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OF TURKU
EFFECT OF ANTIMYCOTICS AND RIFAMPICIN ON THE PHARMACOKINETICS OF BUPRENORPHINE AND THE FEASIBILITY OF SUBLINGUAL FENTANYL FOR PROCEDURAL SEDATION
Mari Fihlman
Moderate
Mild
TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
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University of Turku

Faculty of Medicine
Anaesthesiology, Intensive Care, Emergency Care and Pain Medicine
Doctoral Programme in Clinical Research
Turku University Hospital, Turku, Finland

Supervised by

Associate Professor Teijo Saari, MD, PhD
Department of Anaesthesiology and Intensive Care
University of Turku and
Turku University Hospital
Turku, Finland

Professor Klaus Olkkola, MD, PhD,
Department of Anaesthesiology and Intensive Care
University of Helsinki and
HUS Helsinki University Hospital
Helsinki, Finland

Adjunct Professor Kari Laine, MD, PhD
Integrative Physiology and Pharmacology
Institute of Biomedicine
University of Turku
Turku, Finland

Reviewed by

Adjunct Professor Maija Kaukonen, MD, PhD, EDIC
Department of Anaesthesiology and Intensive Care
HUS, Helsinki University Hospital
Helsinki, Finland

Adjunct Professor Jari Lilja, MD, PhD
Department of Psychiatry
HUS, Helsinki University Hospital
Helsinki, Finland

Opponent

Professor Miia Turpeinen, MD, PhD
Institute of Biomedicine
University of Oulu and
Oulu University Hospital
Oulu, Finland

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To my family

UNIVERSITY OF TURKU
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Anaesthesiology, Intensive Care, Emergency Care and Pain Medicine
MARI FIHLMAN: Effect of antimycotics and rifampicin on the pharmacokinetics of buprenorphine and the feasibility of sublingual fentanyl for procedural sedation
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ABSTRACT

Buprenorphine and fentanyl are opioids, which have been clinically used for decades. Buprenorphine is traditionally prescribed for maintenance therapy in opioid dependent patients and to a lesser extent in the treatment of acute pain. Fentanyl is the most widely used perioperative opioid. In recent years new dosage forms have been introduced for both of these drugs. The use of buprenorphine in the treatment of chronic pain has increased with the introduction of sublingual and transdermal formulations. Good results have been obtained with the administration of sublingual fentanyl in the treatment of cancer breakthrough pain.

Some interaction studies have been made using high-dose buprenorphine and antiretrovirals, but there are few studies evaluating the drug-drug interactions between low-dose buprenorphine and known CYP3A4 inhibitors and inducers. In this thesis three studies were conducted to study the interactions between buprenorphine, using three different administration routes, and two CYP3A4 inhibitors, voriconazole and posaconazole and the CYP3A4 inducer, rifampicin.

Voriconazole increased significantly the plasma concentration of sublingually and orally administered buprenorphine. Posaconazole also increased the plasma concentration of sublingually administered buprenorphine but the effect was not as evident as that encountered with voriconazole. Rifampicin decreased the plasma concentrations of sublingually administered buprenorphine, but it had no effect after the opioid's intravenous administration.

The aim of the fourth study was to evaluate the efficacy and safety of a sublingually administered fentanyl tablet in patients having colonoscopy. Patients often experience colonoscopy painful and unpleasant. Intravenous sedation increases the costs of colonoscopy significantly because patients need monitoring during sedation and recovery. The use of the sublingual administration route could offer a cost-effective alternative to intravenous sedation.

This study showed that 100 micrograms of sublingual fentanyl was ineffective for the treatment of pain during colonoscopy. Nonetheless, it was observed that very few procedures had to be interrupted and the pain that patients experienced was mostly moderate. This raises the question of whether we should treat patients for anxiety and distress instead of pain.

KEYWORDS: buprenorphine, voriconazole, posaconazole, rifampicin, pharmacokinetics, drug-drug interaction, pain, colonoscopy, sublingual fentanyl, analgesia, endoscopy

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
Anestesiologia, tehohoito, ensihoito ja kivunhoito
MARI FIHLMAN: Antimykoottien ja rifampisiinin vaikutus buprenorfiinin farmakokinetiikkaan ja sublinguaalisen fentanyylin soveltuvuus paksusuolen tähystyksen esilääkkeeksi.
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TIIVISTELMÄ

Buprenorfiini ja fentanyyli ovat opioideja, jotka ovat olleet kliinisessä käytössä vuosikymmeniä. Buprenorfiinia käytetään yleisimmin opioidiriippuvaisten potilaiden vieroitus- ja korvaushoidossa ja jonkin verran akuutin kivun hoidossa. Fentanyyli on eniten käytetty perioperatiivinen opioidi. Molemmista lääkkeistä on viime vuosina tullut markkinoille uusia annostelumuotoja. Buprenorfiinin käyttö kroonisen kivun hoidossa on lisääntynyt sublinguaalisen ja transdermaalisen annostelumahdollisuuden myötä. Sublinguaalisen fentanyylin käytöstä on saatu hyviä tuloksia syövän läpilyöntikivun hoidossa.

Kirjallisuus ei juurikaan tunne buprenorfiinin interaktioita muiden kuin HI-virusinfektioon käytettävien lääkkeiden kanssa ja näissä tutkimuksissa on ollut käytössä buprenorfiinin korkeampi korvaushoitoannos. Tämän tutkimuksen kolmessa työssä tutkittiin eri annostelureittejä annetun buprenorfiinin farmakokineettisiä ja farmakodynaamisia yhteisvaikutuksia CYP3A4-entsyymin toimintaa estävien vorikonatsolin ja posakonatsolin kanssa sekä CYP3A4-entsyymin toimintaa kiihdyttävän rifampisiinin kanssa.

Vorikonatsoli lisäsi merkittävästi sublinguaalisesti ja oraalisesti annostellun buprenorfiinin pitoisuuksia plasmassa. Myös posakonatsoli lisäsi sublinguaalisesti annostellun buprenorfiinin pitoisuutta plasmassa, mutta vaikutus oli huomattavasti pienempi kuin vorikonatsolilla. Rifampisiini pienensi sublinguaalisesti annostellun buprenorfiinin pitoisuutta veressä, mutta sillä ei ollut vaikutusta suonensisäisesti annostellun buprenorfiinin pitoisuuksiin.

Neljännessä työssä arvioitiin kielen alle annostellun fentanyylin tehoa ja turvallisuutta paksusuolen tähystyksen esilääkkeenä. Paksusuolen tähystys koetaan hyvin kivuliaana ja epämiellyttävänä tutkimuksena. Suonensisäinen sedaatio ja kivunlievitys kuitenkin nostavat merkittävästi toimenpiteen kustannuksia ja lisäävät siihen kuluvaa aikaa, koska potilaat tarvitsevat suoniyhteyden ja heitä täytyy seurata sedaation aikana ja sen jälkeen.

Tämä tutkimus osoitti, että kielen alle annostellulla fentanyylillä annoksella 100 µg ei pystytä lievittämään potilaiden kokemaa kipua paksusuolen tähystyksen aikana. Tutkimus osoitti myös sen, että kipu on harvoin tutkimuksen rajoittava tekijä ja herätti ajatuksia siitä, tulisiko pyrkiä hoitamaan potilaiden kokemaa ahdistusta ja epämukavuuden tunnetta kivun sijaan.

AVAINSANAT: Buprenorfiini, vorikonatsoli, posakonatsoli, rifampisiini, farmakokinetiikka, lääkeinteraktio, kipu, kolonoskopia, sublinguaalinen fentanyyli, tähystystoimenpide

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Abbreviations

ASA	American Society of Anesthesiology
AUC_{0-t}	area under plasma concentration-time curve from zero to t hours
AUC_m/AUC_p	metabolite-to-parent drug area under plasma concentration-time curve ratio
B3G	buprenorphine-3-glucuronide
CI	confidence interval
CL	plasma clearance
C_{max}	peak plasma concentration
CPT	cold pain threshold
CYP	cytochrome P450
DDI	drug-drug interaction
DFI	drug-food interaction
DSST	digit symbol substitution test
EDTA	ethylenediaminetetraacetic acid
F	oral bioavailability of drug
FDA	Food and Drug Administration
GMR	geometric mean ratio
HPLC	high performance liquid chromatography
k_e	elimination rate constant
LC-MS	liquid chromatography - mass spectrometric method
LC-MS/MS	liquid chromatography – tandem mass spectrometric method
LLQ	lower limit of quantification
ln	natural logarithm
MWT	Maddox Wing Test
NRS	numerical rating scale
N3G	norbuprenorphine-3-glucuronide
P-gp	P-glycoprotein
SD	standard deviation
$t_{½}$	elimination half-life
t_{max}	time to peak concentration
UGT	UDP-glucuronosyl transferase
VAS	visual analogue scale

VRS	verbal rating scale
WHO	World Health Organisation

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals I-IV:

I Fihlman M, Hemmilä T, Hagelberg NM, Kuusniemi K, Backman JT, Laitila J, Laine K, Neuvonen PJ, Olkkola KT, Saari TI. Voriconazole more likely than posaconazole increases plasma exposure to sublingual buprenorphine causing a risk of a clinically important interaction. Eur J Clin Pharmacol. 2016 Nov;72(11):1363-1371

II Fihlman M, Hemmilä T, Hagelberg NM, Backman JT, Laitila J, Laine K, Neuvonen PJ, Olkkola KT, Saari TI. Voriconazole greatly increases the exposure to oral buprenorphine. Eur J Clin Pharmacol. 2018 Aug 30

III Hagelberg NM, Fihlman M, Hemmilä T, Backman JT, Laitila J, Neuvonen PJ, Laine K, Olkkola KT, Saari TI. Rifampicin decreases exposure to sublingual buprenorphine in healthy subjects. Pharmacol Res Perspect. 2016 Nov 3;4(6)

IV Fihlman M, Karru E, Varpe P, Huhtinen H, Hagelberg N, Saari T.I, Olkkola K.T. Feasibility of transmucosal sublingual fentanyl tablet in procedural pain treatment in colonoscopy patients. Manuscript

1 Introduction

The number of clinically used medicines and their formulations increase year by year. Although buprenorphine and fentanyl are traditional opioids their clinical applications have become more diverse in recent years because of the development of new dosage forms. The use of buprenorphine has increased in the treatment of chronic pain when sublingual and transdermal administration have become available. Sublingually administered fentanyl has been found to be effective and safe in the treatment of cancer breakthrough pain.

It is very common that several drugs are used concomitantly and the risk of drug-drug interactions (DDIs) has increased (Åstrand et al. 2007). Most DDIs are harmful, but some of them lead to serious adverse effects (Bucşa et al. 2013). The chemical properties of drugs and many patient-related factors, such as the patient's age, gender, weight and concomitant diseases, affect the pharmacokinetics of the drug. One of the most common causes for harmful DDIs is inhibition of cytochrome P-450 (CYP) mediated metabolism of the drug (Pelkonen et al. 2008). Recent studies have also shown that other systems, such as membrane transporters and UDP-transferases (UGTs) can have their role in drug metabolism and interactions (Chang, Moody, and McCance-Katz 2006; Hassan et al. 2009).

Buprenorphine is a semisynthetic partial μ-opioid receptor agonist. It is widely used in the treatment of opioid withdrawal symptoms and in the maintenance therapy of opioid-dependent patients. In much lower doses, it is prescribed as an analgesic agent and in recent years transdermal formulations have increased its use in the treatment of moderate chronic pain (Fredheim et al. 2010; Zin, Chen, and Knaggs 2014). Some interaction studies have been conducted using high-dose buprenorphine and antiretrovirals (McCance-Katz et al. 2007; 2006), but the interactions of low-dose buprenorphine are largely unknown.

The bioavailability of oral buprenorphine is very low due to first-pass metabolism. Sublingual buprenorphine has higher bioavailability, although data from different studies are very variable (Bullingham et al. 1982; Kuhlman et al. 1996; Mendelson et al. 1997). The principal metabolic pathway, N-dealkylation of buprenorphine is catalysed mainly by cytochrome P450 (CYP) 3A4 (Cone et al. 1984). Some transporters such as P-glycoprotein and UGTs can play a role in the

pharmacokinetics of buprenorphine and its metabolites (Chang, Moody, and McCance-Katz 2006; Alhaddad et al. 2012; Brown et al. 2012). Since strong opioids like buprenorphine can exert serious adverse effects such as respiratory depression, it is important to study these potentially hazardous DDIs with drugs which are known to inhibit or induce CYP-mediated metabolism.

The development of medicine and technology has enabled more and more diseases to be diagnosed at an early stage. Most of the diagnostic imaging and procedures can be performed without anaesthesia, but nowadays patients are more aware of the possibility of receiving pain relief or sedation. Implementation of sedation demands that these patients are monitored during and after the procedure and obviously this increases costs and time spent handling one patient.

Colonoscopy is an invasive procedure that can cause pain and discomfort to the patient. Most patients value analgesia during colonoscopy (Subramanian, Liangpunsakul, and Rex 2005) but instead sedatives are still commonly used to decrease anxiety and to treat pain during colonoscopy (Porostocky et al. 2011; Froehlich et al. 2006). Fentanyl is a rather short-acting opioid and a transmucosal sublingual delivery form has been developed to improve the management of breakthrough pain in cancer patients. Analgesia by administering a transmucosal tablet during colonoscopy is a novel approach and low doses of intravenous fentanyl seem to be effective in achieving a satisfactory level of comfort during colonoscopy (Lazaraki et al. 2007). A single dose of sublingual fentanyl does not require follow-up after the procedure, and thus it was hypothesized that sublingual fentanyl could be a non-invasive and cost-effective way to provide adequate analgesia and increase patient satisfaction during colonoscopy.

2 Review of the Literature

2.1 Opioids studied

2.1.1 Buprenorphine

Buprenorphine was approved for clinical use in the United Kingdom in 1978 as an injectable formulation for the treatment of moderate to severe pain and a sublingual tablet form was launched in 1981 (Cowan 2007). Buprenorphine has been used to treat heroin addiction since 1996 when it was first introduced in France for this purpose. Buprenorphine, a derivative of oripavine has unusual receptor-binding properties. Buprenorphine is a partial μ-opioid receptor agonist which antagonizes the κ-opioid receptor and acts as an agonist at the δ-opioid receptor and the opioid receptor-like receptor (Dum and Herz 1981; Leander 1987). The analgesic efficacy of buprenorphine is 20-40 times higher than morphine and it produces long-lasting subjective and physiological effects (Mattick et al. 2003). The possibility to administer the drug once a day or even less frequently is a great benefit when treating chronic pain or opioid dependency. Buprenorphine is considered safe in clinical use because of its ceiling effect. The ceiling effect is evident i.e. increasing the drug dose no longer exerts any effect on an important dependent variable, in this case depression of respiration. It is well known that the most common severe adverse effect of opioids is respiratory depression (Helpern and Rho 1967) and it is recognized that both sublingual and intravenous administration routes of buprenorphine even at high doses have good safety margin for respiratory depression because of the ceiling effect (Umbricht et al. 2004; Walsh et al. 1994). It has been shown that after the administration of 16 mg sublingual buprenorphine respiration was maximally suppressed and higher doses of buprenorphine did not cause more intense respiratory depression (Walsh et al. 1994). There are some studies suggesting that this ceiling phenomenon might be due to pharmacokinetic factors (Harris et al. 2004) whereas others have found indications that the ceiling effect is most likely caused by pharmacodynamic adaptation, at least up to the dose of 12 mg (Huestis et al. 2013).

2.1.2 Pharmacokinetics of buprenorphine

Buprenorphine undergoes extensive metabolism; in particular, considerable first pass metabolism. Buprenorphine has a very low oral bioavailability (around 10-16%). Sublingual bioavailability is higher (30-55%) but different studies report very variable data (Bullingham et al. 1982; Kuhlman et al. 1996; Mendelson et al. 1997; Nath et al. 1999). Absorption to systemic circulation is slow and the mean time to reach the maximum concentration after sublingual administration has been claimed to lie in a range of 40 – 210 minutes (Kuhlman et al. 1996; Nath et al. 1999; Bullingham et al. 1981).

Buprenorphine has a large volume of distribution, which is estimated to be 188-335L following intravenous administration (Kuhlman et al. 1996; Bullingham et al. 1980). Buprenorphine is highly lipophilic and it is extensively bound to plasma proteins (96%) (Elkader and Sproule 2005).

The main metabolic pathway (65%) of buprenorphine is N-dealkylation to an active metabolite norbuprenorphine. This pathway is catalysed mainly by cytochrome P450 (CYP) 3A4, but also by CYP3A5 and CYP2C8 (Iribarne et al. 1997; Moody et al. 2002; Picard et al. 2005; Chang, Moody, and McCance-Katz 2006). Buprenorphine and norbuprenorphine are further conjugated to buprenorphine-3-glucuronide (B3G) and norbuprenorphine-3-glucuronide (N3G) by UGTs (Chang, Moody, and McCance-Katz 2006). These metabolites have receptor binding properties and pharmacological activity according to animal studies (Brown et al. 2011). Other oxidized and hydroxylated metabolites are formed by other metabolic pathways (Chang, Moody, and McCance-Katz 2006; Picard et al. 2005). (Fig. 1.) The elimination half-life of buprenorphine is long and there is considerable variation in values obtained. Sublingual buprenorphine is reported to have a mean elimination half-life from plasma of 37 hours (Elkader and Sproule 2005).

Buprenorphine is mainly excreted as metabolites in bile (80-90%) and urine (10-30%) (Brewster, Humphrey, and McLeavy 1981; Cone et al. 1984). The majority of the metabolites are excreted into the biliary system and they can be subject to enterohepatic circulation (Brewster, Humphrey, and McLeavy 1981). Subsequent studies have also shown, that many opioids are substrates of transporter proteins, such as P-glycoprotein, which can affect their metabolism (Dagenais, Graff, and Pollack 2004; Kharasch et al. 2003; Drewe et al. 2000).

The main metabolite of N-dealkylation, norbuprenorphine is found in high concentrations in urine and urine toxicology tests are frequently used for patients in buprenorphine maintenance therapy for the determination of the adherence to treatment. If buprenorphine is administered by a route that bypasses first-pass metabolism totally (eg. intravenously or subcutaneously), the formation of norbuprenorphine is significantly lower (Kuhlman et al. 1996).

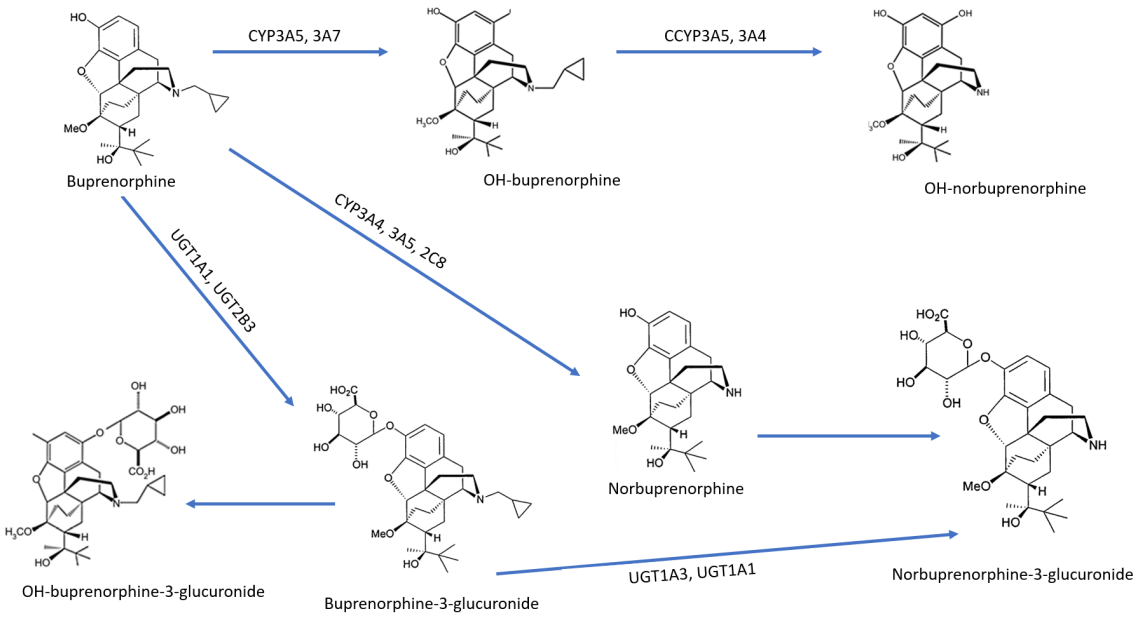

Figure 1. Metabolism of buprenorphine. Modified from Vicencio-Rosas et al. 2018.

2.1.3 Clinical use

Treatment of opioid dependence

Buprenorphine was approved for the treatment of opioid addiction in the United States in October 2002. It had been already used for this purpose in France since 1996. Buprenorphine has many features that make it an excellent drug for the treatment of opioid dependence. It does not induce significant physical dependence and there is a small possibility of lethal overdose without concomitant use of other drugs or alcohol (Mello and Mendelson 1985). Sublingual buprenorphine has a long elimination half-life and dosing once a day or even less frequently is possible. Buprenorphine is a rather safe drug and it has a lower risk of causing respiratory depression than full opioid agonists (Umbricht et al. 2004). Many opioid dependent patients fail in their attempt to stop opioid use. It has been shown that long term maintenance therapy with buprenorphine is feasible and effective in many respects (Gossop et al. 1989; Fudala et al. 2003). In a recent analysis conducted in France, patients who discontinued prescribed buprenorphine treatment were 29 times more likely to die compared to patients who stayed in the buprenorphine treatment programme (Dupouy et al. 2017).

The most common sublingual doses used in maintenance therapy are 8-16 mg. Studies have shown that moderate-to-high doses have significantly higher efficacy

than lower doses (1-3 mg) (Ling et al. 1998; Ahmadi 2003). Sublingual buprenorphine has been even administered successfully three times a week in maintenance therapy (Schottenfeld et al. 2000; Pérez De Los Cobos et al. 2000).

Sublingual form of buprenorphine where naloxone is combined with buprenorphine (Suboxone®) to reduce the intravenous misuse of buprenorphine, is commonly used in maintenance therapy. Naloxone has poor bioavailability when administered sublingually, but if buprenorphine-naloxone is taken inappropriately e.g. by parenteral routes, the presence of naloxone in the bloodstream will induce withdrawal symptoms (Chiang and Hawks 2003; Weinhold et al. 1992).

The most novel approach in the treatment of opioid dependence are the long-acting formulas approved recently. The subdermal buprenorphine implant was approved in the USA in May 2016 and in European Union in June 2019. It is designed to provide a constant low-level dose of buprenorphine for six months for patients in maintenance therapy (Smith et al. 2017). The product consists of 4 thin rods each containing 80 mg (total 320 mg) of buprenorphine. With this new product a steady-state concentration slightly less than that produced by 8 mg daily sublingual buprenorphine can be achieved. This is recommended for patients who are already stable with 8 mg or less daily sublingual buprenorphine (Ling et al., 2010). Another recently approved long-lasting formula is a monthly subcutaneous injection depot which was approved in the USA in late 2017. It is available in two doses: 100 mg and 300 mg. The recommended dosing regimen is two 300 mg monthly doses followed by 100 mg doses thereafter (Coe, Lofwall, and Walsh 2019). This injectable product produces much higher plasma concentrations of buprenorphine and therefore it is recommended for patients who already have higher daily buprenorphine doses and greater physical dependency. Another subcutaneous buprenorphine formula is approved in the European Union and is already in clinical use in Finland. Available dosage range of this buprenorphine formula is from 8 mg to 128 mg and it is administered first weekly and after achieving the steady state the administration can be implemented monthly.

These new products could alleviate many patient concerns such as having their prescription stolen, needing to safely store their medicine away from children and travelling while carrying controlled, and in some countries, illegal, substances.

Acute pain

Buprenorphine has been thought to be a safe drug because of its ceiling effect on respiratory depression. Only in recent years have we learned that there is no ceiling effect for the analgesic effect of buprenorphine (Dahan et al. 2006). For this reason buprenorphine is considered to be very useful in the management of acute pain and in fact, it has been shown that there is no difference in the analgesia provided by

either buprenorphine or morphine (White et al. 2018). The duration of one dose is 6-8 hours and adverse effects are less common than with morphine (Walsh et al. 1994).

Buprenorphine is used for the treatment of acute pain intravenously at a dose of 0.3 mg and sublingually at a dose of 0.2-0.4 mg. Buprenorphine is a very potent analgesic, with an intravenous dose of 0.3 mg being equivalent to 10 mg of morphine in patients who are not dependent on opioids. It has been demonstrated that buprenorphine is effective in the treatment of acute pain even when administered via intrathecal (Celleno and Capogna 1989), epidural (Inagaki, Mashimo, and Yoshiya 1996), subcutaneous or intra-articular (Varrassi et al. 1999) route or when combined with regional anaesthesia (Candido et al. 2002).

Chronic pain

The use of strong opioids has increased in the treatment on non-malignant moderate to severe pain (Breivik et al. 2006). New dosage formulations of buprenorphine have increased the interest to use buprenorphine in the treatment of chronic pain.

Sublingual buprenorphine has been found to be effective in the treatment of chronic pain (Cote and Montgomery 2014). Due to its unique pharmacological profile, buprenorphine has an increased efficacy in treating neuropathic pain (Pergolizzi et al. 2008; Davis 2012). It is safe to use because of the ceiling effect for respiratory depression when used without other central nervous system depressants (Johnson, Fudala, and Payne 2005; Pergolizzi et al. 2008). The adverse effects in sublingual buprenorphine therapy have been found to be similar to standard opioid therapy (Cote and Montgomery 2014).

Transdermal drug delivery systems, so called opioid patches offer an ideal route of administration to achieve minimal variation in opioid plasma levels. When the drug is administered transdermally, the duration of the analgesic effect is longer and there are fewer adverse effects. Buprenorphine is an ideal drug for transdermal delivery because of its good lipophilicity (Sittl, Griessinger, and Likar 2003; Johnson, Fudala, and Payne 2005).

In Finland, transdermal buprenorphine is available with several different patch strengths ranging from 5 µg/hour to 40 µg/hour. Transdermal buprenorphine patches have been found to be effective and well-tolerated in the treatment of malignant and non-malignant chronic pain (Sittl, Griessinger, and Likar 2003; Griessinger, Sittl, and Likar 2005). Transdermal buprenorphine has also been found to be safe in patients who have renal insufficiency (Hand et al. 1990) as well as in elderly patients (Likar et al. 2008).

Buccal buprenorphine was approved for clinical use in the USA in 2015. It was developed for the treatment of chronic pain and is approved for the treatment of pain severe enough to require long term opioid therapy where alternative treatment

opioids are inadequate. It is made from a flexible, water-soluble polymeric film, which ensures rapid absorption and provides a possibility to titrate doses in a flexible manner (Aiyer et al. 2018). This formulation has been found to be promising in the treatment of chronic back pain (Rauck et al. 2016).

Other indications

Buprenorphine is currently investigated for the treatment of depression (Karp et al. 2014) due to its ability to bind also to kappa opioid receptors. There is some evidence that kappa receptors are involved in the stress system and in the pathophysiology of depression (Crowley and Kash 2015). Low dose buprenorphine has been found to be effective and well-tolerated in reducing depressive symptoms even in patients with treatment-resistant depression (Karp et al. 2014; Ehrich et al. 2015; Serafini et al. 2018). Furthermore, there are indications that buprenorphine could significantly reduce suicidal ideation (Striebel and Kalapatapu 2014; Ahmadi, Sarani, and Jahromi 2020).

2.1.4 Sublingual fentanyl as an analgesic agent

Fentanyl has a long history as the most common intraoperative opioid. Fentanyl has a significant role in the treatment of acute and chronic pain and it can be administered intravenously, transdermally and transmucosally (Stanley 2014). The primary sites of therapeutic action of fentanyl are the μ-opioid receptors in the central and peripheral nervous system (Darwish et al. 2007). Fentanyl is a very potent analgesic agent and it is flexible to use because there are various formulations available. A broad range of drug-drug interactions influence significantly its serum concentrations. Fentanyl is highly lipophilic allowing it to diffuse easily across biological membranes (Stanley 2005).

Sublingual fentanyl oral dosage forms are approved for the treatment of breakthrough pain in cancer patients already receiving other forms of opioid therapy (Portenoy et al. 2006; Weinstein, Messina, and Xie 2009). It has been administered also to patients with severe non-malignant chronic pain and it has been found to be effective, safe and well-tolerated (Portenoy et al. 2007; Simpson et al. 2007). The use of sublingual fentanyl has been shown to improve the quality of life in patients suffering from breakthrough pain (Guitart et al. 2015; Cánovas-Martínez et al. 2015). It has been proven to be safe also in elderly patients (Guitart et al. 2019).

Sublingual administration of fentanyl is beneficial due to the rapid onset of action and the avoidance of extensive and variable CYP3A4 mediated metabolism in gut and liver (Zhang et al. 1997). Bioequivalence of buccally and sublingually administered fentanyl was studied in healthy subjects by using a single fentanyl dose

of 400 µg. The systemic exposure following buccal and sublingual administration was found to have similar effects (Darwish et al. 2008). The drug was also well tolerated and patients experienced no severe adverse effects. The most common adverse effects after administration of sublingual fentanyl include nausea, vomiting, somnolence and constipation, which are commonly observed with opioid analgesics (Guitart et al. 2013).

The bioavailability of buccal fentanyl is approximately 65 % (Darwish et al. 2007). After absorption, fentanyl is known to exhibit a quick onset and a short duration of drug effect. It has been shown that after sublingual administration of fentanyl, the first detectable concentrations in plasma are observed in 8-10 minutes and the maximum concentration is reached in 40-50 minutes (Lennernäs et al. 2005). Patients receiving sublingual fentanyl for breakthrough cancer pain have reported the first effect of the drug within 5 minutes of administration and a maximum effect within 30 minutes (Überall and Müller-Schwefe 2011). N-dealkylation is the major route of fentanyl metabolism to norfentanyl (Labroo et al. 1997). Norfentanyl has been recovered in plasma and in urine.

Transmucosal fentanyl has also been evaluated as a premedication in patients undergoing surgery in general anaesthesia and patients having bone marrow aspiration and biopsy. It was found to be effective in decreasing anxiety before general anaesthesia (Singh, Choubey, and Mehra 2017) but it did not reduce the pain during bone marrow aspiration and biopsy (Kuivalainen, Ebeling, and Rosenberg 2013).

2.2 Drug-drug interactions associated with buprenorphine

2.2.1 Cytochrome P450 (CYP) enzymes

The family of CYP enzymes has a significant role in drug metabolism. CYP-enzymes are predominantly located in liver, but also in intestine, lungs and other organs. There are at least 30 different CYP-enzymes which have been identified (Dresser, Spence, and Bailey 2000) and these enzymes are responsible for the oxidative biotransformation of drugs. CYP3A4 metabolizes the greatest number of drugs and together with CYP2D6, CYP2B6, CYP2C9, CYP2C19 and CYP2D6 they are responsible for more than 90% of known oxidative drug metabolism reactions (Pelkonen et al. 2008; Wienkers and Heath 2005). DDI studies have focused on drugs that are substrates, inhibitors or inducers of CYP enzymes because the inhibition or induction of CYP enzymes is the main reason for numerous DDIs (Michalets 1998). Most drugs are metabolized through several CYP forms and drugs that are

metabolized by a single CYP form are more susceptible to drug interactions (Pelkonen et al. 2008).

Enzyme inhibition is usually reversible and it can be divided into competitive, non-competitive, uncompetitive and mixed-type inhibition. Inhibition is competitive when substrate and inhibitor bind to the same position of the enzyme. The active binding site of substrate and inhibitor differ from each other in the non-competitive mode of inhibition. When inhibition is uncompetitive, the inhibitor binds to the enzyme-substrate complex, but not to the free enzyme entity. Both competitive and non-competitive inhibition are observed in mixed-type inhibition. (Pelkonen et al. 2008).

Induction is another type of drug interaction, where drug stimulates excess production of a CYP isoenzyme and the result is increased metabolism of a second agent (DuBuske 2005). This can lead to decreased plasma concentrations and reduced efficacy.

N-dealkylation, the main metabolic pathway of buprenorphine is catalysed mainly by CYP3A4 (Iribarne et al. 1997; Kobayashi et al. 1998). In fact, buprenorphine itself has been found to inhibit CYP3A4 and CYP2D6 *in vitro*, but with therapeutic concentrations of buprenorphine there are no significant interactions with other CYP-metabolized drugs to be expected (Umehara, Shimokawa, and Miyamoto 2002; Zhang et al. 2003). However, it can be presumed that the concomitant use of buprenorphine with drugs which are inducers or inhibitors of CYP3A4 enzyme would lead to an altered pharmacokinetic profile of buprenorphine.

There are some studies where DDIs of high-dose buprenorphine and HIV protease inhibitors have been evaluated. These studies have shown that atazanavir alone and with ritonavir increase the concentrations of buprenorphine and its metabolites in plasma (McCance-Katz et al. 2007). In that study, the authors discussed the possible mechanisms for the increased concentrations of buprenorphine and its metabolites. The most straightforward explanation would be an increased bioavailability of the drug when first-pass metabolism was blocked but it was also possible that the increased concentration of metabolites of buprenorphine might reflect a diversion of buprenorphine metabolism from dealkylation to glucuronidation via inhibition of CYP3A4. Indinavir is also a potent inhibitor of buprenorphine N-dealkylation. Saquinavir has been studied *in vitro*, but it was weaker competitive inhibitor and it was claimed that it probably would not inhibit buprenorphine *in vivo* (Iribarne et al. 1998).

Some *in vitro* studies have shown that ketoconazole, a recognized CYP3A4 inhibitor, is a potent inhibitor of buprenorphine N-dealkylation (Cowan 2003). According to the product monograph of Suboxone® (Suboxone Summary of Product Characteristics), the daily administration of ketoconazole during buprenorphine

maintenance treatment leads to an increase of the C_{max} and AUC of buprenorphine in plasma. Another study explored the effect of ketoconazole on the pharmacokinetics of transdermally administered buprenorphine. They found no significant DDI between ketoconazole and transdermal buprenorphine and the explanation for this finding was assumed to be the lack of pre-systemic metabolism when buprenorphine is administered transdermally (Kapil et al. 2012).

It is estimated that among the opioid users and patients in maintenance treatment psychiatric disorders are very common (Regier et al. 1998). However, there are no clinical interaction studies made with drugs used to treat these disorders. There is only one report in the literature; this is an *in vitro* study with fluoxetine and it showed that fluoxetine-induced CYP2D6 inhibition would be unlikely to significantly affect the metabolism of buprenorphine *in vivo* (Iribarne et al. 1998).

The concomitant use of benzodiazepines and buprenorphine has been reported to lead to serious, sometimes even fatal, interactions, (Reynaud et al. 1998). Benzodiazepines are not considered to be CYP3A4 inhibitors, although some of them are substrates for this enzyme (Saari et al. 2006; 2008). As stated, it has also been predicted that buprenorphine does not significantly inhibit CYP3A4 (Umehara, Shimokawa, and Miyamoto 2002). These interactions are thus more likely to be pharmacodynamic in their nature resulting from respiratory depression.

The first clinical interaction study where withdrawal symptoms were found among the patients using high-dose buprenorphine was published in 2011 (McCance-Katz et al. 2011). In that study, rifampicin was administered orally with a clinically used dose for 15 days. Rifampicin decreased the concentration of sublingual buprenorphine significantly and caused withdrawal symptoms to patients. Rifabutin was also studied with the same method and it was found to decrease the concentrations of buprenorphine as well, but the effect was milder than after rifampicin and did not cause withdrawal symptoms in the patients.

2.2.2 P-glycoprotein

It is well known that CYP enzymes play a major role in drug metabolism and pharmacokinetic drug interactions. However, there are some interactions that cannot be explained exclusively by the inhibition or the induction of the CYP enzymes and it has become apparent that additional mechanisms, e.g. those involving membrane transporter proteins, are also involved in many interactions. P-gp is one of the drug transporter systems, which is thought to participate in some DDIs and DFIs. P-gp is an energy dependent transmembrane efflux protein driven by ATP hydrolysis. It is found in many tissues throughout the body and it is responsible for the transport of many drugs (Ayrton and Morgan 2001). For example, it has been found to be one of the several transmembrane efflux transporter proteins in the blood brain barrier. The

absorption, distribution, and excretion of drugs can be altered when active drug transporter systems are inhibited or induced. Many drugs and foods that affect CYP enzymes have also an effect on P-gp (Lin 2003; Yasuda et al. 2002). For example, while rifampicin is known to be a strong inducer of CYP3A4, it also enhances the activity of P-gp (Greiner et al. 1999; Niemi et al. 2003). When drug metabolism is not extensive, transporter proteins probably play the primary role in the absorption and excretion of various substances. P-gp is found in high levels in the small and large intestine, in the luminal membranes of renal proximal tubules and in the biliary canalicular membrane of hepatocytes. The presence of P-gp in these tissues suggest that it facilitates excretion of substances into urine, bile and into the intestinal lumen (DuBuske 2005). The normal transport function of P-gp may be interfered by other drugs and this can lead to clinically significant alteration in serum drug concentrations.

Several opioids are known to be substrates of P-gp, including morphine, methadone and fentanyl (Dagenais, Graff, and Pollack 2004). The role of P-gp in the transport of buprenorphine is not clear. *In vitro* studies in rodents suggest that norbuprenorphine, but not buprenorphine, is a substrate of P-gp (Hassan et al. 2009; Brown et al. 2012).

2.2.3 UGTs

UDP-glucuronosyl transferases (UGTs) play a significant role in the second metabolic pathways of 20-30 % of the currently marketed drugs (Stingl et al. 2014). After the CYP enzymes UGTs hold the second place as the primary metabolic pathway (Wienkers and Heath 2005; Williams et al. 2004). Buprenorphine and norbuprenorphine undergo glucuronidation by UGTs to B3G and N3G (Bruce et al., 2006). UGT2B7 is responsible for more than 40% of buprenorphine glucuronidation while norbuprenorphine glucuronidation is mainly mediated by UGT1A3 (Rouguieg et al. 2010). Glucuronidation is considered as a detoxification and inactivation pathway but in a recent study both B3G and N3G were found to have receptor binding and pharmacological activity (Brown et al. 2011). In a recent study the possibility to increase oral bioavailability of buprenorphine by inhibiting UGT enzymes was examined (Maharao, Venitz, and Gerk 2019). In this study, the authors found that with the concomitant use of dietary compounds, that are known to inhibit buprenorphine metabolism by inhibiting UGTs, it was possible to achieve higher and less variable bioavailability of orally administered buprenorphine. The UGTs are also induced and inhibited by the same drugs that affect the activity of CYP enzymes. Rifampicin is known to induce the activity of UGTs (Niemi et al. 2003) and according to semi-physiological population pharmacokinetic model voriconazole is a UGT2B inhibitor in the gut and liver (Frechen et al. 2013). It is assumed that

inhibition of one metabolic route might cause a diversion to other routes and if metabolites are pharmacologically active the clinical effect of the drug may be significantly altered.

2.3 CYP inhibitors

2.3.1 Voriconazole

Voriconazole is a second generation triazole antimycotic, a derivative of fluconazole. It has been in clinical use since 2001. Voriconazole has a very broad spectrum of antifungal activity and it has become the first-line drug for the treatment of invasive aspergillosis (Boucher et al. 2004). It has also been approved for treatment of candicemia in non-neutropenic patients. However, there are increased number of reports of voriconazole resistance in invasive aspergillosis (Resendiz-Sharpe et al. 2019).

Voriconazole has a high oral bioavailability of over 90 % after oral administration, and it is absorbed rapidly within 2 hours (Purkins et al. 2003). Food delays absorption significantly and therefore voriconazole should be taken in an empty stomach (Purkins et al. 2003). Steady-state concentrations are reached in 5-7 days when voriconazole is administered orally. By using a loading dose, the time to steady-state can be reduced to 1-2 days. There is extensive variability in concentrations of voriconazole and this can be due to CYP2C19 polymorphism (Purkins et al. 2003).

Plasma protein binding of voriconazole is independent of the plasma concentration and the binding rate is found to be 58%. Voriconazole has been shown to penetrate in many tissues, such as the lungs and the central nervous system (Lutsar, Roffey, and Troke 2003; Capitano et al. 2006). Cerebrospinal fluid concentrations of voriconazole are found to be 50% of plasma concentrations and even higher in brain tissue.

Voriconazole is distributed widely to tissues and its volume of distribution is approximately 4.6 L/kg. The mean elimination half-life of voriconazole is 6 hours after steady-state is achieved (Jeu et al. 2003).

There is a broad range of drug-drug interactions which influence significantly serum concentrations of voriconazole. Voriconazole is a substrate for P450 isoenzymes and therefore many drug-drug interactions must be considered. Voriconazole has a narrow therapeutic index and it displays non-linear pharmacokinetics. Co-administration of voriconazole with other drugs that are substrates of the CYP metabolic enzymes may lead to clinically relevant toxicity if the therapeutic index of the drug is narrow. Voriconazole is known to be a competitive inhibitor of many CYP enzymes and this inhibition has been detected in

several drug-drug interaction studies (Saari et al. 2007; Hagelberg et al. 2009; Saari et al. 2008).

The most common adverse effect of voriconazole is visual disturbances and it has been reported that almost 30 % of patients experienced a change in colour vision and blurred vision and this typically lasted 30 minutes and resolved spontaneously. Elevations in liver function markers and skin reactions have also been reported to be quite common adverse effects during voriconazole therapy (Jeu et al. 2003; Denning et al. 2002).

2.3.2 Posaconazole

Posaconazole was approved for clinical use in September 2006 and it was developed for prophylaxis and treatment of fungal infections in immunocompromised individuals such as patients with hematologic malignancies and allogenic stem stell transplant recipients. Posaconazole has been found to be more effective than fluconazole (Ullmann et al. 2007) and it improves the overall survival in patients with acute leukemia or myelodysplastic syndrome patients undergoing intensive chemotherapy (Cornely et al. 2007). Delayed release tablets of posaconazole were released for clinical use in November 2013 and an intravenous formulation for the treatment of invasive aspergillosis in March 2014.

The relative bioavailability of oral posaconazole has been observed to be significantly increased when the daily dose is divided into several smaller doses. The relative bioavailabity was increased by 98% when administered as two different doses 12 hours apart comparing to single dose administration (Ezzet et al. 2005). In addition, concomitant food intake with posaconazole increases the bioavailability of posaconazole significantly (Courtney et al. 2004) and whenever possible posaconazole should be administered with a full meal. The maximum plasma concentration of posaconazole is reached in 5-8 hours following single dose administration (Courtney et al. 2003). Different studies report the median t_{max} to be 3-6 hours and it takes 10 days to reach steady-state concentrations with oral twice-daily dosing (Courtney et al. 2003; 2004; Ezzet et al. 2005).

Posaconazole undergoes a very extensive degree of binding to plasma proteins (>98%) and the binding is independent of concentration. The values for volume of distribution at steady-state have ranged from 5L/kg to 25L/kg (Courtney et al. 2003; Krieter et al. 2004). This suggests extensive penetration into intracellular spaces. However, posaconazole is found to penetrate poorly into cerebrospinal fluid because of its high degree of protein binding (Perfect et al. 1996).

CYP enzymes do not participate significantly in the metabolism of posaconazole. Posaconazole is primarily an inhibitor of CYP3A4 and does not have an effect on the other studied CYP isoenzymes (1A2, 2C8, 2C9, 2D6 and 2E1) (Wexler et al.

2004). Posaconazole passes into plasma after absorbtion and then it is widely distributed to the tissues and thus slowly eliminated. It has been found that UGTs are responsible for most of the metabolism of posaconazole (Ghosal et al. 2004).

2.4 CYP inducer

2.4.1 Rifampicin

Rifampicin was discovered in 1965. It was first clinically used in Italy in 1968 and it was approved in the USA in 1971. Rifampicin was introduced as a part of combination therapy for tuberculosis and it shortened the duration of treatment from 18 to 9 months (Zumla, Nahid, and Cole 2013). Rifampicin is mainly bacteriocidal antibiotic and its effect is based on the inhibition of the bacterial DNA-dependent RNA polymerase activity (Campbell et al. 2001). In addition to the treatment of tuberculosis, rifampicin is often used in the treatment of staphylococcus infections (Turnidge and Grayson, 1993).The optimal dosage of rifampicin has not been definitely established and the current recommendation from the guideline of the WHO is still the same as it was at the time of the introduction of rifampicin (Van Ingen et al. 2011). Rifampicin has a very wide spectrum, but because of high amounts of resistant bacterial strains it is often used as a combination with other antibacterial agents.

When administered on an empty stomach rifampicin is almost completely absorbed (Acocella 1978). The peak plasma concentration of rifampicin after single oral dose is achieved in 2 hours. Rifampicin has a high degree of binding to plasma proteins (~80%). High concentrations of rifampicin have been detected in various tissues, such as cerebrospinal fluid. The strong induction of CYP3A4 by rifampicin has been detected one day after the first administration of the drug.

Rifampicin is mainly excreted into bile by liver but also into urine by kidneys. The main metabolite of rifampicin is desacetylrifampicin, which is an active but weaker antimicrobial agent than the parent drug (Acocella 1978). The elimination half-life of rifampicin can be shortened to 2-3 hours due to its significant autoinductive effect (Loos and Musch, 1985). Severe adverse effects during rifampicin treatment are rare, but urine, feaces, saliva, tears and sweat may be colored reddish. This is a reversible effect and disappears after discontinuation of medication.

Many clinically relevant interactions of rifampicin have been reported in the literature (Saarikoski et al. 2013; Backman et al. 1998). Rifampicin is known to be one of the strongest inducers of orally administered substrates of CYP3A4 and P-glycoprotein. This can even lead to a total loss of effect of some drugs if they are taken in combination with rifampicin (Villikka et al. 1997). It has also been shown

that the oral bioavailability of digoxin, a substrate of P-gp, was significantly reduced after concomitant rifampicin administration in healthy subjects (Greiner et al. 1999). Rifampicin induces also other CYP enzymes such as CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19 and CYP3A5(Niemi et al. 2003).

2.5 Colonoscopy

2.5.1 Pain during colonoscopy

Colonoscopy is considered as an uncomfortable and often painful procedure for the patient. The cause of pain during colonoscopy is mainly due to the stretching of the mesenteric attachments. The minor cause for pain is the pressure of air distension (Waye 2002). Several studies have found female gender, younger age, lower BMI, irritable bowel, anxiety and anticipated discomfort and technically difficult insertion to be independent factors related to the patient's discomfort during colonoscopy (Elphick et al. 2009; Park et al. 2007). The poor quality of bowel preparation and a less experienced colonoscopist have been associated to reduced completion rate and increased ceacal intubation time (Cirocco and Rusin, 1995). A history of gynaeco-pelvic surgery has also been related to higher discomfort during colonoscopy (Park et al. 2007).

The reliable assessment of pain is difficult because pain is such a subjective, personal and private experience. However, a valid assessment of pain is essential for effective pain management and for successful clinical trials. There are some well-known scales for the assessment of pain intensity. Both visual analogue (VAS) and numerical rating scales (NRS) have been found to be valid (Jensen, Miller, and Fisher 1998; Ferreira-Valente, Pais-Ribeiro, and Jensen 2011) and superior to a four point verbal categorical rating scale (VRS) (Breivik, Björnsson, and Skovlund 2000). When assessing postoperative pain, the NRS and VAS have been shown to give almost identical values in the same patient. There are some studies though that seem to indicate that NRS may be slightly more sensitive than VAS (Ferreira-Valente, Pais-Ribeiro, and Jensen 2011). Furthermore, a NRS with numbers starting from 0 and ending at 10 is thought to be more practical and easier to understand for most people than VAS. NRS is easier to use and no clear vision, paper or pen are needed. NRS can also be used during a telephone interview (Breivik et al. 2008). When pain is assessed with the NRS scale, no pain is defined as 0, mild pain as 1-3, moderate pain as 4-6, severe pain as 7-9 and the worst pain imaginable as 10 (Fig 2).

Colonoscopy was developed to be a non-sedated procedure. However, procedural difficulties, pain and uncomfortable experiences by patients have led to the introduction of sedation prior to colonoscopy. Non-sedated colonoscopy has acquired a negative popular image (Leo 2004). However, there are many ways other

than medicinal sedation to make this procedure more comfortable and less painful for the patient. By using a small-calibre colonoscope the mean pain scores were found to be significantly lower during the procedure (Sato et al. 2013). Transcutaneous electrical nerve stimulation (TENS) has been reported to be effective in relieving pain during colonoscopy (Amer-Cuenca et al. 2011). It has also been shown that using water instead of air in ceacal intubation reduces the need of sedation and the degree of pain (Lin et al. 2013). Several studies also suggest that listening to music during colonoscopy can relieve the patient's anxiety and pain (Ko, Leung, and Wong 2019; Ko et al. 2017).

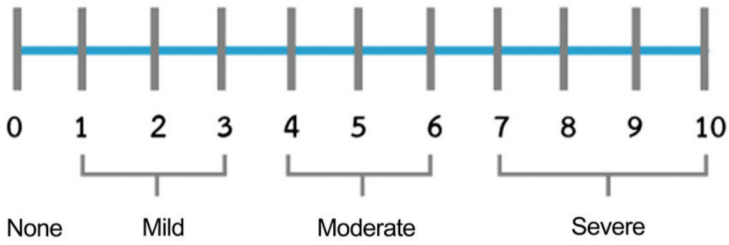

Figure 2. Numerical rating scale 0-10 for pain.

2.5.2 Sedation and analgesia

By applying sedation to colonoscopy it is possible to minimize the discomfort and pain experienced by the patient (Vargo et al. 2002; Terruzzi et al. 2001). At its best, sedation can facilitate the work of the endoscopist and decrease the duration of procedure. However, the risk of cardiorespiratory complications is increased when sedation is used (Ristikankare et al. 2000; Rex, Imperiale, and Portish 1999). Sedation also increases the costs of colonoscopy because of the need of monitoring, more staff as well as longer recovery time (M. Ristikankare et al. 1999; Rex, Imperiale, and Portish 1999). Most of the colonoscopies are performed as outpatient procedures and thus the sedation used must ensure safety but also allow rapid recovery of patients.

Definitions for different levels of sedations have been published by American Society of Anesthesiology (ASA) (Early et al. 2018). The sedation levels are divided into minimal, moderate and deep sedation. Moderate sedation, also called conscious sedation, is the most commonly used level of sedation and it is usually induced by the combination of midazolam and fentanyl. At the level of moderate sedation, the patient maintains ventilatory and cardiovascular function and can respond to verbal stimuli adequately.

There are remarkable differences in sedation practices between countries. In some European countries most of the colonoscopies are done without sedation

(Froehlich et al. 2006) while in the USA and UK, sedation is used in almost all colonoscopies (Bowles et al. 2004; Cohen, Wecsler, and Gaetano 2006). These differences are explained by cultural considerations, patient attitudes and expectations, budgets and resources (Terruzzi et al. 2001). A large multicentre European survey on sedation practices for colonoscopy reported that from 6000 colonoscopy cases 53 % received moderate sedation, 30 % deep sedation and 17 % without sedation (Froehlich et al. 2006).

The most commonly used drugs for sedation are midazolam and opioids, usually fentanyl or pethidine, or a combination of these agents (Froehlich *et al.*, 2005). It has been shown that with relatively small doses of fentanyl or alfentanil combined with midazolam adequate sedo-analgesia and high patient satisfaction can be achieved (Usta et al. 2011). It has also been suggested that sedation improves the overall quality of colonoscopy (Salvador Baudet and Aguirre-Jaime 2019). On the other hand, routinely administering midazolam sedation did not increase patient tolerance nor did it make colonoscopy technically easier in a previous Finnish study (Ristikankare et al. 1999). There are a few studies where opioid alone has been used during colonoscopy but more commonly the opioid has been combined with midazolam or propofol. However, in one study a small dose of intravenous fentanyl was found to provide adequate pain relief during colonoscopy (Lazaraki et al. 2007). Nitrous oxide has also been reported to be effective for pain relief during colonoscopy, it is even thought to provide better pain relief and faster recovery than the midazolam-fentanyl combination (Maslekar et al. 2009; Wootton 1998).

A recent meta-analysis suggested that propofol would be superior to traditional sedative agents. Recovery and discharge times were shorter and the satisfaction score was greater than with benzodiazepines (Zhang, Zhu, and Zheng 2018). However, propofol sedation is associated with longer recovery times as compared with sedation with midazolam and fentanyl in elderly patients (Lovett et al. 2017). The use of propofol doses that provide deep sedation might predispose patients to an increased risk of perforation (Adeyemo et al. 2014).

Dexmedetomidine is a rather new sedative agent which has minimal adverse effects on respiratory function. It has been shown that dexmedetomidine sedation during colonoscopy achieves higher satisfaction and lower NRS scores than midazolam (Dere et al. 2010). Dexmedetomidine has also been compared to small doses of intravenous fentanyl and there were no differences in either patient or colonoscopist satisfaction with the procedure nor in the duration of colonoscopy, but mean pain score during colonoscopy was lower when dexmedetomidine was used (Amri et al. 2018). However, there are many studies that advocate that colonoscopy can be successfully completed without sedation (Leung 2011; Ylinen et al. 2009; Ristikankare et al. 1999; Iqbal et al. 2016).

2.5.3 Recovery after procedure

Sedation during colonoscopy increases the costs and the time spent in the procedure. Non-sedated colonoscopy naturally offers the possibility to discharge the patient immediately after the procedure and the patient is able to leave without requiring an escort and to drive home. There is a group of patients who value the possibility to return to their daily activities as quickly as possible (Subramanian, Liangpunsakul, and Rex 2005). However, the majority of the patients undergoing colonoscopy prefer sedation during the procedure. Ideal sedation should provide good analgesia and relief of discomfort, but the drug effect should be short and should not cause mental or psychomotor impairment after the end of the procedure.

Most often sedation is carried out with low-dose midazolam alone or combined with an opioid. Sarasin et al. reported that midazolam and propofol caused an equivalent impairment of cognition and psychomotor functions, but the duration of the effect of midazolam was longer (Sarasin, Ghoneim, and Block 1996). When compared to midazolam, dexmedetomidine was found to provide better sedation and lower pain scores but there were no differences between the groups when comparing recovery times (Dere et al. 2010). Patient-controlled nitrous oxide has been claimed to be effective during colonoscopy and it allowed a faster recovery compared to midazolam-fentanyl sedation (Maslekar et al. 2009). The mean time to discharge was 28 minutes in the nitrous oxide group and 51 minutes in the midazolam fentanyl group and the recovery of function at discharge was found to be 100 % in nitrous oxide group and 87.3 % in midazolam-fentanyl group.

It has been reported that single use of intravenous fentanyl in colonoscopy was effective and could significantly shorten recovery times (Lazaraki et al. 2007). Patients received either a mean dose of 4.6 mg of intravenous midazolam or 36 µg of intravenous fentanyl. The mean recovery time was 5.6 minutes in the fentanyl group and 16 minutes in the midazolam group. To the best of our knowledge, there are no studies where other than intravenous formulation of fentanyl has been evaluated in patients undergoing colonoscopy.

Propofol was found to offer a faster and more predictable recovery in meta-analysis of 36 randomized studies (McQuaid and Laine 2008). In another meta-analysis of 22 randomized controlled trials propofol was associated with both shorter recovery and discharge times (Wang et al. 2013). A recently conducted meta-analysis suggested that propofol would be superior to traditional sedative agents in the terms of shorter recovery and discharge times (Zhang, Zhu, and Zheng 2018). However, in the elderly patient population propofol was reported to prolong the recovery time compared to a combination of midazolam and fentanyl (Lovett et al. 2017). The mean recovery time was estimated to be 50 minutes in the propofol group as compared to 31 minutes in patients administered both midazolam and fentanyl. Poulos et al. also compared propofol and midazolam-fentanyl sedations but the result

was opposite, recovery in the propofol group was shorter (Poulos et al. 2013). The patients in this latter study were relatively young, the mean age of the cohort was 56 to 57 years. Propofol has also been used for procedural sedation in the combination with short acting opioids. Interestingly, propofol combined with alfentanil was found to cause less cognitive dysfunction than propofol alone or when combined with fentanyl (Doğanay et al. 2017). There was no difference in patient satisfaction between the groups. The median propofol consumption was 150 mg in the alfentanil group, 100 mg in the fentanyl group and 230 mg in the propofol group, respectively. Alfentanil combined with midazolam was also reported to provide shorter sedation than fentanyl combined with midazolam (Usta et al. 2011). Borrat et al. used computerized tests to evaluate the recovery of cognitive function after deep propofol and remifentanil sedation (Borrat et al. 2019). They found that cognitive function had completely recovered in all patients 40 minutes after propofol and remifentanil infusions.

2.5.4 Patient satisfaction

Patient comfort during the colonoscopy procedure is important for patient satisfaction (Maslekar et al. 2010) and willingness to undergo a repeat examination if needed (Hoffman, Butler, and Shaver 1998). The assessment of comfort is, however, as complex as the assessment of pain because the experience is subjective and patients' expectations and tolerance differ. In a recent study significant discomfort was associated with longer colonoscope insertion times and longer colonoscope withdrawal times (Ball et al. 2015). Interestingly, in that study, patients receiving no sedation were least likely to feel significant discomfort. It has also been indicated in other reports, that routinely administered low-dose midazolam does not relieve the discomfort during colonoscopy (Elphick et al. 2009; Ristikankare et al. 1999). In a study where intravenous dexmedetomidine and intravenous fentanyl were compared for sedation during colonoscopy, although the mean pain score was lower in the dexmedetomidine group, there were no significant differences in the patients' satisfaction between the groups (Amri et al. 2018). When compared to midazolam, higher satisfaction scores were obtained with the application of dexmedetomidine (Dere et al. 2010). There are not many studies where an opioid has been used as a single drug for sedation. Lazaraki et al. reported that a small dose of intravenous fentanyl produced significantly lower discomfort scores than obtained with intravenous midazolam alone (Lazaraki et al. 2007). In the fentanyl group the mean discomfort score was 0.4 whereas it was 1.0 in the midazolam group.

There are countries, where most of the colonoscopies are done without sedation. In Germany, sedation is used in only 5% of colonoscopies (Froehlich et al. 2006). There is no recent data about sedation practices in Finland, but 20 years ago, most

colonoscopies were performed without sedation (Ristikankare and Julkunen 1998). However, globally most patients prefer sedation during colonoscopy. Subramanian et al. used a questionnaire to reveal the pre-procedure patient values regarding sedation use for colonoscopy (Subramanian, Liangpunsakul, and Rex 2005). A total of 210 American patients participating in that study placed the highest valuation on experiencing no pain during procedure, waking up promptly after the procedure and for going to sleep and not waking until the procedure was over. There was a small group of patients, 6.2 % of the participating subjects, who preferred colonoscopy without sedation. Norwegian group assessed patient satisfaction with on-demand sedation and they also wanted to identify factors related to moderately or severely painful colonoscopy (Seip et al. 2010). They gathered 12354 patient reports from nine endoscopy centres. The mean rate of painful colonoscopies was 34% and sedation had been used on average in 34% of colonoscopies. However, high sedation rates were not associated with low rates of painful colonoscopies. Patient satisfaction with service and information given was greater than 95% for all centres.

Several meta-analyses have shown that when sedation is implemented with propofol significantly higher satisfaction scores are achieved compared to traditional sedation with midazolam and opioid (Zhang, Zhu, and Zheng 2018; Wang et al. 2013; McQuaid and Laine 2008). High patient satisfaction has also been associated with the use of nitrous oxide (Maslekar et al. 2009) and patient controlled analgesia (Külling et al. 2004; Usta et al. 2011). Both are considered safe and effective during colonoscopy. It is also possible to achieve good patient satisfaction without sedation; there are several non-medical methods, such as hypnosis, music, TENS and the use of a small calibre colonoscope, which may reduce the amount of discomfort and increase patient satisfaction during colonoscopy (Leung 2008).

3 Aims of the Study

New dosage forms of buprenorphine have increased the use of low-dose buprenorphine in the treatment of chronic pain. High doses of buprenorphine are used to treat opioid dependence and some interaction studies of high-dose buprenorphine have been conducted. However, currently the literature holds very little information about interactions occurring with low dose buprenorphine.

Colonoscopy is considered an unpleasant and painful procedure. Traditionally, colonoscopies have been performed without sedation in Finland, but globally, most patients prefer sedation. Intravenous sedation increases the costs and length of the procedure. Sublingually administered fentanyl is a non-invasive method capable of relieving pain and making the procedure more comfortable for the patient. Compared to intravenous sedation, the sublingual administration route could be more cost-effective and easier to implement.

The specific aims for these studies were:

1. To study the possible effects of voriconazole and posaconazole on the pharmacokinetics and pharmacodynamics of sublingual buprenorphine (Study I)
2. To determine the possible effect of voriconazole on the pharmacokinetics and pharmacodynamics of oral buprenorphine (Study II)
3. To evaluate the effect of rifampicin on the pharmacokinetics of sublingual and intravenous buprenorphine (Study III)
4. To examine how the route of buprenorphine administration affects the pharmacokinetic interactions of buprenorphine (Studies I-III)
5. To evaluate the efficacy and safety of sublingually administered fentanyl tablet in patients undergoing colonoscopy (Study IV)

4 Materials and Methods

4.1 Interaction studies

4.1.1 Subjects

Altogether 36 healthy male and female volunteers participated in interaction studies I-III. The demographic details of subjects are shown in Table 1.

We recruited 12 healthy non-smoking volunteers into each of three studies. Recruitment was carried out by emails directed to university students. If subjects were interested in the study, they contacted the investigator by phone or email and received more information about the study. If they still were interested to participate, they were invited to attend a personal visit.

Table 1. Characteristics of volunteers (mean (range)) in Studies I-III.

	Sex F/M	Age years (range)	Weight kg (range)	BMI kg/m^2 (range)
I	4/8	20 (19-23)	67(52-81)	22 (20-25)
II	4/8	22 (18-29)	71 (57-90)	23 (21-28)
III	6/6	21 (19-23)	73 (57-95)	23 (19-26)

F = female; M = male; BMI = body mass index

During the personal visit volunteers were informed about the details of the study protocol. Clinical examination including blood pressure in the sitting position and routine laboratory tests including complete blood count (hemoglobin, hematocrit, differential white blood cell count and platelet count), serum aspartate aminotransferase, alanine transferase, alkaline phosphatase, blood urea nitrogen and creatinine and urine tests for glucose, proteins, drugs with addiction potential (amphetamine, cannabis, cocaine, opioids, phencyclidine, methadone, dextropropoxifen and benzodiazepines), were performed to evaluate the participants' physical health. Their medical history was also obtained and all participants were found to be in good physical health. Urine toxicology and

pregnancy tests were negative and ECGs were within normal limits. The Finnish translation of the Abuse Questions (Table 2) (Michna et al. 2004) was used to evaluate the risk of participants to develop opioid abuse and the risk was found to be low for every participant. Volunteers were not allowed to drink coffee, tea, energy drinks or grapefruit juice for 4 weeks prior to and during the study. Female participants were given instructions to use safe non-hormonal contraception during the study because hormonal contraceptives were not allowed. All subjects gave their written informed consent and the subjects were given instructions on how to perform the pharmacodynamic tests.

The exclusion criteria included concomitant drug therapy, previous history of intolerance to any of the drugs studied, past history of significant disease, alcoholism, drug abuse or psychological or emotional problems, blood donation within 4 weeks prior to the study, and participation in any other studies involving drug products within one month prior to the current study.

Table 2. Abuse Questions by Michna 2004 (Michna et al. 2004).

1.	Is there a history of alcohol or substance abuse in your family, even among your grandparents, aunts, or uncles?
2.	Have you ever had a problem with drugs or alcohol or attended an Alcoholics Anonymous or Narcotics Anonymous meeting?
3.	Have you ever had any legal problems or been charged with driving while intoxicated or driving while influence?

4.1.2 Study design

The data was collected between March 2011 and February 2014. All three studies were carried out using a randomized, balanced, placebo-controlled, cross-over design. Study I consisted of three phases, Study II consisted of two phases and four phases were used in Study III. There was a four weeks' drug-free period in all studies between the phases.

Pre-treatment in Studies I-III

The investigator distributed the research medicines and placebos to volunteers and instructed them to take the pre-treatment at home according to the protocol. Study drugs and placebos were packed in identical plastic containers by a hospital pharmacist who was not involved in the study. Posaconazole was delivered in its original container, but the drug label was removed. The hospital pharmacist delivered the drugs and placebos according to a randomization list. The numbers of drug tablets or placebo capsules per day during the pre-treatment phases were

similar. Adherence with the medicine/placebo dosing schedule was assessed using mobile phone text messages. After taking each dose, the subjects sent a mobile phone text message to one of the investigators. The investigator contacted the subject if no text message was received within 15-20 min after the scheduled dosing time and reminded him/her to take the dose. Voriconazole and posaconazole concentrations were determined in Study I and voriconazole concentrations in Study II. The dosing schedule of the pre-treatments is shown in Table 3.

In Study I the volunteers ingested orally voriconazole (Vfend 200 mg tablet; Pfizer, Sandwich, Great Britain), posaconazole (Noxafil 40 mg/ml oral suspension; Merck Sharp & Dohme, Hoddesdon, Great Britain) or placebo for 5 days twice daily. In Study II voriconazole (Vfend 200 mg tablet; Pfizer, Sandwich, Great Britain) or placebo were administered orally for 5 days twice daily. The pre-treatment used in Study III was either oral rifampicin (Rimapen 600 mg® tabl, Orion, Finland) or placebo once daily for seven days in a randomized order.

Table 3. Design of studies I-III.

	Pre-treatment		**Buprenorphine**
Study	**CYP3A4 inhibitor or inducer**	**Dosing schedule**	**Dosing schedule**
I	**Phase 1** Voriconazole 200 mg tabl	2 tabls at 8 A.M and 8 P.M on day 1 1 tabl at 8 A.M. and 8 P.M. on day 2-4 1 tabl 10 A.M. and 8 P.M. on day 5	0.4 mg SL at 11 A.M. on day 5
	Phase 2 Posaconazole oral suspension 40 mg/ml **Phase 3** Placebo caps	10 ml at 8 A.M. and 8 P.M. on day 1-4 10 ml 10 A.M. and 8 P.M. on day 5	0.6 mg SL at 11A.M. on day 5 (placebo phase)
II	**Phase 1** Voriconazole 200 mg tabl	2 tabls at 8 A.M and 8 P.M on day 1	0.2 mg P.O. at 11 A.M. on day 5
	Phase 2 Placebo caps	1 tabl at 8 A.M. and 8 P.M. on day 2-4 1 tabl 10 A.M. and 8 P.M. on day 5	3.6 mg P.O. at A.M. on day 5 (placebo phase)
III	**Sublingual part**		
	Phase 1 Rifampicin 600mg tabl **Phase 2** Placebo caps	1 tabl at 8 P.M. for 7 days	0.8 mg SL at 11 A.M. on day 7 0.6 mg SL at 11A.M. on day 7 (placebo phase)
	Intravenous part		
	Phase 3 Rifampicin 600mg tabl **Phase 4** Placebo caps	1 tabl at 8 P.M. for 7 days	0.4 mg IV at 11 A.M. on day 7

Administration of buprenorphine

The volunteers spent the study days involving the dosing with buprenorphine in the study facility located in the Department of Pharmacology. The days started at 8 a.m. and the volunteers spent the next 23 hours in this facility.

The volunteers fasted overnight (8 h) before the administration of buprenorphine. Standardized meals were served 4 and 8 h after buprenorphine administration. Volunteers were allowed to drink small amounts of water between the meals, but no other drinks were allowed. For nausea and vomiting, intravenous tropisetron was used, if needed.

A single dose of 0.4 mg (0.6 mg during placebo phase) of sublingual buprenorphine (Temgesic 0.2 mg and 0.4 mg tablets; RB Pharmaceuticals Limited, Slough, Great Britain) was administered on the 5th day of pre-treatment in Study I. In Study II all subjects ingested a single dose of 0.2 mg (3.6 mg during placebo phase) of oral buprenorphine (Temgesic®0.2 tablet RB Pharmaceuticals Limited, Slough, Great Britain) at 11.00 on an empty stomach. Buprenorphine was packed in soluble capsules at the pharmacy to prevent absorption from mucous membranes. In Study III, the subjects were given on the 7th day of pre-treatment sublingually 0.6 mg or 0.8 mg buprenorphine (Temgesic 0.2 mg® resoriblets; RB Pharmaceuticals Limited, Slough, Great Britain) after placebo or rifampicin, respectively. In the second part of the Study III, subjects received an intravenous bolus of 0.4 mg buprenorphine (Temgesic 0,3 mg/ml® inj; RB Pharmaceuticals Limited, Slough, Great Britain) after rifampicin or placebo. The dosing schedule of buprenorphine is illustrated in Table 3.

Pharmacokinetic and pharmacodynamic assessments

Blood samples (10 ml) were collected into ethylenediaminetetraacetic acid containing tubes immediately before and 30 min, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 18 h after the administration of buprenorphine for pharmacokinetic measurements. Plasma was separated within 30 min and stored at -70 °C until analysis. Urine was collected up to 18 hr after buprenorphine administration. Urine aliquots were stored at -70 °C until analysis. In Study III, another venous cannula was inserted into the opposite forearm to allow intravenous administration of buprenorphine.

Adverse effects were evaluated using a questionnaire before, and 3 and 6 hours after buprenorphine administration. The subjective effects of buprenorphine were evaluated using a 100-mm visual analogue scale. The Maddox wing test (MWT) was used to measure the central coordination of extraocular muscles (Hannington-Kiff 1970) and pupil size was measured with Cogan's pupillometer (Cogan 1941). A digit symbol substitution test was used to estimate central processing of sensory information by recording the number of correct symbols substituted in 3 min (Stone

1984). The analgesic effect was evaluated using the cold pressor test. Pharmacodynamic reactions were evaluated prior to and at 1, 2, 3, 4, 5, 6, 8, 10 and 12 h after buprenorphine administration.

4.1.3 Determination of plasma drug concentrations

Determination of buprenorphine and norbuprenorphine

The plasma drug concentrations were analysed in the Department of Clinical Pharmacology, at the University of Helsinki, Helsinki, Finland. Mass spectrometric detection of buprenorphine and norbuprenorphine was carried out using an API 3000 Triple Quadrupol tandem mass spectrometer (Applied Biosystems MDS Sciex, Toronto, ON, Canada) as previously described (Ceccato et al. 2003) with minor modifications. The internal standards (buprenorphine-D4 and norbuprenorphine-D3) were added to samples, quality control samples and reference standards before the subsequent pre-analytical procedures.

Plasma and urine samples (0.5 ml) were prepared by use of a Bond Elut C8 solid phase extraction (Agilent Technologies, Lake Forest, CA, USA). Gradient chromatography was carried out using a Model 1100 Series liquid chromatograph (Agilent Tehcnologies) equipped with a binary pump, a vacuum degasser, a thermostatted column compartment and an autosampler. Atlantis HILIC Silica analytical column (2.1x100 mm; Waters, Milford, MA) with precolumn (2.1 mmx10 mm; Waters) were used at 30 ºC. The mobile phase A consisted of a mixture of acetonitrile: methanol: 10 mM ammonium formate + 0.2% formic acid (90:5:5, v/v/v), and the mobile phase B of 10 mM ammonium formate + 0.2% formic acid. The gradients were: 0-0.5 min B=0%, 0.5-5 min B→40%, 5-8 min B=40%, 8.0-8.1 min B→0%, 8.1-20 min B=0%. The flow rate was 0.2 ml/min. The mass spectrometer was operated in the positive multi-reaction monitoring (MRM+) detection mode with electro-spray ionization. The selected ion transitions used for quantification were: m/z 468.3 to m/z 55.1 for buprenorphine, m/z 414.3 to m/z 340.2 for norbuprenorphine, and m/z 472.3 to m/z 59.2 and m/z 417.3 to m/z 83.2 for the internal standards, respectively.

The lower limit of quantification (LLQ) for plasma buprenorphine was 0.02 ng/ml, and for norbuprenorphine 0.05 ng/ml. For urine buprenorphine and norbuprenorphine the LLQ was 0.5 ng/ml. The inter-day coefficients of variation (CV%) were for plasma buprenorphine 8.0% at 5.3 ng/ml, 8.7 % at 0.5 ng/ml and 6.1% at 0.05 ng/ml, and for norbuprenorphine 3.7% at 4.8 ng/ml, 8.7% at 0.48 ng/ml, and 11.9%% at 0.048 ng/ml.

Voriconazole and posaconazole

Plasma concentrations of voriconazole and posaconazole in the samples taken on day 5 before the administration of buprenorphine were determined by a liquid chromatograph equipped with a Waters Symmetry C8 column (Waters) and UV-detection at 255 nm as described before (Chhun et al. 2007). Diazepam was used as the internal standard, the limit of voriconazole and posaconazole quantification was 10 ng/ml. The CVs for voriconazole and posaconazole were below 10% at relevant plasma concentration range, i.e. for voriconazole 7.5% at 4000 ng/ml, 3.0% at 1100 ng/ml, and 5.5% at 110 ng/ml, and for posaconazole 5.0% at 4000 ng/ml, 1.7% at 1100 ng/ml, and 9.4% at 110 ng/ml.

4.1.4 Pharmacokinetic calculations

The peak plasma concentrations (C_{max}) and the corresponding time to C_{max} (t_{max}) of buprenorphine and norbuprenorphine were observed directly from the data. The areas under the buprenorphine and norbuprenorphine plasma concentration–time curves (AUC) from 0 to 18 h ($AUC_{0–18}$) were calculated by noncompartmental methods using WinNonlin pharmacokinetics program (version 4.1; Pharsight, Mountain View, CA). The terminal log-linear part of each concentration–time curve was identified visually, and the elimination rate constant (k_e) was determined from the logarithmically transformed data using linear regression analysis. The $t_{½}$ was calculated using the equation $t_{½} = ln2/k_e$. The cumulative amount of unconjugated buprenorphine and unconjugated norbuprenorphine excreted into urine was calculated from 0 to 18 h (A_e), and the renal clearance (Cl_{renal}) using the equation $= A_e/AUC_{0-18}$. All pharmacokinetic parameters were normalized for a buprenorphine dose of 1.0 mg.

4.1.5 Pharmacodynamic measurements

Pharmacologic responses were evaluated prior to and at 1, 2, 3, 4, 5, 6, 8, 10 and 12 h after buprenorphine administration. Adverse effects were evaluated using a questionnaire before, and 3 and 6 hours after buprenorphine administration.

Subjective effects

The subjective effects of buprenorphine were evaluated using 100-mm visual analogue scales for the following seven items: drowsy/alert, very poor performance/very good performance, no drug effect/very strong drug effect, relaxed/anxious, unpleasant feeling/pleasant feeling, no nausea/very strong nausea, calm/restless. The participants were asked if they were experiencing the following

adverse effects: dizziness, weakness, fever, headache, increased sweating, nausea, anxiety, sleeping disorders, dryness of the mouth, coordination disorder and tiredness.

Maddox Wing Test

The Maddox wing test was used to measure the central coordination of extraocular muscles (Hannington-Kiff 1970). The subject looked into the Maddox Wing apparatus and oblique and vertical wings divided their vision. In this test, the left eye sees a horizontal numbered scale and the right eye sees an arrow. Divergence of the eyes resulted in an image such as the arrow would move. The number at which the arrow seems to point when stopped is registered and this indicates the diopters.

Cogan's pupillometer

Pupil size was measured with Cogan's pupillometer (Cogan 1941) as a measure of opioid effect. Subjects looked through black plastic sheet (Cogan's pupillometer) with one eye in stable light conditions. In the sheet there was a column of small hole pairs at an increasing distance of 0.5 mm from each other. The volunteers found the first hole-pair where a separate view of each hole could be seen. The size of this hole-pair in millimetres represented the pupil size.

Digit symbol substitution test

A digit symbol substitution test was used to estimate central processing of sensory information by recording the number of correct symbols substituted in 3 min using pencil and paper (Stone 1984). A model of nine digits with corresponding symbols was presented at the top of the paper. A total of 300 digits (9 different) were organized in 12 rows on each paper in a randomized order. To prevent learning the order of the symbols was changed at every testing time point. Subjects had 3 minutes time to substitute digits with correct symbols and the number of correct symbols was recorded.

Cold pain sensitivity

The analgesic effect was evaluated using the cold pressor test. The subject immersed his/her hand up to the wrist in ice-cold water at a temperature of 0–2 °C. The time from the immersion to the first sensation of pain was defined as the cold pain threshold. Subjects reported the pain intensity and unpleasantness at 30 s and 60 s after immersion on a numerical rating scale (0 = no pain or unpleasantness, 100 =

maximal pain or unpleasantness). If pain became intolerable, the pain intensity was recorded as maximal (100).

4.2 Clinical study

4.2.1 Subjects

Altogether 158 patients undergoing diagnostic or therapeutic colonoscopy in the Department of Endoscopies in the University Hospital of Turku were recruited to participate in this study. Male and female patients aged 18 to 80 years, with physical status (ASA) classified as I–III according to the American Society of Anesthesiologists' guidelines, body mass index (BMI) < 35 and a weighing over 50 kg scheduled for routine diagnostic or therapeutic colonoscopy were eligible for the study. Patients with previous gastrointestinal surgery, sleep apnea, chronic obstructive pulmonary disease, SpO2 <90%, pregnancy or nursing or concomitant drug therapy known to cause significant enzyme induction or inhibition of CYP 3A4 were excluded. Further exclusion criteria were a history of intolerance to the study drug or related compounds, a history of alcoholism, drug abuse, psychiatric, psychological or other emotional problems that were likely to invalidate informed consent. Patient characteristics are summarized in Table 4. Subjects were informed about the study before the procedure and they were told that participating was fully optional and participating or refusal would not affect their treatment in any way.

Table 4. Patient demographic characteristics in Study IV.

	Placebo	**Fentanyl**
Mean age, years (±SD)	59.9 ± 13,5	57.9 ± 13.6
Male/female, n	39/33	39/33
Mean height, cm (±SD)	170 ± 9.7	172 ± 8.9
Mean weight, kg (±SD)	79.3 ± 14.8	82.9 ± 19.5
Median length of the procedure, min (range)	15 (5-40)	20 (5-50)
Median time between the end of colonoscopy and hospital checkout, min (range)	25 (5-90)	25 (9-60)

4.2.2 Study design

A randomized double-blind and placebo-controlled study design was used. Subjects were randomized to receive either sublingual Fentanyl (Abstral ® 100 µg,

ProStrakan) or a placebo ten minutes before the procedure. The patients were randomized into two groups by using the sealed envelope technique. All patients, investigators, and staff members involved in the conduct of the study were blinded to treatment assignment. Patients were instructed not to swallow the tablet but to allow it to dissolve completely in the sublingual cavity without chewing or sucking. Patients were not allowed to eat or drink anything until the sublingual tablet had completely dissolved.

The patients assessed the average pain using a numerical rating scale (NRS 0-10) during the procedure and at the end of colonoscopy. Adverse effects of opioids (nausea/drowsiness) and patients' subjective effects were recorded at the end of colonoscopy. The patients also scored their overall satisfaction with the procedure prior to discharge. The adverse effects of opioids were evaluated using NRS (0-10) for the following items: drowsiness (alert / very drowsy), pleasantness (very unpleasant / very pleasant feeling), and nausea/vomiting (no nausea / very strong nausea). Furthermore, the endoscopist and the assisting nurse evaluated using NRS whether the patient seemed to experience pain, the level of sedation, nausea and judged the overall flow of the procedure at the end of colonoscopy. The endoscopist also estimated the level of technical difficulties associated with the colonoscopy.

SpO_2 and respiratory rate were followed throughout the procedure. If the peripheral arterial oxygen saturation decreased below 90 % or respiratory rate decreased below 8 per min, additional oxygen was given. In case of excessive opioid effects, 0.1 mg of naloxone was to be administered.

The patients were interviewed by telephone on the first day after the procedure. The patients assessed their anxiety before the procedure by using a scale from 1 to 4 (1= no anxiety, 4= maximal anxiety). Patients evaluated how well they could remember events during and after the colonoscopy on a scale from 1 to 4 (1=remember everything, 4= cannot remember anything). The level of abdominal pain was assessed using a scale from 1 to 4 (1= no pain, 4=a lot of pain). Patients were also asked whether they had experienced any adverse effects during the day after the procedure such as abnormal tiredness, nausea or dizziness and evaluated these symptoms from 1 to 4 (1= no drowsiness/nausea/dizziness, 4= great amount of drowsiness/nausea/dizziness). Patients assessed the unpleasantness of the colonoscopy from 1 to 4 (1= not at all, 4= very unpleasant).

4.3 Statistical analysis

Based on previous studies (Hagelberg et al. 2009; Hynninen et al. 2007; Saari et al. 2010) it was estimated that 10 subjects would be required to detect a 30% difference in the $AUC_{0-\infty}$ of buprenorphine at a power of 80% and a level of significance $P < 0.05$. Enrolling 12 subjects allowed a 20% dropout rate.

The data from interaction studies were evaluated for the normality of distribution using probit plots and the Shapiro–Wilk's W-test. Data were log-transformed for analysis but are reported as nontransformed results. The $AUC_{0-\infty}$ of buprenorphine was the primary outcome variable in Studies I and III and the $AUC_{0\text{-}18}$ of buprenorphine in Study II. Geometric mean ratios with 90% CIs were calculated for the pharmacokinetic variables. A lack of interaction was assumed if the 90% CI of the geometric mean ratios for pharmacokinetic variables were within the acceptance limit of 0.8–1.25. Differences in pharmacokinetic variables between study drug and placebo phases were analysed using paired Student's t-test except for t_{max} which was analysed using the Wilcoxon signed-ranks test. In Study II, the Pearson product moment correlation coefficient was used to investigate the possible relationship between the ratios of the AUC_{0-18} of buprenorphine during the treatment phase (voriconazole) to the AUC_{0-18} of buprenorphine during the control phase, as well as to the C_{trough} of voriconazole before the administration of buprenorphine. Differences were regarded as statistically significant at $p < 0.05$. The results are expressed as mean values ± SD. The possible association of plasma buprenorphine concentrations with psychomotor and analgesic effects were also calculated using the Pearson's product moment correlation coefficient. The results are expressed as mean values ± SD. All data were analysed using SYSTAT for Windows (version 10.2; Systat Software, Richmond, CA) in Studies I and III and R software (version 3.2.0) and ggplot2 (version 2.1.0) was used for statistical analysis and graphical presentation in Studies II and III.

A total of 150 patients was planned to be enrolled in Study IV. The sample size was determined based on results of previous studies (Pambianco et al. 2016; Amer-Cuenca et al. 2011) with similar design and was expected to provide adequate data to examine the applicability of sublingual fentanyl during colonoscopy. The primary efficacy endpoint was the amount of pain as assessed with the NRS score. The primary efficacy analysis was summarized descriptively for overall success and within each category by treatment group. P values from chi-square tests (or Fisher exact tests as appropriate) or an analysis of variance model with treatment as the main overall effect with pairwise comparisons being conducted for descriptive purposes.

4.4 Ethical considerations

All study protocols were approved by the Ethics Committee of the Hospital District of Southwest Finland and by the Finnish National Agency for Medicines. The trials were registered before patient enrolment at clinicaltrials.gov and in the EudraCT database. Verbal and written information was delivered to volunteers in Studies I-III before they decided to participate in the study. They gave written informed consent

before starting the study. A written informed consent was obtained from each patient in Study IV. Volunteers and patients were told that they could withdraw from the study at any time. The dosages of the drugs were considered safe and the studies were conducted in facilities where any serious adverse effect could be treated appropriately.

5 Results

5.1 Interaction studies

5.1.1 Pharmacokinetic results

Mean changes in the pharmacokinetic parameters of buprenorphine and norbuprenorphine during the treatment periods are shown in Figures 3 and 4. The effects of pre-treatments on the pharmacokinetics of buprenorphine are summarized in Table 5.

Effect of voriconazole on sublingually administered buprenorphine

Voriconazole elevated the plasma concentrations of sublingually administered buprenorphine significantly. Compared to the placebo phase, the mean $AUC_{0-\infty}$ of sublingually administered buprenorphine was increased by voriconazole by 1.80-fold (GMR 1.80; 90% CI of GMR: 1.45, 2.24; $p<0.001$). The presence of voriconazole increased the C_{max} of sublingually administered buprenorphine by 1.37-fold (GMR 1.37; 90% CI of GMR: 1.05, 1.79; $p<0.001$) and the mean $t_{½}$ from 7.9 h to 11.0 h ($p<0.001$). During all three study phases, in Study I, when buprenorphine was administered sublingually, the plasma concentrations of norbuprenorphine were around or below the LLQ in the most plasma samples.

Effect of voriconazole on orally administered buprenorphine

When buprenorphine was administered orally, voriconazole was found to increase the plasma concentrations of buprenorphine and norbuprenorphine significantly. The mean AUC_{0-18} of oral buprenorphine was increased by voriconazole by 4.3-fold (90% CI 2.7, 6.7 $p<0.001$). Voriconazole increased the C_{max} of oral buprenorphine 3.9-fold (90% CI 2.6, 5.9; $p<0.001$). Voriconazole slightly prolonged the $t_{½}$ of oral buprenorphine ($P < 0.05$) but had no significant effect on the t_{max} of orally administered buprenorphine. When buprenorphine was administered orally, voriconazole increased the mean AUC_{0-18} of norbuprenorphine nearly 4-fold (90% CI 3.0, 5.3; $p<0.001$), and its C_{max} 3.3-fold (90% CI 2.4, 4.4; $p<0.001$).

Effect of posaconazole on sublingually administered buprenorphine

Posaconazole increased the exposure to sublingual buprenorphine, but the effect was rather small. Compared to the placebo phase, the mean $AUC_{0-\infty}$ of sublingually administered buprenorphine was increased by the presence of posaconazole by 1.25-fold (90% CI 1.03-1.52; p=0.016). Posaconazole increased the C_{max} of sublingual buprenorphine by 1.20-fold (0.97-1.48) but the effect was not statistically significant (p=0.206). Posaconazole had no effect on the $t_{½}$ of sublingual buprenorphine. Posaconazole tended to decrease the excretion of norbuprenorphine into urine.

Effect of rifampicin on sublingually administered buprenorphine

Rifampicin reduced the exposure to sublingual buprenorphine. When compared to placebo, the mean $AUC_{0–18}$ of sublingual buprenorphine was decreased by rifampicin by 25% (GMR: 0.75; 90% CI of GMR: 0.60, 0.93). The bioavailability of sublingually delivered buprenorphine decreased by rifampicin from the control value of 22 to 16%, but the influence was not statistically significant (GMR: 0.84; 90% CI of GMR: 0.62, 1.13).

Effect of rifampicin on intravenously administered buprenorphine

Compared to placebo, the presence of rifampicin did not exert any statistically significant effect on the plasma buprenorphine concentrations after intravenous buprenorphine administration.

Effects on the renal excretion of buprenorphine and norbuprenorphine

Voriconazole increased the cumulative amount of norbuprenorphine excreted in urine by 1.6-fold (90% CI 1.18-2.12; p<0.001), when buprenorphine was administered sublingually. In no study phase, in Study I, could the concentrations of parent buprenorphine in urine be reliably quantified as they were much lower than those of norbuprenorphine. Voriconazole increased the amount of unconjugated buprenorphine excreted in urine (p<0.001) but had no significant effect on its Cl_{renal} when buprenorphine was administered orally, because also the $AUC_{0–18}$ of norbuprenorphine was increased. The A_e of unchanged unconjugated buprenorphine was less than 0.1% of the dose during 18 hours even during the voriconazole phase. When buprenorphine was administered orally, voriconazole enhanced the A_e of unconjugated norbuprenorphine by 1.5-fold only (p<0.02) and voriconazole significantly (P < 0.001) reduced its Cl_{renal}.

The cumulative excretion of free, nonconjugated norbuprenorphine in urine was decreased by rifampicin by 65% after sublingual (GMR: 0.35; 90% CI of GMR:

0.24, 0.51) and by 52% after intravenous administration of buprenorphine (GMR: 0.48; 90% CI of GMR: 0.39, 0.58), but the effect on buprenorphine excretion was less consistent.

The mean C_{trough} of voriconazole on day 5 was 1522 ng/ml and the mean C_{trough} of posaconazole on day 5 was 967 ng/ml in Study I. The mean plasma concentration of voriconazole (C_{trough}) was 1022 ng/ml in Study II.

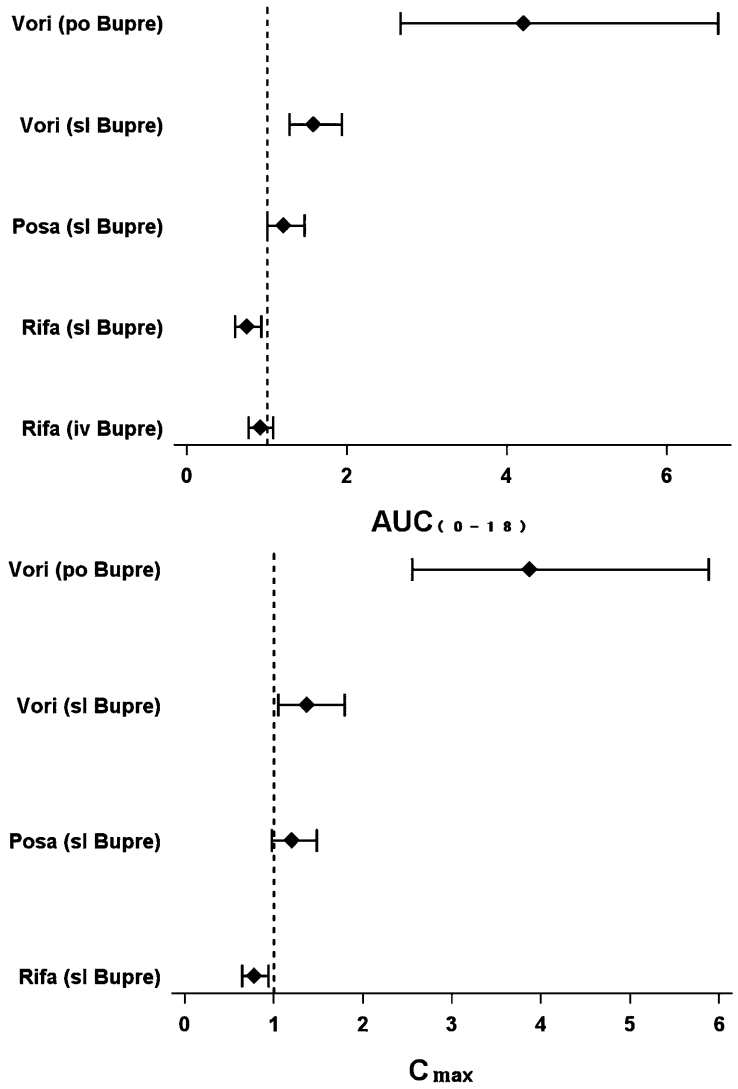

Figure 3. The mean $AUC_{(0\text{-}18)}$ and C_{max} of buprenorphine after pre-treatment with oral voriconazole (vori), posaconazole (posa) or rifampicin (rifa) expressed as geometric mean ratios with the 90% confidence interval. Values are normalized for a buprenorphine dose of 1.0 mg. Bupre = Buprenorphine, po = per oral, sl = sublingual, iv =intravenous.

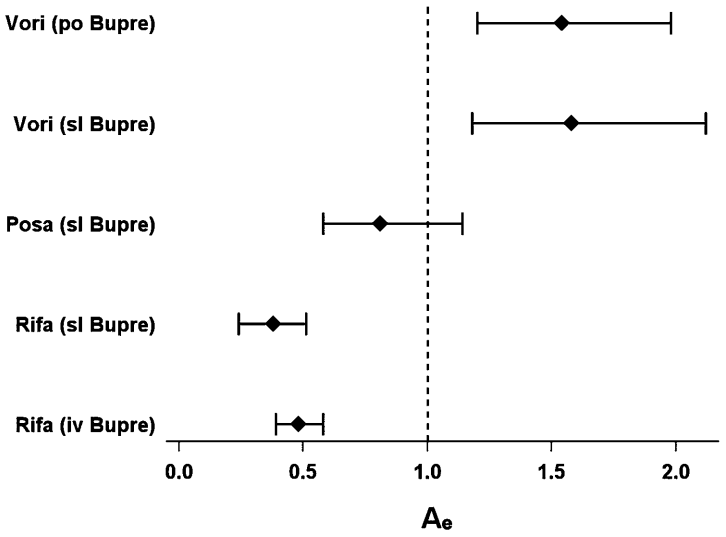

Figure 4. The mean amount of norbuprenorphine excreted into urine (A_e) within 18 h after pre-treatment with oral voriconazole (vori), posaconazole (posa) or rifampicin (rifa) expressed as geometric mean ratios with the 90% confidence interval. Values are normalized for a buprenorphine dose of 1.0 mg. Bupre = Buprenorphine, po = per oral, sl = sublingual, iv =intravenous.

Table 5. Pharmacokinetic parameters of buprenorphine after sublingual (sl), oral (po) or intravenous (iv) buprenorphine administration on the fifth day of pre-treatment with oral placebo (plac), voriconazole (vori), posaconazole (posa) or on the seventh day of pre-treatment with oral placebo or rifampicin (rifa). Values are normalized for a buprenorphine dose of 1.0 mg. Data are shown as mean ± standard deviation (SD), and as *P* values in parenthesis compared to placebo - except for the $t_{max,}$ which is given as median and range.

Study		C_{max} (ng/ml)	t_{max} (h)	$AUC_{(0-18)}$ (ng. h/ml)	$t_{½}$(h)	A_e (µg)
I	Plac (sl Bupre) Vori (sl Bupre) Posa (sl Bupre)	0.70±0.20 0.96±0.27 (0.013) 0.84±0.27 (0.159)	2.0 (1.0-3.0) 2.0 (1.5-3.0) (0.40) 2.0 (1.5-3.0) (0.667)	4.1±1.2 6.5±1.7 (<0.001) 5.0±1.3 (0.026)	7.9±2.8 11.0±3.9 (<0.001) 8.1±2.9 (0.991)	5.7±2.2 9.0±3.1 (<0.001) 4.8±2.2 (0.239)
II	Plac (po Bupre) Vori (po Bupre)	0.057±0.031 0.22±0.23 (<0.001)	0.5 (0.5-18) 2 (0.5-10) (0.06)	0.43±0.26 2.1±1.4 (<0.001)	9.1±2.4 14.5±6.8 (0.042)	0.10±0.063 0.53±0.29 (<0.001)
III	Plac (sl Bupre) Rifa (sl Bupre) Plac (iv Bupre) Rifa (iv Bupre)	0.36±0.15 0.30±0.17 (0.041) - -	1.5 (1-3) 2 (1-3)	1.64±0.74 1.36±0.87 (0.035) 5.32±3.18 4.53±1.64 (0.37)	- - - -	4.35±1.85 1.47±0.66 (<0.001) 4.6±1.9 2.3±1.1 (<0.001)

$C_{max,}$ peak plasma concentration; $t_{max,}$ concentration peak time; $AUC_{(0-18)}$, area under curve from 0 to 18 h; $t_{½}$, elimination half-life; A_e, amount of norbuprenorphine excreted into urine within 18 h.

5.1.2 Pharmacodynamic results

Between the study phases, there were no statistically significant differences in the pharmacological effects of buprenorphine. There was a linear correlation between the plasma buprenorphine concentration and the pharmacological drug effect. Due to different buprenorphine doses, it was not possible to make a relevant comparison of pharmacological effects caused by sublingual and oral buprenorphine.

Adverse effects

Most of the subjects experienced some mild and moderate adverse effects, but there were no severe adverse effects. Mild dizziness, sedation and nausea were the most common adverse effects. During Studies I and II, there were no adverse effects encountered that would have required treatment.

In study III, adverse effects were more frequent, especially when buprenorphine was administered intravenously. All subjects experienced mild-to-moderate adverse effects. Some of the subjects needed medication (tropisetron) to treat the nausea occurring after buprenorphine. Intravenous administration of buprenorphine caused more nausea than its sublingual counterpart. During the intravenous part of the study, itching and urticaria also were encountered and eight subjects needed medication (cetirizine hydrochloride) for these symptoms.

5.2 Clinical study

The patient, endoscopist and assisting nurse assessed subjective parameters (pain, sedation, nausea, dizziness, co-operation, unpleasantness) by using a numerical rating scale (0-10). The patients assessed subjective parameters (nausea, dizziness, stomach pain, unpleasantness) by using a numerical rating scale (0-4) in a post-procedure interview by telephone interview on the first day after the procedure.

5.2.1 Pain and sedation scores

There was no difference between the placebo and intervention groups in the level of pain and sedation. Patients assessed their average and maximum pain during colonoscopy. The median pain [IQR] experienced by the patients was 4.5 [2-7] in the intervention group and 5 [3-6.5] in the placebo group. The median values for pain were 5 in female and 4 in male patients but there was no statistically significant difference between male and female patients. The maximum pain patients experienced was 8 [5-9] in the placebo group and 7 [4.8-8] in intervention group. The endoscopist and assisting nurse also assessed the average pain of the patients. The endoscopist assessed median pain to be 5 [2-7] in the placebo group and 5.5 in

[3-8] in the fentanyl group. The corresponding values estimated by the assisting nurse were 6 [2-7] and 6 [3-8], respectively.

The median self-assessed level of sedation using the NRS was 0 [0-0] in both groups. The endoscopist assessed the sedation level to be 0 [0-1] in both groups. The assisting nurse assessed the sedation level to be 0 [0-1] in the placebo group and 1 [0-2] in the fentanyl group.

5.2.2 Adverse effects

No desaturation events were recorded in either of the groups. Respiratory rates were above 8 per minute and naloxone was not needed in any of the patients. There was no nausea in either group. Patients assessed nausea on the numerical rating scale from 0 to 10 and the median was 0 [0-0] in the placebo group and 0 [0-1] in the intervention group. Furthermore, according to endoscopist's or assisting nurse's assessment, the patients did not suffer from nausea.

The post-procedural interview during the following day after colonoscopy showed no differences in patient experiences between the intervention and placebo groups. The patients assessed their nausea to be 1 [1-1] in both groups.

5.2.3 Success of the procedure and recovery after colonoscopy

Three procedures had to be interrupted in both groups. Excessive pain interrupted the procedure in one patient in the intervention group and in two patients in the placebo group. The median length of the procedure was 15 (range 5-40) minutes in the placebo group and 20 (range 5-50) minutes in the fentanyl group, respectively. There were no significant differences between the two groups in the times between the end of colonoscopy and hospital discharge. The median time between these two events was 25 (range 9-60) minutes in the intervention and 25 (range 5-90) minutes in the placebo group. Patients were asked to assess the post-procedural stomach pain on a scale of 1-4 on the following day after the colonoscopy. The median stomach pain was 1 [1-2] in both groups. They were also asked how well they remembered the previous day's events and there was no difference between the groups.

The assessment of subjective parameters by patient, endoscopist and nurse using the numerical rating scale (0-10) are summarized in Table 6.

Table 6. Assessment of subjective parameters by patient, endoscopist and nurse using the numerical rating scale (0-10). Data are shown as median and interquartile range.

Parameter	Patient			Endoscopist			Nurse		
	Fentanyl	Placebo	p-value	Fentanyl	Placebo	p-value	Fentanyl	Placebo	p-value
Progression of procedure	NA	NA	-	9 [8-10]	9 [8-10]	0.992	8 [7-9]	9 [7-9]	0.834
Co-operation	NA	NA	-	10 [9.75-10]	10 [9.75-10]	0.132	10 [9-10]	10 [9-10]	0.752
Average pain	4.5 [2-7]	5 [3-6.5]	0.852	5 [2-7]	5.5 [3-8]	0.132	6 [2-7]	6 [3-8]	0.716
Maximum pain	7 [4.75-8]	8 [5-9]	0.212	NA	NA	-	NA	NA	-
Sedation	NA	NA	-	0 [0-1]	0 [0-1]	0.910	1 [0-2]	0 [0-1]	0.093
Nausea	0 [0-1]	0 [0-0]	0.255	0 [0-0]	0 [0-0]	0.568	0 [0-0]	0 [0-0]	0.603
Unpleasantness	4 [2-6]	5 [3-7]	0.369	NA	NA	-	NA	NA	-
Drowsiness	0 [0-0]	0 [0-0]	0.595	NA	NA	-	NA	NA	-

NA = Not applicable

6 Discussion

6.1 Interaction studies

6.1.1 Methodological considerations

The three interaction studies were conducted using a single-blinded, randomized, balanced cross-over study design. On the basis of previous drug-drug interaction studies (Nieminen et al. 2009; Saari et al. 2006), it was calculated that 10 subjects would be needed to detect a 30 % difference in the area under the concentration-time curve ($AUC_{0-\infty}$) of buprenorphine at a power of 80% and a level of significance of $P<0.05$. To allow for possible dropouts, 12 healthy non-smoking volunteers were recruited to each of the three studies. Each of the volunteers served as their own control which minimized the effect of inter-individual variability and the number of volunteers could be kept relatively low. This was an academic study and we had no possibility to use identical placebo tablets, especially when posaconazole is administered as a mixture. It was impossible to use a double-blinded study design and even though volunteers were not told which drug they received it is theoretically possible that they would guess the pre-treatment used. Our primary aim was to study the pharmacokinetics of buprenorphine. Nonetheless, it was unlikely that the method of blinding would affect the outcome.

We had a four weeks' interval between the study phases. This was considered sufficient to eliminate any possible carry-over effects. The same wash-out period was chosen in all of the three studies to minimize the possible effects of menstrual cycle on the results of female volunteers although studies have found no significant differences in the pharmacokinetics of CYP3A4 substrates during different hormonal stages (Kharasch et al. 1997).

Before administering the substrate drug, it would be preferable to reach the steady state of the inhibitor or inducer in use. Therefore, we provided a loading dose when voriconazole was administered and according to the literature, steady-state should be achieved on day two although there is wide variability between individuals in terms of concentrations (Purkins et al. 2003). With posaconazole, it takes 10 days to reach steady-state concentrations with oral twice-daily dosing (Courtney et al. 2003). The posaconazole pre-treatment was only for 5 days, because it would have

been unethical to expose healthy volunteers to such a long antifungal treatment. However, interactions with posaconazole have also been described after short dosing period (Krishna et al. 2012).

With rifampicin, a true steady-state was not achieved due to its autoinduction, which occurs over 2 weeks. The repeated administration of rifampicin reduces its oral bioavailability and increases its clearance (Loos and Musch 1985).

The compliance was assured for voriconazole and posaconazole with determination of their concentrations from plasma samples taken before administration of buprenorphine. In Study III, it was not possible to determine the rifampicin concentration in blood but in all of the three studies, compliance with pre-treatment was also controlled with SMS technology. If the message was delayed, the subject was reminded to take the pre-medication.

The dose of buprenorphine was low, because all the volunteers were opioid naïve and we wanted to ensure their safety. In Study I and in the first two phases of study III, buprenorhine was administered sublingually. Volunteers were instructed to let the tablet dissolve completely under the tongue, but we cannot rule out the possibility that part of the drug was swallowed. In Study II, buprenorphine was administered orally and there were extensive differences between the buprenorphine doses in the placebo and intervention phases. We assumed low oral bioavailability and chose a higher buprenorphine dose in the placebo phase. In the voriconazole phase, we wanted to keep the dose small because of the possibility of strong inhibition of the metabolism of buprenorphine.

The pharmacodynamic effects of buprenorphine were evaluated with methods used in earlier interaction studies with opioids (Saari et al. 2010; Saarikoski et al. 2013; Nieminen et al. 2010). We used VAS-scores, Maddox Wing Test, Cogan's pupillometer, digit symbol substitution test, cold pressor test and recorded adverse effects in every study. We used the cold pressure test, because it is known to be a sensitive model for opioid induced analgesia in healthy volunteers (Posner et al. 1985) and it is also straightforward to conduct. There was a linear correlation between the plasma buprenorphine concentration and the pharmacological effect in all pharmacodynamic variables, but their relevant comparison between the study phases was not possible due to the different buprenorphine doses in these different trials.

Almost every subject experienced some mild or moderate adverse effects. The most common adverse effects were mild dizziness and nausea. Especially in Study III where buprenorphine was administered intravenously, the volunteers relatively frequently experienced adverse effects. In Study III, tropisetron was used to treat nausea which theoretically might have affected the results. However, its effect on our results was most likely minimal because tropisetron is a substrate and not an inhibitor of CYP2D6 (Ho and Gan 2006). Itchiness and urticaria were treated with

cetirizine a drug which has a negligible interaction with liver enzymes (Cheng 2008), and therefore the provision of cetirizine most likely did not influence the results of the present study.

6.1.2 Pharmacokinetic considerations

Effect of CYP3A4 inhibition

Voriconazole, a strong CYP3A4 inhibitor, affected significantly the pharmacokinetics of sublingually and orally administered buprenorphine. In contrast, the effect of posaconazole on the exposure of sublingually administered buprenorphine was not significant.

Compared to placebo, voriconazole increased the mean $AUC_{0-\infty}$ of sublingual buprenorphine by 1.80-fold and its C_{max} by 1.37-fold. Voriconazole increased the mean AUC_{0-18} of oral buprenorphine 4.3-fold and its C_{max} 3.9-fold compared to placebo. Compared to placebo, posaconazole increased the mean $AUC_{0-\infty}$ of sublingual buprenorphine by 1.25-fold and its C_{max} by 1.20-fold. In previous studies examining drug-drug interactions between HIV protease inhibitors and high-dose sublingual buprenorphine, ritonavir increased the AUC of buprenorphine significantly (57%) (McCance-Katz et al. 2006). Atanavir alone increased the buprenorphine AUC value by 93%; when atanavir was given together with ritonavir buprenorphine's AUC was elevated by 67%, and the sedative effect of buprenorphine was also significantly increased. These interactions with buprenorphine are of the same order as those observed in the present study.

There are several previous studies where voriconazole and posaconazole have been found to inhibit the metabolism of CYP3A4 substrates. Voriconazole has been found to increase the peak concentration and AUC values of oral midazolam by 3.8- and 10.3-fold, respectively (Saari et al. 2006). It has been shown that posaconazole at a daily dose of 400 mg increased the AUC of oral midazolam by 6.2-fold and C_{max} by 2.4-fold (Krishna et al. 2009). Voriconazole increased also the peak concentration of oral oxycodone by 1.7-fold and its AUC by 3.6-fold (Hagelberg et al. 2009). The presence of voriconazole increased the exposure to sublingual buprenorphine significantly less than it has been reported to alter that of orally delivered midazolam. Sublingual buprenorphine seems to be less susceptible to the effects of drugs affecting intestinal and hepatic CYP3A4 during the first-pass; this is probably due to its partial bypassing of the intestinal first-pass metabolism.

The urinary excretion of norbuprenorphine was also measured. This metabolite can be excreted into urine to some extent also in the unconjugated form because it is less lipophilic than the parent compound, buprenorphine. Surprisingly, the amount of norbuprenorphine excreted into urine during 18 hours after sublingual

buprenorphine dosing was increased by voriconazole by 58%. It would be expected that voriconazole would decrease the CYP3A4-mediated N-dealkylation of buprenorphine to norbuprenorphine because voriconazole is a strong inhibitor of CYP3A4. On the other hand, posaconazole is also a strong and selective CYP3A4 inhibitor but posaconazole actually decreased the excretion of norbuprenorphine into urine, consistent with inhibition of its CYP3A4-mediated formation. Inhibition of CYP3A4-mediated N-demethylation and the strong inhibition of CYP2C9 and CYP2C19 mediated alternative pathways by voriconazole may partially explain why voriconazole increased the urinary excretion of norbuprenorphine and increased buprenorphine concentrations much more than posaconazole. Norbuprenorphine is known to be a substrate of P-gp (Tournier et al. 2010). Posaconazole is a potent inhibitor of P-gp, while voriconazole is a weak inhibitor of this transporter. This may partially explain the smaller effect of posaconazole on the buprenorphine plasma concentrations and urinary excretion of norbuprenorphine compared to voriconazole. In addition, the increased urinary excretion of the metabolite may involve unidentified membrane transporter mechanisms. When buprenorphine was administered orally, voriconazole increased the amount of unconjugated buprenorphine excreted in urine ($p<0.001$). Voriconazole had no significant effect on Cl_{renal} of buprenorphine but it reduced the Cl_{renal} of norbuprenorphine. Norbuprenorphine, but not buprenorphine, is a substrate of the efflux transporter P-gp, so the reduction of Cl_{renal} can be explained by the inhibition of membrane transporters.

The effects of voriconazole on parent buprenorphine can be mainly explained by inhibition of CYP3A4 during the first pass and elimination phases. Inhibition of CYP3A4 should decrease the N-dealkylation of buprenorphine to norbuprenorphine. However, the substantial increases in the AUC and C_{max} of norbuprenorphine suggest the presence of additional mechanisms. Buprenorphine and norbuprenorphine are also glucuronidated by UGTs. Buprenorphine is mainly glucuronidated by UGT2B7, while norbuprenorphine glucuronidation is predominantly mediated by UGT1A3 (Rouguieg et al. 2010) The effects of posaconazole, voriconazole and their metabolites on the different UGTs and glucuronidases are not known. However, voriconazole has been claimed to act as an UGT2B inhibitor in the gut and liver, according to a semi-physiological population pharmacokinetic model (Frechen et al. 2013).

These results seem to emphasize the significant role of CYP3A-mediated first-pass metabolism of buprenorphine, which is only partially bypassed by sublingual administration. The bioavailability of orally administered buprenorphine is low (~15 %), but sublingual administration increases the drug's bioavailability up to 30-60% (Mendelson et al. 1997; Nath et al. 1999). Both the C_{max} and AUC of buprenorphine were clearly increased after voriconazole and the present results clearly suggest that

concomitant treatment with strong CYP-inhibitors may increase the bioavailability of sublingual buprenorphine. Most probably, voriconazole caused increased exposure by inhibiting both the intestinal and hepatic CYP3A enzymes, increasing both the C_{max} and $t_{½}$ of buprenorphine. In addition, other mechanisms such as inhibition of P-gp and UGTs may also be involved.

Effect of CYP3A4 induction

Rifampicin decreased the mean AUC_{0-18} of sublingual buprenorphine by 25%. The bioavailability of sublingual buprenorphine tended to decrease from 22% to 16% with rifampicin, but the change was not statistically significant. Rifampicin did not exert a statistically significant effect on the concentrations of intravenously administered buprenorphine. Rifampicin decreased the cumulative excretion of free, non-conjugated norbuprenorphine in urine by 65% after sublingual, and by 52% after intravenous administration, but the effect on buprenorphine excretion was less consistent. The induction of CYP3A4 activity by rifampicin in the intestinal wall and liver is the most likely the explanation for this finding, but enhancement of UGT or P-gp activities may also be play a role. A previous study has shown that rifampicin 600 mg administered daily for 15 days decreased the mean AUC of high-dose buprenorphine by 70% and withdrawal symptoms were frequent. (McCance-Katz et al. 2011). In this present study, the effect of rifampicin on the exposure to sublingually administered buprenorphine was smaller. The large difference between buprenorphine doses in these two trials and the shorter duration of rifampicin treatment may explain these discrepant findings.

Sublingually administered buprenorphine only partially avoids the induction of CYP3A4-mediated gastrointestinal metabolism by rifampicin. Hence, the sublingual route of administration of buprenorphine is more vulnerable to the effects of an interaction with rifampicin than the intravenous counterpart. Rifampicin has been found to decrease exposure to many other substrates of CYP3A4. Rifampicin decreased the AUC of oral and intravenous oxycodone by 86% and 53%, respectively,(Nieminen et al. 2009) and it has been found to decrease the AUC of oral tramadol by 59% and intravenous tramadol by 43% (Saarikoski et al. 2013). Rifampicin was also reported to enhance the activities of UGTs and P-gp (Greiner et al. 1999; Niemi et al. 2003; Soars et al. 2004). Buprenorphine and norbuprenorphine are conjugated to B3G and N3G by UGTs and it is possible that the pharmacokinetic changes seen in this study are due to the enhanced activity of UGTs evoked by rifampicin (Chang Y 2009). The role of the P-gp in the transport of buprenorphine in humans is less clear although *in vitro* studies in rodents suggest that norbuprenorphine, but not buprenorphine is a substrate for P-gp (Hassan et al. 2009; Brown et al. 2012).

The amount of unconjugated norbuprenorphine in urine was decreased by rifampicin when the participants were administered both sublingual and intravenous buprenorphine. This may be due to a shift in the metabolic pathway towards hydroxylation of buprenorphine or norbuprenorphine by CYP3A4. The induction of further metabolism of norbuprenorphine by UGTs after rifampicin pretreatment is also possible (Chang, Moody, and McCance-Katz 2006; Chang and Moody 2009).

6.1.3 Pharmacodynamic considerations

These studies were designed to explore the pharmacokinetics of buprenorphine. However, we also wanted to collect pharmacodynamic data to evaluate the pharmacological effect of buprenorphine in healthy volunteers. There was a linear correlation between the plasma buprenorphine concentration and the pharmacological effect in all pharmacodynamic variables, but their relevant comparison between the study phases was not possible due to the different buprenorphine doses given in the trials. When buprenorphine was administered sublingually or orally almost every subject experienced some mild or moderate adverse effects. The most frequent adverse effect was sedation, followed by ataxia, dizziness and nausea but in Studies I and II and the first two phases of Study III, these adverse effects were transient and did not require any treatment. When buprenorphine was administered intravenously, adverse effects were more frequent and more intense and several patients needed medication to relieve nausea or itching.

6.1.4 Limitations of the study

There are limitations in these studies; we normalized the pharmacokinetic values to a buprenorphine dose of 1 mg, because these studies were designed mainly to evaluate the pharmacokinetics of buprenorphine and its susceptibility to DDIs. However, dose normalization cannot be used for assessing pharmacodynamical results and subjective adverse effects. If buprenorphine had nonlinear pharmacokinetics, the use of different doses of buprenorphine during various phases of the study might have biased the dose-corrected results. In humans, there is no indication for nonlinear buprenorphine pharmacokinetics over a wide dosage range from 0.06 to 12 mg (Huestis et al. 2013; Bai, Xiang, and Finn 2016; McAleer et al. 2003), although the pharmacokinetics of buprenorphine has been reported to be nonlinear in rats (Gopal, Tzeng, and Cowan 2002). We took blood samples for 18 hours and a longer sampling time could have increased the reliability in the pharmacokinetic calculation, especially in determining the elimination half-life.

6.1.5 Clinical aspects

These present results show that the interaction between voriconazole and sublingual buprenorphine may have a considerable clinical relevance in individual patients. Exposure to sublingual buprenorphine increases significantly even during a short treatment with clinically used doses of voriconazole. The exposure to buprenorphine may increase by more than 100% in some individuals receiving voriconazole. When triazole antifungals, especially voriconazole, are used with sublingual buprenorphine, careful patient monitoring is recommended. It is less likely that posaconazole would evoke a clinically significant interaction with sublingual buprenorphine. Patients receiving high-dose buprenorphine maintenance therapy often miss-use other opioids and benzodiazepines intravenously. This exposes them to various infections including fungal infections. If voriconazole is used to treat fungal infection with a patient receiving high-dose sublingual buprenorphine therapy, the dose of buprenorphine might even need to be reduced to the half of the normal dose.

In clinical use, buprenorphine is not administered orally, but part of the sublingually administered drug can be swallowed. This study shows that voriconazole increases the bioavailability of oral buprenorphine significantly and concomitant use of voriconazole and sublingual buprenorphine may result in a clinically relevant interaction.

In study III, rifampicin decreased the bioavailability and exposure to a low dose of sublingual buprenorphine but did not affect the exposure to intravenous buprenorphine. This interaction may diminish the effects of sublingual buprenorphine. A previous study revealed that when opioid-dependent subjects on stable doses of sublingual buprenorphine/naloxone were treated with oral rifampicin for 15 days, a 70% decrease in the mean AUC of buprenorphine was detected, and withdrawal symptoms were frequent (McCance-Katz et al. 2011). This present study showed that rifampicin has no effect on the concentrations of buprenorphine when the latter drug was administered intravenously. This finding is clinically important, because sublingual buprenorphine is more commonly used in the treatment of opioid dependence, opioid withdrawal symptoms and pain than its intravenous counterpart. If concomitant use of buprenorphine and rifampicin is necessary, any risk of interaction could be avoided, by choosing an intravenous route of administration of buprenorphine. However, it is not possible to successfully administer buprenorphine intravenously to patients receiving maintenance therapy with high sublingual buprenorphine doses. Furthermore, these patients are prone to staphylococcal infections because they often use other opioids and benzodiazepines intravenously. If rifampicin treatment is needed during a high dose sublingual buprenorphine therapy, the dose of buprenorphine should be significantly higher than normally. Another option could be transition to subcutaneous injection depot formula of

buprenorphine. These new dosage forms of buprenorphine bypass the extensive first-pass metabolism of buprenorphine completely and they are probably less prone to CYP-mediated interactions.

6.2 Clinical study

6.2.1 Methodological considerations

The aim of this study was to evaluate the efficacy of a transmucosal fentanyl tablet compared to placebo in patients undergoing colonoscopy. A total of 150 patients was planned to be enrolled in this study. The sample size was determined based on results of previous studies (Pambianco et al. 2016; Amer-Cuenca et al. 2011) with a similar design and was expected to provide sufficient data to reveal the applicability of sublingual fentanyl for relief of discomfort during colonoscopy. The patients were randomized into two groups by using the sealed envelope technique. All patients, investigators, and staff members involved in the conduct of the study were blinded to treatment assignment. The manufacturer of Abstral ® 100 µg provided identical placebo tablets, so the blinding was adequate. Patients received the sublingual tablet of Abstral ® 100 µg or the identical placebo ten minutes before the procedure. It has been shown that first detectable drug concentration in blood after administration of a 100 µg sublingual dose of fentanyl is reached in 10.7 minutes (Lennernäs et al. 2005). However, the maximum drug concentration in blood is reached in 39.7 minutes and most of the colonoscopies in this study were rather short. The median length of the procedure was 15 minutes in the placebo group and 20 minutes in the fentanyl group. Patients could have had better pain relief during the procedure, if there would have been more time between the administration of the drug and the beginning of the colonoscopy. Patients were instructed not to swallow the tablet but allow it dissolve completely. Patients were not allowed to drink or eat anything until the sublingual tablet was dissolved, but we cannot rule out the possibility that part of the drug was nonetheless swallowed.

Sublingual administration of fentanyl was chosen to avoid the need for intravenous access. The bioavailability of sublingual fentanyl is approximately 70%. For safety and ethical reasons, we wanted to keep the dose of fentanyl relatively low, especially when most patients were opioid naïve. Sublingual fentanyl with the dose of 100 µg has been shown to be effective and safe in average-sized adults and also in elderly patients with comorbidities (Rauck et al. 2016; 2017). However, the bioavailability of sublingual fentanyl varies considerably, and we cannot rule out the possibility that the dose was too low, at least in some of the patients.

All colonoscopies were performed by one of the three experienced endoscopists. We tried to avoid a confounding factor i.e. that the skill level of endoscopist would

affect our results, by limiting the number of endoscopists to three. It has been shown that significant discomfort during colonoscopy is associated with longer colonoscope insertion times and longer colonoscope withdrawal times (Ball et al. 2015). In this study, there were no major variations in the duration of the colonoscopies.

6.2.2 Measuring pain and sedation

In this study, the primary outcome variable was the pain experienced by the patient. Pain is difficult to measure, because the experience is subjective, but NRS has been found to be valid for measuring pain (Jensen, Miller, and Fisher 1998; Ferreira-Valente, Pais-Ribeiro, and Jensen 2011). The same numerical rating scale was used to assess patients' sedation, unpleasantness, co-operation, progression of the procedure and adverse effects even though it has not been validated to measure these variables. There are some studies though, that seem to indicate that NRS is slightly more sensitive than VAS (Ferreira-Valente, Pais-Ribeiro, and Jensen 2011) and in this study, we chose NRS because it is more practical and easier to understand for most people than VAS. NRS is also easier to use, when no clear vision, paper or pen are needed.

When pain is assessed using a numerical rating scale, no pain at all is expressed as 0 and worst pain imaginable is designated to be 10. Patients were instructed to use the scale correctly before any assessments were made. In this study, the median pain experienced by the patients was 4.5 [2-7] in the intervention and 5 [3-6.5] in the placebo group. In a previous study by Lazaraki et al. patients received either a small dose of intravenous fentanyl or midazolam and the mean pain score was 2.59 in the fentanyl group and 4.43 in the midazolam group when pain was assessed on a scale of 0-10 (Lazaraki et al. 2007). When 1000 mg of intravenous paracetamol and 0.5-1 µg/kg of intravenous fentanyl were compared in patients undergoing colonoscopy, patients assessed the mean pain to be 4.00 after paracetamol and 3.77 in fentanyl (Ahmadi et al. 2015). Thus, in our study, the median pain scores were similar to those reported elsewhere. The median pain was considered to be moderate, as on NRS pain a rating between 4 and 6 is thought to represent moderate whereas pain 7-10 is classified as severe.

The maximum pain patients experienced in placebo group was 8 [5-9]; in the intervention group it was 7 [4.75-8]. Here, the maximum pain was measured during the colonoscopy because afterwards many patients might remember the degree of the pain in a different way.

The median self-assessed sedation level using the NRS-scale was 0 in both groups. The sedation level assessed by the endoscopist was 0 [0-1] in both groups and the corresponding value assessed by the assisting nurse was 0 [0-1] in the

placebo group and 1 [0-2] in the fentanyl group. The comparison of sedation levels to other studies is difficult, because most of the studies have combined the opioid with midazolam to achieve sedation (Holloway and Logan 1990; Usta et al. 2011). There are very few studies where an opioid has been used alone to relieve pain during colonoscopy.

In this study there were no differences in the placebo and intervention groups in the levels of measured pain. Patients were not sedated in either group. As there were no differences in the placebo and intervention groups, the patients did not experience any relief in their procedural pain from the pre-medication with sublingual fentanyl. However, only three procedures needed to be interrupted in both groups. Excessive pain interrupted the procedure in one patient in the intervention group and two patients in the placebo group. We did not administer any rescue medicine and the procedure was simply interrupted if the patient experienced unbearable pain.

Our results suggest that pain is seldom the limiting factor for success in colonoscopy, while discomfort and anxiety might be of more importance. It has been shown that there is no correlation between lower pain scores and patient satisfaction during colonoscopy (Amri et al. 2018). Higher patient satisfaction scores are achieved with deeper sedation with propofol (Wang et al. 2013; Zhang, Zhu, and Zheng 2018; McQuaid and Laine 2008).

6.2.3 Limitations of the study

Recruitment period was very long in this study. Patients were recruited to participate in this study between April 2012 and December 2018. The main reason for this was patients' unwillingness to undergo colonoscopy without sedation and the prohibition to drive car after administration of the study drug. Another factor affecting recruitment was that the endoscopy unit changed location several times during our study and there were limited possibilities for patient recruitment during certain times.

Patients received the drug ten minutes before the procedure. It has been shown that the peak drug concentration in blood after 100 µg of sublingual fentanyl is reached in 39.7 minutes with the first detectable concentration in 10.7 minutes, on the average (Lennernäs et al. 2005). Here, the median length of the colonoscopy was rather short, 15-20 minutes. Patients could have had better pain relief during the procedure, if there had been a longer time between the administration of the drug and the beginning of the colonoscopy. In this study, the dose of sublingual fentanyl was 100 µg, which was considered to be adequate based on previous reports. The bioavailability of sublingual fentanyl is approximately 70% but it is known that the bioavailability varies considerably between individuals and we cannot rule out the possibility that at least in some of the patients, the dose was too low. However, regarding the intravenous route, a single dose of 36 µg of intravenous fentanyl has

been found to be sufficient prior to colonoscopy (Lazaraki et al. 2007) and compared to this study, the effective dose of fentanyl after 100 µg sublingual administration should have been enough. On the other hand, the fentanyl dose was the same for all the patients. It could have been more beneficial to adjust the fentanyl dose according to the patients' weight. For this purpose fentanyl tablets should have been split and administering the exact dose would have been impossible.

The sublingual route is an effective way to administer some drugs. The drug's effect appears rapidly and extensive first-pass metabolism by CYP enzymes is partly avoided which is particularly useful for those drugs which undergo extensive first-pass metabolism. Unfortunately, the patients in this study were not familiar with the sublingual administration of the drug and even though they were instructed to let the tablet dissolve completely, it is possible that even a considerable part of the fentanyl dose was swallowed.

6.2.4 Future challenges – sedation or analgesia

Patients in the present study did not benefit from 100 µg of sublingual fentanyl before colonoscopy. Patients in both placebo and intervention groups reported a moderate degree of pain. Regardless, almost all procedures were performed successfully. The number of interrupted colonoscopies was similar in both groups. The intervention had no significant effect on the satisfaction of the endoscopist. Sublingual fentanyl did not cause any significant adverse effects or sedation, and the hospital stay was not prolonged.

The results of this study suggest that pain is seldom the limiting factor for success in colonoscopy, while discomfort and anxiety might be of more importance. Patients placed the highest value on experiencing no pain during the procedure in a study, which asked about pre-procedure patient values regarding sedation for colonoscopy. (Subramanian, Liangpunsakul, and Rex 2005). However, significantly higher patient satisfaction scores were reached when propofol was used for sedation during colonoscopy (Zhang, Zhu, and Zheng 2018; Wang et al. 2013; McQuaid and Laine 2008). Nonetheless, lower pain scores do not automatically mean better patient satisfaction (Amri et al. 2018). The second and third most valued property among patients in the study of Subramanian et al. was waking up promptly after the procedure combined with going to sleep and not waking until the procedure was over. Propofol provides a rapid onset of sedation and patients recover quickly after propofol sedation (McQuaid and Laine 2008; Zhang, Zhu, and Zheng 2018). In this present study, the patients did not feel sedated in either of the groups and both the endoscopist and the assisting nurse also assessed the level of patient sedation to be 0 in both groups. Moderate or consciousness-maintaining sedation has been found to be safer than deep sedation and it also resulted in better cost-efficiency (Lim et al.

2019). There are very few studies in which only analgesic drugs have been used to treat pain during colonoscopy and there are even fewer placebo-controlled studies. In most of the studies, comparing different opioids during colonoscopy, the opioids have been used in combination with either midazolam or propofol (Doğanay et al. 2017; Deng et al. 2017; Usta et al. 2011). Even in a study where intravenous fentanyl alone was used, it was compared to midazolam and not to placebo (Lazaraki et al. 2007). The comparison of sedation levels to other studies is therefore difficult. We are not aware of any studies, where pre-medication before colonoscopy was given by any route other than intravenously.

In global terms, most of the patients undergoing colonoscopy prefer sedation but there are countries where sedation is rarely used during colonoscopy (Froehlich et al. 2006). However, there is a small group of patients who are motivated to go through the procedure without sedation and interestingly, it has been found that patients who choose not to have sedation are those least likely to experience significant discomfort during the procedure (Ball et al. 2015).

This present study indicates that sublingual fentanyl, at least as a low-dose monotherapy, seems to be ineffective for producing a suitable level of sedation and/or analgesia for patients undergoing colonoscopy. The literature at the moment suggests that the greatest patient satisfaction scores are achieved when sedation is implemented with propofol or dexmedetomidine (Dere et al. 2010; Wang et al. 2013; McQuaid and Laine 2008). It might be beneficial also to offer all patients in all countries the possibility to undergo colonoscopy without sedation. However, more studies where only analgesic drugs are used are needed before any final conclusion on this issue can be drawn.

7 Conclusions

1. Compared to placebo, voriconazole increased the mean area under the plasma concentration-time curve ($AUC_{0-\infty}$) of sublingual buprenorphine by 1.80-fold, its peak concentration (C_{max}) by 1.37-fold and its half-life ($t_{½}$) by 1.37-fold. Posaconazole increased the $AUC0_{0-\infty}$ of sublingual buprenorphine 1.25-fold. Most of the plasma norbuprenorphine concentrations were below the limit of quantification (0.05 ng/ml). Voriconazole, unlike posaconazole, increased the urinary excretion of norbuprenorphine by 1.58-fold but there were no quantifiable amounts of the parent buprenorphine in urine. The plasma buprenorphine concentrations correlated with the pharmacological effects, but these effects did not differ significantly between the voriconazole, posaconazole and placebo phases.
2. Voriconazole increased the mean area under the plasma concentration-time curve (AUC_{0-18}) of oral buprenorphine by 4.3-fold, its peak concentration (C_{max}) by 3.9-fold and elevated its excretion into urine. Voriconazole also markedly enhanced the C_{max}, AUC_{0-18} and the A_e of unconjugated norbuprenorphine, but decreased its renal clearance. The effects of voriconazole on parent buprenorphine can be mainly explained by inhibition of CYP3A4, but there are indications of additional mechanisms. Mild dizziness and nausea occurred during both placebo and voriconazole phases
3. Rifampicin decreased the mean area under the dose-corrected plasma concentration time curve (AUC_{0-18}) of sublingual buprenorphine by 25%. The presence of rifampicin reduced the bioavailability of sublingual buprenorphine from 22% to 16%. The plasma concentrations of intravenously administered buprenorphine were not influenced by rifampicin. After sublingual and intravenous administration of buprenorphine, the amount of norbuprenorphine excreted into urine decreased by 65% and 52% in the presence of rifampicin, respectively. Adverse effects were frequent.

4. The effects of voriconazole, posaconazole and rifampicin on parent buprenorphine can be mainly explained by inhibition and induction of CYP3A4, but there are indications of additional mechanisms. The activities of UGTs an P-gp can be enhanced by rifampicin, voriconazole and posaconazole and this can influence the metabolism of buprenorphine.
5. Concomitant use of voriconazole or rifampicin and sublingual buprenorphine may result in clinically relevant interactions. Buprenorphine doses should be adjusted properly if concomitant use is necessary.
6. Patients do not benefit from a dose of 100 µg of sublingual fentanyl before undergoing colonoscopy. There were no differences between placebo and the intervention groups in any of measured variables. The median pain experienced by patients, measured with an NRS-scale was 4.5 in the intervention group and 5 in the placebo group. Neither sedation, desaturation nor signs of a decreased respiratory rate were observed in either of the groups. The majority of the colonoscopies could be completed even though patients did not benefit from medication.

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