Can postoperative analgesia be improved by the choice and timing of analgesics?

Studies on nonsteroidal analgesics and opioids with special focus on opioid-induced hyperalgesia

Thesis for the degree Ph.D.

Cand.med.

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Harald Lenz

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2. Abbreviations

ACL	Anterior Cruciate Ligament
ASA	American Society of Anaesthesiologists Physical Status
BBB	Blood-Brain Barrier
BIS	Bispectral Index
BMI	Body Mass Index
CNS	Central Nervous System
CPT	Cold Pressor Test
COX	Cyclooxygenase
DRG	Dorsal Root Ganglion
ECG	Electrocardiogram
EPT	Electrical Pain Threshold
GABA	Gamma-Amino Butyric Acid
HR	Heart Rate
i.v.	Intravenous
LMA	Laryngeal Mask
LSH	Laparoscopic Supracervical Hysterectomy
MAP	Mean Arterial Pressure
MEPT	Maximum Electrical Pain Threshold
NCA	Nurse-Controlled Analgesia
NMDA	N-methyl-D-aspartase
NO	Nitric Oxide
N_2O	Nitrous Oxide
NRM	Nucleus Raphe Magnus

NSAID	Nonsteroidal Anti-Inflammatory Drug
OIH	Opioid-Induced Hyperalgesia
PAG	Periaquaductal Gray Matter
PCA	Patient-Controlled Analgesia
PKC	Protein Kinase C
PM	Painmatcher
PONV	Postoperative Nausea or Vomiting
RCT	Randomized Controlled Trial
RVM	Rostral Ventral Medulla
SBP	Systolic Blood Pressure
SpO_2	Pulse Oximetry
TCI	Target Controlled Infusion
TLH	Total Laparoscopic Hysterectomy
VAS	Visual Analog Scale
VRS	Verbal Rating Score

3. List of papers

Paper I

Lenz H, Raeder J, Hoymork SC: Administration of fentanyl before remifentanil-based anaesthesia has no influence on post-operative pain or analgesic consumption. Acta Anaesthesiol Scand 2008; 52:149-54.

Paper II

Lenz H, Raeder J: Comparison of etoricoxib vs. ketorolac in postoperative pain relief. Acta Anaesthesiol Scand 2008; 52:1278-84.

Paper III

Lenz H, Sandvik L, Qvigstad E, Bjerkelund CE, Raeder J: A comparison of intravenous oxycodone and intravenous morphine in patient-controlled postoperative analgesia after laparoscopic hysterectomy. Anesth Analg 2009; 109:1279-83.

Paper IV

Lenz H, Raeder J, Draegni T, Heyerdahl F, Schmelz M, Stubhaug A: Modulation of remifentanil-induced postinfusion hyperalgesia by parecoxib or ketorolac in humans. (Submitted)

4. Introduction

4.1 Pain pathways

A consequence of a surgical procedure is tissue damage and direct mechanical nerve stimulation. Tissue damage leads to the release of inflammatory mediators such as histamine, substance P, bradykinin and prostaglandins with systemic effects on the central nervous system (CNS) and pain modulation. The inflammatory mediators also activate the peripheral nociceptors locally, and the nociceptive signals are transmitted to the CNS through the Aβ, Aδ and C nerve fibres. Aβ fibres have a large diameter and are highly myelinated. They have a low activation threshold, and are therefore responsible for tactile information. Aδ fibres have a higher activation threshold. Their myelin sheath is thinner than in Aβ fibres, and their conduction speed is therefore slower. C fibres are unmyelinated, and the slowest conductive nerve fibres. They have a high activation threshold, and therefore need strong stimuli to be activated. Such stimuli are often harmful as they may result in tissue damage. Aδ and C fibres respond to noxious stimuli like mechanical, thermal or chemical stimuli.[1] The noxious signals from peripheral somatic and visceral sites end in the dorsal horn of the spinal cord (fig. 1).
In the dorsal horn, there is an integration of peripheral nerve transmission and descending pain modulatory signals.
The noxious signals from the dorsal horn are then transmitted on the contralateral part of the medulla through the spinothalamic, the spinoreticularis and spinomesencephalic tracts to the brainstem. The noxious signals are further transmitted through the thalamus, and the signals finally end in the cortex and result in a conscious perception of pain. In the brainstem there are collateral branches to the periaquaductal gray matter (PAG) where a regulation of nociception takes place. From the periaquaductal gray matter there are branches to the

nucleus raphe magnus (NRM), which again has a controlling function on neurons in the medulla through descending pathways.

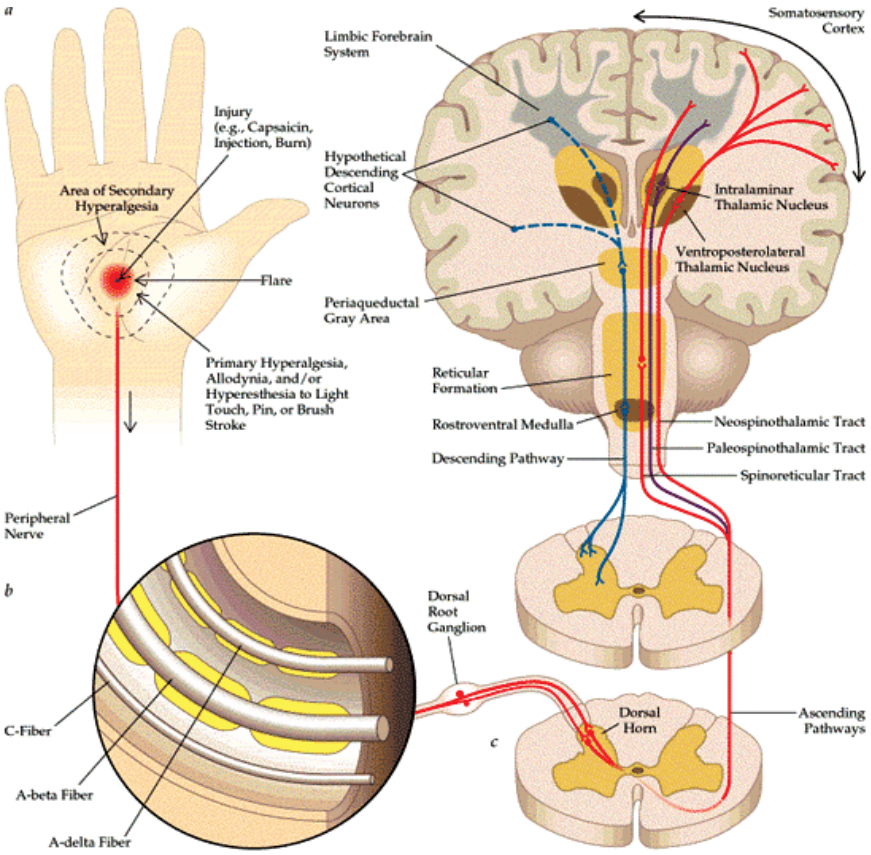


Fig. 1

Noxious stimuli are transduced into electrical activity at the peripheral terminals of Aβ, Aδ and C nerve fibres. This activity is conducted to the dorsal horn of the spinal cord through the dorsal root ganglion. The noxious signals are then transmitted on the contralateral part of the medulla through the spinothalamic, the spinoreticularis and spinomesencephalic tracts to the brainstem. The noxious signals are further transmitted through the thalamus, and to the cortex, where the sensation of pain is experienced. With permission from Medscape®.

A continuous feedback mechanism regulates the nociceptive activity between the connections in the brainstem and the medulla. In the brainstem there are also connections to the centres which regulate the blood pressure, heart rate and respiration. These connections form the basis for the immediate increase in blood pressure, heart rate and respiration rate in the case of acute noxious stimulation.

4.2 Postoperative pain and analgesia

Pain after surgery has a major effect on patient recovery, and may have implications on patient safety, the perceived patient care quality as well as health care economics. The most common complications of ineffective pain control include immobilization, poor wound healing, chronic pain, deep vein thrombosis, pneumonia, coronary ischemia and insomnia.[2-4] Persistent pain in patients after surgery is reported to be between 10-50%, and major chronic pain is reported in about 2-10% of these patients.[4]

Postoperative pain is one of the most common concerns and fears among surgical patients.[5] Even though there has been a focus on postoperative pain the last decades, a national survey in the United States demonstrated that 86% of the patients reported moderate, severe or extreme pain after surgery.[5]

Pain and pain complications have both medical and financial implications; the patients have to stay longer in the hospital, and for some readmission to hospital is necessary, which may lead to dissatisfaction with the medical care.[6]

There may be a lot of reasons for why postoperative analgesia still is suboptimal in many patients: poor understanding of pain physiology, lack of efficient analgesics or other preventive and therapeutic measures as well as suboptimal application of present knowledge into the individual patient. Poor application of present knowledge and treatment options may

be a result of insufficient training of healthcare personnel and patients, fear of serious adverse effects and economic restrictions on drug and personnel expenses.

The development of hyperalgesia during a surgical procedure has recently attained much interest in the field of pain physiology; what causes hyperalgesia and may it be prevented? Early multimodal analgesia also seems to be beneficial for enhanced quality of recovery.[7] Paracetamol, nonsteroidal anti-inflammatory drugs, local anaesthesia and opioids play an important role in multimodal analgesia.[7] Opioids are still useful in general anaesthetic techniques and as treatment of severe postoperative pain, but their role in the development of hyperalgesia as well as their bothersome adverse effects makes the use of them controversial. Our focus has been to look into different aspects of basic pain physiology, i.e. opioid-induced hyperalgesia (OIH) and possibilities to prevent OIH, as well as optimal use of some present analgesic drugs, i.e. opioids and cyclooxygenase inhibitors.

4.3 Nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids

Nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are widely used in postoperative pain management, and their analgesic efficacy is well documented.[8-10]

NSAIDs have demonstrated opioid-sparing effects after surgery,[11-13] and have also an additive effect when administered in combination with paracetamol.[14;15]

The opioid-sparing effects of NSAIDs has been demonstrated in a systematic review of COX-2 inhibitors.[16] On average, the opioid consumption in this review was significantly reduced by 35%, but a significant reduction in opioid-related adverse effects was not shown. The authors of this review describe the reporting quality with respect to opioid-related adverse effects as poor. This is interesting, because in a clinical setting the points of interest are the adverse effects leading to torments for the patients, longer stay in the recovery unit

etc., not the total amount of opioids used per se. In a systematic review Marret E et al. demonstrated that NSAIDs significantly decreased postoperative nausea, vomiting and sedation.[17] In this review, the morphine consumption was positively correlated with the incidence of nausea and vomiting.

Therefore, it is important that clinical trials do not only register opioid consumption and analgesic effect, but also opioid-related adverse effects.

The primary analgesic mechanism of NSAIDs is through inhibition of the cyclooxygenase (COX) enzyme. Cyclooxygenase facilitates the production of prostaglandins, which are important mediators of inflammation and pain (fig. 2).

Two cyclooxygenase enzymes have been discovered; COX-1 and COX-2.[18] COX-1 facilitates the platelet aggregation[19] and gastric mucosal protection,[20] and COX-2 is an important mediator of inflammation, pain and fever.[21;22]

This has resulted in the development of selective COX-2 inhibitors. The advantage of COX-2 inhibitors is the possibility to avoid the tendency for bleeding, which may be very important in some types of surgery. In addition, gastrointestinal wounds and bleedings are less frequent with the use of COX-2 inhibitors compared to non-selective NSAIDs.[23-26] A selective COX-2 inhibition results in a more specific action on inflammation and pain. Numerous studies have confirmed that selective COX-2 inhibitors and non-selective NSAIDs have similar analgesic efficacy.[27-30]

Traditionally, NSAIDs are considered to be peripherally acting drugs, but evidence has also clearly demonstrated analgesic efficacy through spinal COX-inhibition.[31;32]

However, the concept of COX-2 as the major factor in NSAID-induced analgesia has been challenged. In rats, experimental studies on incisional pain have demonstrated activation of COX-1 in the spinal cord, and less pain behaviour after intrathecal injection of ketorolac

compared to a selective COX-2 inhibitor,[33;34] whereas basically spinally COX-2 was activated in an inflammatory pain model.[35]

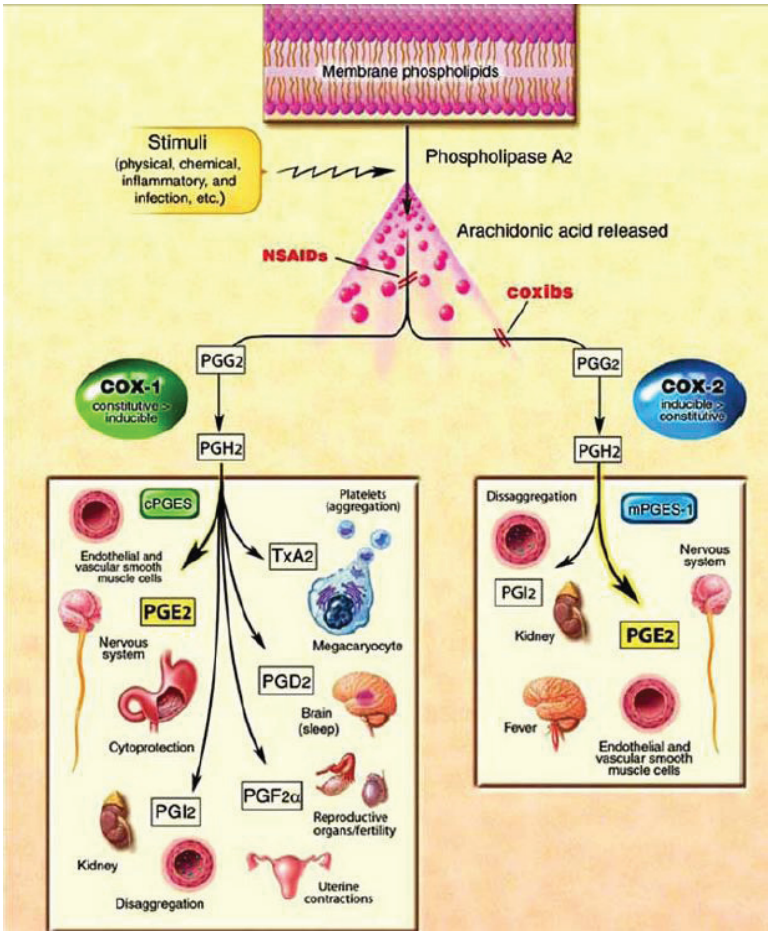


Fig. 2

The differential activation of two major COX enzymes involved in arachidonic metabolism. Arachidonic acid is liberated from membrane phospholipids by phospholipase A_2 in response to inflammatory stimuli, and then converted to PGG_2 and PGH_2 successively be prostaglandin G/H synthases, which are termed as cyclooxygenases and exist in two major isoforms, cyclooxygenase-1 and 2. PGH_2 is further converted by tissue-specific isomerases to several different prostanoids. With permission, Lee Y et al.: Curr Pharm Design 2005; 11:1737-55.

This may indicate that COX activation is different in different pain models. The analgesic efficacy of various cyclooxygenase inhibitors seems to be more complex than previously thought, and hopefully further investigations can result in a more detailed clarification of the analgesic mechanisms of cyclooxygenase inhibitors.

In this thesis two NSAIDs with different selectivity in inhibiting the COX-1 and COX-2 enzymes were compared to investigate the possibility of improving postoperative pain in a day-surgery unit (paper II). COX-2 inhibitors are presumed to have similar efficacy as traditional NSAIDs, but whether timing of nonsteroidal anti-inflammatory drugs is of importance in improving postoperative pain is still a question that needs to be answered. In paper II, the NSAIDs were administered ahead of surgery to ensure maximum effect before incision (preemptive analgesia). Preemptive analgesia remains controversial in managing postoperative pain. In a meta-analysis Ong et al.[36] demonstrated that preemptive NSAIDs reduce analgesic consumption and delay the time to the first rescue analgesic request postoperatively. There was no improvement in postoperative pain scores. Another review did not find any significant evidence of better postoperative pain relief by administering NSAIDs as preemptive medication.[37]

As described above, experimental studies in rats after incisional pain have demonstrated activation of COX-1 in the spinal cord, and less pain behaviour after intrathecal injection of ketorolac before incision compared to a selective COX-2 inhibitor. Therefore, it would be interesting to investigate, in a clinical setting, if there are any differences between a COX-1 inhibitor and a COX-2 inhibitor administered as preemptive medication with respect to postoperative pain and analgesic consumption.

Opioids

The opium poppy is known from Mesopotamia since 3-4000 years ago. All antique civilizations have descriptions of the use of the opium poppy, especially as a tranquillizer and

sleep-inducing drug. The name opium has its origin in the Greek word opos meaning juice. In 1806, a pure substance was isolated from the opium poppy and named after the Greek God of dreams: Morpheus.

Opioids are a generic term for all compounds with the ability to bind the opioid receptors. Opiats are natural opium alkaloids isolated from the opium poppy, like morphine and codeine.

Opioids can be classified in several ways:

1) By the way they are produced**:**

   - Naturally occurring: Morphine and codeine.

   - Semisynthetic: Heroin, oxycodone and buprenorphine.

   - Synthetic: Alfentanil, fentanyl, ketobemidone, methadone, pethidine, remifentanil and sufentanil.

2) By the type of receptor action:

   - Agonists: Alfentanil, codeine, fentanyl, ketobemidone, methadone, morphine, oxycodone, pethidine, remifentanil and sufentanil.

   - Mixed agonists/antagonists: Buprenorphine and nalbuphine.

   - Antagonists: Naloxone and metylnaltrexone.

3) By their origin:

   - Endogenous opioids: Enkephalin, endorphin and dynorphin.

   - Exogenous: Opioid drugs.

There are several different opioid receptors: μ (my), δ (delta), κ (kappa) and ORL1 (nociceptin/orphanin FQ).

The most common opioids are selective μ-opioid receptor agonists: alfentanil, codeine, fentanyl, ketobemidone, methadone, morphine, remifentanil and oxycodone. Opioid receptors

are widely distributed throughout the CNS; e.g. in the substantia gelatinosa, the periaquaductal gray matter (PAG), the thalamus, the amygdala and the cortex (fig. 3).

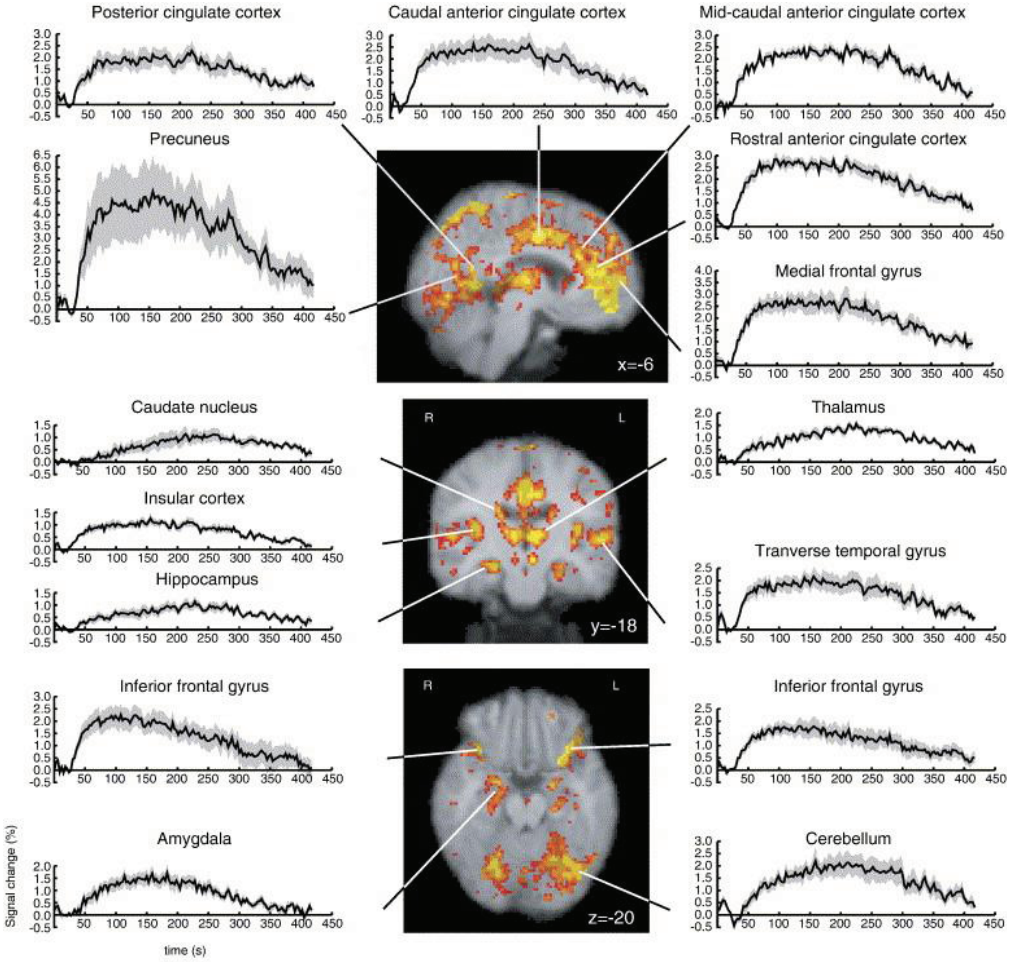


Fig. 3

Group average (fixed effect) activation maps and time courses of signals (±1 SEM, gray area) in response to intravenous remifentanil boluses. The time courses show the average signal changes over the three repetitions of remifentanil administration and voxels within the region of interest in six subjects. The intravenous injection of the drug occurred at 0 s.
With permission, Leppä et al.: Neuroimage 2006;31:661-9.

There are also opioid receptors in the gut[38;39] and in inflammatory tissue.[40]

The CNS is the main target for opioids. Opioids inhibit the ascending transmission of noxious stimuli in the dorsal horn. Opioids can also activate the pain inhibitory system by inhibiting the activity of GABAergic neurons. This is mediated in the PAG through descending pathways in the rostral ventral medulla, and inhibits nociceptive responses in the spinal dorsal horn.

Opioids have a large number of adverse effects like nausea, vomiting, itching, dizziness, sedation, hallucinations, urinary retention, sleep disturbances, respiratory depression etc. It is therefore important that the patients are not "overloaded" with opioids. An enhanced use of opioids increases the risk of adverse effects.

Different opioids have different pharmacological properties, and choosing the right opioid for the specific surgical procedure may be of importance to achieve better postoperative analgesia and less adverse effects.

Two common used opioids are morphine and oxycodone.

Morphine is the "gold standard" among the opioids. It is a classical μ-receptor agonist, and the most commonly used opioid worldwide. Morphine has an active metabolite, M-6-G, which accumulates in the patients suffering from renal failure, and in these patients care should be taken to avoid an overdose of morphine. Morphine has low lipid solubility compared to many other opioids, and is therefore slow-acting because the blood-brain barrier transport is slow.

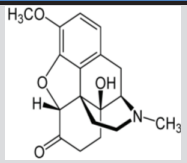
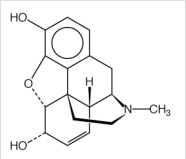
Oxycodone is an old opioid with a growing clinical use the last years. The pharmacological effects of oxycodone have been supposed to be typical of a μ-opioid, closely resembling morphine.[41] Traditionally, it has been presumed a 1:1 ratio in analgesic potency between morphine and oxycodone intravenously and intramusculary in postoperative pain.[42;43] These studies have been performed on various types of surgery, with both somatic and visceral pain.

However, one study on patients undergoing abdominal surgery demonstrated a 2:3 ratio in analgesic potency between oxycodone and morphine intravenously. In addition, the patients who received oxycodone were less sedated.[44] This may suggest a potential better analgesic efficacy of oxycodone in visceral pain with less adverse effects. In a multi-modal, tissue-differentiated experimental pain model in humans, equipotent doses of oxycodone and morphine demonstrated that oxycodone had a better analgesic effect in visceral pain.[45;46] Even though these studies may indicate that oxycodone is more efficient in the treatment of visceral pain compared to morphine, this question is still unsettled.

In paper III, these two opioids were compared with respect to postoperative pain and adverse effects. The approach in this study was to investigate whether one of those opioids was more efficient in the treatment of postoperative pain presumed to be dominated by visceral pain stimulation.

The pharmacological characteristics and differences between oxycodone and morphine are listed in table 1.

Table 1

	Oxycodone	Morphine
Chemical structure		
Receptor binding profile	μ-receptor agonist[47;48]	μ-receptor agonist
Receptor affinity (to μ-receptor)	> 20 times less than morphine[49]	Higher affinity to the μ-receptor than oxycodone[49]
Receptor activation	3-8 times higher concentration is needed to activate the G-protein compared to morphine ([^{35}S]GTPγ assay)[49-51]	Lower concentration to activate the G-protein than oxycodone[49-51]
Analgesic efficacy in postoperative pain	Intravenous: Between 1:1 and 1:1.5[42-44;52] Epidural: Less potent compared to morphine (8.4-9.8:1)[53] Oral: Controlled-release (CR) oxycodone 1.8 times more potent than CR morphine in total effect[54]	Intravenous: Between 1:1 and 1.5:1[42-44;52] Epidural: More potent compared to oxycodone[53] Oral: Less potent than oxycodone[54]
Adverse effects	Classical μ-opioid-related adverse effects, but less hallucinations[55-57] and itching[55] (less histamine release) than morphine	Classical μ-opioid-related adverse effects. More hallucinations and itching than oxycodone[55-57]
Metabolites	O-demethylation in the liver to oxymorphone (no analgesic efficacy)[58] and N-demethylation to noroxycodone (no analgesic efficacy)[50]	Metabolized in the liver to M-6-G (analgesic efficacy), M-3-G (no analgesic efficacy) and normorphine (analgesic efficacy).[59]
Volume of distribution	2-3 L/kg[60]	1-4 L/kg[59;61]
Elimination	Excreted in urine. Oxycodone and noroxycodone as unconjugated, and oxymorphone as conjugated[62]	Excreted mainly through urine[59]
Peak plasma concentration following i.v. administration	Within 25 min[41;60]	Within 20-30 min[63;64]
T ½ following intravenous administration	Approximately 2-3 hours[60]	Approximately 2-3 hours[61;65]
Protein binding (in vitro)	Approximately 38%[66]	Approximately 31%[66]
Lipid solubility	Similar to morphine[66]	Low lipid solubility compared to most others opioids (e.g. fentanyl)[66]
Blood-Brain Barrier transport	Active influx of oxycodone into the CNS?[67;68]	None known active influx
Oral bioavailability	Approximately 60%[62]	18-24%[69;70]

4.4 Opioid-induced hyperalgesia (OIH)

There is growing evidence that opioids, in addition to alleviate pain, can facilitate pain.[71] This phenomenon is called opioid-induced hyperalgesia (OIH). Hyperalgesia is defined as hypersensitivity to nociceptive stimuli, and this is due to the activation of pro-nociceptive mechanisms (sensitization of pro-nociceptive pathways). It is sometimes difficult to differentiate between hyperalgesia and tolerance. Hyperalgesia is a leftward shift of the stimulus-pain curve (fig. 4 A). The result is that a non-painful stimulus may become noxious (allodynia), or that a normally painful stimulus increases in intensity. Tolerance is a loss of analgesic opioid efficacy over time due to the use of opioids. As a consequence, larger doses of opioids are necessary to achieve the same efficacy (desensitization of anti-nociceptive pathways). Tolerance is a rightward shift of the opioid dose-effect curve (fig. 4 B), where the opioid looses its potency.

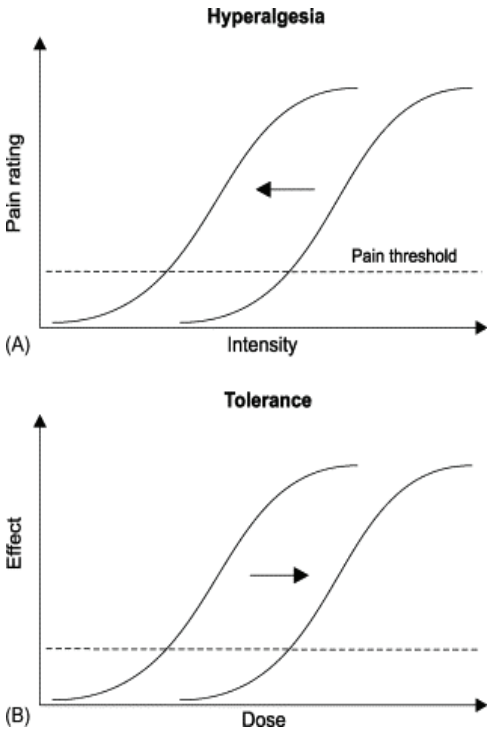


Fig. 4

A) Hyperalgesia is a leftward shift of the stimulus-pain curve, e.g. a non-painful stimulus becoming noxious (allodynia) or that a normally painful stimulus increases in intensity.

B) Tolerance is a rightward shift of the dose-effect curve, where the drug looses its potency.

With permission, Koppert W: Acute Pain 2007; 9:21-34.

Opioid-induced hyperalgesia is explained as when patients receiving opioids become more sensitive to pain as a consequence of the opioid therapy itself. The evidence of OIH and the possibility to prevent OIH can be divided into four types of studies:

1. Studies on former opioid addicts

2. Animal experimental studies

3. Human experimental studies

4. Studies on surgery patients

1. Studies on former opioid addicts

Several studies on current and former opioid addicts have been carried out.[72-75]

Three of these studies have compared either former addicts on methadone to former addicts free of methadone,[72] or former addicts on methadone to a control group (healthy volunteers).[73;75]

The subjects were tested for electrical pain and cold pressor pain. The subjects on methadone detected pain significantly earlier and had significantly lower pain tolerance than the control group or former addicts free of opioids.[73;75]

From this, one may conclude that current opioid addicts are hyperalgesic, and that the condition is reversible with the withdrawal of the opioid therapy (methadone).

2. Animal experimental studies

Several studies with different models in rats have clearly demonstrated that opioids like heroin, morphine and fentanyl induced hyperalgesia, and that activation of the NMDA receptor in the medulla seems to play a key role in the development of opioid-induced hyperalgesia.[76-84]

In these studies, treatment with NMDA receptor antagonists like ketamine and MK-801(dizocilpine maleate) prevented the development of hyperalgesia. It has also been

demonstrated that opioids, like remifentanil, activates the NMDA receptor in the dorsal horn neurons.[85]

Prostaglandins, like PGE_2, can stimulate glutamate release from astrocytes and from the spinal cord dorsal horns with subsequent activation of the NMDA receptors.[86;87] Subsequently, cyclooxygenase inhibitors were found to antagonize this NMDA receptor activation.[88;89] Therefore, it is not surprising that COX-2 inhibition attenuated the level of thermal hyperalgesia induced by paw carrageenan injection.[35]

In rats, OIH induced by subcutaneous fentanyl was prevented by administration of intraperitoneal or intrathecal gabapentin.[90] Gabapentin has a binding site to the alpha-2-subunit of the calcium channel,[91] and the antinociceptive efficacy of gabapentin seems to depend on the affinity to this receptor site.[92] The mechanism by which gabapentin prevents OIH is not totally understood. The underlying hypothesis is that gabapentin inhibits the glutamate release by binding to the alpha-2-delta subunit of spinal voltage-gated calcium channels. As opioids increase the level of presynaptic glutamate, this may explain way gabapentin has the ability to reduce OIH.

In rats, magnesium also seems to prevent OIH after fentanyl administration.[93] The main mechanism seems to be through a voltage-gated antagonist action at the NMDA receptor, and magnesium is therefore considered as a NMDA receptor antagonist.[94]

Nitrous oxide (N_2O) is a NMDA antagonist,[95] and in rats treated with N_2O, fentanyl-induced hyperalgesia in inflammatory and incisional pain models was reduced.[96] Sevoflurane also seems to have a weak anti-hyperalgesic effect.[97]

3. Human experimental studies

Different experimental pain models have been performed in human volunteers.

a) Short-term infusion of remifentanil with electrical pain. To provoke pain and secondary hyperalgesia, two microdialysis fibres equipped with internal stainless steel wires are inserted

intradermally in the central volar forearm, and a constant current stimulator then provokes pain. This model has been proven to create a stable area of secondary hyperalgesia to punctate stimuli by an activation of primarily mechanoinsensitive "silent" C-nociceptors.[98] In this model, remifentanil induced postinfusion hyperalgesia,[99;100] and different drugs have been tested to investigate the possibility to prevent/diminish this postinfusion hyperalgesia. Drugs like ketamine[99;101] and parecoxib[102] have reduced the area of secondary hyperalgesia to punctate stimuli.

b) Short-term infusion of remifentanil with heat-capsaicin model. Sensitization is induced by heating the forearm skin with a thermode at 45 °C. Capsaicin cream applied on the skin induces pain and primary and secondary hyperalgesia. The area of secondary hyperalgesia and allodynia can then be measured before, during and after remifentanil infusion. This model demonstrated that during remifentanil infusion, the area of secondary hyperalgesia was reduced,[103] and after withdrawal, the areas of secondary hyperalgesia and allodynia were enlarged.[104]

c) Short-term infusion of remifentanil with electrical pain (applied on the anterior tibial muscle) and pressure pain test. In this study, remifentanil induced hyperalgesia and tolerance only in the pressure pain test and was not suppressed by ketamine.[105]

d) Morphine has demonstrated hyperalgesia in the cold pressor test.[106]

<u>Summary of the results from experimental pain models on OIH in humans:</u>

Both the electrical model, the cold pressor model, the heat model and the mechanical (pressure) model demonstrate remifentanil-induced hyperalgesia. OIH in humans can be prevented by administration of ketamine, a NMDA receptor antagonist. COX-2 inhibition also seems to have the possibility to prevent OIH. The mechanism behind this is probably through the NMDA receptor; prostaglandins, like PGE_2, can stimulate glutamate release from

astrocytes and from the spinal cord dorsal horns with subsequent activation of the NMDA receptors.[86;87] Subsequently, cyclooxygenase inhibitors can antagonize this NMDA receptor activation.[88;89]

4. Studies on surgery patients

In clinical trials, it is difficult to demonstrate OIH directly. This is due to the lack of good models to differentiate between OIH and acute tolerance. The studies that have been performed demonstrate a more indirect evidence of OIH. In surgery patients, several studies have been performed comparing a "low dose" opioid group vs. a "high dose" opioid group. Three of these studies demonstrated higher opioid consumption and higher pain scores postoperatively in the "high dose" group.[107-109] One study did not demonstrate increased postoperative opioid consumption or pain scores in the group receiving remifentanil, when compared to a group receiving sevoflurane.[110] An important objection to this study is that both groups received 50% nitrous oxide in oxygen. Nitrous oxide is a NMDA antagonist,[95] and may therefore have protected the remifentanil group from developing OIH.

These four studies did not differentiate between OIH and acute tolerance, as both the amount of postoperative opioid consumption and pain scores was used as main result parameters. To address this problem another clinical trial has tried to estimate the area of hyperalgesia and allodynia around the wound postoperatively. The investigators demonstrated that the "high dose" opioid group had a significantly larger area of pinprick hyperalgesia and allodynia near the wound compared to the "low dose" opioid group.[111] In this study, there was also a third group receiving a sub-analgesic infusion of ketamine in addition to "high dose" opioid. Ketamine prevented peri-incisional allodynia and hyperalgesia, and enhanced the opioid consumption postoperatively.

One study has demonstrated that lornoxicam, a non-selective NSAID, significantly diminished the acute opioid tolerance and/or hyperalgesia caused by fentanyl.[112]

Interestingly, this study suggests that administration of only three boluses of fentanyl 3 µg/kg i.v. during approximately 45 min leads to enhanced postoperative opioid consumption compared to placebo (0.9% NaCl).

The mechanisms of OIH:

It seems that OIH can be induced by peripheral, spinal and systemic administration of opioids.[71] Most of the studies on OIH have been done with µ-opioid receptor agonists. The dorsal horn of the medulla plays a crucial role in the development of OIH (fig. 5).

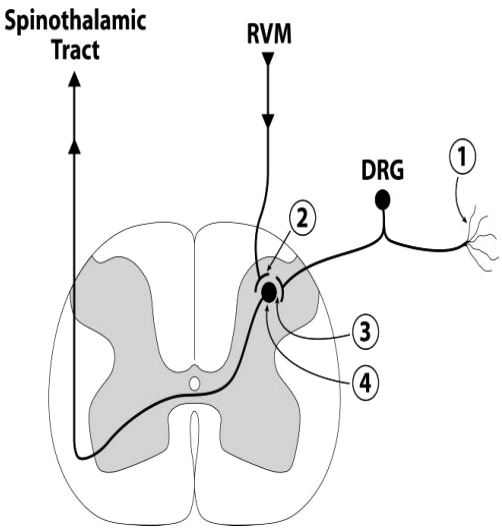


Fig. 5

1. Sensitization of peripheral nerve endings.
2. Enhanced descending facilitation of nociceptive signal transmission.
3. Enhanced production and release as well as diminished reuptake of nociceptive neurotransmitters.
4. Sensitization of second-order neurons to nociceptive neurotransmitters.

The figure does not illustrate all the potential mechanisms underlying opioid-induced hyperalgesia, but rather depicts those that have been more commonly studied.
DRG = Dorsal Root Ganglion; RVM = Rostral Ventral Medulla.
With permission, **Angst MS, Clark JD: Anesthesiology 2006; 104:570-87.**

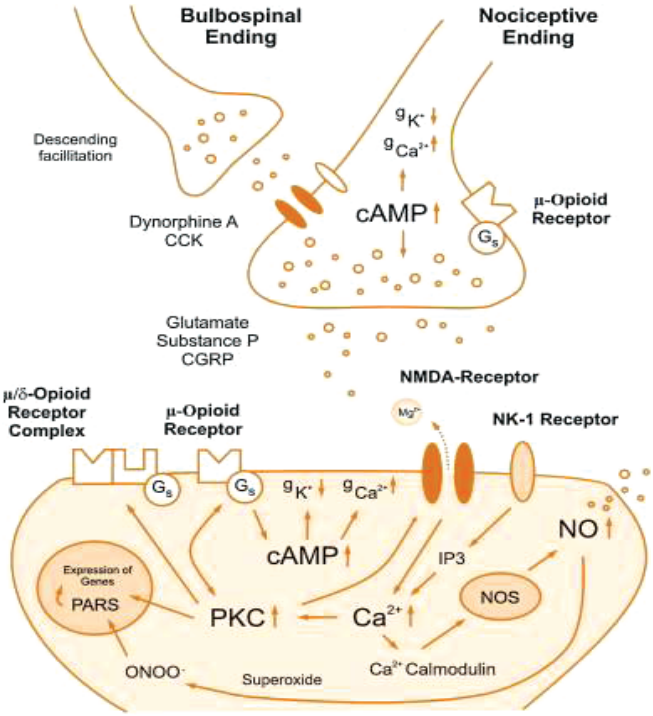


Fig. 6

Schematic illustration of the pronociceptive mechanisms mediated by μ-agonists. The increase of cyclic adenosine monophosphate (cAMP) causes a heightened release of excitatory amino acids. In addition to the increase on cAMP, the activation of protein kinase C (PKC) plays a major role in the postsynaptic processes. The phosphorylation of the NMDA receptors causes an increase of intracellular calcium (Ca^{2+}) with a heightened production of nitric oxide (NO).
With permission, Koppert W, Schmelz M: Best Pract Res Clin Anaesthesiol 2007; 21:65-83.

The NMDA receptor seems to play the most important role in the development of OIH (fig. 6). Opioids bind the NMDA receptor (postsynaptic), and this leads to the generation of NO. Nitric oxide then diffuses out of the postsynaptic neuron enhancing presynaptic release of glutamate. Glutamate then activates the NMDA receptor, and the NMDA receptor is amplifying the afferent pain input, leading to hyperalgesia.

Based on current knowledge, how do we deal with OIH in surgery patients today?

In a practical, clinical setting it is difficult to differentiate between OIH and acute tolerance in surgery patients. Still, it is important for the clinician to know that with the administering of large doses of opioids the patient is likely to experience more pain and needs more opioids postoperatively, which is not a desirable situation. If the planned surgical procedure is very painful or will last for several hours, there is an increased likelihood that large doses of opioids will be used, and strategies to reduce opioid dosing are necessary.

Strategies to reduce peroperative opioid consumption:

a) If possible, inhalation gases should be used.

Inhalation gases has an analgesic effect,[113] and by using inhalation anaesthetics, the opioid consumption may be reduced.

b) Use of local and regional anaesthesia.

Use of local anaesthetics infiltration or regional blocks may reduce peroperative opioid consumption,[114] and thereby reducing the risk of postoperative OIH.

Preincisional intervention with epidural reduced postoperative opioid consumption and hyperalgesia definited by the von Frey pain threshold near the wound.[115] A more aggressive use of epidural anaesthesia during surgery seems therefore to be preferable. The systemic use of intraoperative opioids can be reduced by using epidural anaesthesia actively as an important analgesic component during surgery.

c) Use of N_2O and sevoflurane.

Nitrous oxide is a NMDA receptor antagonist,[95] and has demonstrated reduced hyperalgesia in opioid-exposed rats.[96;116] There is also evidence that sevoflurane has antihyperalgesic effect.[97] As far as we know, no clinical study on surgery patients investigating N_2O with respect to OIH has been performed.

d) Use of ketamine.

Ketamine is the most potent NMDA receptor antagonist in clinical use. Joly et al.[111] administered ketamine 0.5 mg/kg as a bolus, followed by an 5 µg/kg/min infusion during surgery and 2 µg/kg/min until 48 h after the end of surgery in a group receiving "high dose" remifentanil. This regimen prevented increased postoperative morphine consumption.
On the other hand, intraoperative infusion of low dose ketamine infusion alone did not prevent remifentanil-induced acute tolerance and/or hyperalgesia.[117;118]
More studies are needed before it is possible to put forth a recommendation of a practical use of ketamine to prevent OIH in surgery patients.

e) Use of NSAIDs.

In an experimental pain model in humans, NSAIDs seem to prevent OIH.[102] One clinical study indicates that NSAIDs may also have this potential in surgery patients.[112]

f) Use of magnesium.

Magnesium is a NMDA receptor antagonist, and seems to prevent OIH after fentanyl administration in rats.[93] One clinical study has also demonstrated less postoperative morphine consumption with infusion of magnesium,[119] but this study was not designed to investigate opioid-induced hyperalgesia and/or tolerance.

g) Opioid rotation

Opioid rotation has been suggested as a treatment to avoid/reduce OIH.[71] There are several reports of cancer patients with escalating opioid doses and pain supposed to be hyperalgesia, who has profited when changing from one opioid to another.[120] Changing from phenantren to peperidin derivatives has been suggested as a treatment to reduce OIH.[71]

Conclusion:

The strongest and most consistent evidences of OIH are derived from studies on normal volunteers and experimental studies in rats exposed to opioids. There is limited evidence for the development of OIH in surgery patients,[121] however several clinical trials indirectly indicate that OIH might be a relevant problem in surgery patients.[107-109;111;112]

In this thesis we have tried to investigate the possibility of reducing postoperative pain and analgesic consumption by pretreating surgery patients with fentanyl before remifentanil-based anaesthesia. This is a kind of opioid rotation or shifting of opioids to avoid possible postoperative opioid-induced hyperalgesia (paper I).

COX-2 inhibitors also seem to prevent/reduce OIH.[102] In paper IV, two different experimental pain models were used to investigate OIH in humans. COX-1 and COX-2 preferring inhibitors were used as pretreatment to investigate any differences in preventing OIH between COX-1 and COX-2 inhibition.

4.5 Measurement of pain in clinical trials

When measuring pain in clinical trials, it is important that the trauma is similar in all patients. This is achieved by only including patients scheduled for the same surgical procedure and involving as few surgeons as possible.

As several factors are involved in the perception of pain, the measurement of pain is complex. Physiological factors,[122] psychological factors,[123;124] etnicity,[125] gender,[126] age[127] and earlier experience with pain[128] are some of the factors having an impact on postoperative pain. In RCTs, confounding factors like these must be eliminated as far as possible. Cultural factors and traditions for pain behaviour are also factors with impact on pain.[125] In Norway, the population is quite conformable compared to many other countries, e.g. the United States. We included patients with a good understanding of the Norwegian language.

This means that the patients in our studies are mostly Caucasians with the same cultural background.

Gender has an impact on postoperative pain, as women are known to experience more postoperative pain compared to men.[126] When both women and men are included in the same RCT, it is important that the gender distribution is similar in the comparing groups.

Age also has an impact on postoperative pain; the postoperative opioid consumption decreases with increased age.[127]

Patients with chronic pain and/or regular use of pain medication should not be included in basic clinical pain trials. These patients often have more postoperative pain and need more opioids to achieve pain relief. If these patients are included and are imbalanced in parallel groups, the results may be unpredictable.

To avoid many of the known confounding factors with respect to postoperative pain, the ideal setting in a clinical trial is the same, standardized procedure with only one gender. In addition, the age distribution should not be too wide. Reduced number of confounders may increase the statistical power and sensitivity in pain studies, but the conclusions may be less valid when extrapolated to groups of patients not being included in the study.

In the three clinical trials (paper I-III), the patients were well medicated with analgesic (local anaesthetics, NSAIDs and paracetamol) and antiemetics (droperidol, ondansetron and propofol anaesthesia). Of course, good basic pain prophylaxis makes it more difficult to actually find any differences in pain and adverse effects like nausea and vomiting between the groups. It is possible that actual differences are not discovered. On the other hand, if differences are found, this may give a stronger indication of actual differences between the comparing groups. It may be argued that differences which only appear in a comparison with inferior pain regimens in placebo groups are not as relevant in clinical practice. In clinical practice we have to look for improvements when new modalities are administered on the top

of present pain regimens. The use of placebo group has also an ethical aspect. Some patients may receive a less efficient pain treatment, and this could be a problem when applying for approval from the ethical committee. This is especially true if the analgesic efficacy has been demonstrated in previous placebo controlled studies, and when the goal of the new study is to put this into a clinical context.

In the clinical studies we chose to mimic the pain treatment that are actually used in our hospital. This makes it easier to extrapolate the results to a real clinical situation.

5. Aims of the thesis

The overall aim of the thesis was to investigate clinical and experimental aspects of improving postoperative analgesia by testing different analgesic drugs and by looking for means of modulation of postoperative opioid-induced hyperalgesia.

In paper II and paper III, two NSAIDs and two opioids, respectively, were compared to investigate the possibility of improving postoperative pain control.

In paper I and paper IV, the aim was to investigate opioid-induced hyperalgesia, and the possibility to reduce or prevent postoperative pain or hyperalgesia by pretreating the patients with opioid (fentanyl) or NSAIDs before remifentanil infusion.

<u>The following hypotheses were tested:</u>

In paper II, etoricoxib (a predominantly COX-2 inhibitor) vs. ketorolac (a predominantly COX-1 inhibitor) was compared. The primary hypothesis was that etoricoxib would provide similar maximum early postoperative analgesia as ketorolac. The secondary hypothesis was that etoricoxib would provide a better analgesic effect after discharge from the hospital.

In paper III, comparison of the analgesic potency, pain scores and adverse effects of intravenous oxycodone vs. morphine was done in a clinical model of postoperative visceral pain. The main hypothesis was that oxycodone and morphine were equipotent as analgesics, in terms of doses measured in mg and with similar efficacy/adverse effect profile.

In paper I, the hypothesis was that pretreatment with fentanyl prior to induction of remifentanil-based anaesthesia would decrease the self-rated pain scores and opioid consumption in the postoperative period.

In paper IV, two different experimental human pain models were used to investigate the possibility of demonstrating remifentanil-induced postinfusion hyperalgesia; a model using

electrically evoked pain and a cold pressor test. At the same time, the subjects were pretreated with parecoxib or ketorolac to investigate the possibility of preventing opioid-induced hyperalgesia with different types of COX-inhibitors. The main hypothesis was that remifentanil would induce postinfusion hyperalgesia in both experimental models. The secondary hypothesis was that parecoxib and ketorolac would prevent or diminish this postinfusion hyperalgesia in a similar way in both experimental models. By comparing parecoxib (a predominantly COX-2 inhibitor) against ketorolac (a predominantly COX-1 inhibitor), we had the opportunity to investigate if there were any differences in preventing remifentanil-induced hyperalgesia by inhibiting either the COX-1 or the COX-2 enzyme.

6. Materials and methods

6.1 Study design, approval and registration

The study design in all four studies was prospective, randomized and double-blind.

In the clinical trials (paper I-III), two groups were compared.

The last trial was also placebo-controlled with a crossover design including healthy volunteers (paper IV). In this trial, each subject went through four sessions: control, remifentanil, parecoxib + remifentanil and ketorolac + remifentanil. Only males were included because the pain threshold level is fluctuating in women depending on where in the menstrual cycle they are. As four sessions were performed, the pain threshold in women may vary from one session to another, and this is a confounding factor.

In all four papers the randomization was based on computer-generated codes stored in sequentially numbered, sealed envelopes. A person, who did not participate in the handling or the assessment of the patients/volunteers, was responsible for preparing these envelopes, and for opening the envelopes and preparing the medication. The appearance of the syringes (or tablets) was the same, and the investigator (and the patient/volunteer) was therefore blinded.

Before start, the studies were approved by the Regional Committee for Medical Research Ethics in South-Eastern Norway and by the local health institution's privacy protection representative. The last trial (paper IV) was also approved by the Norwegian Medicines Agency before start, as the study involved the use of drugs in volunteers and not for an approved clinical indication with approved doses.

All trials have been registered in ClinicalTrials.gov. ClinicalTrials.gov is a service of the U.S. National Institutes of Health. It is a registry of clinical trials conducted around the world, and it is currently compulsory to register clinical trials before start. If not, the possibility to publish the results is limited.[129;130]

6.2 Patients and volunteers

In the clinical trials (paper I-III), adult persons (18-70 yr) were recruited after a written informed consent had been obtained. The exclusion criteria were regular use of paracetamol, NSAIDs, corticosteroids, antiemetics or opioids. Contraindications for NSAIDs, obesity (paper I) and pregnancy (paper II) were also exclusion criteria. All the patients were ASA physical status I–II.

In paper IV, volunteers were recruited after a written informed consent had been obtained. Most of these volunteers were healthy male students, with no known drug allergy or no use of medication during the experiment. Alcohol or drug abuse was also exclusion criteria.

6.3 Surgery and anaesthesia in paper I-III

In paper I, all patients underwent ACL repair. Both men and women were included.

In paper II, women scheduled for ambulatory, laparoscopic gynaecological surgery were included. All kinds of minor to moderate day surgical procedures were performed.

In paper III, women scheduled for LSH and TLH were included. All patients had benign conditions.

Anaesthesia in the clinical trials (paper I-III) was TCI propofol and remifentanil, except from paper I where μg/kg/min for remifentanil infusion was used. All patients received paracetamol as basic pain prophylaxis.

In paper II and III, the patients also received a NSAID either before or during surgery. Local anaesthesia (bupivacain) was administered in all the clinical trials. In the trials only including women, the patients received antiemetic prophylaxis (droperidol, ondansetron).

6.4 Measurement of pain

In the three clinical trials (paper I-III), either VAS and/or VRS was used. VAS is a 100 mm long visual analog scale, where 0 mm corresponds to no pain, and 100 mm corresponds to the worst pain imaginable. VRS is a five-point verbal rating scale; 0: no pain, 1: slight pain, 2: moderate pain, 3: severe pain, and 4: most intense pain.

The measurement of pain is complex (see chapter 4.5). However, we used quite simple methods to estimate pain postoperatively. VAS and VRS are well established methods, and their reliability is well documented.[131-134] These methods are easy to understand and to use in a postoperative setting.

In paper I-III, patients with chronic pain and/or regular use of analgesics were excluded.

In paper I and III, PCA for postoperative pain management was used. PCA makes the patients more autonomous, and this can also be used to tell something about pain indirectly, as more pain will result in more opioid use.

In paper II, NCA was used for postoperative pain management. In this trial, the patient had to ask for rescue medication or score VAS ≥ 30 mm to get opioid medication. This might be a more inaccurate way to treat pain, but in a day surgery unit where the patients often do not suffer from strong pain, it is a practical way of handling postoperative pain instead of cumbersome pumps and algorithms. It has been shown that with dedicated nurses, like in our trial, NCA is experienced as an equally satisfactory method of treating pain compared to PCA.[135;136]

In paper III, we tried to create an "ideal" setting to avoid confounding factors with respect to pain. Laparoscopic hysterectomy is a standardized procedure, performed by few surgeons. In addition, all the patients are women at approximately the same age. Painmatcher® was used to discover possible differences in preoperative pain threshold between the two groups. A possible difference in pain threshold between the two groups would have been a confounding

factor. The principle of use of Painmatcher® is to grasp the left hand side electrodes between the left thumb and the index finger. When the patients push down the electrodes, this initiates a continuously ascending electrical stimulus.[137] Painmatcher® has been found highly reliable in evaluating pre- and postoperative pain.[138] In the first test, the patient had to keep the pressure until she felt pain (EPT- electrical pain threshold). In the second test, the patient had to keep the pressure to the maximum tolerable pain (maximum electrical pain threshold - MEPT).

In paper IV, we induced pain in healthy volunteers. For practical reasons, a verbal rating scale (0-10) was used in both experimental models (electrical pain and cold pain). During the experiments, both hands were "tied up" - with ongoing electrical pain at one underarm, and the other arm exposed to ice water. The use of a linear visual analog scale would have been difficult, because the participant then had to use one hand to move the pointer.

6.5 Statistical methods

Two parallel groups were compared in the clinical trials (paper I-III). Data were analyzed using an independent sample t-test for parametric data, the Mann-Whitney U test for non-parametric data and the χ^2-test for categorical data. Bonferroni's correction was performed on repeated pain scores values in paper I and II. In paper III, repeated measures analysis of variance (ANOVA) and area under the curve (AUC) were used for VAS scores. Repeated measures ANOVA were also used for the sedation scores in this trial.

Paper IV was a randomized, double-blind, placebo-controlled trial with a crossover design. Previous trials of the electrical pain model have demonstrated that the area of pinprick hyperalgesia decreases from one session to another.[139] Thus, data regarding areas of secondary hyperalgesia were normalized to achieve the same point of reference in the participants from all of the four treatments by setting the mean of both baseline measurements (15 and 30 min) of pinprick hyperalgesia after onset of electrical stimulation,

to 100%. The changes from this baseline were transformed to areas under the curve (AUC) for each period.

We compared the infusion period (30-60 min), the postinfusion period with stimulation (60-150 min), and the postinfusion period without electrical stimulation (150-210 min). The changes in percentage were not normally distributed, therefore non-parametric; two related samples Wilcoxon tests were performed. We also calculated the AUC of VRS scores in the electrical pain and the cold pressor test. These results were normally distributed, and paired samples T-tests for each group were performed. Paired samples T-tests were performed on MAP, HR and SpO_2. All data were processed in the SPSS statistical software version 14.0 and 16.0 (SPSS Inc., Chicago, IL). The significance level was set to 0.05.

7. Results

7.1 Paper II and paper III

In paper II, one hundred thirty-three women scheduled for ambulatory, laparoscopic gynaecological surgery were included in this randomized, double-blind study. Group E received etoricoxib 120 mg orally as premedication and Group K received ketorolac 30 mg i.v. after induction of anaesthesia.

The first four hours postoperatively, the opioid consumption in Group K was significantly less than in Group E (Group K 83 ± 65 µg and Group E 123 ± 91 µg fentanyl [mean (SD), P = 0.004]).

VAS was significantly lower in Group K 30 min after the end of surgery (Group K 31.3 ± 19.7 mm and Group E 43.8 ± 16.9 mm [mean (SD), P < 0.001]). Discharge readiness was significantly shorter in Group K (222 ± 40 min) compared to Group E (244 ± 47 min) [mean (SD), P = 0.004]. There were no differences in pain scores or rescue pain medication at 24 and 48 h postoperatively. Group E had less nausea in the 4-24 h period, 9 vs. 22 patients (P = 0.023).

In paper III, ninety-one women admitted for LSH or TLH were randomized to either intravenous oxycodone or morphine before the end of laparoscopic hysterectomy, and then continued with patient-controlled analgesia (oxycodone or morphine) for 24 h postoperatively.

Preoperative electrical pain threshold (EPT) and maximum electrical pain threshold (MEPT) were similar in the two groups.

The accumulated opioid consumption was significantly less in the oxycodone group compared to the morphine group; 13.3 ± 10.4 mg vs. 22.0 ± 13.1 mg (P = 0.001). The pain

scores were significantly lower in the oxycodone the first hour postoperatively (P = 0.037), and sedation was significantly lower during the 24 h postoperative period (P = 0.006).

7.2 Paper I and paper IV

In paper I, one-hundred patients admitted for anterior cruciate ligament (ACL) repair were included and randomized in a double-blind study. Group Pre received fentanyl 1.5 µg/kg i.v. and Group Post received placebo prior to the remifentanil infusion. At the end of surgery, Group Pre received fentanyl 1.5 µg/kg and Group Post received fentanyl 3.0 µg/kg i.v. There were no differences in postoperative pain or analgesic consumption between the two groups during the first four hours postoperatively. Group Post had significantly less pain in the 4-24 h period after surgery, with a median VRS score of 'slight pain' vs. 'moderate pain' in Group Pre (P < 0.05). In this period, the opioid consumption was similar in both groups.

In paper IV, sixteen male volunteers were enrolled to demonstrate remifentanil-induced postinfusion hyperalgesia in an electrical pain and a cold pain model.

Pinprick hyperalgesia (electrical pain): All groups developed stable and similar pinprick hyperalgesia areas during the first 30 min of electrical stimulation. During the infusion-period, the areas under the curve (AUC) for all treatment groups receiving remifentanil were significantly smaller compared to AUC in the control group.

This antihyperalgesic effect was only present during the infusion. In the postinfusion period, the areas of pinprick hyperalgesia exceeded control values in the remifentanil group (P = 0.039). Pretreatment with parecoxib prevented remifentanil-induced postinfusion hyperalgesia compared to the remifentanil group (P = 0.044). Pretreatment with ketorolac did not prevent postinfusion hyperalgesia compared to the remifentanil group (P = 0.53).

After the electrical stimulation was switched off, there were no significant differences between the four groups.

Cold pressor test (CPT): The AUC values in the first CPT (before any drugs were administered) were similar in all groups. The CPT at the end of the infusion demonstrated significantly lower VRS scores in all three groups receiving remifentanil compared to placebo ($P < 0.001$). The CPT 1 h after the end of the infusion demonstrated significantly higher VRS scores in the remifentanil group compared to the control group ($P = 0.017$). Pretreatment with ketorolac resulted in significantly lower VRS scores compared to the remifentanil group ($P = 0.046$). Pretreatment with parecoxib demonstrated not significant lower VRS scores compared to Group R ($P = 0.18$).

8. Discussion

8.1 Paper II and paper III, different COX-inhibitors and opioids

In these two clinical trials, different COX-inhibitors and opioids were compared in an attempt to improve postoperative analgesia in specific clinical models. The choice of different analgesic agents, included in the multimodal concept of postoperative analgesia, has become more patient and procedure tailored in recent years (www.postoppain.org). The choice of analgesics depend on several different factors. The type of surgery is an important determinant; the extent and type of tissue and cell damage involved, the potential of strong nerve stimulation or damage and the risk of bleeding. Patient related aspects are also important: the age and gender of the patient as well as the individual risks of specific adverse effects such as asthma, gastrointestinal ulcer, renal dysfunction etc. The surgical setting has also an impact; an inpatient will have access to intravenous administration and professional surveillance, this is not the case with an ambulatory patient after discharge.

In these two studies paracetamol and local anaesthetics (bupivacain) were used to mimic a realistic clinical situation with new drugs administered on the top of established routines. The use of proper, basic non-opioid analgesics in all patient groups will reduce the need of opioid rescue medication and the risk of potentially serious adverse effects. However, as mentioned previously, this pragmatic approach may reduce the sensitivity for detecting differences between the study groups.

Hypothesis paper II:

The primary hypothesis was that etoricoxib would provide similar maximum early postoperative analgesia as ketorolac. The secondary hypothesis was that etoricoxib would provide a better analgesic effect after discharge from the hospital.

Presurgical injection of ketorolac 30 mg i.v. resulted in less accumulated opioid consumption during the first 4 h postoperatively, compared to etoricoxib 120 mg orally administered at least 1 h before surgery. The patients receiving ketorolac also experienced less pain at 30 min after the end of surgery.

Previous studies comparing etoricoxib to non-selective or predominantly COX-1 selective NSAIDs in clinical postoperative pain management have demonstrated similar efficacy of the different drugs.[27;28;140]

Zhu et al. used an experimental model of incisional pain in rats, which would be similar to a postoperative clinical situation. They demonstrated significant activation of COX-1 in the spinal cord with incisional trauma, and less pain behaviour after preoperative intrathecal injection of ketorolac than of a selective COX-2 inhibitor.[33;34] In most studies comparing non-selective NSAIDs to COX-2 inhibitors, the drugs were administered after surgery. It is possible that presurgical administration of a COX-1 preferring NSAID, like ketorolac, can slow down the central sensitization by inhibiting COX-1 in the dorsal horn of the medulla resulting in less pain postoperatively.[33] To our knowledge three, randomized, double-blind studies with such preoperative administration of either a non-selective NSAID or a COX-2 inhibitor have been conducted.[141-143]

Pickering et al. compared paracetamol in combination with either rofecoxib, ibuprofen or placebo.[143] Ibuprofen/paracetamol significantly reduced the need of early supplementary analgesics compared to rofecoxib/paracetamol. Pain scores were also significantly lower in the ibuprofen group at the time of administration of rescue pain medication.

Morse et al.[141] compared ibuprofen 400 mg vs. rofecoxib 40 mg orally as premedication for mandibular third molar surgery. The ibuprofen group had lower pain scores every time they scored the patients (not significant; n.s.), and 25% of the patients in the ibuprofen vs. 50% in the rofecoxib group needed rescue medication (n.s.).

Ng et al.[142] administered ketorolac 30 mg or parecoxib 40 mg at induction of anaesthesia in patients undergoing laparoscopic sterilization. The pain scores were lower in the ketorolac group on awakening and at 1 h postoperatively, but no differences in the need of rescue medication were seen.

These studies, including our work, may indicate that pretreating patients with a COX-1 preferring NSAID before surgery may lead to lower pain scores and less need of rescue medication in the early postoperative phase.

We compared one drug administered orally and one drug administered intravenously, and this may be criticized. Intravenous administration is a more predictable way of achieving a rapid and more adequate plasma concentration than oral administration. However, the oral medication in our trial was administered at a mean of 116 min before the start of surgery, and none of the patients received the tablets less than 60 min before the start of surgery, which would ensure full absorption and efficacy.[144] However, in some of the patients anaesthesia actually started less than 60 min after the administration of etoricoxib. Anaesthesia per se may lead to delayed emptying of the stomach, and thus to a potential delayed maximum plasma concentration of etoricoxib in some patients.

In paper II, the setting is ambulatory surgery where the timing aspects are crucial. The time from the arrival of the patient in the hospital to the start of anaesthesia and surgery is short, and administration of premedication at the right time is often difficult to achieve. To ensure that premedication tablets are completely absorbed and have maximum effect before the start of anaesthesia, may be important. For etoricoxib, maximum plasma concentration is reached after 60 min,[144] but there are probably important individual differences. Even though almost 2 h (mean) elapsed from premedication to the start of surgery in this trial, the patients receiving etoricoxib had more pain and needed more opioids postoperatively compared to those

receiving ketorolac. The administration of premedication more that two hours before the start of anaesthesia in a day-surgery unit is unrealistic.

Etoricoxib 120 mg orally and ketorolac 30 mg i.v. were chosen, as these are the recommended maximal doses according to the approval of the Norwegian government medicines agency.

For etoricoxib it has been demonstrated that no stronger effect is seen by increasing the oral dose beyond 120 mg in adults.[140] For ketorolac, the initial dosing after marketing of the drug was 40-60 mg i.v as a singel dose with a possibility to repeat the dose, but after reports of severe adverse reactions and deaths the maximum dose was set to 90 mg i.v. /day (30 mg every 8th hour) in adults.[145]

Surprisingly, there were no differences in pain scores or need of rescue medication at 24 h and 48 h postoperatively. The recommendation for ketorolac is dosing every 8 h, for etoricoxib every 24 h. Thus, with 2 doses of each drug administered according to the recommendations, ketorolac should not be expected to have efficacy throughout the first night and during the subsequent 24-48 h interval. The second ketorolac dose was administered just before discharge because of the need of an i.v. access. In our trial, that corresponded to 3-6 h after the first dose, and this should be even less prone to last until the registration at 24 h. The lack of prolonged effect of etoricoxib may be explained by a low baseline pain score and a low amount of rescue medication in both groups. In addition, all patients received paracetamol 1 g x 4 daily during the study period as a part of a basic pain prophylaxis.

The etoricoxib group had significantly less nausea 24 h after surgery. This result is difficult to explain based on pain scores and use of rescue medication in the corresponding time period. It can be due to subtle non-significant differences in pain, mobilization, hydration or other PONV risk factors between the groups, or this result may be a coincidence.

We demonstrated significantly less time to discharge from the hospital in the ketorolac group compared to the etoricoxib group. We interpret this as a result of less pain and less need of opioid rescue medication in the ketorolac group during this part of the postoperative periode.

Hypothesis paper III:

The main hypothesis was that oxycodone and morphine were equipotent analgesics in a study of clinical visceral pain, in terms of doses measured in mg and with similar effect/adverse effect profile.

In this clinical model of visceral pain, the patients in the oxycodone group needed significantly less accumulated oxycodone compared to the accumulated morphine consumption in the morphine group (13 mg vs. 22 mg). This 2:3 ratio between oxycodone and morphine has been demonstrated previously in an other clinical model of visceral pain.[44] In contrast, clinical studies comparing these two drugs in a postoperative setting with both somatic and visceral pain have found a 1:1 ratio.[42;43]

Our findings are supported by experimental studies in humans, which confirm that oxycodone is superior to morphine in visceral pain.[45;46]

Oxycodone is clearly a μ-receptor agonist, as discribed in chapter 4.3., table 1. Studies in rats suggest that oxycodone also has κ-opioid receptor agonist properties,[146-148] even though this is highly disputed,[149] and not demonstrated in humans. The κ-opioid receptor is involved in visceral pain,[150;151] and if oxycodone has κ-opioid receptor agonist properties this may explain why oxycodone has some advantages in the treatment of visceral pain compared to morphine.

In addition, we found a significantly longer time to the first PCA oxycodone request after the end of surgery. Based on this, we may conclude that the effect of the first standard dose of oxycodone administered by the end of surgery lasts longer, or that the drug is more potent, or both.

Oxycodone's affinity to the μ-opioid receptor is > 20 times less than morphine.[49]

The oxycodone concentration needed to activate the G-protein as measured by the [^{35}S]GtyS agonist-stimulated binding is 3-8 times higher compared to morphine.[49;50] In spite of this, in our trial it seems that oxycodone is more potent than morphine, and has less adverse effects in terms of less sedation.

Recent studies in rats indicate that oxycodone is actively transported through the BBB (blood-brain barrier).[67;68] With the same unbound blood concentrations of oxycodone and morphine, the unbound concentration of oxycodone in the brain is six times higher than morphine.[68]

This may explain why oxycodone seems to be more potent than morphine, but it does not explain the different ratio between oxycodone and morphine in patients undergoing surgery with mainly visceral pain compared to patients undergoing surgery with both somatic and visceral pain.

The first hour postoperatively, the pain scores were significantly lower in the oxycodone group in spite of the use of PCA. This may again be explained by the possibility that oxycodone might be more potent that morphine in visceral pain, or that the onset of analgesia in the morphine group after PCA dosing is slower. Morphine is generally considered to be a slow-acting drug, but the few clinical studies on this issue suggest a fairly similar time to onset (about 5-8 min) and peak effect (about 20-30 min) for both drugs administered as i.v. bolus.[152;153] In a clinical postoperative pain study, Kalso et al. demonstrated that oxycodone achieved faster pain relief and lasted longer than morphine.[44] This is in accordance with our results, indicating a faster onset of analgesia with oxycodone than morphine.

After two hours the differences in pain scores between the oxycodone and morphine groups disappeared. As oxycodone passes the blood-brain barrier faster than morphine,[67;68] this might explain the gap between pain scores during the first postoperative hour. As morphine

slowly penetrates into the CNS, it would take some time before the pain scores are reduced to the same level as in the oxycodone group.

8.2 Paper I and paper IV, opioid-induced hyperalgesia

Opioid-induced hyperalgesia might influence postoperative pain in terms of stronger pain and a higher need of analgesics.[107-109;111] It is therefore important to explore different approaches to reduce OIH.

Paper I did not elucidate OIH development, as there was no control group with less potential of developing OIH. To demonstrate that these patients actually developed OIH/acute tolerance, a third group with inhalation anaesthetic instead of opioid, or on top of low-dose opioid should have been included. However, when considering the induction of OIH after only 30 min of low dose remifentanil in paper IV, it is likely that the patients in both our groups in paper I developed OIH as they received high doses of remifentanil for approximately 90 min.

Hypothesis paper I:

Pretreatment with fentanyl before induction of remifentanil-based anaesthesia would decrease the self-rated pain scores and opioid consumption in the postoperative period.

The idea of pretreatment with one opioid before using another opioid during anaesthesia to avoid OIH/acute tolerance was based partly on studies on opioid rotation in cancer patients,[71;120] as described in chapter 4.4. Opioid rotation of pure agonists has been demonstrated to be successful strategies in decreasing OIH.[154]

The question remains as to whether the use of a pure opioid agonist, with different receptor-binding properties and a longer duration of action than remifentanil, would be beneficial in this context. The initiation of study I was also encouraged by widespread, non-documented practice in many Norwegian departments to administer fentanyl before remifentanil in order

to reduce the remifentanil dose, smoothen the recovery and potentially reduce opioid-induced hyperalgesia.

We did not manage to demonstrate reduced postoperative pain or rescue opioid consumption after remifentanil-based anaesthesia when pretreating the patients with fentanyl 1.5 µg/kg i.v. This negative result may be due to the fact that the dose of fentanyl was too low. The pretreatment dose of 1.5 µg/kg did not have any effect on remifentanil consumption during surgery compared to the group which did not receive fentanyl before start. The higher fentanyl dose (Group Pre: 1.5 µg/kg vs. Group Post: 3.0 µg/kg) at the end of surgery resulted in less pain 24 hours postoperatively in Group Post, which is beyond the expected duration of effect from such a dose. One explaination may be a potentially better immediate analgesic protection with the higher dose, which reduce the wind-up and activation of pain enhancement mechanisms otherwise seen in the postoperative period.

Changing from phenantren to peperidin derivatives has been suggested as a treatment to reduce OIH.[71] McDonnell et al. tried to pretreat patients with morphine (phenantren derivative) 150 µg/kg before remifentanil (peperidin derivative)-based anaesthesia. They did not manage to demonstrate reduced pain scores or analgesic consumption postoperatively, even though morphine is a longer-acting opioid compared to fentanyl.[155]

Paper I demonstrates that the practice of pretreating the patients with low-dose fentanyl has no beneficial impact on postoperative pain or analgesic consumption.

Hypothesis paper IV:

The main hypothesis was that remifentanil would induce postinfusion hyperalgesia in both experimental models. The secondary hypothesis was that parecoxib and ketorolac would prevent or diminish this postinfusion hyperalgesia in both experimental models.

Two different experimental models (electrical model and cold pressor model) were used to demonstrate OIH. As NSAIDs are widely used in clinical postoperative pain, it is interesting

to investigate whether these drugs can prevent OIH, as OIH may increase postoperative pain and analgesic consumption.

Parecoxib, a relatively selective COX-2 inhibitor,[156] blocked the opioid-induced enlargement of a hyperalgesic area, suggesting that OIH may be stimulated by spinal COX-2 activity in humans.[102]

Both COX-1 and COX-2 are expressed in the spinal cord.[34;157;158] There is growing evidence suggesting that spinal COX-inhibition plays an important role in producing antinociception and reducing hypersensitivity.[34;88;159] There is also evidence for an up-regulation of prostaglandin E_2 in the CNS after surgery.[88;160] Therefore, spinal COX-inhibition may be of importance in preventing acute hyperalgesia after surgery. It would be of interest to investigate whether a COX-1 preferring inhibitor, like ketorolac,[161] also would reduce OIH.

The timing of the administration of a COX-inhibitor seems to be important in reducing OIH. Parecoxib was either administered just before remifentanil infusion or approximately 30 min before remifentanil infusion in the study of Tröster et al.[102] Only the parecoxib dose administered 30 min before infusion reduced the postinfusion hyperalgesia.[102]

Therefore, in our study, ketorolac and parecoxib were administered 15 min before the electrical stimulus was switched on, and 45 min before remifentanil infusion (fig. 1 in paper IV). Ketorolac 30 mg i.v. and parecoxib 40 mg i.v. were chosen, as these are the recommended maximum doses according to the approval from the Norwegian government medicines agency.

This trial demonstrated that remifentanil induced postinfusion hyperalgesia in both experimental pain models (electrical pain and cold pain).

Administration of parecoxib before remifentanil infusion, prevented remifentanil-induced hyperalgesia only in the electrical pain model. This has been demonstrated in an previous

study.[102] Surprisingly, ketorolac prevented remifentanil-induced hyperalgesia only in the cold pain model.

While the cutaneous hyperalgesia is mediated by cutaneous "silent" mechano-insensitive C-nociceptors,[162] the cold pressor pain is mediated by nociceptors in the veins.[163]

This different peripheral activation may explain the different effect of the two NSAIDs in the two modalities.

The pain scores in the cold pressor test (postinfusion) are relatively similar between parecoxib and ketorolac, even though only the pain scores in the ketorolac group were significantly lower compared to the remifentanil group. These results may suggest that COX-2 rather than COX-1 inhibition may be most important in reducing opioid-induced central sensitization in these models of experimental pain. However, we do not know to which extent these experimental pain models can be extrapolated to a situation with clinical postoperative pain.

It is also interesting to note that hyperalgesia was produced with a fairly low dose of remifentanil administrated for a short period. Although this was an experimental model, the results may be added to the ongoing discussion as to how much and how long remifentanil needs to be administered during clinical anaesthesia for significant hyperalgesia to develop. It is also interesting to note that in our experimental model the hyperalgesia was shortlasting (fig. 4 paper IV) and modest. Thus, the impact on pain in a clinical postoperative situation may not be evident or measurable unless a very sensitive and non-confounding study design is employed.

9. Conclusions

9.1 Paper II and paper III

In paper II, administration of ketorolac 30 mg i.v. before the start of surgery resulted in significantly less pain 30 min after the end of surgery, significantly less opioid consumption during the first 4 h postoperatively, and significantly faster postoperative discharge readiness compared to oral etoricoxib 120 mg administered as premedication.

With a repeated dose of ketorolac before discharge, there were no differences in pain or rescue analgesic consumption until the next day. Administration of etoricoxib 120 mg in Group E at 24 h postoperatively did not reduce pain scores or need of rescue medication in the subsequent 24-48 h period compared to ketorolac, but less nausea was observed in the 4-24 h period. Thus, in terms of clinical analgesic effect there is no rationale to change from ketorolac to etoricoxib, although other aspects of adverse effects, costs and mode of administration are also valid in this context.

In paper III, the accumulated oxycodone consumption was significantly lower compared to the accumulated morphine consumption. In addition, the oxycodone group had less pain during the first postoperative hour, and was less sedated throughout the entire postoperative period. It is our conclusion that PCA oxycodone is a better alternative than PCA morphine in terms of clinical analgesic effect and less sedation after this kind of procedure.

9.2 Paper I and paper IV

Pretreatment with fentanyl 1.5 µg/kg i.v. (Group Pre) did not reduce postoperative pain or analgesic consumption (0-4 h) after 90 min of remifentanil-based anaesthesia with remifentanil 0.43 µg/kg/min. Group Post had significantly less pain in the 4-24 h period after

surgery, with a median VRS score of ‘slight pain’ vs. ‘moderate pain’ in Group Pre ($P < 0.05$). The oxycodone consumption was similar in both groups.

We conclude that there is no rationale to use low dose fentanyl as pretreatment before remifentanil infusion in this setting, but rather that fentanyl should be administered in an adequate dose at the end of the surgical procedure.

In paper IV, postinfusion remifentanil-induced hyperalgesia was demonstrated in both experimental pain models. Parecoxib prevented hyperalgesia in the electrical model, and ketorolac prevented hyperalgesia in the cold pressor test. Our results may suggest that COX-2 rather than COX-1 inhibition is of major importance to reduce opioid-induced central sensitization.

10. Future perspectives

10.1 NSAIDs

Non-selective NSAIDs and COX-2 inhibitors have been investigated in a large number of studies with respect to perioperative analgesia. In 2009, Scott Reuben, a leading investigator was disclosed for data fabrication,[164] and a large number of his articles has been retracted.[165] Several of Reuben's works are of controversial topics related to NSAIDs and COX-2 inhibitors.

Reuben has reported that NSAIDs may have a preemptive effect, but this has been questioned by other investigator groups.[37] Further studies are therefore needed to either disprove or certify this allegation.

The clinical effect of NSAIDs and COX-2 inhibitors on bone and tissue healing is another important topic that needs clarification. One of Reuben's articles demonstrated no differences in the bone fusion rate after 1 year, with the use of perioperative celecoxib.[166] This topic needs more investigation even though another group have also demonstrated no differences in bone fusion rates with the use of ketorolac.[167]

The role of NSAIDs and multimodal analgesic regimens in preventing chronic pain after orthopaedic surgery also remain unsettled,[4;168] and needs further studies.

10.2 Oxycodone

Oxycodone is an old opioid which has gained new interest during the last decade.[41] Its possible superior effect in visceral pain has particularly been investigated.[45;46] Human studies have clearly demonstrated that oxycodone is a selective μ-opioid receptor agonist,[49;50;169] but its affinity to the μ-opioid receptor is 20 times less than the affinity of morphine.[49] Based on this, it is difficult to explain that oxycodone and morphine have approximately the same

potency in different clinical settings. A Swedish group has demonstrated a potential active transport mechanism of oxycodone through the BBB,[67;68] which may in part explain this gap between the weak affinity to the μ-opioid receptor and oxycodone's potency in the clinic. However, it does not explain the different ratio between oxycodone and morphine in patients undergoing visceral surgery vs. somatic surgery.[43;44;52] Whether this is a real difference or not, is difficult to conclude from these studies, as they have quite different design.

To rule out this doubt, a future study comparing morphine and oxycodone should actually contain two clinical trials with equal design. One study with somatic pain postoperatively and one study with visceral pain postoperatively.

10.3 Opioid-induced hyperalgesia

The strongest evidence that opioids induce hyperalgesia in humans originates from studies of healthy volunteers exposed to opioid infusion.[121] The main problem is to demonstrate OIH in clinical studies, where there might be a lot of confounding factors compared to the controlled situation in an experimental design. We also need to get a better understanding of which experimental pain models that are most relevant for clinical post-surgical pain. It is also important to document the potential clinical implications of OIH. The main challenge in the future is do develop a good model being able to differentiate OIH from acute tolerance in a clinical setting. If this is achieved, we would hopefully be able to develop different types of clinical interventions to reduce or avoid OIH.

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Title

Modulation of remifentanil-induced postinfusion hyperalgesia by parecoxib or ketorolac in humans.

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Abstract

Background: Opioids may enhance pain sensitivity, called opioid-induced hyperalgesia (OIH). Spinal cyclooxygenase activity may play a role in the development of OIH. The aim of this study was to demonstrate remifentanil-induced postinfusion hyperalgesia in an electrical pain and a cold pain model. We also investigated if pretreatment with parecoxib or ketorolac could prevent remifentanil-induced hyperalgesia.

Methods: Sixteen healthy males were enrolled in this randomized, double-blind, placebo-controlled study in a crossover design. Each subject went through four sessions: control, remifentanil, parecoxib + remifentanil and ketorolac + remifentanil. Each session started with a cold pressor test (CPT). The subjects received a bolus of either saline, parecoxib 40 mg or ketorolac 30 mg intravenously. Transcutaneous electrical stimulation induced acute pain and stable areas of pinprick hyperalgesia, which were assessed before, during and after a 30-min infusion of either remifentanil or saline. The CPT was repeated at the end of the infusion and one hour thereafter.

Results: The areas of pinprick hyperalgesia were reduced during the infusion of remifentanil, but increased significantly thereafter. Pretreatment with parecoxib prevented this enhanced postinfusion area of hyperalgesia, but ketorolac did not. Pain ratings in the CPT one hour after ended infusion of remifentanil were significantly higher compared to control. Pretreatment with ketorolac prevented these enhanced pain scores, but parecoxib did not.

Conclusions: Postinfusion remifentanil-induced hyperalgesia was demonstrated for both the electrically induced pain and the cold pressor pain. Parecoxib prevented hyperalgesia in the electrical model, and ketorolac prevented hyperalgesia in the CPT.

Introduction

Opioids are the cornerstone in the treatment of moderate to severe pain. In addition to alleviate pain, there is growing evidence that μ-opioids may reduce the pain threshold, resulting in enhanced pain when the opioid effect diminishes after end of administration.[1-5] This phenomen is known as opioid-induced hyperalgesia (OIH). Large doses of μ-opioids during surgery seem to enhance pain after emergence from anesthesia and the patients need more opioids postoperatively.[6-8]

Activation of the N-methyl-d-aspartate (NMDA)-receptor complex by μ-receptor agonists seems to be one underlying mechanism of this hyperalgesia development,[4,9,10] and OIH can be prevented by administrating ketamine, an NMDA receptor antagonist.[2,4,5,11]

Prostaglandins, like PGE_2, can stimulate glutamate release from astrocytes and from the spinal cord dorsal horns with subsequent activation of the NMDA receptors.[12,13] Subsequently, cyclooxygenase inhibitors were found to antagonize this NMDA receptor activation.[14,15] Since the NMDA receptor is involved in OIH, it may be possible to reduce OIH by cyclooxygenase (COX) inhibitors. Parecoxib, a relatively selective COX-2 inhibitor,[16] blocked the opioid-induced enlargement of a hyperalgesic area, suggesting that OIH may be stimulated by spinal COX-2 activity in humans.[17] Both the COX-1 and COX-2 variant of the COX-enzyme are expressed in the spinal cord, and COX-1 activation has also been shown to be important in pain development after surgery.[18-20] Therefore, it would be of interest to investigate whether a COX-1 preferring inhibitor, like ketorolac,[21] also could reduce OIH.

In this study we investigated whether parecoxib and ketorolac could prevent OIH. We used two different experimental pain models; one model using electrical stimulation to induce pain and secondary mechanical hyperalgesia[22,23] and another model inducing pain from cold stimuli (cold pressor test - CPT).[24]

The cold pressor pain has been shown to be opioid sensitive.[25] By adding CPT as a second pain stimulus, we wanted to study whether postinfusion hyperalgesia also include acute pain ratings to this tonic, painful stimulus and could be modulated by COX-antagonists.

Materials and Methods

The protocol of this randomized, double-blind, placebo-controlled study with a crossover design in volunteers was reviewed and approved by the Regional Committee for Medical Research Ethics in Eastern Norway and the Norwegian Medicines Agency. The study was registered in ClinicalTrails.gov (ID: NCT 00785863).

Sixteen healthy male subjects were enrolled. None of the subjects had any known drug allergy or used any other kind of medication before or during the experiments. Alcohol or drug abuse were exclusion criteria. All subjects were familiarized with the experimental models by a pre-study session.

To provoke pain and secondary hyperalgesia we used a well established intra-dermal electrical pain model.[2,4,17,22] This model has been proven to create a stable area of secondary hyperalgesia to punctate stimuli by an activation of primarily mechanoinsensitive "silent" C-nociceptors.[23] These nociceptors are activated at high current densities.[26]

Two microdialysis fibers equipped with internal stainless steel wires were inserted intradermally in the central volar forearm. The intradermal length of each fiber was approximately 10 mm, and the distance between the fibers about 5 mm.

We applied monophasic, rectangular electrical pulses of 0.5 ms duration with alternating polarity via a constant current stimulator, Digitimer DS7A (Digitimer, Hertfordshire, UK) at 2 Hz. The current intensity was gradually increased during the first 15 min of the stimulus administration to induce a pain score of 6 on a verbal rating score (VRS) going from 0 to 10 (0 = no pain, 10 = worst pain imaginable). The subjects were allowed to use a decimal to indicate one level between integers (i.e. 0.5, 1.5, etc.), making it a 21-points scale.

The current was adjusted so that the subject scored VRS = 6 after 15 min, and this current intensity was kept constant for the rest of the stimulation period; totally 150 min (fig. 1).

Each subject went through four separate sessions with an interval of at least one week between each session.

The control group (Group C) received a 0.9% NaCl bolus intravenously and an infusion of 0.9% NaCl (fig. 1). The remifentanil group (Group R) received a 0.9% NaCl bolus intravenously and an infusion of remifentanil. The parecoxib + remifentanil group (Group PR) received a 40 mg parecoxib bolus intravenously and an infusion of remifentanil. The ketorolac + remifentanil group (Group KR) received a 30 mg ketorolac bolus intravenously and an infusion of remifentanil.

10 ml syringes for bolus of 0.9% NaCl, parecoxib or ketorolac were used. The parecoxib and ketorolac syringes were diluted with 0.9% NaCl, so all syringes contained the same amount of clear liquid (10 ml).

The infusion time of remifentanil or saline was 30 min. 50 ml syringes with the same amount of clear liquid were used. We used TCI-effect site target control infusion, Minto-model,[27,28] starting with 1.0 ng/ml for the first 2 min, thereafter 2.5 ng/ml for the rest of the infusion time of 30 min (fig. 1). By using effect-TCI we reached a steady-state level faster than using µg/kg/min infusion, which earlier studies have used.[2,4,17]

During the infusion of remifentanil or 0.9% NaCl the investigator asked about possible opioid side effects (e.g. nausea, dizziness, pruritus).

Non-invasive blood pressure, electrocardiography and pulse oximetry were monitored continuously during the study.

During the ongoing electrical pain stimulus, the subjects scored VRS every 5 min. In addition, the area of pinprick-hyperalgesia was determined by using a 26 g von Frey filament. The hyperalgesia areas were determined by measuring in four linear paths parallel and orthogonally to the axis of the forearm from distant starting points toward the stimulation site (step size 5 mm), until the subject reported increased pain sensation. In the measuring of the

area of secondary hyperalgesia, both diameters ($D/2 \times d/2 \times \pi$) were used. Area of secondary hyperalgesia was determined every 15 min, from the start of the electrical stimulation (time = 0 min) until one hour after the end of the electrical stimulation period (210 min).

The subjects also underwent the CPT,[24] and pain was reported using VRS, as in the electrical pain model. They performed 3 CPTs for each of the four sessions: one test before any drugs were administered, one test just before the end of the remifentanil/saline infusion, and one test one hour after the end of the remifentanil/saline infusion (fig. 1). The last CPT was performed one hour after the end of the infusion, because presumably there should be virtually no remifentanil left in the circulation or in the brain, based on the elimination algorithm in the Minto model.[27,28]

The water in the CPTs had a temperature between 0.5-1.5 °C. The hand was kept in the water for a maximum of 120 sec at each test. The subjects were asked to score pain (VRS) every 10 sec. If the subject was unable to keep the hand in the water for 2 min (the pain was unbearable), the rest of the values were scored to 10.

Statistics

Sample size was calculated based on results from a previous study on area of post-infusion hyperalgesia.[17] Assuming a SD for the difference between treatments of 10%, a paired t-test (alfa = 0.05, two-sided) with 16 paired observations would yield 96% power to detect a mean difference of 10% , and 80% power to detect a difference of 7.5% (SamplePower 2.0). Based on these calculations, we decided to include 16 subjects.

Earlier studies using this electrical pain model have demonstrated that the area of pinprick hyperalgesia decreases from one session to another session despite the same intensity in electrical stimulation and pain ratings.[29]

Therefore, data regarding areas of secondary hyperalgesia were normalized to achieve the same point of reference in subjects from all of the four treatments by setting the mean of both baseline measurements of pinprick hyperalgesia, i.e. 15 and 30 min after onset of electrical stimulation, to 100%. The changes from this baseline were calculated as areas under the curve (AUC) for different time periods.

We compared the infusion period (30-60 min), the postinfusion period (60-150 min), and the postinfusion period without electrical stimulus (150-210 min). The areas under the curve for change in area of hyperalgesia (percentage changes) were not normally distributed, therefore non-parametric, two-sided Wilcoxon tests were performed.

AUC of VRS for the electrical pain and the CPT were also calculated. These results were normally distributed, and paired samples T-tests for each group were performed.

Paired samples T-tests were performed on MAP, HR and SpO_2.

Data were analyzed in SPSS 16.0. The significance level was set to 0.05.

Results

All subjects participated in all sessions as planned without dropouts or interfering medication. There were no correlation between mean electrical current (mA) needed for VRS = 6 after 15 min and mean VRS for the first cold pressor test in the individual test person (P = 0.52, by Pearson correlation test).

Side effects and vital function monitoring values

The vital function monitoring values (SpO_2, MAP and HR) are shown in fig. 2. All subjects developed side effects during remifentanil infusion (table 2). The side effects never interfered with the subjects' ability to answer the questions from the investigators.

Mean arterial blood pressure measured just after the second CPT increased significantly compared to MAP measured before the CPT in Group C, but the increase was significantly reduced in the three groups receiving remifentanil (fig. 2). The post-infusion CPT (third CPT) induced unchanged blood pressure increase in Group C, but in Group R and Group PR the increase remained significantly lower. Only in Group KR the blood pressure increased to a similar level as in Group C (fig. 2).

Pain ratings

To achieve a pain rating of VRS 6, the average current was increased to 31.2 ± 22.5 mA (mean ± SD) during the first 15 min of the electrical stimulation (table 1). After keeping the current constant, the pain ratings decreased significantly at 30 min, to VRS 5.1 ± 0.07 (mean ± SEM). No significant differences were found between the four groups (fig. 3).

During infusion of remifentanil/saline, the pain ratings decreased significantly in the groups receiving remifentanil compared Group C (control), $P < 0.001$ for all three groups (fig. 3).

There were no significant differences in VRS between the three groups receiving remifentanil

during the 30 min of infusion. After the end of the infusion, the pain ratings increased and reached control values. In the Group KR (ketorolac + remifentanil), the pain ratings (VRS) exceeded the ratings in Group C and became significantly higher during the rest of the electrical stimulation (P = 0.036, by paired samples T-test).

Pinprick hyperalgesia

All groups developed stable pinprick hyperalgesia areas during the first 30 min of the electrical stimulation. The areas measured 65.3 (10.9) cm^2 in Group C, 71.2 (8.2) cm^2 in Group R, 73.3 (5.9) cm^2 in Group PR and 72.7 cm^2 (6.9) in Group KR (mean ± SEM). There were no significant differences between the groups (paired samples T-test).

During the remifentanil/saline infusion-period the areas under the curve (AUC) for all three treatment groups receiving remifentanil became significantly smaller compared to control (P < 0.001 in Group PR and Group KR, P = 0.025 in Group R, fig. 4). There were no significant differences between the groups receiving remifentanil, albeit the reduction of hyperalgesic areas appeared to be more pronounced when COX-inhibitors were co-administered.

This antihyperalgesic effect was only present during the infusion. After the end of the infusion, the areas of pinprick hyperalgesia exceeded control values in Group R, P = 0.039 (60-150 min – post infusion period). Pretreatment with parecoxib prevented postinfusion remifentanil-hyperalgesia compared to Group R, P = 0.044. Pretreatment with ketorolac did not prevent postinfusion hyperalgesia compared to Group R, P = 0.53.

After the electrical stimulation was switched off (150-210 min – stop electric stimulus period), there were no significant differences in the areas of pinprick hyperalgesia between the four groups (fig. 4). The remifentanil induced hyperalgesia (Group R) has returned to baseline values (Group C).

Cold pressor test

The AUC values of the first CPT (before any drugs were administered) remained similar between all sessions (fig. 5A). In the Group C, there were no significant differences between the three consecutive CPTs.

The CPT at the end of the infusion (second CPT) demonstrated similar and significant lower VRS in all three groups receiving remifentanil compared to second CPT in Group C ($P < 0.001$, fig. 5B).

The CPT 1 h after the end of infusion showed significantly higher VRS in Group R compared to Group C ($P = 0.017$, fig. 5C). Pretreatment with ketorolac (Group KR) resulted in significantly lower VRS compared to Group R ($P = 0.046$), whereas pretreatment with parecoxib did not ($P = 0.18$).

There were no significant differences between Group C, Group PR and Group KR at the third CPT.

Discussion

We were able to reproduce significant hyperalgesia after cessation of a 30 min infusion of remifentanil as assessed by increased area of secondary mechanical hyperalgesia as demonstrated in earlier studies.[2,4,17] In parallel, pain ratings to noxious cold stimuli increased in the remifentanil group compared to control, reflecting hyperalgesia in the cold pressor test. Increased pain after cessation of opioid application can be interpreted as acute tolerance or OIH.[1] The duration of remifentanil application in our study was too short to investigate tolerance.[30] Previous studies in healthy volunteers did not observe remifentanil-induced tolerance even at application times of 90 min.[2] Thus, in our study, post-infusion hyperalgesia developed as measured by pain ratings to electrical stimulation and area of secondary mechanical hyperalgesia. Hyperalgesia for electrical pain has been demonstrated previously,[2-4,17] but not for heat stimuli.[2]

While confirming that remifentanil induced increase of secondary mechanical hyperalgesia, we additionally found post-infusion hyperalgesia in the CPT, as might have been expected according to previous results.[30,31]

Our results confirm that low-dose remifentanil (target 2.5 ng/ml) and short infusion (30 min) result in detectable hyperalgesia. However, the magnitude of hyperalgesia seems to be limited and the duration shortlasting, as the areas of hyperalgesia returned to control values after the electrical pain was swift off (fig. 4).

Opioid-induced NMDA activation or internalization of μ-opioid receptors have been suggested as the etiology of OIH.[32]

Recently, intracellular recordings of dorsal horn neurons have shown that withdrawal of remifentanil can acutely induce long-term potentiation (LTP) in spino-thalamic tract projection neurons that was sensitive to NMDA blockers.[33] Increased pain ratings to CPT and

electrical stimuli as well as larger areas of secondary mechanical hyperalgesia are in accordance with these results.

Administering parecoxib before remifentanil infusion, prevented remifentanil induced hyperalgesia only in the electrical pain model. This has been demonstrated in an earlier study.[17] Surprisingly, ketorolac prevented remifentanil induced hyperalgesia only in the cold pain model.

The secondary mechanical hyperalgesia is induced by sensitizing spinal input from "silent" mechano-insensitive C-nociceptors,[26] that renders the dorsal horn hypersensitive to A-delta nociceptor input.[34] In contrast, the cold pressor pain is mediated by tonic discharge of nociceptors in the veins.[35] This different peripheral activation may explain the different effect of the two NSAIDs on the two modalities.

Both COX-1 and COX-2 are expressed in the spinal cord.[18-20] There is growing evidence suggesting that spinal COX-inhibition plays an important role in producing antinociception and reducing hypersensitivity.[14,18,36,37] There is also evidence for an up-regulation of prostaglandin E_2 in CNS after surgery.[14,38] Therefore, spinal COX-inhibition may be of importance in preventing acute hyperalgesia after surgery.

So far, there are few studies on OIH in a clinical incision pain model, but one study demonstrated increased pain sensitivity assessed by peri-incisional allodynia and hyperalgesia after large-dose intraoperative remifentanil.[11] In that study ketamine prevented peri-incisional allodynia and hyperalgesia.

To our knowledge no clinical study has tried to do the same with a COX-inhibitor. However, one study has demonstrated that lornoxicam, a combined COX-1 and COX-2 inhibitor, significantly diminished the acute opioid tolerance and/or hyperalgesia caused by fentanyl.[39]

The ratings of electrically induced pain after end of remifentanil infusions in the study from Tröster et al.[17] exceeded the pain scores compared to their control group. This hyperalgesic

effect remained stable for the rest of the observation period. We could only demonstrate this hyperalgesic effect in the ketorolac group (fig. 3). We hypothesize that the CPTs may have disturbed the pain ratings from the electrical pain scores, accordning to the classical gate-theory.[40] The CPT is a painful test, and many of the subjects had considerably lowered scores from the stable electrical pain stimulation after the CPTs.

An interesting observation is that, in addition to higher electrical pain scores in Group KR after remifentanil-infusion, this group also had a significantly higher MAP after the last CPT compared to Group PR and Group R (fig. 2). Blood pressure control and descending pain inhibition share common pathways and mechanisms in a complex and not fully understood way. The fact that the ketorolac group had higher MAP after the last CPT (DNIC-diffuse noxious inhibitory control-procedure) and higher electrical pain scores after infusion compared with the remifentanil and the parecoxib group indicates that ketorolac may block descending inhibition induced by cold pressor test and that mechanisms shared with blood pressure control is involved (eg. NA-mechanisms).

There was no correlation between mean electrical current (mA) needed for VRS = 6 after 15 min and mean VRS for the first cold pressor test in the individual test person. This is in accordance with results from an animal study, which demonstrates a lack of correlation of sensitivity to nociception in different pain models.[41]

An important question is the relevance of our results for clinical postoperative pain. The measurement of pain to cold-, electrical-, heat- and pressure-stimuli are only experimental tests that will not ideally mimic clinical pain conditions; on the other hand, using surgical incision is un-feasible in volunteers.

An animal, incisional pain model was linked to spinal COX-1 activation,[18] whereas COX-2 was activated in an inflammatory pain model.[42] Comparable data from humans do not exist.

Certainly more research should be done in this area, preferably with clinical models of real surgical pain.

In conclusion, we have demonstrated postinfusion remifentanil-hyperalgesia in electrically induced pain and cold pressor pain. Our results may suggest that COX-2 rather than COX-1 inhibition is of major importance to reduce opioid-induced central sensitization.

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Table 1

Age, weight, height and mean electrical current in the four sessions of the subjects.

No.	Age, yr	Weight, kg	Height, cm	Current, mA
1	31	70	177	28.6 ± 21.7
2	24	93	188	18.2 ± 6.4
3	35	100	179	68.3 ± 17.3
4	35	88	189	83.9 ± 14.4
5	22	94	194	14.3 ± 4.5
6	41	78	181	15.6 ± 1.8
7	24	92	189	5.8 ± 2.0
8	23	83	185	46.4 ± 10.8
9	24	94	173	42.4 ± 4.1
10	25	62	173	40.2 ± 16.3
11	29	74	187	15.3 ± 3.1
12	27	80	174	26.6 ± 3.1
13	50	112	190	30.2 ± 6.0
14	21	79	189	34.2 ± 2.5
15	26	63	179	12.2 ± 3.8
16	22	73	173	17.0 ± 2.9
Mean ± SD	29 ± 8	83 ± 14	183 ± 7	31.2 ± 22.5

Data are presented as (mean ± SD).

Table 2

Side effects during drug infusions.

	Saline	Remifentanil	Parecoxib + Remifentanil	Ketorolac + Remifentanil
Sedation	0	14	11	12
Pruritus	0	10	9	8
Nausea	0	1	3	1
Dizziness	0	6	7	9

Number of subjects who reported side effects (n = 16).

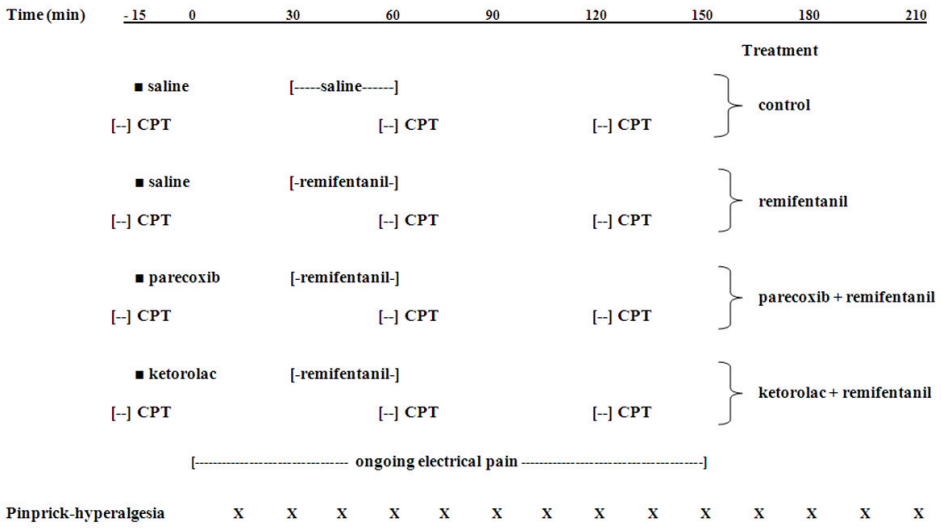

Fig. 1. Schematic illustration of the experimental protocol. Four treatments were performed in a randomized order on each subjects. Every treatment started with a cold-pressor test (CPT, [--]). The subjects then received an intravenous bolus of either 0.9% NaCl, 30 mg ketorolac or 40 mg parecoxib (■). The electrical stimulus started 15 minutes after the bolus. After 30 minutes of electrical stimulus a 30 minutes-infusion of 0.9% NaCl or remifentanil was carried out. At the end of each infusion and one hour after the end of infusion, a CPT was performed. The electrical stimulus was on for 150 minutes. Pinprick hyperalgesia was performed every 15 minutes, from 15 minutes after start of electrical stimulus to one hour after the end of electrical stimulus.

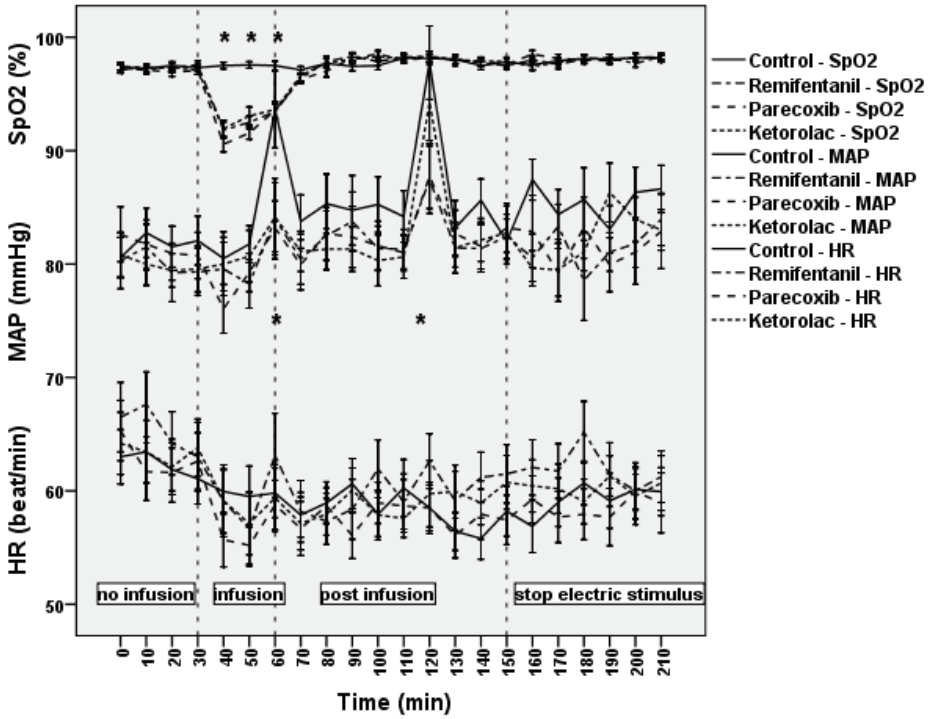

Fig. 2. Infusion of remifentanil resulted in a significant decrease in oxygen saturation (SpO_2), * P < 0.001. Mean arterial pressure (MAP) measured just after the second and third cold pressor test (CPT) had a significant increase in all groups compared to MAP measured before each CPT. Group C (control) had an increase in mean MAP of 12 mmHg (* P = 0.001) and 14 mmHg (* P < 0.001) after the second and third CPT respectively. The three groups receiving remifentanil had an increase in mean MAP of 4 mmHg (* P = 0.002) after the second CPT. Group C had a significant higher increase in MAP compared to the three groups receiving remifentanil, * P = 0.03.

After the last CPT, MAP remained significantly lower in Group R (remifentanil) and in Group PR (parecoxib + remifentanil) compared to Group C, * P = 0.001 and * P = 0.002 respectively. There was no significant difference between Group C and Group KR (ketorolac + remifentanil), P = 0.23. Group KR had a significant higher MAP compared to Group R and Group PR, * P = 0.011 and * P = 0.015 respectively (paired samples T-test). There were no significant differences in heart rate (HR) between the groups during the whole study-periode. The data are expressed as mean ± SEM.

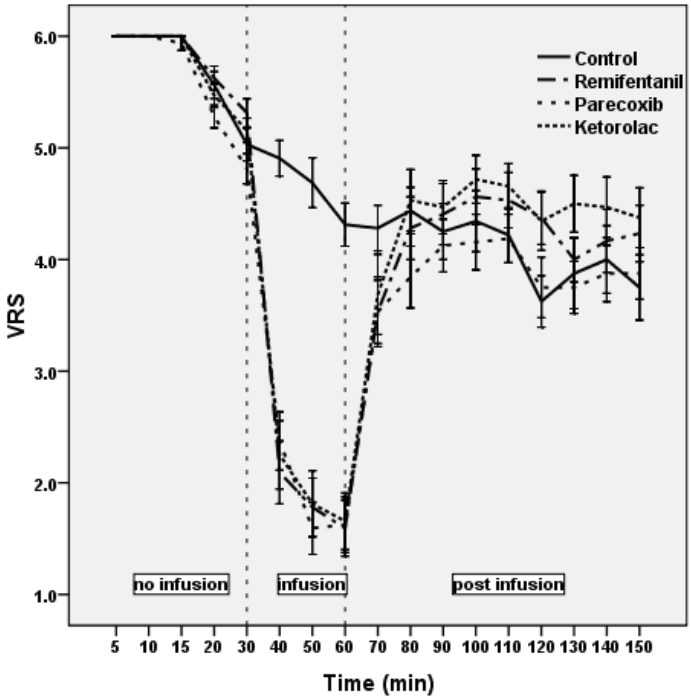

Fig. 3. After keeping the current constant, the pain ratings decreased significantly, reaching 5.1 ± 0.07 (mean ± SEM) at 30 minutes. No significant differences between the four groups. During infusion, VRS (verbal rating score) decreased significantly between the three groups receiving remifentanil compared to control, $P < 0.001$. No significant differences in VRS between the three groups receiving remifentanil. After cessation of the infusion, VRS increased and reached control values. In Group KR (ketorolac + remifentanil) VRS exceeded control values and became significantly higher during the rest of the time with electrical stimulus, $P = 0.036$. The data are expressed as area under the curve (AUC) ± SEM.

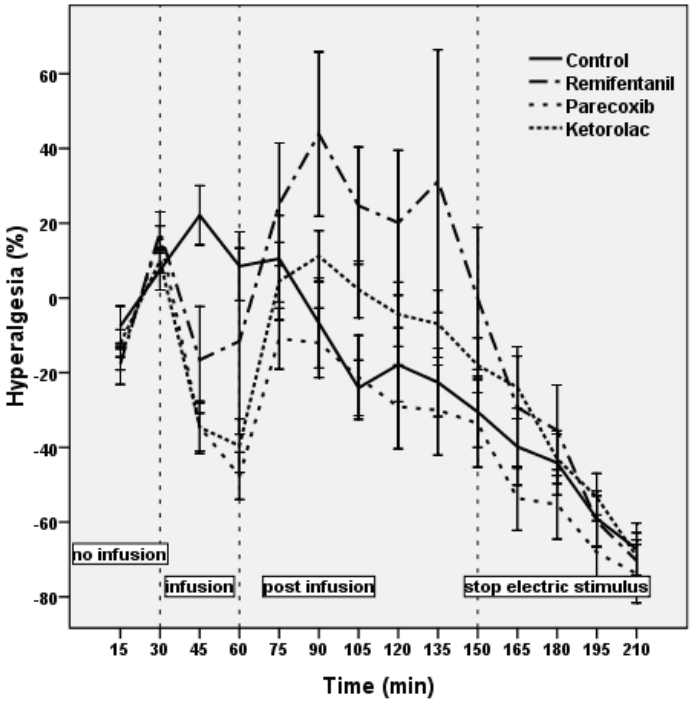

Fig. 4. The data were transformed to areas under the curve (AUC) for each period: infusion-periode (30-60 minutes), the post-infusion periode with electrical stimulus (60-150 minutes) and the post-infusion periode without electrical stimulus (150-210 minutes). Non-parametric tests with Wilcoxon were performed because the percentage changes were not normal distributed. The AUC in the 30-60 minutes periode was significantly less in Group R compared to Group C ($P = 0.025$), and Group PR and Group KR compared to Group C, $P < 0.001$. No significant differences between the groups receiving remifentanil. The areas of pinprick hyperalgesia exceeded control values in Group R in the 60-150 minutes period, $P = 0.039$. Pretreatment with parecoxib prevented postinfusion remifentanil-hyperalgesia ($P = 0.044$, compared to Group R). Pretreatment with ketorolac did not prevent postinfusion hyperalgesia ($P = 0.53$, compared to Group R). After the electrical stimulation was switched off, (the 150-210 minutes periode) there were no significant differences between the four groups.

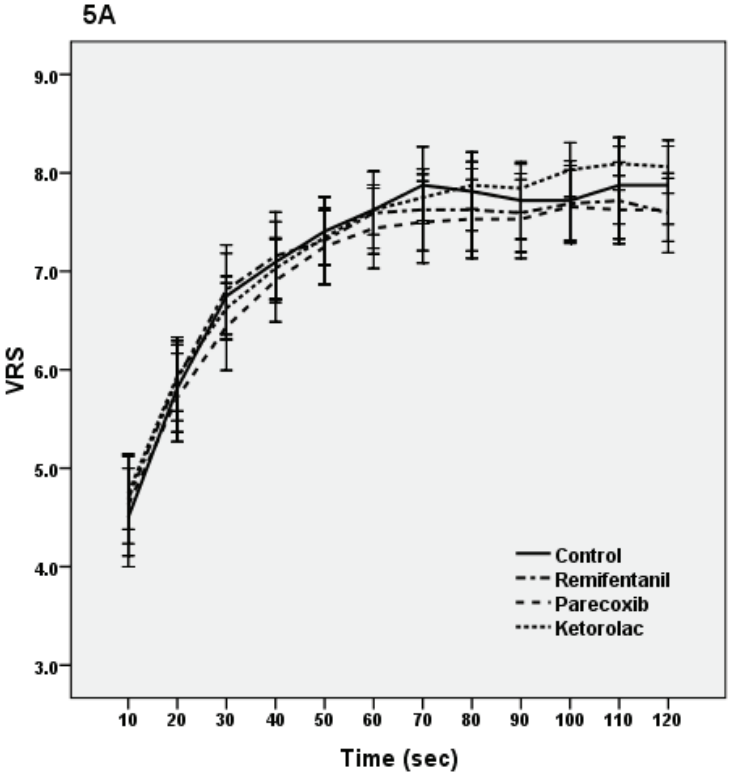

Fig. 5A. The first cold pressor test (CPT) was similar within all participants in all of the four sessions. In Group C (control) there were no significant differences between CPT no. 1, 2 or 3.

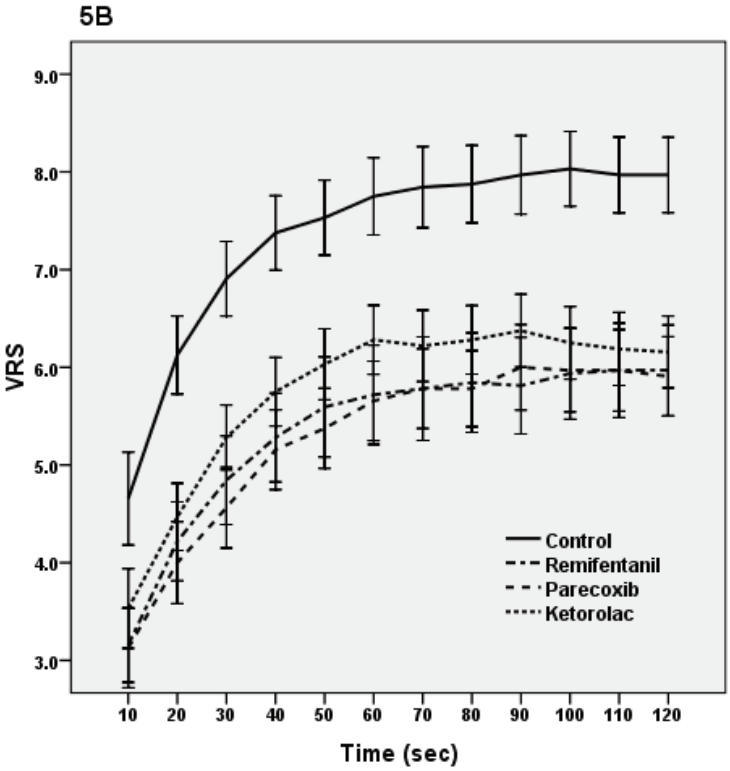

Fig. 5B. The CPT at the end of the infusion demonstrated significantly lower VRS in all three groups receiving remifentanil compared to control, $P < 0.001$. No significant difference between the three groups receiving remifentanil.

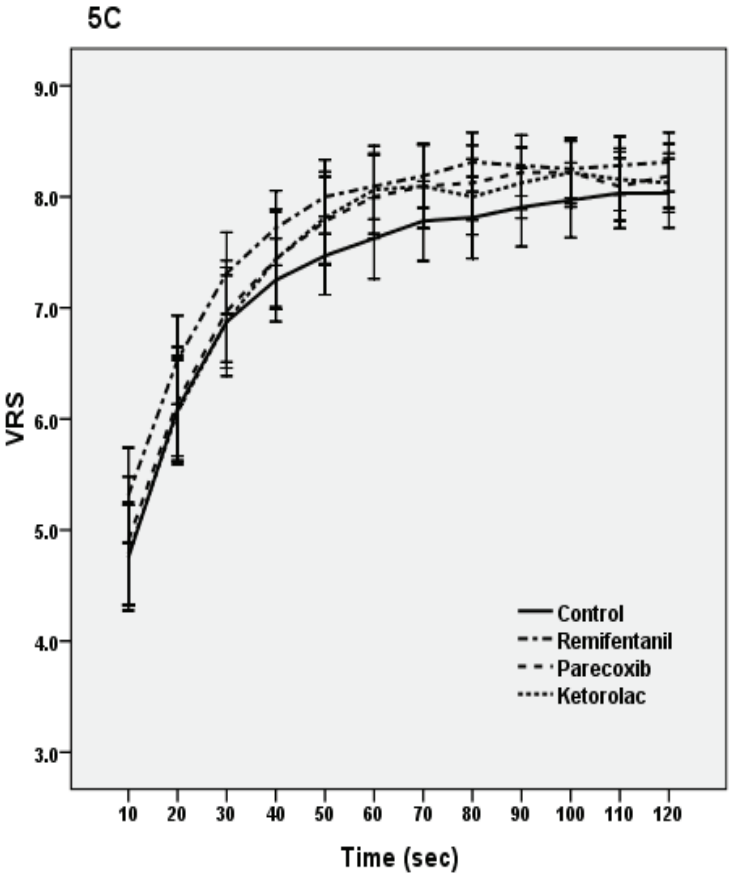

Fig. 5C. The CPT 1 h after cessation of infusion demonstrated significantly higher VRS in Group R (remifentanil) compared to Group C (control), P = 0.017. Pretreatment with ketorolac (Group KR) demonstrated significantly lower VRS compared to Group R, P = 0.046. There were no significant differences between Group C, Group PR (parecoxib + remifentanil) and Group KR. The data are expressed as area under the curve (AUC) ± SEM.