2018

Oxycodone pharmacokinetics and fetal exposure after intravenous or epidural administration to the ewe

Kinnunen, Mari

Wiley

Tieteelliset aikakauslehtiartikkelit
© Nordic Federation of Societies of Obstetrics and Gynecology
All rights reserved
http://dx.doi.org/10.1111/aogs.13378

https://erepo.uef.fi/handle/123456789/6706
Downloaded from University of Eastern Finland's eRepository
Oxycodone pharmacokinetics and fetal exposure after intravenous or epidural administration to the ewe

Running headline: Oxycodone in pregnant sheep

Mari Kinnunen¹, Hannu Kokki¹, Heidi Hautajärvi², Heikki Huhta³, Veli-Pekka Ranta⁴, Juha Räsänen⁵, Hanna-Marja Voipio⁶ & Merja Kokki⁷

¹School of Medicine, University of Eastern Finland, Kuopio, ²Admescope Ltd, Oulu, ³Department of Surgery, University of Oulu, Oulu, ⁴School of Pharmacy, University of Eastern Finland, Kuopio, ⁵Department of Obstetrics and Gynecology, Helsinki University Hospital, Helsinki, ⁶Laboratory Animal Center, Department of Experimental Surgery, University of Oulu and Oulu University Hospital, Oulu, ⁷Department of Anesthesia and Operative Services, Kuopio University Hospital, Kuopio, Finland

Corresponding author:

Merja Kokki

Anesthesia and Operative Services, Kuopio University Hospital, PO Box 100, 70029 KYS, Finland

Email: merja.kokki@kuh.fi

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/aogs.13378

This article is protected by copyright. All rights reserved.
Conflicts of Interest notification

The authors have no conflicts of interest.

Abstract

Introduction There are limited data of oxycodone pharmacokinetics during pregnancy and on fetal exposure after maternal administration. The present study describes the pharmacokinetics of intravenous oxycodone in pregnant sheep and fetal exposure after intravenous and epidural administration. Material and methods 10 pregnant sheep received 0.1 mg·kg⁻¹ oxycodone intravenously -bolus, and blood samples were collected up to 24 hours. Seven days later, the ewes were randomized to receive 0.5 mg·kg⁻¹ oxycodone intravenously (n=5) or epidurally (n=5) as a single bolus, before laparotomy for placement of catheters into the fetal superior vena cava and carotid artery. Paired maternal and fetal blood samples were taken when the fetal arterial catheter was in place and at the end of surgery. Maternal blood samples were taken up to 24 hours. Results After 0.1 mg·kg⁻¹ oxycodone intravenously, the median clearance was 5.2 L·h⁻¹·kg⁻¹ (range, 4.6-6.2), but the volume of distribution varied between 1.5 and 4.7 L·kg⁻¹. The area under the curve was 17 h·ng·mL⁻¹ (14-19) and the plasma concentration at 2 minutes 60 ng·mL⁻¹ (50-74). Following administration of 0.5 mg·kg⁻¹ intravenously v. or epidurally, oxycodone concentrations were similar in the maternal and the fetal plasma. Accumulation of oxymorphone in the fetus occurred; fetal-to-maternal ratios were 1.3-3.5 (median 2.1) in the IV-group and 0.9-3.0 (1.3) in the EPIDURAL-group. Conclusions We determined the pharmacokinetics of oxycodone in pregnant sheep. We showed accumulation of oxymorphone, which an active metabolite of oxycodone, in the fetus. Therefore, further studies in human pregnancies are required to evaluate the safety of oxycodone.

Keywords

Oxycodone; Oxymorphone; Pharmacokinetics; Analgesia; Pregnancy; Fetus
Abbreviations

PK, pharmacokinetics;
i.v., intravenous;
LLoQ, lowest limit of quantification,
C\textsubscript{max}, peak concentration;
T\textsubscript{max}, time to peak concentration;
T\textsubscript{1/2}, terminal half-life;
AUC\textsubscript{t}, area under the curve from time zero to the last observed concentration;
AUC\textsubscript{inf}, area under the curve from time zero to extrapolated to infinity;
Cl, clearance;
V\textsubscript{ss}, apparent volume of distribution at steady state;
P, plasma;
F/M-ratio, fetal-to-maternal ratio

Key message

Oxycodone pharmacokinetics in pregnant ewe was determined. After maternal oxycodone administration, fetal accumulation of oxymorphone, an active metabolite of oxycodone, was observed.
Introduction

Pregnant women may need analgesia during pregnancy, and most are given analgesics during delivery (1,2). Some women undergo urgent non-obstetric surgery during pregnancy, and some life-threatening birth defects may necessitate fetal surgery before birth (3,4). In these cases, appropriate pain management is necessary during surgery and postoperatively.

Abdominal surgery is the most common surgical procedure in pregnant women (3). Epidural analgesia is the golden standard for pain management after laparotomy and in labor (2). When epidural analgesia is used, a local anesthetic is often combined with an opioid agonist to enhance the analgesic effect, decrease the required amount of local anesthetic and improve patient satisfaction (5). Epidural puncture is contraindicated in some patients and parturients, for example, in patients receiving anticoagulant medication or having other bleeding disorders. In these cases, analgesics must be given intravenously (i.v.) or by other administration routes (6-8).

Oxycodone is an opioid agonist that has been used for managing moderate and severe pain for a century. During the last two decades, the global use of oxycodone has increased extensively (9). Abdominal surgery, both open and laparoscopic, and labor are associated with significant visceral pain (10). Oxycodone is highly effective opioid for visceral pain (11), and thus, it is assumed to be a feasible opioid analgesic in pregnant women for management both peri- and postoperative pain in non-obstetric surgery and labor pain (6,9).

Fetal exposure is a concern when using opioids during pregnancy. Oxycodone, like other opioids, crosses freely the placenta (6,12), and this becomes clinically important because higher doses can cause fetal sedation and compromise respiratory and neurological function immediately after birth.

To our knowledge, there are no previous studies of pharmacokinetics (PK) of oxycodone in pregnant ewes. The aims of this experimental study with pregnant sheep were, firstly, to describe the PK of i.v. oxycodone in the ewe, and secondly, to evaluate the fetal exposure to oxycodone and its metabolites in late pregnancy. Our study hypothesis was that the fetal exposure would be similar to maternal exposure after oxycodone administration to the ewe.
Material and methods

The present study is a part of the KuBiCo (Kuopio Birth Control) consortium (www.KuBiCo.fi), which consists of scientists from University of Eastern Finland, Kuopio University Hospital, Institute of Health and Welfare and Istekki Ltd. 10 time-mated Åland landrace ewes (Lammastila Sikka Talu, University of Turku, Rymättylä, Finland) were used in this study at the Department of Experimental Surgery, Laboratory Animal Center, University of Oulu and Oulu University Hospital, Oulu, Finland. Animals were monitored daily by veterinarian, animal technicians and investigators for signs of pain, distress, injury or disease. The ewes with either singleton or twin pregnancy were 3–11 years old with 118–127 gestational days (term 145 days) and with a median weight of 54 kg (51–60 kg).

In the first part of the study, oxycodone PK was measured seven days before surgery. Oxycodone hydrochloride trihydrate (Oxanest®, Takeda Oy, Helsinki, Finland) 0.1 mg·kg⁻¹ i.v., diluted with NaCl 9 mg·mL⁻¹ to 10 mL, was given via the left external jugular vein. The dose corresponds to 0.0867 mg·kg⁻¹ of oxycodone hydrochloride. The blood samples for oxycodone and its metabolites concentration analyses were taken from an indwelling cannula from the contralateral, external jugular vein. Baseline blood sample was collected before the oxycodone administration, and thereafter blood samples were taken at 2, 10, 30 and 60 minutes, and 2, 4, 7, 10 and 24 hours after the 1-minute i.v. bolus.

The second part was an open, randomized study with two parallel groups. The sheep were randomized into the IV- and the EPIDURAL-groups. Randomization was performed using a random organization generator (www.randomization.com). Oxycodone was diluted with NaCl 9 mg·mL⁻¹ into a solution of 5 mg·mL⁻¹ oxycodone. A single 1-minute 0.5 mg·kg⁻¹ oxycodone hydrochloride trihydrate bolus (corresponding to 0.434 mg·kg⁻¹ oxycodone hydrochloride) was administered i.v. or epidurally at the anesthetized ewe at the beginning of surgery.

A standardized general anesthesia was used. Before the surgery, the ewes were premedicated with an intramuscular ketamine 2 mg·kg⁻¹ and midazolam 0.2 mg·kg⁻¹. Anesthesia was induced with i.v. propofol 4-5 mg·kg⁻¹ and maintained with sevoflurane 1.5–2.5% in an oxygen–air mixture with positive pressure ventilation via an endotracheal tube. Transdermal fentanyl patches (2 µg·kg⁻¹·h⁻¹) were attached 1 hour before the surgery, and additional intramuscular fentanyl (2 µg·kg⁻¹) was administered during recovery, if needed for rescue pain management. Maternal heart rate, arterial blood pressure, end tidal partial pressure of
carbon dioxide (etCO$_2$) and oxygen saturation (SpO$_2$) were monitored continuously during anesthesia (AS3 Patient Monitor, Datex-Ohmeda, Helsinki, Finland).

The surgical procedure included the placement of catheters into the fetal internal jugular vein and carotid artery. The surgical procedure has been described in detail earlier (13). In short, a midline abdominal incision was made to access the uterus. After hysterotomy, fetal head and upper body were delivered, and catheters were inserted into the carotid artery and the internal jugular vein, placing the catheter tips in the ascending aorta and the superior vena cava.

Maternal blood samples were collected from the external jugular vein before the oxycodone administration, and 2, 10, 30 and 60 minutes, and 2, 4, 7, 10 and 24 hours after the oxycodone bolus. In addition, two parallel maternal and fetal blood samples were taken; the first when the fetal catheters were in place and the second at the end of surgery. The fetal blood samples were obtained from the arterial catheter. The blood samples were taken into EDTA tubes, turned 6-8 times and then centrifuged at 2500 g for ten minutes. Following this, the separated plasma was divided into two Eppendorf-tubes and stored at – 70 °C until analysis in a single patch in Admescope Ltd. (Oulu, Finland).

Oxycodone concentration was measured using an ultra-performance liquid chromatography mass spectrometry system (14). The linear calibration ranges (ng·mL$^{-1}$) were fitted as follows: oxycodone 0.05-1000, oxymorphone 0.1-500, noroxymorphone 0.2-1000, and noroxycodone 0.05-100. Accuracies were between 101-124% at the lowest limit of quantification (LLoQ) and 85-112% above the LLoQ. Precisions were 0.9-14% over the entire range of calibration. All concentrations of oxycodone and its metabolites are reported as corresponding hydrochlorides.

Statistical analyses

No formal sample size calculation was performed, but a sample of 10 pregnant sheep available was considered to provide pertinent data on the oxycodone PK in pregnant sheep and for the fetal exposure evaluation. Peak concentration ($C_{\text{max}}$), time to peak concentration ($T_{\text{max}}$), terminal half-life ($T_{1/2}$), area under the curve from time zero to the last observed concentration ($AUC_t$) and extrapolated to infinity ($AUC_{\text{inf}}$), clearance (Cl) and apparent volume of distribution at steady state ($V_{\text{ss}}$) were calculated based on noncompartmental analysis using Phoenix WinNonlin version 6.3 software (Certara, Princeton, NJ, USA). $AUC_t$
was calculated using the linear trapezoidal rule. Descriptive results are presented as median with minimum and maximum.

**Ethical approval**

The study protocol was reviewed and approved by the National Animal Experiment Board of Finland (ESAVI/3510/04.10.03/2011). The animal care and experimental procedures were conducted according to the national legislation (15,16) and the EU Directive 2010/63/EU (17).

**Results**

There were no protocol deviations likely to affect the integrity of the data. The maternal P-oxycodone (plasma oxycodone) concentrations after 0.1 mg·kg⁻¹ oxycodone i.v. are presented in figure 1. Median of T₅₀ was 0.64 h (minimum-maximum 0.33-4.4) and median of AUCₜ 16.6 h·ng·mL⁻¹ (13.9-18.8) (table 1). Last observed P-oxycodone above the LLoQ was 4.0 h (2.0-10.0) after the oxycodone administration. One sheep was an outlier, probably due to unintentional extravascular administration of oxycodone, and the data were not included in the PK analysis. On that sheep, Cₘₐₓ of oxycodone was 4.2 ng·mL⁻¹ at 60 minutes after the oxycodone administration (figure 1, sheep 6).

The maternal P-oxycodone concentrations after 0.5 mg·kg⁻¹ i.v. bolus are presented in figure 2. Median of maternal T₅₀ was 5.0 h (0.90-5.7) and plasma concentration at 2 minutes was 605 ng·mL⁻¹ (516-817). Oxycodone concentrations were observed up to 7-24 h after oxycodone administration. The median fetal P-oxycodone concentration was 10.8 ng·mL⁻¹ (1.7-18.9), and the fetal-to-maternal ratio (F/M-ratio) was 1.01 (0.77-1.95) (figure 3). Parallel maternal-fetal blood samples were taken at 55-158 minutes (median 103) after the oxycodone bolus.

The maternal P-oxycodone concentrations after 0.5 mg·kg⁻¹ epidural bolus are presented in figure 4. Median of maternal T₅₀ was 3.8 h (0.69-10.5), Cₘₐₓ 78 ng·mL⁻¹ (16-128) and Tₘₐₓ 0.52 h (0.18-2.0). Last observed oxycodone concentrations above the LLoQ were at 7-24 h after the oxycodone dosing. The median fetal P-oxycodone concentration was 11.8 ng·mL⁻¹ (6.2-22.4) and the F/M-ratio 0.64 (0.47-1.04, n=3) (figure 3). Parallel maternal-fetal samples were taken at 63-161 minutes (median 115) after the oxycodone bolus. Two fetuses died to bleeding complications during the surgery before the oxycodone blood samples could be obtained.

This article is protected by copyright. All rights reserved.
In the parallel maternal-fetal blood samples, in the IV-group the oxymorphone concentration ranged between 3.8 and 12.5 ng·mL\(^{-1}\) (median 7.2) in the maternal plasma and between 9.2 and 40.1 ng·mL\(^{-1}\) (median 15.8) in the fetal plasma. In the EPIDURAL-group, the maternal plasma concentration of oxymorphone ranged between 3.6 and 20.4 ng·mL\(^{-1}\) (median 9.4) and the fetal plasma concentration of oxymorphone between 4.5-54.0 ng·mL\(^{-1}\) (median 10.9, n=3), respectively. The oxymorphone F/M-ratio in the IV-group was 2.10 (1.34-3.52) and that in the EPIDURAL-group 1.29 (0.86-2.96, n=3) (figure 3). The plasma concentrations of the other metabolites of oxycodone were low; P-noroxycodone below 2.3 ng·mL\(^{-1}\) and P-noroxymorphone below the LLoQ.

**Discussion**

To the best of our knowledge, this was the first study to evaluate oxycodone PK in pregnant sheep. The plasma clearance of oxycodone was relatively similar across the ewes, but there was a substantial interindividual variation in the \(V_{ss}\) both after 0.1 mg·kg\(^{-1}\) and 0.5 mg·kg\(^{-1}\) i.v. doses. There was also large variability in the terminal half-life and this is partly explained by the fact that P-oxycodone remained above the LLoQ for a highly variable time interval (2 to 6 hours) in different ewes. Therefore, it is likely that the terminal half-life did not represent the true elimination half-life in all cases. Plasma clearance was 2-fold higher after 0.1 mg·kg\(^{-1}\) i.v. oxycodone compared to Cl after 0.5 mg·kg\(^{-1}\) bolus. After the smaller oxycodone dose, the P-oxycodone concentrations remained above the LLoQ for a shorter time interval and it was likely that the true elimination phase was not observed in all ewes, which led to an underestimate of AUC and an overestimate of Cl. Furthermore, sheep were under general anesthesia during the 0.5 mg·kg\(^{-1}\) oxycodone i.v., which might decrease Cl.

The fetal P-oxycodone concentrations were mainly similar compared to those in the maternal plasma in samples obtained 1-2.5 hours after oxycodone administration. Few higher fetal P-oxycodone concentrations were observed in the IV-group, the highest F/M-ratio being 1.95, but not in the EPIDURAL-group. In our previous study with human parturients, P-oxycodone was similar in the maternal and the umbilical plasma, and no high oxycodone F/M-ratios were observed (6). One of the limitations of the present study was that the first parallel blood samples were taken when the fetal catheters were in place and the second at the end of surgery. As these times vary from pair to pair, the calculation points vary accordingly.
The novel and clinically important finding of the present study was that the fetal plasma concentrations of oxymorphone, an active metabolite of oxycodone, exceeded those in the maternal plasma. Oxymorphone concentrations in the fetal plasma were indeed 2.1-fold higher after i.v. administration and 1.3-fold higher after epidural administration than in the maternal plasma. To the best of our knowledge, there are no previous studies showing fetal oxymorphone accumulation. Oxymorphone is rarely used for labor analgesia (18), but it is metabolized from oxycodone via CYP2D6 in humans. Oxymorphone accumulation to fetus is a concern, because oxymorphone has almost 50-fold higher affinity for the µ-opioid receptor compared to oxycodone. It is assumed that high oxymorphone concentrations are associated with an increased risk for adverse effects in newborn (19).

Possible explanations for oxymorphone accumulation are related to its metabolism and increased fetal uptake. In sheep, fetal development and activity of CYP enzymes are slower than in humans (20). In human oxycodone metabolism, CYP3A4 pathway to noroxycodone is the most significant, whereas CYP2D6 metabolism to oxymorphone has a minor role. In the present study, P-noroxycodone remained low, while oxymorphone was the primary metabolite. Differences in human and sheep pharmacokinetics, and immature CYP activity in sheep fetuses may partly explain the high fetal oxymorphone concentrations observed. Possible fetal uptake warrants further studies. Oxymorphone placental permeability has not been established, but opioids in general cross freely the placenta because they have low molecular weight and are highly liposoluble (21).

In human parturients after 2-5 mg i.v. oxycodone, umbilical oxymorphone concentrations were below 0.12 ng·mL⁻¹ (6). In that study, the blood samples were taken 408 minutes (102-1619) after the last oxycodone dose, which is significantly later compared to the fetal blood samples of the present study (55-161 minutes). In another study of infants at gestational age 23-42 weeks receiving 0.1 mg·kg⁻¹ i.v. oxycodone, the peak P-oxymorphone was below 2.5 ng·mL⁻¹ (22). Thus, the fetal P-oxymorphone concentrations observed here are relatively high and warrants further studies to confirm the clinical relevance in human pharmacotherapy.

Oxycodone PK have been evaluated in non-pregnant sheep. Villesen et al. measured oxycodone concentrations in the sagittal sinus and abdominal aorta in non-pregnant sheep after 0.6 mg·kg⁻¹ i.v. oxycodone and found C_max of 720 ng·mL⁻¹ in arterial samples and 380 ng·mL⁻¹ in plasma obtained from the sagittal sinus (23). In the Villesen’s study, the analysis method was less sensitive than that used in the present study. They reported that oxycodone
concentrations were below the LLoQ (50 ng·mL\(^{-1}\)) at 45 minutes after dosing in each sheep. In the present study, with a more sensitive method (LLoQ 0.5 ng·mL\(^{-1}\)), we could detect oxycodone in 9/10 ewes at 4 hours after 0.1 mg·kg\(^{-1}\) i.v. oxycodone and up to 24 hours after 0.5 mg·kg\(^{-1}\) i.v. or epidural oxycodone.

Neurotoxicity is a concern with any compound administered intrathecally. In fact, there are few studies investigating epidural administration of oxycodone. Epidural oxycodone is assumed to have a potential for intrathecal use. In our previous human study, 0.1 mg·kg\(^{-1}\) epidural oxycodone after gynecological surgery provided more effective analgesia and 320-fold higher oxycodone concentrations in cerebrospinal fluid compared to 0.1 mg·kg\(^{-1}\) i.v. oxycodone (14). No severe adverse effects were observed.

In the present study, the fetal P-oxycodone was lower than the maternal P-oxycodone after epidural administration. In the ewes, median AUC\(_{\text{inf}}\) was 125 h·ng·mL\(^{-1}\) after epidural administration and 154 h·ng·mL\(^{-1}\) after i.v. administration with 0.5 mg·kg\(^{-1}\) oxycodone dose, respectively, suggesting that the bioavailability after epidural administration was approximately 80%. Assuming that there is no significant drug metabolism in the epidural injection site, the expected bioavailability is 100%. However, future studies are needed to verify our observed value. Kokki et al. (14) found a similar high bioavailability in non-pregnant women undergoing lower abdominal surgery. To the best of our knowledge, there are no human studies of epidural oxycodone in parturients.

There are several limitations in this experimental study. Firstly, the number of sheep was small, and because of the loss of two fetuses in the EPIDURAL-group, there were only three ewe-fetus-pairs for comparison. However, 10 pregnant sheep available was considered to provide sufficient experimental data of oxycodone PK and fetal exposure in sheep. Secondly, results observed with a pregnant sheep model should be applied to pregnant women with great caution. This data should be considered as experimental; therefore further human data are needed. However, there are only limited possibilities for evaluation of human maternal and fetal pharmacokinetics of opioids and this necessitates experimental research.

In conclusion, the pharmacokinetics of oxycodone in pregnant sheep were described for the first time. In particular, oxymorphone accumulation to the fetus was observed after i.v. and epidural administration of oxycodone to the ewe. Further studies are required to evaluate the clinical relevance of these results with this sheep model.

This article is protected by copyright. All rights reserved.
Funding

The study was funded with grant from Olvi foundation, Iisalmi, Finland.

References


15. Parliament of Finland. Act on the protection of animals used for scientific or educational purposes. 497/2013.

16. Finnish Government. Decree on the protection of animals used for scientific or educational purposes. 564/2013.


This article is protected by copyright. All rights reserved.

Legends of figures

Figure 1. The maternal plasma concentrations of oxycodone after 0.1 mg·kg\(^{-1}\) intravenous oxycodone.

Figure 2. The maternal plasma concentrations of oxycodone after 0.5 mg·kg\(^{-1}\) intravenous oxycodone.

Figure 3. Fetal-to-maternal ratios (F/M-ratio) of A, B) oxycodone and C, D) oxymorphone plasma concentrations after intravenous or epidural administration to the ewe. Each symbol corresponds a single F/M-ratio of parallel fetal and maternal blood samples. Two parallel blood samples were obtained from each fetus-ewe-pair; the first when the fetal catheters were in place, and the second at the end of surgery.

Figure 4. The maternal plasma concentrations of oxycodone after 0.5 mg·kg\(^{-1}\) epidural oxycodone.
Table 1. Pharmacokinetic variables after oxycodone administration. Data are presented as median (minimum-maximum).

<table>
<thead>
<tr>
<th>Variable</th>
<th>I.V. 0.1 mg·kg(^{-1}) (n=9)</th>
<th>I.V. 0.5 mg·kg(^{-1}) (n=4)</th>
<th>EPI 0.5 mg·kg(^{-1}) (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest observed concentration (ng·mL(^{-1}))</td>
<td>60.2 (49.8-73.5)</td>
<td>605 (516-817)</td>
<td>78.1 (16.3-128)</td>
</tr>
<tr>
<td>(T_{\text{max}}) (h)</td>
<td></td>
<td></td>
<td>0.52 (0.18-2.0)</td>
</tr>
<tr>
<td>(\text{Cl} \text{ (L·h}^{-1}·\text{kg}^{-1}))</td>
<td>5.2 (4.6-6.2)</td>
<td>2.8 (2.7-3.2)</td>
<td>3.5 (3.3-5.2) (n=3)(^a)</td>
</tr>
<tr>
<td>(V_{\text{ss}} \text{ (L·kg}^{-1}))</td>
<td>1.8 (1.5-4.7)</td>
<td>2.0 (1.1-2.5)</td>
<td>Not determined</td>
</tr>
<tr>
<td>(T_{1/2} \text{ (h)})</td>
<td>0.64 (0.33-4.4)</td>
<td>5.0 (0.90-5.7)</td>
<td>3.8 (0.69-10.5) (n=3)(^a)</td>
</tr>
<tr>
<td>(\text{AUC}_{\text{last}} \text{ (h·ng·mL}^{-1}))</td>
<td>16.6 (13.9-18.8)</td>
<td>154 (133-161)</td>
<td>82.7 (29.1-132)</td>
</tr>
<tr>
<td>(\text{AUC}_{\text{inf}} \text{ (h·ng·mL}^{-1}))</td>
<td>16.7 (14.0-18.8)</td>
<td>154 (133-161)</td>
<td>125 (83.7-132) (n=3)</td>
</tr>
</tbody>
</table>

\(^a\)Apparent clearance is calculated for epidural administration.

Abbreviations: \(T_{\text{max}}\) = time to peak concentration, \(\text{Cl}\) = plasma clearance, \(V_{\text{ss}}\) = volume of distribution at steady state, \(T_{1/2}\) = terminal half-life, \(\text{AUC}_{\text{last}}\) = area under the concentration curve from oxycodone administration to the last measured concentration, \(\text{AUC}_{\text{inf}}\) = area under the curve extrapolated to infinity.