Regional Anaesthesia

Central nervous system penetration of oxycodone after intravenous and epidural administration

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Editor’s key points
- Epidural opioids may provide effective analgesia, potentially by a direct spinal effect.
- This study primarily aimed to explore the spinal pharmacokinetics of epidural oxycodone.
- Cerebrospinal fluid oxycodone levels were ≈320 times higher for epidural compared with i.v. administration.
- Rescue analgesia was significantly reduced in patients receiving epidural compared with i.v. oxycodone.
- Further studies are needed to establish the safety and efficacy of epidural oxycodone.

Background. Despite being increasingly used for pain management, only two studies, with controversial results, have evaluated the epidural use of oxycodone.

Methods. Twenty-four women, aged 26–64 yr, undergoing elective gynaecological surgery were enrolled in this randomized, double-blinded, parallel group study. The subjects were administered either i.v. oxycodone and epidural placebo (IV group; n=12) or epidural oxycodone and i.v. placebo (EPI group; n=12) after operation. Oxycodone was administered as a single dose of 0.1 mg kg\(^{-1}\). An epidural catheter for drug administration was placed at T12/L1 and a spinal catheter for cerebrospinal fluid (CSF) sampling at L3/4. Plasma and CSF were frequently collected for the analysis of oxycodone and its major metabolites. The primary outcomes were the peak concentration (\(C_{\text{max}}\)), time to peak concentration (\(T_{\text{max}}\)), and the exposure (AUC\(_{\text{last}}\)) of oxycodone in CSF and plasma. The secondary outcome was the analgesic efficacy, measured as the total dose of rescue fentanyl during the first four postoperative hours.

Results. In the EPI group, the median oxycodone \(C_{\text{max}}\) and AUC\(_{\text{last}}\) in the CSF were 320- and 120-fold higher, respectively, compared with the IV group. The total dose of rescue fentanyl was significantly lower in the EPI group (seven subjects needed 16 doses) than in the IV group [12 subjects needed 71 doses (\(P=0.001\)]]. No serious or unexpected adverse events were reported.

Conclusions. Epidural oxycodone provides much higher CSF concentrations and possibly better analgesic efficacy than does i.v. oxycodone.

Clinical trial registration. EudraCT reference number: 2011-000125-76.

Keywords: analgesia, epidural, analgesics, opioid; administration, i.v.; oxycodone, pharmacokinetics

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Oxycodone is a semisynthetic \(\mu\)-opioid receptor agonist that is increasingly being used by mouth and i.v. for acute and chronic pain management.1-2 CYP3A and CYP2D6 metabolize oxycodone to generate the active metabolites oxymorphone and noroxymorphone, along with the inactive metabolite noroxycodone.3-6 Surprisingly, no data have been reported on the penetration of oxycodone and its metabolites into the human central nervous system (CNS), even though this information would prove valuable in the interpretation of the efficacy and safety data on oxycodone. In clinical studies, the cerebrospinal fluid (CSF) concentrations of the drug are typically used as a surrogate for CNS exposure.5

There is little information on the epidural administration of oxycodone. Two previous studies compared epidural oxycodone with epidural morphine in postoperative pain treatment, and a 10- or two-fold dosing rate of oxycodone provided analgesic effects similar to morphine, with a fairly similar frequency and severity of adverse events.6-7 In one of these studies, i.v. oxycodone served as an open control for epidural oxycodone, and epidural oxycodone seemed to present no advantages over i.v. oxycodone.5 However, this result is inconclusive because the comparison was not blinded.

The present study was planned to clarify the conflicting issue, with the primary aim of verifying the CSF and plasma...
pharmacokinetics of oxycodone and its major metabolites after i.v. and epidural administration. The secondary aim was to compare the efficacy and safety of epidural oxycodone with i.v. oxycodone in patients undergoing gynaecological surgery.

Methods
The study was approved by the Research Ethics Committee of the Hospital District of Northern Savo, Kuopio, Finland (ref: 30/2011), registered with EudraCT (ref: 2011-000125-76), and conducted in accordance with the Declaration of Helsinki. The Finnish Medicines Agency was notified (ref: 27/2011). The study was carried out at the Kuopio University Hospital, Finland, and patients were recruited between May and August in 2011. The study design was a prospective, randomized, double-blinded clinical trial with two parallel groups. The patients were administered either i.v. oxycodone and epidural placebo (IV group) or epidural oxycodone and i.v. placebo (EPI group) after operation. The sample size was not formally calculated; instead, 12 patients in both the IV and EPI groups were considered to provide sufficient data for a pharmacokinetic comparison and for a pilot comparison regarding efficacy and safety.

Inclusion and exclusion criteria
Patients aged 18–65 yr undergoing elective gynaecological surgery with planned postoperative epidural analgesia were screened. We did not enrol subjects who were unwilling to give consent, who had allergy/hypersensitivity to oxycodone or other ingredients in the formulations, had reduced respiratory function, had defects in the vertebral column that were likely to hinder the placement of epidural and spinal catheters, were pregnant or nursing, had a tendency for bleeding or were currently on an anticoagulant therapy, or who had used oxycodone during the previous week, or MAO, CYP3A, or CYP2D6 inhibitors during the previous month.

Enrolment, randomization, and blinding
Thirty-four patients were asked, and 24 patients agreed to participate and gave written informed consent. The reasons for denying participation included an unwillingness to receive any extra procedures (n=4), a fear of headache or a history of post-dural puncture headache (n=3), too many confusing words in the patient information letter (n=1), a serious illness (n=1), and no specific reason (n=1). The subjects were randomly allocated to either the IV group (n=12) or the EPI group (n=12).

Randomization was performed with a random organization generator with a block size of 12 using the closed, opaque envelope method (www.randomization.com). The patients, the care providers, and the outcome assessors were blinded to allocation. A nurse who, after consent, opened the envelope and then prepared the oxycodone and placebo dosage forms but did not otherwise participate in the study was the only one who knew the allocation.

Catheter placement, anaesthesia, and surgery
Patients were premedicated by mouth with 10 mg diazepam and 2 g paracetamol 1 h before the anaesthesia. An epidural catheter was placed at interspace T12/L1 or L1/2 and tested for i.v. or spinal misplacement with 5 ml of lidocaine (10 mg ml⁻¹) with epinephrine (10 μg ml⁻¹). One subject in the EPI group (Patient no. 1) had the epidural catheter replaced as the first was inserted invasurally. A spinal catheter was inserted via a 21 G Sprotte needle at interspace L3/4 for CSF sampling.

The anaesthesia was standardized. At induction, patients were administered i.v. midazolam (1–2 mg), propofol, and remifentanil infusion. Tracheal intubation was facilitated with rocuronium 0.5 mg kg⁻¹. The anaesthetic level was maintained at the response and state entropy level of 40–60 (GE Healthcare, Helsinki, Finland), with sevoflurane in oxygen in air. Airway gases, arterial pressure, heart rate, muscle relaxation, and central temperature were monitored continuously. At the end of the anaesthesia, remifentanil infusion and sevoflurane inhalation were discontinued, muscle relaxation was reversed with sugammadex 1 mg kg⁻¹, and the tracheal tube was removed with TOF value ≥0.9. Thirteen patients had laparoscopic surgery, and 11 patients had laparotomy. Background analgesia with paracetamol (1 g t.i.d. i.v.) was started at the end of the surgery.

Postoperative oxycodone administration
The nominal dose was 0.1 mg kg⁻¹ oxycodone hydrochloride trihydrate (Oxanest® 10 mg ml⁻¹, Leiras, Espoo, Finland) diluted to 10 ml with saline. The actual dose was obtained by rounding the calculated dose in milligrams up to the full number, and the maximum dose was restricted to 10 mg. The nominal dose corresponds to 0.087 mg kg⁻¹ oxycodone hydrochloride. The placebo was 10 ml saline. Oxycodone and placebo formulations were both clear, colourless liquids, thus ensuring the blinding. The IV group received i.v. oxycodone and epidural placebo, and the EPI group received epidural oxycodone and i.v. placebo. The oxycodone and placebo doses were administered simultaneously as 5 min infusions after the patient had arrived in the recovery room and had emerged from anaesthesia, having a response entropy value ≥90.

Sampling and drug analysis
Blood samples (5 ml) were obtained into EDTA tubes from an indwelling catheter placed on the cubital vein of the contralateral arm to study drug infusion. The baseline sample was obtained before the oxycodone administration and then at 2, 5, 15, 30, and 45 min, and 1, 2, 4, 8, 12, and 24 h after the end of the infusion. CSF samples (1 ml) were withdrawn via the spinal catheter parallel to the blood draws. Blood and CSF samples were centrifuged at 21°C and 1200g for 10 min, and the separated plasma and CSF were stored at −70°C until analysis.

Plasma samples of 500 μl were mixed with 200 μl of internal standard solution (54 nM dextromethorphan in water) and
50 μl of 40% phosphoric acid, shaken for 3 min, and centrifuged at 13 200g for 10 min. The supernatants were extracted using cation exchange 96-well plates (Waters Oasis MCX, Waters Corp., Milford, PA, USA). The wells were preconditioned with 1 ml of methanol and 1 ml of water, and 500 μl of samples were loaded into the wells, followed by a wash with 1 ml of 0.1 M HCl and 800 μl of 50% aqueous methanol. The samples were eluted twice with 600 μl of 5% NH₄OH in methanol, and the combined eluates were evaporated under N₂ flow at 40°C, followed by reconstitution to 200 μl with 50% aqueous methanol. The CSF samples (30–500 μl) were treated as described above, except they were reconstituted to 200 μl with 50% methanol in 150 mM phosphate-buffered saline.

An ultra-performance liquid chromatographic system (Waters Acquity UPLC, Waters Corp.) with an autosampler, column oven and vacuum degasser was used together with a 2.1 × 50 mm, 1.7 μm particle size column (Waters BEH C18, Waters Corp.) and a precolumn filter. The temperature of the column oven was 35°C, and the injection volume was 8 μl. The aqueous eluent phase (A) was 5 mM ammonium bicarbonate (pH 9.8), and the organic phase (B) was methanol. A gradient elution with 2–2–80–90% methanol in 0–1–2.5–3.5 min was applied, followed by a 1 min equilibration. The eluent flow rate was 0.5 ml min⁻¹. The data were acquired using a triple quadruple mass spectrometer equipped with a Z-spray electrospray source (Waters Quattro Ultima, Waters Corp.), using selected reaction monitoring (SRM). A positive ionization mode was used with a capillary voltage of 600 V. Argon was used as a collision gas, with the collision-induced dissociation gas cell pressure of 2.1 × 10⁻⁶ mbar. The desolvation temperature was 400°C, and the source temperature was 150°C. Nitrogen was used as a drying gas at a flow rate of 900 litre h⁻¹ and as a nebulizer gas at a full flow rate. The monitored SRM transition reactions were m/z 288 → 213 (collision energy 28 eV, cone voltage 25 V) for noroxymorphone, m/z 302 → 187 (25 eV, 26 V) for noroxycodone, m/z 302 → 242 (26 eV, 26 V) for oxymorphone, m/z 316 → 298 (18 eV, 30 V) for oxycodone, and m/z 272 → 215 (24 eV, 28 V) for the internal standard dextromethorphan. Dwell times of 60–100 ms were used for each SRM reaction. The precursor ions were chosen with one unit mass resolution. Quantitation was based on the peak area ratios of the analyte and the internal standard. The mass spectrometer and ultra-performance liquid chromatography system were operated with the Masslynx 4.1 software (Waters Corp.).

The concentrations of oxycodone, noroxycodone, oxymorphone, and noroxymorphone are reported as hydrochlorides. At the lower limit of quantification, the accuracy of the assay was 80–120% and the coefficient of variation below 20%. The calibration ranges (ng ml⁻¹) for the plasma samples were the following: oxycodone 0.2–500, noroxycodone 0.5–200, oxymorphone 0.2–100, and noroxymorphone 0.2–200. The calibration ranges (ng ml⁻¹) for the CSF samples were the following: oxycodone 0.1–500, noroxycodone 0.05–100, oxymorphone 0.1–500, and noroxymorphone 0.05–500. The quality control (QC) samples containing all of these compounds at 1, 10, and 50 ng ml⁻¹ were prepared in blank plasma or blank CSF matrix and analysed in triplicate in each batch. The CSF matrix contained 1 mM MgCl₂, 2.7 mM KCl, 147 mM NaCl, and 0.5% blank human plasma. The batch was accepted for each analyte if at least six measured concentrations in nine QC samples were within 85–115% of the nominal concentration and the possible deviations occurred at different nominal concentrations. No batches needed to be rejected.

**Pharmacokinetic outcomes**

The primary outcomes of the study were the measured peak concentration (Cmax), time to peak concentration (Tmax), and area under the concentration curve from drug administration to the last measured concentration (AUClast) of oxycodone in the CSF and the plasma. These parameters were calculated based on non-compartmental analysis using the WinNonlin software (ver 5.3; Pharsight Corp., St Louis, MO, USA). The linear trapezoidal rule was used for AUC calculations. For the EPI group oxycodone concentrations, a total of 24 CSF samples from eight subjects were above the upper limit of quantification even after a 20-fold dilution (>10 000 ng ml⁻¹). These concentrations were set to 10 000 ng ml⁻¹, and the first occurrence in each patient was defined as Tmax. Dilutions higher than 20-fold were not made. In addition, the terminal elimination half-life (T1/2) and the AUC extrapolated to infinity (AUCinf) were calculated. The extrapolated portion in AUCinf was always below 10%. However, T1/2 and AUCinf were not determined for the EPI group from the CSF data because the terminal elimination phase typically started at 8–10 h and the number of data points was not sufficient for most patients. In the EPI group, the T1/2 and AUCinf from the plasma data for one patient (Patient no. 3) were not calculated because there was no clear log-linear terminal elimination phase. For the IV group, plasma clearance (CL) and volume of distribution at steady state (VSS) were determined. The metabolite concentrations were low in plasma and CSF and even below the lower limit of quantification in several samples. Therefore, only the range of the measured Cmax values for the metabolites is presented in this report. All of the measured metabolite concentrations are presented in Supplementary Appendices S1 and S2.

**Efficacy and safety outcomes**

The secondary outcome was the analgesic efficacy of oxycodone, measured as the total number of rescue fentanyl doses administered during the first four postoperative hours. The need for rescue fentanyl was determined as described below. Pain was measured with an 11-point numeric rating scale (NRS) 0–10 (0, no pain; 10, most pain) at rest, when coughing, and when the wound area was compressed with a 20 N force (2 kg pressure with three fingers for a 10 cm² area), every 15 min during the first four postoperative hours. Fentanyl (50 μg) was administered if the pain at rest was ≥3/10 or when coughing or during wound compression ≥5/10.

After the 4 h period, epidural pain treatment was continued with an admixture of levobupivacaine (0.5 mg ml⁻¹), fentanyl (4 μg ml⁻¹), and epinephrine (2 μg ml⁻¹) as a routine treatment of the hospital, using an infusion rate of 2–8 ml h⁻¹.
and 2 ml boluses as needed to keep the pain scores < 3/10 at rest and < 5/10 during coughing and wound compression. Oxycodone was not administered to the patients until the last 24 h samples were withdrawn and the spinal catheter removed.

Arterial pressure, heart rate, peripheral oxygen saturation, and exhaled CO2 were monitored up to 24 h. Adverse events were recorded by active and passive surveillance, and recurrent events were calculated as a single event.

Statistical analysis
The data were stored and the calculations were made using the Statistical Package for Social Sciences software (IBM SPSS Statistics 19, IBM Corp., Armonk, NY, USA). Data are presented as the number of cases and median (range) unless otherwise specified. Differences in pharmacokinetic and other continuous parameters between the IV and EPI groups were analysed with the Mann–Whitney U-test and in proportions with the Pearson χ² test. The differences in Tmax in CSF samples were not tested, since unambiguous Tmax could not be determined for eight patients in the EPI group as described above. The AUCinf values in the plasma and the CSF were compared within the IV group using the Wilcoxon signed-rank test. P-values of < 0.05 were considered statistically significant.

Results
Patients were enrolled and analysed as shown in Figure 1. There was one major protocol deviation. One patient in the IV group (Patient no. 7) unintentionally received 5 mg oxycodone orally at 18 and 20 h after the study drug was administered, and therefore, AUClast (primary outcome), T1/2, and AUCinf in the CSF and the plasma were not calculated for this patient. There were minor deviations of a few minutes in the CSF and the plasma sampling, but despite these deviations, the pharmacokinetic data were considered to be adequate.

Patient characteristics and surgical data were similar in the IV and EPI groups (Table 1).

Pharmacokinetics
In the EPI group, the median oxycodone Cmax and AUClast in the CSF were 320- and 120-fold compared with the IV group, respectively (Table 2, Figs 2 and 3). In terms of the raw numbers, these differences were even larger because oxycodone concentrations in 24 CSF samples from eight patients in the EPI group were more than 10 000 ng ml⁻¹ but were set to this value. These concentrations were measured within the time interval of 0.2 – 1.1 h after the drug administration in seven patients and additionally at 2.0 h in one patient, respectively. The measured Tmax for the remaining four patients were 0.6, 0.8, 0.9, and 4.0 h, respectively. The median oxycodone Cmax and AUClast in plasma of the EPI group were 50% and 128% of those in the IV group, respectively, but the difference in AUClast was not statistically significant.

In the IV group, the median (range) oxycodone CL and Vss were 0.54 (0.26–0.95) litre h⁻¹ kg⁻¹ and 2.1 (1.2–3.0) litre kg⁻¹, respectively, and the oxycodone AUCinf in the CSF was...
similar to the AUC_{inf} in the plasma (median 187 vs 160 h ng ml\(^{-1}\), Table 2; \(P=0.13\)).

In both groups, the metabolite concentrations in the plasma and the CSF were much lower than oxycodone concentrations (Table 2 and Supplementary Appendices S1 and S2). Oxymorphone could be measured only occasionally and at low concentrations.

**Analgesic efficacy**

Significantly less fentanyl was needed for rescue analgesia in the EPI group. Seven out of 12 patients in the EPI group were given 16 doses of fentanyl for rescue analgesia during the first four postoperative hours and all 12 patients in the IV group needed rescue fentanyl, which was a total of 71 doses (\(P<0.001\) for doses and \(P=0.012\) for proportion of subjects). The median for the rescue analgesia doses was 1 (0–5) in the EPI group and 6 (2–10) in the IV group. The time from oxycodone administration to the first fentanyl dose was similar in the two groups (Fig. 4).

**Adverse effects**

In the EPI group, eight patients reported a total of 13 adverse effects: pruritus (n=6), nausea (n=3), headache (n=2), and pain in the neck and shoulders (n=2). In the IV group, eight patients reported a total of nine adverse effects: pruritus (n=2), nausea (n=4), headache (n=1), dizziness (n=1), and pain in the urethra (n=1). One patient in the EPI group had an epidural blood patch due to post-dural puncture headache.

**Discussion**

The penetration of oxycodone into the human CSF was quantified for the first time in this study. Lumbar epidural administration resulted in a more than 300-fold peak concentration and a more than 100-fold exposure (AUC_{last}) of oxycodone in the lumbar CSF compared with i.v. administration. In addition, these preliminary data indicate that epidural oxycodone may provide a better analgesic efficacy than i.v. oxycodone, based on the reduced consumption of rescue fentanyl. Both the

<table>
<thead>
<tr>
<th>Variable</th>
<th>IV group (n = 12)</th>
<th>EPI group (n = 12)</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodone</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Plasma</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>(C_{\text{max}}) (ng ml(^{-1}))</td>
<td>58.0 (34.9–135) (12)</td>
<td>28.8 (13.5–77.3) (12)</td>
<td>&lt;0.001</td>
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<td>(T_{\text{max}}) (h)</td>
<td>0.1 (0.1–0.6) (12)</td>
<td>2.1 (0.6–4.2) (12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AUC_{last} (h ng ml(^{-1}))</td>
<td>157 (90–339) (11)</td>
<td>201 (142–501) (12)</td>
<td>0.079</td>
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<tr>
<td>AUC_{inf} (h ng ml(^{-1}))</td>
<td>160 (97–343) (11)</td>
<td>203 (147–420) (11)</td>
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<td>(T_{1/2}) (h)</td>
<td>3.0 (2.0–4.2) (11)</td>
<td>3.8 (3.1–5.1) (11)</td>
<td>0.019</td>
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<tr>
<td>CSF &amp; Noroxycodone</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>(C_{\text{max}}) (ng ml(^{-1}))</td>
<td>30.7 (18.9–39.7) (12)</td>
<td>10 000 (982–10 000) (12)*</td>
<td>&lt;0.001</td>
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<tr>
<td>(T_{\text{max}}) (h)</td>
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<td>0.6 (0.2–4.0) (12)</td>
<td>Not tested</td>
</tr>
<tr>
<td>AUC_{last} (h ng ml(^{-1}))</td>
<td>185 (112–260) (11)</td>
<td>22 600 (8320–41 600) (12)</td>
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<td>AUC_{inf} (h ng ml(^{-1}))</td>
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<td>Noroxycodone</td>
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<td>Plasma (C_{\text{max}}) (ng ml(^{-1}))</td>
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<td>3.7 (2.3–8.1) (12)</td>
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<tr>
<td>CSF (C_{\text{max}}) (ng ml(^{-1}))</td>
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<tr>
<td>Oxymorphone</td>
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<td>0.3 (0.2–0.4) (4)</td>
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<td>CSF (C_{\text{max}}) (ng ml(^{-1}))</td>
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<td>Noroxymorphone</td>
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<td>Plasma (C_{\text{max}}) (ng ml(^{-1}))</td>
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<td>1.2 (0.6–2.0) (12)</td>
<td>Not tested</td>
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<tr>
<td>CSF (C_{\text{max}}) (ng ml(^{-1}))</td>
<td>0.1 (0.05–0.2) (11)</td>
<td>0.1 (0.07–0.2) (11)</td>
<td>Not tested</td>
</tr>
</tbody>
</table>
treatments were well tolerated, and no serious or unexpected adverse events were noted.

After epidural administration, oxycodone permeated rapidly into the lumbar CSF, and the peak concentration was observed before 1.1 h in most patients. Subsequent to the epidural dose, oxycodone concentrations in the CSF were much higher than in the plasma, and the median CSF/plasma ratios for $C_{\text{max}}$ and AUC$_{\text{last}}$ were 350 and 110 (using the median values in Table 2), respectively, whereas the corresponding ratios after the i.v. dose were 0.53 and 1.2, respectively. This ratio is desirable in order to elicit a local analgesic effect in the spinal cord.

The plasma pharmacokinetics of oxycodone in the IV group were similar to those reported for young adult volunteers. After i.v. administration, the oxycodone AUC$_{\text{int}}$ was similar in the CSF and plasma. Based on pharmacokinetic concepts, the data suggest that CSF and total plasma concentrations would be fairly similar during long-term i.v. or oral medication (steady state). Microdialysis experiments previously conducted in rats showed that the free oxycodone concentration in the brain at the steady state was triple the free blood concentration, and some evidence of active uptake of oxycodone into the rat brain was found. However, further detailed studies on the CSF and, if possible, on the extracellular fluid in the brain would help confirm whether there is active uptake of oxycodone into the human CNS.

The contribution of active metabolites, oxymorphone and noroxymorphone, to the analgesic efficacy may be evaluated by comparing their concentrations and analgesic potencies with oxycodone. Oxymorphone and noroxymorphone have 8–44 and 2–3 times higher affinity than oxycodone,
respectively, for the human \( \mu \)-opioid receptor binding and activation, as confirmed by in vitro assays.\(^4\) In rats, the intrathecal oxymorphone and noroxymorphone are up to several hundred times more potent analgesics than intrathecal oxycodone,\(^{13-15}\) whereas the corresponding clinical data in humans are not available. In our study, the oxycodone concentration in the CSF after epidural administration was typically 1000–10 000 times higher than oxymorphone and noroxymorphone concentrations, and the contribution of these metabolites to the local analgesic effect in the spinal cord was most likely negligible. However, the i.v. results were not as clear. Earlier, the central opioid effects of oral oxycodone were attributed mainly to the parent compound,\(^4\ 16\ 17\) and it was recently estimated that on average, oxycodone itself is responsible for 83% and 95% of the analgesic effect during oral and i.v. administration, respectively.\(^{18}\)

Previously, the efficacy and safety of epidural oxycodone were evaluated in two studies. Bäcklund and colleagues\(^5\) compared epidural oxycodone with i.v. oxycodone in patients undergoing a major abdominal surgery. They found that epidural oxycodone seemed to have no advantages over i.v. oxycodone during a 24 h infusion (0.03 mg kg\(^{-1}\) h\(^{-1}\) preceded by 0.15 mg kg\(^{-1}\) bolus). Their results differ from ours, which may be explained by the differences in the patient groups and the experimental designs. Bäcklund and colleagues\(^5\) measured the efficacy and safety outcomes during a period when the oxycodone concentration in the plasma was practically at a steady state, 40–80 ng ml\(^{-1}\) with both routes of administration, and the i.v. oxycodone served as an open control group for epidural oxycodone, indicating that the comparison was not blinded.

The primary aim of the study conducted by Bäcklund and colleagues\(^5\) was to compare epidural oxycodone with epidural morphine. In this primary comparison, a 10-fold infusion rate of epidural oxycodone provided analgesia similar to epidural morphine and with similar adverse events. Later, Yanagidate and Dohi\(^7\) found that epidural oxycodone was as effective as epidural morphine during the first 3 days after gynaecological surgery, when the infusion rate of oxycodone was doubled compared with morphine (12 vs 6 mg day\(^{-1}\); \(\approx 0.01\) vs 0.005 mg kg\(^{-1}\) h\(^{-1}\)). They also found that oxycodone caused fewer adverse events than morphine.

A limitation in our pharmacokinetic data was that the highest oxycodone concentrations in the CSF after epidural dosing could not be precisely quantified because of insufficient dilution of the samples, and this constraint needs to be addressed in future studies. It is also important to study the rostral spread of oxycodone in the CSF after epidural administration to evaluate whether oxycodone may reach the breathing centre and cause late respiratory depression similar to that described for morphine.\(^{19\ 20}\)

The main limitation of our study with regard to efficacy and safety is that the number of patients was relatively small in this pharmacokinetic study, and further studies with a larger cohort are needed to evaluate the clinical feasibility of epidural oxycodone. The oxycodone formulation, Oxanest\(^6\), used in this study is a preservative-free injection for parenteral use; it contains only aqua as a diluent. Although it is used for intrathecal analgesia, no formal neurotoxicity studies have been performed.

In conclusion, our data show that epidural oxycodone provides much higher CSF concentrations than does i.v. oxycodone. However, from a safety and efficacy point of view, these results should be considered as preliminary. At this time, epidural administration should be considered experimental, and more safety data from carefully supervised clinical studies are needed before the safety and reliability of this administration route could be established.

**Supplementary material**

Supplementary material is available at British Journal of Anaesthesia online.

**Authors’ contributions**

M.Ko.: study design, data collection, data analysis, patient recruitment, writing up of the first draft of the paper with P.V., and final approval of the version to be published. P.V.: study
design, data analysis, writing up of the first draft of the paper with M.Ko., and final approval of the version to be published. M.Ku.: study design, data collection, data analysis, patient recruitment, revising the article critically for important intellectual content, and final approval of the version to be published. V.P.R.: study design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. K.R.: study design, data analysis, revising the article critically for important intellectual content, and final approval of the version to be published. H.H.: Data analysis, oxycodone and metabolites laboratory analysis, revising the article critically for important intellectual content, and final approval of the version to be published. H.K.: study design, data collection, data analysis and interpretation, patient recruitment, revising the article critically for important intellectual content, and final approval of the version to be published.

Declaration of interest

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