Epidural Oxycodone for Acute Pain

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Oxycodone is a feasible opioid for epidural analgesia. Pruritus and PONV may be reduced with epidural oxycodone compared to epidural morphine. Epidural analgesia is commonly used in labour analgesia and in postoperative pain after major surgery. It is highly effective in severe acute pain, has minimal effects on fetus and newborn, may reduce postoperative complications, and enhance patient satisfaction. In epidural analgesia, low concentrations of local anaesthetics are combined with opioids. Two opioids, morphine and sufentanil, have been approved for epidural use, but there is an interest in evaluating other opioids as well. Oxycodone is one of the most commonly used opioids in acute pain management.

epidural analgesia oxycodone

1. Historical Aspects of the Pharmacology of Epidural Opioids

The clinical practice of spinal opioid administration for pain relief is based on observations in animals that opioid receptors exist not only in the supraspinal sites, but also in the substantia gelatinosa in the dorsal horn and in the dorsal root ganglia of the spinal cord [1][2]. Clinical use of epidural opioids began in the late 1970s, when analgesia with epidural morphine was introduced by Behar and colleagues [3].

Epidural morphine initially garnered interest because a single injection could produce long-lasting analgesia without hampering motor function, which is common with epidural local anaesthetics. However, late respiratory depression, assumedly caused by the rostral migration of morphine in cerebrospinal fluid (CSF), became a concern regarding epidural morphine soon after its introduction in clinical use. Thereafter, there has been interest in studying other opioids in epidural analgesia [4].

The lipophilic opioids fentanyl and sufentanil have become commonly used epidural opioids since the 1990s. Their epidural administration offers similar analgesia with a lower dose and less adverse drug events compared to intravenous (i.v.) administration [5][6][7][8]. Fentanyl and sufentanil have a relatively short duration of analgesic action after single injection, and that is why they are used mainly as continuous infusions [9][10].

Experimental ones in the 1990s and early 2000s have shown that liposolubility is a major determining factor in PK and the clinical effects of epidural opioids [11]. When opioids are injected epidurally, they must penetrate the meninges, CSF and spinal cord white matter to reach their site of action in the spinal cord. After epidural administration, opioids are also absorbed into epidural fat and into the systemic circulation. Lipophilic opioids

accumulate into lipid-rich tissues such as epidural fat and spinal cord white matter. Consequently, their exposure in CSF and the extracellular space of the spinal cord is lower than that of hydrophilic opioids [11][12].

In humans, it has been found similar results. Lipophilic opioids are more readily cleared from CSF than hydrophilic opioids. The clearance from CSF is 27 μg min^{-1} kg^{-1} for sufentanil and 2.8 μg min^{-1} kg^{-1} for morphine after intrathecal administration [13][14].

This higher clearance from CSF has been assumed to explain why late respiratory depression is less common with lipophilic opioids. As lipophilic opioids are readily cleared from CSF, their cervical CSF concentrations are lower than those of morphine after epidural administration [15][16][17]. However, early respiratory depression is a concern with lipophilic opioids, which may be explained by rostral spread in CSF and absorption into the systemic circulation [17].

The CSF bioavailability of epidural opioids is substantially lower than that of local anaesthetics and α-2 adrenergic agonists.

2. Oxycodone

2.1. General

Oxycodone is a commonly used opioid worldwide. Oxycodone has some advantages over morphine: higher per oral (p.o.) bioavailability, faster onset of analgesia, higher efficacy in visceral pain, less histamine release and fewer hallucinations [18][19][20][21]. Patient satisfaction is also higher in patients receiving oxycodone than in those receiving morphine [22]. Due to its high bioavailability, oxycodone is suitable for p.o. and transmucosal administration, and it is also given intramuscularly, i.v. and subcutaneously. In contrast to these administration routes, there have been limited data on the spinal use of oxycodone until recent years [23].

2.2. Experimental Animal Studies

The first data on neuraxial administration of oxycodone in animals were published in the early 1990s. Plummer (1990) and Pöyhiä & Kalso (1992) found that after intrathecal administration, the antinociceptive effect of morphine (hot-plate and tail-flick tests) was 14 times more potent than that of oxycodone in rats. The onset of the antinociceptive effect was faster with oxycodone but it was also of shorter duration compared to morphine. [24][25]. In line with earlier data in rats, it was later found that the median effective dose (ED50) for the antinociceptive effect (tail-flick test) for intrathecal oxycodone was 15 times higher than that of morphine in mice [26]. In contrast to intrathecal administration, after subcutaneous and intraperitoneal administration, oxycodone was 2–4 times more potent than morphine [25].

This discrepancy in the route-dependent antinociceptive efficacy of oxycodone is thought to result from its active uptake in the blood–brain-barrier (BBB) [27][28], but a relatively low μ-opioid receptor binding affinity and ability to activate the G-proteins [26][29][30][31][32][33].

In rat central nervous system (CNS) tissue, oxycodone has a lower efficacy and potency to activate G-proteins than morphine and oxymorphone, especially in the periaqueductal grey and spinal cord. The antinociceptive efficacy and potency of intrathecal oxycodone is also lower compared to intrathecal oxymorphone [34].

Two recent experimental ones in 2018 and 2019 by Kinnunen and colleagues have evaluated the epidural administration of oxycodone. Pregnant sheep were given an epidural loading dose of 0.1 $mg \cdot kg^{-1}$ oxycodone followed by either a continuous infusion or repeated boluses of epidural oxycodone for five days. After five days, arterial blood samples were collected, the animals were killed and CSF and CNS tissue samples were obtained for analysis. Cervical CSF samples were obtained by cisternal magna punctures and CNS tissue samples were obtained from the cortex, thalamus, cerebellum and spinal cord. Oxycodone concentrations in the spinal cord were up to 400 times higher than brain concentrations. In humans, opioid concentrations in CSF are proposed as a surrogate of CNS exposure [35]. By Kinnunen and colleagues, cervical CSF concentrations were similar to plasma oxycodone concentrations, and CSF concentrations correlated but did not predict tissue concentrations. Oxymorphone, one of oxycodone's active metabolites, accumulated in the ewes' CNS tissues and fetal plasma. These data suggest that epidural oxycodone can provide segmental spinal analgesic efficacy [36][37].

2.3. Clinical Cases

The first clinical case on epidural oxycodone was published in 1997 by Bäcklund and colleagues. In that study, 33 patients undergoing elective major abdominal surgery with combined epidural and general anaesthesia were randomised to receive either epidural morphine (n = 13) or epidural oxycodone (n = 16). In an open control group, 11 patients were given i.v. oxycodone at a similar dose. Epidural morphine and oxycodone had similar analgesic efficacy at a dosing ratio of 1:8.4 to 1:9.8. Adverse drug events were similar between the epidural groups. Compared to epidural opioids, mild respiratory depression was more common in subjects receiving i.v. oxycodone. Postoperative pain scores were mainly similar between groups, but dynamic pain during coughing was more severe in subjects receiving epidural morphine than in the two oxycodone groups at 14 h postoperatively, and at 17 h, dynamic pain was more severe in subjects receiving i.v. oxycodone than in the two epidural groups [38].

There were limitations in the one by Bäcklund and colleagues. Firstly, the correct placement of an epidural catheter was not tested appropriately. Second, a prolonged, 3–5 h fentanyl infusion (2 $\mu g\ kg^{-1}\ h^{-1}$) was used for intraoperative analgesia. This long intraoperative fentanyl infusion should have affected postoperative pain scores for several h, as the elimination half-life of fentanyl is relatively long (4 h). In addition, ketorolac was used for rescue analgesia, and the dose was substantially higher in the morphine group compared to the epidural oxycodone group. Lastly, the comparison between epidural morphine and epidural oxycodone was double-blinded whereas the i.v. oxycodone group was an open control, which renders the comparison between epidural and i.v. oxycodone inconclusive [38].

Later, for the one by Yanagidate & Dohi (2004), it was found that epidural oxycodone and epidural morphine may be equianalgesic at a 1:2 ratio. In this, 75 women undergoing elective gynaecological surgery with combined epidural and general anaesthesia were randomised to receive either epidural oxycodone or epidural morphine in a

double-blinded manner. Fentanyl boluses were used for intraoperative analgesia but the total doses were substantially lower (200 µg) than those by Bäcklund and colleagues [38][39]. However, consistent with the one by Bäcklund and colleagues, the use of adjuvant analgesics was not standardised. In support of the feasibility of epidural oxycodone, adverse drug events, PONV and pruritus were less severe with epidural oxycodone than with epidural morphine [39].

A decade ago, Kokki and colleagues (2014) conducted a PK one on epidural and i.v. oxycodone in 24 women undergoing gynaecological surgery under general anaesthesia and epidural analgesia for postoperative pain management. At the end of surgery, the subjects were randomised to receive a single bolus injection of oxycodone 0.1 mg kg^{-1} either epidurally or i.v. In both groups, a matching placebo injection was given by the other administration route to ensure blinding. Plasma and CSF samples were obtained via an indwelling cannula and a spinal catheter at multiple time points during the first 24 h to measure concentrations of oxycodone and its metabolites. The peak concentrations (maximum concentration, $C_{max)}$ and area under the curve (AUC) in CSF after epidural administration were increased 320- and 120-fold compared to i.v. administration. The need for rescue analgesia was reduced in the epidural group compared to the i.v. group, supporting the superior analgesic efficacy of epidural oxycodone. [40]

In a small observational study, patients undergoing total hip arthroplasty (*n* = 11) had epidural anaesthesia with 15 mL bupivacaine 0.25% and oxycodone 5 mg. All patients were co-administered i.v. ketoprofen (a nonsteroidal anti-inflammatory drug, NSAID) 100 mg at every 12 h, and subcutaneous morphine for rescue analgesia when the pain score on an 11-point numerical rating scale (NRS) was >3. Analgesia lasted for a mean of 10 [minimum 5, maximum 24] h. One patient was given naloxone for pruritus and two patients had bradycardia, but otherwise epidural oxycodone was well tolerated. This small one with no control group renders it difficult to draw conclusions on whether oxycodone may have prolonged epidural bupivacaine analgesia or not, and whether the coadministration of oxycodone with bupivacaine is safe in this kind of patient population [41].

Sng and colleagues (2016) randomised *n* = 100 parturients undergoing caesarean section under spinal anaesthesia with hyperbaric bupivacaine 12 mg and fentanyl 15 µg to receive either epidural morphine 3 mg or epidural oxycodone 3 mg after delivery in a double-blind manner. Per oral paracetamol 1 g three times daily (tds), mefenamic acid (NSAID) 500 mg tds and tramadol 50 mg as needed were used for multimodal analgesia. The need for rescue tramadol during the first 24 postoperative h was higher (*n* = 9 (18%) vs. *n* = 2 (4%)) and pain scores were higher in the oxycodone group compared to the morphine group, but patient satisfaction was similarly high in the two groups. Two patients in the morphine group need treatment for pruritus and two patients had antiemetics for protracted PONV [42].

Zhong and colleagues (2020) randomised 40 parturients to receive 10 mL of epidural ropivacaine 1 mg mL^{-1} with or without oxycodone 2 mg for labour analgesia in a double-blind study. An epidural test dose of 3 mL lidocaine 15 mg mL^{-1} was used to exclude inadvertent intrathecal catheterization, but as no adrenaline was used, the test dose did not exclude inadvertent i.v. catheterization. Appropriate location of the catheter in epidural space was determined by loss of sensation to cold at Th10 dermatome and achievement of a visual analogue pain (VAS)

score < 3 (onset of analgesia). Pain scores were similar between the two groups for the first 2 h, but thereafter until the time of cervical dilatation of 10 cm, pain scores were lower in the oxycodone group. The oxycodone group also needed fewer epidural boluses and the time to the first dose of rescue analgesia (VAS > 3) was 5–6 h longer in the oxycodone group than in the control group, 6.5 h and 1.1 h, respectively. Four parturients in the oxycodone group but none in the control group had pruritus. Otherwise, there were no differences in adverse drug events [43].

Recent randomised clinical trials (RCTs) have indicated that the analgesic efficacy of epidural oxycodone is superior to i.v. oxycodone in postoperative analgesia [44][45]. Ninety women undergoing gynaecological surgery under general anaesthesia were randomised to epidural or i.v. oxycodone 0.1 mg kg^{-1} postoperatively. Background multimodal analgesia was standardised; i.v. paracetamol 1 g tds and i.v. dexketoprofen 50 mg tds; and rescue analgesia i.v. fentanyl 50 µg. After the first 4 h, epidural infusion of levobupivacaine, fentanyl and adrenaline were initiated for all patients. The primary outcome measure was the need for rescue analgesia during the first 4 postoperative h. Pain scores were measured at rest as well as dynamic pain during coughing and during wound compression. The need for rescue i.v. fentanyl during the first 4 postoperative h was lower after epidural oxycodone than after i.v. oxycodone, regardless of surgical technique, laparotomy (n = 30) [44] or laparoscopy (n = 60) [45]. Resting and dynamic pain scores were lower in the epidural group during the first postoperative h, but similar between groups thereafter. Adverse drug events were similar in the two groups. PONV was most common, n = 18 and n = 18 in the two groups respectively. Eight women in the epidural groups and 6 women in the i.v. groups had a respiratory rate < 10 min^{-1}, but none of them needed any interventions. Pruritus was reported to be two times more common in the epidural group, with 52%, compared to the i.v. group with 23%.

In these two double-blind, double-dummy, randomised studies the correct placements of epidural catheters were verified by administering lidocaine 50 mg with adrenaline 50 µg, and testing the loss of sensation to cold. Moreover, intraoperative analgesia was provided with remifentanil infusion, and the infusion rate was adjusted with the Surgical Pleth Index (Carescape™ B650; GE Healthcare, Helsinki, Finland). As the elimination half-life of remifentanil is 12–30 min, it is unlikely that the intraoperative opioid had affected recovery after surgery very much [46]. As the background multimodal analgesia was also strictly standardised, the authors concluded that their results should be on a sound basis [44][45].

A recent double-blind, three-arm dose-response one assessed whether adding oxycodone to epidural ropivacaine may decrease the dose of local anaesthetics required for surgical anaesthesia. Patients (n = 141) undergoing high ligation and stripping of the great saphenous vein were allocated to two active groups: epidural oxycodone 2.5 mg and epidural oxycodone 5.0 mg, and to a control group with no additive to ropivacaine. The volume of epidural injection was 15 mL in all three groups. The median effective concentration (EC50) of ropivacaine was assessed by an up-and-down sequential method. In the two oxycodone groups, the EC50 of ropivacaine was 4 mg/mL, significantly less than that in the placebo group with 5 mg/mL. A clinically meaningful finding was a relatively short duration of analgesic action in the epidural oxycodone 5 mg group; time to VAS score >4 was 3 h after epidural injection compared to 9 h in the control group and 10 h in the epidural oxycodone 2.5 mg group [47].

2.4. Population Pharmacokinetics

Population pharmacokinetic–pharmacodynamic (PK-PD) modelling improves the understanding of analgesic drug action, explains interindividual variability and improves the ability to titrate drugs to the desired effect [48]. A few population PK models have been published for epidural oxycodone.

A five-compartment model described the time concentration data of i.v. and epidural oxycodone accurately and precisely. The epidural space served as a depot compartment, from which the drug could transfer into the central compartment and CSF compartment. Covariates did not correlate with PK parameters and were not modelled [49]. Another population PK model with three compartments suggested that 60% of epidural oxycodone initially penetrates into CSF and 40% is absorbed into the systemic circulation [45].

A universal population PK model was recently developed to describe oxycodone plasma concentrations across a wide range of ages and body sizes after i.v., intramuscular, buccal, nasogastric and epidural administration. A three-compartment model with first-order elimination best described the data. Clearance matured with age, reaching 90% of typical adult values by the age of one year. Allometric scaling using total body weight better explained clearance than fat-free mass [50]. This model enabled the authors to give oxycodone dose recommendations to achieve analgesic concentrations in plasma [51]. Previously, two- or three-compartment models have been used to describe oxycodone time concentration data after i.v. administration [52][53].

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