Oxycodone for the treatment of postoperative pain

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Introduction: Pain is a likely outcome of any surgical procedure. In several countries the use of oxycodone has surpassed that of morphine in postoperative pain management.

Areas covered: This review summarizes the recent pharmacological and clinical data on oxycodone use for postoperative pain management. The benefits and the impact oxycodone may have on outcome in different patient groups is addressed. As oxycodone is available on different pharmaceutical formulations and as a new combination product with naloxone, the different approaches that may be used with oxycodone in postoperative pain management are also reviewed.

Expert opinion: The recent interest in oxycodone is based on its favorable pharmacokinetics and pharmacodynamics, especially in the central nervous system. Moreover, relatively high enteral bioavailability allows an easy switch from one drug formulation to another during the course of pain management. Oxycodone is highly effective and well tolerated in different types of surgical procedures and patient groups, from preterm to aged patients. In the future, the use of transmucosal administration and enteral oxycodone–naloxone controlled-release tablets is likely to increase, and an appropriate concurrent use of different enteral drug formulations will decrease the need for more complex administration techniques, such as intravenous patient-controlled analgesia.

Keywords: analgesics, elderly, obstetrics, opioid, oxycodone, pain, postoperative

Introduction

Pain is the most common adverse effect of surgery, and postsurgical pain is so severe that four out of five patients need analgesics after the procedure. Sufficient pain relief is essential not only to prevent unnecessary suffering but also to hasten recovery and the patient’s outcome after surgery. Increasing evidence shows that severe, undertreated acute pain may not only delay discharge and increase the need for hospitalization after surgery, but also is a risk factor for persistent postoperative pain [1]. Severe postoperative pain may have a significant impact on patients’ short- and long-term quality of life and may also cause significant healthcare cost to the community and, thus, should always be treated appropriately when it occurs. Because postoperative pain is the likely outcome after surgery, proactive approaches for pain control should be applied for all surgical patients [2].

Opioids are the most commonly used medications for the treatment of acute severe pain. They provide effective analgesia without loss of touch, proprioception and muscle strength. To provide adequate analgesia without severe adverse effects, the mechanism of opioid action, adverse effects and differences among opioids should be understood. The main concern for effective analgesia with opioids is, in 2012, as it was 40 years ago, an underestimation of the pain or overestimation of the duration of action of opioids and fear of the risk of abuse [3].
Oxycodone (6-deoxy-7, 8-dihydro-14-hydroxy-3-O-methyl-6-oxomorphine; Box 1) is a semisynthetic thebaine derivative μ-opioid receptor agonist, which has been in clinical use since 1917 (4). It has been the most commonly used analgesic for the management of postoperative and other acute pain in adults since the 1960s in Finland [5], and over the past two decades oxycodone use has surpassed that of morphine in several countries [6].

Oxycodone has been administered to surgical patients by different administration routes: intravenous [7], intramuscular [8], intranasal [7], transmucosal [9], subcutaneous [10], rectal [11], epidural [12] and oral [8,10,13,14]. For oral administration immediate-release solutions and immediate- and controlled-release tablets and capsules are available.

The main pharmacological effects of oxycodone and other opioids are mediated via opioid receptors in the cell membranes of presynaptic nerve endings in the CNS. These opioid receptors belong to G-protein-coupled receptor family (μ-, δ- and κ-opioid receptors) [15].

Intravenous oxycodone has been considered to have a similar potency to intravenous morphine in patients undergoing superficial or orthopedic surgery [16,17]; and in visceral pain less intravenous oxycodone than morphine is needed for sufficient analgesia in patients undergoing intra-abdominal surgery [18]. The potent opioid effect is also confirmed in children [19,20].

Clinical data indicate that, although there is a significant interindividual variation in oxycodone need in postoperative pain management, most patients may have sufficient analgesia after major surgery with 40 – 60 mg oxycodone i.v. (enteral: 60 – 100 mg) during the first 24 h after surgery. After moderate surgery, 20 – 30 mg i.v. (enteral: 25 – 50 mg) is often sufficient and in minor surgery one, two or three doses of 2 – 3 mg i.v. (enteral dose: 5 – 20 mg) should be sufficient (Table 1).

The purpose of this review is to summarize the recent pharmacological and clinical data on oxycodone use in postoperative pain management.

2. Chemistry and basic pharmacology

The oxycodone molecule consists of two planar and two aliphatic rings (Figure 1). It is a white, odorless crystalline powder derived from opium alkaloid thebaine. Oxycodone hydrochloride dissolves in water and is slightly soluble in alcohol [4]. Oxycodone has liposolubility similar to morphine; oxycodone and morphine are both significantly less lipid soluble than fentanyl. The protein binding, mainly albumin, of oxycodone (40 – 50%) is close to that of morphine (38%) and it is not affected by α1-acid glycoprotein [21].

Oxycodone is an μ-opioid receptor agonist, but it has a considerably lower μ-opioid receptor-binding affinity than morphine and oxymorphone, one of its own metabolites. Oxycodone also binds to κ-opioid and δ-opioid receptors, but with a lower affinity than to μ-receptors. The effects of oxycodone may be mediated by not only μ-receptors but also κ-opioid receptors, but this is still controversial issue [22].

2.1 Pharmacokinetics

Oxycodone is extensively metabolized in the liver. The principal oxidative metabolic pathways of oxycodone are N-demethylation to noroxycodone and O-demethylation to oxymorphone; 6-keto reduction to oxycodol accounts for < 10%. Oxycodone and its metabolites undergo additional 6-keto reduction and conjugation with glucuronic acid and are secreted into the urine. Binding to μ-opioid receptors in nerve endings in the CNS...
metabolizers (≥ 90%) [24] with highly variable CYP2D6 function [25,26]. However, in postoperative pain management polymorphism of CYP2D6 seems not to affect the analgesic efficacy of oxycodone [27].

After methylation, oxycodone and its metabolites undergo more 6-keto reduction and conjugation with glucuronic acid. Most oxycodone and noroxycodone is excreted in the urine as a free (unconjugated) form, but oxymorphone is mainly excreted in a conjugated form [8]. Oxycodone is extensively metabolized and only 8 – 14% is excreted unchanged or conjugated to urine as a parent compound [14]. The amount of first-pass metabolism in the intestinal mucosa is minimal.

The volume of distribution of oxycodone is 2 – 3 liters/kg, the clearance 0.7 – 0.8 liters/min and the elimination half-life ($t_{1/2}$) 2 – 3 h after intravenous administration. After immediate-release tablets, $t_{1/2}$ is 3 h and after controlled-release tablets 4 – 5 h. The maximum plasma concentration ($C_{max}$) is reached within 1.3 and 2.6 h after immediate- and controlled-release tablets, respectively. The maximum concentrations after immediate-release tablets are twice as
Oxycodone has a relatively high oral bioavailability (between 45 and 87%) [8,9,28]. Transmucosal administration is also an attractive administration route in acute pain management with oxycodone. Bioavailability is less after intranasal dosing of oxycodone than that after oral transmucosal administration: the intranasal bioavailability of oxycodone was 46% with a high interindividual variation [7] and 55% after oral transmucosal administration [9,29]. Oral administration is a feasible route because oxycodone has a neutral taste and thus is easily accepted by patients [29].

Gender seems to affect the pharmacokinetics of oxycodone. In healthy female volunteers, the clearance is 25% slower than that in male volunteers. The exposure of oxycodone is the greatest in elderly women and lowest in young men [30].

In patients with renal failure the elimination of oxycodone and its metabolites is impaired, the clearance is significantly smaller and volume of distribution is greater than in healthy volunteers with normal renal function [31]. In end-stage renal failure the interindividual variability of oxycodone exposure is great and, thus, in these patients, lower doses should be used, and close follow-up is needed when repeated doses are used.

Because oxycodone is metabolized in the liver, hepatic function has a significant impact on the pharmacokinetics and pharmacodynamics of oxycodone. In hepatic insufficiency, volume of distribution is higher and clearance of oxycodone is lower than in healthy subjects with normal liver function. In end-stage liver disease the t1/2 of oxycodone is lower than in healthy subjects with normal liver function, volume of distribution is higher and clearance of oxycodone is significantly impaired, the clearance is significantly lower than in healthy volunteers with normal liver function [31]. In end-stage renal failure the interindividual variability of oxycodone exposure is great and, thus, in these patients, lower doses should be used, and close follow-up is needed when repeated doses are used.

As the analgesic action of oxycodone is mainly due to the parent compound rather than its metabolites, drugs affecting the CYP3A and 2D6-mediated metabolism have important effects on the pharmacokinetics of oxycodone, but the pharmacodynamic effects of oxycodone may not alter. Rifampicin induces CYP3A4 and can increase the metabolism of oxycodone and decrease its efficacy as an analgesic [33]. On the other hand, drugs that block the CYP3A4-mediated metabolism of oxycodone (e.g., voriconazole), can, at least in theory, increase the effects of oxycodone [34].

3. Clinical use

3.1 Efficacy in acute postoperative pain

Intravenous oxycodone is an effective treatment for acute postoperative pain. In one of the earliest studies comparing morphine and oxycodone in patients with corrective breast or lumbar spinal surgery in which patients used intravenous patient-controlled analgesia (PCA) for postoperative pain relief, a similar amount of morphine and oxycodone was needed for sufficient analgesia [17]. In a subsequent study in patients scheduled for the abdominal surgery, intravenous oxycodone provided faster pain relief with smaller doses than morphine, indicating a potency ratio of oxycodone and morphine of 2.3 [18]. In a recent study in patients with laparoscopic hysterectomy, similar intravenous PCA opioid consumption, pain scores and adverse-effect profile were found in patients randomized to oxycodone or morphine [35]. This indicates that not only the type of surgery but also the extent of surgery may affect the comparison of different opioid analgesics.

A Cochrane review has evaluated the efficacy of single-dose, immediate-release oxycodone in postoperative pain management. It was concluded that oxycodone is an effective analgesic in acute postoperative pain and that oxycodone is two to three times stronger than codeine. Moreover, the efficacy of oxycodone was found to increase when combined with paracetamol [36].

The efficacy of controlled-release oxycodone in postoperative pain has been demonstrated in several studies [37,38]. However, the use of prolonged-release oxycodone in postoperative pain should be qualified, and controlled-release tablets are not recommended for preoperative use or for the first 24 h postoperatively, firstly because the gastrointestinal function during the immediate perioperative period is altered and, secondly, in acute pain controlled-release tablets are not a feasible dosage form for the dose titration.
Fewer data are available on spinal use of oxycodone and the data are inconsistent. When oxycodone or morphine were administered epidurally to surgical patients, the final epidural dose ratio between morphine and oxycodone was 1:9 to provide comparable analgesia, indicating less intraspinal potency than morphine. During the infusion, plasma concentrations of oxycodone were similar with intravenous and epidural administration [12]. A more recent study in patients undergoing gynecological surgery indicates that oxycodone may have some efficacy in epidural use. In that study, an epidural bolus dose of oxycodone 4 mg followed by a continuous epidural infusion of 12 mg/24 h was found equally efficacious to morphine 2 + 6 mg/24 h, but at a 2 + 6 mg/24 h dose oxycodone was inferior to epidural morphine. However, safety was better with oxycodone and adverse effects were less common with epidural oxycodone than with morphine [39].

3.2 Ear, nose and throat surgery

In ear, nose and throat (ENT) surgery perioperative bleeding is a main concern and in patients with nasal polyposis and ASA (Acetylsalicylic acid)-induced asthma nonsteroidal anti-inflammatory analgesic drugs (NSAIDs) are contraindicated. Paracetamol affects thrombocyte function, though to a lesser extent than NSAIDs. In risky operations and in at-risk patients NSAIDs and paracetamol should be given only after primary hemostasis has been developed. Thus, opioids are often the first-line analgesics in postoperative pain management in ENT surgery.

Oxycodone has been used in a variety of ENT procedures; after myringotomy and adenoïdectomy one or two doses of 0.05 mg/kg i.v. may be sufficient, but after tonsillectomy postoperative pain is more severe and the need for opioid analgesics is higher [40]. Endoscopic sinus surgery causes less pain than throat surgery. If nonopioid analgesics are contraindicated, most patients need one or two 2-mg i.v. doses of oxycodone during the first hours after surgery [41].

Oxycodone need during the first 24 h after tonsillectomy is 0.25 – 0.3 mg/kg of body weight. Nonopioid analgesics improve analgesia both at rest and during swallowing and have a significant opioid-sparing efficacy. In patients with scheduled nonopioid analgesics for background analgesia, the need for oxycodone during the first 24 postoperative hours is 0.15 – 0.2 mg/kg i.v. [42,43].

Most tonsillectomies are performed as day cases. Typical doses of oxycodone in adult patients during the first 6 h after tonsillectomy are i) up to 10 mg i.v. (i.e., 0.1 – 0.15 mg/kg) if no background analgesia has been used; ii) 5 – 6 mg i.v. in conjunct with either paracetamol or NSAID; and iii) 2 – 3 mg i.v. with a combination of paracetamol and NSAID [42-46].

In tonsillectomy patients not only background analgesia but also the surgical technique may affect the need for rescue oxycodone. In patients with a recently launched tissue welding technique, only one or two 2-mg i.v. doses of oxycodone may provide sufficient postoperative analgesia after tonsillectomy [47].

3.3 Thyroid surgery

Oxycodone has performed well in superficial surgery like thyroid surgery. In most of these studies oxycodone has been used as a part of a multimodal approach. In a placebo-controlled, double-blinded study the need for oxycodone during the first 24 h after thyroid surgery was 10 – 12 mg both in the active group – cyclo-oxygenase-2-inhibitor etoricoxib 120 mg was given by mouth 60 min before anesthesia – and in the placebo group [48]. In another recent study with no background nonopioid analgesia, the oxycodone consumption was similar. In contrast to the study hypothesis, the need for oxycodone was not higher in poor metabolizers for CYP2D6 (13 mg/24 h) than that in extensive metabolizers (16 mg/24 h). This indicates that in acute pain management the analgesic action is from the parent compound and the active metabolites do not have any clinically meaningful impact on analgesic efficacy [27].

In an earlier study the mean of oxycodone consumption during the first 24 h after thyroid surgery was higher (0.33 – 0.35 mg/kg) [49]. In the Jokela et al. study [49], a conventional open surgical technique was used, while in the Smirnov et al. study [48], ultrasonography scissors were used for tissue preparation. Thus, the twofold higher need for oxycodone in the Jokela et al. study [49] indicates that that the surgical technique may have a significant impact on patient recovery and need for postoperative opioids.

3.4 Breast surgery

The analgesic efficacy of oxycodone has been compared with that of tramadol in patients with breast surgery. Patients were randomized to receive either oxycodone 20 mg or tramadol 200 mg controlled-release tablets on a 12-h schedule. Pain scores at rest and during coughing, and the incidence of postoperative nausea and vomiting (PONV) were similar with both drugs during the first 24 h after surgery. In numeric values the need for rescue analgesia was less in the oxycodone group, but because of a small sample size the difference was not statistically significant. Based on the results, a potency ratio of 1:10 was estimated for oxycodone:tramadol [50]. In an earlier study in patients with maxillofacial surgery a potency ratio of 1:8 for oxycodone:tramadol was reported by Silvasti et al. [51]. A most important finding was that oxycodone was associated with significantly less PONV than tramadol, indicating that oxycodone is better tolerated.

In a multimodal pain treatment model, in which patients in the intervention group were provided a single paravertebral injection of bupivacaine, the need for oxycodone during the first hours after surgery was significantly less than that in the no-injection group, 5 vs 9 mg, respectively [52].

3.5 Gastrointestinal surgery

Gastrointestinal surgery is associated with both wound pain and visceral pain, and oxycodone has been shown to have highly potent analgesic action in these cases.
Contrary to common belief, the need for opioid analgesics in the early recovery period after cholecystectomy is not less after laparoscopic surgery than after open surgery [52-54]. Later in recovery opioid consumption is significantly less in patients having had laparoscopic surgery than in those having had open cholecystectomy [55].

Recent studies support existing data that there is a significant interindividual variation in the need for oxycodone for sufficient analgesia [53,54]. Preoperative patient history also seems to affect the need for opioid analgesics. In a recent study the need for oxycodone was two times higher in patients who had surgery due to chronic cholecystitis compared with patients having minilaparotomy cholecystectomy due to simple gallstone disease [56]. Consistent with Harju et al. [53], in another study in patients with laparoscopic cholecystectomy there was a high interindividual variation for the need for oxycodone: for some patients oxycodone 10 mg i.v. was sufficient, while some needed 40 mg i.v. [57].

Different combinations of background analgesics did not affect significantly the oxycodone consumption during the early phase of recovery after laparoscopic cholecystectomy. The mean dose of oxycodone was between 18 and 22 mg in patients with coxib, paracetamol or dexamethasone, or different combinations of these three drugs [58].

### 3.6 Orthopedic surgery

High analgesic efficacy of oxycodone has been shown also in orthopedic surgery. Postoperative pain after bone surgery is often severe. In patients with first metatarsal bone osteotomy and paracetamol 1 g t.i.d. for background analgesia, the mean oxycodone consumption during the first 72 h after surgery was 59 mg in patients with dexamethasone 9 mg by mouth and 83 mg in patients with no dexamethasone supplementation [59].

Intravenous oxycodone has been found to be a highly effective mode to treat early pain after more extensive orthopedic surgery; a high analgesic efficacy has been demonstrated in acromioplasty [60], spine surgery [61,62] and knee [63] and hip arthroplasty [38]. In lumbar disc surgery, controlled-release oxycodone 20 mg b.i.d. by mouth reduced the need for intravenous PCA morphine during the first 24 h after surgery (26, vs 52 mg in the placebo group); a similar morphine-sparing efficacy was found also for the 25 - 48 h post surgery (i.v. PCA morphine 13 mg in the patients with oxycodone vs 33 mg in the placebo group). In both groups, the patients had paracetamol 1 g i.v. every 6 h for background analgesia. In patients with oxycodone the incidence of PONV was lower, bowel function recovered earlier and the patient satisfaction with pain management was higher than in the control group [62].

### 3.7 Eye surgery

In contrast to efficacy comparison in patients with breast surgery, in which the analgesic oxycodone-to-tramadol ratio was 1:8 – 1:10 [50,51], in eye surgery oxycodone seems to be more effective. In retinal surgery, controlled-release oxycodone 10-mg tablets were compared with a drug combination of tramadol 100 mg/metamizol 1 g i.v. The oxycodone-treated patients rated quality of analgesia significantly higher than the tramadol/metamizol-treated patients. The incidence of adverse effects and number of patients discontinuing study medication were less with oxycodone, indicating that in eye surgery oxycodone could be superior to tramadol [64].

### 3.8 Gynecological surgery

Women report more severe pain and have greater analgesic responses to opioids than men, indicating that there are sex differences in nociceptive responses and pain perception [65]. However, in postoperative pain perception and opioid consumption, gender seems not to be as important a predictor as traditionally believed [66].

Oxycodone has been evaluated in gynecological surgery and caesarean section most often combined with paracetamol or NSAIDs. The theoretical background behind oxycodone use as part of multimodal analgesia [67] is that higher doses of opioids increase the risk for opioid-induced hyperalgesia and other adverse effects [68].

In North America oxycodone is commonly used as a combination product with ibuprofen or paracetamol. Both oxycodone 5 mg/ibuprofen 400-mg tablets and oxycodone 5 mg/paracetamol 325-mg tablets provide enhanced analgesic action compared with pure opioid-based analgesia in women undergoing abdominal or pelvic surgery [69-71]. In one study in 60 women undergoing elective laparoscopic surgery, preoperative administration of oxycodone 15 mg by mouth did not enhance analgesia achieved with ibuprofen 800 mg [72]. However, the mean of oxycodone’s $C_{\text{max}}$ was low at 10.0 mg/ml (range 4.6 - 14.7 ng/ml) and $T_{\text{max}}$ was 4.8 h (range 2 - 8 h), indicating that in most patients subtherapeutic concentrations were achieved [19] and that peroral administration was not optimal in this indication, because PONV, anesthesia and surgery delay and decrease the absorption of peroral medicines [9,99].

In laparoscopic hysterectomy consistent effects of different types of adjuvant analgesics on oxycodone need have been shown. In three studies in which a similar protocol was used, oxycodone was administered by intravenous PCA pump (oxycodone 1 mg/ml and droperidol 0.05 mg/ml, oxycodone i.v.-bolus dose 0.04 mg/kg and a lockout time of 8 - 10 min). In the control groups the total dose of oxycodone during the first 24 h after surgery was 0.45 - 0.55 mg/kg. Paracetamol 1 g every 6 h [73], pregabalin 600 mg by mouth before surgery [74] and dexamethasone 15 mg i.v. [75] provided a similar opioid-sparing efficacy; the total dose of oxycodone was 0.34 mg/kg/24 h in all three studies. However, the individual variation in oxycodone need was significant, and the need for intravenous PCA oxycodone varied more than 10-fold, being between 0.1 and 1.3 mg/kg/24 h.

An early finding that after major abdominal surgery less oxycodone than morphine is needed for pain relief [18] has been confirmed recently by Lenz and colleagues [35] in...
patients with laparoscopic hysterectomy. The consumption of oxycodone with intravenous PCA (13 mg/24 h) was significantly less than that of morphine (22 mg/24 h).

3.9 Thoracic and cardiac surgery

Opioids are a basis in the treatment of postoperative pain after thoracic surgery. However, adverse effects of opioids such as sedation, respiratory depression, biliary spasm, gastrointestinal dysfunction and PONV necessitate the use of adjuvant analgesics to reduce opioid consumption and adverse effects.

In coronary artery bypass grafting (CABG) surgery patients the mean need for intravenous PCA oxycodone is 50 – 60 mg during the first 24 postoperative hours and it decreases on the following days. As in other indications, in CABG surgery interindividual variation in opioid need is significant. In a recent study, the range of intravenous oxycodone need for initial titration for comfort in the ICU was 0 – 16 mg; intravenous PCA oxycodone consumption during the first 24 h between 6 and 94 mg, and for postoperative hours 25 – 48 between 8 and 110 mg; the cumulative consumption during the first 48 h was between 14 and 239 mg [76]. In another study S-ketamine provided a modest oxycodone-sparing efficacy: mean intravenous PCA oxycodone consumption was 103 mg/48 h in the S-ketamine group and that in the placebo group 125 mg/48 h [77]. In another study, contrary to the study hypothesis, the choice of intraoperative opioid did not affect postoperative oxycodone need; oxycodone consumption in patients with intraoperative sufentanil ranged between 42 and 219 mg/48 h and in patients with remifentanil between 29 and 166 mg/48 h [78].

Cardiothoracic surgery, like gastrointestinal surgery, is a condition in which the switch from parenteral administration to enteral dosage forms should be carefully considered. Once patients are able to tolerate analgesics by mouth, the oral route is preferred because it is more convenient, noninvasive and less expensive. However, when oxycodone or any other opioids are swallowed soon after surgery, first delayed and then abrupt absorption of an increased amount of opioids when gastrointestinal function is restored should be taken in account. During the first 48 h after cardiac surgery absorption of oral drugs is low [79], and thus the use of tablets should be postponed after that period. Later, when gastrointestinal function is restored, peroral preparations may perform sufficiently [80]. Use of oxycodone by mouth for postoperative pain management after cardiothoracic surgery warrants additional studies, and oral transmucosal administration should be tested also in this patient population.

3.10 Neurosurgery

Pain following craniotomy is common and often moderate or severe; 60% of patients have significant pain after craniotomy [81].

In some institutions opioids are avoided in craniotomy patients because of their risk to cause respiratory depression, PONV and sedation, which may interfere with the neurological examination [80]. However, lower doses of oxycodone have been well tolerated also in neurosurgery. In one study in adult patients, intravenous oxycodone with PCA-device settings of bolus dose 0.03 mg/kg, lockout time 10 mins, no background infusion and a maximum of three boluses/ hour provides an effective and well-tolerated analgesia. Less oxycodone was used during the first 24 h after cranial surgery in patients with ketoprofen 100 mg i.v. t.i.d. (20 mg/24 h) than those with paracetamol 1 g t.i.d. (37 mg/24 h), respectively. No severe or serious drug-related adverse effects were reported [82]. In another small study, the need for oxycodone 5 mg/paracetamol 325 mg tablets was less in patients with COX-2-inhibitor rofecoxib (mean dose of oxycodone 32 mg by mouth) than that in those with no rofecoxib (68 mg) [83].

These results indicate that small doses of opioids can provide safe and effective pain relief also in craniotomy patients. However, more studies in intracranial surgical patients are needed, because sample sizes in the published studies have been small.

4. Oxycodone in elderly patients

The average age of the population is increasing in all countries, and the number of aged (≥ 80 years) surgical patients is the fastest-growing patient group. Pain management in aged patients is complicated owing to age-related changes in pharmacokinetics, and multipharmacy, which is common in the elderly [84].

Age affects the pharmacokinetics of oxycodone. In the elderly, oxycodone exposure is up to 80% greater and clearance is 30% lower than in young adults and, thus, at 8 h after oxycodone administration plasma oxycodone concentration is twofold higher in aged subjects than in young adults [30,54,85].

Multipharmacy is an issue because concomitant medications may alter oxycodone pharmacokinetics. CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, ritonavir and grapefruit juice) have been evaluated in young healthy adults and in the elderly. CYP3A4 inhibition increases exposure to oxycodone and its active metabolite, oxymorphone, in the two age groups in a similar manner. However, neither age nor CYP3A4 inhibition influence oxycodone effects in cold pain threshold, cold pain intensity, self-rated behavioral measurements, pupil size, Maddox wing test or the digit-symbol substitution test [86]. CYP3A4 inducers, such as rifampicin and St John’s Wort, enhance elimination and decrease oxycodone exposure. Similar to CYP3A4 inhibition, CYP2D6 inhibition (e.g., paroxetine) prolongs oxycodone elimination twofold and increases oxycodone exposure twofold, but with no pharmacodynamic consequences when single doses are used in acute pain management.

Intravenous oxycodone is a feasible opioid analgesic for postoperative pain management in the elderly. In cardiac surgery patients, the mean effective analgesic concentration of oxycodone is similar in young adults and in the elderly. In a recent study, three doses of oxycodone 0.05 mg/kg i.v. were given for patients recovering from cardiac surgery. The
older patients had less pain but were more sedated after the third oxycodone dose than the younger patients. However, fentanyl concentrations were significantly higher in the elderly for several hours after surgery, and in that study this is the most likely cause for the greater sedative effect observed [87].

Oxycodone by mouth has been evaluated in the elderly for postoperative pain management after knee or hip arthroplasty. In one study, oxycodone controlled-release tablets were equally effective with intravenous PCA morphine in patients with hip and knee arthroplasty. Although pain scores were similar in the two groups the amount of rescue analgesics during the hospital stay was lower and the duration of hospital stay was shorter (5.5 vs 6.4 days) with controlled-release oxycodone tablets than with intravenous PCA morphine. Adverse effects, somnolence and constipation, were more common with oxycodone, but PONV was more common with morphine [88]. In a recent study in 114 elderly patients, 20-mg oxycodone controlled-release tablets b.i.d. with immediate-release oxycodone for rescue analgesia was compared with intravenous PCA morphine after total hip arthroplasty. There were no differences in pain scores at during the first 72 h after surgery. Patients taking intravenous PCA morphine received more antiemetics than patients taking oxycodone [38].

Pain relief with oxycodone 10 mg b.i.d. by mouth as part of a multimodal approach was as effective as epidural ropivacaine in patients after radical retropubic prostatectomy. However, the safety profile of oxycodone was better than that of epidural ropivacaine. Epidural infusion was terminated before the end of the planned 3-day study period in 8/20 patients, with adverse effects, loss of sensory function, hypotension or poor efficacy being the most common reasons [89].

Although oxycodone can be used in elderly patients, postoperative pain management approaches in frail elderly patients have not been established and more studies are needed on the use of oxycodone in this special patient group.

5. Patient controlled analgesia

Oxycodone is the drug of choice for PCA opioid administration in Finland [5]. The common starting doses for opioid-naive patients are a bolus dose of 0.02 – 0.03 mg/kg with a lockout time of 10 min and a maximum of four doses in an hour. Patient preference for intravenous PCA is higher compared with conventional regimens. However, evidence does not support the common belief that intravenous opioid PCA would provide better analgesia than other opioid regimens. If there is enough nursing staff, and appropriate use and combination of different oxycodone formulations is applied in multimodal analgesia, the superiority of intravenous PCA oxycodone may be less evident. Also, the evidence regarding PCA opioid consumption is contradictory; both no change and an increase in consumption have been reported [90].

In a multimodal analgesia, oxycodone controlled-release tablets provide similar or slightly more effective analgesia than intravenous opioid PCA. In a recent study in patients with hip arthroplasty, oral oxycodone, as a component of multimodal pain management, at a mean dose of 103 mg/50 h, provides similar pain relief and outcome as intravenous PCA with morphine [38]. The feasibility of oral multimodal pain management with controlled-release multimodal pain management with controlled-release oxycodone tablets has been shown also in patients with spine surgery. In a recent study, the need for intravenous PCA morphine was less and the pain-related interface with walking, coughing and deep breathing was also less in patients using a multimodal approach than that in patients with intravenous morphine [63].

Oxycodone intravenous PCA is a feasible mode for example in orthopedic surgery. Recently it has been evaluated in 45 patients with acromioplasty. For concomitant analgesia these patients received one of a single-injection interscalene plexus block, a subacromial bursa block or placebo. Oxycodone consumption was greatest in the placebo (27 mg) and subacromial block (24 mg) groups, but with plexus block the need for oxycodone was significantly less (6 mg i.v.) [60]. Intravenous PCA oxycodone with or without concomitant NSAIDs (ketoprofen or diclofenac) was evaluated in 64 knee arthroplasty patients. Both NSAIDs had an oxycodone-sparing efficacy: oxycodone consumption in the ketoprofen group was 43 mg, in the diclofenac group 45 mg and in the placebo group 61 mg [63].

Respiratory depression is a major concern with opioid analgesics. An important safety issue for oxycodone is fast onset of action after intravenous administration. Olkkola et al. [19] have shown that after oxycodone 0.1 mg/kg i.v. the maximum mean end-tidal carbon dioxide concentration and minimum mean ventilatory rate occurs within 8 min after oxycodone administration, and that the minimum mean peripheral arteriolar oxygen saturation occurs even earlier, at 4 min after oxycodone dosing in children recovering from deep-inhalation anesthesia. There are other isolated reports suggesting that, besides a faster onset of intrinsic antinociceptive effect, oxycodone administration also demonstrates a rapid onset of its respiratory effects, if any, compared with some other opioids. This has been shown also in healthy adult volunteers having stable inhalation anesthesia. In a recent study, oxycodone produced dose-dependent respiratory depression across the doses evaluated [91].

One of the main safety issues with PCA systems is the stability of compounds in the syringes and the reservoirs. The microbial and physicochemical stability of oxycodone hydrochloride solutions in PCA reservoirs have been noted for different diluted solutions [92].

The complex programming processes in setting up and potential technical errors in using the equipment are risk factors for medication errors when PCA-pumps are used for intravenous administration of opioids. Based on recent studies in postoperative analgesia with controlled-release oxycodone tablets which show equal efficacy with fewer adverse effects and technical problems than with opioid PCA, the use of
controlled-release oxycodone as part of multimodal analgesia is recommended.

6. Intraspinal administration

Neuraxial opioids are commonly used in postoperative pain management, and both intrathecal [93] and epidural opioids [94] have been shown to provide potent analgesic efficacy either alone or combined with local anesthetics.

There are no reports of intrathecal efficacy of oxycodone, and only two studies have evaluated epidural use of oxycodone— with contradictory results. In the first study, in patients after major abdominal surgery, no advantage was found in epidural administration of oxycodone (dose: 65 mg/24 h) compared with intravenous oxycodone (dose: 72 mg/24 h). In the control group, epidural morphine provided significant analgesic efficacy with a total dose of 8 mg/24 h. There were no differences with pain scores at rest but dynamic pain, pain during coughing, was better controlled with epidural oxycodone than with morphine. The adverse-effect profiles were similar in the three study groups [12].

A more recent study indicates that oxycodone may have analgesic efficacy also when administered into the epidural space. Yanadig...[39] studied epidural oxycodone in patients undergoing gynecological surgery. Postoperative pain was treated with: i) oxycodone 2-mg epidural bolus followed by continuous epidural infusion of 6 mg/24 h; ii) oxycodone 4-mg epidural bolus followed by 12 mg/24 h infusion; and iii), in the control group, morphine 2-mg bolus and 6 mg/24 h infusion. Oxycodone 4 + 12 mg was equally efficacious, but oxycodone 2 + 6 mg was inferior to morphine 2 + 6 mg. Safety was better with oxycodone and adverse effects were less common with epidural oxycodone [39].

More clinical studies of epidural and intrathecal use are warranted, as oxycodone may have more favorable CNS pharmacokinetics than other opioids [95,96].

7. Adverse effects of oxycodone

Adverse effects of oxycodone are typical of opioid agonists, with CNS depression and gastrointestinal dysfunction the most commonly reported. In acute pain management, appropriate patient monitoring may detect potential adverse reactions early. However, in significant overdoses, respiratory depression and cardiovascular collapse may result, and prompt treatment should be initiated to establish open airway, assisted ventilation and circulatory support. Repeated doses of naloxone 0.4 – 2 mg i.v. may be administered. In acute pain management, if the patient is not monitored, the outcome after opioid-induced respiratory depression can be fatal [97] (H Kokki, personal communication).

One of the most common adverse effects of opioids is gastrointestinal dysfunction including constipation, abdominal fullness and sense of incomplete bowel emptying, which are often associated also with urinary disorders. These adverse effects are thought to be mediated by stimulation of opioid receptors in the gastrointestinal tract and in the bladder [98]. Constipation may be prevented with laxatives, but constipation may persist despite appropriate laxative use. In chronic pain management there is good evidence that oral naloxone could reverse oxycodone-associated bowel dysfunction [99], and our initial experiences in acute pain management are encouraging on both bowel and bladder dysfunction reversal.

There seem to be some differences in adverse drug reactions associated with different opioids. Several reports indicate that oxycodone may cause fewer hallucinations and nightmares than morphine [10,100,101]. Oxycodone decreases arterial blood pressure less compared with morphine in equianalgesic doses [18]. This may be related to the fact that oxycodone does not release significant amounts of histamine as does morphine. Lesser release of histamine may explain also why itching is less common with oxycodone compared with morphine, although other mechanisms are also involved [13,102]. An in vitro study indicated that oxycodone may not suppress the immune system as much as morphine [103]. However, the clinical significance of this finding remains unclear in acute postoperative pain management. In acute use, physical dependence and withdrawal syndrome are not common but should be taken in account if the need for oxycodone is prolonged.

Oxycodone is extensively metabolized by CYP2D6 and CYP3A enzymes and it is thus prone to drug interactions. The inhibition of metabolizing enzymes may lead to clinically relevant increase in oxycodone concentrations, and inhibition of these enzymes decreases oxycodone exposure. Whether these interactions are associated with any safety concerns in clinical practice remains an open question because in acute postoperative pain management oxycodone should always be titrated to the effect [104]. Because the lipophilicity of oxycodone is relatively low, its penetration into the CNS is limited. Simultaneous use of other drugs affecting the CNS or CNS drug penetration may potentiate the effects of oxycodone [13,105].

Opiates are the main problem drugs among persons receiving treatment for drug abuse in Europe, as they are in many countries [6]. Oxycodone is a pure opioid agonist and it is associated with abuse potential. In 2010 in the USA, there were just under 600000 new nonmedical users of oxycodone [6]. Abuse potential should be taken in account when prescribing oxycodone for patients with known abuse risks. Formulations that provided stable concentrations or are combined with opioid antagonist naloxone should be safer in acute pain management in risk patients. Oxycodone is most often abused intravenously or by snorting [106]. In the future there will be new tamper-resistant oxycodone formulations available for clinical use which should decrease the risk for oxycodone abuse.

8. Future aspects

Enteral bioavailability of oxycodone is relatively high and thus it is likely that in the future enteral administration will be the most popular route to administer oxycodone for postoperative pain. The indications to use intravenous PCA for oxycodone...
administration will decrease and focus more on major surgery. Emerging data seem to indicate that optimal pain control can be achieved by combining a scheduled controlled-release formulation with immediate-release oxycodone as needed for rescue analgesia, pointing to a new standard for the near future.

In all postoperative patients, the gastrointestinal tract does not function optimally for oral administration of analgesics. Recently, an orodispersible tablet, approved in some countries, provides a promising option for oxycodone administration in this situation. Transmucosal use of oxycodone facilitates the optimal dose titration with orodispersible tablets in the early phase of recovery and is a feasible formulation for rescue analgesia in the later course of recovery. Moreover, some patients cannot or are not allowed to swallow drugs (PONV, gastrointestinal surgery patients with gastric suction, children, the elderly, etc.), and in these patients oral transmucosal administration should be an optimal route.

Experimental studies indicate that a sublingual spray solution dosage form with adjusted pH may provide fast onset of pain relief. The pH of the solution is important because it affects transmucosal absorption. In the future, oxycodone spray solution may provide an easy and economical way for postoperative pain treatment in the early phase of recovery [87].

Opioids are associated with high incidence of adverse effects. In the first hours after surgery respiratory depression and risk for PONV are the two most common concerns. Thus, close monitoring and an appropriate combination of nonopioid analgesics as part of multimodal approach will decrease the need for oxycodone and are likely to reduce the risk of serious complications. Later in the course of recovery, bowel dysfunction is the most harmful adverse effect for patients. In this instance, the new controlled-release combination depot tablet, containing oxycodone and naloxone in a 2:1 ratio, is promising. Our own initial experiences in acute pain management have been encouraging so far. In our quality assurance project in pain management we found that in patients on opioids before spine surgery switching to oxycodone–naloxone improved not only bowel function but also bladder function (data not shown). Additional studies are needed to show how well the oxycodone–naloxone product will fit with postoperative pain management protocol.

Opioids are associated with abuse risk, and this should be taken in account also in postoperative pain management while prescribing oxycodone. Oxycodone formulations less prone to abuse are under development.

9. Expert opinion

In Finland, oxycodone has been the most popular opioid in acute pain management for the last 50 years, and in pediatric pain management we have 30 years’ experience with oxycodone. During the last decade the use of oxycodone has surpassed that of morphine in several other countries [6], and it is likely to increase in the future. The new interest in oxycodone is based on the favorable pharmacokinetics and pharmacodynamics of oxycodone especially in the target site, in the CNS. The analgesic efficacy of parenteral oxycodone is similar to that of morphine in somatic pain and superior in visceral pain. Moreover, the onset of analgesic action is relatively fast and the relatively high enteral bioavailability allows an easy switch from one drug formulation to another during the course of pain management. Other reasons why oxycodone use is increasing in postoperative pain management is that oxycodone does not release histamine, and the risk for some other adverse effects such as nightmares and hallucinations is low.

Oxycodone is highly effective and well tolerated in different types of surgical procedure and in different patient groups. Its use is relatively safe also in special patient groups and in patients with renal or hepatic failure, and age is no contraindication for oxycodone – it is used both in preterm neonates and in elderly patients.

In future the use of oral transmucosal administration and swallowed oxycodone–naloxone controlled-release tablets is likely to increase. Appropriate concurrent use of these drug formulations will decrease the need for more complex administration techniques, such as intravenous PCA. The transmucosal bioavailability of oxycodone is high and new transmucosal formulations, orodispersible tablets and pH-adjusted liquids should provide feasible options for effective pain management in patients with impaired gastrointestinal function and in patients who should not or do not swallow drugs. A new combination product, a controlled-release oxycodone–naloxone tablet, may make it possible to overcome some of the harmful adverse effect of opioids, for example bowel and bladder dysfunction. The oxycodone–naloxone combination should be useful also in surgical patients because anesthesia, perioperative bed rest and surgery itself impair bowel and bladder function. Controlled-release tablets will provide a constant background oxycodone concentration and a immediate-release transmucosal formulation may offer a fast-acting option for rescue analgesia.

The use of these new products in postoperative pain management warrants additional studies. More data are needed in pharmacokinetic–pharmacodynamic interactions of oxycodone with other analgesics and perioperative medications. For effective and safe use of oxycodone, and for other opioids as well, it is important to know the analgesic concentrations at the target sites. We need to know the minimal analgesic concentrations for different types of surgery and different type of analgesic combination. For example, ketamine, an N-methyl-D-alanine receptor antagonist, is a useful concomitant compound with some other opioids in postoperative pain management. Whether this is the case with oxycodone should be evaluated. More data are needed also on intraspinal use of oxycodone because our current knowledge is sparse and controversial.

Declaration of interest

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Oxycodone hydrochloride trihydrate

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