Department of Anaesthesiology and Intensive Care Medicine,
Töölö Hospital,
Helsinki University Central Hospital,
Helsinki, Finland

Patient-controlled postoperative analgesia: comparison of efficacy, side-effects and safety of various regimens

Marja Silvasti

ACADEMIC DISSERTATION

To be presented, with the assent of the Faculty of Medicine, University of Helsinki, for public examination in the Auditorium of Töölö Hospital, Helsinki University Central Hospital, Helsinki, on April 28th, 2001, at 12 noon.

Helsinki 2001

Supervisor

Docent Mikko Pitkänen
Department of Anaesthesiology and Intensive Care Medicine
Töölö Hospital
Helsinki University Central Hospital
Helsinki, Finland

Reviewers

Docent Irma Tigerstedt
Department of Anaesthesiology and Intensive Care Medicine
Pain Clinic
Helsinki University Central Hospital
Helsinki, Finland

Professor Arvi Yli-Hankala
Department of Anaesthesia
Tampere University Central Hospital
Tampere, Finland

Opponent

Docent Olli Kirvelä
Department of Anaesthesiology and Intensive Care Medicine
Eye Hospital
Helsinki University Central Hospital
Helsinki, Finland

ISBN 952-91-3297-2
ISBN 951-45-9903-9 (pdf version)
http://ethesis.helsinki.fi
Yliopistopaino
Helsinki 2001

'How to barbecue an elephant?
Slice by slice!'

To Tomi

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications, which will be referred to in the text by their Roman numerals I-V.

I Silvasti M, Rosenberg P, Seppälä T, Svartling N, Pitkänen M.
Comparison of analgesic efficacy of oxycodone and morphine in postoperative intravenous patient-controlled analgesia.
Acta Anaesthesiologica Scandinavica 1998; 42: 576-580.

II Silvasti M, Tarkkila P, Tuominen M, Svartling N, Rosenberg PH.
Efficacy and side effects of tramadol versus oxycodone for patient-controlled analgesia after maxillofacial surgery.
European Journal of Anaesthesiology 1999; 16: 834-839.

III Silvasti M, Svartling N, Pitkänen M, Rosenberg PH.
Comparison of intravenous patient-controlled analgesia with tramadol versus morphine after microvascular breast reconstruction.
European Journal of Anaesthesiology 2000; 17: 448-455.

IV Silvasti M, Pitkänen M.
Continuous epidural analgesia with bupivacaine-fentanyl versus patient-controlled analgesia with i.v. morphine for postoperative pain relief after knee ligament surgery.
Acta Anaesthesiologica Scandinavica 2000; 44: 37-42.

V Silvasti M, Pitkänen M.
Patient-controlled epidural analgesia versus continuous epidural analgesia after total knee arthroplasty.
Acta Anaesthesiologica Scandinavica 2001, in press.

ABBREVIATIONS

ASA	the classification of physical status (I-V) according to the American Society of Anesthesiologists (*American Society of Anesthesiologists 1963; Schneider 1983*)
DSST	Digit Symbol Substitution Test
ECG	electrocardiogram
EPI	continuous epidural infusion (Study V)
F5	continuous epidural infusion with bupivacaine 1 mg/ml and fentanyl 5 µg/ml (Study IV)
F10	continuous epidural infusion with bupivacaine 1 mg/ml and fentanyl 10 µg/ml (Study IV)
G	Gauge (international calibre unit)
5-HT	5-hydroxytryptamine, serotonin
i.m.	intramuscular(ly)
i.v.	intravenous(ly)
ME(A)C	minimum effective (analgesic) concentration
NSAID	non-steroidal anti-inflammatory drug
PCA	patient-controlled analgesia
PCEA	patient-controlled epidural analgesia
p.o.	peroral(ly)
PONV	postoperative nausea and vomiting
S	continuous epidural infusion with saline (Study IV)
s.c.	subcutaneus(ly)
SD	standard deviation
VAS	visual analogue scale
VRS	verbal rating scale

1. ABSTRACT

Patient-controlled analgesia (PCA) has been used for the past 30 years as an alternative method to administer postoperative analgesia. PCA allows patients to self-administer small boluses of opioids, providing better dose titration and regulation. The quantity of analgesic available to the patient is limited by the prescribed PCA variables; demand dose size, lockout period and hourly or 4-hourly limits. The aim of the present series of studies was to examine which analgesic: oxycodone, morphine or tramadol, would be the best alternative in PCA after orthopaedic, maxillofacial or plastic surgery. In addition, a comparison was made of epidural bupivacaine-fentanyl infusion along with i.v. PCA, and along with patient-controlled epidural analgesia (PCEA).

A total of 274 patients were assigned to receive opioids by either i.v. patient-controlled analgesia (220 patients), epidural infusion (64) or patient-controlled epidural analgesia (27). In patients undergoing a plastic reconstruction of the breast or a major operation on the vertebral column, the hypothesis was tested that the efficacy of oxycodone differs from that of morphine in postoperative pain treatment with i.v. PCA. In a prospective, double-blind, randomized study, tramadol was compared with oxycodone in PCA after maxillofacial surgery. Sixty women scheduled to undergo microvascular breast reconstruction under standard general anaesthesia were enrolled in a study on the performance of i.v. PCA with tramadol or morphine, and drug- and technique-related side-effects were compared. The efficacy, safety, side-effects, and patient satisfaction of epidural bupivacaine-fentanyl analgesia and intravenous PCA with morphine were compared after elective anterior cruciate ligament reconstruction of the knee. The efficacy of bupivacaine-fentanyl PCEA and continuous epidural infusion with the same mixture for treatment of pain after total knee arthroplasty were compared.

Analgesia was similar with oxycodone, morphine or tramadol in PCA. There appears to be no clear advantage to using one opioid over the others, with each producing a similar incidence of side-effects, except that tramadol was associated with a disturbingly high incidence of nausea and vomiting. To diminish the nausea and vomiting associated with PCA, it is recommended to add a prophylactic antiemetic to i.v. opioid PCA.

PCEA compared with continuous bupivacaine-fentanyl epidural infusion provided equal analgesia but was associated with a dose-sparing effect of 40%.

PCA and PCEA were shown to achieve high patient satisfaction, but despite this, a significant number of patients experienced troublesome side-effects, especially nausea and vomiting. The incidence of serious complications such as respiratory depression with hypoxaemia or pneumonia was low both with i.v. PCA with three different analgesics and with PCEA.

2. INTRODUCTION

Despite constantly increasing understanding of pain mechanisms and improved technology in pain therapy for the anaesthetist, the provision of adequate postoperative pain relief is still a challenge. Unfortunately, postoperative pain relief, which is conventionally provided by parenteral medication, is often incomplete (*Keeri-Szanto and Heaman 1972; Tammisto 1978; Tammisto and Tigerstedt 1982; Ready 1999*). As far as we know, conventional prescription of opioids—to be given by nurses 'as required'—seldom produces an adequate level of analgesia. In addition, it is impossible to accurately predict what analgesic dosage will be required to provide sufficient pain relief or how much pain a patient will experience after an operation. Adequate pain control may even improve recovery from surgery by reducing stress and improving pulmonary function (*Craig 1981; Bonica 1987; Kehlet 1989, 1994; Scott and Kehlet 1988*). Optimal postoperative analgesia may also reduce postoperative complications and shorten postoperative recovery (*Kehlet 1994; de Leon-Casasola et al. 1994*).

Patient-controlled analgesia (PCA) has become an established technique for the treatment of postoperative pain (*Sechzer 1968; Scott 1970; Keeri-Szanto 1971; Tammisto 1978; Ready 1990; Zimmermann and Stewart 1993; Lehmann 1995).* It has been shown to offer a number of advantages, including good analgesia, avoidance of fluctuations in analgesia, lower total analgesic dosage, and improved patient satisfaction. This method allows self-administration of small, frequent doses of analgesics to maintain a state of constant pain control.

The effectiveness and safety of PCA with a number of opioids have already been demonstrated (*Lehmann 1995; Ready 2000*); however, the optimal opioid has not yet been found. The typical side-effects of opioids, such as nausea and vomiting, sedation, respiratory depression, and pruritus may sometimes hamper the successful application of PCA (*Nottcutt and Morgan 1990; Lehmann 1993; Baxter 1994*). On the other hand, oxycodone, which is the most commonly used parenteral opioid for postoperative pain in Finland (*Pöyhiä 1994*), has not yet been studied for its efficacy in PCA.

The concept of patient-controlled epidural analgesia (PCEA) is derived from PCA, and PCEA has been successfully used for obstetric analgesia (*Gambling et al. 1988; Viscomi and Eisenach 1991; Parker et al. 1992b; Parker and White 1992*). PCEA may also be suitable for postoperative analgesia after orthopaedic operations (*Liu et al. 1998*). As with PCA, it allows the patient to be in control of the dosing and timing of analgesia.

The purpose of the present study was to evaluate the potency, efficacy, and side-effects of three analgesics, e.g., oxycodone, morphine, and tramadol, in PCA and to compare continuous epidural infusion, i.v. PCA, and PCEA in postoperative analgesia. Patient satisfaction with i.v. PCA and PCEA, and the safety of these methods in postoperative pain management were also investigated.

3. REVIEW OF THE LITERATURE

3.1. PATIENT-CONTROLLED ANALGESIA (PCA)

3.1.1. Principles and development of PCA

Traditional techniques for the provision of postoperative analgesia by intermittent i.v. or i.m. injections of an opioid drug do not meet the needs of every patient. Patient-controlled analgesia (PCA) allows patients to self-administer small boluses of opioids, providing better dose titration and regulation (*Bennett et al. 1982b*). This avoids the 'peak and valley' effects encountered with conventional i.m. administration of analgesics. Stable drug plasma concentration is an important goal of postoperative pain management. When using PCA, the plasma concentration at which the patient becomes sufficiently uncomfortable to make a dose demand has become known as the minimum effective (analgesic) concentration (ME(A)C) (*Dahlström et al. 1982; Gourlay et al. 1988; Lehmann 1995; Woodhouse and Mather 2000*). Intrapatient variation in MEC for morphine in the treatment of postoperative pain has been relatively small (*Dahlström et al. 1982*), but interindividual variation in the plasma concentration of opioid required to achieve adequate pain relief has been large (*Dahlström et al. 1982; Gourlay et al. 1988).* As a result, self-administration of opioids after abdominal and orthopaedic surgery has been characterized by considerable variability in individual morphine consumption (*Lehmann et al. 1985*).

An important advantage of PCA is its ability to minimize the time-delay between perception of pain and administration of medication (*Lutz and Lamer 1990*).

The first attempts to establish i.v. PCA were made in the late 1960s, after PCA with intermittent i.v. doses of narcotic analgesics was first described by Philip Sechzer (*Sechzer 1968, 1971, 1990*), who reported that such a patient-controlled analgesic-demand system for the alleviation of pain and for the reliable measurement of pain and pain relief had been under study since 1965. In this system, patients when they felt pain during recovery from surgery were instructed to press a button. When this button was pressed, a nurse observer administered 1 ml of a pethidine- or morphine-containing solution (*Sechzer 1968, 1971*). At the same time, the concept of PCA was developed independently in the U.K. by Scott, who permitted the patients to operate a hinge-lever spring clamp that restrained the i.v. drip flow of pethidine, so patients controlled their own i.v. infusion rate of analgesic (*Scott 1970*). In 1970, Forrest and his co-workers described a more sophisticated apparatus (Demand Dropmaster), which, after the patient pressed the button on a handgrip device, automatically dispensed i.v. analgesic drugs on demand (*Forrest et al. 1970*). Keeri-Szanto eventually developed a commercial machine with an electrically controlled syringe pump (*Keeri-Szanto 1971*). The analgesic efficacy of PCA has been demonstrated to be superior to that obtained with intermittent i.m. injections (*Keeri-Szanto and Heaman 1972*). After this, several experimental systems for the self-administration of analgesics have been described (*Evans et al. 1976; Tammisto 1978; Hull et al. 1979; Hull and Sibbald 1981; Rosenberg et al. 1984*). Tammisto developed a Finnish PCA apparatus with a special but simple technique for improving the safety of the pain management (*Tammisto 1978*). When the development of microprocessors improved the technology of PCA pumps, the clinical use of PCA became more popular and widespread (*Kay 1981; Rowbotham 1992a*).

PCA is an effective and safe means to provide pain relief for cancer patients (*Citron et al. 1986*), and the technique has been proven beneficial in

patients ranging in age from children as young as 5 years to frail, elderly men (*Egbert et al. 1990; Irwin et al. 1992*).

In patients undergoing bone marrow transplantation and in women after abdominal hysterectomy, PCA therapy decreases the morphine requirement compared to that in a continuous morphine infusion (*Hill et al. 1990; Parker et al. 1991*).

The continuous background infusion of morphine during PCA analgesia has been studied extensively, and shown to increase morphine consumption, sedation, and respiratory depression without improving pain relief or patient satisfaction (*Owen et al. 1989b; Wu and Purcell 1990; Parker et al. 1991, 1992a; Tigerstedt et al. 1991; Russell et al. 1993; Baxter 1994; Etches 1994*). On the other hand, following abdominal surgery, a continuous morphine infusion of 1 mg/h with i.v. PCA (morphine 1 mg bolus and 5 min lockout period) has improved analgesia during the first 24 hours. This method was associated with a greater incidence of complications than with i.v. PCA alone (*Dawson et al. 1995*). In the light of all this, the efficacy of combining a continuous infusion with i.v. PCA is uncertain.

Patient-controlled analgesic administration offers the best individualization, and in addition, PCA should be considered for those patients with the most resistant pain (*Tammisto 1978; Tammisto and Tigerstedt 1982*).

3.1.2. PCA versus i.m. opioids

Several reports indicate that PCA is superior to i.m. supplementation of the same opioid (*Bennett et al. 1982a; Bollish et al. 1985; Hecker and Albert 1988; Wasylak et al. 1990; Wheatley et al. 1992; Boulanger et al. 1993; Thomas et al. 1995*). However, other studies could demonstrate no difference between the pain ratings of the PCA and i.m. groups (*Ellis et al. 1982; Dahl et al. 1987; Albert and Talbott 1988; Ferrante et al. 1988; Kleiman et al. 1988; McGrath et al. 1989*). No statistical difference existed between the two groups in the quantity of morphine used in the postoperative period in three of these studies (*Dahl et al. 1987; Ferrante et al. 1988; Kleiman et al. 1988*).

3.1.3. PCA versus epidural analgesics

Several studies have shown superior pain relief with epidural analgesia than with systemic opioids (*Hjortsø et al. 1985; Loper et al. 1989; Weller et al. 1991; Cade et al. 1992; Benzon et al. 1993; Eriksson-Mjöberg et al. 1997; Boylan et al. 1998; Singelyn et al. 1998*). These studies have included very different regimens. Both morphine and lipophilic opioids epidurally have usually been compared with i.v. PCA morphine for postoperative pain relief after various operations.

Epidural morphine provided greater pain relief at rest and upon coughing than did i.v. PCA morphine after cholecystectomy (*Loper et al. 1989*) and after anterior cruciate ligament repair (*Loper and Ready 1989*). After total hip or total knee arthroplasty, patients receiving continuous epidural morphine recalled having less pain between observations than did those receiving i.v. PCA morphine (*Weller et al. 1991*). Similarly, after total knee arthroplasty, continuous epidural analgesia with 0.125% bupivacaine with sufentanil 0.1 µg/ml and clonidine 1 µg/ml at the rate of 10 ml/h provided better pain relief and faster postoperative knee rehabilitation than did i.v. PCA with morphine (*Singelyn et al. 1998*). A thoracic epidural fentanyl infusion was significantly better than i.v. PCA morphine in providing pain relief after thoracotomy (*Benzon et al. 1993*).

Continuous i.v. infusions of lipophilic opioids (fentanyl, alfentanil) and an epidural technique have been found to be equally effective (*Ellis et al. 1990; Loper et al. 1990; Camu and Debucquoy 1991*). When compared with continuous i.v. fentanyl, continuous epidural fentanyl infusion offers no clinical advantages for the management of postoperative pain after caesarean section (*Ellis et al. 1990*) or after repair of the anterior cruciate ligament of the knee (*Loper et al. 1990*), and the side-effect profile between the two routes of

administration was similar in both these two studies. I.v. and epidural infusions of alfentanil after abdominal hysterectomy were equally effective for providing pain relief, and the incidence of opioid-related side-effects was similar (*Camu and Debucquoy 1991*). Glass and colleagues, comparing i.v. PCA with fentanyl to epidurally administered fentanyl, showed that onset of adequate analgesia was slower via the epidural route, but no significant difference in analgesia between the two routes of administration resulted (*Glass et al. 1992*). Nor, after 60 minutes, did plasma fentanyl concentrations differ. These findings thus reflect the high lipophilicity of fentanyl, which rapidly diffuses out of the epidural space causing a systemic effect.

When epidural opioids were compared to i.v. PCA after caesarean section, patients who had i.v. PCA reported greater satisfaction; PCA was an attractive alternative (*Eisenach et al. 1988; Harrison et al. 1988*). After another study involving caesarean section, PCA with combined continuous infusion and demand dosing of pethidine was superior to continuous infusion of epidural morphine (*Smith et al. 1991*).

3.1.4. Choice of analgesic

The most popular opioid in PCA has been morphine (*White 1988; Stanley et al. 1996*), but also most other opioids have been tested (*Lehmann 1995*). Ideally, the analgesic for PCA should have a rapid onset of analgesic action, be highly efficacious in relieving pain, have an intermediate duration of action (30-60 min), produce no tolerance or dependence, and have no or minimal side-effects or adverse drug interactions (*White 1988; Etches 1999*).

3.1.4.1. Morphine

Pharmacokinetics and pharmacodynamics of morphine

Opioids are capable of producing analgesia over a wide range of doses (*Inturrisi 1984*). As the dose is increased, analgesia improves linearly, virtually to the point of loss of consciousness (*Inturrisi 1984*). Dahlström and co-workers (*1982*) discovered that the measured plasma concentrations of morphine which resulted in subjectively satisfactory analgesia were 21 ± 12 ng/ml. On the other hand, Graves and colleagues (*1985*) defined a minimum effective plasma morphine concentration of 20-40 ng/ml. The maximum plasma morphine concentration was 82 ng/ml (*Graves et al. 1985*). Morphine is considered to be the standard opioid to which all other opioids are compared.

Morphine is metabolized primarily in the liver by conjugation to form water-soluble morphine-3- and morphine-6-glucuronides, which are morphine's main metabolites. The 3-glucuronide is devoid of analgesic activity and has poor affinity to opioid receptors (*Pasternak et al. 1987*). The other important metabolite of morphine, the 6-glucuronide (*Osborne et al. 1990; Portenoy et al. 1992*), has been found to be twice as potent as morphine when either is given s.c. in mice (*Paul et al. 1989*), but when morphine-6-glucuronide was injected either intracerebroventricularly or intrathecally in mice, it was approximately 90 and 650 times, respectively, more potent as an analgesic than morphine (*Paul et al. 1989*). In rats, morphine-6-glucuronide microinjected into the periaqueductal gray matter had 20-fold greater potency than did morphine (*Pasternak et al. 1987*). Similarly, in healthy volunteers, when electrical and cold pain tests were used, a single bolus dose of morphine-6-glucuronide 5 mg i.v. had significant analgesia on a visual analogue scale (*Buetler et al. 2000*). In addition, morphine-6-glucuronide had high affinity to μ-receptors, but not to δ- or κ-receptors (*Pasternak et al. 1987*). The kidneys excrete both these metabolites, and patients with renal disease are at risk for prolonged effects (*Osborne et al. 1986, 1993*).

Postoperative pain relief with morphine

In the relief of postoperative pain after elective cholecystectomy, continuous infusion of morphine was inferior to the traditional intermittent i.m. bolus administration technique (*Marshall et al. 1985*). This could be attributed to the apparent rapid development of tolerance in patients who

received the infusion; in addition, continuous infusion of morphine failed to reduce the dose of morphine required.

After abdominal operations, the routine use of a continuous morphine infusion in combination with the standard PCA regimen did not improve pain management when compared with PCA alone (*Owen et al. 1989b; Wu and Purcell 1990; Parker et al. 1991, 1992a; Russell et al. 1993; Baxter 1994; Etches 1994*). The pattern of hourly morphine consumption has been found to follow a diurnal rhythm, with peak times of demand at 9.00 and 20.00 hours (*Burns et al. 1989*).

Relatively healthy patients undergoing elective hysterectomy have experienced little difference between pethidine and morphine with respect to analgesia, to nausea and vomiting, to sedation and satisfaction when using i.v. PCA with either morphine (bolus dose 2 mg, lockout time 10 min) or pethidine (bolus dose 20 mg, lockout time 10 min) (*Stanley et al. 1996*). The morphine: pethidine potency ratio was in this study 1:9.4.

After major knee surgery, i.v. PCA with morphine was less effective at rest and during continuous passive motion than was analgesia provided by continuous epidural infusion with a combination of 1% lidocaine, 0.03 mg/ml morphine, and 2 µg/ml clonidine administered at 0.1 ml/kg/h, but side-effects such as urinary retention, dysesthesia, and arterial hypotension were encountered more frequently in the continuous epidural infusion group (*Capdevila et al. 1999*).

After elective cholecystectomy, i.v. PCA with morphine did not cause more nausea and vomiting than the conventional i.m. method (*Robinson and Fell 1991*). Morphine is the opioid most commonly used for PCA (*Etches 1999*). Typically given as a 1-mg to 2-mg bolus in adults, analgesia is rapid in onset and of intermediate duration (*Etches 1999*).

3.1.4.2. Oxycodone

Pharmacokinetics and pharmacodynamics of oxycodone

Oxycodone (6-deoxy-7,8-dehydro-14-hydroxy-3-O-methyl-6-oxomorphine or 14-hydroxy-7,8-dihydrocodeinone) is a semisynthetic opioid prepared from a naturally occurring opium alkaloid, thebaine.

Back in 1959, Brittain suggested that oxycodone had a potency similar to that of morphine. In a nonrandomized clinical trial of 600 patients treated with i.m. oxycodone for postoperative pain, he evaluated oxycodone 10 mg as being as effective as morphine 10 mg or pethidine 100 mg (*Brittain 1959*). Similarly, after abdominal surgery, 0.1 mg/kg of oxycodone i.v. has been shown to be as effective as 1 mg/kg of pethidine i.v. in postoperative pain relief (*Takki and Tammisto 1973*).

Likewise, Morrison and co-workers (*1971*) confirmed that oxycodone 10 mg, pentazocine 20 mg, and a combination of morphine 10 mg and cyclizine 50 mg (Cyclimorph®) showed nearly the same analgesic effectiveness, although not better than the standard pethidine dose of 100 mg.

On the other hand, in the immediate postoperative period after major abdominal surgery, the equianalgesic dose ratio of i.v. oxycodone and morphine has shown a ratio of 2:3 (oxycodone had analgesic potency 1.5 times that of morphine) (*Kalso et al. 1991*), whereas in cancer pain, oxycodone has shown, with systemic administration, an analgesic potency 0.7 times that of morphine (*Kalso and Vainio 1990; Kalso et al. 1990*). Moreover, as early as 1978, Beaver and co-workers showed that for cancer pain i.m. oxycodone is less potent than morphine (*Beaver et al. 1978*). In practice, the typical i.m. and i.v. doses of oxycodone used by Finnish anaesthetists have been close to those of morphine (*Pöyhiä 1994*). However, for acute postoperative pain after major abdominal surgery, the equianalgesic dose ratio of epidurally administered oxycodone to morphine has been shown to be 8:1 (*Bäcklund et al. 1997*). The reason for this great difference in dose ratio may be that the µ-receptor affinity of oxycodone is clearly lower (*Kalso et al. 1990; Ross and Smith 1997*). The other reason may be that part of the analgesic potency of oxycodone in man is attributable to the action of its metabolites (*Kalso et al. 1990*).

Noroxycodone (*Weinstein and Gaylord 1979*) and oxymorphone (*Baselt and Stewart 1978*) are the two major metabolites of oxycodone in man.

Metabolism of oxycodone in animals and in man occurs mainly in the liver, and proceeds by *N*-demethylation (noroxycodone), *O*-demethylation (oxymorphone), 6-ketoreduction, and conjugation with glucuronic acid (*Ishida et al. 1982; Pöyhiä et al. 1992b; Otton et al. 1993*). In vitro studies indicate that *O*-methylation of oxycodone to oxymorphone is catalyzed by cytochrome P450 2D6 (CYP2D6) in the liver (*Otton et al. 1993*).

Of these two metabolites, only oxymorphone has been shown to have clinically significant opioid agonist activity in humans; it is a μ-opioid receptor agonist with a relative potency estimated as approximately 14 times that of oxycodone when both drugs are administered parenterally (*Beaver et al. 1978*). However, in healthy adults, plasma concentration of this metabolite after i.v., i.m., or oral administration of oxycodone has been negligible (*Pöyhiä et al. 1991, 1992b; Kaiko et al. 1996*). In contrast, although the analgesic potency of noroxycodone, which has only weak affinity for μ-opioid receptors (*Chen et al. 1991*), has not been established in humans, in animal studies it is a considerably weaker analgesic than is either oxycodone or morphine (*Weinstein and Gaylord 1979; Leow and Smith 1994*). Probably, oxycodone itself is primarily responsible for the analgesic effect after oral oxycodone administration (*Kaiko et al. 1996*). Recent investigations have shown that the antinociceptive effects of oxycodone are mediated by CNS κ-opioid receptors, in contrast to morphine, which interacts primarily with μ-opioid receptors (*Ross and Smith 1997; Black and Trevethick 1998*).

Elimination of oxycodone has been shown to be impaired both in end-stage liver cirrhosis and in uremic patients, and the excretion of its metabolites in uremic patients is severely impaired (*Kirvelä et al. 1996; Tallgren et al. 1997*).

Although the adverse effects of oxycodone are quite similar to those of morphine (*Kalso and Vainio 1990; Kalso et al. 1991*), morphine seemed to cause more sedation than did oxycodone (*Kalso et al. 1991*). On the other hand, some evidence exists that oxycodone might cause slightly more profound respiratory depression than morphine (*Mildh et al. 2000*). In patients with pain following cholecystectomy, degree of sedation with pethidine and oxycodone was similar (*Takki and Tammisto 1973*).

Pöyhiä and colleagues (*1992a*) have discovered that after oral oxycodone, no histamine liberation could be detected in either plasma or urine. On the contrary, morphine and pethidine have been found to liberate histamine from mast cells (*Rosow et al. 1982; Flacke et al. 1987*).

Postoperative pain relief with oxycodone

Oxycodone has been in clinical use since 1917, and in Finland is the most commonly used parenteral opioid for severe acute postoperative pain (*Pöyhiä 1994*). Oxycodone by 1990 was also a popular drug for PCA in Finland (*Pöyhiä 1994*). Due to its high bioavailability (60%) (*Pöyhiä et al. 1992b*), it has been successfully and widely used also for the management of chronic pain and terminal cancer pain (*Inturrisi 1984; Leow et al. 1995; Heiskanen and Kalso 1997; Bruera et al. 1998*).

In patients undergoing endoscopic anterior cruciate ligament reconstruction using a patellar tendon autograft, i.m. ketorolac supplemented by oral oxycodone provided comparable analgesia with fewer side-effects than i.v. PCA with morphine (*Popp et al. 1998*).

For pain control after craniotomy, i.v. PCA with oxycodone supplemented with either ketoprofen or paracetamol was a suitable method; the small doses of oxycodone (0.03 mg/kg) used were found to cause no respiratory depression or excessive sedation (*Tanskanen et al. 1999*).

3.1.4.3. Tramadol

Pharmacokinetics and pharmacodynamics of tramadol

Tramadol is a weak centrally acting analgesic drug with a low affinity for μ-opioid receptors (*Lehmann 1994; Eggers and Power 1995; Duthie 1998; Budd and Langford 1999*). In addition, it also inhibits the neuronal reuptake of noradrenaline and 5-hydroxytryptamine (5-HT) (*Raffa et al. 1992; Driessen et al. 1993*), and it facilitates 5-HT release (*Driessen and Reimann 1992; Bamigbade et al.*

1997). Clinical studies have confirmed that the analgesic effect of tramadol is apportioned between its opioid and monoaminergic components (*Desmeules et al.* 1996). Tramadol is a racemic mixture: each enantiomer has different opioid-binding affinity and they also differ in their inhibition of monoaminergic re-uptake, with the (+)enantiomer inhibiting predominantly 5-HT uptake, and the (-)enantiomer inhibiting noradrenaline uptake (*Raffa et al. 1993*).

Tramadol is metabolized in the liver by the cytochrome P450 enzyme system (CYP2D6) to form at least 11 metabolites, of which O-desmethyltramadol predominates and has a higher affinity than tramadol for opioid receptors (*Sevcik et al. 1993; Poulsen et al. 1996*).

Although the potency ratio between tramadol and pethidine has been calculated to be 0.94 (*Vickers et al. 1992*), tramadol 0.6 mg/kg was shown to cause no respiratory depression, as did an equipotent dose of pethidine (*Tarkkila et al. 1998*). Likewise, an equianalgesic dose of tramadol has much less effect on the respiratory centre than morphine (*Vickers et al. 1992*).

Postoperative pain relief with tramadol

Tramadol is minimally sedative and does not cause constipation, but in parenteral use is associated with more nausea and vomiting than either morphine or codeine (*Hopkins et al. 1998; Ng et al. 1998*). Moreover, when used in PCA for postoperative pain treatment, tramadol causes nausea and vomiting relatively often (*Stamer et al. 1997*).

In a large, multi-centre, double-blind, controlled trial, in which the analgesic efficacy of tramadol was compared to that of morphine given in repeated i.v. boluses as required to control postoperative pain following abdominal surgery over 24 hours, tramadol was less sedative than morphine (*Vickers and Paravicini 1995*).

In PCA after colorectal or head and neck surgery, a mixture of tramadol and droperidol is associated with reduced incidence and severity of nausea and vomiting, when compared with tramadol alone (*Ng et al. 1997*). The quality of analgesia and degree of sedation between the two groups were similar.

Investigations of tramadol have shown that doubling the demand dose in PCA results in significantly higher efficacy without doubling the total consumption of analgesic (*Lehmann et al. 1986*).

Tramadol is useful in the treatment of mild to moderate acute or chronic pain, as well as in postoperative and obstetric pain and in pain of other origins including neuralgia, arthritis, and post-traumatic pain (*Lee et al. 1993*).

3.1.5. Bolus dose

The size of the demand dose is of great importance for successful PCA. The correct demand dose for most of the opioids used is unknown. The optimal dose of morphine to start with could be anything from 0.5 to 4 mg (*Bennett 1986*; *Rosen 1986; Lehmann 1993; Etches 1999; Ready 2000*). The optimal demand dose may be defined as the minimum dose to produce appreciable analgesia consistently without causing either subjective or objective side-effects (*Owen et al. 1989a*). In a comparison of i.v. morphine of 0.5, 1.0, and 2.0 mg bolus dose sizes, Owen and colleagues (*1989a*) found 1.0 mg to be closest to optimal. Unfortunately, one size of demand dose does not suit all patients.

A variable bolus dose of morphine in i.v. PCA provided adequate postoperative analgesia (*Love et al. 1996*). In that study, patients could choose a bolus dose of either 0.5, 1.0, or 1.5 mg morphine by pressing a small, medium, or large button, on a handpiece. This system offered no advantage over conventional analgesia, because no difference occurred in the ease of controlling pain, in the satisfaction with pain control, in the experience of pain on movement, in the quality of sleep, in the severity of nausea, or in the incidence of vomiting between the variable dose PCA and conventional PCA (*Love et al. 1996*). If the bolus dose is too large, patients may become drowsy after each dose and not request additional boluses until they awaken.

When the demand dose of tramadol was 18.5 mg, only 5% of patients had unsatisfactory pain relief, but with a smaller demand dose of 9.6 mg

tramadol, 38% patients reported unsatisfactory pain scores (*Lehmann et al. 1986*).

3.1.6. Lockout time

The minimum allowable period between PCA bolus doses is the lockout time, which must be pharmacokinetically appropriate for the opioid used. If adequate analgesia is not achieved, the lockout time should be shortened or the bolus dose increased. The purpose of the lockout period is to make sure that most of the effect of a bolus dose has been experienced before a further dose can be obtained.

Only a few investigations define optimum lockout periods (*Smythe et al. 1993; Badner et al. 1996*). Smythe and co-workers found no significant differences in the efficacy or toxicity of three i.v. morphine PCA regimens. The three morphine regimens were: 1 mg with a 6 min lockout, 2 mg with a 12 min lockout and 2 mg with a 20 min lockout. Similarly, when a small dose of morphine (1 mg) and a short lockout period (6 min) in PCA has been compared to larger doses and longer lockout periods, no difference in analgesia and side-effects appeared between the groups (*Badner et al. 1996*). Lockout times in the range 5 to 20 minutes should be appropriate in most cases (*Lehmann 1993; Etches 1999; Ready 2000*).

Evidence from an investigation with fentanyl supports the opinion that patients do make demands at essentially consistent blood concentrations (MEAC). However, these diminish with time, probably as the pain stimulus decreases (*Gourlay et al. 1988*).

It is important to make sure that no delays occur in drug transport into the patient's circulation. Therefore, a three-way stopcock should be connected directly to the i.v. cannula to ensure a minimum lockout period.

3.1.7. Hourly or 4-hourly limits

The safety of postoperative PCA management is confirmed by setting hourly or 4-hourly total dose limits for the PCA pump. Whether the inclusion of these limits is of any benefit to patients has not been convincingly shown because few patients reach these limits. On the other hand, the sedative and respiratory effects of PCA opioids seem to appear in most patients at doses far less than the dose limits prescribed (*Etches 1999*).

In fact, accurate scientific data for setting the variables of i.v. PCA analgesia, drug choice, incremental dose, lockout interval, and maximum dose have been lacking (*Mather and Owen 1988*).

3.1.8. Duration of administration

In most studies, PCA is administered for 24 to 48 hours. On the other hand, some retrospective studies disclose that i.v. PCA therapy has been utilized for an average of 68 hours (range 8-144) (*Wermeling et al. 1987, 1992*). The consumption of i.v. PCA morphine during 72 postoperatively hours was retrospectively analyzed in the audit of 1,233 Chinese patients (*Tsui et al. 1996*). It is difficult to decide exactly when i.v. PCA therapy should be changed to oral analgesics (*Owen et al. 1988*). On the other hand, PCA therapy is sometimes discontinued because of significant side-effects or because at the patient's request.

3.2. RISKS AND SIDE-EFFECTS OF PCA

In addition to analgesic efficacy, choice of analgesic therapy should be based on the incidence and nature of side-effects, as well as on the patient's preference for the method. PCA with an opioid is associated with the usual opioid-related side-effects, such as nausea and vomiting, urinary retention, and pruritus, as well as the most feared one, i.e., respiratory depression. In meta-analysis of 15 randomized control trials, patients using PCA obtained better pain relief than those receiving conventional i.m. analgesia, without an increase in adverse effects (*Ballantyne et al. 1993*). This benefit is, however, only weakly supported by meta-analysis, because only 3 of 15 studies provided data on patient satisfaction, and these three studies together included only 216 patients (*Ballantyne et al. 1993*).

This kind of systematic analysis may also provide important information about side-effects and problems of PCA (*Brown 1993*).

3.2.1. Nausea and vomiting

For patients using i.v. PCA, reported frequencies of nausea and vomiting vary between 10% and 88% (Table 1). In the systematic review by Tramèr and Walder (*1999*), the incidence of nausea and vomiting after various kinds of operations in patients receiving no prophylactic antiemetic treatment added to their PCA morphine was approximately 50%.

Three different doses, 0.5, 1, and 2 mg, of morphine administered via PCA, caused no difference in the incidence of nausea, vomiting, or administration of antiemetics (*Owen et al. 1989a*). The incidence of nausea and vomiting associated with the increased dose of i.v. PCA tramadol was higher than with i.v. PCA morphine (*Ng et al. 1998; Pang et al. 1999*) and resulted in a decrease in patient satisfaction (*Pang et al.1999*).

No differences appeared the occurrence of side-effects such as nausea and vomiting between PCA and i.m. dosing of opioids (*Tamsen et al. 1979; Dahl et al. 1987; Kleiman et al. 1988*). However, nausea was significantly less frequent in the regular i.m. morphine group than with fentanyl administered by i.v. PCA, the reason for which may be that two different opioids were being compared (*Welchew 1983*).

After cholecystectomy, for patients receiving epidural morphine or i.v. PCA morphine no significant difference existed with respect to incidence of nausea (*Loper et al. 1989*). Similar results were reported after anterior cruciate ligament repair (*Loper and Ready 1989*). On the other hand, after lower abdominal surgery, nausea was reported more frequently by patients using i.v. diamorphine PCA than by those with continuous epidural infusion of 0.15% bupivacaine with 0.01% diamorphine (*Madej et al. 1992*). A possible explanation for more nausea in the i.v. group in this study could be the increased opioid consumption in the PCA group (*Madej et al. 1992*).

Postoperative nausea and vomiting (PONV) are frequently caused by opioids, although the aetiology of PONV is multifactorial. Women are more likely to experience nausea and vomiting (*Wheatley et al. 1991; Cohen et al. 1994; Larsson and Lundberg 1995; Myles et al. 1997*), and those undergoing

Table 1. Incidence (%) of postoperative nausea and vomiting (PONV) with i.v. PCA.

Analgesic	No. of pat.	Surgery	Nausea	Vomiting	Reference
Morphine	40	Abdominal, orthopaedic	10*		Lehmann et al. 1985
Morphine	15	Abdominal	27	27	Robinson and Fell 1991
Morphine	30	Gynaecologic	88*		Semple et al. 1992
Morphine	27	Gynaecologic	56	11	Williams et al. 1993
Morphine	1 233	Miscellaneous	35	18	Tsui et al. 1996
Morphine	50	Laparoscopic	16	32	Naguib et al. 1998
Morphine	40	Orthopaedic	28	5	Pang et al. 1999
Oxycodone	45	Neurosurgical	18	NR	Tanskanen et al. 1999
Tramadol	60	Abdominal, orthopaedic	20*		Lehmann et al. 1986
Tramadol	50	Laparoscopic	18	32	Naguib et al. 1998
Tramadol	40	Orthopaedic	48	28	Pang et al. 1999

*nausea and vomiting together, NR = not reported

gynaecological operations, breast surgery or middle ear surgery seem to have the highest incidence of PONV (*Wheatley et al. 1991; Cohen et al. 1994; Honkavaara et al. 1994; Larsson and Lundberg 1995*).

In general, opioid premedication has been more frequently associated with postoperative nausea and vomiting than are benzodiazepines (*Larsson and Lundberg 1995*).

3.2.2. Urinary retention

The use of i.v. morphine or pethidine hydrochloride PCA after elective open cholecystectomy has been associated with greater urinary retention than was the case for i.m. morphine or pethidine hydrochloride (*Petros et al. 1992*). Similarly, urinary retention after open appendicectomy was 13 times as likely to occur in patients who had i.v. morphine or pethidine hydrochloride PCA as in those with i.m. analgesic administration of morphine or pethidine hydrochloride (*Petros et al. 1993*). It should be noted that in that study the increased amount of analgesic agent given postoperatively was related to urinary retention. Patients who used PCA after abdominal or vaginal hysterectomy were 5.7 times as likely to have urinary retention as those given an i.m. agent, but the amount and type of analgesic agent given postoperatively had little influence on the risk of retention (*Petros et al. 1994*). These studies by Petros and co-workers included no report of measurement of analgesia, but none of these studies showed any significant difference between total doses of analgesics. The morphine:pethidine potency ratio in these studies was considered to be 1:8.

After cholecystectomy there was no significant difference with respect to the incidence of urinary retention between epidural morphine and i.v. PCA morphine (*Loper et al. 1989*). On the other hand, patients receiving epidural morphine after anterior cruciate ligament repair had a significantly higher incidence of moderate urinary retention than did patients receiving i.v. PCA with morphine (*Loper and Ready 1989*).

3.2.3. Pruritus

Opioid analgesics, regardless of the route of administration, can produce troublesome pruritus. The incidence of pruritus varies greatly. Only 5% of patients receiving i.v. PCA morphine after caesarean section experienced treatable pruritus (*Eisenach et al. 1988*); 28% of patients using i.v. PCA with morphine after thoracotomy had pruritus (*Benzon et al. 1993*).

Some authors have found no significant difference in incidence of pruritus in patients receiving either epidural or i.v. PCA opioids (*Loper and Ready 1989; Wheatley et al. 1990; Madej et al. 1992*). On the other hand, there are also studies showing opioid epidural analgesia to cause more frequent pruritus than does i.v. PCA with an opioid (*Eisenach et al. 1988; Harrison et al. 1988; Loper et al. 1989; Smith et al. 1991; Weller et al. 1991*). In these studies, 27% to 85% of patients receiving epidural morphine complained of bothersome pruritus, whereas the incidence of pruritus in i.v. PCA varied from none to 60% (*Eisenach et al. 1988; Harrison et al. 1988; Loper et al. 1989; Smith et al. 1991; Weller et al. 1991*).

3.2.4. Respiratory depression

Fortunately, respiratory depression and hypoxaemia are quite rare postoperative complications with adequate opioid administration and supervision (*Ready et al. 1988; Etches 1994*). Usually, patients who titrate their own analgesics do not overmedicate themselves, and PCA doses as high as 108 mg/hour morphine have safely been administered (*Wermeling et al. 1986*). Naturally, excessive self-administration of i.v. PCA opioid may result in respiratory depression. In healthy volunteers this respiratory depression was clearly indicated by elevated levels of end-tidal CO_2-levels 3 to 4.5 hours after the administration of i.m. oxycodone (0.13 mg/kg) (*Saarialho-Kere et al. 1989*). Morphine- and oxycodone-induced respiratory depression was characterized by changes in breathing pattern, including a decrease in minute ventilation and in respiratory rate and a later increase in tidal volume

(*Leino et al. 1999*). Likewise, when postoperative patients used i.v. morphine PCA, substantial nocturnal hypoxaemia caused by hypoventilation could be measured with continuous pulse oximetry; oxygenation could be improved by providing supplemental oxygen (*Stone et al. 1999*). In healthy male volunteers given oxycodone and morphine in a random, cross-over, double-blind fashion, oxycodone caused a more profound respiratory depression, indicated by diminished alveolar ventilation and decreased arterial oxygen tension (*Mildh et al. 2000*). Pain itself stimulates breathing, so that risk for respiratory depression may be greater in volunteer studies without pain stimulation than with postoperative patients. On the other hand, opioid therapy can improve ventilation by diminishing pain during deep breathing and coughing (*Lange et al. 1988; George et al. 1994*).

An equianalgesic dose of tramadol has much less effect on the respiratory centre than does morphine (*Vickers et al. 1992*). In fact, tramadol causes little or no respiratory depression (*Paravicini et al. 1982*). Tarkkila with his colleagues found the respiratory effects of tramadol to be similar to those of placebo in spontaneously breathing anaesthetized patients, and equianalgesic doses of oxycodone or pethidine caused significant respiratory depression compared with that from tramadol (*Tarkkila et al. 1997, 1998*).

During the first year of the Acute Pain Service in the York District General Hospital (U.K.) four of the 510 patients (0.8%) receiving i.v. PCA with morphine had oversedation with airway obstruction that required treatment with i.v. naloxone, three of whom had respiratory depression associated with a ventilatory frequency less than 10 breaths per minute (*Wheatley et al. 1991*). Etches (*1994*) reported an incidence of severe respiratory depression associated with PCA of 0.5%. This finding is in agreement with two other reports (*Macintyre et al. 1990; Fleming and Coombs 1992*). In a Canadian survey, the incidence of severe respiratory depression with the use of PCA was as low as 0.03% (*Zimmermann and Stewart 1993*). In an audit of 1,233 Chinese patients using i.v. morphine PCA, bradypnoea and oxygen desaturation were reported in 0.5% and 1.6%, respectively (*Tsui et al. 1996*).

Factors increasing the potential for respiratory depression can be divided into 'patient related' and 'technique related' (*Baxter 1994*). The main causes of patient related factors include advanced age, respiratory failure, hypovolaemia, and concurrent use of other sedative medication (*Ready et al. 1988; Baxter 1994*). The technique related factors include use of a continuous infusion, operator error, and equipment failure (*Baxter 1994*).

The use of background infusion with PCA may be associated with a higher incidence of severe respiratory depression than for PCA alone (*Notgutt and Morgan 1990; Schug and Torrie 1993*), because continuous opioid infusion lacks the inherent safety of patient feedback provided by PCA. On the other hand, Doyle and co-workers (*1993a*) found that inclusion of a background infusion of morphine 4 µg/kg/h in a PCA regimen for children did not increase the incidence of side-effects and was associated with less hypoxaemia and a better sleep pattern than without any background infusion. In another study by the same group, a background infusion of morphine 20 µg/kg/h produced a significant increase in morphine consumption without improving analgesia, and there was a significant increase in the incidence of opioid-induced side-effects such as respiratory depression, sedation, and nausea or vomiting (*Doyle et al. 1993b*).

Operator errors resulted in severe overdosing of patients, with the attendant risk of clinically significant respiratory depression and apnoea (*White 1987*). Unfortunately, errors in programming are quite easy to make, because of the design of many electronic PCA devices. Erroneous excessively large bolus doses of opioids to elderly or hypovolaemic patients have been important contributing factors in respiratory complications (*White 1987*). The most serious event occurred when a PCA pump began to administer boluses independently of the patient trigger (*Notgutt and Morgan 1990*). Similarly, profound respiratory depression and oversedation occurred during malfunction of the PCA pump in four other cases (*Thomas and Owen 1988; Christie et al. 1990; Notcutt et al. 1992*).

Respiratory depression was not observed in neurosurgical patients receiving 1-mg bolus doses

of morphine with PCA (*Stoneham et al. 1996*). The study by Tanskanen and her colleagues (*1999*) evaluating the feasibility and safety of PCA with oxycodone in neurosurgical patients revealed no evidence of respiratory depression or excessive sedation, presumably because the i.v. bolus dose of oxycodone in this study was only 0.03 mg/kg. The potential for overdosing patients may thus be minimized if small bolus doses are used with an adequate lockout period between successive doses.

A study in which continuous pulse oximetry was used after lower abdominal surgery suggested that i.v. PCA with diamorphine was less likely to cause hypoxaemia than was epidural infusion of diamorphine (*Wheatley et al. 1990*). Another study concluded that patients receiving opioids by any route after caesarean section were potentially at risk for respiratory depression (*Brose and Cohen 1989*). However, there occurred a higher incidence of brief periods of severe desaturation following continuous epidural morphine or i.m. pethidine, but only prolonged periods of mild desaturation following i.v. PCA with pethidine (*Brose and Cohen 1989*).

3.2.5. Sedation

Sedation can occur with all opioids and is dose-related (*Inturrisi 1984*). Postoperative opioid use and side-effects are often influenced by the patient's age. After abdominal hysterectomy, patients over 70 had a higher incidence of excessive sedation and confusion than did patients under 40, despite receiving less analgesic medication with a continuous infusion of morphine by the standard PCA method or with PCA alone (*Parker et al. 1991*). It has been reported that for postoperative pain after caesarean sections, i.v. PCA with pethidine provided less sedation and more immediate pain relief than did i.m. pethidine injection (*Rayburn et al. 1988*).

3.3. PATIENT SATISFACTION WITH PCA

In general, patient satisfaction with PCA has been high (*Tamsen et al. 1982; Ferrante et al. 1988; Smith et al. 1991*). Retrospective data from 1,233 Chinese patients who utilized i.v. morphine PCA showed that 77% were satisfied with the use of PCA and with their pain relief (*Tsui et al. 1996*). Ferrante and co-workers (*1988*) also had patients rating PCA as superior to i.m. opioid administration with regard to pain relief.

Patient satisfaction with postoperative analgesic care is a complex issue; several factors other than analgesia, such as surgery, incidence of side-effects, and patient-care in the perioperative period may play a role in patients' assessment of the success of postoperative pain management. The most common reason for dissatisfaction has been inadequate pain relief (*Tsui et al. 1996*).

A meta-analysis by Ballantyne and colleagues (*1993*) showed PCA to be associated with a small improvement in pain relief, but with an increase in patient satisfaction. Patients who can control their own level of pain through self-medication by using PCA may choose to use less of the drug and accept higher pain levels rather than experience more adverse effects. Eisenach and co-workers (*1988*) showed that after caesarean section, i.v. PCA with morphine produced better pain relief and satisfaction than i.m. morphine, although both groups tolerated some pain and used only a small portion of the maximum prescribed narcotic. In that study, decreased pain scores correlated with patient satisfaction within the entire study population, but the relationship differed among groups (*Eisenach et al. 1988*); for example, among women who reported the highest satisfaction, pain scores were significantly higher in the PCA group than in the epidural morphine group. A adequacy of pain relief, feeling safe, and a lack of side-effects seem to be predictors of patients' feeling 'extremely positive' about PCA (*Chumbley et al. 1999*).

In a prospective study of a total of 916 patients, of whom 711 received i.v. morphine PCA and 205 received epidural morphine analgesia following a wide variety of gynaecological, urological, orthopaedic, and general surgical procedures, overall satisfaction was high (*Egan and Ready 1994*). However, in that study, the major disadvantage for the PCA group was the lack of effective analgesia in the recovery room immediately following

surgery and before PCA was instituted, and for the epidural group unpleasant side-effects.

3.4. SAFETY OF PCA

The most important problems in safety of PCA are operator and technical errors, which may lead to overdosing and significant complications (*White 1987; Grey and Sweeney 1988; Grover and Heath 1992*).

Before loss of consciousness occurs, undesirable effects such as notable sedation, mental clouding, nausea and vomiting, and/or respiratory depression occur, which may impose a practical limit on the use of PCA, in order to ensure the safety (*Inturrisi 1984*).

3.5. PATIENT ACCEPTANCE AND ABILITY TO USE PCA

In a prospective study of 230 adult women after abdominal hysterectomy, only 2% of the patients had difficulty in using the PCA device (*Parker et al. 1991*). On the other hand, 15 to 20% of 60 patients recovering from balanced general anaesthesia after elective abdominal or orthopaedic surgery had irremediable difficulties in handling equipment known as the On-Demand Analgesia Computer (ODAC) used for the i.v. self-administration of tramadol: some elderly patients in particular were unable to perform the task of pressing the button twice within one second (*Lehmann et al. 1986*).

3.6. PATIENT-CONTROLLED EPIDURAL ANALGESIA (PCEA)

3.6.1. PCEA in obstetric pain

PCEA for labour analgesia was introduced by Gambling and co-workers (*1988*), and several studies demonstrating the efficacy of PCEA in labour have shown this technique to offer an alternative method for continuous epidural analgesia (*Gambling et al. 1988, 1993; Viscomi and Eisenach 1991*). PCEA with hydromorphone has also appeared to be a suitable alternative to conventional i.v. PCA after caesarean section and has offered the advantages of less opioid medication and a more rapid recovery (*Parker and White 1992*).

Purdie and colleagues (*1992*) compared three techniques used to provide epidural analgesia during the first stage of labour: 1) 0.25% plain bupivacaine 10 ml with top-ups on patient demand delivered by the midwife, 2) continuous infusion of 0.125% plain bupivacaine 10 ml/h, and 3) PCEA delivering 3 ml boluses of 0.25% bupivacaine. Each technique produced comparable analgesia, and achieved equivalent maternal satisfaction with no difference between mode of obstetric delivery, and no complications (*Purdie et al. 1992*). However, careful monitoring of the upper level of the epidural block was required, because in seven of 75 mothers in the PCEA group, the block height was above T7 (*Purdie et al. 1992*).

PCEA with hydromorphone has also been shown to be a safe and effective method of providing pain relief after elective caesarean delivery with epidural bupivacaine, although the addition of 0.08% bupivacaine or a basal infusion of hydromorphone, or both, increased side-effects without improving the patients' pain relief (*Parker et al. 1992b*). One double-blind study, which was designed to determine the best dose variables for PCEA and to compare PCEA with continuous infusion epidural analgesia during the first stage of labour, revealed that PCEA was a safe and effective alternative to continuous epidural infusion, irrespective of the initial dose variables selected (*Gambling et al. 1993*). In that study, five groups of parturients self-administered 0.125% bupivacaine with 1:400 000 adrenaline and fentanyl 2.5 µg/ml using PCA pumps supplying 2 to 6 ml bolus doses at 10- to 30-minute lockout times.

A continuous background infusion has been shown not to be essential to achieve good analgesia with PCEA for labour and delivery, but a trend has appeared towards an increased necessity for physician-administered supplemental bupivacaine in the use of pure PCEA without background infusion (*Ferrante et al. 1994*).

High patient satisfaction has been reported among parturients using PCEA (*Gambling et al. 1990, 1993; Paech 1991; Viscomi and Eisenach 1991; Purdie et al. 1992*). It has been discovered that PCEA in obstetric analgesic practice is at least as effective as the continuous epidural infusion system in producing analgesia and has the advantages of increased satisfaction and of reduction in the local anaesthetic required (*Curry et al. 1994*). A prospective, randomized study of PCEA and midwife-administered intermittent bolus epidural analgesia with 0.125% bupivacaine plus fentanyl has been reported to produce the same median hourly pain scores, similar ratings for analgesia, and similar satisfaction (*Paech et al. 1995*); maximum pain scores were higher in those receiving midwife-administered intermitted bolus epidural analgesia, and incidence of urinary catheterization was significantly more common in those using PCEA.

3.6.2. PCEA in postoperative analgesia

There is only a limited history of the use of PCEA for postoperative pain excluding obstetrics. However, in recent years, studies have been done of PCEA after orthopaedic operations or after thoracotomy. Nolan and co-workers (*1992*) demonstrated the effectiveness and safety of PCEA in 11 patients following post-traumatic pelvic reconstruction, finding that PCEA did not significantly reduce analgesic requirements in comparison to continuous infusion epidural analgesia. One reason for this was the small size of the groups. A greater degree of desaturation after upper abdominal surgery has been discovered in patients who received a continuous epidural fentanyl infusion with nurse-controlled supplements than when fentanyl administration was patient-controlled (*Owen et al. 1993*): PCEA with fentanyl was more effective and less of the drug was required than for continuous epidural infusion. In a comparison of PCEA with morphine and bupivacaine to PCEA with fentanyl and bupivacaine, postoperative analgesia after major abdominal surgery, proved to be excellent in both groups; but incidence of nausea was less in the patients receiving fentanyl (10%) with PCEA than morphine (45%) with PCEA (*Özalp et al. 1998*). In that study, pruritus occurred less often in the fentanyl group (5%) than in the morphine group (30%).

After total hip arthroplasty, i.v. PCA with morphine; PCEA with 0.125% bupivacaine, sufentanil 0.1 μg/ml, and clonidine 1 μg/ml; and continuous '3-in-1' block, all provided comparable pain relief (*Singelyn and Gouverneur 1999*). The PCEA was programmed to give a continuous infusion of 0.125% bupivacaine, sufentanil 0.1 μg/ml and clonidine 1 μg/ml at 5 to 7 ml/h, and the PCEA bolus of 2.5 ml/30 min. Another study involving patients after total joint arthroplasty, demonstrated a significant synergistic effect of a combination of 0.125% levobupivacaine and 4 μg/ml fentanyl, compared with either drug alone, when utilizing PCEA (*Kopacz et al. 1999*). In a large study of 1,030 surgical patients, PCEA provided effective and safe postoperative analgesia on hospital wards (*Liu et al.1998*).

4. AIMS OF THE STUDY

The main purpose of the present study was to investigate and to improve patient-controlled analgesia (PCA) in postoperative pain management.

The specific aims of the study were:

1. to compare the potency, efficacy, side-effects, and pharmacokinetics of the two opioids morphine and oxycodone, and the weak opioid μ-receptor agonist tramadol in i.v. PCA, after breast and back surgery, after maxillofacial surgery, and after microvascular breast reconstruction (I-III).

2. to compare the efficacy, safety, side-effects, and patient satisfaction with i.v. PCA and epidural analgesia after anterior cruriate ligament reconstruction of the knee (IV).

3. to compare the efficacy of patient-controlled epidural analgesia (PCEA) with bupivacaine and fentanyl to that of continuous epidural infusion of bupivacaine and fentanyl for the control pain after knee arthroplasty (V).

4. to evaluate the safety of and patient satisfaction with i.v. PCA and PCEA (I-V), and to elucidate the clinical feasibility of PCEA in postoperative management of pain in elderly patients (V).

5. PATIENTS AND METHODS

5.1. STUDY PATIENTS

The studies were carried out in the Department of Anaesthesiology of Töölö Hospital (I-V) and the Surgical Hospital (II) of Helsinki University Central Hospital. All studies were prospective, randomized, and double-blind. The study protocols were approved by the Ethics Committees of the Helsinki University Central Hospital. A total of 274 patients were involved in the five different studies (Table 2), with only ASA I-III patients accepted. In addition, exclusion criteria included clinical or laboratory contraindications to epidural catheter insertion (IV-V), inability to use the PCA device, or allergy to any of the study medications. Before entering the study, every patient provided a written (I, III-V) and/or verbal (I-V) informed consent.

5.2. PREMEDICATION

Oral diazepam 0.15 to 0.2 mg/kg was given as premedication approximately 60 min before induction of anaesthesia (I-IV). In Study V, diazepam 5 to 10 mg, depending on both weight and age, was given orally as premedication approximately 1 h before induction of anaesthesia.

5.3. ANAESTHETIC METHODS

5.3.1. General anaesthesia (I-III)

A standardized general anaesthetic technique was used in Studies I to III. After glycopyrrolate 0.2 mg i.v., anaesthesia was induced with thiopental 4 to 6 mg/kg (I, III) or propofol 2 mg/kg (II) and together with fentanyl 2 µg/kg (I), 3 µg/kg (III) or alfentanil 0.5 to 1 mg (II). Tracheal intubation was facilitated by vecuronium 0.1 mg/kg (I, III) or atracurium 0.5 mg/kg (I) or suxamethonium 1.5 mg/kg (II). Muscle relaxation was maintained with intermittent doses of vecuronium (I-III) or atracurium (I), and the degree of relaxation was measured by train-of-four monitoring with a peripheral neurostimulator. Anaesthesia was maintained with enflurane in 30% oxygen and 70% nitrous oxide (I) or isoflurane (1-1.5%) in a mixture of 65 to 70% N_2O in oxygen (II, III). Supplemental doses of fentanyl 1 to 2 µg/kg hourly (I, III) or alfentanil 0.5 mg were given for analgesia if the systolic arterial pressure rose 20% over the basic value (II). In Study III, after induction of anaesthesia a gastric tube was inserted for the

Table 2. Summary of study characteristics.

	N	Surgery	Intervention
Study I	50	reduction mammaplasty / lumbar spinal fusion	PCA: oxycodone / morphine
Study II	54	maxillofacial surgery (osteotomies)	PCA: tramadol / oxycodone
Study III	60	microvascular breast reconstruction	PCA: tramadol / morphine
Study IV	56	ligament reconstruction of a knee	PCA* / epidural#
Study V	54	total knee arthroplasty	PCEA# / epidural#
Total	274		

* morphine, # bupivacaine and fentanyl

evacuation of stomach contents. All the women in Study III had a urinary catheter in place for more than 24 h. Electrocardiogram, heart rate, noninvasive arterial pressure (I, II) or invasive arterial pressure (III), peripheral oxyhaemoglobin saturation, end-tidal carbon dioxide, and inspiratory oxygen concentrations were monitored continuously throughout anaesthesia (I-III). Haematocrit was maintained at 0.30 to 0.35, and red cell concentrates were given if necessary (I-III). At the end of the surgery, residual neuromuscular blockade, measured by train-of-four monitoring with a peripheral neurostimulator, was antagonized with 0.4 mg glycopyrrolate followed by 2 mg of neostigmine (I-III).

5.3.2. Combined spinal epidural anaesthesia (IV-V)

The epidural catheter was inserted with a 16- or 18-G Tuohy needle in the L2-L3 interspace with the patient in the lateral position before surgery. The midline approach with 'loss of resistance' technique was used. The catheter was inserted 3 to 5 cm past the needle tip into the epidural space. An epidural test dose of 4 ml lidocaine 10 mg/ml with adrenaline 10 µg/ml was administered through the catheter to rule out intravascular or intrathecal position of the catheter. Then a subarachnoid puncture was performed in the midline at the L3-L4 interspace with a 27-G needle, and spinal anaesthesia was induced with 3 ml of plain bupivacaine 5 mg/ml, 5 min after the epidural test dose. If the level of anaesthesia after this initial dosage was below the L1 dermatome or if the patient complained of pain, supplementary doses, 10 ml of lidocaine 10 mg/ml with adrenaline, were given through the inserted epidural catheter. During the operation, diazepam 2.5 to 5 mg i.v. (IV-V) or midazolam 1 mg i.v. (V), or small doses of propofol for sedation (IV-V), and fentanyl 0.05 to 0.1 mg i.v. (IV-V) for analgesia were given when required. In the operating room and in the recovery room noninvasive blood pressure (oscillotonometry), ECG, heart rate, and SpO_2 were monitored. No urinary bladder catheter was used. Intravenous fluids (Ringer's acetate, 6% hydroxyethyl starch) and erythrocyte concentrate transfusions were given on an individual basis, as required by clinical judgement. If systolic arterial pressure decreased below 95 mmHg, ephedrine 5 to 10 mg i.v. was given. All the patients had a pneumatic tourniquet around the thigh inflated 300 to 350 mmHg during the operation. In the recovery room, after the level of anaesthesia had decreased below L1, another test dose of 8 ml lidocaine 10 mg/ml with adrenaline was given through the epidural catheter to confirm its proper position (V). Low molecular weight heparin (LMWH), enoxaparin 40 mg (Klexane®) once a day beginning 12 to 16 h before anaesthesia, was used for thromboprophylaxis.

5.4. ADJUNCTIVE MEDICATIONS

At the end of anaesthesia, for postoperative prophylactic analgesia, paracetamol 500 mg rectally (III) or ketoprofen 100 mg i.v. (IV) was given, and both types of medication were continued three times a day. After the operation all the patients in Study V received paracetamol 1 g orally three times a day starting in the postanaesthesia care unit. In Study II, to diminish postoperative oedema, every patient received dexamethasone 8 mg twice a day, from the evening before the operation to the first postoperative day. In addition, in Study II, diclofenac sodium 1 mg/kg i.m. was given before incision and at the end of anaesthesia.

5.5. PAIN RELIEF

During the preoperative visit, patients were instructed in the use of a PCA pump. Immediately after completion of surgery, the patients were connected to the pump via an intravenous line with a one-way (anti-reflux) rotating valve (Vygon®, Laboratories pharmaceutics, France) (I-IV). The pump was either a Graseby 3300 PCA pump (Graseby Medical Ltd, UK) (I, III-V) or Abbott Pain Management Provider APM (Abbott Laboratories, North Chicago, IL, USA) (II). No basal infusion was used (I-IV). In Study V, the PCEA pump was set to deliver both an infusion

and a bolus in both the groups to provide blindness for the study. In Studies II to III, loading of the analgesic was utilized. The patient, anaesthetist, and nurses were blinded to the contents of the PCA or PCEA syringe (I-V). The lockout period of the PCA pump was 5 min in Studies I to III.

Study I:

Patients were randomly assigned to receive a drug solution which contained either oxycodone 3 mg/ml or morphine 4.5 mg/ml by the PCA pump, which was set to deliver a bolus dose of 30 µg/kg oxycodone or 45 µg/kg morphine. Patients could take a maximum of 6 bolus doses per hour.

Study II:

During the immediate recovery period, either i.v. tramadol 10 mg or oxycodone 1 mg increments were administered every 2 min until the patient was pain-free or fell asleep. Then the PCA pump was connected, and patients were randomly assigned to receive a drug solution that contained either 6 mg/ml tramadol or 0.6 mg/ml oxycodone; the bolus dose was tramadol 300 µg/kg or oxycodone 30 µg/kg. Maximum dosage per 4 hours was tramadol 4 mg/kg or oxycodone 0.4 mg/kg.

Study III:

When the patient requested pain medication, the anaesthetist gave the study drug, tramadol 10 mg or morphine 1 mg i.v., every 2 min until pain control was judged by the patient to be satisfactory. After this initial dose, the PCA pump was connected. The PCA drug solution contained either tramadol 20 mg/ml or morphine 2 mg/ml. The PCA pump was set to deliver a bolus dose of 450 µg/kg tramadol or 45 µg/kg morphine. Patients could take a maximum of six bolus doses per hour.

Study IV:

Patients were randomly divided into three groups. Each patient could use an i.v. PCA device with 40 µg/kg bolus doses of morphine with a lockout period of 10 min and a maximum dose of 240 µg/kg/h. Patients in the F10 group received a continuous epidural infusion with bupivacaine 1 mg/ml and fentanyl 10 µg/ml, patients in the F5 group received bupivacaine 1 mg/ml and fentanyl 5 µg/ml, and patients in the S group received saline.

Study V:

In both groups the epidural solution contained 1.1 mg/ml bupivacaine and 5 µg/ml fentanyl. The PCEA group could demand a bolus of 0.05 ml/kg of the solution, with a lockout interval of 10 min, and a total dose limit of three bolus doses per hour. The EPI group received a continuous infusion of 0.1 ml/kg/h of the same bupivacaine-fentanyl solution, and only a minimal extra bolus of 0.2 ml with the same lockout interval. The 10-min lockout period was chosen to ensure adequate time for the bolus to work before a further dose was allowed.

Start time, the amount, and the number of PCA demands and bolus doses with the time administered were automatically recorded. All other postoperative medication was recorded from the drug chart.

5.5.1. Loading dose

In Studies II and III, when the patient requested pain medication, the anaesthetist gave the study drug i.v. in a double-blind fashion every 2 min until the patient was pain-free or fell asleep. The evaluated drugs and doses were tramadol 10 mg (II, III), oxycodone 1 mg (II), and morphine 1 mg (III). The maximum doses of loading were tenfold.

5.5.2. Rescue medication

In Study I, if the patient tried to take over 6 bolus doses per hour the PCA pump sounded an alarm, the anaesthetist was called and observed the grade of sedation and pattern of breathing, and the clamp of the pump was released for another dose of opioid. In Studies II to V, the rescue analgesic was oxycodone 0.1 to 0.15 mg/kg i.m. Droperidol 10 µg/kg i.v. or i.m. was given in the case of prolonged emesis or vomiting.

5.6. POSTOPERATIVE FOLLOW-UP

Patients were assessed for pain, side-effects, and satisfaction at predetermined timepoints, 3 h (I, IV, V), 9 h (I, IV, V), 20 h (IV, V), and 24 h (I). In Study II, an interview was done at 2 h after commencing PCA and on the ward at 21.00 hours, and at 9.00 hours the next morning. In Study III, a trained nurse interviewed the patients 2 h after PCA had been started, and on the ward at 20.00 hours, at 8.00 hours the next morning, at 20.00 hours the next evening, and finally at 8.00 on the second morning after operation. In Studies I, II and IV, the interviewer was the anaesthetist, but in Studies III and V, a trained nurse.

5.6.1. Assessment of postoperative analgesia

The intensity of pain was evaluated with a 50-cm visual analogue scale (VAS) (Figure 1) (*Tigerstedt et al. 1988b*). A red and white ruler, 50 cm long and 10 cm broad, was employed, with an increasing red field representing pain intensity and a centimetre scale on the reverse side (0=no pain, 50=worst possible pain) (*Tigerstedt et al. 1988b*). Use of this ruler was explained to all the patients during the preoperative visit.

The intensity of pain following surgery was assessed by the patient himself at rest and during activity, during arm or leg lifting (I, III-V) or during mouth opening (II). In Studies II, III and V, pain was assessed also on a 4-point verbal rating scale (VRS) (0=no pain, 1=slight pain, 2=moderate pain, 3=severe pain).

5.6.2. Assessment of the spread of analgesia, motor block, and sensory block (IV-V)

Cephalad dermatomal extension of sensory analgesia was assessed by pinprick, and the degree of motor block of the lower extremities was recorded by criteria slightly modified from those described by Bromage (*1965*) (0=no motor block, 1=inability to raise extended legs, 2=inability to flex knees, 3=inability to flex angle joints) at 3 h, 9 h, and 20 h in Studies IV and V.

5.6.3. Assessment of side-effects and satisfaction

The incidence of nausea, vomiting, pruritus, and sedation was recorded in all the studies. In Studies I, II, IV, and V urinary retention was also recorded and was treated, as needed, with urinary catheterization. Patients were asked in all the studies to indicate their satisfaction with regard to pain relief (0=no pain relief, 1=fair pain relief, 2=good pain relief, 3=excellent pain relief). Reported reasons for dissatisfaction were recorded.

5.6.4. Assessment of psychomotor recovery with DSST (III)

Psychomotor recovery was measured with the Digit Symbol Substitution Test (DSST) (*Wechsler1958; Stone 1984*) (*Appendix 1*), which measures changes in sensory processing performance and in subjects' ability to concentrate, although a motor component (hand and finger movements) is also involved. This is a simple pen-and-paper test shown to be sensitive to the effects of drugs that influence cerebral function (*Hindmarch 1980; Stone 1984*). Subjects were presented with sheets of paper containing 200 randomized digits (1-9) arranged in 8 rows on each page. During a period of 90 s, the subjects were asked to replace the digit with a predetermined symbol, indicated by a code at the top of each page. The code was changed between tests to reduce the learning effect. The score was the number of symbols correctly produced by the subject. This test was assessed preoperatively for baseline values and twice after the operation, 3 h after the end of anaesthesia, and on the first postoperative morning at 9.00 hours.

5.6.5. Blood sampling and laboratory methods

In Study I, venous samples for the determination of plasma concentrations of oxycodone and morphine were drawn twice, just before the patient left the recovery room and on the morning following the operation. The plasma was separated and stored at -20°C until analyzed. Plasma oxycodone concentrations were determined in duplicate by gas chromatography (*Kalso et al. 1990*). The lower assay limit of the method was 3 ng/ml and the daily coefficient of variation was 6.6% at a concentration of 17.7 ng/ml (n = 10). The plasma concentrations of morphine and morphine-6-glucuronide were assayed by use of reversed-phase ion-pair high-performance liquid chromatography (HPLC) (*Svensson et al. 1982*). The lower limit of detection of morphine and morphine-6-glucuronide was approximately 1 ng/ml, and the coefficient of variation was less than 5% for both substances. Concentrations of morphine-3-glucuronide were not reported in the results, because this lacks any analgesic activity (*Pasternak et al. 1987*).

In Study III, samples for arterial blood-gas analyses were collected from a radial artery catheter at least twice during the operation, and 30 min and 2 h after analgesic loading in the recovery room, where each woman breathed 35% oxygen through a Venturi mask.

5.7. STATISTICAL METHODS

Student´s *t*-test was used for comparison of demographic parametric data. Comparison of two groups with nonparametric values was done with Chi-square analysis or Fisher´s exact test in small sample sizes or the Mann-Whitney *U*-test. The Kruskal-Wallis one-way analysis of variance was used for comparison of VAS scores in several groups (IV). Correlations between VAS and plasma concentrations of morphine, morphine-6-glucuronide, and oxycodone were tested with simple regression analysis in Study I.

Statistical analyses were performed by SigmaStat for Windows, version 2.0 (Jandel Corporation, San Rafael, CA, USA). Parametric values were expressed as mean ± standard deviation (SD) and nonparametric values as median (range).

In Study V, the number of patients needed was determined by power analysis. With a chosen power of 0.80 and at a significance level of 0.05, the sample size was calculated to demonstrate a 22% difference in consumption of bupivacaine-fentanyl solution for postoperative pain. The values for standard deviation required for the calculation were based on our earlier experiences on the need for epidural solution. In all studies, a *P* value less than 0.05 was considered statistically significant.

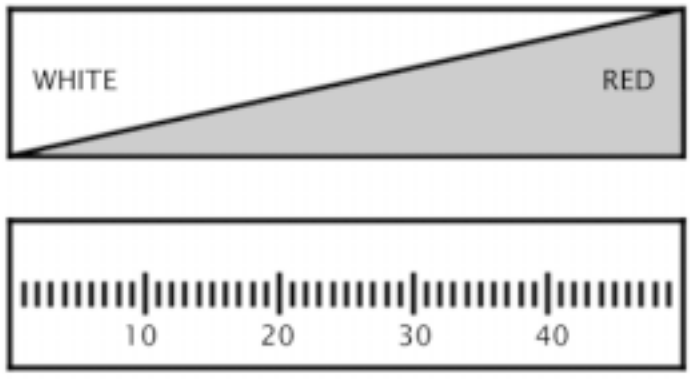


Figure 1. Modified Visual Analogue Scale (0-50 cm).

6. RESULTS

6.1. DEMOGRAPHIC AND ANAESTHESIA DATA OF THE PATIENTS

In all these studies, groups were comparable regarding age, weight, height, and gender (Table 3). In Study I, one patient in the oxycodone group was excluded from the study because of malfunctioning of the PCA pump. In Study II, the PCA treatment was discontinued in two patients in the oxycodone group. In Study III, five women in the tramadol group and two women in the morphine group had to be reoperated upon during the first postoperative 24 h. In Study IV, one patient felt intense pain in his back when the epidural infusion began and was excluded from the study. In Study V, four patients were excluded due to technical difficulties in epidural catheterization, and one patient due to missing data.

The distribution of type of operations was comparable between the treatment groups in Studies I and II. In the other studies, operations of all the patients were similar. Duration of anaesthesia in Study III, duration of surgery in Studies I to III, and loss of blood in Studies II and III were almost identical. The total peroperative alfentanil dosage in Study II and fentanyl dosage in Studies I and III did not differ between the groups. The median of maximum cephalad level of subarachnoid analgesia was similar in the groups 60 min after induction of spinal anaesthesia in Studies IV and V. Three patients in both the F10 and the F5 group, and two patients

Table 3. Demographic data of the patients: means ± SD.

	Gender (F/M)	Age (yr)	Weight (kg)	Height (cm)
Study I				
Oxycodone	19/5	39±11	76±15	169±6
Morphine	20/5	44±11	78±12	166±8
Study II				
Tramadol	18/9	30±10	66±12	169±9
Oxycodone	15/10	29±10	63±12	171±10
Study III				
Tramadol	25/0	50±5	73±11	165±5
Morphine	28/0	51±6	68±8	165±5
Study IV				
F10	5/14	30±8	78±15	173±10
F5	6/12	32±8	79±12	176±7
Saline	4/14	31±8	77±12	176±9
Study V				
PCEA	21/5	71±11	70±9	165±10
EPI	20/3	74±8	70±10	163±8

F10 = bupivacaine 1 mg/ml + fentanyl 10 µg/ml, F5 = bupivacaine 1 mg/ml + fentanyl 5 µg/ml, PCEA = patient-controlled epidural analgesia, EPI = continuous epidural infusion

in the S group needed an additional bolus of lidocaine 10 mg/ml with adrenaline through the epidural catheter during the operation in Study IV. Two patients in the PCEA group and one patient in the EPI group were given an additional bolus of lidocaine 10 mg/ml with adrenaline in Study V. Need for sedation or i.v. analgesics during the operation was identical between the groups in Studies IV and V.

Need for ephedrine intra- and postoperatively was similar in both groups in Study V. Seven patients in both groups were given atropine for bradycardia intra- and postoperatively in Study V.

6.2. POSTOPERATIVE PAIN RELIEF (I-V)

6.2.1. Analgesic efficacy of oxycodone, morphine, and tramadol (I-III)

Amounts of i.v. oxycodone and morphine of PCA needed in the recovery room and on the ward were similar (I). Need for oxycodone or morphine for pain relief at different time intervals was equal in milligrams in the two groups and within the surgical subgroups, surgeries being a plastic reconstruction of the breast or a major operation on the vertebral column, such as lumbar laminectomy and spinal fusion. The potency ratio of tramadol to oxycodone was found to be approximately 8:1 (II), and the potency ratio of tramadol to morphine between 8.5:1 (loading) and 11:1 (PCA). Analgesic requirements of the different opioids in Studies I to III are presented in Table 4.

In Studies I to III, no significant difference appeared between the two analgesic groups in median VAS scores for degree of pain at rest or during activity (Table 5). VRS scores were similar at rest and during activity in both groups in Studies II and III.

In Studies I to III, median VAS scores at rest on the ward were 3 to 15 (6-30%), which can be considered adequate pain relief (*Ready and Rawal 1996*). The highest median VAS scores during Study I were 26 (52%) in the morphine group and 19 (38%) in the oxycodone group. In Study II, the corresponding numbers were 13 (26%) in the tramadol and 15 (30%) in the oxycodone group, and in Study III 22 (44%) in the tramadol and 21 (42%) in the morphine group.

6.2.2. Quality of analgesia and spread of motor and sensory block (IV-V)

In Study IV, nine patients in the F10 group, seven in the F5 group, but only one in the S group needed no PCA morphine during the study ($P<0.05$).

Table 4. Analgesic consumption (mg) in Studies I-III: means (95% confidence interval for mean).

	A	B	C	D
Study I				
Oxycodone	—	16 (10;22)	13 (8;17)	35 (23;47)
Morphine	—	16 (10;22)	12 (8;16)	27 (18;36)
Study II				
Tramadol	38 (26;50)	39 (19;58)	42 (27;58)	81 (50;111)
Oxycodone	3 (2;4)	4 (2;6)	7 (4;9)	12 (6;17)
Study III				
Tramadol	51 (34;69)	115 (69;162)	29 (12;45)	180 (96;264)
Morphine	6 (5;8)	8 (4;12)	2 (1;3)	20 (13;28)

A = during loading, B = in recovery room, C = in the evening, D = during the night

Table 5. Median VAS scores in centimetres (0-50) in Studies I-III.

		In recovery room	That evening	Next morning
Study I				
Oxycodone	R	18 (0-39)	15 (0-40)	13 (0-44)
Morphine	R	14 (0-39)	10 (0-28)	9 (0-46)
Oxycodone	A	20 (0-45)	24 (0-40)	26 (0-48)
Morphine	A	19 (0-47)	16 (0-38)	13 (0-50)
Study II				
Tramadol	R	8 (0-28)	9 (0-26)	3 (0-29)
Oxycodone	R	8 (0-30)	10 (0-28)	5 (0-27)
Tramadol	A	11 (0-38)	13 (0-39)	8 (0-40)
Oxycodone	A	15 (0-30)	15 (0-31)	12 (0-33)
Study III				
Tramadol	R	12 (0-32)	10 (0-30)	12 (0-21)
Morphine	R	16 (0-40)	11 (0-27)	9 (0-25)
Tramadol	A	—	—	14 (0-40)
Morphine	A	—	—	20 (0-37)

R = at rest, A = during activity

Both epidural infusions (F10, F5) provided better analgesia than did epidural saline plus i.v. PCA (S) ($P<0.05$), when VAS scores were compared (Table 6). Medians of the maximum cephalad level of the block during the postoperative period varied from L1 to L3 in the F5 and F10 groups, but in the S group 16/18 had no sensory block 20 h after starting the epidural infusion (Table 7). Three patients in the F10 group, three in the F5 group and ten patients in the S group had complete recovery of the motor block 20 h after starting the epidural infusion in Study IV. Those three patients in the F10 group needed 0 to 12 mg of morphine, those three in the F5 group needed 0 to 12 mg of morphine, but those ten in the S group needed 21 mg to 117 mg of morphine during the study period.

In Study V, pain scores evaluated by VAS and VRS in the PCEA and EPI groups were similar (Table 6). In the PCEA group, 9/26 patients and 11/23 in the EPI group had no demonstrable motor block at the end of the study period, whereas ten patients in the PCEA group and six in the EPI group had a motor block score 2. The spread of sensory analgesia in both groups was similar in Study V (Table 7).

6.2.3. Rescue medication

In Study I, six patients in the oxycodone group and one in the morphine group demanded the predetermined six bolus doses per hour. In Study II, one patient in the tramadol group made demands for more than the 4-h limit of the PCA pump. In Studies II to IV, i.v. PCA opioids provided sufficient analgesia, and no rescue medication was needed. In Study V, 73% of the patients in the PCEA group and 74% patients in the EPI group needed additional oxycodone doses for analgesia during the study. In the PCEA group, eight patients and eleven patients in the EPI group needed more than two oxycodone doses, but the mean number of oxycodone doses per patient in both groups was two in Study V.

6.3. SIDE-EFFECTS

Incidence of nausea was slightly greater in the tramadol than in the oxycodone or morphine groups in Studies II and III (Table 8). Study I revealed no statistically significant difference between the groups in the number of patients who were nauseated or

Table 6. Median VAS scores in centimetres (0-50) in Studies IV-V.

		In recovery room	That evening	Next morning
Study IV				
F10	R	0 (0-22)	0 (0-8)	0 (0-22)
F5	R	0 (0-16)	0 (0-15)	0 (0-26)
Saline	R	0 (0-19)	10 (0-26)	10 (0-19)
F10	A	0 (0-28)	0 (0-20)	0 (0-32)
F5	A	0 (0-33)	0 (0-30)	0 (0-35)
Saline	A	0 (0-20)	19 (1-50)	20 (0-38)
Study V				
PCEA	R	14 (0-47)	20 (1-35)	14 (0-34)
EPI	R	10 (0-37)	10 (0-34)	12 (0-30)
PCEA	A	18 (0-47)	25 (1-47)	30 (0-50)
EPI	A	14 (0-40)	20 (0-40)	23 (0-40)

F10 = bupivacaine 1 mg/ml + fentanyl 10 µg/ml, F5 = bupivacaine 1 mg/ml + fentanyl 5 µg/ml, PCEA = patient-controlled epidural analgesia, EPI = continuous epidural infusion,
R = at rest, A = during activity

Table 7. Maximum cephalad level of block (medians) in Studies IV-V.

	In recovery room	That evening	Next morning
Study IV			
F10	L1	L2	L2
F5	L1	L2	L3
Saline	L2	norm*	norm*
Study V			
PCEA	L2	L4	L5
EPI	L2	norm*	norm*

F10 = bupivacaine 1 mg/ml + fentanyl 10 µg/ml, F5 = bupivacaine 1 mg/ml + fentanyl 5 µg/ml, PCEA = patient-controlled epidural analgesia, EPI = continuous epidural infusion,
* normal skin sensation

vomited. In Study II, during the analgesic loading or immediately after it, four patients in the tramadol but none in the oxycodone group needed droperidol for nausea. However, in Study III during loading 48% of women in the tramadol and 4% of women in the morphine group suffered from nausea and were given droperidol ($P < 0.05$). No difference appeared in incidence of urinary retention in Studies I, II, IV, and V (Table 8).

No evidence of respiratory depression or excessive sedation existed in Studies I, II, IV, and V. In Study III during loading, three patients in the morphine group had low PaO_2 values but had no need for respiratory support. In Study I, one patient in the morphine group developed septic fever on the day after the operation, and in Study III, one woman caught pneumonia on the second day after the operation. In Studies IV and V, no infection of

Table 8. Patients (%) with side-effects and complaints about the analgesic therapy during Studies I-V.

	Nausea and vomiting	Urinary retention	Pruritus
Study I			
Oxycodone	18 (75)	3 (13)	4 (17)
Morphine	17 (68)	3 (12)	6 (24)
Study II			
Tramadol	18 (67)	1 (4)	3 (11)
Oxycodone	11 (44)	1 (4)	1 (4)
Study III			
Tramadol	14 (78)	—	5 (28)
Morphine	17 (68)	—	10 (40)
Study IV			
F10	11 (58)	8 (42)	6 (32)
F5	6 (33)	5 (28)	3 (17)
Saline	4 (22)	3 (17)	0 (0)
Study V			
PCEA	13 (50)	8 (31)	0 (0)
EPI	14 (61)	11 (48)	1 (4)

F10 = bupivacaine 1 mg/ml + fentanyl 10 µg/ml, F5 = bupivacaine 1 mg/ml + fentanyl 5 µg/ml, PCEA = patient-controlled epidural analgesia, EPI = continuous epidural infusion

epidural catheterization was discovered.

In Study V, four patients were unable to operate the apparatus correctly. In addition, one patient in the PCEA group confused the button of PCEA apparatus with the call bell.

6.4.PSYCHOMOTOR RECOVERY WITH DSST AND SEDATION (III)

The DSST after the operation could be adequately performed at the three planned times in 14/18 patients in the tramadol and 17/25 in the morphine group, with no difference in DSST between groups. In the morphine group, four patients who could not focus their vision and four other patients who were deeply sedated could not perform the DSST and in the tramadol group, four deeply sedated patients were unable to perform the DSST test.

6.5. PLASMA CONCENTRATIONS OF OPIOIDS (I)

In the recovery room, the mean plasma level of morphine was 32 ng/ml (range 0-235 ng/ml), and of morphine-6-glucuronide was 27 ng/ml (range 0-82 ng/ml). At the end of the study, the mean morphine concentration was 22 ng/ml (<1-102 ng/ml), and the mean morphine-6-glucuronide concentration 27 ng/ml (range <1-106 ng/ml). In the recovery room, the mean oxycodone concentration was 38 ng/ml (range 0-100 ng/ml) and at 24 h 38 ng/ml (range <3-98 ng/ml).

No correlation between VAS scores and plasma concentrations of opioids and their metabolites could be found.

6.6. PATIENT SATISFACTION

In Study I were three dissatisfied patients: two in the morphine and one in the oxycodone group. In Study II, all patients, except one in the oxycodone group, were satisfied with their pain therapy. In Study III, in the tramadol group five women among those twelve patients who suffered nausea during loading and had received droperidol wanted to discontinue PCA treatment on the ward later because of PONV. Altogether in Study III, seven patients in the tramadol and three in the morphine group wanted to discontinue the use of PCA method before the end of the study because of prolonged PONV.

All patients, except one in each epidural group in Study IV were satisfied with the pain therapy; 8% of the patients in the PCEA group and 0% of patients in the EPI group was dissatisfied with the pain relief in Study V. There were two patients in each group who could not describe the quality of their pain relief in Study V.

7. DISCUSSION

7.1. THE RESEARCH METHODOLOGY

All the studies were performed in a prospective, randomized, and double-blind fashion with standardized anaesthetic techniques used in all cases. The intraoperative doses of analgesics in Studies I to III, and the method of combined spinal epidural anaesthesia in Studies IV to V, were also standardized in order to compare the analgesic efficacy of opioids and compare the different analgesia methods. During the induction of anaesthesia, during surgery, in the recovery room, and on the ward, the patients were observed according to clinical routine.

7.1.1. Measures of analgesia

The objective measurement of pain is quite difficult, but it has been shown that of the various methods for measuring pain, the visual analogue scale (VAS) seems to be the most sensitive (*Huskisson 1974; Revill et al. 1976; Tigerstedt and Tammisto 1988*). A 50-cm scale was used in the recovery period for its presumed greater accuracy compared to that of a 10-cm scale (*Tigerstedt et al. 1988b*). For a better visual display of VAS, a ruler 50 cm long and 10 cm broad was used, with an increasing red field representing pain intensity. Such a large and coloured ruler may offer additional reliability in measurement of the intensity of pain in the postoperative period when the psychomotor skills of the patients are restricted because of drugs and the strange environment.

The efficacy of analgesics can be estimated when analgesic consumption by use of PCA is analyzed in comparable groups of patients (*Lehmann 1993, 1995*). Equal pain relief by i.v. PCA with the various different opioids investigated was achieved in Studies I to III.

7.1.2. Measurements of plasma concentrations of opioids

The methods of analysis of Study I, reversed-phase ion-pair high-performance liquid chromatography (HPLC) and gas chromatography, have been considered to be valid and reliable (*Navaratnam and Fei 1984*). Although the concentrations of opioids and metabolites produced a large variation in Study I, the results can, however, be considered clinically relevant and may reflect the great individual range in need for analgesics. The plasma concentrations of those opioids that cause sufficient analgesia have varied greatly (*Graves et al. 1985; Kalso et al. 1990; Eriksson-Mjöberg et al. 1997*).

7.2. POSTOPERATIVE ANALGESIA

Opioids were administered in Studies I to IV by i.v. PCA at dosages adjusted for weight, but the efficacy of a morphine dose is reported to be unrelated to factors other than age (*Macintyre and Jarvis 1995*). These investigators found that at least the loading dose should be adjusted by age and that during the first 24 hours after surgery, age was the best predictor of morphine requirements. Older patients required considerably less opioid than did young patients. However, in that investigation age was shown to have only a limited influence on morphine requirements between ages 20 and 60, and almost all the patients in the present Studies I to IV fell within this range.

Providing adequate preoperative information about PCA results in diminished anxiety for patients and a reduction in the amount of pain that patients experience (*Jones 1988; Chumbley et al. 1998*). In the present studies, all the patients were preoperatively informed about the PCA treatment and were instructed in the use of a PCA pump.

It was interesting to note that some patients considered some pain to be an acceptable part of postoperative care. Higher doses of opioids do cause more side-effects: higher doses of morphine than in the present studies have caused sedation during recovery-room observation (*Kalso et al. 1991*). On the other hand, some patients obtain complete analgesia, whereas others do not. This has been reported also in other studies (*Purdie et al. 1992*). Many other investigators have also found that patients will remain in mild or even moderate pain without making the maximum number of demands for PCA available to them (*Owen 1989a, 1990, 1995; Lehmann 1993, 1995; Doyle et al. 1994; Taylor et al. 1996*). The VAS scores during movement were the highest, probably because the patients appeared willing to tolerate more pain temporarily or because they did not realize that they would need more opioids before an unexpected painful movement.

Psychological factors and the occurrence of side-effects have been shown to have some predictive value for MEC and the requirements of the maintenance dose (*Gourlay et al. 1988*). In Study I, the mean concentrations of morphine were clearly above one reported MEC, 16 ng/ml (*Dahlström et al. 1982*). A similar range of plasma concentrations of morphine was discovered earlier during i.v. morphine dosing (*Murphy and Hug 1981*). In Study I, VAS scores of pain were low at the time that concentrations of morphine were measured, the opioid levels can possibly be regarded as indicators of the success of the analgesic therapy. On the other hand, the oxycodone plasma levels (I) corresponded to those seen previously after i.m. administration of routinely used oxycodone doses (*Pöyhiä et al. 1992b*). This indicates that patients controlled their use of the PCA system. There occurred no accumulation of the opioids in Study I.

The earlier reported equianalgesic dose ratio, 2:3, between i.v. oxycodone and i.v. morphine (*Kalso et al. 1991*), could not be confirmed in Study I. In the study by Kalso and co-workers, patients were followed for only two hours in the recovery room, and opioids were given by nurses. These patients had undergone major abdominal surgery, after which, the major component of the immediate postoperative pain is typically visceral pain. In animal studies, it has been suggested that κ-opioid agonists produce visceral analgesia (*Schmauss and Yaksh 1984; Burton and Gebhart 1998; Simonin et al. 1998*). Because the nociceptive effects of oxycodone are mediated by κ-receptors (*Ross and Smith 1997*), in the study by Kalso and co-workers, oxycodone provided postoperative analgesia after abdominal surgery at smaller doses than for morphine (*Kalso et al. 1991*). In Study I, also during the recovery period, were mean amounts of opioids similar.

The potency ratio of tramadol to oxycodone was approximately 8:1, and of tramadol to morphine was between 8.5:1 (loading) and 11:1 (PCA). These fell within the expected ratio range 6:1 to 12:1, which was based on comparisons of tramadol with morphine (*Lehmann et al. 1990; Stamer et al. 1997*).

Even though rather many patients in Study IV experienced complete recovery from the sensory and motor block at 20 hours after start of the epidural infusion, their pain relief was adequate. Because PCEA allows patients to tailor the block to their own requirements, some patients used very little bupivacaine, whilst others used more bupivacaine to achieve a good block (*Purdie 1992*). It appears that patients try to obtain as good analgesia as possible without unpleasant side-effects.

In Study V, bupivacaine-fentanyl consumption during the 20 hours was less in the PCEA group than in the EPI group. Similarly, a significant dose-sparing effect has been found to be associated with the use of demand-dose PCEA as compared with standard continuous epidural infusion for analgesia during labour and delivery (*Ferrante et al. 1991, 1995*) and after abdominal surgery (*Boudreault et al. 1991*). In those studies, the reductions in analgesic requirement were not associated with a reduction in the cephalad extension of sensory blockade, in degree of motor block or in pain scores. In those studies, epidural fentanyl was not administered alone but with bupivacaine, and the combination was proposed to result in a greater degree of analgesia while reducing side-effects (*Fischer et al. 1988; Breivik et al. 1995; Niemi and Breivik 2001*). For certain patients, a continuous epidural infusion may

be the most practical way to accomplish adequate postoperative analgesia. Modern pharmacological means for the reinforcement of the epidural analgesic effect include the addition of such drugs as adrenaline (*Breivik et al. 1995; Niemi and Breivik 1998*) or clonidine (*Eisenach et al. 1996; Paech et al. 1997, 2000; Curatolo et al. 2000*) to local anaesthetic or opioid solutions.

The role of nonsteroidal anti-inflammatory drugs (NSAIDs) in reducing the need for opioids has been verified in several studies, and the concomitant use of NSAIDs with opioids has been recommended (*Kostamovaara et al. 1996; Gillies et al. 1987*). We thus used NSAIDs and paracetamol in Studies II to V. In Study III, only a small amount of paracetamol was used, because larger doses of paracetamol, as well as NSAIDs, might have caused reversible platelet dysfunction and produced disturbances in haemostasis (*Niemi et al. 2000*).

7.3. SIDE-EFFECTS

There seems to be no clear advantage in using one opioid over the others, when each produces a similar incidence of postoperative nausea and vomiting (*Kalso et al. 1991; Stanley et al. 1996*). In accordance with earlier studies (*Vickers and Paravicini 1995; Ng et al. 1998; Pang et al.*1999), i.v. tramadol PCA was associated with a disturbingly high incidence of nausea and vomiting also in the present studies (II, III).

Opioid-related side-effects, especially nausea and vomiting, remain the most harmful problems in pain management with PCA. Although in all the present studies, PCA proved to be an effective method in postoperative pain treatment, it was, in fact, depressing to realize that PONV were such common side-effects with the use of PCA or PCEA.

For this, several potential explanations exist, including increased use of the opioid and lack of prophylactic antiemetic medication (*Tigerstedt et al. 1988a; Sharma and Davies 1993; Tramèr and Walder 1999*). In some cases, nurses may be reluctant to administer special antiemetic medication (*Semple et al. 1992*), and patients may be unable to request antiemetic medication.

Side-effects such as PONV were obviously important and troublesome complications of PCA in the present studies. In future, therefore, much more effort has to be put into reducing PONV incidence. It is important to treat such side-effects either prophylactically or immediately post-operatively once the symptoms appear (*Korttila et al. 1985; Rowbotham 1992b; Lamond et al. 1998*). Tigerstedt and her colleagues found that for reducing nausea droperidol at the end of surgery was effective (*Tigerstedt et al. 1988a*). According to a systematic review by Tramèr and Walder (*1999*), droperidol was the best documented drug, and its antiemetic efficacy was clinically relevant as a prophylactic antiemetic.

The explanation for the relatively high incidence of PONV, at least in study III, may be related to the fact that all the patients were women, who are more likely than men to experience nausea and vomiting (*Cohen et al. 1994; Larsson and Lundberg 1995*).

In fact, one way to avoid these adverse effects and to provide superior pain relief is to use opioid-sparing strategies that reduce opioid requirements (*Kehlet and Dahl 1993; Etches et al. 1999*). For this purpose, the most commonly used supplemental analgesic drugs are NSAIDs and paracetamol. For instance, following total hip or knee replacement, i.v. ketorolac has reduced i.v. morphine requirements by PCA up to 44%, and improved analgesia, as well as being associated with reduced incidence of PONV compared with that with placebo (*Etches et al. 1995*).

Because of these unpleasant opioid-related side-effects, patients may refuse to continue PCA treatment. As we know, postoperative nausea is a very complex symptom with many factors other than opioids contributing to its aetiology, and patients respond individually to PCA opioids.

Study IV, with epidural fentanyl infusion compared to PCA morphine alone, showed a clear tendency towards greater number of various systemic opioid side-effects without any respiratory depression with the higher concentration of epidurally administered fentanyl. In general, lipophilic opioids in low concentrations rarely

cause respiratory depression, but nausea, vomiting, and pruritus are relatively common side-effects (*Rawal 1996*).

Neither the best antiemetic prophylaxis nor the best rescue medication for PCA-related PONV has been established (*Woodhouse and Mather 1997; Tramèr and Walder 1999*).

Tramadol has been found to be minimally sedative (*Hopkins et al. 1998*). However, Study III showed no difference in performance of the DSST test between the tramadol and morphine groups. Sedation or blurred vision prevented performance of the DSST test in 22% and 32% of the tramadol and morphine patients, respectively (NS), some of them because of marked sedation probably mainly due to the analgesic.

In the present studies, respiratory depression and sedation caused no problems, probably because most of the patients did not titrate themselves totally pain-free. Postoperatively, because patients remained on the ward, where they were not monitored with pulse oximetry, in some cases transient hypoxaemia may have occurred undetected.

7.4. SAFETY

An advantage with PCA is avoidance of wide swings in plasma analgesic concentration compared with the situation in i.m. dosing, although with continuous epidural infusion a steady state in concentration of local anaesthetics and opioids would be better maintained. PCA may be a disadvantage during the night-time, when plasma opioid concentrations decrease below presumed analgesic levels, causing the patient to awaken in pain.

PCEA seemed to be a safe and useful method also among elderly knee arthroplasty patients (V). The number of epidural catheter-related problems in Study V was 4/54 (7%), lower than in the study by Andersen et al. (*2000*), where 17% of the patients after transabdominal surgery had the epidural catheter reinserted due to misplacement or malfunction of the catheter.

With proper epidural dosing, the sensory block height remained at low dermatomal levels (IV-V). According to Purdie and co-workers (*1992*), the upper level of the epidural block in obstetric patients during PCEA with 0.125% bupivacaine was observed to be above T7 in seven of 75 mothers; so careful regular monitoring of the upper level of the epidural block is required.

Some of the elderly patients were shown to have difficulties in conceptualizing the working principle of the PCEA apparatus. There exists a high incidence of postoperative confusion even in elderly non-demented patients following major surgery, regardless of the route of analgesic administration (*Williams-Russo et al. 1992*).

In one study, postoperative fever was reduced to a greater degree in the PCA group than in the i.m. group, and a significant reduction was also noted in the postoperative pulmonary complication rate, as evidenced by radiographic findings in the PCA group (*Lange et al. 1988*). These investigators speculate that the additional benefit from using PCA is that the patient assumes control of his or her well-being, and this provides a spontaneous mechanism of self-care (*Lange et al. 1988*).

Several published and anecdotal reports of pain management with opioids and concomitant use of benzodiazepines or barbiturates describe patients who ceased breathing (*Bailey et al. 1990; Baxter 1994; Avramov et al. 1996*). For this reason, concurrent administration of other centrally acting drugs such as sedatives and hypnotics should be avoided.

Respiratory rate is a simple parametre and easy to monitor. Although commonly used, as in the present studies, respiratory rate alone is, however, a relatively poor indicator of respiratory depression (*Ready et al. 1988; Whipple et al. 1994; Leino et al. 1999*). More sensitive methods of monitoring analgesic drug-induced respiratory effects are continuous pulse oximetry, intermittent blood gas analyses, and monitoring of apnoea and CO_2 response (*Moon and Camporesi 2000*), although these methods are often rather impractical on the ward. The most important method is to monitor the patients' level of consciousness.

The risks of human error and complications were minimized during the present studies, because a strict, standardized means of monitoring of pain

and pain therapy was followed, and side-effects of pain therapy were monitored frequently. The anaesthetist's having checked the patient and the PCA pump regularly may be one reason for avoidance of such problems as program errors.

7.5. PATIENT SATISFACTION

Patients' general satisfaction in all the studies regarding the postoperative analgesia was good. The adequacy of pain relief and patients' feeling safe may have caused this positive attitude (*Chumbley et al. 1999*). In addition, frequent assessment by the staff might have a favourable impact on patients' satisfaction (*Jamison et al. 1997*). Dissatisfaction with i.v. PCA has been shown to be highly correlated with pain intensity, patients' perceptions of support, their expectations of recovery, and their anxiety (*Jamison et al. 1993*). On the other hand, positive results obtained may be the consequence of patients' reluctance to criticize their treatment and the fact that the immediate surgical outcome happened to be good. It has been shown that 5 to 20% of patients complained strongly about lack of pain relief, and PCA should be considered for those patients with the most resistant pain (*Tammisto 1978; Tammisto and Tigerstedt 1982*).

8. CONCLUSIONS

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

1. The analgesic efficacy of oxycodone and morphine in i.v. patient-controlled analgesia after plastic reconstruction of the breast and major surgery on the vertebral column was similar. The potency ratio of tramadol to oxycodone was found to be approximately 8:1, and the potency ratio of tramadol to morphine between 8.5:1 and 11:1. No correlation existed between the analgesia scores and plasma concentrations of opioids and their main metabolites. Analgesia was similar with oxycodone, morphine or tramadol by PCA. No difference appeared as to side-effects except for nausea and vomiting. Tramadol was shown to be associated with a disturbingly high incidence of nausea and vomiting both after maxillofacial surgery and after microvascular breast reconstruction, probably in part, because most of the former and all of the latter patients were women.

2. Epidural infusion of fentanyl (1 µg/kg/h or 0.5 µg/kg/h) and (bupivacaine 0.1 mg/kg/h) provided better pain relief but led to more side-effects than was the case with i.v. morphine PCA after knee ligament surgery. A tendency was seen towards more side-effects with the higher concentration of epidurally administered fentanyl (1 µg/kg/h).

3. Bupivacaine-fentanyl patient-controlled epidural analgesia after total knee arthroplasty provided postoperative analgesia similar to that of continuous bupivacaine-fentanyl infusion with significantly (40%) smaller doses of epidural infusion.

4. Carefully and correctly applied, PCA and PCEA are safe and effective. In addition, PCEA proved to be a safe and useful method among elderly patients. The risk for clinically significant postoperative respiratory depression appears to be very low. Almost all patients were satisfied with their pain therapy provided by i.v. PCA with morphine and oxycodone, and also by epidural infusions with bupivacaine-fentanyl solutions. However, women's satisfaction with i.v. PCA with tramadol was poorer, the major reason for which was the disturbingly high incidence of PONV.

9. CLINICAL IMPLICATIONS

Patient-controlled analgesia (PCA) provides good postoperative analgesia, but as is the case also with i.m. opioids, it is associated with a high incidence of postoperative nausea and vomiting. Major improvements in postoperative pain therapy are i.v. opioid PCA as well as continuous epidural infusions of local anaesthetics and opioids. The two methods are in most cases alternatives.

I.v. PCA is technically simple and easy to apply, because postoperatively i.v. fluid infusions are usually given as a routine. Epidural analgesia is nowadays a common and elegant technique in postoperative pain treatment. PCEA is not a routine method, however, and although similar in principle to i.v. PCA, it also involves the problems and risks of epidural puncture and catheterization.

Because the use of PCA is not without side-effects and risks, frequent general observation by nurses on the ward is thus important. In addition, sometimes during treatment it may be necessary to alter the PCA program, to change the amount of the bolus dose or duration of the lockout interval. In some cases, it may also be more useful to change the i.v. PCA opioid to another.

10. ACKNOWLEDGEMENTS

This present study was carried out at the Department of Anaesthesia and Intensive Care, Töölö Hospital, Helsinki University Central Hospital. The clinical part of Study II was carried out to a great extent at the Surgical Hospital, Helsinki University Central Hospital.

I wish to express my sincere gratitude to all those who helped me in this project, especially to:

Professor Emeritus Tapani Tammisto, the former Head of the Department of Anaesthesia, University of Helsinki, for giving me excellent facilities to perform this study.

Professor Per Rosenberg, Head of the Department of Anaesthesia, University of Helsinki, for his collaboration, for his so-positive attitude towards research and for his valuable comments during all the phases of the study. His vast experience and knowledge of the scientific and clinical work has provided superb support throughout this project.

The former and present Heads of the Department of Anaesthesia of Töölö Hospital, Docents Ulla Karhunen and Klaus Olkkola, for giving me the opportunity to work in Töölö Hospital and for providing research facilities in Töölö Hospital.

Above all, Docent Mikko Pitkänen, my teacher and supervisor, for his guidance into clinical scientific work, his never-failing support, and his encouragement during various phases of this study. He has placed his invaluable experience at my disposal whenever I needed it. And he never pushed me too hard to finish my studies. Finally, Mikko!

Nils Svartling, M.D., Ph.D., for fruitful criticism and everlasting friendship. His motivating way to advise me and numerous inspiring discussions have been important in the realization of this study. He has continuously encouraged me to complete this work, and pushed me when needed. Nisse, as well as my supervisor, Mikko, worked intensively to enrol all the eligible patients into these studies.

Docent Irma Tigerstedt and Professor Arvi Yli-Hankala, as my official referees appointed by the Faculty of Medicine, University of Helsinki, offered constructive criticism of this manuscript. I am very grateful to them for their valuable suggestions, comments, and most pleasant discussions during the preparation of the final manuscript.

Docent Marjatta Tuominen and Docent Pekka Tarkkila, my co-authors, for their valuble contributions during Study II. Marjatta initially organized the study, and fruitful discussions with Pekka gave me special motivation.

Professor Sirpa Asko-Seljavaara, Head of the Department of Plastic Surgery, for giving me the possibility to perform three of these studies, I to III, in her department, and for her positive attitude towards my research.

Professor Seppo Santavirta, Head of the Department of Orthopaedics and Traumatology, Töölö Hospital, and Professor Juhani Ahonen, the former Head of the Department of Surgery of Surgical Hospital, for providing me the opportunity to perform a part of this research at the Surgical Hospital.

Docent Timo Seppälä, for providing facilities for the measurement of plasma oxycodone concentrations.

Juhani Haasio, M.D., Ph.D., for his assistance and experience in problems with computers. For the most part, the layout of this book is the result of Jussi's work. His help is highly appreciated.

Docent Tarja Randell and Päivi Tanskanen, M.D., the first neuroanaesthetists in Finland, for their priceless help and support. Their magnificent ability to raise my spirits even during the darkest moments of this study is sincerely acknowledged. And I owe many thanks to Tarja, for much advice with statistical problems.

All my colleagues and friends in the Department of Anaesthesia, for their encouragement, co-operation, and interest in my work.

All the nursing staff in the operating rooms and on the wards, for their excellent assistance and support, and positive attitude toward clinical research. The anaesthesia nurses are warmly acknowledged for their excellent collaboration. Without them this study would not have been possible.

Carol Norris, Ph.D., for editing of the English language of this thesis and for her flexibility.

Aira Edelman, M.Sc., for skilful laboratory analysis.

Leena Lajunen, for her help in finding and obtaining copies of several references.

All the patients who volunteered in these studies.

My friends outside of the science. Especially the Levi's Ladies, Helena Hänninen, M.D., Päivi Jutela, M.D., Eini Nikander, M.D., and Paula Pihlaja, M.D., for their cheerful company and for keeping me in touch with other perspectives of life during these years. In addition, I am grateful to Paula for enhancing my physical condition in the form of our weekly tennis.

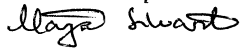
Special thanks go to the three Leenas: Eeva-Leena Järnefelt, Marja-Leena Hyrkkänen, and to Anna-Leena Yliniemi, 'my little sister', for their friendship and support throughout these years.

My warmest thanks to my mother Aino, father Kalle, and brother Pekka, for their support and optimism and for their willingness always to help me when needed.

Last but not least, my dear Tomi Lundell, M.Sc., for his love and support during this study, for constructive criticism, especially after his personal field-testing of PCA last spring, and for his everlasting 'PITKÄPINNA'.

This study was supported by grants from the Viipuri Tuberculosis Foundation, the South Karelian Doctor Unit, Finnish Breast Cancer Group, the Biomedicum Helsinki Foundation and the Finnish Medical Society Duodecim, all of which are gratefully acknowledged.

Helsinki, March 19th, 2001



Marja Silvasti

11. REFERENCES

Albert JM, Talbott TM. Patient-controlled analgesia *vs.* conventional intramuscular analgesia following colon surgery. *Dis Colon Rectum* 1988; 31: 83-86.

American Society of Anesthesiologists. New classification of physical status. *Anesthesiology* 1963; 24: 111.

Andersen G, Rasmussen H, Rosenstock C, Blemmer T, Engbæk J, Christensen M, Ørding H. Postoperative pain control by epidural analgesia after transabdominal surgery. Efficacy and problems encountered in daily routine. *Acta Anaesthesiol Scand* 2000; 44: 296-301.

Avramov MN, Smith I, White PF. Interactions between midazolam and remifentanil during monitored anesthesia care. *Anesthesiology* 1996; 85: 1283-1289.

Badner NH, Doyle JA, Smith MH, Herrick IA. Effect of varying intravenous patient-controlled analgesia dose and lockout interval while maintaining a constant hourly maximum dose. *J Clin Anesth* 1996; 8: 382-385.

Bailey PL, Pace NL, Ashburn MA, Moll JWB, East KA, Stanley TH. Frequent hypoxemia and apnea after sedation with midazolam and fentanyl. *Anesthesiology* 1990; 73: 826-830.

Ballantyne JC, Carr DB, Chalmers TC, Dear KBG, Angelillo IF, Mosteller F. Postoperative patient-controlled analgesia: meta-analyses of initial randomized control trials. *J Clin Anesth* 1993; 5: 182-193.

Bamigbade TA, Davidson C, Langford RM, Stamford JA. Actions of tramadol, its enantiomers and principal metabolite, O-desmethyltramadol, on serotonin (5-HT) efflux and uptake in the rat dorsal raphe nucleus. *Br J Anaesth* 1997; 79: 352-356.

Baselt RC, Stewart CB. Determination of oxycodone and a major metabolite in urine by electron-capture GLC. *J Anal Toxicol* 1978; 2: 107-109.

Baxter AD. Respiratory depression with patient-controlled analgesia. (Editorial). *Can J Anaesth* 1994; 41: 87-90.

Beaver WT, Wallenstein SL, Rogers A, Houde RW. Analgesic studies of codeine and oxycodone in patients with cancer. II. Comparisons of intramuscular oxycodone with intramuscular morphine and codeine. *J Pharmacol Exp Ther* 1978; 207: 101-108.

Bennett RL. Experience with patient-controlled analgesia at the University of Kentucky. *Semin Anesth* 1986; 5: 112-115.

Bennett RL, Batenhorst RL, Bivins BA, Bell RM, Graves DA, Foster TS, Wright BD, Griffen WO Jr. Patient-controlled analgesia. A new concept of postoperative pain relief. *Ann Surg* 1982a; 195: 700-705.

Bennett R, Batenhorst R, Graves D, Foster TS, Baumann T, Griffen WO, Wright BD. Morphine titration in postoperative laparotomy patients using patient-controlled analgesia. *Curr Ther Res* 1982b; 32: 45-52.

Benzon HT, Wong HY, Belavic AM Jr., Goodman I, Mitchell D, Lefheit T, Locicero J. A randomized double-blind comparison of epidural fentanyl infusion versus patient-controlled analgesia with morphine for postthoracotomy pain. *Anesth Analg* 1993; 76: 316-322.

Black D, Trevethick M. The kappa opioid receptor is associated with the perception of visceral pain. *Gut* 1998; 43: 312-313.

Bollish SJ, Collins CL, Kirking DM, Bartlett RH. Efficacy of patient-controlled versus conventional analgesia for postoperative pain. *Clin Pharm* 1985; 4: 48-52.

Bonica JJ. Importance of effective pain control. *Acta Anaesthesiol Scand* 1987; 31 (Suppl. 85): 1-16.

Boudreault D, Brasseur L, Samii K, Lemoing J-P. Comparison of continuous epidural bupivacaine infusion plus either continuous epidural infusion or patient-controlled epidural injection of fentanyl for postoperative analgesia. *Anesth Analg* 1991; 73: 132-137.

Boulanger A, Choinière M, Roy D, Bouré B, Chartrand D, Choquette R, Rousseau P. Comparison between patient-controlled analgesia

and intramuscular meperidine after thoracotomy. *Can J Anaesth* 1993; 40: 409-415.

Boylan JF, Katz J, Kavanagh BP, Klinck JR, Cheng DCH, DeMajo WC, Walker PM, Johnston KW, Sandler AN. Epidural bupivacaine-morphine analgesia versus patient-controlled analgesia following abdominal aortic surgery. Analgesic, respiratory, and myocardial effects. *Anesthesiology* 1998; 89: 585-593.

Breivik H, Niemi G, Haugtomt H, Högström H. Optimal epidural analgesia: importance of drug combinations and correct segmental site of injection. *Baillière's Clin Anaesthesiol* 1995; 9: 493-512.

Brittain GJC. Dihydrohydroxycodeinone pectinate. *Lancet* 1959; II: 544-546.

Bromage PR. A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine in epidural analgesia. *Acta Anaesthesiol Scand* 1965; 16 (Suppl.): 55-69.

Brose WG, Cohen SE. Oxyhemoglobin saturation following cesarean section in patients receiving epidural morphine, PCA, or im meperidine analgesia. *Anesthesiology* 1989; 70: 948-953.

Brown BW Jr. Meta-analysis and patient-controlled analgesia.(Editorial). *J Clin Anesth* 1993; 5: 179-181.

Bruera E, Belzile M, Pituskin E, Fainsinger R, Darke A, Harsanyi Z, Babul N, Ford I. Randomized, double-blind, cross-over trial comparing safety and efficacy of oral controlled-release oxycodone with controlled-release morphine in patients with cancer pain. *J Clin Oncol* 1998; 16: 3222-3229.

Budd K, Langford R. Tramadol revisited. (Editorial II). *Br J Anaesth* 1999; 82: 493-495.

Buetler TM, Wilder-Smith OHG, Wilder-Smith CH, Aebi S, Cerny T, Brenneisen R. Analgesic action of i.v. morphine-6-glucuronide in healthy volunteers. *Br J Anaesth* 2000; 84: 97-99.

Burns JW, Hodsman NBA, McLintock TTC, Gillies GWA, Kenny GNC, McArdle CS. The influence of patient characteristics on the requirements for postoperative analgesia. A reassessment using patient-controlled analgesia. *Anaesthesia* 1989; 44: 2-6.

Burton MB, Gebhart GF. Effects of *kappa*-opioid receptor agonists on responses to colorectal distension in rats with and without acute colonic inflammation. *J Pharmacol Exp Ther* 1998; 285: 707-715.

Bäcklund M, Lindgren L, Kajimoto Y, Rosenberg PH. Comparison of epidural morphine and oxycodone for pain after abdominal surgery. *J Clin Anesth* 1997; 9: 30-35.

Cade L, Ashley J, Ross AW. Comparison of epidural and intravenous opioid analgesia after elective caesarean section. *Anaesth Intens Care* 1992; 20: 41-45.

Camu F, Debucquoy F. Alfentanil infusion for postoperative pain: a comparison of epidural and intravenous routes. *Anesthesiology* 1991; 75: 171-178.

Capdevila X, Barthelet Y, Biboulet P, Ryckwaert Y, Rubenovitch J, d'Athis F. Effects of perioperative analgesic technique on the surgical outcome and duration of rehabilitation after major knee surgery. *Anesthesiology* 1999; 91: 8-15.

Chen ZR, Irvine RJ, Somogyj AA, Bochner F. Mu receptor binding of some commonly used opioids and their metabolites. *Life Sci* 1991; 48: 2165-2171.

Christie JM, Greenstein AS, Rafii A. A respiratory arrest with patient controlled analgesia. *Anesthesiology Review* 1990; 17: 45-48.

Chumbley GM, Hall GM, Salmon P. Patient-controlled analgesia: an assessment by 200 patients. *Anaesthesia* 1998; 53: 216-221.

Chumbley GM, Hall GM, Salmon P. Why do patients feel positive about patient-controlled analgesia? *Anaesthesia* 1999; 54: 386-389.

Citron ML, Johnston-Early A, Boyer M, Krasnow SH, Hood M, Cohen MH. Patient-controlled analgesia for severe cancer pain. *Arch Intern Med* 1986; 146: 734-736.

Cohen MM, Duncan PG, DeBoer DP, Tweed WA. The postoperative interview: assessing risk factors for nausea and vomiting. *Anesth Analg* 1994; 78: 7-16.

Craig DB. Postoperative recovery of pulmonary function. *Anesth Analg* 1981; 60: 46-52.

Curatolo M, Schnider TW, Petersen-Felix S, Weiss S, Signer C, Scaramozzino P, Zbinden AM. A direct search procedure to optimize combinations of epidural bupivacaine, fentanyl, and clonidine for postoperative analgesia. *Anesthesiology* 2000; 92: 325-337.

Curry PD, Pacsoo C, Heap DG. Patient-controlled epidural analgesia in obstetric anaesthetic practice. *Pain* 1994; 57: 125-127.

Dahl JB, Daugaard JJ, Larsen HV, Mouridsen P, Nielsen TH, Kristoffersen E. Patient-controlled analgesia: a controlled trial. *Acta Anaesthesiol Scand* 1987; 31: 744-747.

Dahlström B, Tamsen A, Paalzow L, Hartvig P. Patient-controlled analgesic therapy, part IV: Pharmacokinetics and analgesic plasma concentrations of morphine. *Clin Pharmacokinet* 1982; 7: 266-279.

Dawson PJ, Libreri FC, Jones DJ, Libreri G, Bjorkstein AR, Royse CF. The efficacy of adding a continuous intravenous morphine infusion to patient-controlled analgesia (PCA) in abdominal surgery. *Anaesth Intens Care* 1995; 23: 453-458.

Desmeules JA, Piguet V, Collart L, Dayer P. Contribution of monoaminergic modulation to the analgesic effect of tramadol. *Br J Clin Pharmacol* 1996; 41: 7-12.

Doyle E, Harper I, Morton NS. Patient-controlled analgesia with low dose background infusions after lower abdominal surgery in children. *Br J Anaesth* 1993a; 71: 818-822.

Doyle E, Mottart KJ, Marshall C, Morton NS. Comparison of different bolus doses of morphine for patient-controlled analgesia in children. *Br J Anaesth* 1994; 72: 160-163.

Doyle E, Robinson D, Morton NS. Comparison of patient-controlled analgesia with and without a background infusion after lower abdominal surgery in children. *Br J Anaesth* 1993b; 71: 670-673.

Driessen B, Reimann W. Interaction of the central analgesic, tramadol, with the uptake and release of 5-hydroxytryptamine in the rat brain *in vitro*. *Br J Pharmacol* 1992; 105: 147-151.

Driessen B, Reimann W, Giertz H. Effects of the central analgesic tramadol on the uptake and release of noradrenaline and dopamine *in vitro*. *Br J Pharmacol* 1993; 108: 806-811.

Duthie DJR. Remifentanil and tramadol. *Br J Anaesth* 1998; 81: 51-57.

Egan KJ, Ready LB. Patient satisfaction with intravenous PCA or epidural morphine. *Can J Anaesth* 1994; 41: 6-11.

Egbert AM, Parks LH, Short LM, Burnett ML. Randomized trial of postoperative patient-controlled analgesia vs intramuscular narcotics in frail elderly men. *Arch Intern Med* 1990; 150: 1897-1903.

Eggers KA, Power I. Tramadol. (Editorial). *Br J Anaesth* 1995; 74: 247-249.

Eisenach JC, Grice SC, Dewan DM. Patient-controlled analgesia following cesarean section: a comparison with epidural and intramuscular narcotics. *Anesthesiology* 1988; 68: 444-448.

Eisenach JC, De Kock M, Klimscha W. α_2-adrenergic agonists for regional anesthesia. A clinical review of clonidine (1984-1995). *Anesthesiology* 1996; 85: 655-674.

Ellis DJ, Millar WL, Reisner LS. A randomized double-blind comparison of epidural versus intravenous fentanyl infusion for analgesia after cesarean section. *Anesthesiology* 1990; 72: 981-986.

Ellis R, Haines D, Shah R, Cotton BR, Smith G. Pain relief after abdominal surgery—a comparison of i.m. morphine, sublingual buprenorphine and self-administered i.v. pethidine. *Br J Anaesth* 1982; 54: 421-428.

Eriksson-Mjöberg M, Svensson J-O, Almkvist O, Ölund A, Gustafsson LL. Extradural morphine gives better pain relief than patient-controlled i.v. morphine after hysterectomy. *Br J Anaesth* 1997; 78: 10-16.

Etches RC. Respiratory depression associated with patient-controlled analgesia: a review of eight cases. *Can J Anaesth* 1994; 41: 125-132.

Etches RC. Patient-controlled analgesia. *Surg Clin North Am* 1999; 79: 297-312.

Etches RC, Warriner CB, Badner N, Buckley DN, Beattie WS, Chan VWS, Parsons D, Girard M. Continuous intravenous administration of ketorolac reduces pain and morphine consumption after total hip or knee arthroplasty. *Anesth Analg* 1995; 81: 1175-1180.

Evans JM, MacCarthy J, Rosen M, Hogg MIJ. Apparatus for patient-controlled administration of intravenous narcotics during labour. *Lancet* 1976; I: 17-18.

Ferrante FM, Barber MJ, Segal M, Hughes NJ, Datta S. 0.0625% bupivacaine with 0.0002% fentanyl via patient-controlled epidural analgesia for pain of labor and delivery. *Clin J Pain* 1995; 11: 121-126.

Ferrante FM, Lu L, Jamison SB, Datta S. Patient-controlled epidural analgesia: demand dosing. *Anesth Analg* 1991; 73: 547-552.

Ferrante FM, Orav EJ, Rocco AG, Gallo J. A statistical model for pain in patient-controlled analgesia and conventional intramuscular opioid regimens. *Anesth Analg* 1988; 67: 457-461.

Ferrante FM, Rosinia FA, Gordon C, Datta S. The role of continuous background infusions in patient-controlled epidural analgesia for labor and delivery. *Anesth Analg* 1994; 79: 80-84.

Fischer RL, Lubenow TR, Liceaga A, McCarthy RJ, Ivankovich AD. Comparison of continuous epidural infusion of fentanyl-bupivacaine and morphine-bupivacaine in management of postoperative pain. *Anesth Analg* 1988; 67: 559-563.

Flacke JW, Flacke WE, Bloor BC, Van Etten AP, Kripke BJ. Histamine release by four narcotics: a double-blind study in humans. *Anesth Analg* 1987; 66: 723-730.

Fleming BM, Coombs DW. A survey of complications documented in a quality-control analysis of patient-controlled analgesia in the postoperative patient. *J Pain Symptom Manage* 1992; 7: 463-469.

Forrest WH Jr., Smethurst PWR, Kienitz ME. Self-administration of intravenous analgesics. *Anesthesiology* 1970; 33: 363-365.

Gambling DR, Huber CJ, Berkowitz J, Howell P, Swenerton JE, Ross PLE, Crochetière CT, Pavy TJG. Patient-controlled epidural analgesia in labour: varying bolus dose and lockout interval. *Can J Anaesth* 1993; 40: 211-217.

Gambling DR, McMorland GH, Yu P, Laszlo C. Comparison of patient-controlled epidural analgesia and conventional intermittent "top-up" injections during labor. *Anesth Analg* 1990; 70: 256-261.

Gambling DR, Yu P, Cole C, McMorland GH, Palmer L. A comparative study of patient controlled epidural analgesia (PCEA) and continuous infusion epidural analgesia (CIEA) during labour. *Can J Anaesth* 1988; 35: 249-254.

George KA, Wright PMC, Chisakuta AM, Rao NVS. Thoracic epidural analgesia compared with patient controlled intravenous morphine after upper abdominal surgery. *Acta Anaesthesiol Scand* 1994; 38: 808-812.

Gillies GWA, Kenny GNC, Bullingham RES, McArdle CS. The morphine sparing effect of ketorolac tromethamine. A study of a new, parenteral non-steroidal anti-inflammatory agent after abdominal surgery. *Anaesthesia* 1987; 42: 727-731.

Glass PSA, Estok P, Ginsberg B, Goldberg JS, Sladen RN. Use of patient-controlled analgesia to compare the efficacy of epidural to intravenous fentanyl administration. *Anesth Analg* 1992; 74: 345-351.

Gourlay GK, Kowalski SR, Plummer JL, Cousins MJ, Armstrong PJ. Fentanyl blood concentration—analgesic response relationship in the treatment of postoperative pain. *Anesth Analg* 1988; 67: 329-337.

Graves DA, Arrigo JM, Foster TS, Baumann TJ, Batenhorst RL. Relationship between plasma morphine concentrations and pharmacologic effects in postoperative patients using patient-controlled analgesia. *Clin Pharm* 1985; 4: 41-47.

Grey TC, Sweeney ES. Patient-controlled analgesia. *JAMA* 1988; 259: 2240.

Grover ER, Heath ML. Patient-controlled analgesia. A serious incident. *Anaesthesia* 1992; 47: 402-404.

Harrison DM, Sinatra R, Morgese L, Chung JH. Epidural narcotic and patient-controlled analgesia for post-cesarean section pain relief. *Anesthesiology* 1988; 68: 454-457.

Hecker BR, Albert L. Patient-controlled analgesia: a randomized, prospective comparison between two commercially available PCA pumps and conventional analgesic therapy for postoperative pain. *Pain* 1988; 35: 115-120.

Heiskanen T, Kalso E. Controlled-release oxycodone and morphine in cancer related pain. *Pain* 1997; 73: 37-45.

Hill HF, Chapman CR, Kornell JA, Sullivan KM, Saeger LC, Benedetti C. Self-administration of morphine in bone marrow transplant patients reduces drug requirement. *Pain* 1990; 40: 121-129.

Hindmarch I. Psychomotor function and psychoactive drugs. *Br J Clin Pharmacol* 1980; 10: 189-209.

Hjortsø NC, Neumann P, Frøsig F, Andersen T, Lindhard A, Rogon E, Kehlet H. A controlled

study on the effect of epidural analgesia with local anaesthetics and morphine on morbidity after abdominal surgery. *Acta Anaesthesiol Scand* 1985; 29: 790-796.

Honkavaara P, Saarnivaara L, Klemola U-M. Prevention of nausea and vomiting with transdermal hyoscine in adults after middle ear surgery during general anaesthesia. *Br J Anaesth* 1994; 73: 763-766.

Hopkins D, Shipton EA, Potgieter D, Van Der Merwe CA, Boon J, De Wet C, Murphy J. Comparison of tramadol and morphine via subcutaneous PCA following major orthopaedic surgery. *Can J Anaesth* 1998; 45: 435-442.

Hull CJ, Sibbald A. Control of postoperative pain by interactive demand analgesia. *Br J Anaesth* 1981; 53: 385-391.

Hull CJ, Sibbald A, Johnson MK. Demand analgesia for postoperative pain. *Br J Anaesth* 1979; 51: 570P-571P.

Huskisson EC. Measurement of pain. *Lancet* 1974; II: 1127-1131.

Inturrisi CE. Role of opioid analgesics. *Am J Med* 1984; 77(3A): 27-37.

Irwin M, Gillespie JA, Morton NS. Evaluation of a disposable patient-controlled analgesia device in children. *Br J Anaesth* 1992; 68: 411-413.

Ishida T, Oguri K, Yoshimura H. Determination of oxycodone metabolites in urines and feces of several mammalian species. *J Pharm Dyn* 1982; 5: 521-525.

Jamison RN, Ross MJ, Hoopman P, Griffin F, Levy J, Daly M, Schaffer JL. Assessment of postoperative pain management: patient satisfaction and perceived helpfulness. *Clin J Pain* 1997; 13: 229-236.

Jamison RN, Taft K, O'Hara JP, Ferrante FM. Psychosocial and pharmacologic predictors of satisfaction with intravenous patient-controlled analgesia. *Anesth Analg* 1993; 77: 121-125.

Jones C. Pain assessment. *Surgical Nurse* 1988; 1: 5-8.

Kaiko RF, Benziger DP, Fitzmartin RD, Burke BE, Reder RF, Goldenheim PD. Pharmacokinetic-pharmacodynamic relationships of controlled-release oxycodone. *Clin Pharmacol Ther* 1996; 59: 52-61.

Kalso E, Pöyhiä R, Onnela P, Linko K, Tigerstedt I, Tammisto T. Intravenous morphine and oxycodone for pain after abdominal surgery. *Acta Anaesthesiol Scand* 1991; 35: 642-646.

Kalso E, Vainio A. Morphine and oxycodone hydrochloride in the management of cancer pain. *Clin Pharmacol Ther* 1990; 47: 639-646.

Kalso E, Vainio A, Mattila MJ, Rosenberg PH, Seppälä T. Morphine and oxycodone in the management of cancer pain: plasma levels determined by chemical and radioreceptor assays. *Pharmacol Toxicol* 1990; 67: 322-328.

Kay B. Postoperative pain relief. Use of an on-demand analgesia computer (ODAC) and a comparison of the rate of use of fentanyl and alfentanyl. *Anaesthesia* 1981; 36: 949-951.

Keeri-Szanto M. Apparatus for demand analgesia. *Can J Anaesth Soc J* 1971; 18: 581-582.

Keeri-Szanto M, Heaman S. Postoperative demand analgesia. *Surg Gynecol Obstet* 1972; 134: 647-651.

Kehlet H. Surgical stress: the role of pain and analgesia. *Br J Anaesth* 1989; 63: 189-195.

Kehlet H. Postoperative pain relief. A look from the other side. *Reg Anesth* 1994; 19: 369-377.

Kehlet H, Dahl JB. The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. *Anesth Analg* 1993; 77: 1048-1056.

Kirvelä M, Lindgren L, Seppälä T, Olkkola KT. The pharmacokinetics of oxycodone in uremic patients undergoing renal transplantation. *J Clin Anesth* 1996; 8: 13-18.

Kleiman RL, Lipman AG, Hare BD, MacDonald SD. A comparison of morphine administered by patient-controlled analgesia and regularly scheduled intramuscular injection in severe, postoperative pain. *J Pain Sympt Manag* 1988; 3: 15-22.

Kopacz DJ, Sharrock NE, Allen HW. A comparison of levobupivacaine 0.125%, fentanyl 4 µg/ml, or their combination for patient-controlled epidural analgesia after major orthopedic surgery. *Anesth Analg* 1999; 89: 1497-1503.

Korttila K, Kauste A, Tuominen M, Salo H. Droperidol prevents and treats nausea and vomiting after enflurane anaesthesia. *Eur J Anaesthesiol* 1985; 2: 379-385.

Kostamovaara PA, Laitinen JO, Nuutinen LS, Koivuranta MK. Intravenous ketoprofen for pain

relief after total hip or knee replacement. *Acta Anaesthesiol Scand* 1996; 40: 697-703.

Lamond CT, Robinson DL, Boyd JD, Cashman JN. Addition of droperidol to morphine administered by the patient-controlled analgesia method: what is the optimal dose? *Eur J Anaesthesiol* 1998; 15: 304-309.

Lange MP, Dahn MS, Jacobs LA. Patient-controlled analgesia versus intermittent analgesia dosing. *Heart Lung* 1988; 17: 495-498.

Larsson S, Lundberg D. A prospective survey of postoperative nausea and vomiting with special regard to incidence and relations to patient characteristics, anesthetic routines and surgical procedures. *Acta Anaesthesiol Scand* 1995; 39: 539-545.

Lee CR, McTavish D, Sorkin EM. Tramadol. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in acute and chronic pain states. *Drugs* 1993; 46: 313-340.

Lehmann KA. Intravenous patient-controlled analgesia: postoperative pain management and reseach. In: Chrubasik J, Cousins M, Martin E, eds. *Advances in Pain Therapy II.* 1st Ed. Berlin: Springer-Verlag 1993; 65-93.

Lehmann KA. Tramadol for the management of acute pain. *Drugs* 1994; 47 (Suppl. 1): 19-32.

Lehmann KA. New developments in patient-controlled postoperative analgesia. *Ann Med* 1995; 27: 271-282.

Lehmann KA, Brand-Stavroulaki A, Dworzak H. The influence of demand- and loading dose on the efficacy of postoperative patient-controlled analgesia with tramadol. A randomized double-blind study. *Schmertz Pain Douleur* 1986; 4: 146-152.

Lehmann KA, Gördes B, Hoeckle W. Postoperative on-demand analgesie mit morphin. *Anaesthesist* 1985; 34: 494-501.

Lehmann KA, Kratzenberg U, Schroeder-Bark B, Horrichs-Haermeyer G. Postoperative patient-controlled analgesia with tramadol: analgesic efficacy and minimum effective concentrations. *Clin J Pain* 1990; 6: 212-220.

Leino K, Mildh L, Lertola K, Seppälä T, Kirvelä O. Time course of changes in breathing pattern in morphine- and oxycodone-induced respiratory depression. *Anaesthesia* 1999; 54: 835-840.

de Leon-Casasola OA, Parker BM, Lema MJ, Groth RI, Orsini-Fuentes J. Epidural analgesia versus intravenous patient-controlled analgesia. Differences in the postoperative course of cancer patients. *Reg Anesth* 1994; 19: 307-315.

Leow KP, Cramond T, Smith MT. Pharmacokinetics and pharmacodynamics of oxycodone when given intravenously and rectally to adult patients with cancer pain. *Anesth Analg* 1995; 80: 296-302.

Leow KP, Smith MT. The antinociceptive potencies of oxycodone, noroxycodone and morphine after intracerebroventricular administration to rats. *Life Sci* 1994; 54: 1229-1236.

Liu SS, Allen HW, Olsson GL. Patient-controlled epidural analgesia with bupivacaine and fentanyl on hospital wards. Prospective experience with 1,030 surgical patients. *Anesthesiology* 1998; 88: 688-695.

Loper KA, Ready LB. Epidural morphine after anterior cruciate ligament repair: a comparison with patient-controlled intravenous morphine. *Anesth Analg* 1989; 68: 350-352.

Loper KA, Ready LB, Downey M, Sandler AN, Nessly M, Rapp S, Badner N. Epidural and intravenous fentanyl infusions are clinically equivalent after knee surgery. *Anesth Analg* 1990; 70: 72-75.

Loper KA, Ready LB, Nessly M, Rapp SE. Epidural morphine provides greater pain relief than patient-controlled intravenous morphine following cholecystectomy. *Anesth Analg* 1989; 69: 826-828.

Love DR, Owen H, Ilsley AH, Plummer JL, Hawkins RM, Morrison A. A comparison of variable-dose patient-controlled analgesia with fixed-dose patient-controlled analgesia. *Anesth Analg* 1996; 83: 1060-1064.

Lutz LJ, Lamer TJ. Management of postoperative pain: review of current techniques and methods. *Mayo Clin Proc* 1990; 65: 584-596.

Macintyre PE, Jarvis DA. Age is the best predictor of postoperative morphine requirements. *Pain* 1995; 64: 357-364.

Macintyre PE, Runciman WB, Webb RK. An acute pain service in an Australian teaching hospital: the first year. *Med J Aust* 1990; 153: 417-421.

Madej TH, Wheatley RG, Jackson IJB, Hunter D.

Hypoxaemia and pain relief after lower abdominal surgery: comparison of extradural and patient-controlled analgesia. *Br J Anaesth* 1992; 69: 554-557.

Marshall H, Porteous C, McMillan I, MacPherson SG, Nimmo WS. Relief of pain by infusion of morphine after operation: does tolerance develop? *Br Med J* 1985; 291: 19-21.

Mather LE, Owen H. The scientific basis of patient-controlled analgesia. *Anaesth Intens Care* 1988; 16: 427-436.

McGrath D, Thurston N, Wright D, Preshaw R, Fermin P. Comparison of one technique of patient-controlled postoperative analgesia with intramuscular meperidine. *Pain* 1989; 37: 265-270.

Mildh LH, Tuomisto LM, Scheinin M, Kirvelä OA. Morphine-induced cardiovascular stimulation: the effects of two doses on healthy subjects. *Anesth Analg* 2000; 91: 51-57.

Moon RE, Camporesi EM. Respiratory monitoring. In: Miller RD, ed. *Anesthesia.* 5th Ed. Philadelphia: Churchill Livingstone 2000; 1255-1295.

Morrison JD, Loan WB, Dundee JW. Controlled comparison of the efficacy of fourteen preparations in the relief of postoperative pain. *Br Med J* 1971; 3: 287-290.

Murphy MR, Hug CC Jr. Pharmacokinetics of intravenous morphine in patients anesthetized with enflurane-nitrous oxide. *Anesthesiology* 1981; 54: 187-192.

Myles PS, Hunt JO, Moloney JT. Postoperative 'minor' complications. Comparison between men and women. *Anaesthesia* 1997; 52: 300-306.

Naguib M, Seraj M, Attia M, Samarkandi AH, Seet M, Jaroudi R. Perioperative antinociceptive effects of tramadol. A prospective, randomized, double-blind comparison with morphine. *Can J Anaesth* 1998; 45: 1168-1175.

Navaratnam V, Fei HK. A review of laboratory methods for the analysis of opiates and diluents in illicit drug traffic. *Bulletin on Narcotics* 1984; 36: 15-23.

Ng KFJ, Tsui SL, Yang JCS, Ho ETF. Comparison of tramadol and tramadol/droperidol mixture for patient-controlled analgesia. *Can J Anaesth* 1997; 44: 810-815.

Ng KFJ, Tsui SL, Yang JCS, Ho ETF. Increased nausea and dizziness when using tramadol for post-operative patient-controlled analgesia (PCA) compared with morphine after intraoperative loading with morphine. *Eur J Anaesthesiol* 1998; 15: 565-570.

Niemi G, Breivik H. Adrenaline markedly improves thoracic epidural analgesia produced by a low-dose infusion of bupivacaine, fentanyl and adrenaline after major surgery. A randomised, double-blind, cross-over study with and without adrenaline. *Acta Anaesthesiol Scand* 1998; 42: 897-909.

Niemi G, Breivik H. Epidural fentanyl markedly improves thoracic epidural analgesia in a low-dose infusion of bupivacaine, adrenaline and fentanyl. A randomized, double-blind crossover study with and without fentanyl. *Acta Anaesthesiol Scand* 2001; 45: 221-232.

Niemi TT, Backman JT, Syrjälä MT, Viinikka LU, Rosenberg PH. Platelet dysfunction after intravenous ketorolac or propacetamol. *Acta Anaesthesiol Scand* 2000; 44: 69-74.

Nolan JP, Dow AAC, Parr MJA, Dauphinee K, Kalish M. Patient-controlled epidural analgesia following post-traumatic pelvic reconstruction. A comparison with continuous epidural analgesia. *Anaesthesia* 1992; 47: 1037-1041.

Notcutt WG, Knowles P, Kaldas R. Overdose of opioid from patient-controlled analgesia pumps. *Br J Anaesth* 1992; 69: 95-97.

Notcutt WG, Morgan RJM. Introducing patient-controlled analgesia for postoperative pain control into a district general hospital. *Anaesthesia* 1990; 45: 401-406.

Osborne R, Joel S, Grebenik K, Trew D, Slevin M. The pharmacokinetics of morphine and morphine glucuronides in kidney failure.*Clin Pharmacol Ther* 1993; 54: 158-167.

Osborne RJ, Joel SP, Slevin ML. Morphine intoxication in renal failure: the role of morphine-6-glucuronide. *Br Med J* 1986; 292: 1548-1549.

Osborne R, Joel S, Trew D, Slevin M. Morphine and metabolite behavior after different routes of morphine administration: demonstration of the importance of the active metabolite morphine-6-glucuronide. *Clin Pharmacol Ther* 1990; 47: 12-19.

Otton SV, Wu D, Joffe RT, Cheung SW, Sellers EM. Inhibition by fluoxetine of cytochrome P450 2D6

activity. *Clin Pharmacol Ther* 1993; 53: 401-409.

Owen H, Kluger MT, Ilsley AH, Baldwin AM, Fronsko RRL, Plummer JL. The effect of fentanyl administered epidurally by patient-controlled analgesia, continuous infusion, or a combined technique of oxyhaemoglobin saturation after abdominal surgery. *Anaesthesia* 1993; 48: 20-25.

Owen H, Kluger MT, Plummer JL. Variables of patient-controlled analgesia 4: the relevance of bolus dose size to supplement a background infusion. *Anaesthesia* 1990; 45: 619-622.

Owen H, Mather LE, Rowley K. The development and clinical use of patient-controlled analgesia. *Anaesth Intens Care* 1988; 16: 437-447.

Owen H, Plummer JL, Armstrong I, Mather LE, Cousins MJ. Variables of patient-controlled analgesia 1.bolus size. *Anaesthesia* 1989a; 44: 7-10.

Owen H, Plummer J, Ilsley A, Hawkins R, Arfeen Z, Tordoff K. Variable-dose patient-controlled analgesia. A preliminary report. *Anaesthesia* 1995; 50: 855-857.

Owen H, Szekely SM, Plummer JL, Cushnie JM, Mather LE. Variables of patient-controlled analgesia 2. concurrent infusion. *Anaesthesia* 1989b; 44: 11-13.

Paech MJ. Epidural analgesia in labour: constant infusion plus patient-controlled boluses. *Anaesth Intens Care* 1991; 19: 32-39.

Paech MJ, Pavy TJG, Orlikowski CEP, Evans SF. Patient-controlled epidural analgesia in labor: the addition of clonidine to bupivacaine-fentanyl. *Reg Anesth Pain Med* 2000; 25: 34-40.

Paech MJ, Pavy TJG, Orlikowski CEP, Lim W, Evans SF. Postoperative epidural infusion: a randomized, double-blind, dose-finding trial of clonidine in combination with bupivacaine and fentanyl. *Anesth Analg* 1997; 84: 1323-1328.

Paech MJ, Pawy TJG, Sims C, Westmore MD, Storey JM, White C. Clinical experience with patient-controlled and staff-administered intermittent bolus epidural analgesia in labour. *Anaesth Intens Care* 1995; 23: 459-463.

Pang W-W, Mok MS, Lin C-H, Yang T-F, Huang M-H. Comparison of patient-controlled analgesia (PCA) with tramadol or morphine. *Can J Anaesth* 1999; 46: 1030-1035.

Paravicini D, Zander J, Hansen J. Wirkung von tramadol auf hämodynamik und blutgase in der frühen postoperativen phase. *Anaesthesist* 1982; 31: 611-614.

Parker RK, Holtmann B, White PF. Patient-controlled analgesia. Does a concurrent opioid infusion improve pain management after surgery? *JAMA* 1991; 266: 1947-1952.

Parker RK, Holtmann B, White PF. Effects of a nighttime opioid infusion with PCA therapy on patient comfort and analgesic requirements after abdominal hysterectomy. *Anesthesiology* 1992a; 76: 362-367.

Parker RK, Sawaki Y, White PF. Epidural patient-controlled analgesia: influence of bupivacaine and hydromorphone basal infusion on pain control after cesarean delivery. *Anesth Analg* 1992b; 75: 740-746.

Parker RK, White PF. Epidural patient-controlled analgesia: an alternative to intravenous patient-controlled analgesia for pain relief after cesarean delivery. *Anesth Analg* 1992; 75: 245-251.

Pasternak GW, Bodnar RJ, Clark JA, Inturrisi CE. Morphine-6-glucuronide, a potent mu agonist. *Life Sci* 1987; 41: 2845-2849.

Paul D, Standifer KM, Inturrisi CE, Pasternak GW. Pharmacological characterization of morphine-6β-glucuronide, a very potent morphine metabolite. *J Pharmacol Exp Ther* 1989; 251: 477-483.

Petros JG, Alameddine F, Testa E, Rimm EB, Robillard RJ. Patient-controlled analgesia and postoperative urinary retention after hysterectomy for benign disease. *J Am Coll Surg* 1994; 179: 663-667.

Petros JG, Mallen JK, Howe K, Rimm EB, Robillard RJ. Patient-controlled analgesia and postoperative urinary retention after open appendicectomy. *Surg Gynecol Obstet* 1993; 177: 172-175.

Petros JG, Rimm EB, Robillard RJ. Factors influencing urinary tract retention after elective open cholecystectomy. *Surg Gynecol Obstet* 1992; 174: 497-500.

Popp JE, Sanko WA, Sinha AK, Kaeding CC. A comparison of ketorolac tromethamine/oxycodone versus patient-controlled analgesia with morphine in anterior cruciate ligament reconstruction patients. *Arthroscopy* 1998; 14: 816-819.

Portenoy RK, Thaler HT, Inturrisi CE, Friedlander-Klar H, Foley KM. The metabolite morphine-6-glucuronide contributes to the analgesia produced by morphine infusion in patients with pain and normal renal function. *Clin Pharmacol Ther* 1992; 51: 422-431.

Poulsen L, Arendt-Nielsen L, Brøsen K, Sindrup SH. The hypoalgesic effect of tramadol in relation to CYP2D6. *Clin Pharmacol Ther* 1996; 60: 636-644.

Purdie J, Reid J, Thorburn J, Asbury AJ. Continuous extradural analgesia: comparison of midwife top-ups, continuous infusions and patient controlled administration. *Br J Anaesth* 1992; 68: 580-584.

Pöyhiä R. Opioids in anaesthesia: a questionnaire survey in Finland. *Eur J Anaesthesiol* 1994; 11: 221-230.

Pöyhiä R, Kalso E, Seppälä T. Pharmacodynamic interactions of oxycodone and amitriptyline in healthy volunteers. *Curr Ther Res* 1992a; 51: 739-749.

Pöyhiä R, Olkkola KT, Seppälä T, Kalso E. The pharmacokinetics of oxycodone after intravenous injection in adults. *Br J Clin Pharmacol* 1991; 32: 516-518.

Pöyhiä R, Seppälä T, Olkkola KT, Kalso E. The pharmacokinetics and metabolism of oxycodone after intramuscular and oral administration to healthy subjects. *Br J Clin Pharmacol* 1992b; 33: 617-621.

Raffa RB, Friderichs E, Reimann W, Shank RP, Codd EE, Vaught JL. Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an 'atypical' opioid analgesic. *J Pharmacol Exp Ther* 1992; 260: 275-285.

Raffa RB, Friderichs E, Reimann W, Shank RP, Codd EE, Vaught JL, Jacoby HI, Selve N. Complementary and synergistic antinociceptive interaction between the enantiomers of tramadol. *J Pharmacol Exp Ther* 1993; 267: 331-340.

Rawal N. Neuraxial administration of opioids and nonopioids. In: Brown DL, ed. *Regional anesthesia and analgesia*, 1st Ed. Philadelphia: W.B. Saunders Co, 1996: 208-231.

Rayburn WF, Geranis BJ, Ramadei CA, Woods RE, Patil KD. Patient-controlled analgesia for post-cesarean section pain. *Obstet Gynecol* 1988; 72: 136-139.

Ready LB. Patient-controlled analgesia - does it provide more than comfort? (Editorial). *Can J Anaesth* 1990; 37: 719-721.

Ready LB. Acute pain: lessons learned from 25,000 patients. *Reg Anesth Pain Med* 1999; 24: 499-505.

Ready LB. Patient-controlled analgesia. In: Miller RD, ed. *Anesthesia.* 5th Ed. Philadelphia: Churchill Livingstone 2000; 2326-2328.

Ready LB, Oden R, Chadwick HS, Benedetti C, Rooke GA, Caplan R, Wild LM. Development of an anesthesiology-based postoperative pain management service. *Anesthesiology* 1988; 68: 100-106.

Ready LB, Rawal N. Anesthesiology-based acute pain services: a contemporary view. In: Brown DL, ed. *Regional anesthesia and analgesia*. 1st Ed. Philadelphia: W. B. Saunders Co, 1996: 632-643.

Revill SI, Robinson JO, Rosen M, Hogg MIJ. The reliability of a linear analogue for evaluating pain. *Anaesthesia* 1976; 31: 1191-1198.

Robinson SL, Fell D. Nausea and vomiting with use of a patient-controlled analgesia system. *Anaesthesia* 1991; 46: 580-582.

Rosen M. Patient-controlled analgesia in practice. *Semin Anesth* 1986; 5: 108-111.

Rosenberg PH, Heino A, Scheinin B. Comparison of intramuscular analgesia, intercostal block, epidural morphine and on-demand-i.v.-fentanyl in the control of pain after upper abdominal surgery. *Acta Anaesthesiol Scand* 1984; 28: 603-607.

Rosow CE, Moss J, Philbin DM, Savarese JJ. Histamine release during morphine and fentanyl anesthesia. *Anesthesiology* 1982; 56: 93-96.

Ross FB, Smith MT. The intrinsic antinociceptive effects of oxycodone appear to be κ-opioid receptor mediated. *Pain* 1997; 73: 151-157.

Rowbotham DJ. The development and safe use of patient-controlled analgesia. (Editorial). *Br J Anaesth* 1992a; 68: 331-332.

Rowbotham DJ. Current management of postoperative nausea and vomiting. *Br J Anaesth* 1992b; 69 (Suppl. 1): 46S-59S.

Russell AW, Owen H, Ilsley AH, Kluger MT, Plummer JL. Background infusion with patient-controlled analgesia: effect on postoperative

oxyhaemoglobin saturation and pain control. *Anaesth Intens Care* 1993; 21: 174-179.

Saarialho-Kere U, Mattila MJ, Seppälä T. Psychomotor, respiratory and neuro-endocrinological effects of a μ-opioid receptor agonist (oxycodone) in healthy volunteers. *Pharmacol Toxicol* 1989; 65: 252-257.

Schmauss C, Yaksh TL. *In vivo* studies on spinal opiate receptor systems mediating antinociception. II. Pharmacological profiles suggesting a differential association of *Mu*, *Delta* and *Kappa* receptors with visceral chemical and cutaneous thermal stimuli in the rat. *J Pharmacol Exp Ther* 1984; 228: 1-12.

Schneider AJL. Assessment of risk factors and surgical outcome. *Surg Clin North Am* 1983; 63: 1113-1126.

Schug SA, Torrie JJ. Safety assessment of postoperative pain management by an acute pain service. *Pain* 1993; 55: 387-391.

Scott JS. Obstetric analgesia. A consideration of labor pain and a patient-controlled technique for its relief with meperidine. *Am J Obstet Gynecol* 1970; 106: 959-978.

Scott NB, Kehlet H. Regional anaesthesia and surgical morbidity. *Br J Surg* 1988; 75: 299-304.

Sechzer PH. Objective measurement of pain. *Anesthesiology* 1968; 29: 209-210.

Sechzer PH. Studies in pain with the analgesic-demand system. *Anesth Analg* 1971; 50: 1-10.

Sechzer PH. Patient-controlled analgesia (PCA): a retrospective. *Anesthesiology* 1990; 72: 735-736.

Semple P, Madej TH, Wheatley RG, Jackson IJB, Stevens J. Transdermal hyoscine with patient-controlled analgesia. *Anaesthesia* 1992; 47: 399-401.

Sevcik J, Nieber K, Driessen B, Illes P. Effects of the central analgesic tramadol and its main metabolite, O-desmethyltramadol, on rat locus coeruleus neurones. *Br J Pharmacol* 1993; 110: 169-176.

Sharma SK, Davies MV. Patient-controlled analgesia with a mixture of morphine and droperidol. *Br J Anaesth* 1993; 71: 435-436.

Simonin F, Valverde O, Smadja C, Slowe S, Kitchen I, Dierich A, Le Meur M, Roques BP, Maldonado R, Kieffer BL. Disruption of the κ-opioid receptor gene in mice enhances sensitivity to chemical visceral pain, impairs pharmacological actions of the selective κ-agonist U-50,488H and attenuates morphine withdrawal. *EMBO J* 1998; 17: 886-897.

Singelyn FJ, Deyaert M, Joris D, Pendeville E, Gouverneur JM. Effects of intravenous patient-controlled analgesia with morphine, continuous epidural analgesia, and continuous three-in-one block on postoperative pain and knee rehabilitation after unilateral total knee arthroplasty. *Anesth Analg* 1998; 87: 88-92.

Singelyn FJ, Gouverneur J-MA. Postoperative analgesia after total hip arthroplasty: IV PCA with morphine, patient-controlled epidural analgesia, or continuous "3-in-1" block?: A prospective evaluation by our acute pain service in more than 1,300 patients. *J Clin Anesth* 1999; 11: 550-554.

Smith CV, Rayburn WF, Karaiskakis PT, Morton RD, Norvell MJ. Comparison of patient-controlled analgesia and epidural morphine for postcesarean pain and recovery. *J Reprod Med* 1991; 36: 430-434.

Smythe M, Haubert K, Hoffman J, Dmuchowski C. Comparison of three morphine regimens in postsurgical patients using patient-controlled analgesia. *Ann Pharmacother* 1993; 27: 691-694.

Stamer UM, Maier C, Grond S, Veh-Schmidt B, Klaschik E, Lehmann KA. Tramadol in the management of post-operative pain: a double-blind, placebo- and active drug-controlled study. *Eur J Anaesthesiol* 1997; 14: 646-654.

Stanley G, Appadu B, Mead M, Rowbotham DJ. Dose requirements, efficacy and side effects of morphine and pethidine delivered by patient-controlled analgesia after gynaecological surgery. *Br J Anaesth* 1996; 76: 484-486.

Stone BM. Pencil and paper tests—sensitivity to psychotrophic drugs. *Br J Clin Pharmacol* 1984; 18: 15S-20S.

Stone JG, Cozine KA, Wald A. Nocturnal oxygenation during patient-controlled analgesia. *Anesth Analg* 1999; 89: 104-110.

Stoneham MD, Cooper R, Quiney NF, Walters FMJ. Pain following craniotomy: a preliminary study comparing PCA morphine with intramuscular codeine phosphate. *Anaesthesia* 1996; 51: 1176-1178.

Svensson J-O, Rane A, Säwe J, Sjöqvist F. Determination of morphine, morphine-3-

glucuronide and (tentatively) morphine-6-glucuronide in plasma and urine using ion-pair high-performance liquid chromatography. *J Chromatogr* 1982: 230: 427-432.

Takki S, Tammisto T. A comparison of pethidine, piritramide and oxycodone in patients with pain following cholecystectomy. *Anaesthesist* 1973; 22: 162-166.

Tallgren M, Olkkola KT, Seppälä T, Höckerstedt K, Lindgren L. Pharmacokinetics and ventilatory effects of oxycodone before and after liver transplantation. *Clin Pharmacol Ther* 1997; 61: 655-661.

Tammisto T. Analgesics in postoperative pain relief. *Acta Anaesthesiol Scand* 1978; Suppl. 70: 47-50.

Tammisto T, Tigerstedt I. Narcotic analgesics in postoperative pain relief in adults. *Acta Anaesthesiol Scand* 1982; Suppl. 74: 161-164.

Tamsen A, Hartvig P, Dahlström B, Lindström B, Holmdahl MH. Patient controlled analgesic therapy in the early postoperative period. *Acta Anaesthesiol Scand* 1979; 23: 462-470.

Tamsen A, Hartvig P, Fagerlund C, Dahlström B, Bondesson U. Patient-controlled analgesic therapy: clinical experience. *Acta Anaesthesiol Scand* 1982; Suppl. 74: 157-160.

Tanskanen P, Kyttä J, Randell T. Patient-controlled analgesia with oxycodone in the treatment of postcraniotomy pain. *Acta Anaesthesiol Scand* 1999; 43: 42-45.

Tarkkila P, Tuominen M, Lindgren L. Comparison of respiratory effects of tramadol and oxycodone. *J Clin Anesth* 1997; 9: 582-585.

Tarkkila P, Tuominen M, Lindgren L. Comparison of respiratory effects of tramadol and pethidine. *Eur J Anaesthesiol* 1998; 15: 64-68.

Taylor NM, Hall GM, Salmon P. Patients' experiences of patient-controlled analgesia. *Anaesthesia* 1996; 51: 525-528.

Thomas DW, Owen H. Patient-controlled analgesia —the need for caution. A case report and review of adverse incidents. *Anaesthesia* 1988; 43: 770-772.

Thomas V, Heath M, Rose D, Flory P. Psychological characteristics and the effectiveness of patient-controlled analgesia. *Br J Anaesth* 1995; 74: 271-276.

Tigerstedt I, Salmela L, Aromaa U. Double-blind comparison of transdermal scopolamine, droperidol and placebo against postoperative nausea and vomiting. *Acta Anaesthesiol Scand* 1988a; 32: 454-457.

Tigerstedt I, Tammisto T. A modified visual analogue scale (VAS) for evaluation of pain intensity during immediate postoperative recovery. *Schmertz Pain Douleur* 1988; 9: 27-31.

Tigerstedt I, Tammisto T, Neuvonen PJ. The efficacy of intravenous indomethacin in prevention of postoperative pain. *Acta Anaesthesiol Scand* 1991; 35: 535-540.

Tigerstedt I, Wirtavuori K, Tammisto T. Conceptualization of pain categories on different visual analogue scales. *Schmertz Pain Douleur* 1988b; 9: 66-69.

Tramèr MR, Walder B. Efficacy and adverse effects of prophylactic antiemetics during patient-controlled analgesia therapy: a quantitative systematic review. *Anesth Analg* 1999; 88: 1354-1361.

Tsui SL, Tong WN, Irwin M, Ng KFJ, Lo JR, Chan WS, Yang J. The efficacy, applicability and side-effects of postoperative intravenous patient-controlled morphine analgesia: an audit of 1233 Chinese patients. *Anaesth Intens Care* 1996; 24: 658-664.

Vickers MD, O'Flaherty D, Szekely SM, Read M, Yoshizumi J. Tramadol: pain relief by an opioid without depression of respiration. *Anaesthesia* 1992; 47: 291-296.

Vickers MD, Paravicini D. Comparison of tramadol with morphine for post-operative pain following abdominal surgery. *Eur J Anaesthesiol* 1995; 12: 265-271.

Viscomi C, Eisenach JC. Patient-controlled epidural analgesia during labor. *Obstet Gynecol* 1991; 77: 348-351.

Wasylak TJ, Abbott FV, English MJM, Jeans M-E. Reduction of postoperative morbidity following patient-controlled morphine. *Can J Anaesth* 1990; 37: 726-731.

Wechsler D. Digit Symbol Test. In: Wechsler D, ed. *The Measurement and Appraisal of Adult Intelligence*. 4th Ed. Baltimore: The Williams & Wilkins Company 1958; 81-82.

Weinstein SH, Gaylord JC. Determination of oxycodone in plasma and identification of a major

metabolite. *J Pharm Sci* 1979; 68: 527-528.

Welchew EA. On-demand analgesia. A double-blind comparison of on-demand intravenous fentanyl with regular intramuscular morphine. *Anaesthesia* 1983; 38: 19-25.

Weller R, Rosenblum M, Conard P, Gross JB. Comparison of epidural and patient-controlled intravenous morphine following joint replacement surgery. *Can J Anaesth* 1991; 38: 582-586.

Wermeling DP, Foster TS, Rapp RP, Kenady DE. Evaluation of a disposable, nonelectronic, patient-controlled-analgesia device for postoperative pain. *Clin Pharm* 1987; 6: 307-314.

Wermeling DP, Greene SA, Boucher BA, Lehman ME, Briggs GG, Bezarro ER, Foster TS. Multicenter evaluation of a patient-controlled analgesia device for the treatment of postoperative pain. *Clin Pharm* 1992; 11: 342-346.

Wermeling DP, Record KE, Foster TS. Patient-controlled high-dose morphine therapy in a patient with electrical burns. *Clin Pharm* 1986; 5: 832-835.

Wheatley RG, Madej TH, Jackson IJB, Hunter D. The first year's experience of an Acute Pain Service. *Br J Anaesth* 1991; 67: 353-359.

Wheatley RG, Shepherd D, Jackson IJB, Madej TH, Hunter D. Hypoxaemia and pain relief after upper abdominal surgery: comparison of i.m. and patient-controlled analgesia. *Br J Anaesth* 1992; 69: 558-561.

Wheatley RG, Somerville ID, Sapsford DJ, Jones JG. Postoperative hypoxaemia: comparison of extradural, i.m. and patient-controlled opioid analgesia. *Br J Anaesth* 1990; 64: 267-275.

Whipple JK, Quebbeman EJ, Lewis KS, Gottlieb MS, Ausman RK. Difficulties in diagnosing narcotic overdoses in hospitalized patients. *Ann Pharmacother* 1994; 28: 446-450.

White PF. Mishaps with patient-controlled analgesia. *Anesthesiology* 1987; 66: 81-83.

White PF. Use of patient-controlled analgesia for management of acute pain. *JAMA* 1988; 259: 243-247.

Williams OA, Clarke FL, Harris RW, Smith P, Peacock JE. Addition of droperidol to patient-controlled analgesia: effect on nausea and vomiting. *Anaesthesia* 1993; 48: 881-884.

Williams-Russo P, Urquhart BL, Sharrock NE, Charlson ME. Post-operative delirium: predictors and prognosis in elderly orthopedic patients. *J Am Geriatr Soc* 1992; 40: 759-767.

Woodhouse A, Mather LE. Nausea and vomiting in the postoperative patient-controlled analgesia environment. *Anaesthesia* 1997; 52: 770-775.

Woodhouse A, Mather LE. The minimum effective concentration of opioids: a revisitation with patient controlled analgesia fentanyl. *Reg Anesth Pain Med* 2000; 25: 259-267.

Wu MYC, Purcell GJ. Patient-controlled analgesia—the value of a background infusion. *Anaesth Intens Care* 1990; 18: 575-576.

Zimmermann DL, Stewart J. Postoperative pain management and Acute Pain Service activity in Canada. *Can J Anaesth* 1993; 40: 568-575.

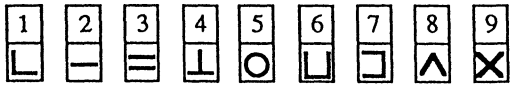
Özalp G, Güner F, Kuru N, Kadiogullari N. Postoperative patient-controlled epidural analgesia with opioid bupivacaine mixtures. *Can J Anaesth* 1998; 45: 938-942.

APPENDIX I

HELSINKI UNIVERSITY CENTRAL HOSPITAL
Töölö Hospital
Department of Anaesthesia
Topeliuksenkatu 5
00250 Helsinki, Finland

DATE:	NAME:
TIME:	

DIGIT 1 2 3 4 5 6 7 8 9

SYMBOL 

2	7	6	5	4	3	9	1	8	3	7	4	6	5	2	9	1	2	8	6	7	5	4	9	3

5	7	6	8	2	9	1	3	4	6	8	7	2	5	1	4	3	9	5	7	8	3	6	5	2

8	4	3	9	7	6	1	5	4	3	7	6	9	1	8	4	3	5	2	7	9	1	8	6	7

6	8	7	2	5	1	4	3	9	1	2	9	8	4	3	6	7	5	2	1	6	4	7	9	3

8	7	2	6	9	5	4	1	3	2	5	8	7	9	6	1	4	3	2	5	7	9	6	8	1

7	1	4	5	8	2	6	9	3	5	3	9	7	2	1	4	6	7	8	2	3	7	9	7	1

9	2	1	4	8	3	7	6	5	1	2	9	3	8	4	7	6	2	5	8	1	7	4	9	3

1	6	4	9	7	3	2	8	6	7	9	3	1	4	8	2	5	9	8	2	4	3	1	7	5

ORIGINAL PUBLICATIONS (I-V)

Errata

Publication I, (Comparison of analgesic efficacy of oxycodone and morphine in postoperative intravenous patient-controlled analgesia). Page 580, the title of the twelfth reference should be: Anesthesiology-based acute pain services: A contemporary view. Also the name of the reference book should be: Regional anesthesia and analgesia.

Publication II, (Efficacy and side effects of tramadol versus oxycodone for patient-controlled analgesia after maxillofacial surgery). Page 838, in Table 3, no. of patients (%) with urinary catheterization in the oxycodone group: 1 (5) should be 1 (4).

Publication IV, (Continuous epidural analgesia with bupivacaine-fentanyl versus patient-controlled analgesia with i.v. morphine for postoperative pain relief after knee ligament surgery). Page 41, the title of the fourteenth reference should be: A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine in epidural analgesia.