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ORIGINAL RESEARCH

Population pharmacokinetics of oxycodone in plasma and cerebrospinal fluid after epidural and intravenous administration

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ABSTRACT

Objectives: To establish the first plasma and cerebrospinal fluid (CSF) oxycodone population pharmacokinetic (PopPK) model after epidural (EPI) and intravenous (IV) oxycodone administration.

Methods: The study was conducted with 30 female subjects undergoing elective gynecological surgery with epidural analgesia. A parallel single dose of EPI oxycodone with IV placebo (EPI group; n = 18) or IV oxycodone with EPI placebo (IV group; n = 12) was administered. An epidural catheter for drug administration was placed at T12/L1 and a spinal catheter for CSF sampling at L3/4. Plasma and CSF for oxycodone analysis were frequently collected. A PopPK model was built using the NONMEM software package.

Results: Plasma and CSF oxycodone concentrations were evaluated using separate central plasma and CSF compartments and separate peripheral plasma and CSF compartments. Epidural space served as a depot compartment with transfer to both the plasma and CSF central compartments. The population parameters for plasma clearance and apparent distribution volumes for central and peripheral compartments for plasma and CSF were 37.4 L/h, 90.2 L, 68.9 L, 0.035 L (fixed based on literature), and 0.039 L, respectively.

Conclusion: A PopPK model was developed and found to precisely and accurately describe oxycodone time-concentration data in plasma and CSF.

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KEYWORDS
Oxycodone; intravenous; epidural; population pharmacokinetics; NONMEM; central nervous system

1. Introduction

Oxycodone is a semisynthetic μ-opioid receptor agonist increasingly used in treatment of acute and chronic pain. In recent years, the consumption of oxycodone has surpassed that of morphine in many countries [1]. Analgesic efficacy of oxycodone is mainly based on parent compound, but it has active metabolites that may contribute to analgesic efficacy [2]. Oxycodone is mainly metabolized via CYP3A4/5 and CYP2D6 into active primary metabolite oxymorphone and less active noroxycodone, which are further metabolized to a secondary metabolite, noroxymorphone that has also some analgesic activity [3]. Opioids exert analgesic action in central nervous system (CNS). Cerebrospinal fluid (CSF) concentrations of drugs are used as surrogates for CNS exposure [4], but no human data in addition to the study of Kokki et al. [5] and Piirainen et al. [6] on CNS penetration of oxycodone and its metabolites have been published.

Oxycodone is most commonly administered by mouth or intravenously (IV) due to high bioavailability and rapid onset of analgesia [7]. Information related to epidural administration of oxycodone in humans is scarce. To date, only six studies have been published [5,6,8–11]. In three of the studies, similar analgesia with epidural oxycodone and epidural morphine was reported but a larger dose of oxycodone was needed [8–10]. In the Kokki et al. study [5] the penetration of oxycodone into CSF was quantified and it reported more than 300-fold higher peak concentration and 100-fold greater exposure of oxycodone in the lumbar CSF compared to IV administration. For a more transferable and detailed quantitative analysis, however, noncompartmental analysis (NCA) used by Kokki et al. [5] is not sufficient. Contrary to the NCA, a compartmental model can be used to predict time-concentration profiles, to simulate alternative scenarios and to focus on details of the underlying system.

Some studies have presented population pharmacokinetic (PopPK) data on oxycodone after IV [12–14] and oral administration [15–17]. The aim of this study is to extend the results of Kokki et al. [5] and establish a population pharmacokinetic (PopPK) model for oxycodone time-concentration data in plasma and CSF after epidural and IV administration. This study is part of a larger project to evaluate the efficacy and safety of epidurally administered oxycodone.

2. Patients and methods

Regarding this PopPK study, data from a randomized, double-blinded clinical trial of oxycodone [5] with six additional patients were analyzed. The study (EudraCT ref: 2011–000125-76) was conducted in accordance with the Declaration of Helsinki and approval of the protocol was granted by the Research Ethics

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Supplementary data for this article can be accessed here.

Committee of the Northern Savo Hospital District, Kuopio, Finland. Notification to the Finnish Medical Agency was made (ref: 27/2011) and the study had institutional approval. Post-operative analgesia of either epidural oxycodone and IV placebo (EPI-group) or IV oxycodone and epidural placebo (IV-group) was administered.

2.1. Clinical trial registration

EudraCT reference number: 2011–000125-76.

2.2. Patients

The study included adult female patients aged between 18 and 65 years undergoing elective gynecological surgery with planned post-operative epidural analgesia. Patients who were unwilling to give consent, who were pregnant or nursing or who had a tendency for bleeding or were currently on an anticoagulant therapy were omitted. Also, patients with allergy or hypersensitivity to oxycodone or other ingredients in the formulations, reduced respiratory function, defects in the vertebral column that were likely to hinder the placement of epidural and spinal catheters, and who had use of oxycodone during the previous week were excluded. Patients who had used MAOI, CYP3A inhibitors or inducers, or CYP2D6 inhibitors during the previous month were excluded due to interaction potential with oxycodone.

2.3. Treatments

The patients received postoperatively a dose of 0.1 mg/kg of oxycodone hydrochloride trihydrate with the maximum dose being restricted to 10 mg. Saline was used as placebo. After arriving in the recovery room, the patient was administered the oxycodone and placebo doses simultaneously as 5 min infusions. The EPI-group received epidural oxycodone and IV placebo and the IV-group IV oxycodone and epidural placebo. Intravenous fentanyl boluses were used as rescue analgesia during the first four postoperative hours followed by an epidural infusion of epinephrine-fentanyl-levobupivacaine-admixture.

2.4. Sampling and analytical methods

Parallel blood (3.5 mL) and CSF (1 mL) samples were withdrawn before and at 2, 5, 15, 30 and 45 min and at 1, 2, 4, 8, 12 and 24 h after the end of the study drug injections.

Samples were analyzed using an ultra-performance liquid chromatographic system with triple quadrupole mass spectrometer (UPLC-MS/MS) as described in Kokki et al. [5]. The limit of detection was 0.1 ng/mL and the limit of quantification (LOQ) 0.2 ng/mL with accuracy of the assay 80–120% and the coefficient of variation below 20%. Dextromethorphan was used as internal standard solution.

2.5. Modeling strategy and PopPK-model

Data were analyzed using NONMEM software (version 7.3; ICON Development Solutions, Ellicott City, MA, USA) with Perl-speaks-NONMEM and Pirana (version 2.9.0) [18]. Data visualization was done with R (version 3.2.3) and Xpose (version 4.5.3). Models were fitted to data using First-Order Conditional Estimation with Interaction (FOCE-I) method in NONMEM. In fitting of the oxycodone data, several structural models were tested. As stated by Kokki et al. [5], the metabolite concentrations were generally low in plasma and CSF, and thus, metabolite modeling was not included in this analysis. First, only the plasma data from the IV route were modeled applying one, two or three compartments in the PopPK model as previously reported in the literature [17-17]. Second, epidural space was added as a depot compartment for the established model and also the plasma data from the epidural route were used. Finally, a CSF compartment was added and full data with plasma and CSF oxycodone concentrations were used. For the central CSF compartment volume, a fixed value of 0.035 L was used [19] and a peripheral CSF compartment to CSF was tested and applied. As an alternative to intercompartmental clearance, separate transfer rate constants between CSF and peripheral CSF compartments as well as CSF and plasma compartments were tested in order to model possible active uptake or efflux. Since plasma AUC of oxycodone is the same after IV and epidural administration [5], a bioavailability term for epidural oxycodone was not applied. PopPK parameters were estimated simultaneously after each model modification. For the statistical models, log-normal distribution of individual parameter values were used to model the between subject variability, that is,

$$P_i = \theta_{pop} \times e^{\eta},$$

where P_i is the parameter value of the i^{th} subject, θ_{pop} the population typical (median) value of the parameter and η is the random effect variable with mean 0 and variance ω^2. For residual variability, proportional, additive and combined error models were tested. Separate residual error models for plasma and CSF concentrations were used.

Model selection was based on visual inspection of goodness-of-fit (observations versus population predictions, observations versus individual predictions and conditional-weighted residuals (CWRES) versus time) plots and objective function values (OFV). The evaluation of predictability of the model was performed by using visual predictive checks [20]. The model was bootstrapped with 1000 replicate datasets to assess nonparametric 95% confidence intervals for the parameters [21].

3. Results

3.1. Demographic data

A total of 30 female patients were included in the study. The study of Kokki et al. [5] with 12 subjects in the EPI-group and 12 subjects in the IV-group was extended by recruiting six new patients into the EPI-group. The original data for the six new patients are given in Supplement 1. The final EPI- and IV-groups are similar in terms of age, weight, and height (Table 1).

3.2. Observed time-concentration data

The dataset consisted of 634 oxycodone concentrations of which 12 from 8 individuals were below the limit of quantification (BLOQ) and 24 from 7 individuals were above the limit of quantification (ALOQ). All ALOQ and 3 out of 12 BLOQ

Table 1. Summary of demographics for patient groups. Data are presented as the median (range).

Variable	IV-group (n = 12)	EPI-group (n = 18)
Age (years)	53 (26–60)	56 (27–64)
Weight (kg)	74 (55–110)	67 (53–100)
Height (cm)	165 (155–176)	161 (155–172)
BMI (kg/m^2)	26.6 (20.5–35.5)	24.2 (18.8–33.1)

concentrations were from CSF samples. Each BLOQ observation was replaced by LOQ divided by two, except that any and all consecutive BLOQ observations after the first one were discarded (the M6-method introduced by Beal [22]). Since it can be assumed that consecutive BLOQ observations reflect true concentrations, which are decreasing, the M6-method can be used. All 24 ALOQ observations (concentration over 10 000 ng/mL) were excluded from the analysis. Hence, the final dataset used for analysis consisted of 607 observations.

3.3. Population pharmacokinetic model

Oxycodone time-concentration data were best described by a model with five compartments (Figure 1). For the plasma data only, the best fit was obtained by 2-compartmental model. Similarly, CSF data were best described with a 2-compartmental model. Epidural space serves as a depot compartment with transfer to both central and CSF compartments. Omitting peripheral CSF compartment yielded significantly higher OFV (ΔOFV = +258).

Of the several residual error models tried, models with only additive error had problems in minimization, so proportional error model was used. The error in models with combined (additive and proportional) or exponential error model was about the same as in when using only proportional error model, so only proportional error model was used. Even though no significant difference in OFV was seen between the model with a single residual error and the model with separate error models for plasma and CSF concentrations, it was decided to use separate error models to emphasize the difference between sampling sites.

Several strategies were tested to model transfer between CSF and plasma compartments. The transfer rate constants indicated a slightly increased values from central compartment to CSF compartment compared with the opposite direction (range 0.0591–0.0612 vs. 0.0465–0.0584), but the difference was not significant. On the other hand, significantly higher OFV (ΔOFV = +200) was obtained when omitting transfer from epidural space to central compartment.

There were no correlations in the final model between etas and covariates (age and weight) (Supplement 2), and, therefore, covariate effects were not modeled.

The final parameter estimates are presented in Table 2. In population parameters, the lowest relative standard error (RSE) was observed in elimination clearance and the highest in intercompartmental clearance between central and peripheral compartment. A relatively high interindividual variability was seen in all parameters, especially in the central volume of distribution. The bootstrap 95% confidence intervals generally agree with the parameter estimates and their RSEs.

Goodness-of-fit plots for the final PopPK model can be seen in Figures 2 and 3 with separate panels for the EPI- and IV-groups. In Figure 2, most predictions are close to the line of identity indicating good agreement between predicted and observed values. In Figure 3, CWRES values are randomly and homogeneously distributed around zero.

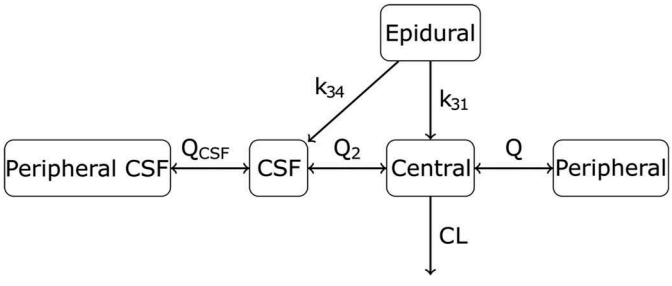

Figure 1. Illustration of the final structural model best describing the data. The intravenous dose was administered to central compartment and epidural dose to epidural compartment. Blood and cerebrospinal fluid (CSF) samples were withdrawn from central and CSF compartments, respectively. CL, clearance; Q, intercompartmental clearance between central and peripheral compartment; Q_2 intercompartmental clearance between central and CSF compartment; Q_{CSF} intercompartmental clearance between CSF and peripheral CSF compartment; k_{31} and k_{34} transfer rate constants from epidural to central and CSF compartments, respectively.

Table 2. Population pharmacokinetic parameters for the final model.

	Population estimates		Bootstrap results	
Parameter	Value	RSE (%)	Median	95% CI
θ_1 (litre/h)	37.4	6.2	37.5	(32.6–42.4)
θ_2 (litre)	90.2	17.6	90.3	(61.5–123.3)
θ_3 (litre)	68.9	18.9	66.2	(43.1–95.5)
θ_4 (litre)	0.035[a]		0.035[a]	
θ_5 (litre/h)	206	39.3	179.7	(70.6–360.1)
θ_6 (litre/h)	0.0537	13.1	0.0562	(0.0439–0.0774)
θ_7 (1/h)	0.749	11.7	0.715	(0.555–0.929)
θ_8 (1/h)	0.0886	19.8	0.0947	(0.0577–0.134)
θ_9 (litre/h)	0.00516	18.3	0.00531	(0.00359–0.00752)
θ_{10} (litre)	0.0385	17.1	0.0404	(0.0283–0.0615)
Interindividual variability (of form $\sqrt{\omega^2}$)				
ω_1	36.2 (%)	22.2	12.5 (%)	(3.1–24.1)
ω_2	76.4 (%)	45.6	59.5 (%)	(9.8–214.6)
ω_3	53.4 (%)	24.0	25.7 (%)	(8.1–67.4)
ω_4	0[a] (%)		0[a]	
ω_5	0[a] (%)		0[a]	
ω_6	33.0 (%)	22.2	10.3 (%)	(2.4–22.9)
ω_7	42.8 (%)	45.6	11.2 (%)	(1.8–33.3)
ω_8	64 (%)	39.4	28.6 (%)	(1.6–100.1)
ω_9	0[a] (%)		0[a]	
ω_{10}	0[a] (%)		0[a]	
Residual variability				
σ_1	29.7	12.8	8.6	(4.4–13.2)
σ_2	33.8	9.6	11.2	(7.3–15.9)

Explanation of indices for θ and ω:
1. Clearance (CL)
2. Central volume of distribution (V)
3. Peripheral volume of distribution (V2)
4. CSF central volume of distribution (V4)
5. Intercompartmental clearance between central and peripheral compartments (Q)
6. Intercompartmental clearance between central and CSF compartments (Q2)
7. Transfer rate constant from epidural to central compartment (k31)
8. Transfer rate constant from epidural to CSF compartment (k34)
9. Intercompartmental clearance between CSF and peripheral CSF compartments (QCSF)
10. CSF peripheral volume of distribution (VPCSF)

[a]indicates that the value was fixed and not estimated, thus having no residual standard error (RSE) or 95% confidence interval (CI). The indices of θ and ω correspond to each other. In residual variability, σ1 describes proportional error for plasma concentration and σ2 for CSF concentrations. Bootstrap analysis was conducted using 1000 samples.

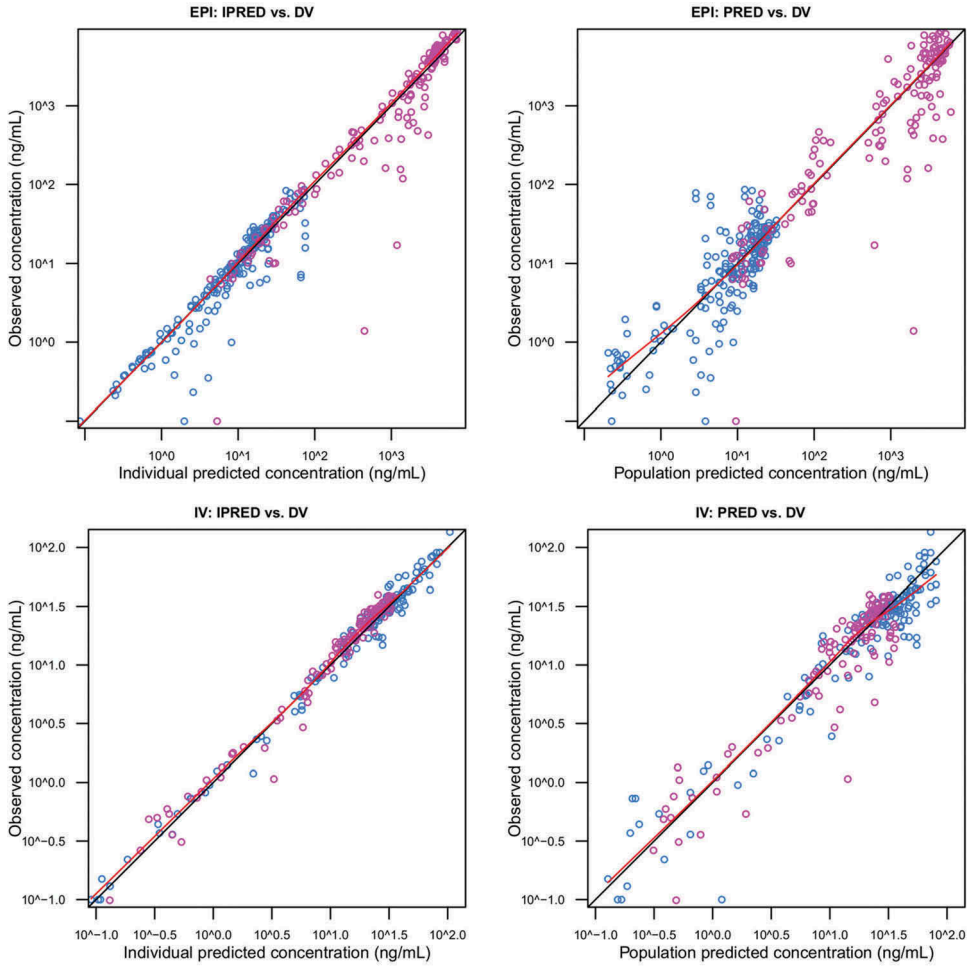

Figure 2. Measured vs. predicted oxycodone concentrations for the individual empirical Bayes estimates (left) and the population model (right). The line of identity is plotted in black and the median of observations in red. EPI, epidural; IV, intravenous; IPRED, Individual predicted concentration; DV, dependent variable, i.e. measured drug concentration.

The visual predictive check (Figure 4) confirms that the model simulations and observed data agree for both groups and both sampling sites.

4. Discussion

The novelty of this study was to establish the first PopPK model for epidurally administered oxycodone. As seen in Figure 1, the final model consists of five compartmentals with one depot compartment for epidural space and two compartments for both CSF and the rest of the body. For IV oxycodone 2-compartmental models have been reported in the literature [14,17]. For the brain and CSF, models with more complexity have been presented in the literature. Westerhout et al. [23] evaluated CSF and brain distribution of paracetamol in rats and show that physiologically based PK (PBPK) modeling can to some extent predict CSF-plasma-ratios observed in human clinical trials [24]. More recently, Yamamoto et al. [25] have shown that a PBPK model based on experimental data derived from rats and in vitro experiments could predict modestly, within 1.6-fold error, free drug concentrations in multiple CNS compartments after IV drug administration in humans. However, the Yamamoto et al. [25] model cannot predict CNS kinetics after epidural drug administration. Omitting transfer from epidural space to plasma significantly weakens the model fit. This can be explained physiologically, as the epidural space contains several structures that may impact PK significantly: nerve roots, fatty areolar tissue and blood vessels that supply the spinal cord and vertebral veins [26].

The PopPK parameter values obtained for clearance and central volume of distribution agree with those reported earlier [27,28]. The volume of CSF near lumbosacral epidural space varies substantially, in adults between 0.01 and 0.06 L [19,29], that may explain the high between-individual variability in CSF concentrations in the present study. As reported by Lee at al [29]. and Sullivan et al. [19], the value of 0.035 L was chosen to represent the lumbosacral CSF volume in order to assume well-stirred model for the first sampling time points. The total volume of CSF is approximately 0.25 L and CSF flows freely in a caudal direction posterior to the spinal cord and in a cephalad direction anterior to the cord [4,30,31]. However, describing CSF concentration of oxycodone using only one compartment was not adequate for the later time points. Therefore, physiology supports the use of peripheral CSF compartment. Had there been more data about CSF concentrations, a more detailed model incorporating separate transfer rate constants could have been used. However, such extensive sampling of CSF in humans is not ethically appropriate and practically feasible. In the study by Kokki et al. [5], 11 mL of CSF per subject was collected.

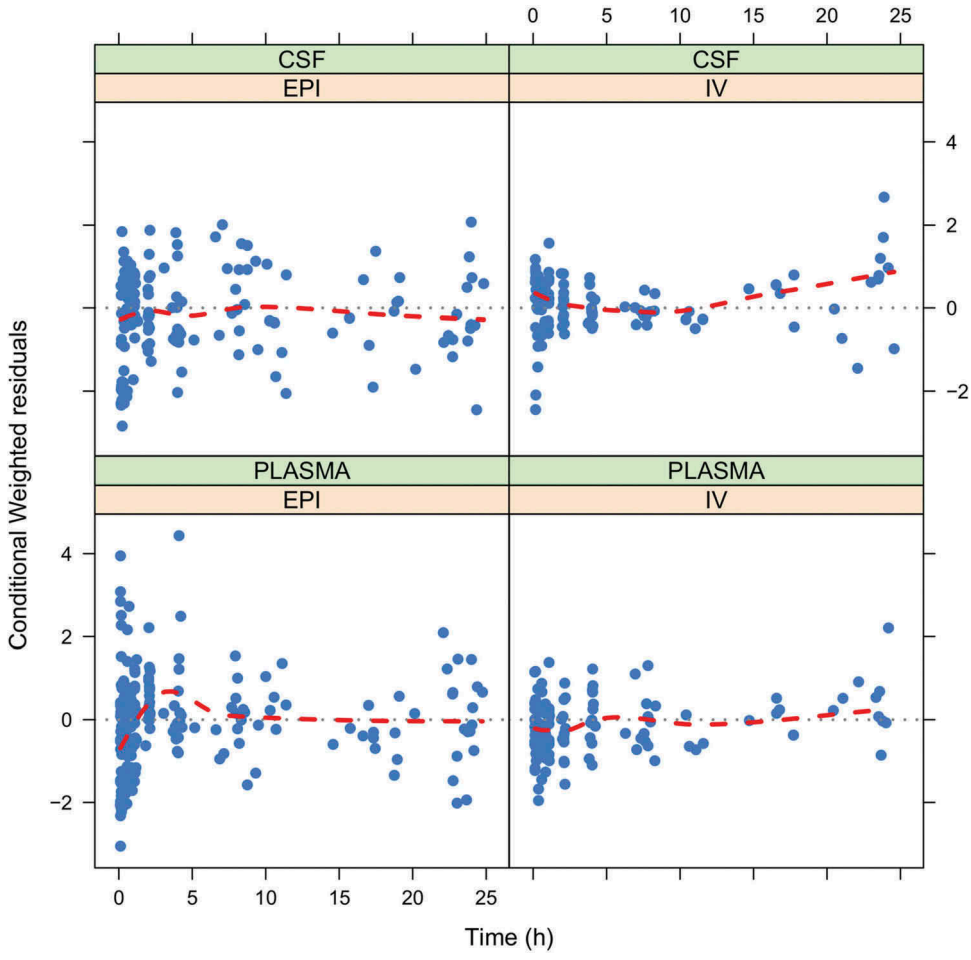

Figure 3. Conditional Weighted Residuals (CWRES) plotted against time for both cerebrospinal fluid (CSF) and plasma concentrations of oxycodone and for both epidural (EPI) and intravenous (IV) groups.

The concentration of oxycodone in CSF after epidural administration is substantially higher compared to plasma samples (e.g. Figure 4). This raises the concern for safety as addressed by Kokki et al. [32]. Recently it was shown that after gynecologic laparotomy, epidural oxycodone provided superior analgesia with similar adverse effects compared to IV oxycodone during early postoperative recovery [6] and in a cell model, it was shown that the neurotoxicity of oxycodone is similar or less than that with morphine [32]. However, more prospective studies are needed to establish the safety and reliability of the epidural administration route.

There are limitations in our study. First, the data for our modeling was taken from Kokki et al. [5] who ran into limitations with oxycodone concentrations ALOQ due to insufficient dilution of the samples as the peak oxycodone concentrations in the CSF were higher than expected, highest >10,000 ng/mL. In the additional data set (n = 6), the peaks in the CSF were between 2,565 and 6,606 ng/mL. Therefore, the few ALOQ concentrations were handled as outliers. Second, it has been suggested that spinal catheters used by Kokki et al. [5] may have produced some observer effect. Some of the oxycodone administered epidurally may have passed into subarachnoid space via the breachment of dura adjacent to the spinal catheter [33]. However, Piirainen et al. [6] later confirmed the superior CSF penetration of epidural vs. IV administration of oxycodone in single lumbar puncture samples. Third, we studied a single dose of oxycodone. It is possible that at steady state both PK and pharmacodynamic (PD) differ from those obtained with a single dose. Further research is needed on this aspect. However, since time to redosing is a clinically relevant endpoint for assessing opioid-induced analgesia, the PK model established in this study could be further extended by incorporating PDs into the model. The extension could be done with repeated time to event (RTTE) rescue fentanyl data collected during the clinical study. Several RTTE studies for morphine have been published [34,35] RTTE model for oxycodone would give better understanding of the efficacy and safety issues related to intrathecal oxycodone. Piirainen et al. [6] evaluated a single injection of either epidural or IV oxycodone in pain management after gynecologic laparotomy. All subjects needed rescue fentanyl during early recovery, but less rescue analgesics were needed in the epidural oxycodone group. Moreover, most subjects needed just one or two doses of rescue fentanyl immediately after the epidural injection and few subsequent doses in average 3 h after the epidural injection of oxycodone. In the IV oxycodone group, the subjects needed rescue fentanyl rather regularly throughout the first postoperative hours.

There has been much discussion about influx transporter for oxycodone in humans, but the data on CNS penetration of oxycodone are inconclusive [36]. In experimental studies in rats, active transport of oxycodone has been shown at the

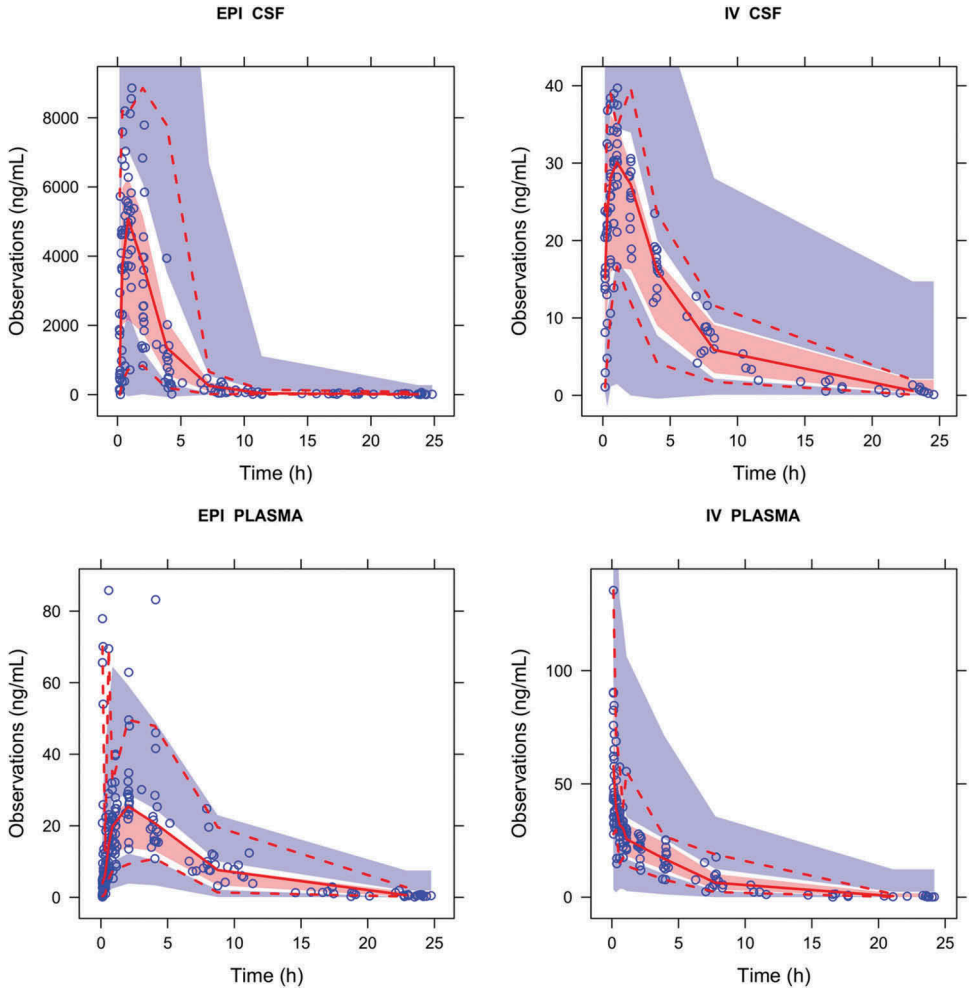

Figure 4. Visual Predictive Check (VPC) for the final population model for the epidural (EPI) – and intravenous (IV) – groups. Blue circles represent the individual observations, solid red line the median observations and dashed red line the 2.5th and 97.5th percentiles of the observations. Blue and red areas represent the 95% confidence intervals for the 2.5th, 50th and 97.5th percentile prediction intervals. CSF, cerebrospinal fluid.

blood-brain barrier [37,38]. In humans, PBPK modeling approach has been used to predict the CNS drug exposure based on CSF concentrations [23,25].

Drug distribution into CSF is a complex phenomenon. After systemic drug administration, blood-CSF barrier in the choroid plexus and blood-arachnoid barrier in the spinal cord region are physical barriers, but also contain transporters [39]. After epidural administration, there is also direct and localized penetration from the epidural space into CSF. The drug concentration in CSF may not reflect brain parenchymal concentrations accurately, and after systemic administration, CSF concentrations may not correlate with analgesia, as shown for oral and subcutaneous morphine [37,40]. However, it is worthy to determine CSF concentrations of opioids to get a better understanding of PK/PD of these compounds in CNS. The spinal cord itself is a major site of action of the opioids, and further studies are needed to evaluate how well do CSF concentrations reflect with those in the spinal cord.

5. Conclusion

A PopPK model was developed and found to describe oxycodone time-concentration data with high precision and accuracy. For assessing oxycodone-induced analgesia, the developed model can act as a key component for future PD-PK modeling of IV and epidurally administered oxycodone.

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Author Contributions

M.L.: conception and design, analysis and interpretation of the data, the drafting of the paper and revising it critically for intellectual content; P.P.: interpretation of the data; the drafting of the paper and revising it critically for intellectual content; H.K.: conception and design, interpretation of the data, the drafting of the paper and revising it critically for intellectual content; C.K.: analysis and interpretation of the data, revising the paper critically for intellectual content; V-P.R.: conception and design, analysis and interpretation of the data, revising the paper critically for intellectual content; P.V.: analysis and interpretation of the data, revising the paper critically for intellectual content; M.K.: principal investigator, conception and design, analysis and interpretation of the data, the final approval of the version to be published. All authors agree to be accountable for all aspects of the work.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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