EFFECTS OF GLUCOCORTICOIDS AND NONSTEROIDAL ANTI-INFLAMMATORY DRUGS ON POSTOPERATIVE AND EXPERIMENTAL PAIN

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From: René Descartes. L'homme de Rene Descartes.
Paris: Charles Angot, 1664

CONTENTS

ACKNOWLEDGEMENTS

LIST OF PAPERS

This thesis is based on the following papers, which are referred to in the text by their Roman numerals:

I   Romundstad L, Stubhaug A, Niemi G, Rosseland LA, Breivik H. Adding propacetamol to ketorolac increases the tolerance to painful pressure. Eur J Pain 2006;10:177-83.

II   Stubhaug A, Romundstad L, Torill Kaasa, Breivik H. Methylprednisolone and ketorolac rapidly reduce hyperalgesia around a skin burn injury and increase pressure pain thresholds . Acta Anaesthesiol Scand. 2007; In press.

III   Romundstad L, Breivik H, Niemi G, Helle A, Stubhaug A. Methylprednisolone intravenously 1 day after surgery has sustained analgesic and opioid-sparing effects. Acta Anaesthesiol Scand. 2004;48:1223-31.

IV   Romundstad L, Stubhaug A, Roald H, Skolleborg K, Haugen T, Narum J, Breivik H. Methylprednisolone reduces pain, emesis, and fatigue after breast augmentation surgery: a single-dose, randomized, parallel-group study with methylprednisolone 125 mg, parecoxib 40 mg, and placebo. Anesth Analg. 2006;102:418-25.

V   Romundstad L, Stubhaug A, Skolleborg K, Roald H, Romundstad P, Breivik H. Chronic pain and sensory changes after augmentation-mammoplasty: Long term effects of preincisional administration of methylprednisolone. Pain. 2006;124:92-9.

Table 1. Overview of the studies

Study	Medication	Design, n analysed	Stimulus/ Type of surgery	Effect variables	Main conclusion
I	• Ketorolac • Propacetamol • Ketorolac + Propacetamol • Placebo	• Experimental • Randomized • Double-blind • Crossover • 16 healthy volunteers	• Painful pressure on base of fingernail	• Pressure pain tolerance threshold (PPTT)	Adding propacetamol to ketorolac increased the PPTT compared with ketorolac alone.
II	• Methylpredn. • Ketorolac • Placebo	• Experimental • Randomized • Double-blind • Crossover • 12 healthy (male) volunteers	• Burn injury • Painful pressure on base of fingernail	• Secondary hyperalgesia Pressure pain tolerance and detection threshold (PPTT and PPDT).	Both methylpredn. ketorolac reduced the area of secondary hyperalgesia. and increased PPTT. Only ketorolac increased PPDT.
III	• Methylpredn. • Ketorolac • Placebo	• Clinical • Randomized • Double-blind • Parallel • 75 patients	• Lower limb orthopaedic surgery	• Postoperative pain (VAS). • Opioid consumption.	Both methylpredn. and ketorolac reduced postoperative pain. Methylpredn., but not ketorolac, reduced opioid consumption for 72 h.
IV	• Methylpredn. • Parecoxib • Placebo	• Clinical • Randomized • Double-blind • Parallel • 204 patients	• Breast augmentation surgery	• Postoperative pain (NRS). • Rescue analgesic consumption. • Composite pain and rescue score. • PONV and fatigue.	Both methylpredn. and parecoxib reduced postoperative pain and rescue analgesic usage. Methylpredn. but not parecoxib, reduced PONV and fatigue.
V	• Methylpredn. • Parecoxib • Placebo	• Clinical • Randomized • Double-blind • Parallel • 175 patients • Follow-up of study IV after 6 weeks and 1 year	• Breast augmentation surgery	• Pain 6 weeks and 1 year after surgery • Sensory changes 6 weeks and 1 year after surgery. • Activities of daily living (ADL) 6 weeks and 1 year after surgery.	The prevalence of non-evoked and evoked pain was 13% and 20% at 1 year. Pain at 6 weeks was the most important risk factor for chronic postoperative pain (OR=18.4). Pain interfered with ADL in 25 % of patients after 6 weeks and 14 % after 1 year. The active drugs did not affect chronic pain. Methylpredn. but not parecoxib reduced hyperesthesia after 6 weeks and 1 year.

NOMENCLATURE AND ABBREVIATIONS

ADL: Activities of daily living

Allodynia: Pain due to a stimulus that do not normally provoke pain

AUC: area under the curve

CI: confidence interval

CB1: Type 1 cannabinoid receptor

CNS: Central Nervous System

COX-1: Cyclooxygenase Isoenzyme-1

COX-2: Cyclooxygenase Isoenzyme-2

COX-2 inhibitor: COX-2 selective inhibitor

Coxib: COX-2 selective inhibitor

Hyperalgesia: A leftward shift of the stimulus response function curve that relates magnitude of pain to stimulus intensity (Meyer et al., 1994). The threshold of pain is lowered and pain to suprathreshold stimuli enhanced.

Hyperesthesia: Increased sensitivity to cutaneous stimulation due to a diminished threshold or an increased response to stimuli.

Hypoesthesia: Impairment of tactile sensitivity; decrease of sensitivity.

Il$_{1\beta}$: Interleukin-1-beta

Il$_6$: Interleukin-6

Il$_{10}$: Interleukin-10

iNOS: Inducible Nitric Oxide Synthase

mPGES-1: microsomal PGE synthase-1

NF-κB: nuclear factor-kappa B

NNT: numbers needed to treat

NMDA: *N*-methyl-D-aspartate

NO: Nitric Oxide

NSAID: Non-Steroidal Anti-Inflammatory Drug, and non selective COX-1 and COX-2 inhibitor

0-10 NRS: 0-10, 11-point, Numerical Rating Score

Odds: The odds of an event are calculated as the number of events (pain) divided by the number of non-events (no pain).

Odds ratio (OR): An odds ratio is calculated by dividing the odds in the treated (analgesic drug) or exposed (acute pain) group by the odds in the control group.

PAR: pain relief

PG: Prostaglandin

PGE$_2$: Prostaglandin E$_2$

PGI$_2$: Prostaglandin I$_2$ (prostacyclin)

Prevalence: The ratio of the number of cases in a statistical population with a disease (chronic pain) at a specified time and the number of individuals in the same population at the same time. In plain English, "prevalence" simply means "proportion" (typically expressed as percentage). Prevalence is distinct from **incidence**, which is a measure of the number of disease cases per unit time.

Primary hyperalgesia: Hyperalgesia in the site of an injury.

Punctate hyperalgesia: Pain evoked by punctate mechanical stimuli (von Frey filaments were used to evoke this sensation of pain).

PPTT: Pressure Pain Tolerance Threshold

0-100 VAS: 0-100 mmVisual Analogue Scale

0-4 VRS: 0-4, 5-point, Verbal Rating Scale

SD: standard deviation

Secondary hyperalgesia: Hyperalgesia in the uninjured area surrounding the injury.

SEM: standard error of the mean

Steroids: A family of different hormones: glucocorticoids, mineralocorticoids, androgens, estrogens, and progestagens. In this thesis the word "steroid" refers to glucocorticoids.

TNF$_\alpha$: Tumor Necrosis Factor-alpha

TOTPAR: total pain relief

INTRODUCTION

The history of anti-inflammatory drugs

The treatment of acute inflammatory pain probably began about 3,500 years ago in ancient Egypt with the use of decoctions or extracts of herbs or plants containing salicylates, such as willow bark or leaves. In 400 BC, Hippocrates advocated the use of willow bark to relieve the pain of childbirth (Brune and Hinz, 2004). In 1897, following the advent of synthetic salicylate, Felix Hoffmann synthesized the acetylated form of salicylic acid (Vane and Botting, 2003). Whether the drug was named "aspirin" from acetyl and the source of salicylic acid, the plant *Spirea ulmaria*, or after St Aspirinius, the patron against headaches, is not known. But it became the most widely used medicine of all time (Brune and Hinz, 2004).

The first nonsteroidal anti-inflammatory drug (NSAID), phenylbutazone, was introduced in 1949, followed by indomethacin in 1963, and by ibuprofen in 1969 (Hart and Boardman, 1963; Adams, 1992). In 1971, Vane discovered the mechanism by which aspirin and indomethacin exerts their anti-inflammatory, analgesic and antipyretic actions (Vane, 1971). He proved that aspirin and other NSAIDs inhibit the enzyme cyclooxygenase (COX). This enzyme catalyzes the formation of prostaglandins (PGs), which cause inflammation, pain and fever (Vane and Botting, 2003). In 1982, Bergström, Samuelson and Vane shared the Nobel Prize in Medicine for these discoveries (Gryglewski and McGiff, 2005).

Acetanilide was developed in 1886 and phenacetin in 1887; both, such as the salicylates, possess antipyretic and analgesic properties (Hinsberg and Kast, 1887). In 1893, another compound was found in the urine of individuals who had taken phenacetin. This compound, now known as paracetamol (acetaminophen in the USA), was discovered to have a prompt analgesic and antipyretic action (von Mering, 1893). In 1948 Brodie and Axelrod established that paracetamol is a major metabolite of both phenacetin and acetanilide. They also found that acetanilide is associated with methaemoglobinaemia, and therefore advocated the use of paracetamol for pain relief (Brodie and Axelrod, 1948). Today paracetamol is commonly given as a basis for

postoperative pain treatment because of its analgesic and opioid-sparing effects, and proven safety at appropriate dosages (Korpela et al., 1999; Breivik et al., 2007).

More than 50 years ago Hench and colleagues discovered the anti-inflammatory and analgesic actions of glucocorticoids (Hench et al., 1949). They had previously noticed that sciatic pain as well as pain and other symptoms of rheumatoid arthritis were often improved during pregnancy and when a patient had jaundice, both situations in which there is an increase of steroids in the body (Hench, 1933). The active substances of the adrenal cortex had then recently been isolated by Reichstein and Kendall and shown to be steroids (Hench et al., 1949). It seemed possible that these might alleviate inflammatory symptoms. Hench and his co-workers found that small doses of cortisone dramatically improved the symptoms of patients with rheumatoid arthritis. For these discoveries Hench, Kendall, and Reichstein were jointly awarded the Nobel Prize in Physiology and Medicine in 1950 (Nobel Archives, Stockholm, 1950). Powerful synthetic glucocorticoids were then developed. Despite the unwelcome side effects associated with long term therapy, they became and remain a mainstay of anti-inflammatory therapy (Saklatvala, 2001).

It was the action of glucocorticoids on prostaglandin production that led to the discovery of cyclooxygenase-2 (COX-2). Many researchers had observed that glucocorticoids could reduce prostaglandin synthesis but that it did not block it completely. Thus, the existence of a COX isoform that is positively regulated by cytokines and negatively regulated by glucocorticoids was suspected. Philip Needleman proposed that there must be 2 enzymes, one whose expression could be blocked by steroids, COX-2, and another whose expression was not effected by steroids, COX-1, and thus was active in spite of exogenous steroids. In 1990, Needleman's group provided proof of the existence of two different enzymes (Needleman and Isakson, 1997). At the same time the inducible COX isoform, COX-2, was isolated. In the early 1990s, the inducible COX-2 isoenzyme was successfully cloned (O'Banion et al., 1992).

It became clear that both COX-1 and COX-2 are constitutively expressed isoforms, and that COX-2 in addition is induced by inflammatory mediators, while COX-1 can be upregulated following tissue injury and in conditions such as gastric ulceration and glomerulonephritis (Svensson and Yaksh 2002; Samad et al., 2002). It was reasoned

that inhibition of COX-2, the expression of which is controlled by cortisone, would be sufficient for anti-inflammatory and analgesic effects but would be free of gastrointestinal and kidney toxicity – a hypothesis that would turn out to be only partly correct (Brune and Hinz, 2004). As a consequence of this discovery, more selective COX-2 inhibitors were developed. They shared most of the effects and adverse effects of the traditional NSAIDs, but did not inhibit platelet aggregation, and decreased but did not eliminate the risk for gastric ulceration (Gilron et al., 2003). However, increased risk of thrombosis and cardiovascular events such as myocardial and cerebral infarction gradually became apparent, and as a result, rofecoxib was withdrawn from the marked (Fitzgerald, 2004) and restrictions on the use of other selective coxibs ensued.

Use of anti-inflammatory drugs for postoperative pain
Among patients, postoperative pain is the most common reason for anxiety before surgery (Warfield and Kahn, 1995). This fear is unfortunately well founded. In a meta-analysis of studies comprising 19,909 patients, 1 in 5 patients experienced severe pain or poor pain relief after surgery (Dolin et al., 2002). In spite of the advances in the availability of acute pain services and our increased knowledge of postoperative pain, this meta-analysis shows that postoperative pain management has improved little during the last twenty years. In 1997, the UK Audit Commission proposed a standard whereby fewer than 20% of patients experience severe postoperative pain after 1997, with a further reduction to 5% by 2002 (Dolin et al., 2002). However, usual practice has not delivered that expectation (The Oxford Pain Internet Site, 2003). Thus, there are discrepancies between ordinary and optimal pain management. The reasons for this are: a) lack of awareness and knowledge of the problem among health professionals; b) inadequate or improper application of the available knowledge, therapies and resources; c) fear of serious side effects and complications; d) voids in knowledge about pain management because of insufficient research (Loeser, 2001; Breivik et al. 2007).

As the health care environment changes, increased pressure are felt to perform operations in the ambulatory setting that would traditionally have been undertaken on inpatients. As a result, physicians are challenged to provide offensive pain control in new settings. Operative and postoperative regional anaesthesia and analgesia, which provide

the best dynamic pain control, are often difficult to carry out when the patient is sent home the same day. Inadequate early postoperative analgesia and adverse events such as nausea and vomiting impede patient flow and reduce the efficiency of a day-case unit. Patients discharged with oral analgesic medication a have higher risk of inadequate analgesia and adverse effects of opioid medication during the first days at home compared with patients cared for in a hospital (Beauregard et al., 1998). Therefore, it is important to optimize the analgesic regime with non-opioid analgesics, reducing the need for opioids and their side effects (Breivik et al., 2007).

Optimal pain relief, reduction of adverse effects such as nausea and vomiting, and shorter duration of convalescence without compromising safety is achievable for most patients with *multimodal* or *balanced* pain relief (Kehlet and Dahl 2003). This approach aims to reduce pain at each step of the pain nociception process by combining analgesics that each operates through a different site or mechanism of action. Multimodal pain treatment postoperatively therefore involves the use of well known agents such as opioids, paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) and the newer cyclooxygenase-2 (COX-2) specific inhibitors (Kehlet, 2004). For more severe postoperative pain, epidural analgesic techniques with local anaesthetics, opioids and adrenaline and peripheral continuous nerve blocks are recommended (Niemi and Breivik 2002; Zaric et al. 2004; Breivik et al., 2007).

Three decades ago opioids *alone* were considered sufficient after surgical procedures (Harcus et al., 1980). NSAIDs and/or paracetamol were mostly used after minor procedures, and they were not routinely used for medium or major procedures. For many patients this resulted in pronounced opioid side effects such as nausea, vomiting, sedation, respiratory depression, prolonged ileus, problems with mobilization, and prolonged convalescence (Kehlet and Dahl, 2003).

Opioids still remain mainstay in postoperative pain management, but paracetamol, NSAIDs and COX-2 inhibitors alone or combined with opioids have been well documented as effective for postoperative analgesia, with few side effects during short time treatment (Hyllested et al. 2002; Barden et al. 2003). Optimal use of non-opioid analgesics, i.e. adequate doses and combinations, has proved to effectively reduce opioid

consumption and thus opioid related side effects such as sedation, nausea and vomiting (Marret et al., 2005; Breivik et al., 2007).

NSAIDs and selective COX-2 inhibitors
Once tissue has been injured by a surgical trauma, multiple chemical mediators are released from damaged and inflammatory cells. The resulting "inflammatory soup" is rich in cytokines, growth factors, bradykinin, purines, amines, lipids, ATP, serotonin, histamine, protons, potassium, prostaglandins and inflammatory enzymes such as inducible nitric oxide synthase (iNOS) and the inducible COX-2 (Fig. 1). At the cellular level, inflamed regions show a substantial influx of inflammatory cells, arterial dilatation, and increased blood flow, fluid and plasma leakage with a resulting oedema. Both the oedema (mechanical pressure) and the inflammatory mediators activate nociceptors, evoking pain (Julius and Basbaum, 2001).
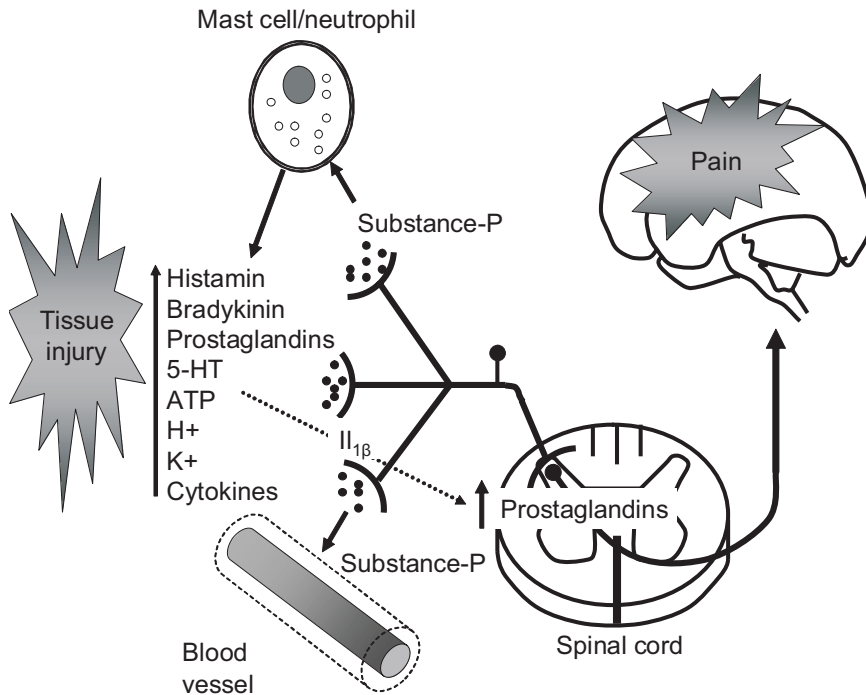
Figure1. Some of the main components of the inflammatory reaction after a tissue injury are shown. Each factor sensitizes the terminals of the nociceptors. Peripheral inflammation induces an increase in spinal prostaglandins contributing to central sensitization. Activation of the nociceptors not only transmits pain signals to the spinal cord and brain but also initiates neurogenic inflammation resulting in vasodilatation, plasma extravasation and activation of mast cells and neutrophils. These cells in turn contribute to additional elements of inflammation.

The efficacy of NSAIDs and selective COX-2 inhibitors (coxibs) is attributed generally to blockade of cyclooxygenase enzymes that convert arachidonic acid (a lipid substrate derived from membrane phospholipids) into inflammatory prostaglandins (Fig. 2). Phospholipase A_2 enzymes liberate free fatty acid from membrane phospholipids and control the flow of arachidonic acid available for prostaglandin synthesis. Prostaglandin E_2 (PGE_2) greatly potentiates the pain produced by pain-producing mediators such as bradykinin or histamine (Simmons et al., 2004) (Fig.1). PGE_2 contributes to peripheral sensitization and hyperalgesia by binding to G-protein-coupled receptors that increase levels of cAMP within nociceptors. Peripheral inflammation mediates via $Il_{1\beta}$ spinal induction of COX-2, increasing spinal PGE_2 (Fig. 2). PGE_2 interacts with receptors on the central terminals of nociceptors and results in central sensitization. PGE_2 stimulation of prostaglandin (EP) receptors in the dorsal horn increase NMDA channel opening, augmenting the excitatory effect of glutamate (Svennson and Yaksh, 2002). This argues that COX inhibitors exert their pain relieving effects by modulating nociception at both peripheral and central sites (Svensson and Yaksh, 2001). There is also strong support for a pronociceptive role of PGI_2 in inflammatory pain (Zeilhofer and Brune, 2006). PGI_2 production catalysed by COX-1 seems to be involved in peritoneal pain (Simmons et al, 2004). Also COX-1 is upregulated in the spinal cord after a peripheral injury (Zhu and Eisenach, 2003; Zhu et al., 2003 and 2005).

A molecular target, through which PGE_2 sensitizes primary sensory fibres, is a voltage gated sodium channel that is resistant to tetrodotoxin (TTX-R Na^+-channel). These TTX-R Na^+-channels contribute considerably to action potential firing rate and duration in small-diameter sensory neurons. PGE_2 increases excitability of dorsal root ganglion (DRG) neurons, by shifting the voltage dependence of the TTX-R Na^+-channel activation in the hyperpolarizing direction. This reduces the extent of membrane depolarisation needed to initiate an action potential (Julius and Basbaum, 2001).
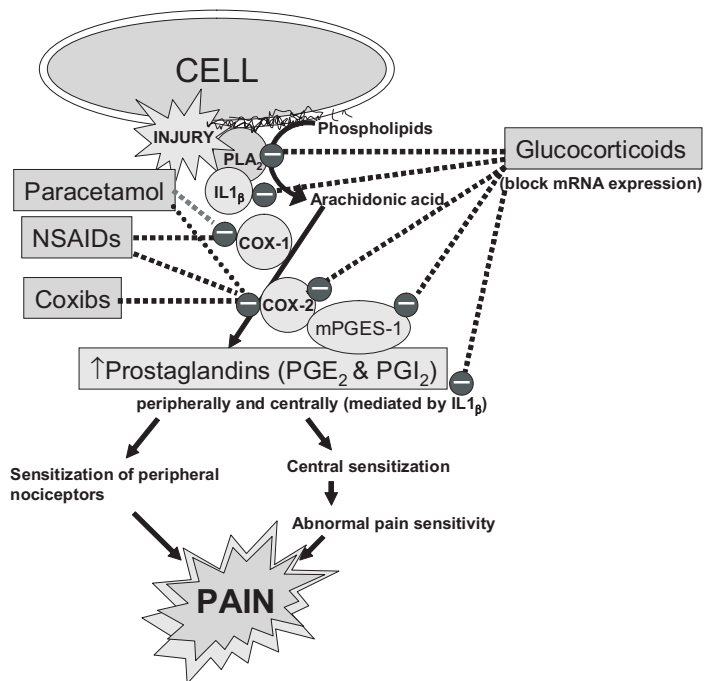
Figure 2

The glucocorticoids and the non-steroid anti-inflammatory drugs share at least one
common mechanism, namely inhibition of cyclooxygenase (COX) enzyme(s) which
reduces the synthesis of prostaglandins, most importantly PGE_2, attenuating peripheral
and central sensitization, and pain. Having more potent anti-inflammatory properties the
glucocorticoids also inhibit other enzymes and signal molecules necessary for
prostaglandin synthesis e.g. phospholipase A , microsomal PGE synthase-1 (mPGES-1)
and cytokines.

Table 2

Mechanisms other than COX/prostaglandin synthesis inhibition contributing to the analgesic effects of anti-inflammatory drugs

NSAIDs/Coxibs	Paracetamol	Glucocorticoids
• iNOS inhibition • indirectly inhibition of NMDA receptors (glutamate)	• iNOS inhibition • 5HT-receptor agonist	• iNOS inhibition • indirectly inhibition of NMDA receptors (glutamate) • Inhibition of TNFα, IL1β, IL6 and NF-κB • induction of IL10 • $\uparrow$glycinergic (inhibitory) activity • $\uparrow$release of GABA and endocannabinoids • $\downarrow$release of peptides from free nerve endings • $\downarrow$ectopic nerve impulses • $\downarrow$neuropathic edema • inhibition of glia activation

NSAIDs inhibit cyclooxygenase 1 (COX-1) peripherally and centrally (Zhu et al., 2003 and 2005) (Fig. 2), as well as cyclooxygenase 2 (COX-2) in the central nervous system (CNS), and peripherally in injured or inflamed tissue (Yaksh et al., 2001) (Fig. 2). The coxibs selectively inhibits COX-2 in peripheral tissues and in the CNS (Yaksh et al., 2001) (Fig. 2). NSAIDs and coxibs also inhibit inducible nitric oxide synthase (iNOS), nitric oxide (NO) being an inflammatory mediator and intracellular signal molecule involved in sensitization of neuronal cells (Table 2) (Amin et al,. 1995; Ryu et al., 2000; Fermor et al., 2002). COX-2 inhibition reduces PGE_2 stimulation of prostaglandin (EP) receptors in the dorsal horn and thereby reduces NMDA channel opening and the excitatory effect of glutamate (Svennson and Yaksh, 2002).

COX-1 in the stomach catalyses the synthesis of prostaglandins that protect the gastric mucosa, COX-1 in thrombocytes increases thromboxane A_2 involved in platelet aggregation, and COX-2 in the kidney produces prostaglandins that are important in maintaining renal blood flow, mediation of renin release, and regulation of salt and water balance (Hinz and Brune, 2002). In these organs the cyclooxygenases are expressed constitutively and are inhibited by NSAIDs. The constitutively expressed COX-2 in the kidney is inhibited by coxibs as well (Svennson and Yaksh, 2002).

These mechanism based effects give rise to some of the most serious side effects of NSAIDs: increased bleeding tendency, gastrointestinal bleeding, salt and water retention, renal failure, hypertension, and aggravation of congestive heart failure from renal salt and water retention. The COX-2 inhibitors give the same renal side effects as the NSAIDs but do not inhibit thrombocyte aggregation (Hinz and Brune, 2002). The coxibs reduce the risk for upper gastrointestinal bleeding compared with NSAIDs, since the prostaglandin that protects the gastric mucosa is COX-1 dependent (Aschroft et al., 2001).

It was somewhat surprising when an increased risk for upper gastrointestinal bleeding compared with placebo was reported after the use of selective COX-2 inhibitors. COX-2 mediated inhibition of micro-vascular angiogenesis has been proposed as a possible explanation (Hinz and Brune, 2002). Another explanation may be that reducing prostaglandin synthesis with COX-2 inhibitors can cause alternative processing of

arachidonic acid via the 5-lipooxygenase pathway, resulting in increased production of proinflammatory and gastrotoxic leucotrienes (Brune and Hinz, 2004).

The COX-2 inhibitors have been attributed with an increased risk for thrombotic events and an increase in the incidence of myocardial and cerebral infarction (Bombardier et al., 2000). A multi-centre study evaluating the effect of rofecoxib on colonic adenomas in 2600 patients was stopped after 18 months and rofecoxib was withdrawn from the marked. This action was taken because of a significant increase, by a factor of 3.9, in the incidence of serious thromboembolic adverse events in the group receiving 25 mg rofecoxib daily compared with placebo (Fitzgerald, 2004). A recent trial investigating the safety of parecoxib and valdecoxib treatment during a 10 days period after coronary bypass surgery concluded that these drugs were associated with an increased incidence of myocardial infarction, cardiac arrest, stroke and pulmonary embolism (Nussmeier, 2005). The reason for this may be that COX-2 catalyses the production of prostacyclin (PGI_2) in blood vessel walls. PGI_2 is a vasodilator and reduces adhesiveness of platelets. When COX-2 is blocked, also PGI_2 production is suppressed, allowing thromboxane to cause platelets to stick together and adhere to endothelium of vessels. Thromboxane also causes blood vessels to constrict. NSAIDs reduce both PGI_2 and thromboxane A_2, and theoretically achieving a better balance between prothrombotic and antithrombotic effects (Mukerhjee et al., 2001). However, despite extensive use of COX-2 inhibitors perioperatively, it is difficult to find any reports on serious renal or cardiovascular complications associated with its short-term use after non-cardiac surgery on healthy patients. In this setting, these side effects are probably of minor concern (White, 2005). This was confirmed by Nussmeier et al. (2006): In a 30 days postoperative follow up after 10 days treatment with valdecoxib and its prodrug parecoxib or placebo (1.062 patients included), they found that adverse events, including cardiovascular and thromboembolic, had similar frequencies among the patients in the different groups. However, after cardiac surgery even short term exposure to coxibs increases risk of complications (Nussmeier et al 2005).

Non-selective NSAIDs such as diclofenac and ibuprofen (which have significant COX-2 inhibiting effects) have also been associated with an increased risk of myocardial infarction (Hippisley-Cox and Coupland, 2005). Long term use of NSAIDs increases

risks of major cardiovascular events such as myocardial and cerebral infarction (Chan et al., 2006). The most comprehensive meta-analysis on cardiovascular side effects after COX-2 specific and non-specific NSAIDs with 150.000 included concludes that selective COX-2 inhibitors are associated with a moderate increase in the risk of vascular events, as are high dose regimens of ibuprofen and diclofenac, but not naproxen (Kearney et al. 2006). However, in this discussion of safety of selective and non-selective COX inhibitors, it should not be forgotten that poor pain relief may entail more complications than those caused by adverse effects of these drugs (Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine, 2005)

NSAIDs that block COX-1 can precipitate bronchospasm. Fortunately, it appears that the most selective COX-2 inhibitors do not have this adverse effect (Stevenson, 2004). Allergy to sulphonamides is a contraindication for some of the coxibs containing sulphonamide groups (celecoxib and valdecoxib). Serious dermatological/allergic reactions have been seen after administration of these drugs to susceptible individuals (Marques et al., 2004). Because of these dermatological adverse effects, the use of valdecoxib was suspended in Europe and USA in 2005 (European Medicines Agency, 2005).

During the last few years nitric oxide (NO)-releasing NSAIDs have been developed. Release of NO as the compounds are broken down, may counteract the NSAID-induced gastrointestinal and cardiorenal toxicity (Fiorucci and Antonelli, 2006).

There are concerns about the negative effect on bone healing of NSAIDs and coxibs. This negative effect on bone healing has been ascribed to the inhibitory effect of prostaglandin production (Reikeraas and Engebretsen, 1998). However, only meagre high quality clinical evidence of this effect has been found. Smoking has major effects on risk of fractures and on bone healing and smoking is therefore an important confounding factor (The Oxford Internet Pain Site, 2004). Apart from indomethacin, or doses of rofecoxib and ketorolac that exceed what is recommended, there is no evidence that NSAIDs or coxibs make any difference to bone healing after surgery or trauma (The Oxford Internet Pain Site, 2004; Reuben et al., 2005). Under unstable conditions (unstable fracture) clinical doses of indomethacin impair bone healing while ketorolac does not. Under stable conditions (rigid osteofixation) ketorolac and indomethacin have

no deleterious effect on bone healing (Elves et al., 1982; Reikeraas and Engebretsen, 1998). Thus, bone healing that occurs by direct (gap) healing seems to be rather resistant to the effects of NSAIDs. NSAIDs and coxibs facilitate postoperative mobilization, which is known to stimulate vascularisation of callus, bone healing and increase fracture strength (Grundnes and Reikeraas, 1991a and 1991b; Kaastad et al., 1996).

Since COX-2 is induced peripherally and centrally during inflammatory conditions, a selective COX-2 inhibitor theoretically would be the drug of choice for postoperative inflammatory pain. However, the specific and non-specific COX inhibitors have similar analgesic effects on postoperative pain (Rømsing and Møiniche, 2004). We have already mentioned that COX-1 is upregulated in the spinal cord after a peripheral injury (Zhu and Eisenach, 2003; Zhu et al., 2003 and 2005). COX-1 can be induced following a spinal cord injury, and other pathological conditions such as gastric ulcer and glomerulonephritis (Samad, 2002). Early after experimentally induced neuropathy, spinal COX-1 expression increases (Zhu and Eisenach, 2003). Inhibition of COX-1 during the early stages in an experimental neuropathic pain model seems to prevent further development of allodynia and hyperalgesia (Hefferan et al., 2003). This suggests a role for COX-1 inhibition in the prevention of postoperative neuropathic pain (Zeilhofer and Brune, 2003; Zhu and Eisenach, 2003).

Due to the focus on COX-2 during the last decade, the importance of COX-1 inhibition in the management of pain may have been underestimated. Ketorolac, a COX-1 preferring inhibitor, has excellent efficacy on acute pain (Rainer et al., 2000). There is evidence that in order to achieve optimal analgesia, inhibition of both COX isoenzymes is advantageous (McCormack and Twycross, 2001; Zeilhofer and Brune, 2003; Zhu and Eisenach, 2003, Zhu et al., 2003 and 2005). However, when it is crucial to minimize bleeding or in order to reduce the risk for gastrointestinal bleeding, a COX-2 selective inhibitor may be the drug of choice (Hegi et al., 2004; Garner et al., 2005).

Paracetamol (acetaminophen)

Such as NSAIDs, paracetamol affects prostaglandin synthesis, particularly in the CNS (Flower and Vane, 1972). Paracetamol inhibits weakly COX-1 and COX-2 in vitro (Fig. 1), but reduces prostaglandin synthesis markedly in vivo, and acts as a COX-2 selective inhibitor of prostaglandin production when the levels of arachidonic acid are low (Botting, 2000; Graham and Scott, 2005). The many similarities between COX-2 selective inhibitors and paracetamol in their clinical effects and adverse effect-profiles may be explained by this (Graham and Scott, 2005). Even though paracetamol is a poorer COX- inhibitor than the NSAIDs and coxibs, very high (toxic) doses eventually lead to complete inhibition of COX-1 and COX-2 throughout the body (Brune and Hinz, 2004). Paracetamol also inhibits inducible nitric oxide synthase (iNOS) (Table 2) (Amin et al,. 1995; Ryu et al., 2000).

Paracetamol exert a central antinociceptive effect via a supraspinal activation of descending serotonergic pathways (Table 2) (Alloui et al., 2002; Bonnefont et al., 2003), possibly mediated through its COX-2 inhibiting effects in the CNS (Graham and Scott, 2005). A recent study has demonstrated that 5-HT antagonists reduce the analgesic effect of paracetamol (Pickering et al., 2006).

Paracetamol has analgesic, antipyretic and anti-inflammatory effects (Skjelbred and Løkken, 1979; Botting, 2000; Bjørnsson et al. 2003). However, authorities and distinguished textbooks of pharmacology such as Goodman & Gilman, still erroneously state that paracetamol, such as the NSAIDs, has little or no anti-inflammatory effect (Hardman et al., 2001; Simmons et al., 2004). This misconception seems to be based on only two trials in patients with rheumatoid arthritis (Boardman and Hart, 1967; Ring et al., 1974). After oral surgery the evidence for an anti-inflammatory effect of paracetamol similar to that of NSAIDs is well documented (Løkken and Skjelbred, 1980, Mburu et al., 1988; Bjørnsson et al., 2003). "The common statement that paracetamol has no anti-inflammatory activity is incorrect" (Graham and Scott 2005).

During the last decade Brune and Botting independently speculated on the existence of a putative COX-3 in the brain, mainly responsible for pain and fever (Botting, 2000; Brune and Hinz, 2004). In 2002 Chandrasekharan described the cloning and expression of an alternatively spliced form of COX-1 from canine cerebral cortex,

named COX-3. This canine COX-3 is inhibited by both paracetamol and NSAIDs
(Chandrasekahran et al., 2002). Later, other investigators found that COX-3 does not
exist in humans (Dinchuc et al., 2003).

Paracetamol dose

Paracetamol overdose is hepatotoxic and extremely dangerous with inadequate treatment.
On the other hand, within the therapeutic range, it is well tolerated, with few side effects.
The analgesic effect of traditional doses (1 g to an adult patient) is slightly less and of
shorter duration than standard doses of an NSAID (Breivik et al., 1999). Clinicians tend
to use too low doses (Breivik et al., 2007). The efficacy of paracetamol can be markedly
improved with higher start doses than previously recommended (Korpela et al., 2001;
Juhl et al., 2006). There is no ceiling of the analgesic effect for acute pain at 1 g: An
initial dose of 2 g paracetamol intravenously to adults gave higher peak effect and longer
duration of analgesia compared with 1 g, without any indication of hepatotoxic effects
(Juhl et al., 2006).

Because of the documented analgesic and opioid-sparing effect postoperatively,
and low toxicity, paracetamol has become a widely used pharmacological base on which
other analgesics are added as needed. In addition to the oral and rectal formulations,
intravenous paracetamol (Perfalgan®) is useful particularly for surgical patients (Breivik
et al., 2007). Rectal administration is slow and often incomplete. The intravenous
administration is particularly advantageous in the immediate postoperative period when
gastric emptying often is delayed (paracetamol is not absorbed from the stomach)
(Breivik et al., 2007).

Combination of an NSAID or a COX-2 inhibitor with paracetamol

There is evidence for more pain relief when combining an NSAID with paracetamol
compared with an NSAID alone in arthritic pain (Buescher and Meadows, 2004). In
animal studies, supra-additive effects (i.e. synergism) between paracetamol and NSAIDs
are well documented (Wong et al., 1983; Fletcher et al., 1997; Hyllested et al. 2002;
Miranda et al., 2006a and b). Of 12 randomised controlled clinical trials, seven
demonstrated significantly better analgesia after combining an NSAID and paracetamol

compared with either drug alone (Stacher et al., 1979; Wong et al., 1983; Fletcher et al., 1997; Breivik et al., 1999; Menhinick et al., 2004; Pickering et al 2002; Hiller et al., 2006), five were inconclusive (Dahl et al., 2004; Hiller et al., 2004; Mathews et al., 1984; Montgommery et al., 1996; Viitanen et al., 2003). Only five RCTs comparing the combination of a coxib plus paracetamol with either drug alone have been performed (Issioui et al. 2002a; Issioui et al., 2002b, Pickering et al., 2002; Miranda et al., 2006; Haglund et al., 2006). In one of these studies celecoxib plus paracetamol were better than placebo but no differences were seen after either drug alone (Issioui et al., 2002b). One study demonstrated significantly improved analgesia when paracetamol was added to rofecoxib (Haglund et al., 2006). A recent experimental study on mice has demonstrated potent supra-additive effects between paracetamol and coxibs (parecoxib) (Miranda et al, 2006).

Some of the trials studying the effect of combining an NSAID or a coxib with paracetamol have too low baseline pain intensity or too low pain intensity in the placebo group (Rømsing et al., 2002). Such trials will have low assay sensitivity and minimal ability to detect even clinically important differences between two active treatments (Stubhaug and Breivik, 1995).

Two systematic reviews concluded that the available research data in this field is limited (Rømsing et al., 2002; Hyllested et al., 2002). We therefore decided to investigate this in a human experimental study (Study I).

Glucocorticoids

The anti-inflammatory properties of NSAIDs, COX-2 inhibitors, and even paracetamol are regarded as essential for their analgesic effects (Bjørnsson et al., 2003; Simmons et al., 2004; Graham and Scott, 2005). Glucocorticoids give even more profound anti-inflammation. In fact they are the most potent anti-inflammatory agents currently available (Newton, 2000), but have not traditionally been regarded as analgesics for acute pain. They reduce pain and swelling after oral surgery, orthopaedic surgery, spinal surgery, adenotonsillectomy, and laparoscopic surgery (Skjelbred and Løkken, 1982; Aasbøe et al., 1998; Holthe and Kehlet, 2002 Bisgaard et al., 2003; Afman et al., 2006).

Postoperatively glucocorticoids have demonstrated analgesic efficacy after both systemic and local administration (Liu et al., 1996; Afman et al 2006). Glucocorticoids also have documented analgesic effect in arthritic pain (Gotzsche et al., 2004), cancer pain (Henriksen et al., 2003), and complex regional pain syndrome (Kalita et al., 2006). In rats methylprednisolone can hinder the development of neuropathic pain after nerve injury (Takeda et al., 2004).

To achieve anti-inflammatory and analgesic effects glucocorticoids bind to intracellular receptors, modify gene transcription, and induce synthesis of proteins (Schleimer, 1993; Barnes, 2005). They reduce the prostaglandin synthesis by inhibiting phospholipase A_2 (PLA_2), and by blocking the expression of COX-2 mRNA in peripheral tissues and in the central nervous system, but do not affect COX-1 (Fig. 2) (O'Banion et al., 1992; Schleimer, 1993; Barnes, 2005). As already mentioned, it was the preventing effect of glucocorticoids on COX-2 expression that led to the detection of COX-2.

Recently PGE_2 synthases have gained much attention as targets for analgesic and antihyperalgesic agents. One membrane bound form, microsomal PGE synthase-1 (mPGES-1), which is closely associated with COX-2, contribute most to pain sensitization and is suppressed by glucocorticoids (Zeilhofer and Brune, 2006).

Other effects contributing to the analgesic effect include the suppression of leucocytes and mediators of inflammatory hyperalgesia such as iNOS, TNF_α, $Il_{1\beta}$ and Il_6, by downregulating the nuclear transcription of their RNA (Table 2) (Schleimer, 1993; Ferreira et al., 1997; Barnes, 2005). Reduced vasodilatation and capillary leakage reduce oedema and pain due to increased pressure in closed compartments (Schleimer, 1993;

Kehlet and Holthe, 2002). Glucocorticoids also inhibit release of neuropeptides from nerve endings, signal transmission in nociceptive C-fibres and ectopic discharge from traumatized nerves (Johansson et al., 1990; Johansson and Bennet, 1997). They also induce expression of the anti-inflammatory cytokine Il_{10} and reduce the activation of nuclear factor-kappa B (NF-κB) (Table 2). Activated NF-κBin the glia induce COX-2 and proinflammatory cytokines that contribute to central neuroplastic changes and thus sensitization, resulting in lower pain thresholds and spontaneous neuronal firing, manifested as allodynia and hyperalgesia (Xie et al., 2006).

Glucocorticoid-induced effects that require protein-synthesis have about 2 hour's latency of onset (Ferreira et al., 1997). In order to take advantage of these anti-inflammatory effects for reduction of postoperative inflammation and pain, preoperative administration of glucocorticoids has been advocated. Therefore, in all previous studies of the analgesic effect of glucocorticoids on postoperative pain, the first dose has been given perioperatively (Holthe and Kehlet, 2002).

However, there are reports of rapid onset of analgesic and anti-hyperalgesic effects of glucocorticoids: After oral surgery significant pain-reduction have been observed before 45 minutes (Skjelbred and Løkken, 1982). Rapid and striking anti-hyperalgesic effects of glucocorticoids have been demonstrated in animals (Ferreira et al, 1997; Roach and Sufka, 2003). These findings indicate specific analgesic and anti-hyperalgesic mechanisms not linked to the anti-inflammatory effects requiring protein-synthesis. Rapid reduction in neural discharge within seconds to a few minutes due to non-genomic effects on membrane receptors is a documented effect of steroids (Falkenstein et al., 2000; He et al., 2003). These rapid non-genomic effects of glucocorticoids (dexamethasone) are due to decreased glutamate release, and increased GABA and endocannabinnoid release (Di et al., 2003 and 2005) (Table 2). By decreasing glutamate and increasing GABA, glucocorticoids would be expected to rapidly cause a marked reduction in excitability of nerve cells *in vivo* (Di et al., 2005).

The FDA has suggested that the oral surgical model is especially appropriate for drugs with anti-inflammatory effects (Ridgway, 2004). Since 1977, 20 RCTs of high quality have been conducted on the effect of steroids on postoperative pain after oral surgery, of which 17 had positive outcome (Romundstad et al., 2005). This is sufficient

evidence to recommend the routine use of a glucocorticoid for the relief of postoperative pain after oral surgery (Holthe and Kehlet, 2002).

Data from four systematic reviews on anti-inflammatory drugs have been used to study the influence of pain models on outcome of analgesic drug trials (Barden et al., 2004). Systematic difference in the estimate of analgesic efficacy between dental and other postsurgical pain models were not found. This analysis supports the idea that it is legitimate to extrapolate efficacy from one acute pain context to another, i.e. a drug, which is analgesic in one setting such as after oral surgery, will also be analgesic in another setting such as general surgery (Barden et al, 2004). Despite this, there have been disagreements on whether glucocorticoids have a clinically important analgesic effect after non-dental surgery. Thus, the effects on pain after major abdominal and other types of surgery have not always been convincing (Holthe and Kehlet, 2002; Bisgaard et al., 2003). Confounding factors such as differences in anaesthesia methods, surgical technique, other adjuvant therapies, other main outcome measures than pain (usually PONV) and small sized studies with low power may all play a role in negative outcome of such studies (Bisgaard, 2006). Other factors may be the dose of glucocorticoid and magnitude of the surgical trauma. Trials using less than dexamethasone 8 mg or methylprednisolone 40 mg are less likely to give quantifiable analgesic effects (Holthe and Kehlet, 2002). During and after major surgery the endogenous glucocorticoids may reach such high levels that the benefit of additional glucocorticoids on pain maybe small (Bisgaard et al., 2003). But even after major surgery benefits have been demonstrated on other variables such as reduced inflammatory response, improved pulmonary function, less fatigue, less PONV, appetite stimulation, and more rapid convalescence (Holthe and Kehlet, 2002; Halvorsen et al., 2003).

A recent meta-analysis on glucocorticoids given for pain after adenotonsillectomy with 626 pediatric patients included concluded that a single intraoperative dose of dexamethasone significantly reduces post-tonsillectomy pain (Afman et al., 2006).

Increasing but insufficient evidence for relief of pain by glucocorticoids after non-oral surgery makes human experimental and clinical studies on the analgesic effects of glucocorticoids necessary. Therefore, we investigated analgesic effects of glucocorticoids after non-oral surgery. Such studies need appropriate baseline pain to secure assay

sensitivity, or if baseline pain can not be assessed, the number of patients expected to have moderate to high pain intensity must be high enough to achieve adequate power (Stubhaug and Breivik, 1995) (see Study II, III, IV and V).

Antiemetic effect of glucocorticoids

Most surgical patients prefer some pain to severe postoperative nausea and vomiting (PONV). PONV is the main cause of delayed discharge from hospital and unanticipated hospital readmission after ambulatory surgery (Sinclair et al., 1999; Tramér, 2004). The mechanisms by which glucocorticoids alleviate nausea are not fully understood, but are probably partly due to central inhibition of inflammatory mediators. Stimulating the release of endocannabinoids and subsequent activation of presynaptic type I cannabinoid receptors (CB1) may also contribute to the antiemetic effect of glucocorticoids (Di et al., 2003 and 2005; Izzo and Coutts, 2005). Glucocorticoid effects on endogenous opioid and serotonergic systems may play a role. Dexamethasone has been shown to have comparable efficacy with the best antiemetics available, i.e. ondansetron (5-HT antagonist) and droperidol (dopamine antagonist) in preventing PONV, and has additive effects when combined with these drugs (Henzi et al., 2000; Eberhart et al., 2000).

Adverse effects of glucocorticoids

A systematic review of data from more than 1,900 patients concluded that perioperative methylprednisolone up to 30 mg/kg, as a single dose, in major surgery, was not associated with any adverse effects (Sauerland et al., 2000). However, it is important to be aware that glucocorticoids can give a marked elevation in blood glucose (Holthe and Kehlet, 2002) with potentially negative consequences in the postoperative phase. In a study on side effects performed on 457 patients with opticus neuritis treated with methylprednisolone 1000 mg i.v. per 24h for three days followed by 1 mg/kg/24h orally for two weeks, two patients had serious but transient adverse effects (psychosis and acute pancreatitis) (Chrousos et al., 1993). The psychological effects, initially consisting of euphoria and a feeling of increased energy, can turn into dysphoria or depression after treatment for more than one week (Plihal et al., 1996). Psychotic reactions have been described even after a single dose, but the risk for this is very small (Sauerland et al.,

2000). We have not found side effect data on repeated administration of steroids over several days postoperatively, or such data on combinations with non-opioid analgesics.

Persistent postoperative pain

Most patients undergoing surgical procedures recover uneventfully within weeks and patient satisfaction is reported to be high (Perkins and Kehlet, 2000). However, chronic postsurgical pain develops in an alarming number of patients (Breivik et al., 2007). Incidences are reported as high as 30-83% after limb amputations, 22-67% after thoracothomies, 12-56% after gall bladder surgery, 4-37% after inguinal hernia repair, and 12-57% after breast surgery (Perttunen et al., 1999; Tasmuth et al, 1999; Perkins and Kehlet, 2000; Macrae, 2001; Kehlet et al., 2006).

After cosmetic breast augmentation, the incidence of persistent postsurgical pain has been reported to be 38% (Wallace et al., 1996). However, that study also included patients with submuscular silicone implants that are known to be more painful than subglandular implants. Prospective studies done by the implant manufacturers INAMED and MENTOR on 2,163 patients, revealed that 5-16% had pain after three years and 7-17% had pain five years after cosmetic breast implant surgery (U.S. Food and Drug Administration, 2004). These results have not been published in any scientific journal.

Surgical nerve injury plays a major role for development of chronic postoperative neuropathic pain (Mikkelsen et al., 2004). After breast cancer surgery, intercostobrachial neuralgia is associated with damage of that nerve, and attempts to preserve the nerve are associated with a lower incidence of pain (Abdullah et al., 1998). Those exposed to cryoneurolysis of intercostal nerves in order to reduce acute pain after thoracotomies had significantly *higher* risk of pain after 12 months (Richardson et al., 1994; Richardson et al., 2000).

Although traumatic nerve dysfunction is associated with chronic pain (Benedetti et al., 1998), nerve damage alone, however, does not always cause pain: The incidence of decreased sensation was 2-4 times higher than the incidence of pain in the distribution of the intercostobrachial nerve after axillary node dissection (Abdullah et al. 1998).

Likewise Benedetti et al. (1998) found chronic pain in only 50% of individuals with dysfunction in intercostal nerves after thoracotomy.

One striking risk factor for chronic postoperative pain is severe and prolonged acute postoperative pain (Perkins and Kehlet, 2000). Those who had most severe postoperative pain, and those who consumed most analgesics during the week after surgery, had a higher risk of having persistent pain (Katz et al., 1996; Perkins and Kehlet, 2000). On the other hand, those treated with NSAIDs and paracetamol, and those given intercostal nerve blocks with local anaesthetics, had lower risk of pain after 12 months (Richardson et al., 1994).

Other risk factors for chronic postsurgical pain include presence of presurgical pain, age, repeat surgery, radiotherapy, neurotoxic cytostatics and genetic factors (Stubhaug, 2005).

Nevertheless, whether acute pain directly causes chronic pain is debated. Acute and chronic pain could be separate consequences of injury as indicated in Fig. 3 (Stubhaug, 2005).
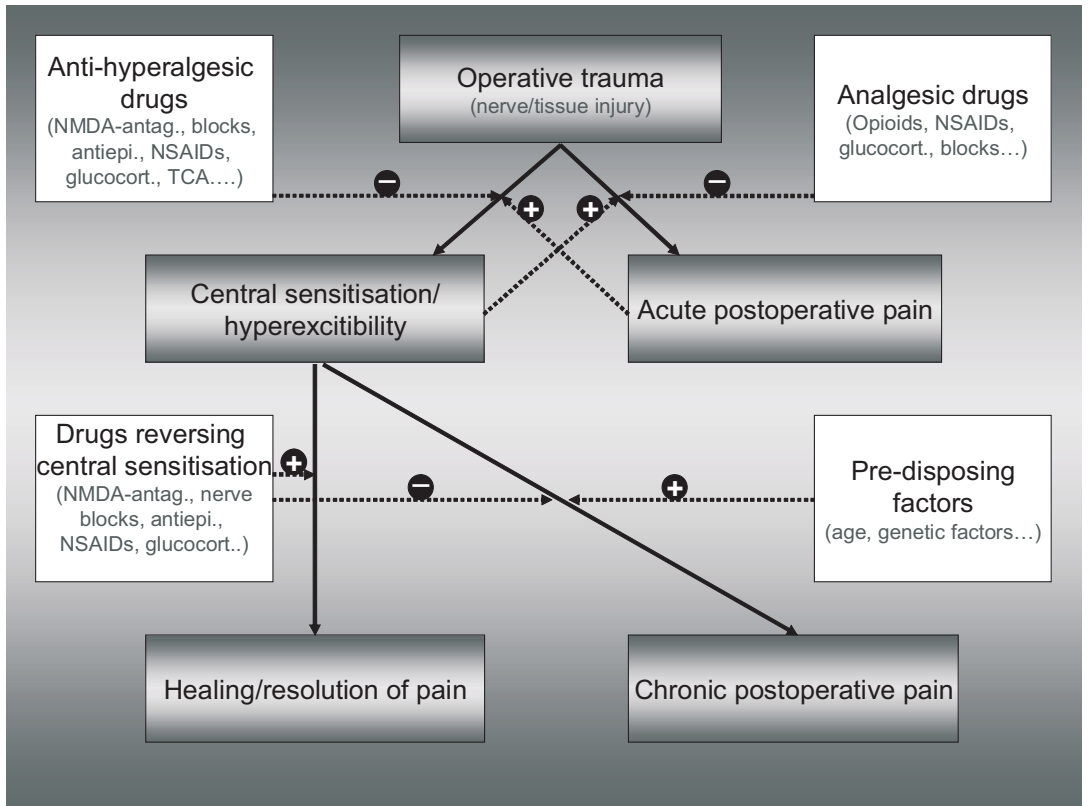
Figure 3.
This is a model proposing the relationship between the operative trauma (tissue/nerve injury), acute pain, central nervous sensitization and development of chronic post-operative pain. Possible augmenting or diminishing factors and treatments are indicated in the figure with the symbols + and - , respectively. Figure adapted from Stubhaug, 2005.

In addition to biological factors, Dworkin et al. (1999) incorporated psychosocial factors in a model of the pathogenesis of chronic pain. Presurgery catastrophizing behaviour is a risk factor for heightened acute postsurgical pain (Pavlin et al., 2005) but not fully investigated in chronic postoperative pain. Younger age, being unmarried, and preoperative anxiety each makes contributions to the persistence of acute postoperative pain (2 – 30 days after surgery) (Katz et al., 2006). However, neither depression nor anxiety is preoperative predictors of chronic pain (> 3 months) after surgery (Katz et al., 1996; Tasmuth et al., 1996). A possible psychological risk factor for persistent postoperative pain is the vague term "psychological vulnerability", also called "neuroticism" (Jess et al., 1998). These are hypervigilant persons who notice internal and external signals better than average; it is conceivable that they make more of the normal postoperative hypersensitivity around a surgical wound and scar. This normal hypersensitivity and soreness is always present for a few weeks after surgery, but slowly weaken and disappear in most patients.

Untreated severe pain is associated with changes in neuronal function, chemical profile and structure, e.g. expression of protein kinase-γ in lamina II in the spinal cord, facilitating AMPA (alpha-amino-methyl-proprionic-acid) and NMDA (N-methyl-D-aspartate) receptor function, gating neural influx of calcium and establishing a state of hyperexcitability (Woolf and Salter, 2000). Loss of inhibitory interneurones, and increase in the number of interneurones involved in pain transmission also contribute to this central sensitization (Basbaum, 1999; Woolf and Salter, 2000; Scholz and Woolf, 2002). Thus, in 1999 Basbaum concluded, "Persistent pain should be considered a disease state of the nervous system, not merely a symptom of some other disease conditions".

Activation of spinal glial cells appears to be a significant mechanism bridging acute pain and nerve damage to chronic pathological pain states (Takeda et al., 2004 and 2005). Activation of spinal glia can release pain-enhancing substances, such as prostaglandins, excitatory amino acids, growth factors and proinflammatory cytokines, establishing and maintaining pathological pain states. Causal association with this activation of glia to pathological chronic pain states is indicated by the fact that pharmacological inhibition of glial activation by glucocorticoids prevents the

development of pathological pain in animal models of chronic neuropathic pain (Takeda et al., 2004) (Table 2).

The concept of preemptive analgesia was introduced by Patrick Wall when he observed that the dose of morphine needed to suppress excitation of central pain receptive neurones was 10-fold less when given before than after the nociceptive stimulus was applied in animal experiments (Wall, 1988). This observation was reinforced by a study indicating a prolonged effect of local anaesthetic blocks on pain after inguinal hernia repair (McQuay et al., 1988). Numerous clinical studies followed, mostly failing to document in patients that pre-treatment with analgesic methods would reduce postoperative pain and requirement for postoperative analgesia. As first pointed out by Breivik et al in 1996, this was a misconception in that any pre-treatment would not last long enough to suppress hypersensitizing nociceptive impulses in the early postoperative period. They concluded that the only way one could hope to suppress central sensitization in patients (as opposed to short term studies in animals) is: "prevention of postoperative pain by pre-treatment and continued optimal treatment" (Breivik et al., 1996). The conclusion of a systematic review done by Møiniche et al in 2002 was negative as to a beneficial effect of preemptive analgesia on postoperative pain. They also suggested that future studies redirect their focus from timing of perioperative analgesia (preemptive analgesia) to "protective analgesia", aimed at the prevention of pain hypersensitivity (pathological pain). These studies should investigate the effect of various anti-hyperalgesic and analgesic drugs for acute postoperative analgesia that is meant to protect the patient against acute inflammatory, acute neuropathic and, hopefully, chronic neuropathic pain. In addition to the traditional anti-inflammatory drugs, drugs that reduce central sensitization and neuropathic pain e.g. ketamine, dextromethorphan, gabapentin, pregabalin, mexiletin, local anaesthetics (centraxial, regional and peripheral blockades) and glucocorticoids have been suggested to have a special role in reducing central sensitization, and thus pathological pain and persistent postsurgical pain and hyperalgesia (Stubhaug et al., 1997; Dahl et al., 2004). Traditional anti-inflammatory analgesics (NSAIDs, coxibs, paracetamol) also reduce central sensitization (Koppert et al., 2003; Sycha et al., 2005; Takeda et al, 2005), Studies are now emerging that indicates reduced risk for development of persistent postsurgical pain and hyperesthesia when more

aggressive anti-hyperalgesic management of acute postoperative pain is offered (Dahl et al., 2004; Power, 2005).

There are studies that have demonstrated long term effect of "protective perioperative analgesia": Epidural analgesia results in reduced pain after 6 months (Richardson, 2000; Sentürk et al., 2002; Tiippana et al., 2003) and even after 12 months (De Kock, 2004). An intraoperative intravenous infusion of ketamine or intrathecal clonidine resulted in significantly reduced pain after six months (DeKock et al. 2001; Lavand'homme et al., 2005; De Kock et al., 2005). Patients undergoing mastectomy or lumpectomy that were treated with eutectic mixture of local anaesthetics (EMLA) before surgery and continuing for six days had a lower incidence and intensity of pain 3 months later compared with placebo (Fassoulaki et al., 2000). Although perioperative treatment with gabapentin and mexiletine did not reduce the incidence or intensity of chronic pain, burning pain was significantly more common in the placebo groups compared with the active drug groups after 3 months (Fassoulaki et al., 2002). A 5-day treatment with the selective COX-2 inhibitor celecoxib, begun before surgery and into the postoperative period in patients with bone donor site pain for spinal fusion, gave significant reduction in acute pain and donor site pain after 1 year (Reuben et al., 2006). Whether glucocorticoids also reduce persistent postoperative pain has not previously been investigated.

Acute postoperative pain is most often regarded as inflammatory and nociceptive pain. But clearly neurogenic mechanisms also contribute in the acute phase and reversible neuropathic type pain may dominate from the late acute phase up to several months (Dahl et al., 2004; Power, 2005). This is expression of a normal, defensive hypersensitivity reaction that is important for maintaining rest and promoting healing of damaged and injured tissues. When postoperative hyperalgesic or allodynic pain persists beyond the usual course of the expected time of healing, or 3 - 6 months, it is defined as "chronic postoperative pain" (Merskey and Bogduk, 1994; Perkins and Kehlet, 2000) and often persists for months and years thereafter. This is somehow due to the processes initiated by peripheral nerve injury and central sensitization occurring at an exaggerated degree and eventually causing maladaptive, dysfunctional adaptations of the neurones of the pain-regulating system in the spinal cord dorsal horn (Basbaum 1999; Woolf and Salter,

2000). No drug has a major influence on healing of peripheral nerves, but anti-hyperalgesic drugs e.g. ketamine and methylprednisolone, can inhibit or impede glia activation and the neuronal mechanisms leading to hyperalgesia and allodynia (Ferreira et al., 1997; Stubhaug et al. 1997; Takeda et al., 2004).

Central sensitization and secondary hyperalgesia

Primary hyperalgesia is the tender, sensitive area directly in and close by the wound, caused by the direct trauma and inflammatory reaction in and near the injured tissue. Secondary hyperalgesia is a wider area around the wound, where there are no visible signs of tissue injury, but where the skin has a lower pain threshold and enhanced pain response to mechanical stimuli such as touching the skin with a von Frey hair. Mechanical secondary hyperalgesia outside the injury is believed to be due to neuroplastic changes in the central pain modulatory systems with sensitization and hyperexcitability of neurones in the dorsal horn of the spinal cord ("central sensitization") (LaMotte et al., 1991, 1992; Baron, 2006). Central sensitization is demonstrated after surgery by the development of such a hyperalgesic area in non-injured tissue around the surgical trauma (Stubhaug et al., 1997).

This area of secondary hyperalgesia normally regresses gradually some time after surgery. However, in patients developing chronic postoperative pain these changes persist and often are aggravated (Dubner and Basbaum, 1994; Eide et al., 1995). It is not unreasonable to assume that there is a relationship between the secondary hyperalgesia around a surgical wound and the persistent abnormal sensations in the unfortunate patients developing chronic postoperative pain (Breivik et al., 1996). De Kock et al. (2005) demonstrated that reducing the area of hyperalgesia with intrathecal clonidine after colectomy did not greatly reduce acute pain, but was associated with a significant decrease in the number of patients who developed residual pain as late as six months after colectomy.

The discharges of afferent C-fibres, set off by the injury, cause a state of central sensitization, whereby dorsal horn neurones, e.g. the wide dynamic range neurones (WDN), become sensitised to input from low threshold mechano-sensitive A-fibres (Simone et al., 1991; Torebjörk et al., 1992; Kilo et al., 1994; Woolf and Salter, 2000).

Receptors for the excitatory amino acids glutamate and aspartate, the NMDA- (*N*-methyl-D-aspartate) and AMPA- (alpha-amino-methyl-proprionic-acid) receptors, play important roles in generation of central sensitization (Woolf and Salter, 2000; Yaksh, 2001; Nozaki-Taguchi, 2002). In human studies the NMDA-antagonist ketamine reduces mechanical secondary hyperalgesia after experimentally induced injuries (caused by first degree burns or capsaicin injection) and after surgical incisions (Ilkjaer et al., 1996; Warncke et al., 1997; Stubhaug et al., 1997).

Clinical evidence suggests that opioids, used during anaesthesia, and for the treatment of moderate to severe pain, can elicit increased sensitivity to noxious stimuli, suggesting that opioids also can activate pain facilitatory mechanisms. This is clearly seen as an enlargement of the area of secondary hyperalgesia when a remifentanil infusion is stopped (Angst et al., 2003). Opioid induced hyperalgesia (e.g. by remifentanil or fentanyl) can be abolished by ketamine or ketorolac, while the α_2-agonist clonidine can reduce the increased pain associated with opioid withdrawal (Kang et al., 2002; Koppert et al., 2003).

Peripheral inflammation leads to central induction of COX-2 (Beiche et al. 1998), and COX-1 (Zhu et al., 2002). This induction is mediated by inteleukin-1beta ($Il_{1\beta}$) (Samad et al. 2001). Central induction of COX, results in increased prostaglandin production. PGE_2 stimulation of prostaglandinE_2 receptors (EP_2) in the dorsal horn will enhance NMDA channel opening, reduce inhibitory transmission of glycinergic interneurones, activate and increase excitability and depolarisation of dorsal horn neurons by opening EP_2 linked ion channels (Woolf and Salter, 2000; Baba et al., 2001; Ahmadi et al. 2002). Thus central release of prostaglandins contributes to the induction of central sensitization and secondary hyperalgesia (Vanegas and Schiable, 2001). Koppert found clear experimental evidence for reduction of secondary hyperalgesia induced by i.v. infusion (clinically used dosages) of the COX-2 inhibitor parecoxib (Koppert et al., 2004).

Glucocorticoids inhibit phospholipase A_2 and block the expression of COX-2 mRNA, and they therefore effectively reduce prostaglandin synthesis and central sensitization in rats (Ferreira et al., 1997). Steroids also inhibit the induction of spinal NO-synthase (iNOS) (Schleimer, 1993). Spinal NO-release contributes to the

development of secondary hyperalgesia following a noxious chemical stimulus (capsaicin) in rats (Wu et al. 2001). Accordingly, glucocorticoids can be expected to reduce central sensitization and secondary hyperalgesia in humans. However, previously published human studies have *not* demonstrated that topical or systemic glucocorticoids suppress secondary hyperalgesia (Pedersen et al. 1994; Werner et al 2002). Theoretically non-selective NSAIDs can have anti-hyperalgesic effects via inhibition of spinal COX-1, COX-2 and iNOS. Intraspinal ketorolac blocks fentanyl-induced hyperalgesia in rats (Kang et al., 2002). Previous studies on NSAIDs have not been able to confirm this anti-hyperalgesic effect in humans (Møinicke et al. 1993; Warncke et al. 1996; Kumar et al., 2006). However, methylprednisolone and NSAIDs have been documented to prevent neuropathic pain in rats (Zhu et al., 2003; Takeda et al., 2004).

If persistent pain after surgery results from central sensitization during an acute pain event, prevention may be possible if this sensitization can be blocked (Breivik et al., 1996; Basbaum, 1999). Thus, if NSAIDs and steroids can be shown to reduce central sensitization also in humans, this would be another argument for their systematic uses perioperatively.

Because of the potential benefits of reducing central sensitization after surgery, we investigated the effects of a glucocorticoid and an NSAID on experimentally induced secondary hyperalgesia (central sensitization) in human volunteers (Study II). We also investigated the effect on acute postoperative pain (Study III and IV) and any long-term effects on chronic postoperative pain and hypersensitivity from a preoperative dose of a glucocorticoid (Study V).

AIMS OF THE THESIS

1. Can any additive analgesic effect between paracetamol and NSAIDs be revealed in a human experimental pain model by addition of paracetamol to ketorolac and measuring the pressure pain tolerance threshold? (Study I)

2. Will a human experimental pain model, measuring pressure pain detection threshold and pressure pain tolerance threshold, reveal any analgesic effects of a glucocorticoid (methylprednisolone) or an NSAID (ketorolac)? (Study II)

3. Does a glucocorticoid (methylprednisolone) or an NSAID (ketorolac) reduce secondary hyperalgesia after a 1°-burn injury? (Study II)

4. Does a glucocorticoid (methylprednisolone) given immediately before day-case surgery reduce acute postoperative pain? (Study IV)

5. Does a glucocorticoid (methylprednisolone) given immediately before day-case surgery reduce nausea, and fatigue compared with a COX-2 inhibitor (parecoxib), and placebo? (Study IV)

6. Does a glucocorticoid (methylprednisolone) when administered one day after surgery reduce acute postoperative pain compared with an NSAID (ketorolac), and placebo, and if so, what is the onset time and duration of analgesic effect? (Study III)

7. What is the prevalence of and risk factors for chronic postoperative pain and sensory changes after cosmetic augmentation-mammoplasty? (Study V).

8. Does a preoperatively administered single dose of a glucocorticoid (methylprednisolone) or a COX-2 inhibitor (parecoxib) reduce persistent postoperative pain and sensory dysfunction? (Study V).

METHODOLOGICAL CONSIDERATIONS

Study design

All studies in this thesis project were prospective, placebo controlled, randomized and double blind trials with one or more active drugs as comparators. Two of the studies had a crossover design (Study I and II), and three had a parallel design (Study III, IV and V). The crossover trial design is the most sensitive trial design and is a within-individual comparison; the subject is his or her own control, and smaller group differences can be detected as the inter-patient variability is eliminated (Cleophas and Zwinderman, 2002; Max, 2002). Crossover studies regularly provide power equivalent to parallel group studies with 5 to 10 times the patient number (Louis et al., 1984; Max, 2002). If there are two or more treatments, every individual gets each treatment, one after the other in a random order to eliminate the effect of calendar time. The treatment periods are separated by a washout period, which allows any residual effects (carry-over effect) of the previous treatment to dissipate. In Study I we had two days washout period, and in Study II we had four days washout periods between the treatments. We used relatively long acting drugs. Thus, it was important to calculate and account for the carry-over effects in the statistical analyses.

In parallel studies each patient is allocated to receive only one of the test drugs. If the population tested is very heterogeneous i.e. differences in age, gender, health status, surgical interventions, baseline pain etc., there will be problems with variability of results, overlap between the groups, and low test power, i.e. no difference can be demonstrated even if a true difference exists (Stubhaug and Breivik, 1995). All patients included in Study I-V were relatively young and healthy. The surgeries performed gave similar baseline pain in Study III. In Study IV/V the surgical procedures were nearly identical, and all included individuals had the same gender and were within the similar age range, minimising variability.

Study I and II were carried out under experimental conditions on volunteers. In experimental studies it is easier than in clinical settings (Study III-V), to control for disturbing (confounding) factors.

Treatment comparisons

An important feature of experimental and clinical trials is that they should be comparative, comparing a standard active drug with a new drug and with placebo. All studies in this thesis were comparative. Without a control treatment, it is impossible to be sure that any response is solely due to the effect of the treatment and the importance of the new treatment can be over-stated. Ideally the controls should be: 1. Standard treatment (active control drug); 2. A negative control (placebo) confirming effect of the standard drug, also confirms assay sensitivity of the trial (Breivik et al., 1998, Stubhaug, 2003).

Knowledge of the placebo response in pain trials is essential. If an analgesic drug trial is comparing two different drugs with no placebo control, there is a possibility of finding no difference. Some will erroneously conclude that the two drugs have equal analgesic effect. In reality no conclusion can be made (Stubhaug and Breivik, 1995).

To give placebo is far from doing nothing (Wall, 1994; Stubhaug, 2003). The placebo response involves release of endogenous substances such as endogenous opioids, dopamine, and serotonin that can provide pain relief (Benedetti et al., 2003). In the clinical trials (Studies III and IV) all subjects were explicitly informed about the rescue analgesic drugs and to ask for these drugs whenever needed. This minimizes the suffering among those receiving placebo *and* those having insufficient pain relief from the active drugs.

Blinding and unblinding

All studies in the present thesis were double blinded. In Study III, a test of unblinding was performed 6 hours after test drug administration. Unblinding is that the test persons (and often the observer) guess if a placebo, or an active drug has been received. An active analgesic drug with subjective effects may strengthen the pain relieving effect by activating potent placebo mechanisms. Such an effect will likely be most pronounced when a drug with a rapid onset of effect is administered (Benedetti et al., 2003). A patient who has received an active analgesic drug, but does not experience a subjective confirmation early (Study III) may more easily guess incorrectly that he has received an inactive drug (placebo). In such a patient the additive analgesic effect of the positive

expectation will be lost, and it can even turn in to a negative effect, a nocebo effect (Benedetti et al., 2003).

Pain measurements

In Study III we used a five point categorical verbal rating scale (VRS) (e.g. 0 = no pain, 1 = weak pain, 2 = moderate pain, 3 = strong pain, 4 = very severe pain) for inclusion, and a 0 – 100 mm visual analogue scale (VAS) for the subsequent pain intensity measurements. In Study IV, the first pain intensity measurements were done in the immediate post anaesthetic period. Because of often experienced difficulties for the patients to use the standard VAS due to possible rest sedation (Sriwatanakul et al., 1983), we used the 0 – 10 (11-point) numeric rating scale (NRS). Here the patient could describe the pain intensity by choosing a number from 0 to 10, which is easier than using the VAS scale (Sriwatanakul et al., 1983).

We used a five point categorical verbal rating scale (VRS) (i.e. 0 = no relief, 1 = slight relief, 2 = moderate relief, 3 = good relief, 4 = complete pain relief) in Study III for the measurement of pain relief.

Derived variables

Dichotomous data from acute pain trials are wanted for meta-analysis of studies on acute pain (Moore et al., 1996). The area under the time-analgesic curve for the pain relief, called total pain relief (TOTPAR), is a derived variable measured by calculating the area under the curve (AUC) for pain relief against time (Mathews et al., 1990). If a patient had complete pain relief immediately, and sustained it for the full six hours of measurement, then the maximum TOTPAR 0-6h would be attained. If a 5 categories 0-4 verbal score was used, the patient would have a score of 4 points times 6 hours, giving a maximal achievable TOTPAR of 24. Another patient who had a score of 12 would have 50% of the maximum TOTPAR, or 50%maxTOTPAR. Such data make it possible to calculate numbers needed to treat (NNT) (Moore et al., 1996). From the proportion having >50%maxTOTPAR >4-6 hours, numbers needed to treat (NNT) can be calculated: NNT = 1/(proportion of patients with >50%maxTOTPAR in an active drug group – proportion of patients with >50%TOTPAR in the placebo group (Moore et al., 1996). This method is

used in the Oxford league table of analgesics (The Oxford Pain Internet Site, 2003). More than 50%maxTOTPAR has been suggested as a parallel to Beecher's "pain half gone" or 50% pain relief (50%PAR) as a benchmark test for analgesics (Beecher, 1955; McQuay and Moore, 1998). In Study III we used to 50%maxTOTPAR to calculate NNT, and compared it with NNT obtained from the more directly derived 50%PAR.

The composite pain intensity and rescue analgesic score
In trials where rescue analgesics is given early to a significant proportion of study patients, the numbers of "true" pain observations after test drugs decline rapidly, and the common method: "Last observation carried forward" (LOCF), will soon be based on very few observations and therefore has reduced validity (Max and Laska, 1991). To solve this problem it is possible to calculate a composite score based on actual pain observations (both before and after rescue, as opposed to LOCF) and rescue analgesic consumption. In Study IV we modified the Silverman method (Silverman et al., 1993) for calculating a composite score as follows:

1. Rank all subjects according to their sum of actual pain intensities observed during the observation time.
2. Express the difference of each treated subject's rank from the mean rank as a percentage of the mean rank.
3. Perform the same steps for rescue analgesic usage.
4. For each subject, the sum of the two % differences calculated for actual pain rank and rescue analgesic usage rank, constitutes the composite score.

Statistical analysis

Non-parametric versus parametric tests

Non-parametric tests are useful when the sample size is so small that it is impossible to assess the distribution of the data, non-numerical categorical data, and when the data are far from normally distributed. However, non-parametric tests are generally wasteful of information; consequently they have less power of detecting a real effect than the equivalent parametric tests if the assumptions underlying the parametric test are satisfied (Petrie, 2003). Biostatisticians claim that parametric tests such as analysis of covariances in a general linear model or a linear mixed model (see later) in most cases are more robust and powerful when repeated measurements are analyzed (Vickers, 2005). In all trials we assessed the distribution of the data with frequency histograms, normal plots and/or Kolmogorov Smirnov test, and we used parametric or non-parametric methods when appropriate.

The statistical tests used

One – Way ANOVA: A one-way analysis of variance that compare means of more than two independent groups of observations by splitting the total variance of a variable into its component parts, each attributed to a particular factor (the independent variable) (Petrie, 2003) (Study IV).

General Linear Model (GLM): Provides regression analysis and analysis of variance (ANOVA) and includes covariates for one or multiple dependent variables by one or more factors and/or variables (Dobson, 2001) (Study III).

Linear Mixed Model: Such as GLM the Linear Mixed Models is also an extension of regression and ANOVA, but this procedure expands the general linear model further so that the data are permitted to exhibit correlated and non-constant variability. The linear mixed model provides the flexibility of modelling not only the means of the data but their variances and covariances as well. This is a variance component model that takes correlations (dependency) due to repeated treatments, and repeated observations in each treatment session on each subject into account (Verbeke and Molenberghs, 1997; Littell

et al., 2000). Unlike standard methods, linear mixed models use all data and give a more accurate analysis.

Multiple measurements on the same subject in crossover trials are much more similar than measurements on different subjects in parallel trials as the inter-individual variability is eliminated. In crossover trials the linear mixed model allows one to model the within-subject variability and dependence and get a picture of change and variance on the subject level (the within-subject variance component), not just the population average pattern of change (the between-subjects variance component). Thus, this statistical analysis is appropriate for a crossover trial with repeated measurements (Brown and Prescott, 1999). The linear mixed model was used in study I and II, which were crossover trials with repeated measurements.

Post-hoc multiple comparisons: Two common multiple comparisons procedures are *Fisher's least significant difference* and the *Bonferroni adjustment.*

Fisher's least significant difference test (Fisher's LSD) starts with an overall F-test (ANOVA) to first test the null hypothesis that all the population means are equal (the omnibus null hypothesis). If the preliminary overall ANOVA analysis is not significant, then neither the omnibus null hypothesis nor any other null hypothesis can be rejected, and further multiple comparisons are not allowed. If the overall ANOVA is significant, then each mean can be compared with each other. There is only a 5% chance that the overall F ratio will reach significance when there are no differences. Some statisticians (Snedecor and Cochran, 1980; Hochberg and Tamhane, 1987; Proschan et al., 1994) refer to this procedure as Fisher's *protected* LSD to emphasize the protection the preliminary F-test provides against type-1 errors. Thus, Fisher's LSD is more than multiple unprotected t-tests. This method is appropriate to use when the compared populations have close similarities, such as is the case in crossover trials (Proschan et al., 1994). We used Fisher's LSD in study I and II, which were crossover trials.

Bonferroni adjustment is done to avoid type-1 errors in multiple comparisons. A Bonferroni adjusted P-value is the P-value multiplied with the number of outcomes being

tested in the multiple comparison test. Some biostatisticians dislike the Bonferroni correction because it is quite conservative and can cause a substantial loss of precision in the research findings (Altman, 1991; Perneger, 1998). However, Bonferroni adjustment is simple, well known, and do not necessarily affect the interpretation of the results. We used Bonferroni adjustments in Study III and IV.

Kruskall – Wallis test: A non-parametric alternative to the one-way ANOVA; used to compare the distributions of more than two independent groups of observations (Petrie, 2003). This test was used in Study III, IV and V.

Mann – Whitney U test: A non-parametric test comparing the distributions of two independent groups of observations. It is equivalent to the Wilcoxon rank sum test and the Kruskal-Wallis test for two groups. If significant differencences between the groups are found with a global Kruskal – Wallis test, subsequent comparisons between the groups with the Mann – Whitney U test can be done (Altman, 1991). This test was used in Study III, IV and V.

Logistic regression: A regression model giving the relationship between a binary dependent variable (pain/no pain) and a number of explanatory variables (Agresti, 1990). It can be considered as a generalized linear model that utilizes the logit as its link function. The logit function is the inverse of the "sigmoid", or "logistic" function. If p is a probability then $p/(1 - p)$ is the corresponding odds, and the logit of the probability is the logarithm of the odds; similarly the difference between the logits of two probabilities is the logarithm of the odds-ratio, thus providing an additive mechanism for combining odds-ratios. This test was used in Study V.

Chi-squared test: Used to analyse frequency data or proportions. It tests the null hypothesis that there is no association between the factors that define a contingency table (Altman, 1991). This test was used in Study III.

Fisher's exact test: A test that evaluates exact probabilities in a contingency table, used when the observed frequencies are small (Altman, 1991). This test was used in Study I, II, III, IV and V.

RESULTS

1. Effect of adding paracetamol (propacetamol) to an NSAID (ketorolac) on the tolerance to painful pressure (Study I)

A prospective, double blind, randomised, placebo controlled, *crossover* study was performed to evaluate the effect of i.v. propacetamol 2g (= paracetamol 1 g) and ketorolac 30 mg, individually and in combination, on PPTT in 16 volunteers on 4 separate days. PPTT was measured 15 minutes before and at 45, 60, 90 and 150 minutes after the start of test drug administration. The pressure stimuli were applied on the base of a fingernail, increasing by 30 kPa/sec until the pressure pain tolerance threshold was reached.

For the total observation period (150 min), only the combination (propacetamol + ketorolac) increased significantly PPTT compared with baseline ($P < 0.04$), while PPTT decreased significantly after placebo ($P < 0.01$). The combination (propacetamol + ketorolac) and ketorolac alone increased PPTT compared with placebo (combination vs. placebo and ketorolac vs. placebo, $P < 0.001$) and with propacetamol (combination vs. propacetamol and ketorolac vs. propacetamol, $P < 0.001$). The combination was significantly better than ketorolac alone ($P < 0.04$). After propacetamol 2g, PPTT did not change significantly neither compared with placebo nor with baseline.

2. Effect of a glucocorticoid (methylprednisolone) and an NSAID (ketorolac) on pressure pain detection and tolerance (Study II)

Effects of ketorolac and methylprednisolone on pressure pain detection threshold (PPDT) and pressure pain tolerance threshold (PPTT) were investigated in 12 male volunteers. A dose of ketorolac 60 mg, methylprednisolone 125 mg, or placebo was administered i.v. on three separate days with four days between in a double blind, placebo-controlled, randomised trial with crossover design. PPDT and PPTT were measured at 15 minutes before test drug infusion was started (baseline), and at 5, 10, 20, 30, 45, 60, 90, and 120 minutes after i.v. test drug injection. Pressure stimuli were applied on the base of a fingernail, increasing until the PPDT and PPTT were reached.

For the total observation period of 120 minutes ketorolac but not methylprednisolone increased PPDT compared with placebo (ketorolac vs. placebo, P < 0.05). No significant differences in PPDT were found between the active drugs. Both active drugs increased PPTT compared with placebo (methylprednisolone, P < 0.01; ketorolac, P < 0.001). Ketorolac increased PPTT significantly more than methylprednisolone (P < 0.05). From 30 minutes PPTT was significantly increased by both active drugs compared with placebo (P<0.05).

3. Effect of a glucocorticoid (methylprednisolone) and an NSAID (ketorolac) on experimental secondary hyperalgesia (Study II)

In Study II primary and secondary hyperalgesia were produced by a 12.5 cm² 1° burn injury on the abdominal skin 45 minutes before injection of the test medicines. Area of secondary hyperalgesia outside the site of injury was quantified by determining the area in which mechanical stimuli with a von Frey hair (50.6 mN) elicited a painful sensation. These measurements were done 30 min after burn injury and 15, 60 and 120 minutes after the drug injections.

Compared with placebo the active drugs reduced the area of secondary hyperalgesia for the total observation period of 120 minutes (methylprednisolone, P < 0.001; ketorolac, P < 0.01). No significant differences in secondary hyperalgesia were found between methylprednisolone and ketorolac. While methylprednisolone reduced the area of secondary hyperalgesia significantly already at 15 minutes and at all single observation time points compared with placebo (P < 0.01), ketorolac reduced the area of secondary hyperalgesia significantly from 60 minutes (P < 0.05)

4. Effect of preincisional methylprednisolone 125 mg or parecoxib 40 mg on acute postoperative pain after breast-surgery (Study IV)

We compared methylprednisolone 125 mg i.v. (n = 68) in a randomized, double blind parallel group comparison with parecoxib 40 mg i.v. (n = 68) and placebo (n = 68) given

immediately before breast augmentation surgery. Methylprednisolone and parecoxib decreased resting pain and dynamic pain intensity (0-10 NRS) from 1-6 hours following surgery compared with placebo (sum pain intensity using the last observation carried forward: methylprednisolone vs. placebo, P<0.03; parecoxib vs. placebo, P<0.001; sum dynamic pain intensity: methylprednisolone vs. placebo, P<0.004; parecoxib vs. placebo, P<0.001). Using a composite score of actual pain intensity and rescue analgesic use, the active drugs were almost identical and significantly superior to placebo (P<0.001). Rescue drug consumption and pain during the first 24 h were similar in the two active drug groups and significantly reduced compared with the placebo group.

5. Effect of preincisional methylprednisolone 125 mg or parecoxib 40 mg on emesis and fatigue after breast-surgery (Study IV)

In Study IV methylprednisolone, but not parecoxib, reduced postoperative nausea and vomiting (P<0.001) and fatigue (P<0.05) compared with placebo.

6. Effect of a glucocorticoid (methylprednisolone) or an NSAID (ketorolac) administered one day after surgery on pain and opioid-usage (Study III)

This was a prospective double blind, single dose, randomized, parallel comparison of intravenous methylprednisolone 125 mg, ketorolac 30 mg as an active control, and placebo in 75 patients with moderate to severe pain one day after orthopaedic surgery. Outcome variables were pain intensity (0-100 VAS), pain relief (0-4 PAR) and rescue opioid consumption.

Methylprednisolone was not significantly different from ketorolac and gave significantly lower pain intensity from one hour (0-6h, P<0.02), and more pain relief 2-6h after test drugs (P<0.05) compared with placebo. After twenty-four hours, pain intensity was lower in both active drug groups compared with placebo (methylprednisolone, P<0.0001; ketorolac, P<0.007). Number needed to treat (NNT) calculated from patients having more than 50% of maximum obtainable total pain relief during the first 6 h (>50%maxTOTPAR$_{6h}$) was 3.6 for methylprednisolone 125 mg and 3.1 for ketorolac 30 mg. NNT calculated from percentage *reporting* at least 50% pain relief for at least 4 hours (>50%PAR$_{4h}$) was 2.8 for both groups. Opioid consumption was significantly

reduced for 72 hours after methylprednisolone compared with ketorolac (P<0.02) and placebo (P<0.003).

7. Prevalence of and risk factors for chronic postoperative pain and sensory changes after augmentation-mammoplasty (Study V)

We studied the prevalence of chronic pain and long term sensory changes after cosmetic augmentation mammaplasty (n included = 219). A questionnaire was mailed 6 weeks and 1 year after surgery. Response rate after 1 year was 80% (n = 175). The prevalence of spontaneous non-evoked pain was 16% after 6 weeks and 13% after 1 year. Evoked pain decreased from 31% at 6 weeks to 20% at 1 year. Pain intensity in those having pain at rest and/or evoked pain was mostly low (1-3 on 0-10 NRS), but after 1 year 0.5% (1 patient) had strong to severe pain at rest (7-10 on 0-10 NRS) and 2.3% (4 patients) had strong to severe evoked pain. Pain interfered with activities of daily living in 25 % of patients after 6 weeks and 14 % after 1 year. Hyperesthesia did not change much from 47% at 6 weeks to 46% at 1 year. Hypoesthesia also showed minimal change: 47% at 6 weeks to 46% at 1 year. Factors associated with increased odds for pain at 1 year were intensity of pain during the first six days after surgery (sum pain intensity) (OR 1.3, 95% CI 1.1 to1.6), pain at 6 weeks (OR 18.4, 95%CI 6.9 to 49.3), hyperesthesia at 6 weeks (OR 2.3, 95% CI 1.1 to 5.1) and hyperesthesia present at 1 year (OR 3.1, 95% CI 1.4 to 6.7).

8. Long term effects of preincisional administration of a glucocorticoid (methylprednisolone) or a COX-2 inhibitor (parecoxib) on persistent postoperative pain and sensory dysfunction after augmentation-mammoplasty (Study V)

In Study V we studied the effects of a single i.v. preoperative dose of methylprednisolone 125 mg (n = 74), parecoxib 40 mg (n = 71), or placebo (n = 74) on persistent postoperative pain and sensory dysfunction after augmentation-mammaplasty. Methylprednisolone but not parecoxib was associated with reduced odds for hyperesthesia at 1 year (OR 0.3, 95% CI 0.1 to 0.6), and significantly reduced the prevalence of hyperesthesia (30%) compared with placebo (56%, P<0.01) and parecoxib

(51%, P<0.04). The active drugs neither affected hypoesthesia nor reduced chronic pain significantly.

DISCUSSION

I will discuss the findings of the five studies of this thesis, according to the objectives of the thesis, as follows:

1. while paracetamol (1g given i.v.) did not have significant effect alone, it increased the elevated pressure pain tolerance threshold caused by the non-selective NSAID ketorolac (30 mg given i.v.) in volunteers

2. while the glucocorticoid methylprednisolone (125 mg i.v.) and the NSAID ketorolac (60 mg i.v.) both increased the thresholds for pressure pain tolerance in male volunteers, only ketorolac increased the pressure pain detection threshold

3. methylprednisolone (125 mg i.v.) and ketorolac (60 mg i.v.) both reduced postburn secondary hyperalgesia in male volunteers

4. methylprednisolone (125 mg i.v.) and parecoxib (40 mg i.v.) given before surgery both reduced acute postoperative pain after breast augmentation surgery

5. methylprednisolone, but not parecoxib, reduced nausea and fatigue after breast augmentation surgery

6. methylprednisolone (125 mg i.v.) and ketorolac (30 mg i.v.) both reduced postoperative pain when given one day after orthopaedic surgery, and methylprednisolone reduced opioid rescue consumption for 72 hours

7. hypoesthesia, hyperesthesia, and persistent pain are common one year after breast augmentation surgery and the risk for chronic pain is increased in those with more severe prolonged acute pain, in those with pain and hyperesthesia at 6 weeks, and co-existent hyperesthesia at 1 year after surgery

8. methylprednisolone reduced hyperesthesia, but did not significantly reduce pain one year after breast augmentation surgery

1. Effect of adding paracetamol (propacetamol) to a non-selective NSAID (ketorolac) on the tolerance to painful pressure (Study I)

While paracetamol alone had no significant effect, the addition of paracetamol to ketorolac was significantly superior to ketorolac alone in this experimental pain model using pressure pain tolerance threshold (PPTT) as outcome measure. This finding indicates an additive effect and a potential advantage of combining paracetamol with ketorolac for acute pain.

Due to a standardised experimental model and a crossover design in the present study, it was possible to detect an interesting difference between the two active treatments at the 0.05 significance level with 16 subjects included. This demonstrates an adequate upside assay sensitivity (Stubhaug, 2003).

When we repeatedly applied high pressure to the base of a fingernail, a significant decrease in PPTT was observed during the placebo sessions indicating development of inflammation and sensitization. If a drug that only had effect on the peripheral sensitization of nociceptors (e.g. via reduction of prostaglandins) were given, the effect would be, in the best case, to bring the PPTT back to baseline. In the present study, the PPTT was not only brought back to baseline by ketorolac and the combination of ketorolac and paracetamol, but the PPTT did in fact increase significantly compared with baseline (a positive effect with time). This happened to a slight degree (not significant) after ketorolac alone, but a marked (and significant) increase in PPTT was observed during the whole observation period when paracetamol was added to ketorolac. Thus, paracetamol, which did not have any significant effect alone, markedly augmented the analgesic effect of ketorolac.

Possible reasons for the observed additive effects of paracetamol and ketorolac are that they most likely do have partly different mechanisms of analgesic action: Ketorolac causes analgesia mainly by inhibiting the COX-1 and COX-2 isoenzymes in peripheral, injured tissue, and in the CNS-pain modulating neuronal mechanisms. Paracetamol does have an effect on the serotonergic pain-inhibiting neuronal mechanisms in the CNS (Pickering et al., 2006). Moreover there are strong arguments for a COX-2 specific inhibition by paracetamol when arachidonic acid concentration is low (Graham and Scott, 2006), such as most likely is the case in the present acute pain model,

creating acute pain by rapidly increasing pressure on sensitive tissues. Drugs that have effect on a process via different mechanisms of action are likely to have supra-additive effects when coadminstered (Berenbaum, 1989).

The present experimental study confirms the results from clinical trials (Breivik et al., 1999; Miranda et al., 2006) finding additive effect of combining paracetamol with an NSAID for relief of acute postoperative pain.

2. Effects of a glucocorticoid (methylprednisolone) and a non-selective NSAID (ketorolac) on pressure pain detection and tolerance (Study II)

Ketorolac but not methylprednisolone increased the pressure pain detection tolerance. Methylprednisolone and ketorolac significantly increased the threshold for pressure pain tolerance. No previous trials have investigated the effect of glucocorticoids on pressure pain thresholds. Study II confirmed other trials documenting analgesic effects from glucocorticoids (Skjelbred and Løkken, 1982; Aasbø et al., 1997; Bisgaard et al., 2003; Afman et al., 2006).

Ketorolac increased the pressure pain tolerance threshold significantly more than methylprednisolone and documented adequate assay-sensitivity of Study II. This effect on pressure pain detection and tolerance of NSAIDs has been documented previously (Study I).

Repetitive painful high pressure stimuli such as PPTT will likely result in an acute inflammatory reaction and peripheral as well as central sensitization and are thus an appropriate model evaluating drugs for postoperative pain (Luginbuhl et al., 2001). However, in the present study PPTT during the placebo sessions did not decrease as it did in Study I. This can indicate that the importance of inflammation and sensitization in this pain model must not be exaggerated. Another explanation for the differences in PPTT between Study I and II in PPTT during the placebo sessions may be that only men were included in Study II, while both men and women were included in Study I. In pressure pain testing males generally have higher thresholds compared with females (Brennum et al., 1989; Chesterton et al., 2003). Pressure pain tolerance threshold (PPTT) seems to correlate better with clinical pain than pressure pain detection threshold (PPDT)

(Luginbuhl et al., 2001). In the present study PPTT differentiated between the active drugs, and appeared to be a more sensitive variable for the test drug effects than PPDT.

3. Effects of a glucocorticoid (methylprednisolone) and a NSAID (ketorolac) on experimental postburn secondary hyperalgesia
(Study II)

Both active drugs reduced the area of secondary hyperalgesia after a skin burn injury, methylprednisolone 125 mg somewhat more, but not significantly more than ketorolac 60 mg. After the skin burn injury, all subjects developed an area of primary hyperalgesia characterised by a lowered heat pain threshold. In all subjects we found an area of secondary hyperalgesia surrounding the site of injury, characterised by increased response to mechanical punctate stimuli. Central sensitization demonstrated by development of secondary hyperalgesia after the burn injury in the present trial, is a clinically relevant measurement of the neuroplastic component of acute pain (Stubhaug et al., 1997).

Effect of methylprednisolone

We found a significant reduction of secondary hyperalgesia already 15 min after administration of methylprednisolone. Glucocorticoid effects requiring protein synthesis have about 2 hour's latency of onset (Ferreira et al., 1997; Hay and de Belleroche, 1998). Our findings indicate rapid analgesic and anti-hyperalgesic mechanisms not linked to peripheral anti-inflammatory or central effects requiring protein synthesis. After oral surgery significant pain-reduction has been observed before 45 minutes (Skjelbred and Løkken, 1982). Rapid and striking anti-hyperalgesic effects of glucocorticoids have been demonstrated in animals (Ferreira et al, 1997; Roach and Sufka, 2003). An explanation for the rapid effect may be a non-genomic steroid action that have been recognised in the past few years and it indicates that rapid steroid effects on central nervous function may occur (Wehling, 1997). These rapid actions seem to be transmitted by specific membrane receptors. Binding sites in membranes have been characterised, and they display binding features compatible with an involvement in rapid steroid signalling (Gerdes, 2000; Falkenstein et al., 2000). The mechanism of action is probably a membrane receptor -

second messenger cascade (Wehling, 1997). Documented rapid non-genomic effects of glucocorticoids (dexamethasone) are decreased glutamate release and increased GABA and endocannabinnoid release (Di et al., 2003 and 2005). By decreasing glutamate and increasing GABA, glucocorticoids would be expected to cause a marked reduction in excitability of nerve cells *in vivo* (Di et al., 2005).

A theoretic possibility therefore, is that both non-genomic and genomic steroid actions are responsible for the analgesic and anti-hyperalgesic effect, where the non-genomic mechanisms lead to the rapid analgesia and anti-hyperalgesia (minutes) and the genomic mechanisms give a sustained analgesia and anti-hyperalgesia (hours - days). Other mechanisms responsible for the anti-hyperalgesic effect of glucocorticoids may be COX-2 inhibition, reduced PGE_2 stimulation of prostaglandin (EP) receptors in the dorsal horn and thereby reduced NMDA channel opening, reducing the excitatory effect of glutamate further (Svennson and Yaksh, 2002). The anti-hyperalgesic effects of central COX-2 and iNOS inhibition have been studied in rats (Wu et al., 2001; Svennson and Yaksh, 2002) and in humans (Koppert et al., 2003; Sycha et al., 2005). Glucocorticoids also induce expression of the anti-inflammatory cytokine Il10 and reduce the activation of nuclear factor-kappa (NF-κB). Activated NF-κBin the glia induce COX-2 and proinflammatory cytokines that contribute to central sensitization, resulting in lower pain thresholds and spontaneous neuronal firing, manifested as allodynia and hyperalgesia (Xie et al., 2006).

No studies have previously found attenuation of secondary hyperalgesia after systemic or topical administration of glucocorticoids in humans (Pedersen et al., 1994; Werner et al., 2002). Achieving the necessary plasma- and CSF-concentration with topical steroids, may be difficult. It is probably necessary to use high enough doses intravenously. Werner et al. used lower doses than we did in the present study (8 mg dexamethasone is equipotent with about 40 mg methylprednisolone).

Chronic neuropathic pain occurs in 5-80% of patients after surgery (Macrae, 2001). If persistent pain after surgery at least in part is associated with CNS sensitization, prevention or at least reduction in severity may be possible if sensitization can be blocked (Perkins and Kehlet, 2000). Recently, De Kock et al. (2005) demonstrated that reducing the area of hyperalgesia with intrathecal clonidine after colectomy did not greatly reduce

acute pain, but was associated with a significant decrease in the number of patients who developed residual pain as late as six months after colectomy. It might be that the area of hyperalgesia could predict patients likely to develop persistent pain after surgery.

Theoretically therefore, anti-hyperalgesic drugs such as steroids may reduce development of chronic posttraumatic pain by reducing central sensitization and secondary hyperalgesia (Stubhaug et al., 1997).

Effect of ketorolac

The present trial is the first to document reduction of secondary hyperalgesia after a non-selective NSAID. COX-2 selective NSAIDs (rofecoxib and parecoxib) and paracetamol have been documented to reduce secondary hyperalgesia in other trials (Koppert et al., 2003; Sycha et al., 2005). Non-selective NSAIDs have anti-hyperalgesic effects in rats in a dose dependent manner (Bianchi and Panerai, 2002; Kang et al., 2002; Burian and Geisslinger, 2005). The analgesic and anti-hyperalgesic effect of NSAIDs in rats seem to be more evident after blockade of both COX-1 and COX-2 (Bianchi and Panerai 2002; Zhu and Eisenach, 2003). However, although non-selective NSAIDs have been shown to have anti-hyperalgesic effect in animals (Svennson and Yaksh, 2002), previous human studies on NSAIDs (ibuprofen and ketorolac) have failed to confirm these findings (Møiniche et al., 1993; Warncke et al. 1996; Petersen et al. 1997; Kumar et al., 2006). These studies differ from the present study in several ways: While we used a high intravenous bolus of ketorolac post injury in a burn model, Warncke et al used topical ibuprofen post-injury or oral ibuprofen 600 mg before injury. Møiniche et al used topical ketorolac before and after injury. Petersen et al used oral Ibuprofen 600 mg before injury. Kumar et al used 60 mg ketorolac i.v. in an intramuscular capsaicin deep tissue model where ketorolac was insensitive as an analgesic. Since previous studies with topical NSAIDS in a similar model were negative, one might speculate that the effects observed in our study were mediated by central nervous mechanisms.

4. Effects of a glucocorticoid (methylprednisolone) or a COX-2 inhibitor (parecoxib) given preincisionally on acute pain after breast-augmentation surgery (Study IV)

A single-dose of i.v. methylprednisolone 125 mg before breast augmentation surgery had a marked analgesic effect, but not significantly different from parecoxib 40 mg i.v. Compared with placebo, the active drugs caused a significantly lower consumption of rescue analgesics on the day of surgery.

This was a single-centre study with a high number of patients (n = 219) of the same gender and within narrow age limits, undergoing a highly standardized surgical procedure by the same two surgeons, producing considerable pain and inflammatory reaction from the surgical tissue trauma. Satisfactory assay-sensitivity was documented by a significant difference in outcome measures between the active control drug (parecoxib) and placebo.

About half of the patients in all groups had taken rescue analgesics during the first two hours postoperatively, partly reflecting the nursing staff routine of offering these ambulatory patients analgesics. This secured pain relief before the patients left the clinic after about 120 minutes after end of surgery. However, a problem in the interpretation of the pain intensity data based on the conventional last observation carried forward (LOCF) method was created. The number of patients that had not taken rescue declined rapidly, and the statistical calculations were therefore based on a decreasing number of real pain observations after test drug only, without the effects of rescue analgesics, reducing the validity of the statistical calculations based on LOCF (Max and Laska, 1991). We therefore calculated a *composite score* from actual pain observations and rescue analgesic consumption during the first 6 hours.

The results from this composite score (modified after Silverman et al., 1993) were similar for the two active drugs and both were significantly superior to placebo, for pain at rest as well as dynamic pain. Thus, in the present trial, the data based on LOCF, and the data based on integration of actual pain and rescue analgesics consumed, led to the same conclusion: both active drugs were significantly better than placebo and not different from each other. However, the integrated assessment differentiated even better between the active drugs and placebo. This was not a surprise since both the actual pain intensity ("raw pain data") and the use of rescue analgesics were significantly lower in

the active drug groups compared with the placebo group. I refer to "METHODOLOGICAL CONSIDERATIONS" for further explanation of the composite score calculations.

Some studies on e.g. major abdominal surgery have not been able to document definite analgesic effect of glucocorticoids (Holthe and Kehlet, 2002). Confounding factors such as differences in anaesthesia methods, surgical technique, other adjuvant therapies, main focus on other outcome variables than pain, and small sized studies with low power, may have contributed to negative outcome in those studies. Trials using less than dexamethasone 8 mg or methylprednisolone 40 mg seem to be less likely to give quantifiable analgesic effects (Holthe and Kehlet, 2002). During and after major surgery the endogenous glucocorticoids reach such high levels that the benefit of additional, exogenous glucocorticoids on pain may be small. But even in major surgery benefits have been demonstrated on other variables such as reduced inflammatory response, improved pulmonary function, less fatigue, increased appetite, less PONV, and more rapid convalescence (Bisgaard et al., 2003; Halvorsen et al., 2003).

5. Effects of a glucocorticoid (methylprednisolone) or a COX-2 inhibitor (parecoxib) given preincisionally on emesis and fatigue after breast-augmentation surgery (Study IV)

In Study IV methylprednisolone reduced the total number of adverse-events, most importantly PONV, during the first 24 hours. PONV is the main cause of delay in discharge from the outpatient department and unanticipated hospital readmission after ambulatory surgery (Sinclair et al., 1999). After breast surgery the incidence of PONV can be 60-80% (Wattwil et al., 2003). In this trial the incidence was 60% in the placebo group. After methylprednisolone PONV was effectively reduced both in incidence (30%) and severity during the first 24 hours compared with placebo. Parecoxib did not reduce PONV compared with placebo. These findings are in agreement with those of Apfel and colleagues (2004).

After even uncomplicated surgery patients can feel tired and washed out. They often need to sit or lie down, and need to sleep more. These symptoms can be defined as

postoperative fatigue (The Oxford Pain Internet Site, 2002). Steroids may cause elevated mood, even euphoria, and a feeling of increased energy (Plihal et al., 1996). This may reduce postoperative fatigue as observed in our study IV with reduced incidence and severity of postoperative fatigue after methylprednisolone compared with placebo. This agrees with the conclusions of a systematic review by Rubin and Hotopf (2002).

6. Effect of a glucocorticoid (methylprednisolone) or an NSAID (ketorolac) administered one day after surgery on pain and opioid-usage (Study III)

On the day after orthopaedic surgery, in patients with moderate to severe pain at rest, i.v. methylprednisolone 125 i.v. mg had a marked analgesic effect similar to that of ketorolac 30 mg i.v., although of slightly slower onset. Compared with ketorolac 30 mg, methylprednisolone 125 mg resulted in somewhat lower pain intensity 24 hours after test medication in spite of significantly less consumption of opioid. This more pronounced opioid-sparing effect of methylprednisolone compared with ketorolac continued during the following two postoperative days.

Satisfactory assay-sensitivity was documented in Study III by a significant difference in outcome measures of the active control drug (ketorolac) compared with placebo.

There is a frequently repeated statement in the literature that steroids have better analgesic effect when it is given at a time point so that inflammation is prevented or reduced, i.e. when it is given early in the inflammatory process, preferably before or at the latest soon after the end of surgery (Holthe and Kehlet, 2002; Bisgaard et al., 2003; Bisgaard, 2006). The anti-inflammatory effect of course is important for analgesia, but by giving a glucocorticoid on the day after surgery to patients with moderate to severe pain, we also expected to be able to measure the onset time of any analgesic effect.

Study III demonstrated clearly that a glucocorticoid can cause pain relief even after the inflammatory pain component with peripheral and central sensitization is well established on the day after orthopaedic surgery. The fairly rapid onset of analgesic effect after methylprednisolone 125 mg i.v., indicates that mechanisms different from the genomic anti-inflammatory mechanisms also must have contributed to the analgesic

effect. The anti-inflammatory effects of glucocorticoids are thought to take about 2 hours to come into full effect after an intravenous dose (Holthe and Kehlet, 2002; Bisgaard, 2006). The prolonged opioid-sparing effect continuing for 72 hours, point to long-lasting effects on postoperative inflammatory pain. This very prolonged opioid-sparing effect can only partly be explained by the duration of biological activity of methylprednisolone, which is estimated to about 36 hours after a dose of 125 mg i.v. (Holthe and Kehlet, 2002). Reduction of sensitization of neurons in the spinal cord (central sensitization) via reducing postoperative secondary hyperalgesia (Study II) may have contributed to this prolonged opioid-sparing effect.

Measuring onset of analgesia by using stopwatches (Laska et al., 1991), noting first perceptible and first meaningful pain relief, discriminated between the rapid onset of ketorolac and the slower onset of methylprednisolone and placebo. But it did not discriminate between the latter two. The majority of patients in all three groups reported meaningful pain relief. This occurred after 5 minutes in the ketorolac group and after 9 minutes in the other two groups. Thus, in Study III, the stopwatch method appeared to be strongly influenced by the early onset subjective placebo effects: Pharmacological onset of analgesia as illustrated by the time course of decreasing pain intensity came somewhat later.

In the present trial we used the pain relief variable to derive the dichotomous variable 50%maxTOTPAR and then calculate NNT (see "METHODOLOGICAL CONSIDERATIONS"). We also calculated NNT from 50%PAR ("pain half gone") to obtain more directly derived variables. Complicated calculations for obtaining new variables can be questioned. The derived variables are not identical with the original variables and information may be lost when making dichotomous outcome measures out of continuous or several categories variables. The NNT values calculated from 50%PAR, and from 50%max TOTPAR were within the confidence intervals found in a meta-analysis published by Smith et al. (2000) using the calculated 50%maxTOTPAR for ketorolac, indicating that more directly derived variables may be at least as good as those obtained from complicated calculated calculations. We suggest that directly reported dichotomous data merit further evaluation in future studies.

7. The prevalence of and risk factors for chronic postoperative pain and sensory changes after cosmetic augmentation-mammoplasty (Study V)

After augmentation-mammoplasty the prevalence of spontaneous non-evoked pain was 16% after 6 weeks and 13% after 1 year. Evoked pain decreased from 31% at 6 weeks to 20% at 1 year. Pain intensity in those having pain at rest and/or evoked pain was mostly low (1-3 on 0-10 NRS), but after 1 year 0.5% had strong to severe pain at rest (7-10 on 0-10 NRS) and 2.3% had strong to severe evoked pain. For these patients activities of daily life were seriously affected by pain. Hyperesthesia did not change much from 6 weeks (31% in the methylprednisolone group, 49% in the parecoxib group, and 57% in the placebo group) to 1 year (30% in the methylprednisolone group, 51% in the parecoxib group, and 56% in the placebo group). Pain interfered with activities of daily living in 25 % of patients after 6 weeks and 14 % after 1 year. Most of the patients were mildly affected and none were severely impaired after 1 year.

The prevalence of pain in Study V was comparable to that reported 1 year after subglandular implants after breast augmentation (21%) in the trial of Wallace et al. from 1996. Large studies done by the implant manufacturers INAMED (901 included) and MENTOR (1,264 included) for FDA approval, but not published in any medical journal, showed pain rates of 5-16% at 3 years and 7-17% at 5 years after cosmetic breast implant surgery (U.S. Food and Drug Administration, 2004). These numbers indicate that pain is relatively common several years after breast augmentation.

The sensory changes documented in the present trial were largely in concert with results from other types of breast surgery. Three months after axillary clearance for breast cancer Abdullah et al. (1998) found an 84% prevalence of sensory deficits in patients in whom the intercostobrachial nerve had been sectioned, and a 54% prevalence of sensory deficits when section of the intercostobrachial nerve had not been documented. One year after breast cancer surgery sensory impairment occurred in 75% after both radical and tissue conserving surgery (Tasmuth et al. 1996).

The sensory deficits in our study, consistent with injury to lateral and cutaneous branches of the 3rd, and/or 4th, and/or 5th intercostal nerves, were in accordance with the

findings of Schlenz et al. (2000). In the present study hypoesthesia seems to indicate nerve transection, as this had not changed much between 6 weeks and 1 year after surgery. Even though local and systemic administration of glucocorticoids in previous trials have improved functional nerve recovery and nerve regeneration (Graham et al., 1973; Lipton et al., 1986; Yates et al., 2004), none of the active drugs affected hypoesthesia in the present trial. However, some patients reporting hyper- or hypoesthesia at 6 weeks did not report this at 1 year, and vice versa, indicating improvement for some, and deterioration for others.

Of those having rest pain or evoked pain at 6 weeks and 1 year, 22 and 21% respectively did not report sensory changes. It might be that hypo- or hyperesthesia was concealed (overshadowed?) by pain in some of these patients. But the subjective experience of coexistent pain and sensory changes is complicated. Trials investigating chronic pain and sensory changes after surgery do not always find a consistent relationship between pain and sensory deficits (Mikkelsen et al. 2003). According to Gottrup et al. (2000), the tolerance for sensory stimuli is lower (hyperesthesia) in areas of pain with a relative preservation of sensory function in the same areas. It thus seems that pain reveals hyperesthesia rather than masking it. In the same study Gottrup found less loss of sensation in patients with pain after surgery. In a recent trial (Kompatsher et al., 2004) 21% of the patients had subjective sensory impairment 2 years after breast augmentation, but all patients had objective sensory impairment. It may be that patients tend to report what bothers them most, but do not meticulously account sensory changes that are not as annoying as pain.

Our study documents that patients having postoperative pain lasting for 6 weeks most likely will have pain also after 1 year (odds ratio 18.4). Acute postoperative pain during the first 6 days and hyperesthesia at 6 weeks also increased the odds for persistent postoperative pain. These results support the findings from previous studies after other types of surgery where the severity and duration of acute postoperative pain are the most striking predictive factors for persistent pain (Katz et al., 1996; Callesen et al., 1999).

Persistent pain and hyperesthesia reported by our patients may indicate central sensitization in the spinal cord dorsal horn, while hypoesthesia indicates peripheral nerve injury (Basbaum 1999; Woolf and Salter, 2000).

8. Effects of a glucocorticoid (methylprednisolone) or a COX-2 inhibitor (parecoxib) on persistent postoperative pain and sensory dysfunction after augmentation-mammoplasty

(Study V)

The prevalence of hyperesthesia was relatively high at 6 weeks and 1 year giving power to detect clinically interesting differences between the groups: Methylprednisolone but not parecoxib reduced hyperesthesia after 6 weeks and 1 year compared with placebo. Methylprednisolone, selective COX-2 inhibitors, and non-selective NSAIDs can inhibit or impede the neuronal mechanisms behind development of central sensitization and secondary hyperalgesia, phenomena which may be associated with hyperalgesia, allodynia and chronic pain (Ferreira et al., 1997; Koppert et al., 2003; Sycha et al., 2005; Study II). Attenuation of hyperesthesia by glucocorticoids has been demonstrated in previous trials. Steroids given after oral and orthognathic surgery have prevented sensory hypersensitivity (Barron et al., 2004; Seo et al., 2004). The present trial supports these findings.

Since methylprednisolone reduced hyperesthesia and hyperesthesia was associated with increased odds for evoked pain, one might expect to find a significant effect of methylprednisolone on evoked pain. But the differences in evoked pain intensity (0-10 NRS) did not reach statistical significance (P=0.085). The number of patients having significant persistent pain was relatively low, giving low power for testing a possible preventive effect on chronic postsurgical pain. Thus, larger studies are needed to test the potential of glucocorticoids for preventing chronic pain after surgery.

CONCLUSIONS

1. Adding paracetamol 1g (as propacetamol 2 g) i.v. to ketorolac 30 mg i.v. markedly augmented pressure pain tolerance threshold caused by ketorolac 30 mg alone. Paracetamol 1g i.v. (alone) did not increase the pressure pain tolerance (Study I).

2. The thresholds for pressure pain tolerance increased significantly after both methylprednisolone 125 mg i.v. and ketorolac 60 mg i.v. Pressure pain tolerance threshold increased significantly more after ketorolac than after methylprednisolone. Ketorolac but not methylprednisolone, gave a significant increase in the threshold for pressure pain detection (Study II).

3. Both methylprednisolone 125 mg i.v. and ketorolac 60 mg i.v. reduced the areas of secondary hyperalgesia after a thermal skin injury (Study II).

4. Compared with placebo, methylprednisolone 125 mg i.v. given immediately before breast augmentation surgery had analgesic and rescue analgesic sparing effects similar to those of parecoxib 40 mg i.v. (Study IV).

5. Methylprednisolone, but not parecoxib, reduced postoperative emesis and fatigue (Study IV).

6. Methylprednisolone 125 mg administered i.v. *one day after* surgery gave similar early reduction of pain and duration of analgesia compared with i.v. ketorolac 30 mg. Methylprednisolone had a slower onset compared with ketorolac. Less pain than placebo 24 hours after methylprednisolone and less opioid consumption for 72 hours compared with ketorolac and placebo indicated a sustained analgesic effect of one dose of methylprednisolone 125 mg (Study III).

7. Chronic pain and sensory changes are common after augmentation mammoplasty and patients having pain at 6 weeks most likely will have pain also at 1 year.

Other factors associated with pain at one year were pain during the first 6 postoperative days, hyperesthesia at 6 weeks, and the presence of hyperesthesia 1 year after surgery (Study V).

8. Although preoperative methylprednisolone significantly reduced the prevalence of hyperesthesia 1 year after augmentation mammoplasty, it had no significant effect on the prevalence of spontaneous or evoked pain at 6 weeks and 1 year after surgery. Parecoxib did not have any effect on chronic pain or sensory changes after surgery (Study V).

CLINICAL IMPLICATIONS

Opioids are effective in relieving severe postoperative pain, but opioids also frequently cause adverse effect in bowel function, nausea and sedation. Such adverse effects are unpleasant and impede rehabilitation after surgery (Breivik et al., 2007). In order to augment non-opioid analgesia for acute pain, it is appropriate to combine an NSAID with paracetamol (Study I). One perioperative dose of a glucocorticoid reduces acute pain, postoperative nausea and vomiting, and fatigue (Study III and IV). This makes glucocorticoids particularly useful in ambulatory anaesthesia (Study IV). Central sensitization (seen as secondary hyperalgesia) appears after a tissue injury and is prevented by both methylprednisolone (glucocorticoid) and ketorolac (NSAID) (Study II). This may reduce the risk of transition of acute pain and hyperesthesia to a chronic condition. This is common after most types of surgery, including cosmetic breast augmentation, as revealed in the present thesis (Study V). However, although persistent sensory changes were significantly reduced, chronic pain was not significantly reduced by methylprednisolone in Study V.

Although the NSAID (ketorolac i.v.) in our studies had a faster onset (Study III) and a more potent analgesic effect compared with a glucocorticoid (methylprednisolone i.v.) in Study II, an appropriate dose of methylprednisolone had analgesic effects that were more sustained after surgery than ketorolac (Study III). None of our studies are large enough to achieve reliable safety data. However based on a meta-analysis (Sauerland et al., 2000) and Study II-V, a single perioperative dose of a glucocorticoid is a safe and valuable adjunct analgesic that also has positive effects on other postoperative symptoms, most importantly fatigue, PONV, and chronic hyperesthesia.

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