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Oxycodone for pain management in the latent phase of labour – a pragmatic trial

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Abstract

Background: Parenteral opioids are used for pain relief in labour but there are little data for oxycodone in this context. The aim of the present study was to evaluate the efficacy, foetal exposure and safety of subcutaneous oxycodone in the latent phase of labour.

Methods: This pragmatic trial included 76 parturients, who received subcutaneous oxycodone for pain relief in the latent phase of labour according to the hospital protocol: an initial dose 0.1 mg·kg\(^{-1}\), and a second dose, 0.05 mg·kg\(^{-1}\), could be administered four hours later. Pain intensity and pain relief were assessed using a numerical rating scale of 0-10. After delivery, blood samples from the maternal and umbilical veins were collected, and plasma concentrations of oxycodone and its main metabolites were quantified using UPLC-MS/MS. The Apgar scores and maternal and neonatal adverse effects were recorded.

Results: The foetal exposure at birth was low, the median oxycodone and oxymorphone umbilical vein plasma concentrations were 1.2 ng·mL\(^{-1}\) (range 0.21-7.8) and 0.14 ng·mL\(^{-1}\) (0-0.26), respectively. Pain scores decreased substantially, from a median pain score of 7/10 before oxycodone to median scores of 5/10 at 30 min after administration, 5/10 at 60 min and 6/10 at 120 min. The median Apgar score was 9 (range 2-10) at 1 min and 9 (6-10) at 5 min. Maternal adverse effects were mild, and there were no oxycodone-related neonatal adverse effects.

Conclusion: Subcutaneous oxycodone provided effective analgesia during the latent phase of labour. Newborn exposure at birth was low, and oxycodone was well-tolerated.

Editorial Comment:
Subcutaneous oxycodone may be a good alternative for analgesia for the first stage of labor. In this unblinded one-armed trial, good analgesia for the period before active labor and low foetal concentrations of oxycodone or important metabolites were demonstrated for the chosen dose of subcutaneous oxycodone.

Introduction

Labour pain can be moderate to severe in the latent phase during contractions.\(^1\) Pain in the latent phase increases maternal anxiety and stress\(^1\) and may delay breastfeeding and increase the risk
for postpartum depression.\textsuperscript{2,3} Therefore, effective and safe methods for pain relief during the entire labour process are required.

Non-pharmacological methods have no or only minor adverse effects and may improve the labour experience, yet they often lack adequate analgesic efficacy.\textsuperscript{4} Neuraxial techniques are the gold standard for labour analgesia, but they are not always feasible and are not commonly used in the latent phase.\textsuperscript{5,6} Systemic opioids are effective, but maternal and foetal adverse effects are a concern, especially with higher doses.\textsuperscript{7} Opioids pass freely across the placenta;\textsuperscript{8} thus, neonates are at risk of developing opioid-related adverse effects. A recent Cochrane review concluded that further studies are needed to verify whether the benefit-risk ratio of parenteral opioids is positive for labour analgesia.\textsuperscript{6}

In 2008, the global consumption of oxycodone for medical use surpassed that of morphine,\textsuperscript{9} but there are only limited data regarding oxycodone use in labour,\textsuperscript{10} and data on the latent phase are scarce for any other opioid as well. In our previous pharmacokinetic study with 15 nulliparous parturients in the active phase of labour, intravenous (i.v.) oxycodone 5 mg had moderate analgesic efficacy and was well-tolerated by both the mothers and the newborns.\textsuperscript{11} Oxycodone concentrations were similar in the maternal and umbilical plasma at birth.\textsuperscript{11} Subcutaneous (s.c.) and i.v. oxycodone has been used for labour analgesia in our hospital for a few years. However, we are not aware of any publications about the use of oxycodone during the latent phase of labour.

In the present pragmatic trial, we first evaluated neonatal exposure to oxycodone and its metabolites at birth after maternal s.c. oxycodone in the latent phase of labour and second, the efficacy and safety of s.c. oxycodone in labour analgesia. Our study hypotheses were that neonatal exposure to oxycodone would be low and comparable to maternal exposure at birth and oxycodone would provide effective analgesia in the latent phase of labour.
Methods

The study protocol was approved by the Research Ethics Committee of the Hospital District of Northern Savo, Kuopio, Finland (date of approval 9.10.2012, no.64/2012), registered in the European Clinical Trials Database (EudraCT no.2012-003189-42) and had institutional approval. The Finnish Medicines Agency was notified (no.93/2012). The study was conducted in accordance with the Declaration of Helsinki. The study is a part of the KuBiCo (Kuopio Birth Control) consortium (www.KuBiCo.fi), which comprises scientists from the University of Eastern Finland, Kuopio University Hospital, Institute of Health and Welfare and Istekki Ltd., Kuopio, Finland.12

We enrolled 80 parturients aged 20-42 years at Kuopio University Hospital between December 2013 and January 2016. These parturients gave written consent after being provided verbal and written information. We did not enrol parturients who were younger than 18 years old, who did not receive oxycodone or who were unwilling to participate.

Oxycodone (Oxanest®; Takeda Oy, Helsinki, Finland) was administered according to the hospital protocol during the first stage of labour: in the latent phase, an initial dose of 0.1 mg·kg^{-1} s.c. injection of oxycodone hydrochloride with a maximum dose of 10 mg was administered, and four hours later, further doses of 0.05 mg·kg^{-1} (maximum 5 mg) could be administered if required, no more frequently than every four hours. Latent phase was defined as the part of first stage of labour, where painful contractions were frequent and cervical changes occurred, and cervical dilatation was up to 4 cm.13 An attending obstetrician who was unaware of whether a parturient was participating in the study decided on oxycodone administration based on the clinical evaluation. During the latent phase, no opioids other than oxycodone were allowed. In the active phase, intrathecal fentanyl could be used as required.

Maternal contraction pain was assessed before and 30, 60 and 120 min after the first oxycodone administration. Pain intensity was evaluated using an 11-point numerical rating scale (NRS, 0=no pain, 10=most pain). The percentage of maximum possible total pain relief score (%maxTOTPAR) was calculated using a trapezoidal rule dividing an actual TOTPAR by a maximum possible TOTPAR.14 In addition, pain relief was assessed 60 min after the first oxycodone dose.
using the NRS (0=no relief, 10=complete relief) and categorial verbal rating scale (VRS, none, slight, moderate, good, complete). Neonatal status was assessed with cardiotocography during labour and the newborn’s outcome with the Apgar scores\textsuperscript{15} and the Neurologic and Adaptive Capacity Score (NACS) at 60-120 min after the birth.\textsuperscript{16} Maternal and foetal adverse effects were recorded.

To evaluate newborn exposure, blood samples from the umbilical cord were collected after delivery when the umbilical cord was clamped and cut. Blood samples from the maternal vein were collected shortly after birth. The blood samples were centrifuged at 2500 g for 10 min, and the separated plasma was collected in Eppendorf tubes and stored at -70 °C until analysis in a single patch at Admescope Ltd., Oulu, Finland.

The concentrations of oxycodone and its main metabolites oxymorphone, noroxymorphone and noroxycodone were analysed with an ultra-performance liquid chromatography mass spectrometry system.\textsuperscript{17} The lower limit of quantification (LLOQ) was 0.1 ng·mL\textsuperscript{-1} for oxycodone and oxymorphone, 0.2 ng·mL\textsuperscript{-1} for noroxycodone and 0.5 ng·mL\textsuperscript{-1} for noroxymorphone. The linear calibration ranges (ng·mL\textsuperscript{-1}) were fitted as follows: oxycodone 0.1-1000, oxymorphone 0.1-500, noroxycodone 0.2-1000 and noroxymorphone 0.5-1000. Accuracies were between 89-125\% at the LLOQ and 75-118\% above the LLOQ. The precisions were 0.5-14\% over the entire range of calibration. All concentrations of oxycodone and metabolites were reported as their corresponding hydrochlorides.

The primary outcome measures were maternal and umbilical plasma concentrations of oxycodone and its main metabolites at birth. Secondary outcome measures were maternal pain intensity and pain relief scores after the first s.c. oxycodone administration, maternal and neonatal adverse effects and newborn Apgar and NACS scores.

No formal sample size calculation was conducted. However, a minimum of 50 parturients was considered to provide sufficient data on neonatal exposure to oxycodone at birth. In normal labour, 95\textsuperscript{th} percentile from latent phase to birth of the neonate is 17.7 hours,\textsuperscript{18} the maximum plasma concentration after s.c. oxycodone 0.1 mg kg\textsuperscript{-1} is 50 ng·mL\textsuperscript{-1},\textsuperscript{19} and the terminal plasma half-life of oxycodone in parturients is 2.6 hours.\textsuperscript{11} Thus, we assumed that we can detect oxycodone from majority of the umbilical samples even in the longest cases of delivery with the
LLoQ of 0.1 ng·mL⁻¹. The data were analysed using the Statistical Package for Social Sciences software (IBM SPSS Statistics 25, International Business Machines Corporation, Armonk, NY, USA). The Pearson correlation coefficients with two-tailed significance testing were used for the correlation evaluation. Pain data were analysed using Friedman’s test and Wilcoxon signed-rank test. For multiple comparisons, Bonferroni correction was applied. A p-value of less than 0.05 was considered statistically significant. The data were presented as a median with minimum and maximum, mean with standard deviation (SD), or number of cases as appropriate.
Results

A total of 80 parturients agreed to participate and provided informed consent. Three parturients were lost to follow-up, and there was one major protocol deviation (i.v. oxycodone instead of s.c. oxycodone was administered for one parturient); a few minor protocol deviations were unlikely to affect the integrity of the data. Hence, 76 parturients were included in the analysis. The parturients’ demographics are presented in Table 1. The babies were born by spontaneous vaginal delivery (n=56; 74 %), vacuum-assisted vaginal delivery (n=10; 13 %), caesarean section (n=8; 10 %) or emergency caesarean section (n=2; 3 %).

The median initial dose of s.c. oxycodone was 8 mg (range 6-10) and the median total dose was 9 mg (6-43). Thirty-five (46%) of the 76 parturients required additional doses of s.c. oxycodone; specifically, one (n=28), two (n=5), three (n=1) or six (n=1) additional doses were administered. The time from the last oxycodone dose to the delivery ranged between 3 h 24 min and 40 h 4 min (median, 11 h 38 min).

Maternal blood samples were obtained from 58 (76 %) parturients and umbilical samples from 61 (80 %) newborns. The plasma concentrations of oxycodone, noroxycodone, oxymorphone and noroxymorphone are presented in Table 2.

There was a moderate negative correlation between time from the last oxycodone dose to delivery and the umbilical concentrations of oxycodone (r=-0.61, p<0.001) and a weak negative correlation for oxymorphone (r=-0.32, p=0.015) (Figure 1). However, there was no correlation between the total dose of oxycodone and the umbilical plasma oxycodone (r=-0.19, p=0.16) or oxymorphone (r=0.14, p=0.32) concentrations.

The median pain intensity in NRS 0-10 was 7 (range 4-10, n=73) before the first oxycodone administration. A significant analgesic action was reported in all postadministration assessments; at 30 min, the median pain intensity in NRS was 5 (0-9, n=50), at 60 min the intensity was 5 (0-10, n=52) and at 120 min the intensity was 6 (0-10, n=51) (Figure 2). The median %maxTOTPAR was 45% (-25% - 100%), while 26 (44%) of the 59 parturients had %maxTOTPAR ≥ 50% and three had a negative value. The median value of pain relief in NRS was 5 (0-10, n=61). Pain relief at 60 min
after the first dose was assessed in VRS for 46 parturients, and it was complete in 9 parturients, good in 14 parturients, moderate in 14 parturients and slight in 9 parturients.

All parturients required additional analgesia as labour progressed into the active phase: epidural analgesia was provided for 67 (88%) parturients, inhaled nitrous oxide for 62 (82%) parturients, pudendal or paracervical block for 22 (29%) parturients, spinal analgesia for three (4%) parturients, and acetaminophen (paracetamol) for one (1%) parturient.

Observed maternal adverse effects (n=30) in 29 (38%) parturients were expected and mild: sedation (n=27), decreased contraction frequency (n=2) and vomiting (n=1).

In neonates, the median Apgar score was 9 (range 2-10) at 1 min and 9 (6-10) at 5 min after birth. The median NACS score was 38 (31-39). Five (7%) of the 76 newborns required follow-up and treatment in the neonatal intensive care unit due to infection (n=2), premature birth (n=1), hypoglycaemia (n=1) and breathing difficulty (n=1). Respiratory depression could possibly be an oxycodone-related adverse effect; however, opioid concentrations in the umbilical vein were very low (0.57 ng·mL⁻¹ for oxycodone and 0.10 ng·mL⁻¹ for oxymorphone) in the newborn with breathing difficulty. Thus, the assessment was that breathing difficulty was unlikely oxycodone-related.

Two babies were delivered by emergency caesarean section. In the first case, the parturient was at 40 weeks’ gestation and had gestational diabetes. She received 9+4.5 mg oxycodone, and the last dose was administered 13 h 11 min before delivery. The section was performed due to decreased foetal capillary pH of 7.04. Her Apgar scores were 6/6, and the newborn was observed for three days in the neonatal intensive care unit due to hypoglycaemia. Her recovery was uneventful. The other emergency caesarean section was performed due to pre-eclampsia in a parturient at 34 weeks’ gestation. She received three 10 mg doses of s.c. oxycodone within 40 h, the last dose at 4 h 15 min before delivery. The oxycodone concentration in the maternal plasma was 15.5 ng·mL⁻¹ and the noroxycodone concentration was 11.1 ng·mL⁻¹ at 75 min after the last oxycodone dose. The other metabolites were < LLoQ. The Apgar scores were 9/9, and the newborn was observed in the neonatal intensive care unit due to prematurity; his recovery was uneventful. In both cases, the emergency caesarean section was considered not related to the oxycodone administration.
Discussion

The novelty of this study is that it measured for the first time newborn exposure to oxycodone after s.c. oxycodone administration to the parturient in the latent phase of labour. Oxycodone was detected in all umbilical plasma samples at birth, and the concentrations were slightly higher than those in the maternal plasma. However, all umbilical concentrations were well below the estimated minimum effective concentration in children, 12 ng·mL$^{-1}$, and mean effective analgesic concentration, 20 ng·mL$^{-1}$, thus, neonatal exposure to oxycodone was considered low. In the present pragmatic trial, umbilical oxycodone concentrations were lower than in our previous study of i.v. oxycodone in the active phase of labour, median 1.2 ng·mL$^{-1}$ vs. 2.7 ng·mL$^{-1}$, respectively, although the total oxycodone dose was higher, 9 mg in the present s.c. study vs. 5 mg in the i.v. study.$^{11}$ The median time from the last oxycodone dose to delivery was 11.6 h, which is almost twice as long as in the previous i.v. study, 6.8 h, and multiple times longer than the oxycodone elimination half-life in parturients, 2.6 h.$^{11}$ This likely explains the low neonatal exposure to oxycodone at birth in the present study.

Umbilical plasma concentrations of oxymorphone, 0.26 ng·ml$^{-1}$ or below, were low but slightly higher than those in maternal plasma, 0.20 ng·ml$^{-1}$ or below. Oxymorphone is an active metabolite that has a 10 to 45 times higher affinity for μ-opioid receptors than oxycodone.$^8$ Therefore, oxymorphone accumulation in the foetus is a concern. In our previous experimental study in pregnant ewes, the foetal-to-maternal ratio of oxymorphone was 2.1 at 60-180 min after i.v. administration and 1.3 after epidural administration to the ewe.$^{22}$ In our earlier clinical study, when oxycodone was administered i.v. in the active phase of labour, oxymorphone concentrations were 0.0-0.12 ng·mL$^{-1}$ in the umbilical plasma and <LLOQ in the maternal plasma at birth.$^{11}$ It is assumed that the route of administration may affect foetal exposure to oxymorphone. There are no data on analgesic oxymorphone concentrations in neonates, but in adults, the maximum plasma concentration of oxymorphone is 0.27 ng·mL$^{-1}$ after the smallest approved dose of 5 mg of extended-release oxymorphone tablet.$^{23}$ Together, oxymorphone seems to accumulate in the foetus, but plasma oxymorphone concentrations remain at safe levels when the total dose of s.c. oxycodone is moderate. If the initial s.c. oxycodone dose is no higher than 0.1 mg·kg$^{-1}$ and subsequent doses of oxycodone no higher than 0.05 mg·kg$^{-1}$ and not
more often than every three hours, it is unlikely that oxymorphone could accumulate into the foetal side for any clinically meaningful amount taking into account the elimination half-life of 6-7 hours for oxymorphone.\textsuperscript{23}

Pain scores decreased substantially after oxycodone administration. The initial dose (0.1 mg·kg\textsuperscript{-1}) decreased pain scores from 7/10 to 5/10, and 26 of the 59 parturients had at least 50\% max\textsuperscript{TOTPAR}. This change in pain score is substantial, since the estimated minimum clinically significant change in NRS is 1.4.\textsuperscript{24} However, in two parturients, pain scores did not change after s.c. oxycodone and three parturients had negative %max\textsuperscript{TOTPAR}, i.e., these three parturients had higher pain scores after oxycodone than before. In the latent phase of labour, uterine contractions cause pressure to the cervix and lower uterine segment, and the parturient senses this as dull, poorly localised visceral pain.\textsuperscript{25} Oxycodone is highly effective in easing visceral pain;\textsuperscript{26} therefore, we assume that oxycodone is a feasible opioid analgesic in the latent phase of labour also. In the present pragmatic trial, 88\% of parturients received epidural analgesia as labour progressed to the active phase. This is more frequent than reported previously in a Finnish study, where 67\% of nulliparous and 23\% of multiparous women were provided epidural analgesia.\textsuperscript{27} High proportion observed here may be associated to inclusion criteria of the study, as we included only parturients receiving oxycodone in the latent phase. This population may require epidural analgesia more often than those who tolerate the latent phase without opioid analgesics. However, this aspect should be addressed in further studies. To the best of our knowledge, there are only two previous studies of oxycodone in labour. In 1965, Hodge compared rectal oxycodone pectinate at a dose of 30 mg to morphine or pethidine and found oxycodone to be less effective than morphine.\textsuperscript{10} However, the dose of morphine was not reported, and no drug concentrations were measured, thus making comparison inconclusive. In our previous study, i.v. oxycodone at a total dose of 2-5 mg decreased pain scores from 7 to 6 in NRS 0-10, and the duration of analgesia was 1.5 h.\textsuperscript{11}

There were no severe oxycodone-related maternal or neonatal adverse effects. The most common maternal adverse effect was sedation, which can be a desired effect in the latent phase of labour as it allows mother to rest before the active phase of labour. Two babies were delivered by emergency caesarean section; the indications were decreased foetal pH and pre-
eclampsia. We assume that these caesarean sections were not related to oxycodone administration. One newborn had respiratory distress that was likely related to delayed adaptation to extra-uterine life. He was monitored for two hours in the neonatal intensive care unit, and his recovery was uneventful. Umbilical plasma concentrations of oxycodone, oxymorphone and noroxymorphone were low, and thus it is unlikely that respiratory distress was related to oxycodone.

One of the strengths of the present pragmatic trial was that oxycodone was administered based on the clinical evaluation of the attending obstetricians, who were unaware of whether a parturient was participating in the study. The study presented as a normal clinical situation in the hospital labour ward. In our labour ward, s.c. oxycodone has been in regular use since 2012. During these years, both midwives and obstetricians have gained substantial expertise on the use of oxycodone in labour pain.

There are some limitations in this study that could be addressed in future studies. For logistic reasons, a few of maternal blood samples were not taken simultaneous to the umbilical samples; thus, comparisons between maternal and umbilical concentrations could not be performed for all mother-neonate pairs. However, childbirth is an emotional experience, and immediate blood sampling after delivery was not appropriate for some parturients in this kind of pragmatic trial. Second, we did not assess the mothers’ satisfaction with analgesia, which is an important outcome in all clinical studies.6

Conclusion

S.c. oxycodone appeared to be a feasible option as an opioid for analgesia in the latent phase of labour. Oxycodone provided substantial analgesic efficacy and was well-tolerated by mothers. Neonatal exposure to oxycodone and its metabolites was relatively low at birth, and no neonatal oxycodone-related adverse effects were observed. However, oxymorphone appeared to accumulate in the foetus, and thus higher doses of oxycodone should be avoided in labour. Further research is needed to evaluate the parturients’ satisfaction with analgesia and to verify safety of s.c. oxycodone in labour.

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Conflict of Interest: The authors have no conflicts of interest.

The full trial protocol can be accessed from the corresponding author.

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References


**Figure legends**

Figure 1. Maternal and umbilical venous plasma concentrations of A) oxycodone and B) oxymorphone after s.c. oxycodone administration to the parturient. The Y-axis represents the time from the last oxycodone dose to the sample collection.

Figure 2. Parturient pain scores before and 30 min, 60 min and 120 min after the first s.c. oxycodone dose. Data are presented as the mean with standard deviation. NRS, numerical rating scale.
Table 1. Parturient demographics. Data are median (range) or number of cases. Ua, umbilical artery; Uv, umbilical vein.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parturients (n=76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>29 (20-42)</td>
</tr>
<tr>
<td>BMI (kg·m$^{-2}$)</td>
<td>30 (23-56)</td>
</tr>
<tr>
<td>Primigravida (n)</td>
<td>41</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>40 (34-41)*</td>
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<tr>
<td>Duration of the 1$^{st}$ stage (hr:min)</td>
<td>11:23 (2:20-32:35)</td>
</tr>
<tr>
<td>Duration of the 2$^{nd}$ stage (hr:min)</td>
<td>0:18 (0:02-1:20)</td>
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<tr>
<td>Ua-pH</td>
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</tr>
<tr>
<td>Uv-pH</td>
<td>7.3 (7.0-7.5)</td>
</tr>
</tbody>
</table>

*Two neonates were preterm (gestational age < 37 weeks).

Table 2. Oxycodone and its metabolite concentrations. Data are presented as the median (minimum-maximum). F/M, foetal to maternal.

<table>
<thead>
<tr>
<th></th>
<th>Maternal plasma, ng·mL$^{-1}$</th>
<th>Umbilical venous plasma, ng·mL$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=58</td>
<td>n=61</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>0.90 (0-17)</td>
<td>1.2 (0.21-7.8)</td>
</tr>
<tr>
<td>Noroxycodone</td>
<td>1.7 (0-14)</td>
<td>2.2 (0-11)</td>
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<tr>
<td>Oxymorphone</td>
<td>0 (0-0.20)</td>
<td>0.14 (0-0.26)</td>
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<tr>
<td>Noroxymorphone</td>
<td>0.63 (0-1.9)</td>
<td>0 (0-1.4)</td>
</tr>
<tr>
<td>Oxycodone F/M -ratio</td>
<td>1.3 (0.36-3.3)</td>
<td>1.3 (0.36-3.3)</td>
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