some evidence exists that volatile agents may cause myocardial depression in the post-bypass phase, but also it has been claimed that volatile agents may protect the myocardium from reperfusion injury (Swyers et al., 2014). A few RCTs and meta-analyses have demonstrated the beneficial effects of volatile agents on cardiac surgical patients (Bignami et al., 2017; Uhlig et al., 2016). However, the most recent large RCT did not confirm these findings (Landoni et al., 2019). The superiority or equivalence either of these two methods is not clear and further research is warranted (Ren et al., 2019).

Monitoring is essential during cardiac anaesthesia. Arterial cannulation, central venous access, bladder catheter, trans-oesophageal ultrasound probe, body temperature probes, and probe for cerebral oximetry are all likely to be needed. The extent of monitoring is related to the complexity of the planned procedure. More extensive monitoring is required in combined valve and bypass surgery, multiple valve surgery, and aortic arch surgery.

2.2.2 On-pump surgery

In an on-pump procedure, the patient is connected to the heart-lung machine through a centrally placed cannulation. This method enables a motionless and rather bloodless operation field when the heart is arrested.

Venous blood is drained into the heart-lung machine through large 8.7-11 mm (26-32 Fr) cannulas. In CABG and AVR procedures, a single 2-stage cannula that has draining holes in its atrial and inferior vena cava parts is used. In mitral and right-sided valve surgery, bi-caval cannulation is needed to isolate the heart from the circulation. In certain cases, a venous connection can be established through the groin with a long cannula which is positioned at the level of the right atrium. An arterial cannula is commonly inserted into the distal ascending aorta or aortic arch. If extensive atherosclerotic changes are present in the ascending aorta, an arterial line can be established in the right axillary artery. In patients who need temporary cardiopulmonary bypass

for rewarming and hemodynamic support, such as hypothermic patients, the arterial line can be established through the groin (Kokki et al., 2018). The cardiopulmonary bypass (CBP) system is illustrated in Figure 1.

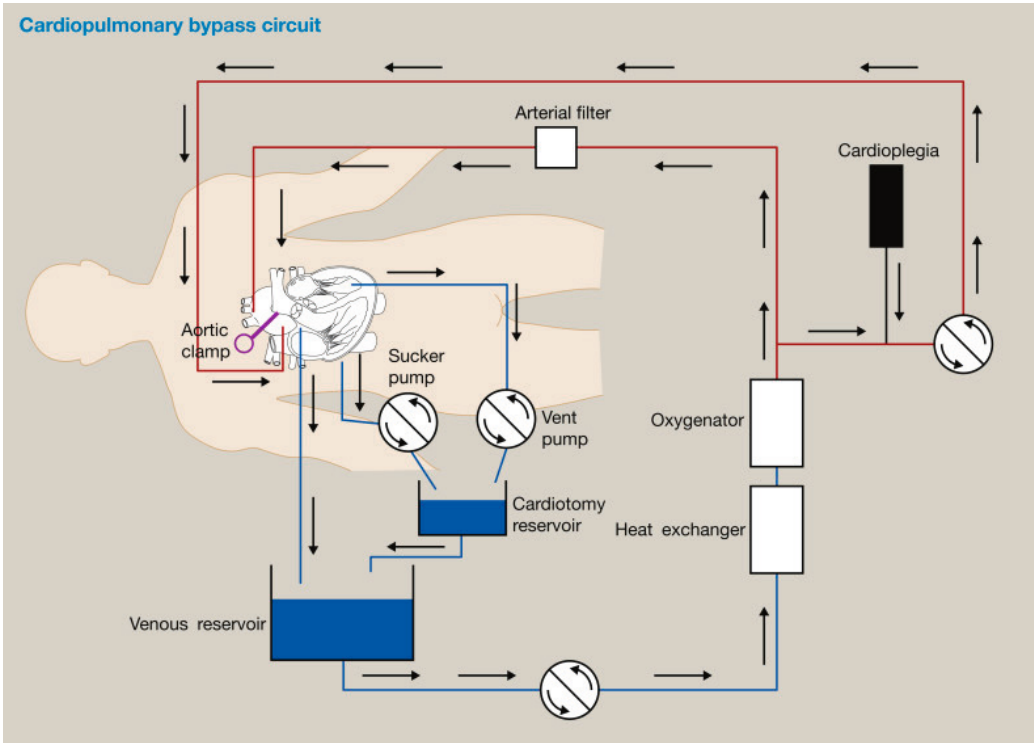


Figure 1. The cardiopulmonary bypass (CBP) system (Kiziltug et al., 2018). Modified by permission of the copyright owner.

The primary function of the CPB system is to provide adequate oxygen delivery to ensure that the body can meet its oxygen demand. Various factors affect the adequacy of perfusion system such as body temperature, body size, and systemic vascular resistance. It is well documented that lactic acidosis occurs when the flow is less than 1.6 L/min/m2 in normothermia (body temperature > 28 °C) but at lower temperatures, the flow can be reduced. A commonly adopted practice is to have flows of 1.8-2.2 L/min/m2. The target of the mean arterial pressure of over 65 mmHg is commonly

recommended (Kiziltug et al., 2018). Maintaining this target pressure often needs the administration of vasoactive drugs.

The major disadvantage of the CPB is its tendency to cause a systemic inflammatory reaction. This reaction is mainly initiated by the interaction between circulating blood and foreign material including air. The contact with foreign materials occurs in cannulas, hoses, blood reservoir, and roller or centrifugal pumps. The contact with air takes place in the venous blood reservoir, and when blood is suctioned back to the circulation from the operation field. Certain measures can be taken to counteract this inflammatory reaction e.g. the use of heparin coated hoses and minimizing their length (Barry et al., 2015). Administration of anti-inflammatory agents like corticosteroids may diminish this reaction but their routine use is not recommended because there is no clear evidence of their positive effect on morbidity or mortality (Kunst et al., 2019; Ng et al., 2020). The CPB can also cause microvascular occlusion, vasoconstriction, fibrinolysis, thrombosis increased vascular permeability and cellular damage (Barry et al., 2015).

Miniaturized extracorporeal circulation (MECC) was introduced into clinical practice in the beginning of 2000s. It has been proved to be applicable also in other cardiac surgical procedures not only in bypass surgery (Anastasiadis et al., 2011; Castiglioni et al., 2007; Liebold et al., 2019). The rationale of MECC is to minimize the systemic inflammatory reaction by using a heparin-coated short circuit, reducing foreign surfaces with low priming volume, and avoiding blood-air contact (Anastasiadis et al., 2013; Ranucci et al., 2019). MECC circuits do not have a venous blood reservoir and the use of cardiotomy suction is minimized. The most recent meta-analysis with 22 778 patients showed that MECC tends to improve perioperative outcomes as compared to conventional CPB in terms of reduced 30-day mortality, less cerebral strokes, less postoperative atrial fibrillation (POAF), less acute kidney injury (AKI) and a reduced need for red blood cell transfusions (Anastasiadis et al., 2016; Ellam et al., 2019; Kowalewski et al., 2016; Rimpiläinen et al., 2011).

Anticoagulation is needed when the patient is connected to a cardiopulmonary bypass circuit to prevent the formation of clots. Intravenous heparin is given at a dose of 300-500 IU/kg with the ACT (activated clotting time) targeted to be at least 400 seconds depending on the CPB equipment

and the ACT system used. During CPB, ACT should be regularly monitored every 30 minutes and additional dosages of heparin may be needed to maintain an adequate ACT level. The required dosage of heparin seems to vary notably between patients because its pharmacodynamics is related to levels of antithrombin III. Anticoagulation is reversed by administration of protamine in the post-bypass phase of the operation.

After aortic cross-clamping, the heart is arrested with a cardioplegic solution. Cardioplegia is essential to protect the myocardium from ischemic injury. Cardioplegia arrests the myocardium in diastole and maintains it in a depolarized state. There are many forms of cardioplegia currently in use. They are mainly classified by temperature (cold, tepid or warm), solution (crystalloid or blood) or substances in solution (Whittaker et al., 2020). The cardioplegic solution is delivered in an antegrade, retrograde or combined manner depending on the planned procedure. Antegrade cardioplegia is administered through a cannula in the ascending aorta or directly into coronary ostias and thus the flow of solution is spread to myocardium via the coronary arteries. Retrograde cardioplegia is given through a catheter placed in the coronary sinus and thus cardioplegia spreads to myocardium via the venous vasculature. The cardioplegia dose is repeated every 20-30 minutes or administered as a continuous flow. Custodiol and del Nido solutions were developed to simplify cardioplegia (Matte et al., 2012; Reidemeister et al., 1967). These solutions achieve cardiac arrest with one single dose of cardioplegia for up to 60 minutes. The superiority of one type of cardioplegia over another has not been clearly documented (An et al., 2019; Fan et al., 2010; Zeng et al., 2014). However, a recent European guideline recommends blood cardioplegia because it minimizes the risk of haemodilution (Kunst et al., 2019).

2.2.3 Off-pump surgery

Coronary artery bypass grafting without the use of a cardiopulmonary bypass is called off-pump bypass graft surgery (OPCAB). The rationale for OPCAB is to minimize mechanical manipulation of the ascending aorta by avoiding central aortic cannulation and cross-clamping. Another potential benefit of equal importance is the avoidance of CPB (Chassot et al., 2004; Kelleher et

al., 2004). It is well documented that CPB elevates the extent of the systemic inflammatory response as well as promoting coagulation disorders and multiple organ dysfunction (Ascione et al., 2000; Diegeler et al., 2000; Raja et al., 2007). It has also been proposed that OPCAB might protect the patient from the postoperative neurocognitive decline, but the evidence for that claim is not convincing (Tamargo et al., 2020).

The anaesthesiologic management of the OPCAB procedure varies somewhat. There are no unanimous guidelines or consensus on the best practise.

Patients often need fluid loading to achieve a more stable haemodynamic state when the heart is manipulated, rotated or lifted. Together with fluid resuscitation, the Trendelenburg position is frequently used to improve the preload during the procedure. Atrial pacing is often applied to increase blood pressure and cardiac output. Constant electrocardiogram (ECG) monitoring during the procedure is mandatory to detect myocardial ischemia because the risk of ischemia is increased in the OPCAB procedure. In some patients, the procedure needs to be converted to on-pump due to hemodynamic instability, global ischemia, malignant arrhythmias, or technical difficulties in achieving adequate revascularization. It is essential that there is a continuous interaction between the surgical and anaesthetic teams during the OPCAB procedure.

2.3 COMPLICATIONS OF CARDIAC SURGICAL PROCEDURES

2.3.1 Arrhythmias and conduction disturbances

Various arrhythmias and conduction disturbances are commonly encountered after cardiac surgical procedures. They represent a major source of morbidity and mortality after cardiac surgery. The need for post-bypass pacing became apparent in the early days of cardiac surgery and led to the development of cardiac pacemakers (Cook et al., 2005).

The aetiology of arrhythmias and conduction disturbances is multifactorial; an underlying chronic degenerative disease of the heart, myocardial ischemia, the method of myocardial protection during aortic occlusion,

direct surgical damage to the conduction system or the use of anti-arrhythmic drugs (Kumbhani et al., 2006). Postoperative electrolyte disorders e.g., hypokalaemia, are common after cardiac surgery and they are known to increase the risk of both atrial and ventricular arrhythmias. The clinical significance of arrhythmias and conduction disturbances is related to their duration, ventricular response rate and underlying cardiac function as well as other comorbidities (Peretto et al., 2014).

The incidence of early post-operative conduction defects has decreased during decades. The reported incidence has varied between 3 and 56 % after CABG (Kumbhani et al., 2006). The impact of transient conduction disturbances on the long-term survival is not clear. Permanent conduction disturbances which need pacemaker implantation do seem to exert a negative impact on survival (Fujita et al., 2019).

Arrhythmias are divided into atrial or ventricular types depending on the initiation site of the arrhythmia; supraventricular i.e., atrial arrhythmias are the most common.

Conduction disturbances are either complete or partial (hemiblocks). Various degrees of atrioventricular conduction disturbances may exist as well as sinus node dysfunction. Right bundle branch block (RBBB) is the most common conduction disturbance encountered after CABG. It is often transient, and its clinical impact is considered to be minimal. The postoperative left bundle branch block and left-sided hemiblocks seem to have more clinical sequelae than the RBBB. Their relationship to increased mortality has been reported in several studies (Regueiro et al., 2016). Atrioventricular conduction disturbances are mainly seen after valve surgery or in patients with severe coronary artery disease affecting the myocardial circulation in the vicinity of the conduction system.

A permanent atrioventricular block is often the result of direct surgical trauma to the conduction system. This may happen in open aortic valve surgery where the close location of the bundle of His with the aortic annulus and surgical sutures predisposes it to damage. Mechanical damage to the bundle of His may also occur in TAVI procedure, where the stretching of anatomical structures by the prosthesis can impact on this structure. Atrioventricular conduction disturbances are also common after mitral valve surgery. They are

often temporary and can be explained by tissue oedema and the stretching of adjacent structures. The bundle of His is generally visible in the tricuspid valve annulus and thus mechanical damage to the conduction system can be avoided by using a partial annuloplasty ring. Nonetheless, mechanical damage to the conduction system is almost inevitable when implanting full annuloplasty rings or valvular prostheses.

2.3.2 Postoperative atrial fibrillation

New-onset postoperative atrial fibrillation (POAF) is the most common arrhythmia after cardiac surgical procedures. The incidence increases with the complexity of the surgical procedure being at the lowest after the pure CABG and highest after the combined CABG and valve surgery (Cox, 1993). In the Society of Thoracic Surgeons Adult Cardiac Surgery Database, it is estimated that POAF occurs in 25 % of cases after isolated CABG, 30 % after isolated valvular procedures and 40-50 % following the combination of CABG and valve procedures (D'Agostino et al., 2018). It is noteworthy that the incidence of POAF has remained unchanged for decades despite rigorous investigation and numerous proposed treatment strategies even with contemporary improvements in cardiac surgical care (Burrage et al., 2019; Creswell et al., 2001; D'Agostino et al., 2016; Shen et al., 2011). The new-onset atrial fibrillation starts typically 2 – 3 days postoperatively after CABG and lasts on average 7 hours (Filardo et al., 2018). According to one large observational study, women seemed to have a lower risk of POAF, but no effect on the long-term survival between the sexes was found (Filardo et al., 2020).

POAF was associated with prolonged hospitalization, complications, decreased quality of life, increased healthcare costs, and long-term mortality (Eikelboom et al.,2020; LaPar et al., 2014; Phan et al., 2015). According to a recent study, POAF was linked with a 4-fold risk of stroke and 3-fold increase in all-cause mortality after CABG (Kosmidou et al., 2018). New-onset POAF doubles the in-hospital risk of stroke (Kaw et al., 2011).

The recurrence of POAF is presumably an under-recognized phenomenon. In one systematic review and meta-analysis, the rate of POAF recurrence among patients who were discharged in sinus rhythm was 28.3 % (Lowres et

al., 2018). The mean time of recurrence was 12 ± 5 days postoperatively. It is noticeable that 40 % to 93 % of episodes were asymptomatic.

Several clinical risk factors for POAF have been recognized, e.g. increasing age, female gender, previous history of AF, increased left atrial size, mitral valve disease, previous cardiac surgery, chronic obstructive pulmonary disease (COPD), Caucasian race, physical inactivity (Jannati, 2019; Tran et al., 2015; Yamashita et al., 2019). Obese patients (body mass index [BMI] > 30 kg/m2) have a 12 % higher risk of POAF compared with non-obese (Hernandez et al., 2013).

The perioperative risk factors of POAF have been recognized. Inflammation has a strong relation to the existence of POAF (Aviles et al., 2003; Boos et al., 2006). Other factors include autonomic stimulation, oxidative stress and atrial stretch related to fluid load (Allessie et al., 2001; Raiten et al., 2015).

Some risk score calculators have been developed to help clinicians to identify those patients who are at an increased risk of POAF (Chen et al., 2020; El-Chami et al., 2012; Gu et al., 2017; Hakala et al., 2002; Mariscalco et al., 2014). However, they seem to have a limited ability to predict POAF in cardiac surgical patients (Cameron et al., 2018).

2.3.2.1 Prevention of atrial fibrillation

Various interventions have been under investigation to prevent POAF. They can be categorized into two groups, either pharmacological or surgical interventions.

The methods of pharmacological intervention have included a prophylactic use of anti-arrhythmic drugs, optimizing electrolytes, use of drugs which reduce systemic or local inflammatory response to the surgical trauma, use of drugs which reduce oxidative stress secondary to the surgery and the choice of vasoactive medication (Arsenault et al., 2013; Burrage et al., 2019).

The strongest evidence of reducing the incidence of POAF is available for ß-blockers and amiodarone (Arsenault et al., 2013). These drugs seem to have an equal effect on reducing the incidence of POAF (Zhu et al., 2012). The current European guideline for the diagnosis and management of atrial fibrillation states that there is very little supportive data for any other pharmacological interventions to be able to prevent POAF (Hindricks et al., 2020).

Surgical therapies have included different forms of atrial over-pacing, surgical manipulation of adjacent tissues to the atrial tissue such as posterior pericardiotomy, removal of an anterior fat pad, and pulmonary vein isolation with different energy forms. The positive effects on the decreased incidence of POAF by some of these surgical manoeuvres have been demonstrated in numerous studies. However, the power of evidence has been so far weak and thus none of these therapies have achieved any guideline recommendations (Arsenault et al., 2013; Burrage et al., 2019).

The avoidance of CPB and thus minimizing the systemic inflammatory response to the surgical trauma has been thought to reduce the incidence of POAF. There is a slight tendency that more studies support rather than disputing this theory, but the evidence is far from unequivocal (Dieberg et al., 2016; Puskas et al., 2015).

2.3.2.2 Treatment of atrial fibrillation

Asymptomatic and self-terminating POAF is a common phenomenon after cardiac surgery. There are two treatment strategies available to patients with POAF: rate control and rhythm control.

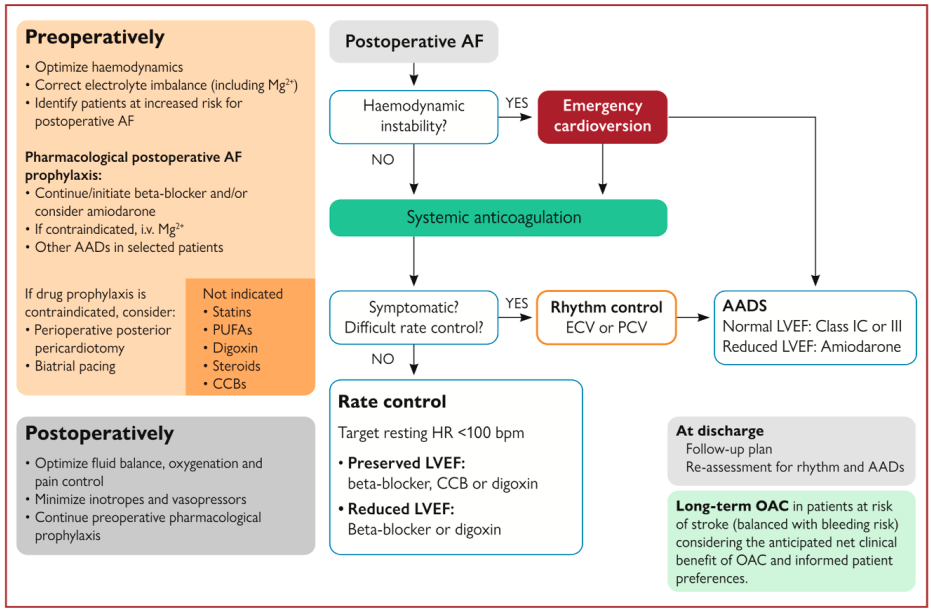
The initial treatment of POAF involves the correction of factors which predispose to POAF, e.g., optimizing fluid balance and electrolytes especially hypokalaemia, oxygenation, pain control, minimizing vasoactive medication and the continuation of preoperative antiarrhythmic medication. Systemic anticoagulation therapy is provided to all patients with POAF to prevent thromboembolic complications. Emergency cardioversion is indicated in patients who are haemodynamically compromised due to POAF.

Rate control is indicated in patients whose underlying cardiac disease is in such a state that preserving sinus rhythm is not evident and it is also an accepted therapy in asymptomatic patients. Rate control is mainly carried out with class II antiarrhythmic drugs, ß-blockers. Other recommended drugs are class IV i.e., calcium channel blockers and class V i.e., digoxin. The target resting heart rate is under 100 bpm (Hindricks et al., 2020).

Rhythm control is indicated in patients with symptomatic POAF and in patients with whom rate control is difficult to achieve (Hindricks et al., 2020). Either electrical or pharmacological cardioversion is used with the goal of

restoring sinus rhythm. Pharmacological intervention is typically started with intravenously administered ß-blockers. Alternatives to class II drugs ß-blockers are a class IC antiarrhythmic drug i.e., flecainide and class III antiarrhythmics amiodarone, sotalol and vernakalant. Nowadays, classes IV and V antiarrhythmics verapamil, diltiazem and digoxin are rarely used.

The management of POAF according to the latest European Society of Cardiology guideline, is presented in Figure 2.



Management of postoperative AF. AAD = antiarrhythmic drug; bpm = beats per minute; CCB = calcium channel blocker; ECV = electrical cardioversion; LVEF = left ventricular ejection fraction; Mg^{2+} magnesium; OAC = oral anticoagulation; PCV = pharmacological cardioversion; PUFA=polyunsaturated fatty acid.

Figure 2. Management of new-onset atrial fibrillation (Hindricks et al., 2020). Modified by permission of the copyright owner.

2.3.3 Other complications

Several complications are distinctive to cardiac surgical procedures. Some of them are life-threatening and demand an immediate response. Many of the others nonetheless exert a negative impact on the patient's long-term survival, and they all increase the costs of healthcare.

Cardiac surgery related neurological complications are often devastating. The clinical appearance varies from slight disorientation to disabling strokes. The reported incidence of postoperative delirium varies from 3 – 52 % (Koster et al., 2011). In the largest reported series in cardiac surgical patients with 16 184 patients, the incidence was estimated as 8.4 % (Bucerius et al., 2004). The predisposing risk factors do display a wide variation. Risk factors, such as the presence of a cognitive impairment, depression, smoking history, a previous stroke and an advanced age deserve special attention from the practical point of view (Koster et al., 2011).

Postoperative strokes are divided into two categories. Early strokes are detectable immediately when the patient is awakening from the anaesthesia. Late postoperative strokes are those occurring later in the postoperative timeframe. The rationale for this division is the difference in pathophysiological mechanisms behind the stroke. An early postoperative stroke is most likely the result of the aortic manipulation and a consequential atheromatous embolism. An increased risk of debris embolization exists in aortic valve surgery in cases where heavily calcified native valves are removed and decalcified. In contrast, atrial fibrillation and a cerebrovascular disease are often behind late postoperative strokes. According to a recent systematic review, the incidence of postoperative strokes is 2 % with equal frequencies in both categories but their impact on the short and long-term survival is clearly detrimental. The operative mortality in patients with early stroke is 29 % and with late stroke 18 %. In the same systematic review, after a follow-up of 8 years, the mortality for early stroke patients was 12 % and 9 % for late strokes respectively (Gaudino et al., 2019; Gaudino et al., 2019).

Postoperative bleeding is common after cardiac surgery with the extent of the bleeding ranging from insignificant to life-threatening. The incidence of severe postoperative bleeding requiring a reoperation varies between 2 and 6 % (Ranucci et al., 2008). Uninterrupted antithrombotic or anticoagulation

drug therapy is well documented to increase the risk for postoperative bleeding and reoperations due to bleeding (Aboul-Hassan et al., 2017; Siller-Matula et al., 2017). Reoperations and an excessive use of blood products have been linked to an increased risk of deep sternal wound infections.

The incidence of post-sternotomy mediastinitis varies between 0.3 and 3.4 % (Goh, 2017). Several factors have been identified as increasing the risk of a deep sternal infection. According to a recent systematic review, the estimation of odd ratios for developing deep sternal infection with diabetes, COPD, obesity, and bilateral internal mammary artery grafting were 1.9, 2.53, 2.26 and 2.49 respectively (Abdelnoor et al., 2019).

The incidence of AKI following cardiac surgery has been estimated as approximately 18 % (Thiele et al., 2015), with the incidence of AKI requiring dialysis at about 2 % in modern series (Kiers et al., 2013). Perioperative AKI has been associated with a high risk of developing a chronic kidney disease. About 64 % of patients with a need for new haemodialysis in the perioperative period will need permanent dialysis. Their prognosis is poor, up to 90 % of them will die within one year (Leacche et al., 2004). The pathogenesis of AKI is multifactorial and not fully understood. Nephrotoxins, regional hypoxia, mechanical blood trauma, embolization, oxidative stress, inflammation, perfusion-reperfusion injury and medications are all factors which contribute to the development of AKI (Thiele et al., 2015). Several clinical risk factors have been recognized: pre-existing kidney disease, COPD, diabetes, reduced left ventricular function, advanced age and female gender. Redo-surgery and the emergent nature of surgery are also well-known risk factors for AKI. There is no specific medication to treat AKI and thus preventive measures should seek to address predisposing factors. Several predictive models for AKI in a cardiac surgical population have been developed (Kiers et al., 2013).

Postpericardiotomy syndrome (PPS) is a well-known complication of cardiac surgery. It was described soon after cardiac operations with the heart-lung machine started in the 1950s. Despite decades of research, the exact pathogenesis underlying PPS is still unclear. The variation of its incidence in published series is wide, between 9 % and 65 % with a median of 16 % (van Osch et al., 2017). The symptoms typically start within a few days or weeks after the operation with pericardial and pleural effusion with fever.

Various inflammatory markers and clinical factors have been investigated as predisposing factors. The individual inflammatory response, perioperative bleeding and coagulation may play an important role in the development of PPS. Steroids as anti-inflammatory agents and colchicine have been traditionally used in the treatment of PPS (van Osch et al., 2017).

Gastrointestinal (GI) complications after cardiac surgery are rather common. In the largest reported study with over 2.7 million CABG patients, their incidence was 4.1 % (Rodriguez et al., 2007). These symptoms have been linked to an increased patient mortality, length of hospitalization and overall costs. Several risk factors have been identified: advanced age (> 65 years), urgent operation, haemodialysis, use of intra-aortic balloon pump as well as complexity and duration of the procedure. Postoperative ileus, abscesses, upper GI-tract ulcerations with/without bleeding and colonic disorders such as diverticulitis and bleeding account for over 80 % of postoperative gastrointestinal disorders (Rodriguez et al., 2007).

2.4 PERI- AND POSTOPERATIVE PAIN IN CARDIAC SURGICAL PATIENTS

2.4.1 Acute pain

Postoperative pain (POP) after cardiac surgery is often severe due to the extensive surgical trauma needed in the exposure of heart and adjacent structures together with a systemic inflammatory response to the surgical trauma. The pain is most intense during the first two days after the operation. Certain factors have been linked to higher levels of POP; younger age, female gender, the presence of preoperative pain and anxiety (Bjørnnes et al., 2016). Inadequate treatment of postoperative pain has been linked to a slower recovery from the operation and to some common early postoperative complications like poorer ventilation and a risk of pneumonia (Bignami et al., 2018). It has also been shown to lengthen the stay in hospital.

According to the International Association for the Study of Pain, pain can be categorized to nociceptive, neuropathic or nociplastic types. Nociceptive pain is a consequence of activated nociceptors due to trauma of non-neural

tissue. Neuropathic pain results from damage to the somatosensory nervous system. Nociplastic pain is a result of altered nociception without any clear evidence of tissue trauma or damage to the somatosensory nervous system. The types of pain can also be categorized into somatic or visceral pain (IASP, 2021).

The pain after sternotomy is of a nociceptive type. It is caused by skin incisions and preparation of subcutaneous fat and muscle tissue, fracture of sternum by the surgical saw, distension of thoracic halves to achieve adequate exposure to the heart, mammary artery dissection and chest drainage tubes. A neuropathic component of sternotomy pain is related to the damage of skin nerves during an incision, possible damage to distal ends of intercostal nerves with the steel wires used for sternotomy closure and the potential distension of axillary neural plexus with the sternotomy spreader. The intercostal nerves can become damaged during a mammary artery dissection (Zubrzycki et al., 2018; Jayakumar et al., 2019).

POP after thoracotomy is also mainly of the nociceptive type. The pain is the result from a similar mechanism to that occurring after sternotomy; skin incision, subcutaneous tissue dissection and spreading intercostal space with surgical instruments and often fractures of costal bones. Pleural drain tubes cause pain mainly by damaging the intercostal nerves. Patients with thoracotomy are much more prone to neuropathic pain than patients with sternotomy due to the anatomical location of the intercostal nerves and the closing technique after thoracotomy (Zubrzycki et al., 2018; Jayakumar et al., 2019).

2.4.2 Persistent pain

Persistent postoperative pain (PPP) has been defined as a pain that lasts for at least 3 months after the operation. Its incidence after cardiothoracic surgery varies quite extensively. According to the most recent systematic review, the incidence of PPP was 37 % within 3 – 6 months, 29 % between 6 and 12 months, 29 % up to 24 months declining to 17 % over 24 months after the cardiac operation (Guimarães-Pereira et al., 2017) (Table 1). Another report described an incidence of 28 – 56 % for up to 2 years postoperatively (Bruce et al., 2003) with the main location of the pain being the sternum followed by the

limbs. As many as 75 % of patients reported the presence of pain in the leg (Bruce et al., 2003). It is noticeable that 40 – 50 % of patients with PPP report the severity of pain as ranging from moderate to severe. The more severe the pain, the higher is the probability that it is a neuropathic type of pain (Guimarães-Pereira et al., 2017). The prevalence of neuropathic aetiology of PPP has been reported in occur in two out of every three cardiothoracic patients (Haroutiunian et al., 2013).

Table 1. The incidence of persistent postoperative pain after cardiac surgery. (Guimarães-Pereira et al., 2017). Modified by permission of the copyright owner.

Estimated incidences of PPPCS and its intensity at 3 to less than 6, 6 to less than 12, 12 to less than 24, and at least 24 mo after CS.

	3 to <6 mo	6 to <12 mo	12 to <4 mo	≥24 mo
PPPCS incidence				
All studies	37% (CI: 32%-42%) $I^2 = 79\%$	29% (CI: 22%-35%) $I^2 = 95\%$	29% (CI: 21%-38%) $I^2 = 97\%$	17% (CI: 8%-25%) $I^2 = 98\%$
Leave-one-out meta-analysis	36%-40%	27%-31%	25%-31%	14%-20%
Studies with quality assessment score > 5 subgroup meta-analysis	40% (CI: 37%-42%) $I^2 = 11\%$	27% (CI: 20%-33%) $I^2 = 95\%$	29% (CI: 20%-38%) $I^2 = 97\%$	17% (CI: 8%-25%)* $I^2 = 98\%$
Observational studies subgroup meta-analysis	40% (CI: 37%-43%) $I^2 = 32\%$	30% (CI: 22%-38%) $I^2 = 94\%$	29% (CI: 20%-39%) $I^2 = 97\%$	17% (CI: 8%-25%) * $I^2 = 98\%$
RCTs subgroup meta-analysis	31% (CI: 15%-48%) $I^2 = 89\%$	26% (CI: 7%-44%) $I^2 = 98\%$	Nonapplicable (only 1 study[3])	Nonapplicable (no study)
PPPCS intensity (patients with PPPCS reporting moderate to severe pain)				
Regarding their average pain	40% (CI: 34%-46%) $I^2 = 53\%$		43% (CI: 31%-56%) $I^2 = 88\%$	50% (CI: 38%-63%) $I^2 = 89\%$
Regarding their worst pain			49% (CI: 42%-56%) $I^2 = 13\%$	53% (CI: 44%-61%) $I^2 = 0\%$

CI, confidence interval; PPPCS, persistent postoperative pain after cardiac surgery; RCT, randomized controlled trial.
* All studies have a quality assessment score >5 and are observational studies.

2.4.3 Pain management

Sufficient analgesia during a cardiac operation is achieved by administration of opioids. Repeated doses or a continuous infusion are administered intravenously during anaesthesia (Barry et al., 2015). In the early postoperative phase in an intensive care unit (ICU), analgesia is achieved mainly by repetitive intravenous doses of opioids (Barr et al., 2013). Peroral analgesic medication is usually started on the first postoperative day even though the absorption of drugs is uncertain. For this reason, patients do need additional pain medication administered repeatedly by either intramuscular, intravenous, or subcutaneous injections. Patient-controlled analgesia (PCA) with opioids

can be started as soon as the patient's cooperation is adequate. Gradually, instead of the medication being administered by injection, it is switched to a peroral form to facilitate pain management.

In addition to pain reducing drugs administered in various ways, there is also a possibility to control pain by utilizing regional anaesthetics and epidural pain control.

All things considered, a multimodal approach most likely achieves the best results in pain management after cardiac surgery (Nachiyunde et al., 2018).

2.4.3.1 Opioid analgesics

Opioid-based analgesics are the primary and the most used form of pain management in cardiac surgical patients (Jayakumar et al., 2019).

During the operation, the main agents in use are fentanyl and its derivatives alfentanil, remifentanil and sufentanil. Their PK properties are such that a continuous infusion or repetitive doses are needed at hourly intervals to maintain an adequate level of analgesia (Barry et al., 2015). The very short-acting opioid remifentanil is always administered as a continuous infusion.

Fentanyl, oxycodone, or morphine are generally used in the early postoperative phase in ICU when the patient is still intubated. In PCA-devices, the most common agents in use are oxycodone and morphine. With patients without self-controlled analgesia, opioids are administered either as injections into the muscular or subcutaneous tissue until the GI-tract recovers after the operation. Peroral opioids can be started after the GI function has recovered. Oxycodone and tramadol are used in their peroral forms. Transdermal opioid patches are not used postoperatively.

2.4.3.2 Non-opioid analgesics

The non-opioid analgesics which have been administered after a cardiac surgery consist of non-opioid peroral pain reducing drugs, regional infiltrated anaesthetics, epidural analgesia, and paravertebral blocks.

The most used peroral drug is paracetamol. Its analgesic potency is somewhat limited, but it is thought to have synergistic properties when combined with opioids in pain relief. Its exact mechanism of action is still partly unknown, but it is believed to inhibit cyclooxygenase enzymes and

prostaglandin synthesis as well as affecting serotonergic pathways in the pain signal transmission pathways (Douzjian et al., 2017).

Non-steroidal anti-inflammatory drugs are commonly utilized after major surgeries. However, their role in postoperative pain management in cardiac surgical patients is controversial. Selective COX-2 inhibitors have been shown to provide adequate postoperative analgesia in cardiac surgical patients but with an unacceptable rate of adverse events, mainly cerebrovascular events, acute kidney injuries, GI-bleeding and increased rate of wound infections (Nussmeier et al., 2005; Ott et al., 2003). However, a non-selective COX-inhibitor, ibuprofen did not show any excessive amount of side-effects after a cardiac surgery with short-term use (Qazi et al., 2015). Another non-selective COX-inhibitor diclofenac, has been demonstrated to provide sufficient postoperative analgesia without an excessive rate of side-effects, when rectally administered (Dhawan et al., 2009).

Thoracic epidural analgesia, paravertebral blocks and regional anaesthetic techniques have been widely studied. Results have been encouraging in terms of pain relief, but their effect on the length of stay in hospital or any major adverse events could not be demonstrated (Bignami et al., 2018). According to a recently up-dated meta-analysis, epidural analgesia after cardiac surgery seemed to reduce postoperative myocardial infarctions, respiratory depression, arrhythmias, time of intubation and pain. The impact on mortality and cerebrovascular events was less certain (Guay et al., 2019). However, anticoagulation therapy after cardiac surgery limits the use of epidural analgesia because of the epidural haematoma risk.

2.4.3.3 Non-pharmacological management

The usefulness of some non-pharmacological therapies in postoperative pain management has been examined. For example, both hand-massage and music therapy postoperatively have shown beneficial effects on the patient's wellbeing, but unequivocal scientific evidence is lacking (Grafton-Clarke et al., 2019; Grafton-Clarke et al., 2019).

In some studies, thoracic supportive vests have been claimed to exert a positive effect on postoperative pain (Caimmi et al., 2017; Laurikka et al., 1998).

Transcutaneous electrical nerve stimulation has demonstrated its ability to reduce pain scores as an adjuvant therapy to conventional pain management (Malik et al., 2018).

2.5 PERIOPERATIVE MEDICATION IN CARDIAC SURGERY

2.5.1 General considerations

Major cardiovascular surgery affects the behaviour of drugs postoperatively. The generally desired route of drug administration is peroral delivery as soon as it is feasible. However, it is well-established that there is a functional depression of GI-tract after major surgery, for example, gastrointestinal motility is often reduced after surgery (Berger et al., 2000; Kennedy et al., 2006). Gastric emptying might be delayed due to the surgery itself, the drugs used or as a consequence of an illness like diabetes (Horowitz et al., 2002). Opioid analgesics cause pyloric spasms thus hampering gastric emptying (Heyland et al., 1996). Changes in splanchnic blood flow, oedema and intestinal ischemia may change local circumstances to such an extent that it affects drug absorption (Thompson, 1995).

2.5.2 Pharmacokinetics

Pharmacokinetics refers to the movement of drugs through the body. Eino Nelson (Nelson, 1961) was among the first scientists to describe that it basically consists of four phases: 1) absorption, 2) distribution, 3) metabolism and 4) excretion, (ADME). The principles of ADME is presented in Figure 3.

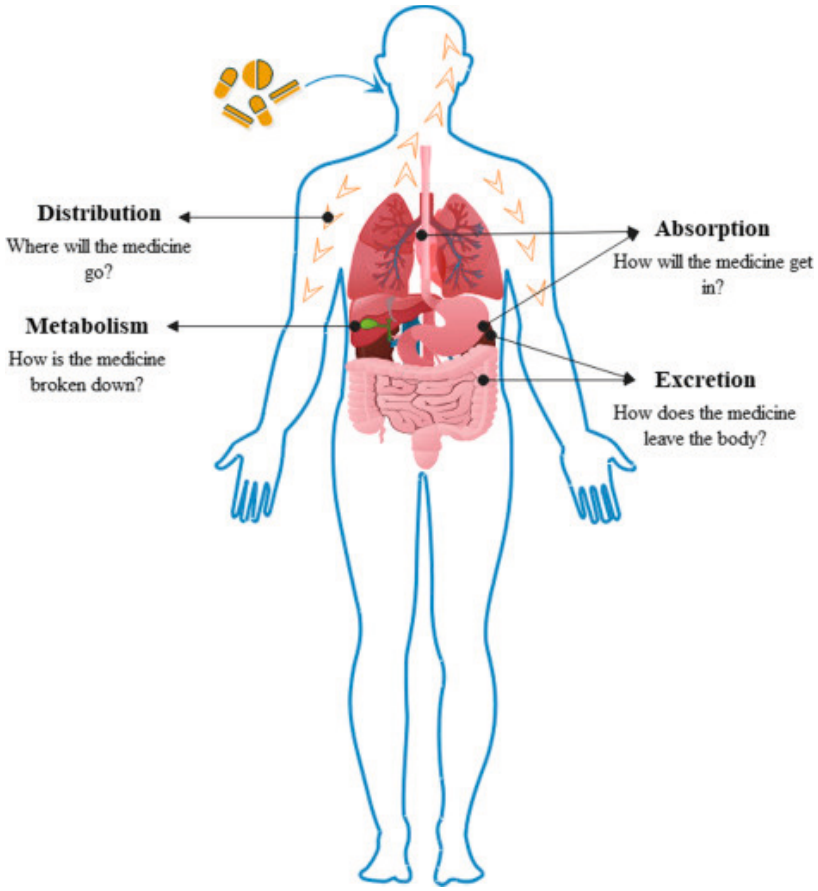


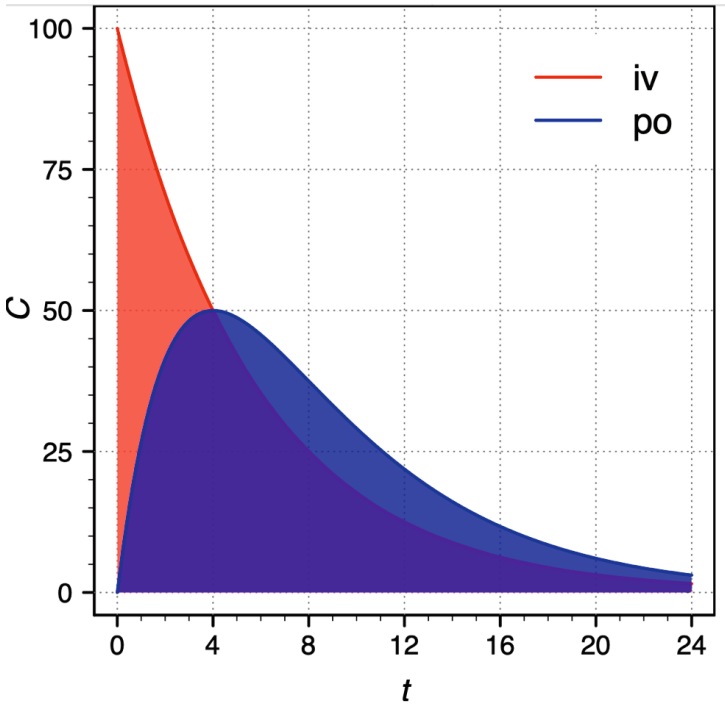
Figure 3. The principles of ADME. (Chandrasekaran et al., 2018). Modified by permission of the copyright owner.

The principal concepts of PK are the clearance (CL) and volume of distribution (V_d). Clearance reflects the volume of blood or plasma from which a substance is completely removed per unit of time. CL is distinctive for each drug, and it is also different in the various organs. V_d is a theoretical variable, and it reflects the volume in which a drug is distributed. It also reflects the water-lipid solubility and thus the tissue permeability of a drug. Most drugs are relatively lipid-soluble and poorly soluble in water. Lipid-soluble drugs have high V_d and water-soluble have low V_d. Octanol-water coefficient (o/w) describes the relationship between fat solubility and water solubility of a substance.

Fentanyl is highly lipid-soluble, its o/w is 399, in contrast, oxycodone is freely soluble in water, its o/w value is 0.7. Propranolol is one of the most lipid-soluble ß-blockers (o/w 399), while metoprolol is more water soluble, (o/w 0.4).

Several other PK parameters describing the behaviour of a drug are obtained from plasma concentrations. C_{max} means the peak plasma concentration after drug administration, t_{max} is the time to reach C_{max}, t½ is the time required for the concentration of the drug to decline to half of its original value, AUC means the area under the curve of a plasma concentration versus time profile.

Bioavailability describes the percentage (or the fraction (F)) of an administered dose of drug that reaches the systemic circulation. Bioavailability is 100 % (F=1) after intravenous administration (Figure 4).



$$F = \frac{AUC_{(PO\text{-}drug)}}{AUC_{(IV\text{-}drug)}}$$

Figure 4. Definition of the bioavailability (F). C = plasma concentration of a drug, t = time after drug administration. Modified by permission of the copyright owner.

Different $t_{½}$ values can be calculated for absorption, $t_{½(abs)}$, distribution, $t_{½(dist)}$ and elimination phase, i.e., the terminal elimination half-life, t½(elm). It is not always feasible to estimate half-lives after an intravenous infusion (Figure 5.). "Context-sensitive half-time" describes the time required for the plasma concentration to decrease by 50% at the termination of the infusion in relation to how long the drug has been infused. For remifentanil, the context-sensitive half-time is independent of the duration of the infusion while for fentanyl, the half-time increases from 24 minutes to 50 and to 280 minutes when the duration of infusion increases from 1 hour to 2 and to 8 hours, respectively (Hughes et al., 1992).

Plasma concentrations do not always describe the absorption of the compounds. For example, after an oral dose, metoprolol is readily absorbed but it appears to undergo a substantial first-pass metabolism in the gut and in the liver, and thus the oral bioavailability is only 40-50 % (Regårdh et al., 1981). First-pass metabolism may occur also in the lung, in the vasculature endothelium and in the central nervous system (Boer et al., 1992).

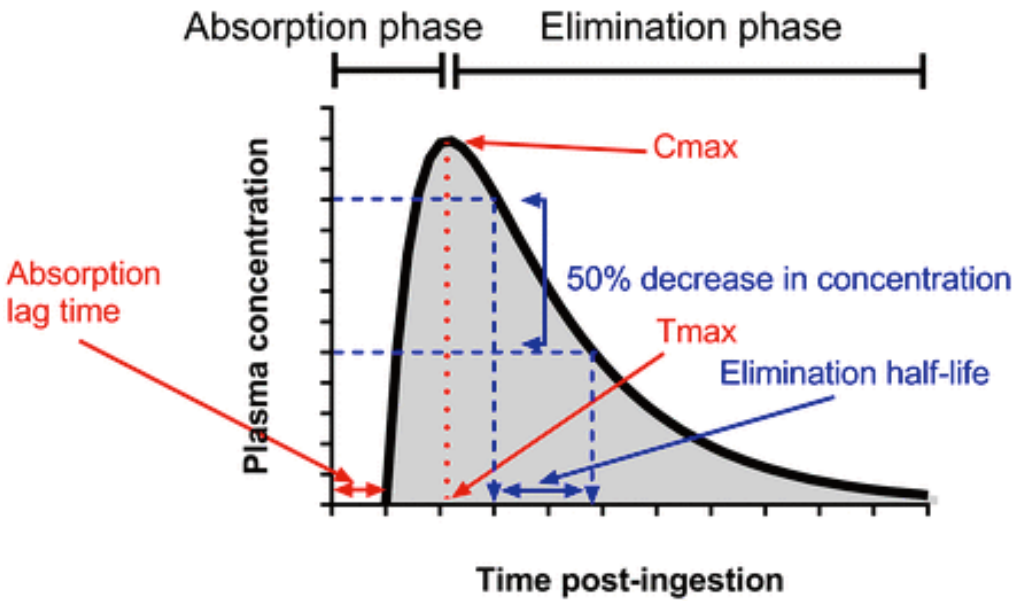


Figure 5. Example of the pharmacokinetic parameters. (Lea-Henry et al., 2018). Modified by permission of the copyright owner.

Pharmacokinetic data can be analysed by various methods. There are two common approaches in PK modelling; one is compartmental modelling, in which the body is considered as either one or more theoretical compartments between which the drug is being transferred. The other approach is a non-compartmental model, in which there is no assumption of compartments. A non-compartmental analysis is methodologically less complex and time consuming compared to compartmental PK models which need advanced mathematical modelling and computing.

2.5.2.1 Non-compartmental pharmacokinetics

Non-compartmental analysis (NCA) describes the degree of exposure to the administered drug. It uses basic mathematical equations to estimate PK parameters unlike compartmental models, which are based on a nonlinear regression analysis. NCA is based on observed drug concentrations over a certain period of time. The most common PK parameters obtained from NCA are C_{max}, t_{max} AUC and $t_{½}$. From the concentration versus time data, a plot describing the PK of a drug can be reconstructed.

2.5.2.2 Compartmental pharmacokinetics

A drug's PK behaviour in the body is often more accurately described with compartmental models. In two or multiple compartmental models, the drug is administered or initially absorbed in a central compartment from where it is eliminated and distributed into peripheral compartment(s). With respect to elimination, the k_0 elimination rate constant is calculated. The drug transfer between the central and peripheral compartments is described with constants k_{12} and k_{21}, with the first describing the transfer from the central compartment to the peripheral compartment and the k_{21} distribution representing the movement from the peripheral to the central compartment. The number of compartments required equals the number of phases of an exponential decline in the plasma concentration.

The pharmacokinetics of some drugs can be described more accurately with physiological perfusion models. These models are useful in the modelling of drugs that affect physiological parameters, e.g., cardiac output, and thus influence their own distribution and elimination. Physiologically based PK

models can be used also to predict a compound's distribution into its sites of action (Yamamoto et al., 2018)

Pharmacokinetics of oxycodone is best described by a two-compartmental model (Kokki et al., 2012) and that of fentanyl with a three-compartmental model (Hudson et al., 1986).

2.5.2.3 Population pharmacokinetics

Population PK describes the behaviour of a drug within a population rather than in a single individual. Compartmental models are used in population PK models. Population PK models are based on sophisticated statistical analyses and mathematical models. The main benefit of this method is that it enables sparse sampling thus reducing the size of the study group and the number of samples to be collected. Samples are taken from different subjects at different time points along the concentration plot. Population PK often utilize pooled data from more than one study. The main restriction to the use of population PK models is the complexity of the mathematical models used in the analyses (Välitalo et al., 2014).

2.5.2.4 Clinical pharmacokinetics

Clinical PK is the application of PK principles to the safe and effective therapeutic management of drugs in an individual patient and in different clinical settings. Protein binding is one of the most important variables in PK as in general, it is only the free, unbound drug that can penetrate into the tissues, act on the therapeutic target site and be eliminated from the body. Several factors, including stress, surgery, and liver or kidney dysfunction may alter the concentration of plasma proteins and therefore these factors may affect not only the PK but also the pharmacodynamics of compounds in the early postoperative period (Meloche et al., 2020).

2.5.3 Mode of drug administration

The bioavailability of a given drug is largely dependent on the route of drug administration. Bioavailability of a drug means the proportion of an administered drug reaching the systemic circulation for an intended action. Intravenously administered drugs have a bioavailability of 100 %; in all

other routes of administration, the bioavailability is lower than this value. However, with administration routes which have low first-pass metabolism, the bioavailability can be near to 100%. However, the routes and drugs undergoing more extensive first-pass metabolism, even though all or most of the compound can be absorbed, the bioavailability can be a mere 50 % or even less.

2.5.3.1 Per oral

Drug administration by mouth is the most common method of giving a drug to a patient. It can be carried out promptly without much effort from the personnel. This delivery route requires compliance from the patient to actually consume the medication in the postoperative period. The major disadvantage of peroral medication in the early postoperative period is the fact that the absorption of drugs might be affected by motility disorders of the GI-tract as well as alterations in the patient's fluid balance and the pH in GI-tract. These changes in physiological parameters may affect a compound's dissolution and the rate of absorption as well as the pass-time in the GI-tract. Some perorally administered drugs undergo substantial first-pass metabolism in the gut and liver, thus affecting their bioavailability. The dosage form affects significantly the PK parameters of compounds administered by mouth, liquids being more rapidly absorbed (Kokki et al., 2012).

2.5.3.2 Intravenous

Intravenous drug dosing is an accurate method of drug administration to the patient. Drugs administered in this way are effective because they avoid any first pass metabolism in liver and thus their bioavailability is 100 %. They are spread immediately throughout the systemic circulation and thus their effect starts rapidly. However, although the bioavailability of intravenous drugs is 100%, the time to gain access into the biophase, e.g., to penetrate the blood brain barrier, may substantially delay the onset of their pharmacodynamic action. Only inhaled drugs can theoretically have a more rapid onset of action. Intravenous administration is an invasive treatment causing more pain and discomfort to the patient and requires more work from the personnel and

also more sophisticated equipment, especially when continuous dosing is required (Thompson et al., 2016).

2.5.3.3 Transmucosal

The most common transmucosal routes of drug administration are conjunctival, intranasal, buccal, sublingual, rectal and vaginal. They all are non-invasive methods, and the onset of drug effect is relatively rapid. Rectally administered drugs bypass 2/3 of the first pass metabolism thus leading to high bioavailability. The good bioavailability is explained by the anatomy of the venous supply to the rectum: veins of the lower part of rectum drain directly into the systemic circulation. A sublingually administered drug is rapidly absorbed to capillaries and subsequently into the systemic circulation thus accounting for the rapid onset of action. With intranasal administration, the absorption is also prompt due to the same mechanism as in sublingual administration. Transmucosal routes of drug administration are highly sensitive to local circumstances at the time of drug administration. These unfavourable circumstances include diarrhoea at the time of rectal dosing, dry mucosae in the mouth or nose, the high level of mucociliary clearance in the nasal cavity. Psychological factors may play an important role with rectal and vaginal administration, especially in children (Kokki et al., 2006). Titrating of a dose is easy for example with the intranasal or buccal route but more complicated in rectal or vaginal routes due to psychological factors.

2.5.4 Perioperative drugs in cardiac surgical patients

The provision of appropriate perioperative medication has been shown to have a positive impact on both the short- and long-term prognosis after cardiac surgery (Iqbal et al., 2015). However, it has been estimated that unawareness of published guidelines exists in the surgical community, leading to non-optimal postoperative medication (Milojevic et al., 2017).

2.5.4.1 Antiplatelet and antithrombotic agents

Antiplatelet drugs are cornerstones for the treatment of an ischemic cardiovascular disease. The most common agent in use is acetylsalicylic acid (ASA, commonly known as aspirin). ASA is an inhibitor of the cyclo-oxygenase

1 (COX-1) enzyme. By preventing the synthesis of the COX-1 product thromboxane A2 in platelets, it inhibits platelet aggregation. Its efficacy in reducing postoperative mortality, myocardial infarctions and strokes is well documented. However, resistance to ASA is a well-known phenomenon with an incidence of 5 - 69 % (Zimmermann et al., 2008). In one recent study, its incidence after CABG was claimed to be as high as 71 % (Wand et al., 2018). The prevalence of laboratory defined ASA resistance has been estimated at around 25 % (Ebrahimi et al., 2020).

$P2Y_{12}$ -receptor inhibitors are another important group of antiplatelet drugs. These agents bind to ADP-receptors in platelets thus preventing aggregation. Clopidogrel is the most widely used drug in this group. Other drugs are prasugrel, ticagrelor and cangrelor. The last two mentioned drugs are in common use after catheter-based procedures but their role after CABG is unclear. Resistance to clopidogrel exists with an incidence of 30 % in a laboratory-based test (Aleil et al., 2005; Snoep et al., 2007).

In certain clinical settings, dual antiplatelet therapy (DAPT) is indicated after CABG. Current guidelines recommend a combination of ASA and clopidogrel for 12 months after CABG for patients with an acute coronary syndrome (ACS). The efficacy of the combination ASA with other $P2Y_{12}$ receptor inhibitors is currently under investigation. The prevalence of resistance to ASA/clopidogrel combination is reported to be 6 % (Gori et al., 2008).

In clinical work, discontinuation of antiplatelet therapy before a planned procedure is important as well as the time-point when therapy is restarted. Patients who have not discontinued antiplatelet medication before the operation tend to bleed more, they need more transfusions and the frequency of reoperations due to bleeding is increased. Despite the bleeding tendency, it is recommended to continue ASA until the surgical procedure unless the patient has a very high risk of bleeding, or the patient refuses blood transfusions or the planned surgery is non-coronary (Sousa-Uva et al., 2018). $P2Y_{12}$ receptor inhibitors in DAPT should be discontinued if clinically possible. The safe discontinuation interval is specific for each drug, usually 5 - 7 days. Current guidelines recommend starting ASA within 24 hours after CABG. If DAPT is indicated, $P2Y_{12}$ -receptor inhibitor could be started when

an additional bleeding risk is considered to be low but within 48 hours after surgery (Sousa-Uva et al., 2018).

Two types of anticoagulation drugs are used in cardiac surgical patients: vitamin K antagonists and non-vitamin K antagonists. The latter are designated as new oral anticoagulants (NOAC). Warfarin is the most used vitamin K antagonist. It is recommended that warfarin treatment should be stopped 5 days before the operation (Sousa-Uva et al., 2018). If the ischemic risk is considered to be high, a bridging therapy with unfractionated heparin (UFH) or a low-molecular-weight-heparin (LMWH) could be initiated. Stopping UFH therapy before the operation is related to its PKs, at least 6 hours before the operation (Sousa-Uva et al., 2018). With a LMWH given twice a day, discontinuation should happen > 12 hours before the operation due to its PKs (Sousa-Uva et al., 2018).

Administration with new oral anticoagulant medications should be stopped 48-96 hours before the operation, depending on the agent in use and the patient's renal function.

The reinstitution of anticoagulation therapy should take place within 24-48 hours after the surgery. If the patient needs anticoagulation therapy because of valvular prosthesis, LMWH or UFH is initiated together with warfarin. It is recommended that warfarin should be continued for up to 3 months after the operation with biological valve prostheses and valve repairs like mitral valvuloplasty. Mechanical valve prostheses need lifelong anticoagulation with warfarin. NOACs have no approval with mechanical valvular prostheses. They can be used in other indications for anticoagulation and are started as soon as an additional bleeding risk is acceptable.

2.5.4.2 ß-blockers

Most patients with ischemic heart disease are prescribed ß-receptor blocking medication. The main benefits of this medication are the drug's ability to reduce the heart's workload, to slow the heart rate, and to reduce blood pressure. Especially patients with a reduced ejection fraction (EF) and a recent myocardial ischemic event benefit from ß-blocking medication (Andersson et al., 2014; Chatterjee et al., 2013; Lin et al., 2010).

In cardiac surgical patients, the use of ß-blocking medication is associated with a survival benefit by reducing postoperative arrhythmias which are a serious cause of increased morbidity (Blessberger et al., 2015). However, in a more recent systematic review, there was no evidence of a benefit from ß-blocking medication in terms of early all-cause mortality, myocardial infarction, cerebrovascular events, hypotension, or bradycardia. A trend towards a reduced incidence of atrial fibrillation and ventricular arrhythmias seemed to exist (Blessberger et al., 2019; Thein et al., 2018).

2.5.4.3 Lipid-lowering agents

Statin therapy is one the cornerstones of medication in patients with an ischemic heart disease. The current European guideline recommends intensive medication with the primary target of low-density lipoprotein (LDL-C) 1.8 mmol/L (Mach et al., 2020) after CABG. If the target is not achieved by statin alone, additional medication is indicated in the form of a cholesterol absorption inhibitor, ezetimibe or even the newest generation proprotein convertase subtilisin/kexin type 9 (PCSK) inhibitors.

There is somewhat conflicting data if one should initiate therapy with a new statin before CABG i.e., does it have beneficial effects on early outcomes after surgery (Billings et al., 2016; Kuhn et al., 2015; Zheng et al., 2016). In conclusion, there is no absolute data supporting a new-onset statin therapy before cardiac surgery, but the guidelines do recommend the continuation of an on-going therapy.

2.5.4.4 Blood pressure medication

The majority of patients with an ischemic heart disease have arterial hypertension as a risk factor for coronary artery disease. According to the most recent European guideline for the management of arterial hypertension, five major drug classes or their combinations are recommended for the treatment of hypertension; angiotensin-converting-enzyme (ACE) inhibitors, ß-blockers, angiotensin-receptor II blockers (ARB), calcium-channel blockers (CCB), and diuretics (Williams et al., 2018).

Because ACEs and ARBs (renin-angiotensin-aldosterone system inhibitors, RAAS) are the most widely used drugs for hypertension, their role during

surgical revascularization or other types of cardiac surgery has been debated (Bhatia et al., 2016; Disque et al., 2016). Preoperative continued use of ACEs and ARBs has been shown to increase several postoperative complications; hypotension, myocardial infarction, renal dysfunction but they do not appear to have any significant effect on overall mortality, postoperative atrial fibrillation or strokes (Zhang et al., 2015). The current consensus is to discontinue ACEs and ARBs 24-48 hours before the operation.

However, there is a strong evidence for a long-term positive effect of RAAS blockers on the patient's survival, especially in those individuals with reduced left ventricular EF and renal dysfunction (Pfeffer et al., 1992; Savarese et al., 2013; Yusuf et al., 1992). Based on this data, RAAS blockers are recommended to be started after the operation but no earlier than 48 hours.

CCBs can be safely used pre- and postoperatively as an additional medication with ß-blockers and RAAS blockers to combat hypertension if needed.

2.5.4.5 Glucose lowering agents

Diabetes mellitus is a significant risk factor for coronary artery disease. Diabetic patients represent up to 40 % of patients undergoing CABG (Raza et al., 2015). In general, an elevated blood glucose concentration (>6.6 mmol/l) is linked to an increased rate of postoperative complications. The preoperative glycated haemoglobin (HbA1c) level describes the average blood sugar level over a period of weeks or months, thus revealing the level of glycaemic control in diabetic patients. Two recent systematic reviews demonstrated a negative impact of increased HbA1c levels on postoperative complications in terms of mortality, strokes, myocardial infarctions, and sternal wound infections (Biancari et al., 2019; Zheng et al., 2017).

Peri- and post-operative hyperglycaemia (> 6.6 mmol/L) is a well-known phenomenon resulting from the body's stress response to surgical trauma. To some extent it protects the patient, but a highly increased blood sugar concentration has been linked to adverse outcomes (Preiser et al., 2016). The degree of glycaemic control peri- and post-operatively is under debate. Tight postoperative glycaemic control may have some beneficial effects but also

it has also been shown to exert a negative impact on the outcome (Finfer et al., 2009; Haga et al., 2011).

Short-acting insulin is used in the management of hyperglycaemia. Oral antidiabetic drugs are recommended to be stopped one day before the surgery. Short-acting insulin is administered either in subdivided subcutaneous injections or as a continuous intravenous infusion with the target of blood sugar concentration of 8.3 – 10 mmol/L (Sousa-Uva et al., 2018). Long-acting insulins and peroral antidiabetics are recommended to be started at 50 % of the preoperative dose after the operation (Sousa-Uva et al.2018).

3 AIMS OF THE STUDY

3.1 GENERAL AIMS OF THE THESIS

This doctoral thesis aims to assess the bioavailability of orally administered metoprolol and oxycodone, and intranasally administered fentanyl in the early postoperative period after CABG surgery. It was hypothesized that better knowledge on the pharmacokinetic properties of these drugs would enhance the prevention and treatment of postoperative atrial fibrillation and pain, and therefore improve patient outcome.

3.2 SPECIFIC AIMS OF THE THESIS (STUDIES I – III)

3.2.1 Aims of study I

Assess the bioavailability of metoprolol in patients undergoing CABG surgery with CPB.

3.2.2 Aims of study II

Compare the bioavailability of peroral oxycodone, co-administered with naloxone, in patients undergoing CABG surgery with or without CPB.

3.2.3 Aims of study III

Assess the bioavailability, safety, and analgesic efficacy of intranasal fentanyl in patients undergoing cardiac surgery.

4 STUDY I: DOES CORONARY ARTERY BYPASS SURGERY AFFECT METOPROLOL BIOAVAILABILITY?

4.1 ABSTRACT

Background: β-blockers are commonly administered in patients with coronary artery bypass surgery (CABG). Despite this therapy, however, the incidence of postoperative atrial fibrillation (AF) is high (9–19%), and it is unknown why the β-blockers do not reduce the incidence of AF more efficiently. In this pharmacokinetics study, in which the patients acted as their own controls, we have evaluated the bioavailability of perioperative metoprolol tablets in CABG surgery patients.

Methods: Twelve male patients, aged 45–64 years, scheduled for CABG surgery were administered an initial 50 mg metoprolol tartrate tablet orally on the morning of the preoperative day and thereafter at 12-h intervals. Regular blood samples were collected up to 12 h after the first administration of the drug on the preoperative day as well on the first and third postoperative days. The plasma concentration for metoprolol was analysed (limit of quantification = 0.001 mg/L) using liquid chromatography-tandem mass spectrometry.

Results: The bioavailability of the metoprolol was significantly less on the first postoperative day, with AUC_{0-12} values ranging from 0.7 to 17.1 (median: 7.2) mg min/L, than on the preoperative day, with AUC_{0-12} values of 5.1– 26.7 (12.6) mg min/L; however, it returned to the preoperative values on the third postoperative day, with AUC_{0-12} values of 3.5–25.2 (15.2) mg min/L. Similar changes were observed in Cmax values: preoperative C_{max} ranged between 0.026 and 0.123 (0.060) mg/L, on the first postoperative day, the C_{max} ranged between 0.003 and 0.093 (0.025) mg/L, and on the third postoperative day, the C_{max} ranged between 0.009 and 0.136 (0.061) mg/L. There was no correlation between the pharmacokinetic parameters and patient characteristics, but both the preoperative C_{max} and C60 correlated significantly with the postoperative

C_{max} (Pearson correlation coefficient: 0.61–0.72). One patient with one of the lowest rates and extent of metoprolol absorption developed AF.
Conclusion: This study indicates that the bioavailability of metoprolol is markedly reduced when administered in tablet form during the early phase after CABG.

4.2 INTRODUCTION

Atrial fibrillation (AF) is a common phenomenon after coronary artery bypass grafting surgery (CABG), with incidence rates of between 10 and 35% (Almassi et al., 1997; Andrews et al., 1991; Aranki et al., 1996; Creswell et al., 2001; De Jong et al., 2000; Hakala et al., 2002; Hravnak et al., 2002; Lahtinen et al., 2004; Omorphos et al., 2004). Postoperative AF is associated with significant postoperative complications, such as increased risk of stroke, which affects the outcome, the need for additional treatment and may lead to prolonged hospital stay which, in turn, increases healthcare costs (Aranki et al. 1996, De Jong et al. 2000, Hravnak et al 2002, Hakala et al. 2002, Lahtinen et al. 2004). Recent meta-analyses have confirmed the efficacy of β-blockers in the prevention of AF after CABG (Crystal et al., 2002; Omorphos et al., 2004), and β-blockers are standardly administered to all patients undergoing CABG. However, the incidence of postoperative AF remains high (8.7–19%) (Omorphos et al. 2004), and it is not yet known why the β-blockers do not reduce the incidence of AF more efficiently.

Gastrointestinal motility may be reduced markedly after surgery, with delays in gastric emptying, and these physiological changes may impair drug absorption (Ogilvy et al., 1995). Berger et al. (2000) found that the absorption of paracetamol administered gastrically was decreased on the first postoperative day after cardiac surgery, mainly because of opioid-related pylorus closure. Based on these findings we hypothesized that the unimpressive efficacy of β-blockers may be a consequence of their poor absorption from the gastrointestinal tract during the early postoperative phase. We therefore designed this prospective study, in which the patients acted as their own preoperative controls, to evaluate the rate and extent

of absorption of metoprolol, a selective adrenergic beta-1-blocking agent with no stimulatory action, in 12 patients undergoing CABG surgery. Patients were given metoprolol tartrate 50 mg tablets twice daily, and the 12-h pharmacokinetic profile of metoprolol was determined on 3 days: the day before surgery, and on the first and third day after CABG. The primary outcome parameter was the 12-h area under the time-concentration curve ($AUC_{0–12}$) for metoprolol.

4.3 MATERIALS AND METHODS

The study population consisted of 12 male consecutive patients, aged 45 to 64 years, who were scheduled for elective CABG in the Kuopio University Hospital. The study was approved by the Research Ethics Committee of the Hospital District of Northern Savo and was conducted in accordance with the Declaration of Helsinki. The patients were given oral and written information on the trial protocol, and they all provided written consent. All patients who were asked agreed to participate. All male patients under 65 years of age were included if they had no contraindication for metoprolol. Patients already using metoprolol were excluded, as were patients with a previous surgery of upper gastrointestinal tract, disease or any other condition that could interfere with the gastric absorption. Patients with hepatic dysfunction and simultaneous use of compounds metabolized in liver via the same enzyme-metabolizing system as metoprolol were also excluded.

Patients came to the hospital on the day before surgery. The patients had fasted for at least 2 h before the metoprolol was administered. Each patient was given one 50 mg tablet of metoprolol tartrate (Metoprolin Ratiopharm; Merckle GmbH, Blaubeuren, Germany) to be swallowed with a glass of water (150 ml) at 8 a.m. After the test drug had been administered, the patients were asked to remain in an upright position for 30 min, either sitting on a chair or walking around the ward. Fasting was continued for 4 h after the test drug administration, and at 12 a.m. the patients were served a light meal. The patients were provided with two additional doses of metoprolol 50 mg before surgery – at 8 p.m. on the day before surgery and at 6 a.m. on the day of the

operation. Metoprolol administration was continued on the first morning after surgery: 50 mg tablets, administered orally at 8 a.m. and at 8 p.m.

Blood samples (3 ml) were obtained with an indwelling catheter inserted in an antecubital vein at baseline, and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8 and 12 h post dose after the 8 a.m. metoprolol administration on the preoperative day and the first and the third postoperative days. The baseline sample was obtained before the administration of metoprolol and the sample at 12 h was obtained before the 8 p.m. administration. Arterial blood pressure and heart rate were recorded after each blood sample. Blood was collected into EDTA tubes, and plasma was obtained within 20 min of collection by centrifugation at 3100 rpm/min for 10 min at +20°C. The separated plasma was stored at +4°C, and the samples were sent to the laboratory packed in an insulated cool container for analysis.

Determination of metoprolol in plasma

Instrumentation. The liquid chromatography-tandem mass spectrometry (LC-MS/MS) instrumentation consisted of a PE Series 200 LC-MS Pump, an autosampler and a PE Sciex API 365 triple stage quadrupole mass spectrometer, equipped with a PE Sciex Turbo Ion Spray interface (Concord, ON, Canada). LC separations were carried out with a 100 × 2.1 -m Genesis C18 column (particle size: 4 µm; Jones Chromatography, Hengoed, UK) and a 40-mm Purospher RP-18 LiChro Cart 4-4 guard column (particle size: 4 µm; Merck, Darmstadt, Germany).

Table 1. Accuracy and precision of metoprolol determination.

Concentration (mg/L)	Accuracy (%)[a]	Within-day CV (%)[a]	Day-to-day CV (%)[b]
0.005	118	10.2	11.5
0.01	103	2.8	13.8
0.05	98	8.7	8.2
0.1	100	8.9	4.6

[a]Based on five parallel determinations
[b]Based on 14 separate determinations over a 2-month period

Extraction procedure. The internal standard dibenzepin (20 µl, 1 µg/mL) was added to serum (1 g), the pH of which was made alkaline by addition of 1 M Tris-buffer (300 µL, pH 11). The sample was extracted with butyl acetate (600 µL) in a vortex-mixer (2 min), and the organic layer was separated by centrifugation. Prior to evaporation, ammonium acetate buffer (75 µL, 10 mmol/L, 0.1% formic acid, pH 3.2) was added to prevent evaporation to dryness. Acetonitrile (75 µL) was then added, and the samples were sonicated (5 min). Following centrifugation, the extract was transferred to an autosampler vial.

LC-MS/MS conditions The mobile phase consisted of acetonitrile and ammonium acetate buffer (10 mmol/L, 0.1% formic acid, pH 3.2), with the following gradient being used: acetonitrile 15 →50% in 10 min, 2 min isocratic, then 50 → 100% in 8 min. Total flow rate through the column was 200 µL/min, and the injection volume was 20 µL. The separation was carried out at 35°C. The needle voltage was 5.2 kV, and the nebulizer gas (air, 60 psi) and curtain gas (nitrogen, 40 psi) were set at 10 and 12 in the SCIEX control software, respectively. The collision cell gas (nitrogen, 40 psi) was set at 2. The Turbo Ion Spray heater temperature was 375°C, and the heater gas flow rate was 7 L/min. Metoprolol was quantified using multiple reaction monitoring (MRM). The ion transition of m/z 268.2 to m/z 121.0 was obtained at a collision energy of 35 eV and monitored with a dwell time of 250 ms.

Validation data. The limit of quantification was 0.001 mg/L. Linear calibration was used throughout the applied concentration range with $R^2 > 0.996$. The accuracy and precision of the method are shown in Table 1.

Pharmacokinetic analysis Pharmacokinetic parameters were calculated based on noncompartmental analysis using WINNONLIN software (ver. 4.0.1;

Pharsight Corp., Mountain View, Calif.) installed on a personal computer. C_{max} is the maximal drug concentration observed and t_{max} is the time to reach this maximal drug concentration. The area under the plasma concentration-time curve from the time zero to 12 hours, $AUC_{0–12}$, was calculated using the linear trapezoidal rule.

Statistics

No formal sample size calculation was performed, but according to the European Medicines Agency guidelines (EMEA 2006) a group of 12 patients can be considered to provide sufficient data on perioperative pharmacokinetics of peroral metoprolol.

Pharmacokinetics variables after the three administrations were analysed with SIGMASTAT software (ver. 2.03 for Windows; SPSS, Chicago, Ill.). Differences according to administration days were assessed with one-way repeated- measures ANOVA using log-transformed $AUC_{0–12}$ and C_{max} values. The Tukey test was used in all pair-wise comparisons. Correlations between pharmacokinetic parameters and patient characteristics were tested with the Pearson's correlation coefficient using the SPSS statistical package (ver. 11.5 for Windows; SPSS Inc.). Differences were regarded as statistically significant if the P value was less than 0.05. Data are expressed as the number of cases and medians are expressed with the range where appropriate.

4.4 RESULTS

All enrolled patients completed the study, and there were no protocol deviations likely to interfere with the study results. Baseline characteristics, and peri- and postoperative variables are shown in Table 2.

There was a significant difference in the bioavailability of metoprolol between the three study days (Table 3). The mean plasma concentration curves on these are shown in Figure 1. On the preoperative day, the $AUC_{0–12}$ values ranged from 5.1 to 26.7 (median: 12.6) mg min/L. On the first postoperative day, these values were significantly lower, 0.7–17.1 (7.2) mg

min/L (first postoperative day vs. first preoperative day: P=0.005), but they returned to the preoperative day values on the third postoperative day, 3.5–25.2 (15.2) mg min/L (third postoperative day vs. preoperative day: P=0.96).

A similar difference was noticed in the maximal drug concentration achieved with metoprolol tablets (Table 3). On the preoperative day, C_{max} ranged from 0.026 to 0.123 (0.060) mg/L, on the first postoperative day, it ranged from 0.003 to 0.093 (0.025) mg/L (first postoperative day vs. preoperative day: P=0.001) and on the third postoperative day, it ranged from 0.009 to 0.136 (0.061) mg/L (third postoperative day vs. preoperative day: P=0.89). Plasma metoprolol concentrations in each patient on the preoperative day and on the first and third postoperative day are shown in Figs. 2, 3 and 4, respectively.

Table 2. Baseline patient characteristics, and peri- and postoperative parameters.

Patient no.	Age (years)	Weight (kg)	Body mass index (kg/m^2)	Dyslipidemy	Arterial hypertension	Diabetes	Dyspepsia	Perfusion time (min)	Oxycodone during the first 24 h (mg)
1	58	81	27	Yes	No	Yes	No	87	37
2	54	84	27	Yes	No	No	Yes	73	45
3	59	86	25	Yes	Yes	No	No	98	31
4	57	131	38	Yes	No	No	No	75	66
5	64	70	25	Yes	Yes	No	No	37	54
6	45	116	37	Yes	No	No	No	68	65
7	57	78	26	Yes	Yes	Yes	Yes	79	29
8	59	93	31	Yes	Yes	No	No	59	50
9	53	90	30	No	Yes	No	No	75	65
10	56	90	30	Yes	No	No	No	91	44
11	57	116	41	Yes	Yes	No	No	72	37
12	61	92	30	Yes	Yes	Yes	No	94	45

Table 3. Individual pharmacokinetic data for study patients on the three study days.

Patient no.	New atrial fibrillation after surgery	C_{max} [a] (mg/L)			$AUC_{(0-12)}$ [d] (mg min/L)		
		Preoperative day	First postoperative day[b]	Third postoperative day[c]	Preoperative day	First postoperative day[e]	Third postoperative day[f]
1	No	0.048	0.030	0.098	11.5	15.5	16.2
2	No	0.055	0.004	0.030	12.2	0.66	12.0
3	No	0.123	0.047	0.084	17.1	11.1	14.9
4	Yes	0.033	0.003	0.041	6.9	1.1	7.8
5	No	0.030	0.031	0.017	8.0	5.9	4.0
6	No	0.116	0.093	0.105	21.7	17.1	15.4
7	No	0.080	0.040	0.059	21.5	8.3	19.3
8	No	0.084	0.009	0.065	26.7	2.2	16.6
9	No	0.026	0.019	0.009	5.1	6.0	3.5
10	No	0.068	0.037	0.136	18.6	11.9	25.2
11	No	0.065	0.020	0.063	13.0	9.4	15.0
12	No	0.033	0.009	0.045	11.2	2.9	16.1

[a]Significant differences between the study days ($P = 0.001$; repeated-measures ANOVA).
[b]Significantly different from the preoperative day ($P = 0.001$; Tukey).
[c]Significantly different from the first postoperative day ($P = 0.002$; Tukey).
[d]Significant differences between the study days ($P = 0.003$; repeated-measures ANOVA).
[e]Significantly different from the preoperative day ($P = 0.005$; Tukey).
[f]Significantly different from the first postoperative day ($P = 0.010$; Tukey).

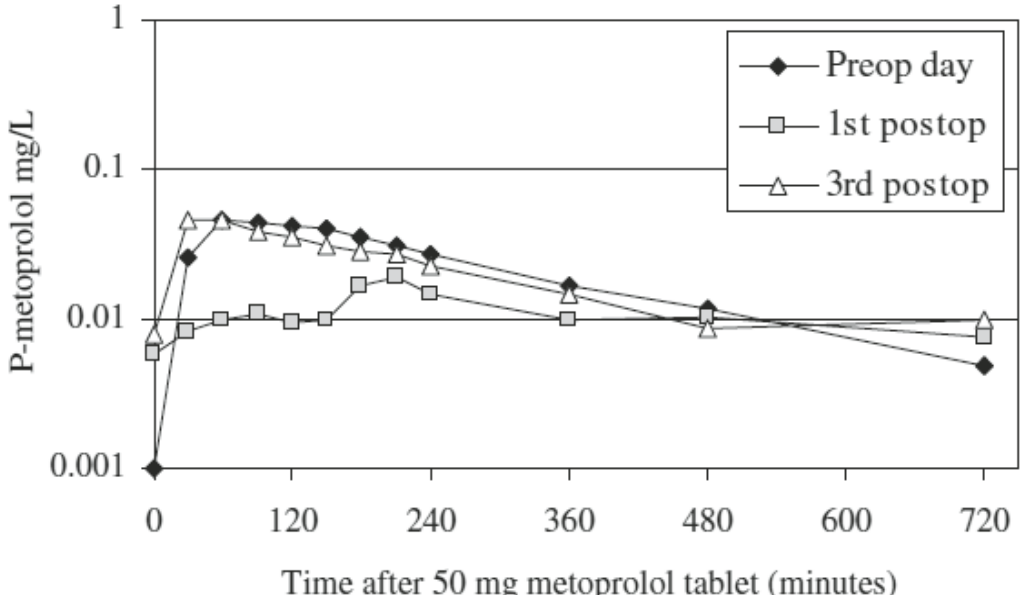


Figure 1. The means of plasma concentrations on the three study days.

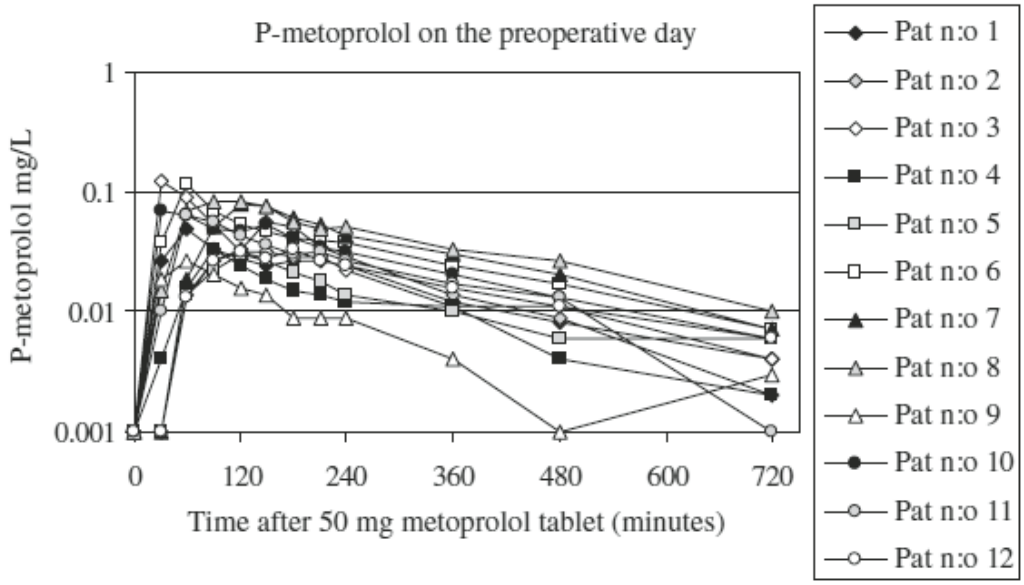


Figure 2. The plasma concentration-time curves on the day before surgery.

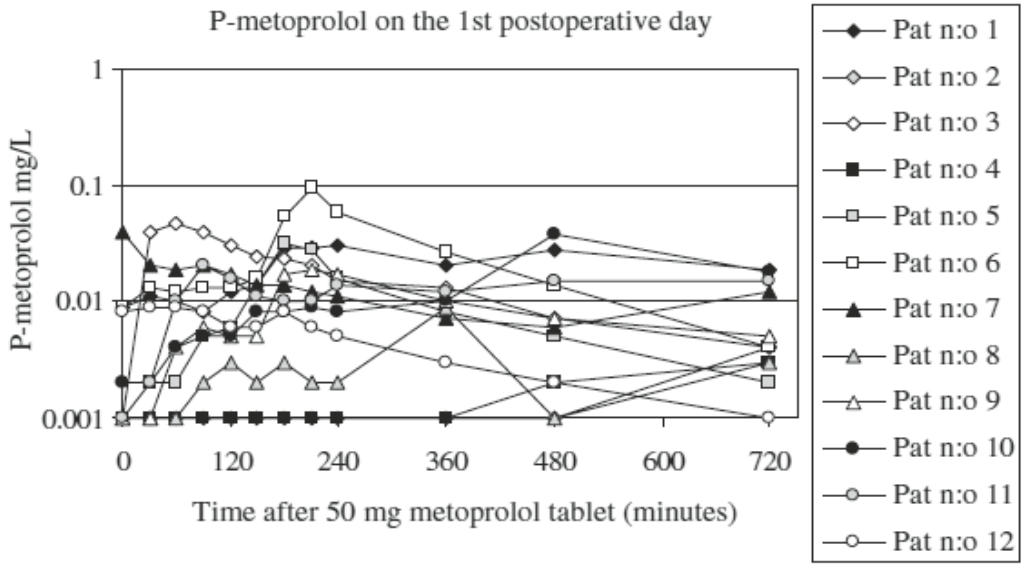


Figure 3. The plasma concentration-time curves on the first postoperative day.

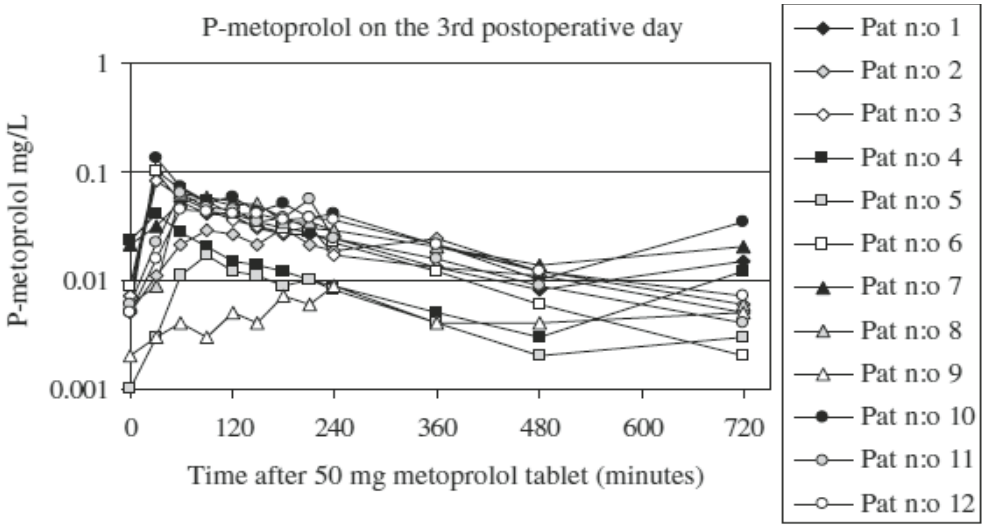


Figure 4. The plasma concentration-time curves on the third postoperative day.

The remaining metoprolol concentration from the previous dose did not usually contribute significantly to AUC_{0-12} and C_{max} values on the first and third postoperative days since the metoprolol concentration before the drug administration (time zero) was below 10% of the observed C_{max} in 15 of all 24 cases and was over 50% in only three cases. The highest contribution of previous dose was observed in the following cases. On the first postoperative day, C_{max} for patient no. 7 occurred at time zero and was attributable to the previous dose. In addition, the zero-time concentration for subject 12 was 89% of C_{max}. For these two subjects, the true difference in AUC_{0-12} and Cmax values between the preoperative and the first postoperative day was even higher than described in Table 3. However, it was not possible to subtract the contribution of the previous dose because plasma concentrations were not determined for the previous dose. In addition, metoprolol did not follow well-defined first order kinetics on the first postoperative day. On the third postoperative day, zero-time concentration for subject 4 was 56% of C_{max}. For this patient, the calculated AUC_{0-12} and C_{max} values on the third postoperative day were slightly higher than those on the preoperative day (Table 3), but the

true values without the contribution of the previous dose would probably have been similar or only slightly lower than those on the preoperative day.

The rate of metoprolol absorption was also significantly slower on the first postoperative day [t_{max}: 0–720 (median: 210) min] than on the preoperative day [t_{max}: 30–180 (75) min] and on the third postoperative day [t_{max}: 30–240 (60) min] (P=0.035).

There was no correlation between the pharmacokinetic parameters and the patient characteristics. However, the preoperative C_{max} did exhibit a significant correlation, with C_{max} on the first postoperative day (r=0.683, P=0.014) and third postoperative day (r=0.611, P=0.035). Of those single measurements on the preoperative day, C60 correlated best with the preoperative day C_{max} (r=0.835, P= 0.001), first postoperative day Cmax (r=0.717, P=0.009) and third postoperative day C_{max} (r=0.712, P=0.009). The preoperative day C_{60} also correlated significantly (r = 0.692, P=0.013) with the $AUC_{0–12}$ value on the first postoperative day.

One patient (no. 4) developed AF. He had one of the lowest $AUC_{0–12}$ values (6.9, 1.1 and 7.8 mg min/L) and C_{max} levels (0.033, 0.003 and 0.041 mg/L) on all three study days.

Recovery from the operation was uneventful in 11 patients. One patient, a 57-year-old man, developed sternal dehiscence that needed reconstructive reoperation on the sixth postoperative day.

4.5 DISCUSSION

The absorption of metoprolol from the gastrointestinal tract is well documented in humans in normal conditions, but less is known about the effects of surgery on the absorption and bioavailability of the drug. Metoprolol is a weak base and its ionization constant (pK_a) is 9.2 (Schoenwald et al., 1983). In the stomach (pH between 1 and 3) the amount of absorbable non-ionized drug is low and, consequently, metoprolol is poorly absorbed from the stomach. On the other hand, metoprolol is well absorbed from the small intestine and the colon. Thus, the gastric emptying rate regulates the absorption rate of metoprolol from the small intestine. The rate but not

the extent of metoprolol absorption is increased by the presence of food in the gastrointestinal tract (Godbillon et al., 1985; Jobin et al., 1985). Despite complete gastrointestinal absorption, only about 50% of single oral doses of metoprolol reach the systemic circulation because of the extensive first pass metabolism (Regårdh et al., 1980).

The results of our study demonstrate that the bioavailability of orally administered metoprolol was negligible in several patients on the first postoperative day after CABG; however, on the third postoperative day, the absorption of metoprolol had returned to the preoperative level in most patients. There may be several reasons for this poor absorption and low bioavailability. Firstly, most patients should have had bowel dysfunction and delayed gastric emptying immediately following surgery. Following surgery, gastrointestinal track motility is impaired because of ileus, pseudo-obstruction and the use of pharmacologic agents (Berger et al., 2000; Kennedy et al., 2006). Secondly, during and after major cardiovascular surgery, structural changes to the intestine may occur because of villous atrophy. In addition, changes in splanchnic blood flow, oedema and mucosal ischemia, all commonly associated with CABG surgery, impair absorption by decreasing the effective absorptive area of the gut and reducing mucosal transport (Heyland et al., 1996; Thompson, 1995). Thirdly, disease may affect gastrointestinal function; for example, a significant percentage of diabetic patients suffer from gastroparesis, which may delay the absorption of tablets that are not easily degraded in the stomach (Horowitz et al., 2002). However, in the present study, diabetes did not affect drug absorption: the rate and extent of metoprolol absorption in the three diabetic patients (patient nos. 1, 7 and 12) was similar or higher than those in the nine patients without diabetes. Finally, perioperative opioids may have exacerbated postoperative ileus in the present study. Oxycodone, an opioid which was used for postoperative pain management in the present study (Table 2), has been shown to decrease the gastric emptying rate on the first postoperative day (Heyland et al. 1996). Theoretically, the reduced peak concentration and AUC of metoprolol on day 1 can be explained by an increase in hepatic clearance and first-pass metabolism. However, this is unlikely because the splanchnic perfusion is decreased immediately after major surgery.

Our results on metoprolol absorption are very similar to those of Berger et al. (2000) on paracetamol absorption. Similar to metoprolol, paracetamol is poorly absorbed from the stomach but is well absorbed from the small intestine (Clements et al, 1978). Berger et al. (2000) found that the absorption of paracetamol administered gastrically was markedly reduced on the first postoperative day after cardiac surgery, whereas the absorption was normal or close to normal on the third postoperative day. After postpyloric delivery, the absorption was normal on both days. Berger et al. (2000) concluded that the reduced absorption following gastric administration on the first postoperative day was mainly due to opioid-related pylorus closure. This may also explain the reduced metoprolol absorption on the first postoperative day in our study since we used an opioid-based protocol for pain relief during the early phase after surgery (Table 2).

It has been shown that the longer the surgical patients are without their regular medicines, the more non-surgical complications these patients suffer (Kennedy et al., 2000). When long-term β-blocking medication is abruptly discontinued, a phenomenon called β-blocking withdrawal effect may occur. This is characterized by increased catecholamine concentrations in the plasma. The withdrawal effect has been proposed as a possible cause of AF after cardiac surgery when β-blocking medication has been stopped at the time of surgery (Kalman et al., 1995; White et al., 1984). Most of the patients undergoing CABG are receiving preoperative β-blocker medication. We hypothesize that even if the peroral administration of metoprolol is continued following CABG, its low bioavailability may lead to an insufficient concentration of metoprolol in the serum and that this could actually resemble the β-blocking withdrawal effect. Thus, the low bioavailability of metoprolol could be one etiological factor of AF after cardiac surgery.

On the basis of our study, which reveals a low bioavailability of peroral metoprolol, intravenously administered β-blockers may be a more effective approach to preventing AF after cardiac surgery. Intravenous administration ensures an adequate plasma concentration, and variations between individuals in maximal plasma concentrations are less likely to occur. The feasibility of using intravenous β-blockade has been reported in two studies (Balcetyte-Harris et al., 2002; Halonen et al., 2006). In one of these

(Balcetyte-Harris et al. 2002), intravenous esmolol was less well tolerated and offered no advantages to standard β-blockade in the prevention of AF after cardiac surgery; in the second, intravenous administration of metoprolol was significantly more effective than its oral administration in the prevention of AF after cardiac surgery (Halonen et al. 2006).

In conclusion, this study indicates that the bioavailability of metoprolol from tablets is markedly reduced in most patients on the first postoperative day after CABG. Consequently, intravenous administration may be needed to achieve sufficient blood concentrations.

Acknowledgements: The study received financial support by a EVO-grant from The Kuopio University Research Foundation. We like to thank Mikko Vahteristo for helpful discussions on the statistical analysis.

5 STUDY II: BIOAVAILABILITY OF OXYCODONE BY MOUTH IN CORONARY ARTERY BYPASS SURGERY PATIENTS – A RANDOMIZED TRIAL

5.1 ABSTRACT

Objective: Pain after coronary artery by-pass (CAB) surgery is severe. Analgesic administration by mouth is unreliable until after gastrointestinal function has recovered. We evaluated the bioavailability of oxycodone co-administered with naloxone by mouth in patients after CAB surgery using either a conventional extracorporeal circulation (CECC) or off-pump surgery (OPCAB).

Methods: Twenty-four patients, 50–73years, 12 with CECC and 12 with OPCAB, were administered a 10/5 mg oxycodone-naloxone controlled-release tablet by mouth on the preoperative day and for the first seven postoperative days (PODs) thereafter. Blood samples were collected up to 24h after the preoperative administration, and then randomly either on POD1 and POD3 or on POD2 and POD4. The oxycodone concentration in plasma was analysed using liquid chromatography-mass spectrometry.

Results: On POD1 oxycodone absorption was markedly delayed in five of six patients after CECC and in all six patients after OPCAB surgery; median of tmax after CECC 630 [range 270–1420] minutes and after OPCAB 1020 [720–1410] minutes, compared to median of 120–315min preoperatively and on POD2-POD4. The carry-over corrected AUC0–24 values on the PODs did not differ from the preoperative values but were higher on POD3 compared with POD1 in both CECC and OPCAB groups. The rate and extent of oxycodone absorption equalled preoperative values on POD2 and onwards in patients with CAB surgery.

Conclusions: Bioavailability of oxycodone by mouth was similar after CAB surgery via CECC or having OPCAB. Data indicate that POD2 is an appropriate time to start oxycodone administration by mouth after CAB surgery.

5.2 INTRODUCTION

Early postoperative pain after coronary artery bypass (CAB) surgery is often severe. In the majority of patients moderate or severe pain persists for the few first days after surgery. In our earlier study, at four days after surgery, half of CAB surgery patients still had severe pain at rest, two-thirds during movement and four out of five patients during coughing. Most of the patients experienced more postoperative pain than they anticipated (Lahtinen et al., 2006).

The need for efficient pain management is essential in CAB surgery patients because severe postoperative pain increases the risks for cardiovascular and thromboembolic complications, pneumonia, delays postoperative rehabilitation, and decreases function and health-related quality of life (Liu et al., 2007). One of the major concerns is that severe acute postoperative pain is associated with an increased risk for persistent pain 12 months after surgery. Data indicate that the longer a patient has severe postoperative pain, the higher the risk for chronic postsurgical pain (Lahtinen et al., 2006).

Early postoperative analgesia after CAB surgery is based on opioid analgesics. Acetaminophen (paracetamol) is often included as a part of a multimodal approach (Lahtinen et al., 2002; Van Driest et al., 2018), but non-steroidal anti-inflammatory drugs are contraindicated in the early phase of recovery (Nussmeier et al., 2005). In the early phase after CAB surgery opioid analgesics are commonly administered parenterally, in co-operative patients via an intravenous (IV) patient-controlled analgesia (PCA) pump, as the absorption of compounds given by mouth is unpredictable (Kokki et al., 2018; Valtola et al., 2007). However, opioid administration by mouth is preferred as soon as gastrointestinal function is restored, because the costs of IV PCA medication are rather high, and the PCA pump and IV lines interfere with patient mobility (Porela-Tiihonen et al., 2017).

Oxycodone is a highly effective opioid analgesics, and its use has surpassed that of morphine by several-fold during the last decade in several countries (Kinnunen et al., 2019). Some recent trials have shown that oxycodone administration by mouth is feasible also in CAB patients (Ruetzler et al., 2014). Moreover, novel controlled-release tablet formulations may allow a

twice daily dosing. In healthy young adults a controlled-release oxycodone tablets the fast absorption component comprised 35% of the dose with an absorption half-life of 0.3 h and the slower absorption component comprised 65% of the dose with an absorption half-life of 4.8 h (Smith et al., 2008). In vitro release rate data correlate well with the rate of absorption data of oxycodone from controlled-release tablets in young adults (Mundin et al., 2012). This kind of tablet formulation could be feasible also in CAB patients, but to the best of our knowledge there are no pharmacokinetic (PK) data that show when gastrointestinal function is recovered after CAB to allow opioid administration by mouth.

Postoperative ileus is common after major surgery. Many surgery- and anaesthesia-related factors contribute to delay gastrointestinal transit, and in addition of anaesthetics and perioperative opioids, surgical stress and associated inflammatory reaction may contribute (Berger et al., 2000). Off-pump CAB surgery (OPCAB) is assumed to be associated with less inflammatory reaction by avoiding the use of a conventional extracorporeal circulation (CECC), maintaining pulsatile blood flow, and generally having lesser need for fluid resuscitation during the operation (Parolari et al., 2003). In this study our hypothesis was that the surgical trauma to the body is less after OPCAB surgery than after CAB surgery with CECC, and as a result, the gastrointestinal function is less disturbed and the absorption of oxycodone by mouth from a controlled-release tablet formulation is restored earlier after OPCAB surgery compared to CAB surgery with CECC. To test this hypothesis, we conducted the present PK study where the primary outcome measure was the absorption of oxycodone co-administered with naloxone by mouth on the preoperative and first four postoperative days (PODs) in patients scheduled for CAB with CECC or OPCAB surgery.

5.3 MATERIALS AND METHODS

Patients. The study population consisted of 24 patients, aged between 50 and 73 years, who were scheduled for elective CAB surgery at Kuopio University Hospital, Kuopio, Finland between November 2015 and December 2016.

The patients were provided oral and written information about the trial protocol, and they all provided written consent by the cardiac surgeon (AV). The study protocol was approved by the Research Ethics Committee of the Northern Savo Hospital District, Kuopio, Finland (24 Jan 2012; Ref. 119 // 2011), the Finnish Medicines Agency was notified (Ref. 63 // 2012), and it was registered in the European Clinical Trials Database (Eudra CT: 2011–004894-96) prior to patient enrolment. The study was conducted in accordance with the Declaration of Helsinki and had institutional approval.

All patients between 18 and 75 years of age were included if they had no contraindication to oxycodone or naloxone. Patients who had used oxycodone during the previous week prior to surgery were excluded, as were patients with a previous surgery of the upper gastrointestinal tract, disease or any other condition that could interfere with gastric absorption, respiratory depression with hypoxia and/or hypercapnia, chronic obstructive pulmonary disease, moderate or severe hepatic or renal impairment, or history of opioid abuse. Patients taking concomitant cytochrome P450 3A4 (CYP3A4) inhibitors (such as ketoconazole), CYP3A inducers (such as rifampin), CYP2D6 inhibitors (such as paroxetine), or MAO-inhibitors were also excluded.

Oxycodone administration. Patients arrived at the hospital on the day before surgery. For the preoperative administration, the patients fasted for at least 3 h before the oxycodone-naloxone administration. Each patient was given a controlled-release (CR) oxycodone-naloxone tablet 10/5 mg (Targiniq, Mundipharma, Vantaa, Finland) by mouth with a glass of water (150 mL) between 8 and 10 a.m. After this, they were asked to remain in an upright position for at least 30 min, either sitting on a chair or walking around the ward. Fasting was continued after the test drug administration, and at noon the patients were served a light meal. After surgery the patients were given a CR oxycodone-naloxone tablet 10/5 mg at 7 a.m. for the first seven PODs after an overnight fast and two hours before breakfast was served.

Blood samples. Patients in both the CECC and OPCAB groups were randomized into two arms. In one study arm, postoperative blood samples were collected on POD1 and POD3, and in the other arm, samples were collected on POD2

and POD4. Thus, blood samples were collected for the PK analysis from each subject on three days: on the preoperative day and on two PODs. The randomization was computer generated (www.randomization.com) by the principal investigator (Figure 1).

Blood samples (3 mL) were obtained with an indwelling catheter inserted into an antecubital vein at baseline (before drug administration), and at 0.25, 0.5, 1, 2, 3, 4.5, 6, 9, 12 and 24 hours after the oxycodone-naloxone administration. The baseline sample was obtained before the 7 a.m. administration, and the 24 h sample was obtained before the next 7 a.m. oxycodone-naloxone administration. Blood was collected into EDTA tubes, and plasma was obtained within 60 min of collection by centrifugation at 2100 g for 10 min at +20 °C. The separated plasma was stored at -76 °C until analysis. Arterial blood pressure, heart rate and rhythm, peripheral capillary oxygen saturation (SpO2), respiratory rate, end-tidal CO2 (ETCO2) and adverse effects were recorded after each blood sample. Pain was also evaluated during the blood collection visits, at rest, with coughing and during a deep breath, using an 11-point numeric rating scale (NRS, 0=no pain, 10=most pain). Morphine consumption for rescue analgesia via the IV PCA pump was recorded in 12-h intervals from 7 a.m. to 7 p.m.

Outcome measures. The primary outcome measure was the area under the oxycodone curve from time zero to 24 h calculated with the carry-over subtraction (corrected $AUC_{0\text{-}24}$; see Pharmacokinetic parameters) on the PODs compared to that on the preoperative day. The secondary outcome measures were the observed AUC0-24 and peak concentration (C_{max}), time to peak concentration (tmax) and terminal half-life ($t_{½}$). For the clinical outcome measure we used pain scores, the consumption of IV PCA morphine for rescue analgesia and adverse events (AE).

Anaesthetic management and extracorporeal circulation. Before surgery, the patients received premedication by mouth: diazepam 0.25 mg/kg up to 20 mg. Nitrides, beta-blockers, statins, cortisone, and medication for chronic pulmonary diseases were given from their drug list. A standardized anaesthesia protocol was used for each patient. Anaesthesia was induced with

intravenous midazolam, sufentanil, propofol and pancuronium. Anaesthesia was maintained with propofol infusion, and sufentanil and pancuronium boluses i.v. Sevoflurane was added if the patient was hypertensive. Customized perfusion sets were used in the CECC group as previously described (Kokki et al., 2018).

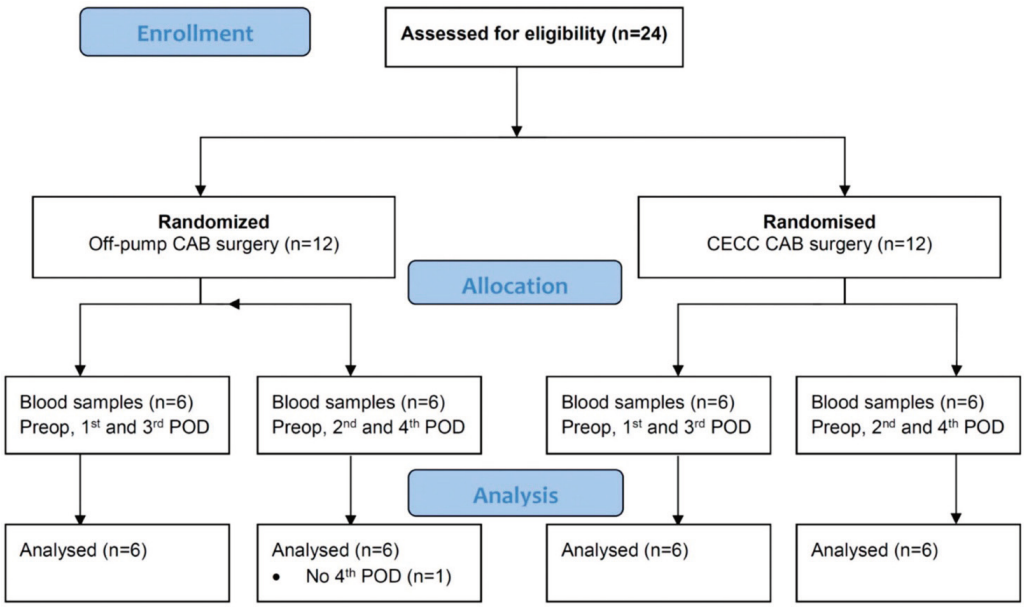


Figure 1. Flow Chart. CECC=conventional extracorporeal circulation; OP-CAB=Off-pump coronary artery bypass surgery; PREOP=preoperative day; POD=postoperative day.

Postoperative pain. Each patient was provided with multimodal postoperative pain management. In addition to seven daily single dose oxycodone-naloxone CR 10/5 mg tablets administered at 7 a.m., the patients received acetaminophen 1 g IV or by mouth three times per day. Regarding rescue analgesia, for the first five PODs, the patients had an IV PCA pump with morphine, single dose 2 mg, lock-out time 10 min, maximum dose 20 mg/4 hours. For patients with meaningful pain, indicated by a pain score >3/10 at rest or >5/10 during coughing or a deep breath, nurses could administer 5

mg IV morphine. Following the study period, the patients were prescribed acetaminophen/codeine 500/30 mg tablets to be used up to 8 tablets/24 hours as required.

Plasma oxycodone and metabolites concentrations. Oxycodone and metabolites concentrations were analysed with an ultra-performance liquid chromatography mass spectrometry system in three patches at Admescope Ltd., Oulu, Finland as previously described in detail (Kokki, et al., 2017). The linear calibration ranges (ng/mL) were fitted as follows: oxycodone 0.02-500, oxymorphone 0.05-200, noroxymorphone 0.1-500, and noroxycodone 0.2-200. Accuracies were between 84-125% at the lowest limit of quantification (LLoQ) and 83-112% above the LLoQ. Precisions were 0.6-17% over the entire range of calibration. All concentrations of oxycodone and its metabolites are reported as free bases.

Pharmacokinetic parameters. The AUC_{0-24}, C_{max}, t_{max}, $t_{1/2}$, and terminal elimination rate constant (Kel) were determined using noncompartmental analysis with Phoenix WinNonlin version 6.3 software (Certara, Princeton, NJ, USA). The observed AUC_{0-24} was calculated using the linear-up and log-down trapezoidal rule, and the carry-over concentration from the previous dose at time zero (C_0) was used as such without any subtraction. The K_{el} and $t_{1/2}$ were determined only when there was a clear log-linear terminal phase.

The carry-over corrected AUC_{0-24} was calculated assuming an exponential decline in the carry-over concentration:

$$\text{Corrected } AUC_{0-24} = \text{Observed } AUC_{0-24} - (C_0 - C2_{4(calc)})/Kel$$

$$C_{24(calc)} = C_0 \times \exp(-K_{el} \times 24 \text{ h})$$

Where $C_{24(calc)}$ is the calculated carry-over concentration at the last sampling time (24 h). In this correction K_{el} was taken from the same dosing event of the individual patient when available, and otherwise from the previous studied dosing event of the same patient.

Pharmacokinetic modelling. A 2-compartment PK model with a lag-time, first-order absorption and first-order elimination was used to describe oxycodone disposition. The model was parameterised in terms of CL (L/h/70 kg), V (L/70

kg), intercompartmental CL (Q, L/h/70 kg), absorption half-life (tabs, h) and absorption lag-time (tlag, h). The absorption lag-time was used to quantify the delay in oxycodone-naloxone controlled-release tablet absorption after cardiac surgery. Data were pooled with those available after in patients given the intravenous formulation after laparotomy (Piirainen et al., 2019) and urological procedures (Kokki et al., 2012; Lamminsalo et al., 2019) to make an estimate of the relative oral relative bioavailability (F). Parameter estimates were scaled using theory based allometry to a 70 kg total body weight individual.

$$Fsize = \left(\frac{WT}{70}\right)^{EXP}$$

Where Fsize is a variable describing the fractional difference from a standard adult weighing 70 kg e.g., CL. EXP describes the allometric exponent; ¾ for functional processes such as CL, 1 for volumes and ¼ for parameters such as half-life which are dependent on the ratio of V over CL. Absorption was assumed independent of size.

Absorption on POD1 was slow and this was quantified by adding an additional factor to account for this delay (Fabs)

$$Tabs = Tabs_{STD}\ x\ Fabs$$

Lag time (Tlag) was also prolonged after cardiac surgery but returned to preoperative values over the 5- day study period. This was quantified using an additional factor (Flag) and a recovery half-time (LagT)

$$Tlag = Tlag_{STD}\ x\ Flag\ x\ e^{-POD\ x\ {Log(2)}/{LagT}\ x\ \left({WT}/{70}\right)^{1/4}}$$

Population parameter estimates were obtained using mixed effects models with ADVAN4 TRANS4 (NONMEM 7.4, ICON Development Solutions, Ellicott City, MD, USA) with first-order conditional estimation and a convergence criterion set to 3 significant digits. Population parameter variability (PPV) was described using an exponential model for the random effect variables (η); these variables were assumed to have a mean of zero and variance denoted by ω^2.

$$P_i = P_{TV}\ e^{\eta i}$$

Where P is the parameter (e.g., CL) for the ith individual, PTV is the typical value for that parameter and η is the random effects variable. Between

occasion variability for CL, V and bioavailability (F) was added to the model because oral oxycodone was administered daily for seven postoperative days. Population parameter variability comprises both between subject variability (BSV) and between occasion variability (BOV); BOV was estimated for CL, V1 and F.

Residual unidentified variability (RUV) was accounted for using a combined residual error model (consisting of additive and proportional error terms) for oxycodone PK. BSV in the residual error model was estimated for each observation. Estimates of the proportional (θ_{RUV_CV}) and additive (θ_{RUV_SD}) residual error parameters were obtained. The population parameter variability of the RUV (η_{PPV_RUV}) was also estimated:

$$SDij = \sqrt{\left(\left(Obs_{ij}.\theta_{RUV_{CV}}\right)^2 + \left(\theta_{RUV_{SD}}\right)^2 \right)}.e^{\eta PPV_{RUV\ i}}$$

Where OBS_{ij} is the observation (oxycodone plasma concentration) in the i^{th} individual at the j^{th} time. Individual predictions of concentration were calculated using the following equation with the random effects (ε) fixed to 1.

$$Y = Obs_{ij} + SDij\ .\varepsilon$$

Model selection. The decrease in objective function value (OBJ; [-2log likelihood]) was used as a guide during the model building process, with a lower OBJ within nested models indicating a superior model. Model selection was also based on inspection of prediction corrected visual predictive check (PC-VPC) plots (Bergstrand et al., 2011) and confidence intervals surrounding parameter estimates obtained by bootstrapping. Bootstrap methods provide a means to evaluate parameter uncertainty. Parameter medians and their associated 95% confidence intervals were obtained after 100 bootstrap replications.

Statistical analysis. No formal sample size calculation was performed but 24 patients was assumed to provide sufficient data on PK after CAB surgery. Statistical analysis was performed with SigmaPlot version 13.0 software (Systat Software, Inc., San Jose, CA, USA). Between-group differences in the preoperative day AUC_{0-24}, C_{max}, and $t_{1/2}$ values were analysed with the Kruskall-Wallis test, and between-day differences in the AUC_{0-24} and C_{max} values within

each group were analysed with the Friedman test. Tukey's test was used in all pair-wise comparisons. Differences were regarded as statistically significant if the P-value was less than 0.05. Data are expressed as the number of cases and median with minimum and maximum values where appropriate.

5.4 RESULTS

Patient characteristics are presented in Table 1. The groups were similar regarding sex, age, and body mass index. There were no blood samples for one subject in the OPCAB group on POD4. Most subjects had carry-over concentration from the previous dose. The median oxycodone C_0 on POD1 was 0.07 [0.0-0.15] ng/mL, POD2 1.8 [0.0-5.0] ng/mL, POD3 1.6 [0.41-5.1] ng/mL and POD4 1.0 [0.39-3.4] ng/mL, respectively.

Table 1. Patient characteristics.

Parameter	Conventional extracorporeal circulation groups		Off-pump groups	
	Samples on POD1 and POD3 $n=6$	Samples on POD2 and POD4 $n=6$	Samples on POD1 and POD3 $n=6$	Samples on POD2 and POD4[h] $n=6$
Sex: male/female	6/–	5/1	6/–	5/1
Age, years	63 [57–73]	61 [50–73]	66 [59–72]	66 [56–70]
Height, m	1.73 [1.63–1.83]	1.72 [1.71–1.82]	1.75 [1.70–1.84]	1.78 [1.61–1.82]
Weight, kg	86 [60–102]	93 [85–99]	81 [65–98]	81 [65–104]
BMI, kg/m^2	27.6 [22.4–34.9]	30.4 [29.1–32.4]	25.8 [21.2–33.7]	25.2 [22.2–35.0]

Data are presented as the number of cases or median [minimum – maximum].
Abbreviations: POD, postoperative day; BMI, body mass index.

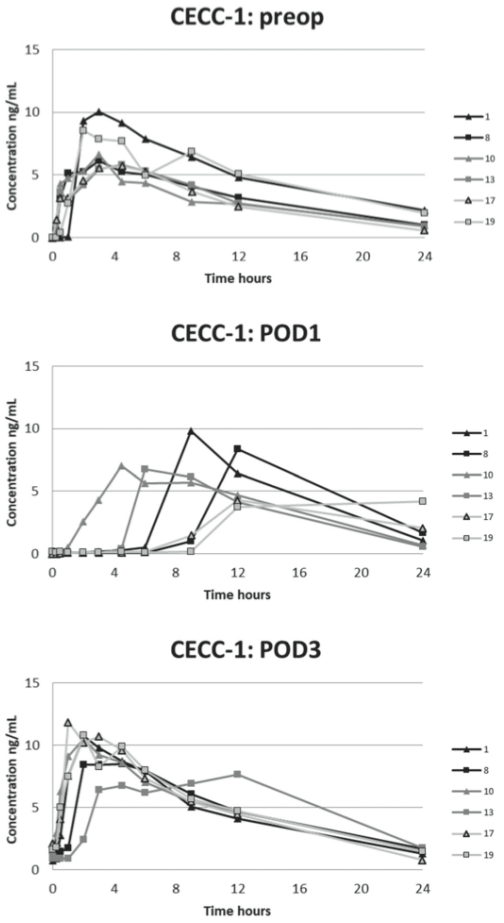


Figure 2. Plasma concentrations of oxycodone in the CECC-group with blood samples in the preoperative, and 1st and 3rd postoperative days.

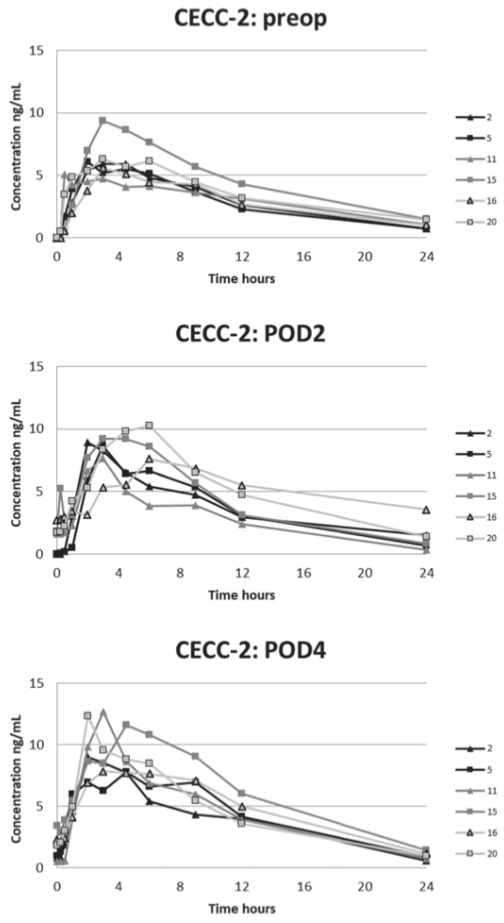
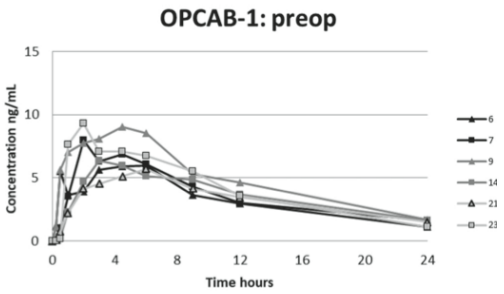
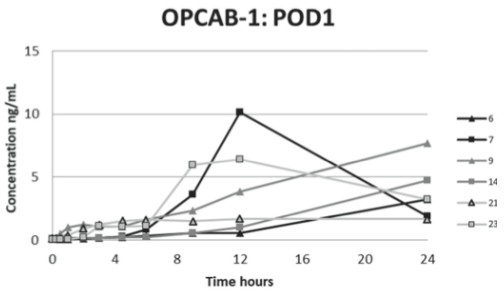


Figure 3. Plasma concentrations of oxycodone in the CECC-group with blood samples in the preoperative, and 2nd and 4th postoperative days.

The plasma oxycodone concentration curves for each patient are presented in Figures 2-5. On POD1 oxycodone absorption was markedly delayed in five of six patients after CECC surgery and in all six patients after OPCAB surgery. On POD1 the median of t_{max} after CECC was 630 [range, 270-1420] minutes and after OPCAB 1020 [720 -1410] minutes, respectively. These values were substantially longer than the preoperative values, t_{max} before CECC was 180 [30-270] minutes and before OPCAC 180 [60-360] minutes (Table 2).





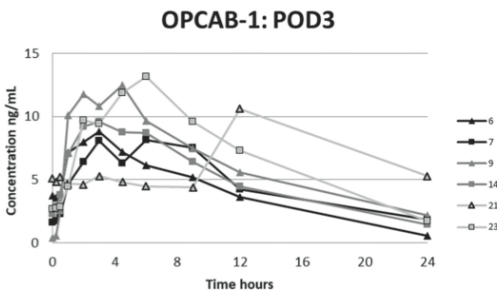
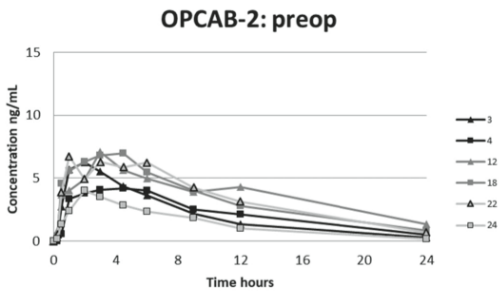
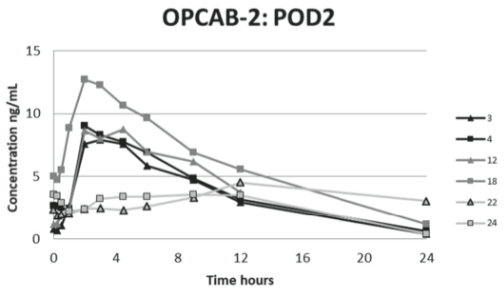


Figure 4. Plasma concentrations of oxycodone in the OPCAB-group with blood samples in the preoperative, and 1st and 3rd postoperative days.





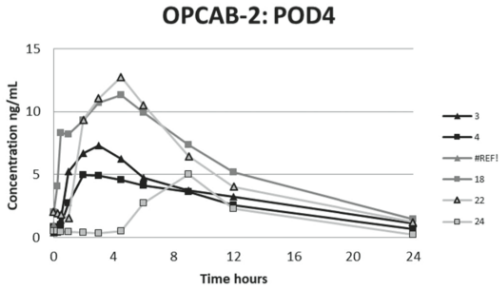


Figure 5. Plasma concentrations of oxycodone in the OPCAB-group with blood samples in the preoperative, and 2nd and 4th postoperative days.

Table 2. Pharmacokinetic parameters for 10 mg oxycodone hydrochloride (9.0 mg free base) after coronary artery bypass surgery in the different treatment groups.

Group	Study day	n	AUC_{0-24} [a] (ng·min/mL)	Corrected AUC_{0-24} [b] (ng·min/mL)	C_{max} [a] (ng/mL)	t_{max} (min)	$t_{1/2}$ (min)
1 (CECC)	Preoperative	6	4250 [3590–6570]	4250 [3590–6570]	6.4 [5.7–10.0]	180 [120–270]	387 [299–481]
	POD1	6	3650 [2760-4550]	3620 [2760–4490]	6.9 [4.2–9.8]	630 [270–1420]	–
	POD3	6	7060 [6450-7270]§§	6130 [5610–6800]§	10.6 [7.7–11.8]*,§	120 [60–720]	437 [376–475] (n = 5)
2 (CECC)	Preoperative	6	3830 [3560-6070]	3830 [3560–6070]	6.0 [5.1–9.4]	180 [30–180]	394 [313–496]
	POD2	6	5600 [3790-7250]	4960 [3140–6070]	8.8 [7.6–10.3]	180 [120–360]	346 [286–968]
	POD4	6	6220 [5270-8610]*	5500 [4920–6990]	10.3 [7.8–12.7]*	180 [120–270]	330 [293–348]
3 (OPCAB)	Preoperative	6	4560 [4280-6480]	4560 [4280–6480]	7.2 [5.7–9.3]	225 [120–360]	417 [378–531]
	POD1	6	3740 [1390-5400]	3690 [1360–5320]	5.6 [1.7–10.2]	1020 [720–1410]	–
	POD3	6	8000 [5620-9520]§§	5990 [3990–8330]§	10.1 [8.1–13.2]§	315 [180–720]	462 [311–463] (n = 5)
4 (OPCAB)	Preoperative	6	3720 [1930-4870]	3720 [1930–4870]	6.5 [4.0–7.1]	150 [60–270]	309 [244–497]
	POD2	6	4570 [3370-8570]	4030 [2100–5990]	8.4 [3.6–12.7]	230 [120–720]	333 [263–394] (n = 4)
	POD4	5	4640 [2190-8170]	4410 [2040–7150]	7.3 [5.0–12.8]	270 [120–540]	374 [195–472]

Data are presented as the median [minimum–maximum] (n for $t_{1/2}$ if different from the group size).
[a]Based on the observed concentrations, [b]the carry-over from the previous doses were subtracted as described in Materials and methods. Abbreviations: POD, postoperative day; CECC, conventional extracorporeal circulation; OPCAB, off-pump coronary artery bypass surgery. Significances: $^{*}p < .05$ vs. Preoperative day; $^{\S}p < .05$ vs. POD1; $^{\S\S}p < .01$ vs. POD1.

Table 3. Peak concentrations of main oxycodone metabolites in plasma.

Group	Study day	C_{max} (ng/mL)		
		Noroxycodone	Oxymorphone	Noroxymorphone
1 (CECC)	Preoperative	6.7 [5.0–10.4]	0.10 [0.07–0.15]	1.3 [0.5–3.1]
	POD1	6.3 [2.7–12.5]	0.12 [0.10–0.19]	1.5 [0.7–1.9]
	POD3	6.0 [3.5–10.1]	0.23 [0.13–0.42]	1.3 [0.8–3.3]
2 (CECC)	Preoperative	7.0 [4.6–8.9]	0.13 [0.0–0.18]	1.0 [0.5–1.5]
	POD2	6.0 [3.2–11.9]	0.21 [0.0–0.30]	1.4 [0.27–1.8]
	POD4	6.3 [2.7–12.5]	0.12 [0.10–0.19]	1.5 [0.7–1.9]
3 (OPCAB)	Preoperative	6.5 [4.5–11.8]	0.18 [0.0–0.26]	1.9 [0.27–3.0]
	POD1	5.3 [1.7–6.8]	0.14 [0.0–0.23]	1.1 [0.18–1.9]
	POD3	5.0 [2.5–9.9]	0.39 [0.0–0.86]	2.1 [0.5–2.9]
4 (OPCAB)	Preoperative	8.9 [4.6–10.4]	0.14 [0.0–0.29]	1.6 [0.27–3.1]
	POD2	9.4 [2.3–17.5]	0.18 [0.0–0.54]	1.7 [0.27–3.8]
	POD4	5.3 [2.5–9.2]	0.28 [0.0–0.69]	1.4 [0.45–2.0]

Data are presented as the median [minimum–maximum].
Abbreviations: C_{max}, peak concentration; POD, postoperative day; CECC, conventional extracorporeal circulation; OPCAB, off-pump coronary artery bypass surgery.

The corrected AUC_{0-24} on the PODs did not differ statistically from the preoperative values (Table 2). However, the corrected AUC_{0-24} and the observed AUC_{0-24} and C_{max} were all higher on POD3 compared with those on POD1 after CECC (group 1) and OPCAB surgery (group 3), respectively. Additionally, C_{max} on POD3 and POD4 was higher than the preoperative value after CECC surgery (groups 1 and 2), as was the observed AUC_{0-24} on POD4 compared with the preoperative value (group 2).

The median observed AUC_{0-24} on POD3 and POD4 were 62-75% higher than the preoperative value in groups 1-3 and 25 % higher in group 4, respectively

(Table 2). This observed accumulation after the surgery was markedly higher than the theoretical 7 % steady-state accumulation calculated with the mean Kel of 0.112 (SD 0.025) 1/h (n=24) on the preoperative day [1/(EXP(-0.112 1/h × 24 h) = 1.07]. A similar trend was seen in C_{max}.

Noroxycodone was the main metabolite and oxymorphone and noroxymorphone were detected only in low concentrations (Table 3).

Table 4. Oxycodone population pharmacokinetic parameter estimates.

			PPV (%)	
Parameter	Estimate	95%CI	BSV	BOV
V1 (L/70 kg)	134	90.9, 157	176	70.9
V2 (L/70kg)	81.9	72.3, 105	83.6	
CL (L/h/70 kg)	43.3	38.5, 49.5	37.0	32.1
Q (L/h/70kg)	155	151, 182	86.7	
Relative bioavailability	0.53	0.48, 0.60	56.6	
tlag (hours)	0.27	0.25, 0.33	–	
Flag	11.8	10.1, 15.1	–	
LagT (days)	1.25	1.2, 1.4	–	
tabs (hours)	1.55	1.4, 2.2	–	
Fabs	3.91	2.6, 4.6	–	
RUV additive (ng/mL)	0.082	0.035, 0.089	η_{PPV_RUV} 0.44	
RUV proportional (%)	21.4	19, 33	–	

Parameter estimates are presented as the medians.
Abbreviations: V, volume of distribution; CL, clearance; Q, intercompartmental clearance; tlag, absorption lag-time; Flag is a scaling parameter applicable to tlag on POD1; tabs, absorption half-time; Fabs is a scaling parameter applicable to tabs on POD1; RUV, residual unidentified variability; CI, confident interval; PPV% (PPV%=$\sqrt{}$variance × 100), population parameter variability; BSV, between subject variability; BOV, between subject variability.

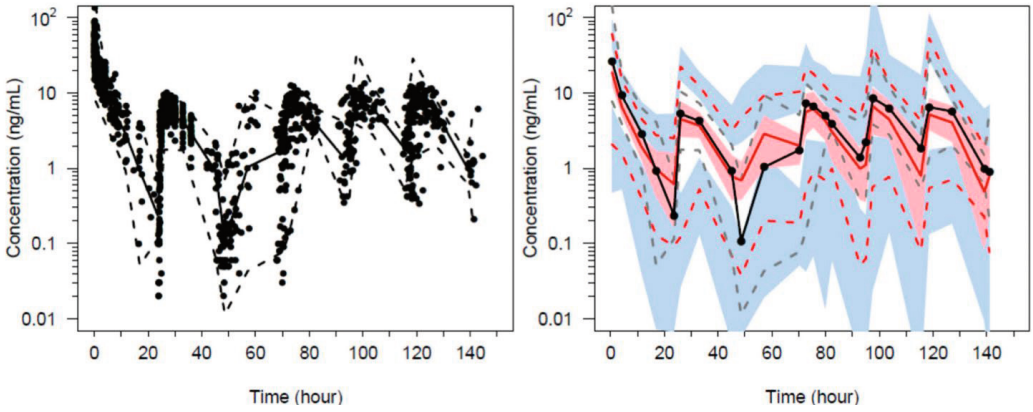


Figure 6. Predicted-corrected visual predictive check (PC-VPC) for the final oxycodone PK model. Plots show median (solid) and 90% intervals (dashed lines). The y axis is presented on a logarithmic scale. Left hand plot shows all prediction corrected observed oxycodone concentrations. Right hand plot shows prediction corrected percentiles (10%, 50%, and 90%) for observations (grey dashed lines) and predictions (red dashed lines) with 95% confidence intervals for prediction percentiles (median, pink shading; 5th and 95th blue shading).

Population parameter estimates for the oxycodone 2-compartment analysis are shown in Table 4 and PC-VPC for the final oxycodone PK model in Figure 6. Data for PK analyses comprised of 1072 oxycodone plasma concentrations. Absorption was slow on POD1 (Fabs= 3.91) as was the lag time (Flag=11.8) that rapidly resolved (lagT=1.25 days). We were unable to define a difference in these parameter estimates in those who had surgery with cardiopulmonary bypass and those without cardiopulmonary bypass.

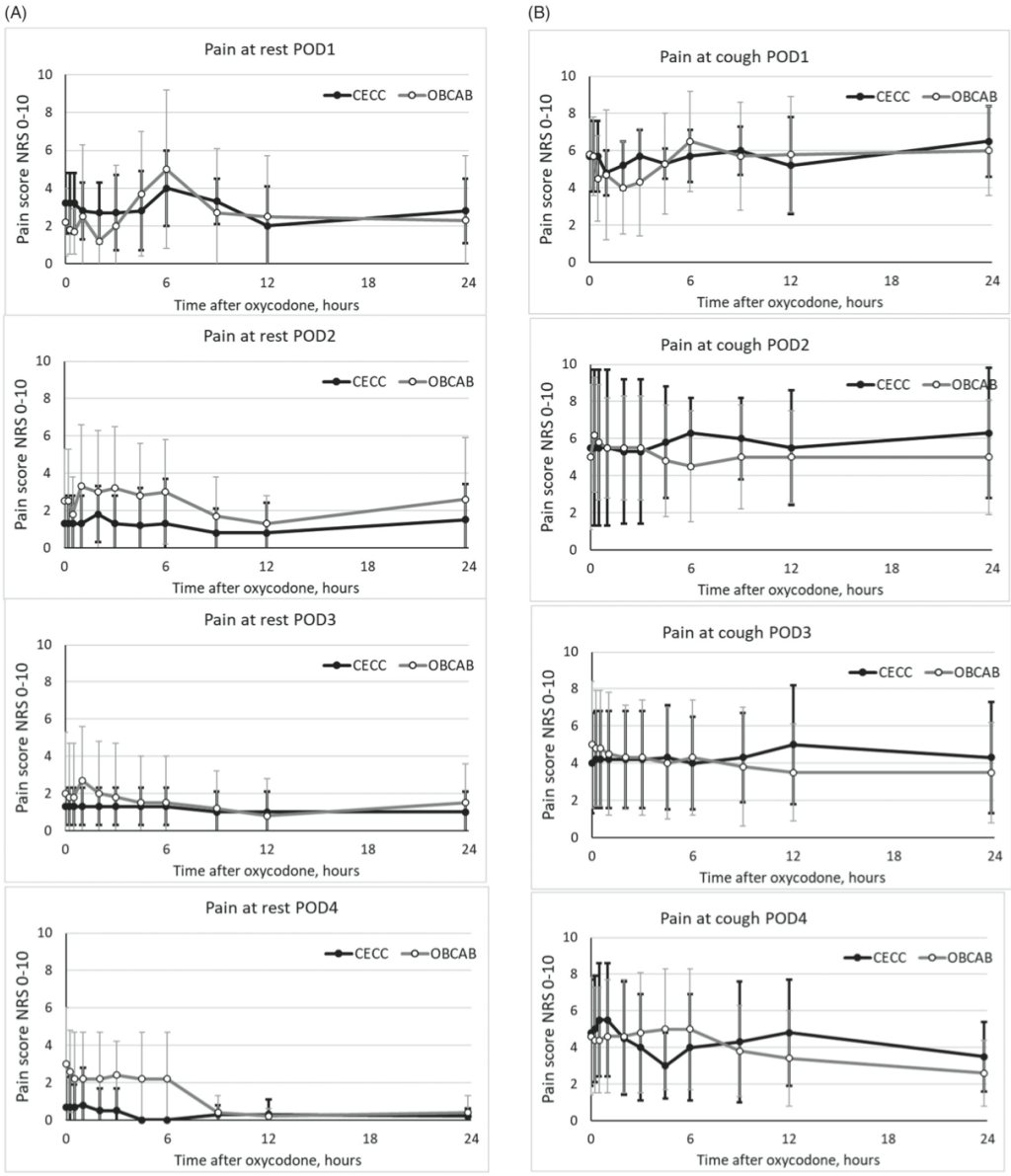


Figure 7. Pain scores in the two groups at rest (A) and with cough (B) in the two groups. Data are presented as the mean and standard deviation.

Pain scores were similar in patients after CECC and OPCAB surgery (Figure 7 A and B). Morphine consumption via an IV PCA pump was similar among patients after CECC and OPCAB surgery. However, the between-subjects variation was large; after CECC surgery, it was between 59 and 199 mg/96 hours, and after OPCAB surgery, it was between 69 and 324 mg/96 hours (Figure 8).

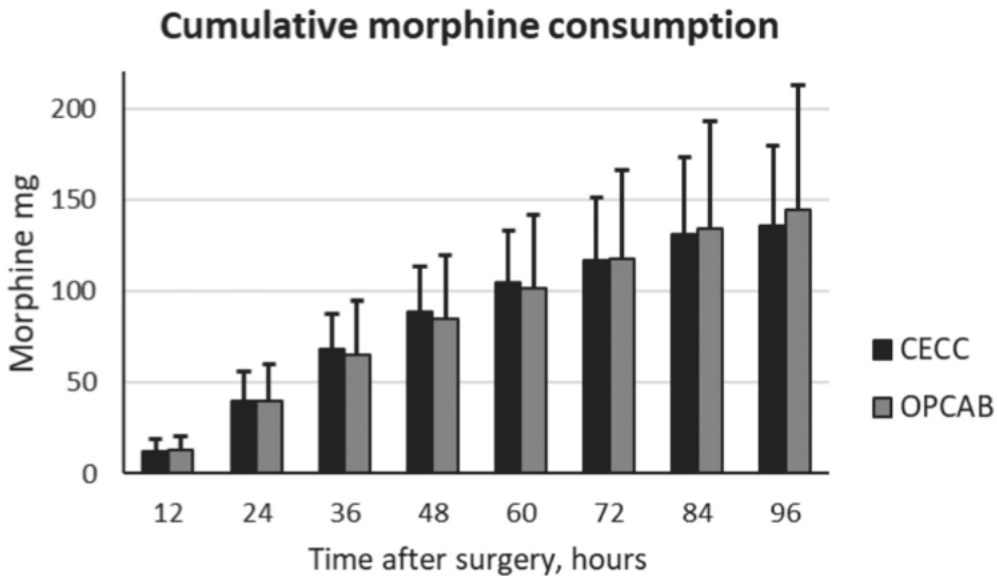


Figure 8. Morphine consumption via IV PCA pump in the two groups. Data are presented as the mean and standard deviation.

Twenty-one subjects (11 in the CECC group and ten in the OPCAB group) developed a total of 38 AEs (n=18 and n=20 in the two groups, respectively), most of which were probably opioid-related. Two patients had low SpO2 (86 and 89% at 2 and 6 hours), and one had a low respiratory rate (7/min at 9 hours) after preoperative oxycodone-naloxone administration, but all had normal $ETCO_2$. They were given supplementary oxygen and recovery was uneventful thereafter. Postoperatively, there were no cases of low respiratory rates or high $ETCO_2$ values, but eight subjects in each group had at least

a single SpO2 value below 90% (the lowest recorded value was 81%) and thus, were given oxygen supplementation. Eight subjects had constipation, four were somnolent, three had postoperative atrial fibrillation, two were confused and two had nausea.

5.5 DISCUSSION

In contrast to our hypothesis, the data of the present study suggest that the recovery of gastrointestinal function and the absorption of ingested oxycodone is similar after OPCAB surgery and after CAB surgery with CECC. The novelty of this study is that the observed and corrected AUC_{0-24} and C_{max} of oxycodone equalled or exceeded the preoperative values on POD2 in four out of six patients in both groups, and it was similar to or higher than the preoperative values on POD3 and POD4 in each patient. Oxycodone-naloxone CR tablets are not recommended within the first 12–24h postoperatively (FIMEA, 2019; Kokki et al., 2012). Consistent with that, our data indicate that the appropriate time to start oxycodone administration by mouth is on POD2 in most patients with CAB surgery.

Oxycodone absorption was markedly delayed in most patients on POD1 after CAB surgery. The median tmax values on POD1 were 3- to 6-fold longer than those observed preoperatively or on POD2-POD4. We assume that this was caused by a slow gastric emptying time in the early phase of recovery. Oxycodone is absorbed mainly in the small intestine, and most of the oxycodone is absorbed before the tablet reaches the colon (Kokki et al., 2012). Following surgery, gastrointestinal track motility is impaired because of an ileus, pseudo-obstruction, and the use of pharmacologic agents. Opioids per se also delay gastric emptying (Berger et al., 2000; Smith et al., 2011). However, the co-administration of naloxone reduces the oxycodone induced slowing of gastrointestinal transit (Smith et al., 2011). Our data suppose that this was also the case in the present study except on POD1, as the rate and extent of oxycodone absorption had already returned to similar or higher than the preoperative values in most patients on POD2. To support the early recovery of gastrointestinal function in the present study, on POD2, POD3 and POD4,

the PK data of oxycodone-naloxone CR tablets were dose-proportional to those reported in healthy subjects (Smith et al., 2011; Smith et al., 2008) and those found in our earlier study with oxycodone CR tablets in elderly patients undergoing cystoscopy under regional anaesthesia (Kokki et al., 2012).

On POD1 oxycodone absorption was markedly delayed in eleven of twelve subjects. There were no differences in $AUC_{0–24}$ and Cmax between the preoperative day and POD1, but the estimated $AUC_{0–24}$, Cmax and tmax values on POD1 are likely to be somewhat inaccurate due to the delayed absorption and the fact that blood samples were not collected during the night (the last two samples were taken at 12 and 24 h). However, even with the inaccurate estimate of $AUC_{0–24}$ on POD1, it is clear that $AUC_{0–24}$ on POD3 was significantly higher than on POD1 as the median observed $AUC_{0–24}$ was approximately twofold. The most likely explanation is that a portion of the doses given on POD1 and POD2 was absorbed with a significant delay leading to an increased drug exposure on POD3 that clearly exceeded the theoretical accumulation factor calculated from the preoperative day data (7% increase). A plausible mechanism is the surgery- and opioid-related pylorus closure (Berger et al., 2000). The delayed absorption after the surgery would also explain the 23–75% increase in median observed $AUC_{0–24}$ on POD2, POD3 and POD4 compared with the preoperative day, respectively, even though a statistical significance was found only in the CECC group 2 between POD4 and the preoperative day.

A 2-compartment PK model with a lag-time, first-order absorption and first-order elimination was used to describe oxycodone disposition and parameter estimates align with findings from other studies where 2-compartment models have been used to describe oxycodone disposition. Use of a 2-compartment model allowed comparison with estimates published by others (Kokki et al., 2012; Lamminsalo et al., 2019; Piirainen et al., 2019). Cardiac surgery is associated with profound changes to physiology (e.g., altered volume of distribution and changes in plasma protein concentrations), changes in gut, renal and hepatic activity; these factors can alter perioperative drug PK (Hall, 1991; Mets, 2000). We assume these factors contribute to the high between subject variability observed on V1, V2 and Q and the BOV on V1. The lag in absorption is likely caused by delayed gastric emptying following cardiac

surgery. There was an increase in the absorption half-time on POD1. The lag time was also prolonged on POD1 (Flag 1⁄4 11.8) but recovered rapidly with a half-time (LagT) of 1.25days. This is likely attributable to the return of normal gut function in the days following cardiac surgery.

In the present study two subjects had nausea, but none had postoperative vomiting, and eight out of the 24 patients had constipation. Opioid induced bowel dysfunction can affect oxycodone absorption by several mechanisms.

Postoperative nausea and vomiting are common complaints and the use of perioperative use of opioids is a known risk factor for postoperative vomiting. If a patient vomits within the first hour after oxycodone CR tablet intake, it is unlikely that any meaningful amount of oxycodone has been absorbed. However, it is not recommended to repeat or to take an extra dose. Pain management should just follow regular dosing schedule (FIMEA, 2019). Since oxycodone is used for postoperative pain, patients should have rescue analgesia available for breakthrough pain in any case. Opioid induced bowel dysfunction inhibits gastric emptying and peristalsis in the gastrointestinal tract. The first may result in delayed absorption of oxycodone due to delayed emptying (see above). Slowing intestinal peristalsis may also increase the retention time of oxycodone in small intestine (Berger et al., 2000). A prolonged transit in small intestine could have been one mechanism for higher extent of oxycodone absorption of oxycodone most evident on POD3 (Mundin et al., 2012). Other mechanism could also be involved, e.g., increased absorption of water, less gastric secretion and saliva production induced by oxycodone. Diet does not affect the PK of CR oxycodone tablets (FIMEA, 2019; Kinnunen et al., 2019; Smith et al., 2008).

Our data are consistent with data that were previously reported in CAB surgery patients who were administered postoperative metoprolol tablets (Kokki et al., 2018; Valtola et al., 2007). The data of those two studies showed that the rate and extent of metoprolol absorption after administration by mouth was markedly decreased in the early phase after CAB surgery. Similar to the results found in the present study, it was shown that the use of CECC in CAB surgery or performing OPCAB surgery does not affect the postoperative absorption of metoprolol, i.e., the restoration of gastrointestinal function.

The absorption of oxycodone from an oxycodone-naloxone CR tablet is biphasic. The initial absorption occurs from the surface of the tablet, following the dissolution of the film coating. The remaining drug substance is absorbed from the matrix, either by dissolution or diffusion from or through the tablet matrix. PK models indicate that the faster absorption accounts for one-third and the slower absorption two-thirds of the total absorption, so that 95% of oxycodone absorption in completed at 24h after administration (Kokki et al., 2012; Mandema et al., 1996). Consistent with that finding, in the present study, most patients had substantial trough concentrations on POD2 and POD3 at 24 h after the previous dose, but on POD1, 48 h after the previous dose, trough concentrations were low (0.17ng/mL or lower). A second peak could be explained, in theory, by enterohepatic circulation. It is not known whether oxycodone undergoes enterohepatic circulation. Morphine and its active metabolites are assumed to undergo substantial enterohepatic circulation and this may account a second peak in serum concentration over time after administration by mouth and increase in relatively potency of repeated doses compared to that of single morphine dose by mouth (Hasselström et al., 1993). The main route of oxycodone excretion is the kidney, 8% as oxycodone and 65% as metabolites, and oxycodone undergoes some first-pass metabolism in the intestine (Kinnunen et al., 2019). Biliary excretion of oxycodone in humans is not known, but animal data indicate that small amount of oxycodone and its metabolites are excreted in faeces (Ishida et al., 1982).

In the present PK study oxycodone-naloxone CR tablets were administered 24-hourly. In clinical practice, oxycodone-naloxone CR tablets are intended for scheduled administration, and the usual starting dose for opioid-naïve patients is 10/5 mg 12-hourly (FIMEA, 2019). In healthy volunteers, steady-state PK of oxycodone CR tablets is achieved after two or three 12- hourly doses (Reder et al., 1996). In the present study, the median of the oxycodone C12 ranged between 3.7 and 5.2ng/mL on POD2, POD3 and POD4. Thus, a higher oxycodone accumulation would have been seen and higher trough concentrations observed if oxycodone-naloxone CR tablets were administered 12-hourly.

In consistent to PK data showing negligible absorption of oxycodone by mouth on POD1, morphine consumption to comfort was similar high to that reported earlier after CAB surgery (Lahtinen et al., 2004; Lahtinen et al., 2002; Lahtinen et al., 2008). Thereafter, as PK data of indicate that oxycodone absorption had restored to preoperative values a parallel decline on the need for rescue PCA-analgesia was observed. Postoperative pain was most severe on POD1, but thereafter pain was rather well controlled. On POD2 and thereafter, majority of patients had just mild pain at rest. However, after thoracic surgery dynamic pain, pain provoked by movement, such as deep breathing or coughing, getting out of bed, or walking are more important parameters than pain at rest (Lahtinen et al., 2004; Lahtinen et al., 2002; Lahtinen et al., 2006, 2008). In the present study dynamic pain was modestly well controlled with co-administration of opioid-analgesics and paracetamol. However, the between-subjects variation on dynamic pain scores was large, and in clinical practice these patients should be identified, have more attention and prescribed personalized pain management with adjuvant analgesia techniques and close follow-up in order to minimize the risk of persistent postoperative pain and other postoperative complications (Fletcher et al., 2015; Lahtinen et al., 2006; Liu et al., 2007).

The main limitations in the present study are a small number of subjects and that the postoperative blood samples were obtained on alternate PODs. However, due to logistical reasons, we were not able to enroll more patients. Moreover, it was considered unethical to obtain several blood samples daily. On each of three study days, a total of eleven blood samples were collected for this study, in addition to those collected for the clinical purposes. Another limitation is that allow the data enabled a standard non-compartmental statistical approach only. A modelling-based approach would have been far more informative and allow for robust conclusions and the potential for simulations to explore alternative dosing practices. Building a population PK model was evaluated but the data on POD1 especially were that heterogeneous that the concentration curves could not be reliably predicted or explained with PK model. Thus, the use of non-compartmental statistical approach is justified, and we believe that non-compartmental

data are sufficient to show that administration by mouth on POD1 cannot be recommended in this context (Välitalo et al., 2014).

One of the limitations is that this PK study does not enable us to draw any pharmacodynamic conclusions because there was no control group; each patient was administered oxycodone-naloxone 10/5mg CR tablets 24-hourly, and there were not follow-up data collected after the first postoperative week. However, similar pain scores and postoperative morphine consumption support the contention that bioavailability was similar between both groups. Opioid-induced bowel dysfunction is one of the concerns with taking postoperative opioids. Previously, we showed that even seven days use of oxycodone-naloxone CR tablets administration may prevent the development or reduce the severity of opioid-induced bowel dysfunction without interfering with the analgesic efficacy of oxycodone compared to oxycodone CR tablets. Moreover, it was found that oxycodone-naloxone tablets had a carry-over effect after seven days use of oxycodone two times a day; surveyed two weeks after opioid cessation, bowel function was superior after seven days of taking oxycodone-naloxone tablets compared to oxycodone tablets (Kokki et al., 2017). In the present study the opioid consumption and pain scores were similar or lower compared to our previous studies in similar settings (P. Lahtinen et al., 2004; Lahtinen et al., 2002; Lahtinen et al., 2008). Thus, it is unlikely that naloxone interfered with the analgesic efficacy of oxycodone.

In conclusion, the postoperative bioavailability of oxycodone from oxycodone-naloxone CR tablets seems to be similar after CAB with CECC and after OPCAB surgery. Second, oxycodone administration by mouth is not recommended on POD1 because the absorption is markedly delayed in the majority of patients, but the rate and extent of oxycodone absorption resumed or exceeded the preoperative values on POD2 and beyond. Thus, the appropriate time to start oxycodone administration by mouth is on POD2 in most patients with CAB surgery.

6 STUDY III: INTRANASAL FENTANYL FOR INTERVENTION-ASSOCIATED BREAKTHROUGH PAIN AFTER CARDIAC SURGE-RY

6.1 ABSTRACT

Background: Cardiac bypass surgery patients have early postoperative interventions that elicit breakthrough pain. We evaluated the use of intranasal fentanyl for breakthrough pain management in these patients.

Methods: Multimodal analgesia (paracetamol 1 g three times a day, oxycodone 2–3 mg boluses with a patient-controlled intravenous pump) was used in 16 patients (age 49–70 years, weight 59–129 kg) after cardiac bypass surgery. Intranasal fentanyl 100 µg or 200 µg was used to manage breakthrough pain on the first and third postoperative mornings in a randomized order. Blood samples were collected for up to 3 h after fentanyl administration, pain was assessed with a numeric rating scale of 0–10. Plasma fentanyl concentration was assayed using liquid chromatography-mass spectrometry. Body composition was measured with a bioelectrical impedance device.

Results: Bioavailability of intranasal fentanyl was high (77%), absorption half-time short (< 2 min) and an analgesic plasma concentration ≥ 0.5 ng/mL was achieved in 31 of 32 administrations. Fentanyl exposure correlated inversely with skeletal muscle mass and total body water. Fentanyl analgesia was effective both on the first postoperative morning with chest pleural tube removal and during physiotherapy on the third postoperative morning. The median time of subsequent oxycodone administration was 1.1 h after intranasal fentanyl 100 µg and 2.1 h after intranasal fentanyl 200 µg, despite similar oxycodone concentrations (median 13.8, range 5.2–35 ng/mL) in both fentanyl dose groups.

Conclusions: Intranasal fentanyl 100 µg provided rapid-onset analgesia within 10 min and is an appropriate starting dose for incidental breakthrough pain in the first 3 postoperative days after cardiac bypass surgery.

6.2 INTRODUCTION

Acute pain after cardiac surgery is often severe, and effective pain management is beneficial for recovery. Severe pain increases the risks for postoperative complications, decreases quality of life and function, and delays postoperative rehabilitation (Lahtinen et al., 2006; Liu et al., 2007). In some patients, pain after surgery lasts beyond the natural healing of the tissues and may become chronic. Acute postoperative pain is one of the known modifiable predictors of persisting postoperative pain. The greater the magnitude of acute pain and the longer it lasts, the more likely are patients to have pain at 12 months after cardiac surgery (Fletcher et al., 2015; Glare et al., 2019; Lahtinen et al., 2006). Most patients need a multimodal approach to pain management in the early postoperative period. Opioids comprise a component of multimodal approach (Lahtinen et al., 2006).

Postoperative patients have both constant pain and sudden flares of breakthrough pain. Breakthrough pain is defined as an acute exacerbation of pain that is inadequately controlled by a stable analgesic regime. Breakthrough pain flares are both predictable and unpredictable. Short-acting opioid analgesics are often the primary treatment for this pain, and compounds that have a fast onset, a short duration of action and a convenient administration route are preferred (Mercadante et al., 2016). Breakthrough pain episodes are often predictable in postoperative surgery patients. Predictable triggers for such pain in cardiac surgery patients are, for example, chest tube removal and postoperative physiotherapy; exacerbation of pain is anticipated, and a short duration of pain predicted.

Opioids differ in lipophilicity, opioid receptor binding affinity and intrinsic activity. These features contribute to differences in absorption, onset, potency, and duration of action (Porela-Tiihonen et al., 2017). Fentanyl is a lipophilic opioid, and it has been approved for intranasal transmucosal

administration in patients with cancer with breakthrough pain. Intranasal fentanyl has a reported high bioavailability of 71%, maximum concentration in plasma is reached within 7 min of administration and the duration of action is approximately an hour (Christrup et al., 2008). Intranasal fentanyl has been used also in non-cancer acute pain (Hansen et al., 2012; Kokki et al., 2015). Intravenous (IV) opioid analgesics (e.g., oxycodone) are commonly used after cardiac surgery via a patient-controlled analgesia (PCA) pump as oral absorption of drugs is unpredictable during the first 48 h after surgery (Kokki et al., 2018; Schuitmaker et al., 1999; Valtola et al., 2007; Valtola et al., 2020). However, patient attachment to a PCA pump can limit mobility. Thus, transmucosal administration of fentanyl is an attractive non-invasive alternative for breakthrough pain in the early postoperative period (Brown et al., 2007; Hansen et al., 2012; Kokki et al., 2015; Porela-Tiihonen et al., 2017).

The aim of the study was to evaluate intranasal fentanyl for incidental breakthrough pain in patients after cardiac surgery. Our hypothesis was that chest pleural and mediastinal drainage tube removal and physiotherapy exacerbate pain in cardiac surgery patients and that while intranasal fentanyl 100 µg should be an effective analgesic to control these pain flares, a fentanyl 200-µg dose would provide a longer duration of analgesic action (Christrup et al., 2008). To test this hypothesis, we investigated exposure to fentanyl at two doses, 100 µg and 200 µg, and observed pain during the chest tube removal on the first postoperative morning and during physiotherapy on the third postoperative morning. Intranasal fentanyl absorption pharmacokinetic (PK) parameters were estimated because these characteristics contribute to the speed of onset of analgesia. Body composition was evaluated to assess this as a PK covariate that might have impact on fentanyl concentration.

6.3 MATERIALS AND METHODS

Patients. Study patients were scheduled for elective cardiac bypass surgery with extracorporeal circulation in Kuopio University Hospital, Kuopio, Finland between February, and June 2019. Patients were provided oral and written information about the trial protocol, and they all gave written consent.

The study protocol was approved by the Research Ethics Committee of the Northern Savo Hospital District, Kuopio, Fin land (Ref. 657//2018), the Finnish Medicines Agency was notified (Ref. 62//2018), and it was registered in the European Clinical Trials Database (Eudra CT: 2018-001280-22). The study was conducted in accordance with the Declaration of Helsinki and had institutional approval.

We enrolled patients aged between 18 and 75 years who had no known hypersensitivity to fentanyl or any ingredient in the intranasal pharmaceutical preparation. Patients were excluded if they had moderate or severe renal or hepatic impairment, sleep apnoea, respiratory depression with hypoxia and/or hypercapnia, chronic obstructive pulmonary disease, or a history of opioid abuse. Patients who were treated with drugs known to inhibit or induce cytochrome P450 (CYP) 3A activity or inhibit CYP2D6 activity (e.g., CYP3A4; carbamazepine, imidazole derivatives and macrolide antibiotics; CYP2D6; paroxetine and quinidine) were excluded.

Anaesthetic management and extracorporeal circulation. Patients arrived at the hospital on the day before the surgery. Each patient was interviewed and examined by a cardiac surgeon (AV) to determine eligibility for the study. Body composition was assessed using a bioelectrical impedance device (medical body composition analyser; seca mBCA 515; seca Deutschland, Hamburg, Germany) to determine height, weight, total body water, fat mass, visceral fat, fat-free mass, and skeletal muscle mass.

Before surgery, the patients received oral premedication: diazepam 0.25 mg/kg up to 20 mg. Nitrides, beta-blockers, statins, cortisone, and medication for chronic pulmonary disease were continued if these were existing routine medications. A standardised anaesthesia protocol was used for each patient. Anaesthesia was induced with IV midazolam (median 5 mg; range 3–5), sufentanil and propofol. Cisatracurium was used as a neuromuscular blocking drug. Anaesthesia was maintained with propofol infusion (1532 mg; 1216–2277), and sufentanil (200 µg; 100–250) and cisatracurium (26 mg; 20–38) boluses. Sevoflurane was added if the patient was hypertensive (n = 7, median 0.25 MAC hours, 0.1–1.29). A conventional extracorporeal circulation was used in all surgeries (Kokki et al., 2018).

Postoperative pain management. All patients had a multimodal, postoperative pain management regime. Patients were given paracetamol 1 g three times a day; the first doses were IV and then by mouth starting on the first postoperative day. Rescue analgesia comprised IV oxycodone boluses; the first doses were given by the intensive care unit nurses and on the surgical ward patients used an IV PCA pump with oxycodone; single dose 2–3 mg, lock-out time 10 min, maximum dose 20 mg/4 h. Patients with insufficient pain relief, indicated by a 11-point numeric rating scale score ≥4/10 at rest or ≥6/10 during coughing or deep breathing, were allowed 6–8 mg of subcutaneous oxycodone by nursing staff. Following the study period, i.e., on the fourth postoperative day, the PCA pump was discontinued, and patients were administered an oxycodone-naloxone tablet 10/5 mg by mouth twice a day together with paracetamol 1 g three times a day for the rest of their hospital stay. Cumulative oxycodone consumption for rescue analgesia via the IV PCA pump was recorded before intranasal fentanyl administrations on the first and third postoperative mornings, and during the first 3 h after the fentanyl administrations.

Intranasal fentanyl administration. The pharmaceutical preparation used in this study was Instanyl® (Takeda, Helsinki, Finland) in two strengths, 100 µg and 200 µg of fentanyl. Each patient was given a single dose of both strengths of medication in a blinded randomised sequence. In group 1, patients were administered the first dose of intranasal fentanyl; 100 µg, on the first postoperative morning 10 min before chest tube removal and the second dose, 200 µg, on the third postoperative morning just before physiotherapy, and in group 2, vice versa; 200 µg on the first postoperative morning and 100 µg on the third postoperative morning (see the flow chart in Fig. 1). Intranasal fentanyl was administered to each patient with the patient's head in an upright position during administration, the first dose in the intensive care unit on the first postoperative morning and the second dose at the surgical ward on the third postoperative morning by the same investigator (AV). The hospital pharmacy covered the nasal spray device labelling with an opaque tape and coded the devices to conceal the treatment allocation.

Randomisation was generated with a random organisation generator (www.randomization.com).

Pain intensity assessment and patient monitoring. Pain intensity before and after chest tube removal on the first postoperative morning and before and during physiotherapy on the third postoperative morning was evaluated during the blood collection visits: (i) at rest, (ii) with coughing; and (iii) during a deep breath, using an 11-point numeric rating scale (0 = no pain, 10 = most pain). Arterial blood pressure, heart rate and rhythm, peripheral capillary oxygen saturation, respiratory rate, end-tidal carbon dioxide and adverse effects were recorded after each blood sample (see below). Adverse effects were sought also from patients' medical records.

Blood samples. Blood samples (3 mL) for the drug assay were obtained from a central venous catheter before drug administration, and at 10, 20, 30, 40, 60, 120 and 180 min after fentanyl administration. Blood was collected into EDTA tubes, and plasma was obtained within 60 min of collection by centrifugation at 2100g for 10 min at + 20 °C. The separated plasma was stored at − 76 °C until analysis in a single batch.

Plasma fentanyl and oxycodone concentrations. Fentanyl and oxycodone concentrations were analysed with a Waters Acquity ultra-performance liquid chromatograph combined with a Waters XEVO-TQ-S triple quadrupole mass spectrometry (Waters, Milford, MA, USA) in one single batch (Heikkinen et al., 2015; Kokki et al., 2014). The lower limits of quantification (LLoQ) were 0.004 ng/mL for fentanyl and 0.1 ng/mL for oxycodone. The linear calibration ranges were fitted as follows: fentanyl 0.004–40 ng/mL and oxycodone 0.1–200 ng/mL. Accuracies ranged for both analytes between 93 and 105% at the LLoQ and between 87% and 110% above the LLoQ. The precisions were 0.8–19% over the entire range of calibration. All fentanyl and oxycodone concentrations are reported as free base.

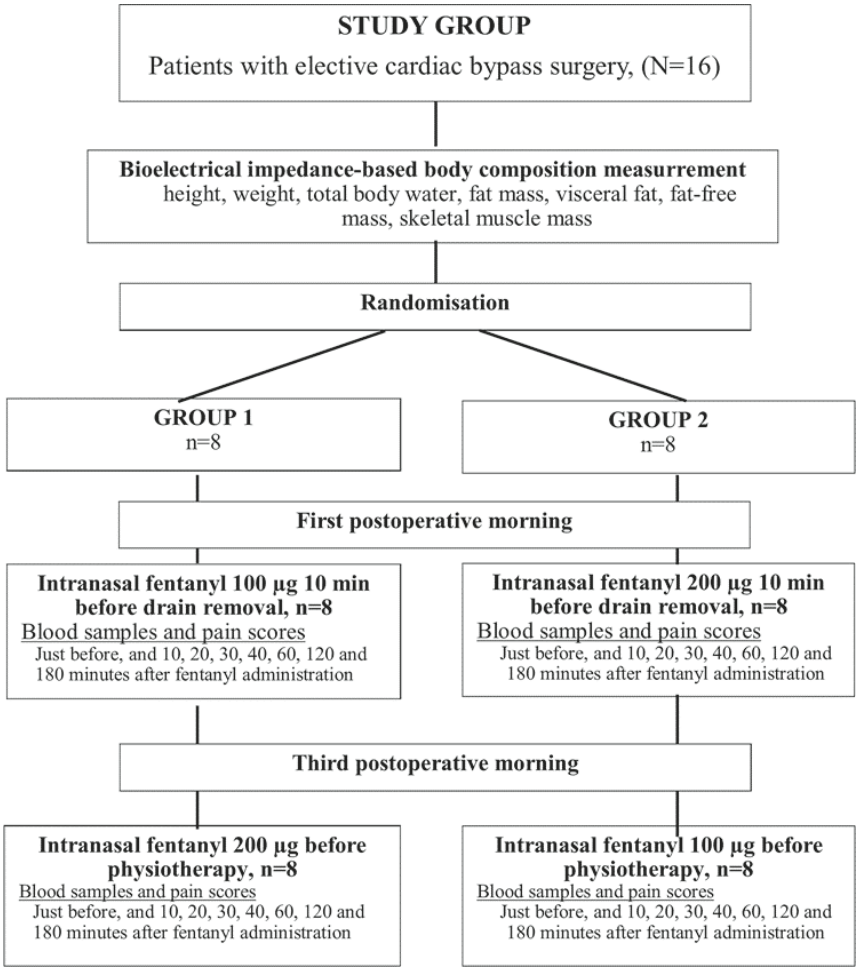


Figure 1. The flow chart of the study.

Pharmacokinetic Modelling. Both non-compartmental and population PK modelling were used. The non-compartmental analysis was performed using Phoenix WinNonlin software version 6.3 (Certara, Prince- ton, NJ, USA). The maximum observed plasma drug concentration (C_{max}), time to C_{max} and area under the plasma concentration–time curve from time zero to the last quantifiable concentration (AUC_{0-180}) were determined. The AUC_{0-180} was calculated using the linear trapezoidal rule. The figures for plasma concentration–time curves were created using the GraphPad Prism version 5 (GraphPad Software Inc., La Jolla, CA, USA). The time period with fentanyl

concentration over 0.5 ng/mL was calculated with a non-compartmental analysis using linear interpolation rule (Phoenix WinNonlin 8.3, Princeton, NJ, USA).

Population parameter estimates were obtained using non-linear mixed-effects models (NONMEM VII; Globomax LLC, Hanover, MD, USA). The population mean parameters, between-subject variance (BSV) and residual variance were estimated using the first-order conditional estimation method using ADVAN 12 TRANS 4 of NONMEM VII. Convergence criterion was 3 significant digits.

The population parameter variability was modelled in terms of random-effect (η) variables. Each of these variables is assumed to have a mean of 0 and a variance denoted by ω2, which is estimated. Population parameter variability comes from two distinct sources: BSV and within-subject variation. If an individual is studied on more than one occasion, then the variability in the occasion-specific individual parameter around the average individual value defines within-subject variation. Within-subject variation should be divided into within-occasion variability and between-occasion variability (BOV) but within-occasion variability for a parameter such as clearance is difficult to estimate. In this study, intranasal fentanyl was given to individuals on two occasions and BOV was estimated. Both BSV and BOV were modelled with an exponential term. We report the estimate of ω for each variability component expressed as a percentage because these quantities are approximate coefficients of variation for a log normal distribution. Residual unidentified variability was described using a combined proportional and an additive residual error model for each observation prediction (ErrPROP, ErrADD).

$$P_i = P_{\text{std}} \times \left(W_i / W_{\text{std}} \right)^{\text{PWR}},$$

Size standardisation. The parameter values were estimated as standardized for a body weight of 70 kg using an allometric model (Anderson et al., 2008).

Where Pi is the parameter in the i^{th} individual, Wi is the weight in the i^{th} individual and P_{std} is the parameter in an individual with a weight W_{std} of 70 kg. The PWR exponent was 0.75 for clearance and 1 for distribution volumes.

Quality of fit. The quality of fit of the PK model to the data was sought by NONMEM's objective function and by visual examination of plots of observed vs predicted concentrations. Models were nested and an improvement in the objective function was referred to the Chi-squared distribution to assess significance, e.g., an objective function change of 3.84 is significant at $\alpha = 0.05$.

Bootstrap methods, incorporated within the Wings for NONMEM program, provided a means to evaluate parameter uncertainty (Efron, 1979). A total of 1000 replications were used to estimate parameter confidence intervals. A visual predictive check (Post et al., 2008), a modelling tool that estimates the concentration prediction intervals and graphically superimposes these intervals on observed concentrations after a standardised dose, was used to evaluate how well the model predicted the distribution of observed plasma concentrations. Simulation was performed using 1000 subjects with characteristics taken from studied patients.

The use of priors. The principle of using prior information is that previous data can be used to support a PK model under which the current data are being analysed (Standing et al., 2010). The parameters (including their uncertainty) of the model derived from the more informative data are then used to analyse the data in question in the context of prior knowledge. The better the prior knowledge, the more the data under analysis will be constrained to be similar to the prior information. Using prior information is done by augmenting the objective function (a measure of fit) derived from the observed data with a penalty function, which is a summary of data from previous (more informative) studies (Gisleskog et al., 2002). Fentanyl priors were sourced from two publications. Loughren estimated fentanyl parameters and their variability in a study investigating the impact of St John's wort on pharmacokinetics (Loughren et al., 2020). Shafer estimated fentanyl parameters using pooled data during infusion (Shafer et al., 1990). Variability was not reported in the article by Shafer and colleagues (Table S1 of the Electronic Supplementary Material [ESM]). Parameter variability estimates for fentanyl (Gepts et al., 1995) were substituted and consequent priors used as a confirmatory analysis for the primary analysis that used priors described by Loughren and colleagues (Table S1). Use of such prior I.V. information

also allowed estimation of the relative bioavailability (FNASAL) of the nasal delivery system.

Compartment model. A three-compartment linear disposition model with first- order absorption and first-order elimination was used to analyse concentration–time profiles. Others had analysed fentanyl using a three-compartment model and that information was used as priors. The model was parameterised in terms of clearance, intercompartmental clearances (Q2 and Q3), three volumes of distribution (V1, V2, V3) and an absorption rate constant. The latter was expressed as an absorption half-time. Intranasal fentanyl bioavailability (FFENTANYL) was constrained between 0 and 1 (Lesaffre et al., 2007), while a logistic distribution was used for its variability to maintain estimates within these limits (Mould et al., 2013).

Pharmacodynamic analysis. The primary pharmacodynamic (PD) outcome measure was the sum of pain intensity difference (SPID) for the time interval from 0 to 180 min after fentanyl administration. The SPID was calculated as weighted sums of the time elapsed since previous assessment and pain intensity difference (PID) at each time point:

$$SPID_t = PID_t \times time_t - time_{t-1} \text{ (minute)},$$
$$PID_t = PI \text{ baseline} - PI \text{ time } (_t),$$

Where PI is the pain intensity on an 11-point numeric rating scale. For each patient, the value for SPID was converted to a percentage of maximum SPID ($\%maxSPID_{0-180}$) by division into the calculated maximum value (McQuay et al., 1998). Exacerbation of pain was defined as %maxSPID ≥−33% and that pain at rest was ≥ 4/10 and dynamic pain was ≥ 6/10 (Farrar et al., 2000). For an estimate of minimum effective concentration (MEC) of fentanyl and oxycodone when co-administered, we used the last plasma concentrations obtained before the first rescue oxycodone dose after fentanyl administration.

Outcome measures. The primary PK outcome measure was fentanyl exposure, $AUC_{0\text{-}180}$ and the primary PD outcome measure was $\%maxSPID_{0\text{-}180}$ during the first 3 h after fentanyl administration.

Statistical analysis. The sample size estimation was based on data presented by Christrup (Christrup et al., 2008). In that study $AUC_{0–180}$ after intranasal fentanyl 100 μg was 48.5 min·ng/mL (standard deviation 10.3) and after fentanyl 200 μg was 77.5 min·ng/ mL (standard deviation 24.1). Based on those data, 14 patients would provide a study power over 0.9 at $\alpha = 0.05$ and show a difference for fentanyl exposure between the two dose levels. The appropriateness of sample size was also confirmed for PD comparisons, in the study from Christrup (Christrup et al., 2008), the mean of SPID0–60 was 120 (standard deviation 71) for intranasal fentanyl 100 μg and that for fentanyl 200 μg was 252 (standard deviation 66).

SigmaPlot version 13 (Systat software, San Jose, CA, USA) was used for statistical analysis. The comparison of the two dosing groups was done using the Mann–Whitney Rank Sum test. The differences in C_{max} and $AUC_{0–180}$ between 100-μg and 200-μg doses were tested with the Wilcoxon signed rank test. Correlations between patient characteristics and C_{max} or $AUC_{0–180}$ were tested with the Pearson's correlation coefficient. The r-values of − 0.29 to + 0.29 were considered to indicate a weak correlation, – 0.49 to − 0.3 or 0.3–0.49 a moderate correlation, − 0.89 to − 0.5 or 0.5– 0.89 a strong correlation, and − 1.0 to − 0.9 or 0.9– 1.0 a very strong correlation. Data are presented as median (minimum–maximum) or number of cases if not otherwise indicated. A p-value of ≤ 0.05 was considered significant.

6.4 RESULTS

Pharmacokinetic data

The PK analysis comprised 16 patients with 256 drug assay observations (Table 1). All 224 plasma fentanyl concentrations measured after drug administration were above the LLoQ. A MEC of fentanyl 0.5 ng/mL (Gourlay

et al., 1988) was achieved in all 16 administrations after intranasal fentanyl 100 µg and in 15 out of 16 administrations after fentanyl 200 µg. Plasma fentanyl concentration was ≥0.5 ng/mL for a median of 25 min (range 11–68 min) after fentanyl 100 µg and 77 min (range 0–180 min) after fentanyl 200 µg, respectively. Raw data are shown in Figure 2 and the C_{max}, time to C_{max} and $AUC_{0–180}$ from the non-compartmental analysis are presented in Table 2. The C_{max} and AUC_{0-180} values after fentanyl 200 µg were divided by the values observed after fentanyl 100 µg to determine a within-subject comparison (200/100 ratio). Patients ID2 and ID11 in Group 1 showed lower fentanyl exposure after intranasal administration of fentanyl 200 µg on the third postoperative morning than after fentanyl 100 µg on the first postoperative morning (within-subject 200/100 ratio of 0.62 and 0.91). Patients ID6 and ID14 in Group 2 showed similar, unexpectedly low fentanyl exposure after 200 µg of fentanyl on the first postoperative morning compared with the 100 µg of fentanyl dose on the third postoperative morning (within-subject 200/100 ratio of 0.56 and 0.89). This BOV was captured in the population PK analysis (Table 3).

Pharmacokinetic parameters are listed in Table 2. A non- compartment analysis demonstrated dose proportionality with C_{max} and $AUC_{0–180}$. In all patients (n = 16), the median C_{max} after fentanyl 100 µg was 1.3 ng/mL and the median $AUC_{0–180}$ was 62.7 min·ng/mL and after fentanyl 200 µg was 2.0 ng/mL (compared to 100 µg p = 0.109) and 107.3 min·ng/mL (p = 0.007), respectively.

Compartmental parameter estimates for the fentanyl three-compartment analysis using Loughren priors are shown in Table 3 and those for the confirmatory analysis using Shafer priors (Shafer et al., 1990) in Table S2 of the ESM. Figure 3 shows satisfactory visual predictive check plots for these PK data. In a body composition review, C_{max} and $AUC_{0–180}$ correlated inversely with total body water, skeletal muscle mass and visceral fat, but not with fat mass (Table S3 of the ESM).

Table 1. Patient characteristics. Data are presented as the number of patients or median [minimum - maximum].

Parameter	Group 1 Intranasal fentanyl on POD1 100 µg and on POD3 200 µg ($n = 8$)	Group 2 Intranasal fentanyl on POD1 200 µg and on POD3 100 µg ($n = 8$)
Sex (male/female)	7/1	6/2
Age (years)	63 [51–70]	65 [49–67]
Height (m)	1.75 [1.64–1.83]	1.73 [1.64–1.84]
Weight (kg)	72 [59–98]	77 [69–129]
BMI (kg/m^2)	24.2 [19.3–32.4]	28.1 [23.5–41.7]
ASA (II/III/IV)	1/5/2	–/7/1
TBW (L)	43.2 [32.7–56.7]	44.4 [34.2–53.9]
SMM (kg)	27.6 [18.7–37.9]	28.5 [20.6–34.8]
FM (kg)	17.7 [8.7–52.3]	22.7 [12.8–31.7]
VAT (L)	3.3 [1.0–10.8]	2.9 [2.1–5.1]

ASA American Society of Anaesthesiologist's physical status classification, *BMI* body mass index, *FM* fat mass, *POD* postoperative day, *SMM* skeletal muscle mass, *TBW* total body water, *VAT* visceral fat

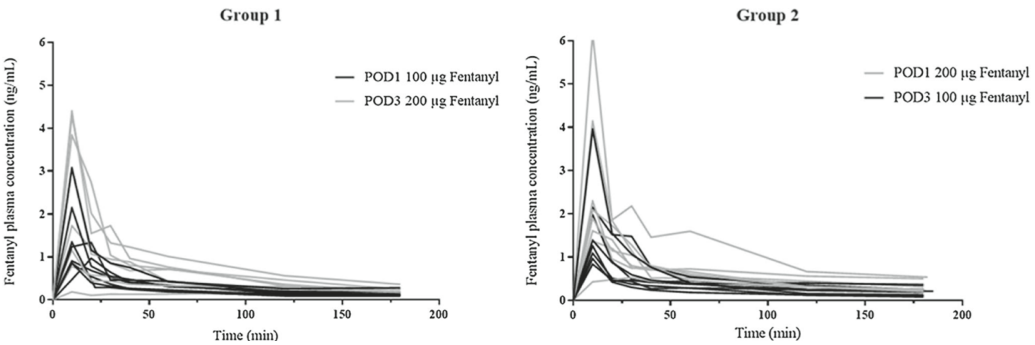


Figure 2. Fentanyl plasma concentrations after intranasal fentanyl 100 µg and fentanyl 200 µg from two dosing sequences plotted against time. In Group 1, patients (n=8) received 100 µg of intranasal fentanyl on the first postoperative morning and 200 µg on the third postoperative morning and in Group 2 (n=8) vice versa. *POD* postoperative day.

Table 2. Pharmacokinetic parameters of intranasally administered fentanyl based on a non-compartmental analysis. In Group 1, patients (n=8) received fentanyl 100 µg on the first postoperative morning and fentanyl 200 µg on the third postoperative morning and in Group 2 (n=8) vice versa.

Pharmacokinetic parameters									
		Intranasal fentanyl dose						Within-subject 200/100 ratio	
		100 µg			200 µg				
	ID	C_{max} (ng/mL)	AUC_{0-180} (min·ng/mL)	t_{max} (min)	C_{max} (ng/mL)	AUC_{0-180}	t_{max} (min)	C_{max}	AUC_{0-180}
Group 1	2	1.4	40.5	10	0.2	25.1	10	0.1	0.6
$n = 8$	4	0.9	37.3	10	3.8	144.3	10	4.5	3.9
	9	0.9	55.2	10	1.7	111.5	10	1.9	2.0
	10	1.0	52.1	20	0.8	58.7	10	0.8	1.1
	11	2.2	71.5	10	1.2	64.9	10	0.5	0.9
	13	1.3	69.0	20	4.4	148.6	10	3.3	2.2
	15	0.9	39.7	10	3.1	103.0	10	3.6	2.6
	16	3.1	103.0	10	4.3	179.8	10	1.4	1.7
Median [minimum–maximum]		1.2 [0.9–3.1]	53.7 [37.3–103.0]	10 [10–20]	2.4 [0.2–4.4]	107.2 [25.1–179.8]	10 [10–10]	1.7 [0.1–4.5]	1.9 [0.6–3.9]
Group 2	1	1.3	68.2	10	1.4	103.1	10	1.1	1.5
$n = 8$	3	1.1	57.2	10	6.2	154.9	10	5.7	2.7
	5	2.0	74.2	10	4.1	224.8	10	2.1	3.0
	6	2.2	112.8	10	0.5	62.9	30	0.2	0.6
	7	1.4	85.5	10	1.6	125.8	10	1.2	1.5
	8	0.8	42.5	10	1.9	103.0	10	2.3	2.4
	12	1.0	38.1	10	2.1	115.1	10	2.2	3.0
	14	4.0	106.0	10	2.3	94.4	10	0.6	0.9
Median [minimum–maximum]		1.3 [0.8–4.0]	71.2 [38.1–112.8]	10 [10–10]	2.0 [0.5–6.2]	109.1 [62.9–224.8]	10 [10–30]	1.6 [0.2–5.7]	2.0 [0.6–3.0]
P-value between groups		0.574	0.234		0.959	0.574		1.0	0.878

AUC_{0-180} area under the plasma concentration–time curve from time zero to time of last quantifiable concentration, *C_{max}* maximum plasma drug concentration, *ID* patient identification number, *POD* post-operative day, *t_{max}* time to reach C_{max} following drug administration

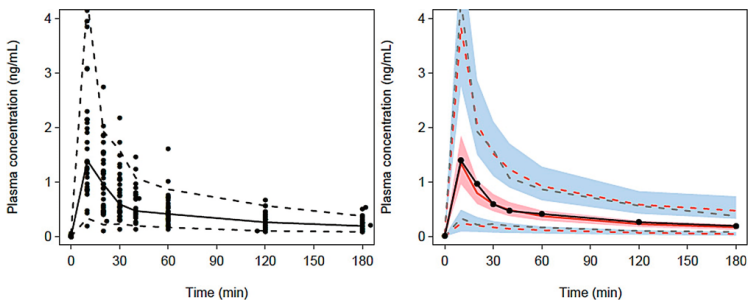


Figure 3. Visual predictive check for the fentanyl pharmacokinetic model. All plots show median and 90 % intervals (solid and dashed lines). The left-hand plot shows all prediction-corrected observed concentrations. The right-hand plot shows percentiles (10%, 50% and 90%) for observations (lines with symbols) and predictions (lines) with 95% confidence intervals for prediction percentiles (shaded areas).

Table 3. Standardized population pharmacokinetic parameter estimates for intranasal fentanyl using Loughren priors (Loughren et al., 2020).

Standardised population pharmacokinetic parameter estimates				
Parameter	Estimate	%BSV	%BOV	95% CI
CL (L/min/70 kg)	0.517	21.1	46	0.199–0.823
Q_2 (L/min/70 kg)	1.06	27.5	–	0.33–1.72
Q_3 (L/min/70 kg)	0.789	41.2	–	0.403–1.169
V_1 (L/70 kg)	31.2	29.9	107	12.2–42.1
V_2 (L/70 kg)	20.1	49.3	–	9.0–29.8
V_3 (L/70 kg)	149	35.6	–	137–157
$T_{abs1/2}$ (min)	1.86	3.2	–	1.10–2.74
F_{NASAL}	0.765	19.7	–	0.414–0.996
Err add (ng/mL)	0.0175	–	–	0.0122–0.0228
Err prop (%)	21.2	–		16.2–23.9

BSV between-subject variability, *BOV* between-occasion variability, *CI* confidence interval of the structural estimate, F_{NASAL} intranasal bioavailability, $T_{abs1/2}$ absorption half-life

A three-compartment linear disposition model with first-order absorption and first-order elimination was used to analyse concentration–time profiles. Population estimates of clearance (CL), intercompartmental clearances (Q_2 and Q_3) and three volumes of distribution (V_1, V_2, V_3), respectively, standardized to a 70-kg person using allometric models

Residual unidentified variability was described by combined proportional and additive residual error model for each observation prediction (Err prop, Err add)

Pharmacodynamic data

The pain scores in the two groups are presented in Fig. 4. The median %maxSPID after fentanyl 100 µg on the first postoperative morning in Group 1 was at rest 11% (− 44% to 86%), during deep breathing 30% (5–81%), and at cough 25% (0–70%), and after fentanyl 200 µg on the third postop erative morning at rest 73% (0–97%), during deep breathing 49% (− 44% to 97%) and at cough 23% (−19% to 56%).

In Group 2, the median %maxSPID on the first postopera tive morning after fentanyl 200 µg was at rest 57% (− 261% to 97%, p = 0.259 compared to Group 1), during deep breathing 53% (− 4% to 81%, p = 0.279) and at cough 29% (− 102% to 67%, p = 1.000), and after fentanyl 100 µg on the third postoperative morning at rest 0% (− 27% to 97%, p= 0.189), during deep breathing 80% (− 165% to 97%, p =0.336) and at cough 2% (− 75% to 80%, p = 0.328).

To compare our PD data with that of Christrup and colleagues in a post hoc analysis, we calculate SPID0–60 for pain at cough. The mean SPID0–60 was 134 (standard deviation 117) after fentanyl 100 μg and that after fentanyl 200 μg was 182 (standard deviation 103), respectively.

Before the first intranasal fentanyl administration on the first postoperative morning, the patients in Group 1 had received 27 mg (10–34) IV oxycodone compared to 30 mg (25–56) in Group 2 (p = 0.195), and before the second fentanyl dose on the third postoperative morning in Group 1 77 mg (42–201) compared to 85 mg (53–131) IV oxycodone in Group 2 (p = 0.950). The median plasma oxycodone con- centration before the first fentanyl administration was 25.4 ng/mL (11.7–41.5) in Group 1 and 34.1 ng/mL (17.6–39.5, p= 0.372) in Group 2, and before the second fentanyl administration in Group 1 was 24.7 ng/mL (10.0–45.6) and 20.5 ng/mL (6.7–67.1, p = 0.912) in Group 2, respectively.

On the first postoperative morning, four patients in Group 1 (fentanyl 100 μg) were administered seven oxycodone doses via a PCA pump during the first 180 min after fentanyl administrations, the median time to the first rescue dose was 81 min (36–120), compared to six patients in Group 2 (fentanyl 200 μg) with seven oxycodone doses and the median time to the first dose was 148 min (45–176) [p = 0.067], respectively. On the third postoperative morning, five patients in Group 1 (fentanyl 200 μg) were administered six oxycodone doses via a PCA pump during the first 180 min after fentanyl administrations, the median time to the first dose was 108 min (52–172), and three patients in Group 2 (fentanyl 100 μg) administered seven PCA-oxycodone doses, the median time to the first dose was 54 min (32–117) [p = 0.393].

The median oxycodone concentration in the preceding blood sample before rescue oxycodone administrations (an estimate of MEC) was 17.7 ng/mL (8.9–33.9) on the first postoperative morning and 11.7 ng/mL (5.2–34.7) on the third postoperative morning, and those for fentanyl 0.31 ng/ mL (0.19–0.73) and 0.36 ng/mL (0.16–0.76), respectively.

Four patients had six adverse effects related to fentanyl administration. One patient had nausea and vomiting 30 min, and confusion 6 h after fentanyl 200 μg. One patient had nausea 5 h after fentanyl 200 μg and another 3.5 h after fentanyl 100 μg. One patient had constipation 28 h after fentanyl 100 μg.

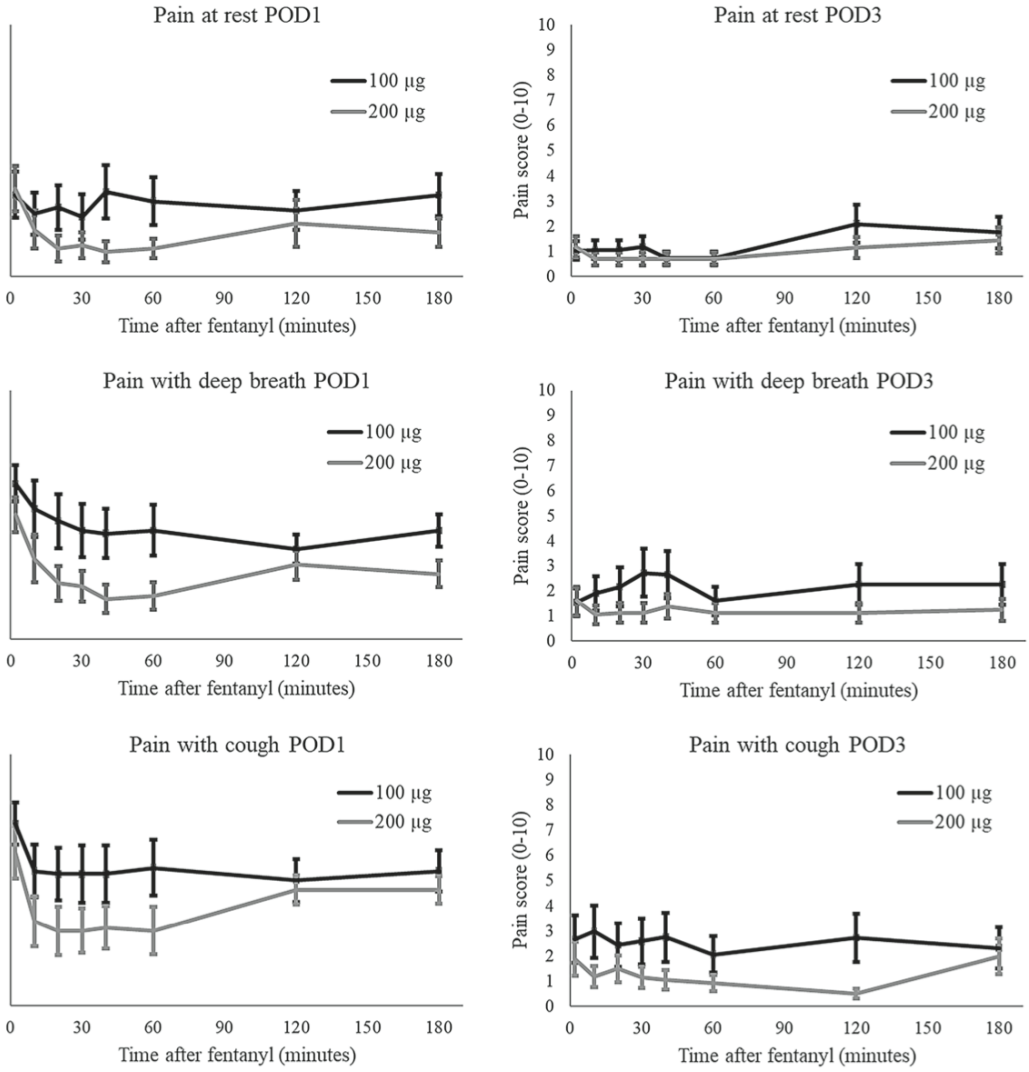


Figure 4. Pain scores on the first and third postoperative day (POD) during the first 3 h after intranasal administration in the two groups, in group 1 (n = 8) intranasal fentanyl 100 µg was administered on the first postoperative morning before chest tube removal and intranasal fentanyl 200 µg on the third postoperative morning, and in group 2 (n = 8) vice versa. Pain was assessed with an 11-point numerical rating scale (0 = no pain, 10 = most pain) at rest, with deep breathing and with cough. Data are mean with the standard error of the mean.

6.5 DISCUSSION

Our data support the use of transmucosal fentanyl for incidental breakthrough pain after cardiac bypass surgery during the first postoperative days. Absorption PK parameter estimates (intranasal bioavailability 0.77, absorption half-time < 2 min) support early analgesic responses and are consistent with those reported in younger healthy adults (Christrup et al., 2008; Striebel et al., 1993). The AUC_{0-180} and C_{max} were dose proportional, and a MEC of fentanyl 0.5 ng/mL observed in patients scheduled for surgical procedures involving an abdominal incision (Gourlay et al., 1988) was reached in almost all (97%) of the patients given intranasal fentanyl 100 µg or fentanyl 200 µg.

We analysed data using both linear compartmental and non-compartmental pharmacokinetics. Priors were used to better characterize absorption parameters (intranasal bioavailability, absorption half-time). Although priors differ for some parameter estimates (e.g., Shafer use infusion data to estimate a bigger V3), absorption parameters were similar in both analyses (Shafer et al., 1990). In the present study, there were low within-subject 200/100 ratios in fentanyl exposure in 4 of 16 participants, consistent with the large BOV noted for clearance estimates and BSV for bioavailability. The nasal route is known to be associated with high BSV and BOV, much of which is attributable to absorption dependent on the anatomy and physiology of this mucosal surface (Grassin-Delyle et al., 2012). However, this variability is accounted for by titration of opioids to effect and intranasal fentanyl, with its rapid absorption, is easy to re-dose if the anticipated effect is not achieved after the initial dose.

The clinical utility of intranasal fentanyl administration was supported by observed analgesic effect: no pain exacerbations were observed during chest tube removal or during physiotherapy and $\%maxSPID_{0-180}$ values after intranasal fentanyl were positive in the majority of patients. Our current analysis indicates intranasal fentanyl 100 µg as an initial dose in the management of incidental breakthrough pain in cardiac surgery patients. In this current study, early pain after cardiac bypass surgery was similar to that reported by others but the pain resolution was faster (Milgrom et al., 2004) using intranasal fentanyl for breakthrough pain.

Pain intensity difference for 0–60 min was similar to those reported by Christrup in patients undergoing third-molar extraction with intranasal fentanyl 100 µg and 200 µg (Christrup et al., 2008). Veldhorst-Janssen have shown that a lower dose of intranasal fentanyl 50 µg 10 min before drain removal in surgery patients was insufficient for effective analgesia (Veldhorst-Janssen et al., 2010). In that study, a two-fold increase in pain scores was recorded during drain removal and this response was similar to that observed in patients administered intranasal placebo. The mean C_{max} fentanyl concentration was 0.22 ng/mL, similar to that reported in a parturient woman after a single intranasal fentanyl 50-µg dose (Kokki et al., 2015). These concentrations are two- to three-fold less than the MEC of fentanyl 0.5 ng/mL (Gourlay et al., 1988).

Intranasal fentanyl in this current study was effective at both doses and the analgesic action was two-fold longer with the higher fentanyl 200-µg dose. The duration of effect of fentanyl 100 µg before the need for oxycodone of 1.1 h was similar to that in Christrup (1.0 h), but with fentanyl 200 µg, the effective duration of 2.1 h was half an hour longer than that reported in patients who had undergone third-molar extraction (Christrup et al., 2008). It should be noted that in the present study fentanyl was co-administered with oxycodone. Before fentanyl administration, the mean oxycodone plasma concentrations were 29 ng/mL on the first postoperative morning and 26 ng/mL on the third postoperative morning, these oxycodone concentrations are similar to the MEC reported in patients with abdominal surgery (Kokki et al., 2012; Kokki et al., 2012; Purdy et al., 2018).

When we compared the oxycodone concentrations after fentanyl administrations and before the next PCA oxycodone doses (our estimate of MEC) to others who have estimated MEC, it was noted that the median oxycodone values of 18 ng/mL on the first postoperative morning and 12 ng/mL on the third postoperative morning are two to three-fold higher than those reported by Pesonen also in cardiac surgery patients (Pesonen et al., 2009). In both studies, the estimates of MEC of fentanyl were similar to those reported earlier in abdominal surgery patients (Gourlay et al., 1988). It is likely that differences in the study designs have contributed to discrepancies. In the current study, assay samples were collected during activities known to

be painful, while Pesonen and colleagues report rescue oxycodone use while patients were lying in bed. Our data indicate that MEC values for dynamic pain are substantially higher than those for pain at rest. This is supported by Cajanus and who has shown that in breast surgery patients an oxycodone MEC value, when administered after fentanyl, was increased by 21% per one-point increase in the dynamic pain intensity score (Cajanus et al., 2018). However, the MEC concentrations obtained in the current study for oxycodone before fentanyl were similar but after fentanyl are substantially lower than those reported in abdominal surgery patients with no concomitant fentanyl. In cholecystectomy and midline laparotomy patients where remifentanil infusion was used for intraoperative analgesia, postoperative MECs of oxycodone 20–30 ng/mL were reported (Kokki et al., 2012; Kokki et al., 2012; Purdy et al., 2018).

The pain model used in the present study, chest tube removal and postoperative physiotherapy are clinically relevant to test the effectiveness of intranasal fentanyl in this patient population. Cardiac bypass surgery patients are exposed to several painful procedures during the first days of recovery and among the most painful and distressing procedures are chest tube removal, turning in the bed, respiratory exercises and mobilization (Milgrom et al., 2004; Puntillo et al., 2018; Puntillo et al., 2014). In the present study, pain scores were recorded both at rest and during activity and were highest during coughing. That was expected as coughing generates excessive force up to 270 N that is an over ten-fold higher force than commonly used in these types of analgesic studies (Gourlay et al., 1988; Kokki et al., 2012; Kokki et al., 2012; Parker et al., 2008; Purdy et al., 2018). The assessment of dynamic pain is important, as severe pain negatively affects function, physical activity and deconditioning after surgery. Deep breathing and coughing are essential to reduce pulmonary complications and early mobilisation reduces the hospital length of stay (Santos et al., 2017).

Fentanyl has a high extraction ratio (Bower et al., 1982) and thus clearance may be impaired with decreased hepatic blood flow consequent to low cardiac output (Wiczling et al., 2016). In the present study, there were no cases of low cardiac output. Moreover, population clearance was similar to that reported by others (Christrup et al., 2008) and there were no obvious outliers, and thus

it is unlikely that surgery or a cardiac bypass has affected that much the PK parameters obtained.

The intranasal fentanyl delivery system can administer an inaccurate dose if not used in an optimal manner. This has probably contributed to low observed fentanyl plasma concentrations and intranasal bioavailability variability. The device contains only a small amount of liquid and if the device is tilted too much, the tube inside the device may not reach liquid content and the spray will not provide the intended amount of fentanyl. Our hospital pharmacy was responsible for covering the bottle with opaque tape thus the delivery mechanism could not be checked during drug dosing, although the intention was to keep the device in an upright position. However, these types of dosing errors were less likely as the patients were able to feel the spray in their nostril and all the administrations were performed by the same investigator who had extensive training with placebo devices before the study. Moreover, the fentanyl exposure of subjects in the present study was similar or higher than that reported by others (Christrup et al., 2008).

In conclusion, our data support the feasibility of transmucosal fentanyl for incidental breakthrough pain in cardiac surgery patients during the first postoperative days. There was no exacerbation of pain after intranasal fentanyl 100-µg and 200-µg administration 10 min before painful procedures, and thus 100 µg should be an appropriate starting dose. As a novel finding, C_{max} and fentanyl exposure correlated inversely with skeletal muscle mass, total body water content and visceral fat.

7 GENERAL DISCUSSION

This thesis was planned to examine some aspects of cardiac surgical treatment and for its part to enhance patient outcome. The rationale to study selected medications that is that they are used in the prevention and management of post-operative atrial fibrillation and pain, both of which predispose cardiac surgical patients to many postoperative complications. A better understanding on the PK properties of these drugs might help in choosing the appropriate route and timing of administration, as well as optimal dosing of these drugs, and plausibly reduce the complication rate.

In the first study, the bioavailability metoprolol was evaluated in elective bypass surgery patients. In the second study, the bioavailability of oxycodone was evaluated by comparing in a randomized setting patients undergoing coronary artery bypass surgery either with or without extracorporeal circulation. In the third study, the efficacy of fentanyl using an alternative and less commonly utilized route of drug administration against incidental breakthrough pain, was examined in cardiac surgical patients.

7.1 BIOAVAILABILITY OF METOPROLOL

Although the absorption of metoprolol from the gastrointestinal tract has been well documented under normal conditions in several publications, it is unclear whether its absorption remains unchanged after major surgery, such as cardiac surgery.

The physico-chemical properties of metoprolol determine that the majority of the absorption takes place in the different sections of small bowel. Since metoprolol is a weak base, this means that of only a small amount of drug will be absorbed in the acidic environment of the stomach (Schoenwald et al., 1983). This is the reason why gastric emptying rate is one of the most important factors regulating metoprolol absorption. Postoperative ileus, pseudo-obstruction and the use of certain drugs may lead to an overall decreased motility of the gastrointestinal tract after cardiac surgery and

thus delay the absorption of metoprolol (Berger et al., 2000; Kennedy et al., 2006). Altered splanchnic blood flow, tissue oedema and ischaemia are also important changes in gastrointestinal structures, which have been shown to decrease the absorptive area of the gut after major surgery (Heyland et al., 1996; Thompson, 1995). If patients are in the supine and left lateral positions in bed, this may also lead to delayed gastric emptying. Diseases like diabetes are related to a decreased rate of gastric emptying. It is also recognized that as little as 50 % of absorbed metoprolol reaches the systemic circulation because of the drug's extensive first pass metabolism.

This study demonstrated that the bioavailability of orally administered metoprolol was markedly impaired on the first postoperative day after cardiac bypass surgery. The decreased bioavailability was apparent in all calculated PK parameters. The bioavailability had returned to normal on the third postoperative day.

This study on the bioavailability of metoprolol confirmed some previously published results on the general response of the gastrointestinal tract to major surgery. Similar changes in the bioavailability of paracetamol have been reported (Berger et al., 2000). The most likely explanation for delayed absorption in this study population is impaired gastric emptying. This is a consequence of the presence of pyloric spasm due to the extensive use of opioids intraoperatively as well as in postoperative pain treatment. The protocol for postoperative pain treatment in our cardiac unit included provision of both oxycodone and paracetamol. All operations were straightforward without the need for extensive fluid resuscitation and none of our patients had a low-output syndrome. Therefore, it is unlikely that systemic dysfunction of gastrointestinal tract might have affected the drug's absorption in this study population.

The pharmacokinetic findings of the present study are clinically relevant. One patient with the lowest concentration of metoprolol developed atrial fibrillation. ß-blocking drugs are the main agents used in the prevention and treatment of postoperative atrial fibrillation. Therefore, since their effect is diminished after peroral delivery in the early postoperative period, the use of other routes of drug administration is indicated (Halonen et al., 2006). Our finding on altered absorption of orally administered metoprolol in the

immediate postoperative period further underlines the need to consider intravenous administration.

There are no relevant limitations of this study except for the small size of the study population and the gender distribution. A group of 12 subjects were considered to give sufficient data on metoprolol's bioavailability according to European Medicines Agency guidelines. All enrolled patients completed the study and no deviations from study protocol were observed. All patients were male and thus the effect of gender remained undetermined.

7.2 EFFECT OF CARDIOPULMONARY BYPASS ON THE BIOAVAILABILITY OF OXYCODONE

Any major surgery may exert a temporary negative impact on the function of the gastrointestinal tract (Ogilvy et al., 1995). There are several recognized surgery and anaesthesia related factors leading to this somewhat inevitable phenomenon e.g. the administered anaesthetics and opioids, surgical stress, as well as the inflammatory reaction induced by the surgical procedure (Berger et al., 2000). Off-pump bypass surgery is thought to cause less of an inflammatory reaction by avoiding the use of an extracorporeal circulation, in which blood flow is laminar and blood is in contact with foreign material. In off-pump surgery, the blood flow remains pulsatile and far less fluid resuscitation is needed (Parolari et al., 2003). The hypothesis in this study was that the recovery of the gastrointestinal tract would be faster in patients operated with the off-pump technique. The recovery was estimated by assessing the bioavailability of oxycodone administered orally. The use of oxycodone as a marker drug is clinically relevant as severe pain is common after sternotomy and needs to be treated with opioids (Lahtinen et al., 2006). The oral administration of analgesics is an attractive option due to its ease of use; however, its early postoperative absorption and efficacy are unknown.

The working hypothesis was not confirmed by the data; there was no difference in the PK parameters between groups of surgeries performed with the extracorporeal circulation or without it. The bioavailability was altered in the majority of patients on the first postoperative day with the

main reason for alteration being delayed absorption. The time to maximal concentration (tmax) on the first postoperative day was 3- to 6-fold longer compared to preoperative values, and values on later postoperative days. This is in accordance with a previous study in which the rate of metoprolol absorption was similarly decreased in the early phases of both CABG and OPCAB surgeries (Kokki et al., 2018). As opposed to metoprolol, however, the maximal drug concentration (Cmax) and total systemic exposure (AUC_{0-24}) were similar to the preoperative day but occurred more slowly and appeared later. Consistent with the altered bioavailability, the need for parallel analgesia with morphine was increased. The morphine consumption and pain scores were similar in both groups.

The novelty of this study is that the observed and corrected AUC_{0-24} and Cmax of oxycodone equalled or exceeded preoperative values on the second postoperative day in four out of six patients in both groups. In addition, these PK parameters were similar or higher in all patients on the third and fourth postoperative days. The increase in PK parameters was higher than the theoretically calculated accumulation factor. The AUC_{0-24} values on the third postoperative day were approximately double the values on the first postoperative day. Compared with the preoperative day, an increase of 23-75 % in median AUC_{0-24} values on postoperative days 2,3 and 4 was found. The pharmacokinetic analysis revealed that these alterations are characteristic for a drug's delayed absorption, most like attributable to delayed gastric emptying (Berger et al., 2000).

The present findings have clinical relevance. If oxycodone is intended to be administered per os on the first postoperative day, there is a heightened risk for complications in terms of drug accumulation. This accumulation may cause respiratory depression, excessive sedation, poor coordination, and disorientation. Based on these findings, oxycodone administration by mouth should not be started earlier than the second postoperative day.

The strength of this study is its prospective randomized design. All operations were performed without notable difficulties and recovery was uneventful in all patients, thus making the study population homogenous. The main limitation of this study is the small number of subjects and the fact that blood samples were collected on alternate days. Due to logistical

reasons, a larger enrolment was not possible. Blood sample collection on the first postoperative day should have been more intensive after the first 12 hours as more intense sampling might have helped in the PK modelling. However, 11 blood samples within 24 hours is relatively high in this kind of trial. The AUC_{0-24} values were so heterogenous on the first postoperative day that was not possible to build a reliable population PK model. The lack of a control group prevented us drawing any pharmacodynamic conclusions. Moreover, only 2 patients out of 24 were female and thus, the effect of gender remains unknown.

7.3 INTRANASAL ROUTE OF FENTANYL ADMINISTRATION

In this study population, intranasally administered fentanyl proved to be a rapid, effective, and well tolerated drug against incidental breakthrough pain. To the best of my knowledge, there are no reports in the medical literature on this route of drug administration in cardiac surgical patients.

This mode of drug administration is known to have a somewhat wide between-patient and on-occasion variability. On the other hand, the analgesic effect of fentanyl is rapid and repetitive dosing is straightforward if anticipated pain relief is not achieved after the initial dosing. We investigated two doses, 100 and 200 µg. These doses were chosen because earlier, a dose of 50 µg was reported as being insufficient to provide sufficient analgesia at the time of drain removal after breast surgery (Veldhorst-Janssen et al., 2010). Sufficient analgesia was achieved with both doses, but the duration of analgesia was two-fold longer with the higher dose. Pain scores in this study population were similar as in other reports (Milgrom et al., 2004). Fentanyl was well tolerated; but 4 patients had opioid-related non-serious adverse effects. Adverse effects included nausea, vomiting, confusion, and obstipation.

Moreover, the study design allowed us to estimate minimal effective concentrations (MEC) of oxycodone and fentanyl when co-administered. It was found that in this study population, MEC values of oxycodone were 2-3 fold higher than in earlier reports (Gourlay et al., 1988; Pesonen et al., 2009), while the MEC value of fentanyl was similar to that previously reported

(Gourlay et al., 1988). The differences can be explained by the fact that in our patients, dynamic pain was evaluated, while other studies assessed pain at rest (Pesonen et al., 2009). Pain during activity such as coughing or breathing exercise is considered a more relevant outcome measure than pain at rest. The fact that only 3 out of the 16 study subjects were female may limit the interpretation of the study's results.

A novel finding emerging from this study was that the body composition may affect the disposition of fentanyl. An inverse correlation with fentanyl bioavailability was detected with body water content, skeletal muscle mass, and visceral fat, but not with fat mass. This leads to the speculation that obese patients may need a smaller body weight-based dosing of lipid-soluble drugs like fentanyl.

7.4 FUTURE ASPECTS

The findings in these studies can be implemented into clinical practise after further research. The results support Enhanced Recovery After Surgery (ERAS) protocols, which are increasingly used to promote recovery from surgery. These protocols encourage the early switch from intravenous lines and devices to the oral administration of medication, fluids, and solids.

On the basis this thesis, it is evident that the bioavailability of drugs is disturbed soon after surgery. Since preventive measures need to be taken against postoperative atrial fibrillation, this goal can be achieved by developing effective protocols of intravenous administration of ß-blocking medication in the early postoperative period. Further research on the postoperative pain management is warranted. The main goal is to achieve sufficient analgesia by non-invasive methods. Therefore, the role of intranasal, sublingual, and buccal routes of drug administration in postoperative pain management needs more investigation.

On the basis of the third study, anthropometric studies are needed in the future when choosing the dose of some drugs, especially those with narrow therapeutic windows like opioids; this is especially the case in obese patients.

8 CONCLUSIONS

The postoperative use of drugs is essential for cardiac surgical patients to enable recovery without undesired events and to ensure long-term benefits from the operation. Drug administration by mouth is preferred and desired due to its convenience both to the patient and the staff. However, the current data indicate that the bioavailability of perorally administered drugs is altered in the early postoperative period. Therefore, other administration routes should be used until the GI-tract has recovered.

In the first study, the bioavailability of metoprolol by mouth after cardiac bypass surgery was evaluated using non-compartmental PK model. Compared to the preoperative day, metoprolol bioavailability was markedly reduced on the first postoperative day. However, it returned to the preoperative level on the third postoperative day.

In the second study, the bioavailability of peroral oxycodone was evaluated. Patients were prospectively randomized to coronary artery bypass grafting either with or without cardiopulmonary bypass. A two-compartmental model was used in the PK analysis. The absorption of oxycodone was markedly delayed in both groups on the first postoperative day leading to drug accumulation on subsequent postoperative days.

In the third study, each patient received after surgery a single intranasal dose of 100 µg or 200 µg of fentanyl, two days apart in random order. A pharmacokinetic evaluation was performed using population pharmacokinetic methods. The bioavailability and PKs were comparable to those reported in healthy adults, with no effect of surgery. The lower dose was sufficient to relieve the breakthrough pain induced by drain removal and physiotherapy.

On the basis of these studies, the following conclusions can be drawn:

1. The bioavailability of metoprolol by mouth was markedly decreased on the first postoperative day, in most patients only returning to the normal level on the third postoperative day. Thus, metoprolol should be administered by the intravenous route in the early phase of the recovery.
2. The absorption of peroral oxycodone is comparably delayed on the first postoperative day after coronary artery bypass grafting with or without extracorporeal circulation. In either case, oxycodone should not be administered by mouth before the second postoperative day due to the risk of drug accumulation and possible overdose.
3. Intranasally administered fentanyl 100 µg is rapid, effective, and well-tolerated medication for incidental breakthrough pain after cardiac surgery.

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ANTTI VALTOLA

The postoperative medication is essential to help recovery from cardiac surgery. The present study investigated the bioavailability of three clinically relevant drugs. The operation delays markedly the absorption of per oral metoprolol and oxycodone for the first two days after the operation. This indicates other routes of administration during the first 48 postoperative hours. Intranasal fentanyl absorption was a rapid and it was efficient and well-tolerated for relieving incidental postoperative pain after cardiac surgery.

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**PUBLICATIONS OF
THE UNIVERSITY OF EASTERN FINLAND**
Dissertations in Health Sciences

ISBN 978-952-61-4260-9

ISSN 1798-5706