British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2017) **83** 791–800 791

PHARMACOKINETICS

Maturation of oxycodone pharmacokinetics in neonates and infants: Oxycodone and its metabolites in plasma and urine

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Received 28 June 2016; **Revised** 12 October 2016; **Accepted** 23 October 2016

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Keywords infant, neonate, oxycodone, pharmacokinetics, preterm

AIMS

This study aimed to characterize the pharmacokinetics of oxycodone and its major metabolites in infants and covered the age range between extremely preterm neonates and 2-year-old infants.

METHODS

Seventy-nine infants (gestational age 23–42 weeks; postnatal age 0–650 days) received intravenous oxycodone hydrochloride trihydrate at a dose of 0.1 mg kg^{-1} during or after surgery. Three to seven blood samples were taken from each infant, and plasma concentrations of oxycodone, noroxycodone, oxymorphone, and noroxymorphone were quantified. The unconjugated forms of these compounds were determined in urine collected after up to 24 or 48 h from 25 infants. Pharmacokinetics was determined using noncompartmental analysis and reported for six clinically relevant age groups based on postmenstrual age.

RESULTS

Oxycodone pharmacokinetics changed markedly with patient age. Preterm neonates were found to have the highest pharmacokinetic variability out of the study population. In extremely preterm neonates (n = 6) median of elimination half-life was 8.8 h (range 6.8–12.5), in preterm (n = 11) 7.4 h (4.2–11.6), and in older neonates (n = 22) 4.1 h (2.4–5.8), all of which were significantly longer than that in infants aged 6–24 months (n = 12) 2.0 h (1.7–2.6). Median renal clearance was fairly constant in all age groups, whereas non-renal clearance markedly increased with age. Noroxycodone was the major metabolite in plasma and urine.

CONCLUSIONS

Oxycodone elimination is slower and pharmacokinetic variability more pronounced in neonates when compared to older infants. These findings highlight the importance of careful dose titration for neonates.

DOI:10.1111/bcp.13164

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- In adults the use of oxycodone has surpassed that of morphine is several countries.
- Oxycodone is increasingly used also in children.
- The pharmacokinetics of oxycodone have been evaluated in infants aged 6 months or older, but the data on newborns are sparse and no data are available for preterm neonates.

WHAT THIS STUDY ADDS

- Pharmacokinetics of oxycodone changes markedly with age.
- The highest between-subject variability was seen in preterm and term neonates.
- Elimination to inactive noroxycodone via CYP3A seems to be the main metabolic route for infants also.

Tables of Links

TARGETS	
GPCR [2]	**Enzymes** [3]
μ receptor	CYP2D6
	Monoamine oxidase A

LIGANDS	
Morphine	Ketoconazole
Oxycodone	Dextromethorphan
Oxymorphone	Phenobarbital
Thiopental	Midazolam
Caffeine	Paracetamol

These Tables list key protein targets and ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [2, 3].

Introduction

Oxycodone is extensively evaluated and increasingly used for acute and chronic pain relief in adults and the elderly [4, 5]. The use of oxycodone has surpassed that of morphine in several countries [6] and today oxycodone is increasingly used also in children [5, 7, 8]. The pharmacokinetics of oxycodone have been determined in approximately 90 infants and children aged between 6 months and 10 years [9–11]. In this age group the pharmacokinetics of oxycodone after intravenous administration is fairly similar to adults, and the between-subject variability is moderate with this administration route [9, 10, 12]. In contrast, the pharmacokinetics of oxycodone in infants under 6 months has not been established. In the only published study on 22 infants aged between 0 and 6 months, the infants under one week of age had the lowest median clearance (CL) of oxycodone together with the longest elimination half-life ($t_{1/2}$), but no clear trend in the maturation was observed due to high between-subject variability [13]. Furthermore, there is no information on either the plasma metabolite profile or the urinary excretion of oxycodone and its metabolites in this age group.

In adults, oxycodone is extensively metabolized in the liver and only approximately 10% of the dose is excreted unchanged in urine [14–16]. The main metabolic route is cytochrome (CYP) 3A-mediated N-demethylation to noroxycodone [16, 17]. Another important pathway is O-demethylation to oxymorphone via CYP2D6. This enzyme is also mainly responsible for converting noroxycodone to noroxymorphone. Noroxycodone is a weak μ-opioid receptor agonist whereas oxymorphone and noroxymorphone are more potent agonists than oxycodone [16, 18]. However, oxymorphone and noroxymorphone probably do not contribute significantly to central opioid effects as their plasma concentrations are much lower than that of oxycodone [16, 19, 20]. They are also more hydrophilic than oxycodone and this feature may limit their uptake into the central nervous system [16, 21].

In infants and children aged between 6 months and 8 years the plasma metabolite profile of oxycodone after buccal and sublingual administration was similar to that in adults after oral administration [11]. Noroxycodone was the major metabolite whereas the concentration of oxymorphone was low (<7% compared to oxycodone). Noroxycodone was also the major metabolite formed *in vitro* by cryopreserved hepatocytes originating from infants, and its formation rate was markedly reduced by CYP3A inhibitor ketoconazole [22].

This study aimed to characterize the maturation of oxycodone pharmacokinetics in infants and covered the age range between extremely preterm neonates and 2-year-old infants. Oxycodone and its major metabolites were determined from plasma and urine. This information is needed for efficient and safe use of oxycodone in infants.

Methods

This study was funded by a governmental research grant number 507A002 from the Hospital District of Northern Savo, Kuopio, Finland. The study protocol was approved by the Research Ethics Committee of the Hospital District of Northern Savo, Kuopio, Finland (No. 6/2012), registered with EudraCT (2011-005612-28, principal investigator HK), and conducted in accordance with the Declaration of Helsinki.

The Finnish Medicines Agency was notified (No. 6/2012) and the study was registered in Clinical Trials database (NCT02564003). The study received institutional approval.

The study was carried out at the Kuopio University Hospital, Finland, and patients were recruited between January 2012 and June 2013. The study design was a prospective, open label clinical trial on the pharmacokinetics of oxycodone in neonates and infants. Some restrictions were set to the design for ethical and logistical reasons. The total number of preterm neonates was limited to 20, and the number of blood samples from preterm neonates and older infants during the first 12 h after dosing was limited to two and five, respectively, with a maximum of three samples/24 h for preterm and seven samples/24 h for older infants. The summary of the study design is presented in Table 1.

Infants scheduled for surgery with planned perioperative or postoperative opioid analgesia were screened if their gestational age (GA) was at least 23 weeks and postnatal age (PNA) below 2 years. We enrolled an infant if the parents gave informed written consent. The infant was excluded if he/she had allergy or hypersensitivity to oxycodone or had received monoamineoxidase-, CYP3A- or CYP2D6-inhibitors during the previous month or other reason that was considered to contraindicate participation. A total of 92 children's parents were asked, of whom 13 declined. The reasons for not wanting to participate included not wanting any extra treatment (n = 5) or additional stress to the child (n = 1), and parents of seven children did not given any specific reason.

The intravenous dose of 0.1 mg kg^{-1} of oxycodone hydrochloride trihydrate (Oxanest® 10 mg ml^{-1}, Oy Leiras Takeda Pharmaceuticals Ab, Helsinki, Finland) was diluted with saline up to 0.5–1 ml in the preterm neonates and 2–5 ml in other infants. The dose selection was based on published pharmacokinetic and pharmacodynamic data of oxycodone in infants [9–13]. The dose was injected over 1 min into a venous line. The dose corresponded to 0.078 mg kg^{-1} oxycodone base and 0.087 mg kg^{-1} oxycodone hydrochloride. Oxycodone was given either before or right after surgery, or before other painful procedures that required opioid analgesia.

Blood samples were taken into EDTA tubes at baseline before oxycodone administration and at predetermined times after drug administration (Table 1). An arterial cannula was inserted in the radial artery to monitor blood pressure, and this cannula was used for blood sampling from preterm neonates and children who required arterial cannulation for clinical reasons. The sample volume was adjusted to patient size. In preterm neonates, sample volume was 200–500 µl, in term neonates 1 ml and in older infants 3 ml, respectively. Blood samples were centrifuged at 21°C and 1200 g for 10 min, and the separated plasma samples were stored at −70°C until analysis.

Urine was collected from 25 children up to 24 or 48 h. Urine was collected only if the subject had a urine catheter for clinical reason. A new collection device, but not a urine catheter, was changed after 24 h if urine collection was continued. The urine volume collected at 0–24 h and 24–48 h was measured and recorded, and paired urine samples (5–10 ml) were taken into polypropene tubes and stored at −70°C.

The concentrations of oxycodone, noroxycodone, oxymorphone and noroxymorphone in plasma and urine were determined using liquid chromatography–mass spectrometry (LC–MS). All the concentrations of oxycodone and its metabolites are reported as free bases.

In the sample preparation, 100 µl of plasma was mixed with 25 µl of internal standard solution (54 nM dextromethorphan in ultrapure water), mixed vigorously, pipetted into Waters Sirocco precipitation plate (Waters Oasis MCX, Waters Corp., Milford, MA, USA) containing 200 µl acetonitrile, vortex-mixed for 5 min, centrifuged for 20 min at 2952 g and pipetted into UPLC-96 well plate to wait for analysis. The standard and quality control samples were prepared by spiking external standard solution into blank plasma and otherwise processed as the samples.

The concentrations of oxycodone, noroxycodone, oxymorphone and noroxoymorphone in plasma were determined using a LC–MS (Waters Acquity UPLC and Waters Xevo TQ-S triple quadrupole MS, Waters Corp., Milford, MA, USA) method. A column with 1.7 µm particle size (Waters BEH C18, Waters Corp., Milford, MA, USA) with precolumn filter was used at 35°C and sample injection volume was 4 µl. A gradient elution system with 0.5 ml min^{-1} flow rate of 1–1–80–90% of methanol in 0–1–2.5–3.5 min in 5 mM ammonium bicarbonate (pH 9.8) was applied, followed by 1 min equilibration. The data for plasma samples were collected using selected ion monitoring (SRM) with positive ionization mode and capillary voltage of 500 V. Nitrogen was used as a cone gas at 150 l h^{-1}, desolvation gas at 1200 l h^{-1} and as a nebulizer gas at full rate. Desolvation and source

Table 1

Patient groups in study design and data analysis

Study design					Data analysis		
Group code	**Postmenstrual age (weeks)**	***n***	**No. of blood samples**	**Blood sampling times (h)**	**Group code**	**Postmenstrual age (weeks)**	***n***
A	24–36.9	20	3	0.57, 12 and 24	A1	24–27.9	6
					A2	28–36.9	11
B	37–52.9	42	5	0.033, 0.25, 4.85, 8.63 and 9.57	B1	37–43.9	22
					B2	44–52.9	13
C	53–65.9	5	5	0.033, 0.58, 4.9, 8.12 and 9.8	C	53–65.9	12
D	66–144	5	5	0.033, 0.53, 4.3, 8.33 and 9.93	D	66–144	12

temperatures were 650°C and 150°C, respectively. Argon was used as a collision gas at 0.18 ml min^{-1} flow rate. The monitored SRM transition reactions were m/z 288 > 213(collision energy 25 eV, cone voltage 40 V) for noroxymorphone, 302 > 284 (16 eV, 40 V) for noroxycodone and oxymorphone, m/z 316 > 241 (30 eV, 40 V) for oxycodone and m/z 272 > 215 (20 eV, 40 V) for internal standard dextromethorphan. Dwell time of 10 ms was applied and the precursor ions were chosen with one mass unit resolution. Quantitation was based on the peak area ratios of the analytes and the internal standard. The mass spectrometer and ultra-performance liquid chromatography system were operated with the Masslynx 4.1 software (Waters Corp., Milford, MA, USA). The method was linear, accurate and precise in the range of 0.05 (used as limit of quantification)–500 ng ml^{-1} for oxycodone, 0.1–200 ng ml^{-1} for oxymorphone, 0.2–500 ng ml^{-1} for noroxycodone and 0.2–200 ng ml^{-1} for noroxymorphone in plasma samples. The intraday and interday accuracies ranged between 88 and 111% and the coefficients of variation were less than 20%. The quality control samples containing all of these compounds at 1, 10 and 50 ng ml^{-1} were prepared in blank plasma and analysed as duplicates in each analytical batch. All the measured concentrations were within 85–115% of the nominal concentration, and therefore, all batches were considered acceptable.

The urine samples were prepared with the same method as used earlier for cerebrospinal fluid samples [21]. The concentrations of oxycodone, noroxycodone, oxymorphone and noroxymorphone (unconjugated without enzymatic hydrolysis) in urine were acquired using a quadrupole time-of-flight mass spectrometer (Waters Xevo G2 Q-TOF-MS, Waters Corp., Milford, MA, USA) in positive ionization mode and with capillary voltage of 500 V. Nitrogen was used as a cone gas and as a desolvation gas at 50 and 1000 l h^{-1} flow rate, respectively. Desolvation temperature of 600°C and source temperature of 150°C was applied. The acquisition was performed in MSe mode with collision energy ramp of 15–35 eV. Leucine encephalin was used as a lock mass compound at a mass range of m/z 100–1000. Acquisition time was 100 ms and the ion chromatogram window applied in quantification was 20 mDa. The method used was linear, accurate and precise in urine samples in the range of 0.2 (used as limit of quantification)–500 ng ml^{-1} for oxycodone, 1–500 ng/mL for oxymorphone, 1–500 ng ml^{-1} for noroxycodone and 2–500 ng ml^{-1} for noroxymorphone, respectively. The intraday accuracies ranged between 92 and 156% at the limit of quantification and 85–111% above the limit of quantitation. The coefficients of variation were less than 30%.

The elimination half-life ($t_{1/2}$), CL and volume of distribution at steady-state (V_{ss}) were determined with noncompartmental analysis (WinNonlin version 6.3; Pharsight Corp., St. Louis, MO, USA) using at least three data points from the terminal log-linear phase. The observed highest concentration (C_{max}) is also reported. From urine data, the percentage of unconjugated oxycodone and unconjugated metabolites from the oxycodone dose was calculated on mole basis for 0–24 and 0–48 h urine collection periods, and renal and non-renal (hepatic) clearance of oxycodone were determined. Oxymorphone or noroxymorphone concentrations in 0–24 h urine was below the limit of quantification of the metabolite in 6 and 13 infants of the total 25 infants, respectively. In these cases, the minimum percentage of the metabolite required for quantification was calculated based on the limit of quantification of each metabolite and the subject's oxycodone dose and urine volume. These calculated values were 0.04–0.26% and they (and not zero) were used in descriptive statistics of oxymorphone and noroxymorphone in 0–24 h urine samples, respectively.

All subjects were monitored by the attending nurses and physicians and any incidences were recorded on patients' records. Any occurrences of suspected adverse effects were also sought at every blood sampling point and before discharge. This was done by interviewing the neonatal intensive care unit nurses and physicians, paediatric surgical ward nurses, and patients' parents. The patients' charts were also evaluated to improve the robustness of the data. The subjects were followed up to 24 h after oxycodone administration. Heart rate, breathing frequency, blood pressure, and carbon dioxide end tidal concentration were measured routinely during anaesthesia, surgery and followed up a minimum of 10–24 h after drug administration. Severe unexpected adverse events (see below) were reported to the Finnish Medicine Agency and research ethics committee within 24 h of the incident.

Statistical analysis

The infants were divided into six clinically relevant age groups based on postmenstrual age (PMA) for descriptive summary of the plasma concentration curves and pharmacokinetic parameters (Table 1). The groups A, preterm neonates, and B, term neonates and infants under 53 weeks PMA, in the study design were divided into two data analysis groups each. Data are given for each group as median and range. The between-group differences in pharmacokinetic parameters obtained with individual noncompartmental analysis were tested using Kruskal-Wallis with Dunn's method for pairwise comparisons (SigmaPlot version 13.0, Systat Software, Inc., San Jose, CA, USA).

Results

Oxycodone was given to 79 infants but data from three subjects were excluded from data analysis groups. The dose of oxycodone hydrochloride trihydrate ranged between 0.086 and 0.126 mg kg^{-1} (median, 0.1). The total number of plasma samples in 76 infants was 397 and the number of blood samples taken from each subject ranged between two and seven (median, five). Oxycodone plasma concentration was below the limit of quantification in two 24-h plasma samples (one, see below). The demographics for the subjects in the data analysis groups are presented in Table 2. All concomitant medications are presented in Table 3.

There were some protocol deviations. The blood sampling was terminated earlier than planned in four subjects. In study design group A, preterm, the first scheduled sample (0.57 h) was taken after a significant delay from two subjects. In groups B–D, older infants, the first scheduled sample (2 min) was not taken from six subjects. Oxycodone was given to four preterm neonates who were receiving

Table 2

Patient characteristics, indication of oxycodone and type of surgery for the data analysis groups

	Groups					
	A1 (*n* = 6)	**A2 (*n* = 11)**	**B1 (*n* = 22)**	**B2 (*n* = 13)**	**C (*n* = 12)**	**D (*n* = 12)**
Postmenstrual age (weeks)	25.9 [24.3–26.9]	31.0 [28.0–36.9]	39.5 [37.4–43.0]	47.7 [44.4–51.9]	56.7 [53.4–65.0]	98.8 [68.6–132.9]
Gestational age (weeks)	25.4 [23.3–26.3]	29.9 [27.1–36.9]	38.2 [30.0–41.6]	39.9 [31.3–41.9]	39.8 [36.0–40.6]	40.0 [31.4–40.0]
Postnatal age (days)	5 [1–15]	1 [0–27]	2 [0–85]	51 [22–144]	122 [96–175]	412 [213–650]
Weight (kg)	0.79 [0.65–1.05]	1.6 [0.52–3.0]	3.4 [2.4–5.2]	5.2 [3.8–6.9]	6.8 [5.0–8.2]	10.7 [7.3–14.0]
Sex (male/female)	3/3	5/6	14/8	12/1	9/3	7/5
ASA I/II/III/IV	–/–/4/2	–/1/7/3	–/5/14/3	–/11/2/–	1/11/–/–	11/1/–/–
Indication for oxycodone						
Sedation	4	8	4			
Surgery	1	3	15	12	12	12
Painful procedure	1		3	1		
Type of surgery						
Gastrointestinal		2	10	9	11	4
Neurosurgery		1	3		1	
Cardiac surgery	1					
Uro-/Gynecological			1			3
Other			1	3		5

Data are median (minimum–maximum) or number of cases. ASA, American Society of Anesthesiologists Physical Status Classification.

Table 3

Concomitant medications. Data are number of subjects

	Group A1 *n* = 6	**Group A2 *n* = 11**	**Group B1 *n* = 22**	**Group B2 *n* = 13**	**Group C *n* = 12**	**Group D *n* = 12**
Antibiotics	6	6	8	4	4	5
Fluconazole	2	2	—	—	—	—
Caffeine	6	7	—	—	—	—
Vasoactive drugs	3	6	—	—	—	—
Non-steroidal anti-inflammatory analgesic	1	1	—	5	8	8
Paracetamol	1	3	4	9	9	9
Midazolam	—	—	18	13	12	12
Thiopental	—	—	16	13	12	12
Local anaesthetics	—	—	11	11	11	10

Most subjects were given several medications. Thiopental and midazolam were used for general anaesthesia or sedation for surgical operations or other minor interventions.

fluconazole (CYP3A inhibitor) for prophylaxis of candidiasis and for one who had received phenobarbital (CYP3A inducer) since birth to prevent epileptic seizures; he was given oxycodone at PNA of 22 days.

Data from three subjects were excluded from data analysis groups. The data of the extremely preterm (GA 27.6 weeks) who had received phenobarbital was excluded because the elimination of oxycodone was very rapid for his age (P-oxycodone at 0.57 h 16.6 ng ml^{-1}, at 12.1 h 0.86 ng ml^{-1}, and at 24 h below the limit of quantification (0.05 ng ml^{-1}), respectively. The terminal half-life calculated from 0.57 and 12.1 h data was 2.7 h). One subject (GA 27.9 weeks, PNA 7 days,

weight 0.44 kg) died (not oxycodone-related) after ductus arteriosus surgery. Oxycodone concentration in his plasma at 0.57 h was 16 ng ml^{-1}. Data from a third subject (GA 42 weeks, PNA 1 day, weight 2.7 kg) were excluded because of exceptionally high oxycodone concentrations throughout the study period (593 ng ml^{-1} at 3 min and 15 ng ml^{-1} at 14.6 h).

Oxycodone in plasma

Oxycodone pharmacokinetics changed markedly with age (Table 4 and Figure 1). There was a significant decrease in the elimination half-life with increasing PMA, and the between-subject variability was highest in the preterm neonates, groups A1 and A2 (Figure 2). The infants receiving prophylactic fluconazole therapy (n = 4) had similar oxycodone pharmacokinetics to other infants in the same age group (Figure 1).

Metabolites in plasma

Noroxycodone was the major metabolite in plasma with most of the observed peak concentrations between 3 and 10 ng ml^{-1} (Figure 3). The shape of the noroxycodone plasma curve changed with age. In older infants, noroxycodone peaked earlier and the elimination was more rapid. The preterm neonates receiving fluconazole had similar plasma concentrations of CYP3A-mediated noroxycodone to other preterm neonates (Figure 3). Oxymorphone and noroxymorphone plasma concentrations were usually below 1.5 ng ml^{-1} (Figure 4).

Oxycodone and metabolites in urine

Urine was collected from 25 infants for 24 h, and in 18 of these infants the collection was continued up to 48 h. Significant fractions of unconjugated oxycodone (median for the first 24 h 12% [minimum–maximum, 0.01–50] and median for the first 48 h 13% [0.01–56]) and noroxycodone (median$_{24h}$ 6.5% [0.2–12] and median$_{0\text{-}48h}$ 7.6% [0.4–17]) were found in the urine of most patients. The fractions of these compounds in urine varied widely in neonates. The three highest fractions of unconjugated oxycodone in 0–24 h urine were 50, 40 and 32%, respectively. The fractions of unconjugated oxymorphone and noroxymorphone in urine were low (<3%). We had urine data in 14 full-term neonates, groups B1 and B2. In these neonates renal and non-renal CL was 0.063 l h kg^{-1} [0.008–0.11] and 0.41 l h kg^{-1} [0.15–0.64] during the first 24 h (n = 14), and 0.07 l h kg^{-1} [0.013–0.11] and 0.41 l h kg^{-1} [0.35–0.64] during 0–48 h (n = 10), respectively. In seven preterm neonates, groups A1 and A2, renal CL was similar to full-term infants, but non-renal CL was less, 0.21 l h kg^{-1} [0.12–0.27] during the first 24 h (n = 7), and 0.18 l h kg^{-1} [0.11–0.22] during 0–48 h (n = 5). In four older infants, groups C and D, renal CL was similar to younger subjects, but non-renal CL was higher, 0.47 l h kg^{-1} [0.31–0.55] during the first 24 h (n = 4), and 0.47 l h kg^{-1} [0.31–0.55] during 0–48 h (n = 3).

Safety

One boy who had operation due to pyloric stenosis had postoperative nausea and vomiting, and urinary retention. One preterm underwent surgery for patent ductus arteriosus, and died at the first postoperative morning. The death was not related to the study drug. This serious adverse event was notified to the Finnish Medicines Agency and research ethics committee within 24 h. No other adverse events were recorded.

Discussion

This study aimed to characterize the maturation of oxycodone pharmacokinetics in infants. Data were analysed from 76 infants including 17 preterm neonates. A clear trend in the maturation was found based on a marked decrease in the elimination half-life. In an earlier study on 22 infants aged between 0 and 6 months, the infants under PNA of 7 days had the lowest median CL of oxycodone together with the longest $t_{1/2}$. In that study, no clear trend in the maturation was observed because of marked between-subject variability. Moreover, only four preterm neonates (GA 33–36 weeks) were enrolled in that study [13].

The pharmacokinetic parameters in infants aged 6–24 months were fairly similar to those reported earlier for infants and children over 6 months [9, 10]. Elimination half-life is similar in the present study and studies by Kokki and colleagues [10, 11]. When compared against another study with older children up to 10 years of age, the $t_{1/2}$ in the present

Table 4

Pharmacokinetics of oxycodone in plasma

	Groups					
Parameter	**A1 (n = 6)**	**A2 (n = 11)**	**B1 (n = 22)**	**B2 (n = 13)**	**C (n = 12)**	**D (n = 12)**
CL (l h kg^{-1})	0.27 [0.2–0.49]	0.27 [0.1–0.52]	0.50 [0.23–0.79]	0.54[c] [0.16–0.94]	0.53 [0.21–1.2]	0.64 [0.53–0.96]
V_{ss} (l kg^{-1})	3.1[a] [2.3–3.6]	2.7[b] [0.56–3.9]	3.0 [1.5–5.4]	2.0[c] [0.59–3.7]	2.2 [0.7–3.8]	1.8 [1.3–2.8]
$t_{1/2}$ (h)	8.8 [6.8–12.5]	7.4 [4.2–11.6]	4.1 [2.4–5.8]	2.7 [2.1–4.2]	2.6 [2.3–3.4]	2.0 [1.7–2.6]

Data are presented as median (minimum-maximum); CL, clearance; V_{ss}, volume of distribution at steady state; $t_{1/2}$, elimination half-life. Statistical analysis of $t_{1/2}$: Groups A1 and A2 were significantly different from groups B2, C and D ($P < 0.05$), respectively. Group B1 was significantly different from group D ($P < 0.05$).

[a] n = 5

[b] n = 10

[c] n = 12

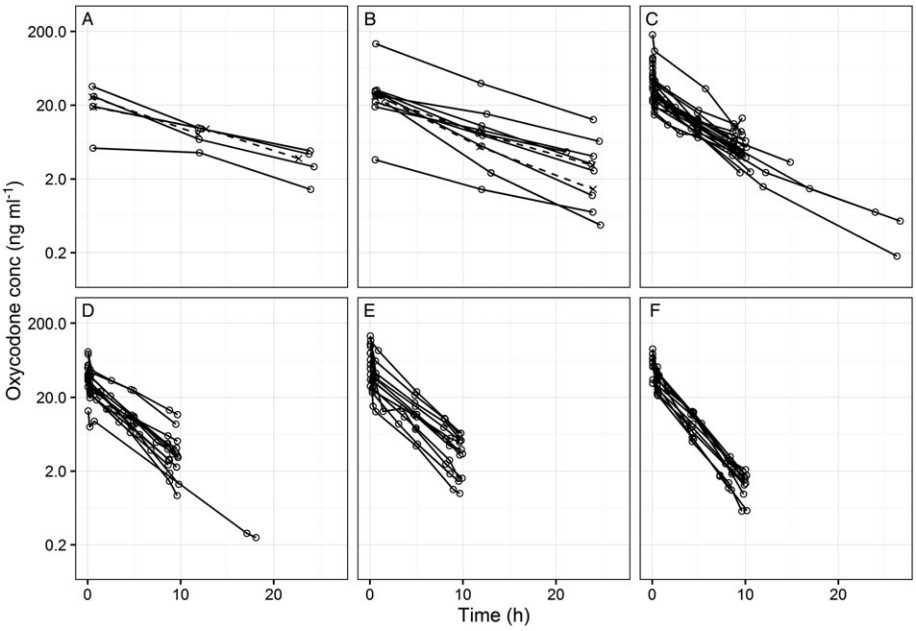

Figure 1

Oxycodone plasma concentrations versus time in different age groups. Group A1 with postmenstrual age of 24–27.9 weeks (A), group A2 with 28–36.9 weeks (B), group B1 with 37–43.9 weeks (C), group B2 with 44–52.9 weeks (D), group C with 53–65.9 weeks (E), and group D with 66–144 weeks (F). In panels A and B the observations marked with (×) and connected with dotted lines came from preterm neonates who were receiving prophylactic fluconazole therapy

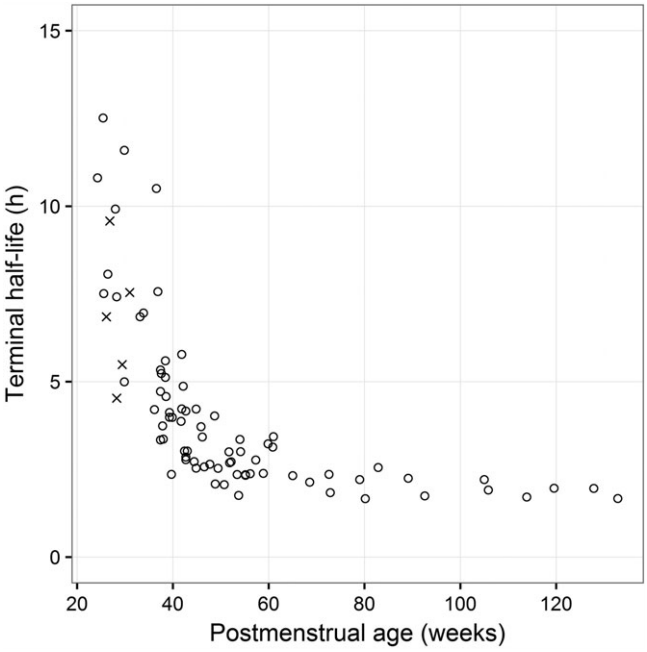

Figure 2

Correlation of postmenstrual age and terminal half-life of oxycodone (n = 76). Terminal half-life was obtained using noncompartmental analysis. Values marked with (×) came from preterm neonates who were receiving prophylactic fluconazole therapy

study (102–156 min) was similar to the study with the older children (73–179 min) [9].

The plasma metabolite profile in the infants was similar to that reported for adults [23, 24]. Noroxycodone, a fairly weak μ-opioid receptor agonist, was the major metabolite whereas the concentrations of more potent metabolites, oxymorphone and noroxymorphone, were very low. This suggests that, similar to adults, oxycodone itself is mainly responsible for the central opioid effects in infants. Unconjugated noroxycodone was also found from urine in significant amounts as seen earlier in adults [14–16, 25]. The metabolite profile in plasma and urine suggests that CYP3A-mediated *N*-demethylation to noroxycodone is the main elimination route also in infants.

In the present study, median fraction of unconjugated oxycodone in 0–24 h and 0–48 h urine was 12 and 13% of the dose, respectively. These values represent the portion of renal CL from the total CL. Our median values are close to the mean values in adults (5–11%) after intravenous, intramuscular and oral administration [14–16]. Renal function is immature in infants and it achieves full capacity not before the PNA of three months, and in preterm infants its maturation may be even more delayed [26, 27]. Our data indicate that immature kidney function may not affect renal clearance of oxycodone that much. In seven preterm and 14 full-tern neonates, median renal clearance was 0.06–0.07 l h kg^{-1}, that is close to the corresponding value in adults (0.06 and 0.11 l h kg^{-1} based on data in [14] and [15]). Based on our data it seems that non-renal (hepatic) clearance is significantly decreased in preterm compared to full-term newborns and older infants. However, we had data only on seven preterm, two of which were extremely preterm. Thus, further data are required before firm conclusions can be drawn.

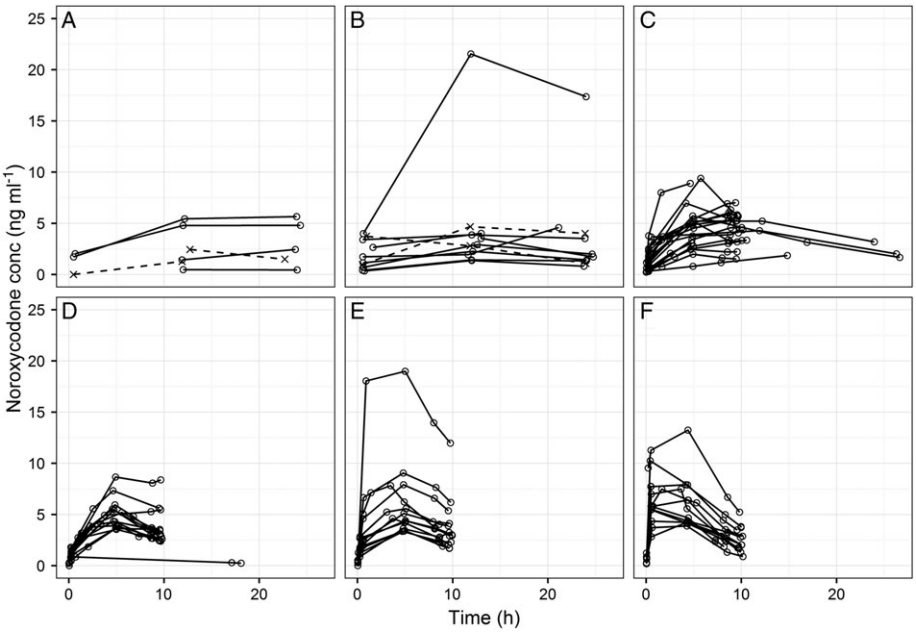

Figure 3

Noroxycodone plasma concentrations versus time in different age groups. Group A1 with postmenstrual age of 24–27.9 weeks (A), group A2 with 28–36.9 weeks (B), group B1 with 37–43.9 weeks (C), group B2 with 44–52.9 weeks (D), group C with 53–65.9 weeks (E), and group D with 66–144 weeks (F). In panels A and B the observations marked with (×) and connected with dotted lines came from preterm neonates who were receiving prophylactic fluconazole therapy

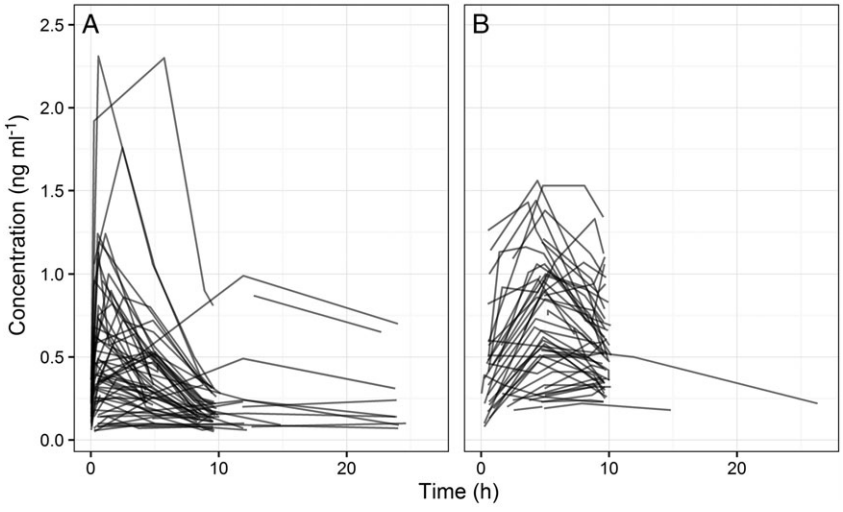

Figure 4

Oxymorphone (A) and noroxymorphone (B) plasma concentrations versus time (n = 76)

Regarding the very high between-subject variability of oxycodone pharmacokinetics in the preterm neonates, we cannot rule out the possibility that some of the extreme pharmacokinetic parameters were partly affected by an experimental error. For example, a preterm infant in group A2 had a very low peak concentration (3.6 ng ml^{-1} at 0.57 h) while having a fairly long terminal half-life ($t_{1/2}$ 9.9 h). This could be explained by assuming that the actual dose delivered was lower than the intended dose. Most of the oxycodone dilutions were prepared by a clinical pharmacist. Unfortunately, a pharmacist was present in the unit only from Monday to Friday between 7 a.m. and 4 p.m., and some of the test drug dilutions were prepared by other staff. It has been shown that preparing recommended doses of parenteral medications of commercially available formulations can be challenging when the required volumes of stock solutions are less than 0.1 ml as it was in this case [28]. In addition, concomitant drug use is a potential reason behind the high

between-subject variability. Midazolam and thiopental were used in most of the older infants but not in preterm, and few drugs, caffeine and vasoactive drugs, were only used in preterm. Moreover, the gender distribution among preterm was equal but most of the older infants were boys. However, we are unaware of any data indicating whether gender may affect pharmacokinetics in infants.

Oxycodone was well tolerated and only few adverse effects were reported. Preterm infants were treated in the neonatal intensive care unit and most were sedated and mechanically ventilated, so some adverse effects may have remained unrecognized. One child who had an operation due to pyloric stenosis suffered from vomiting and urinary retention, both well-known opioid-related adverse effects. These symptoms were mild and self-limiting, not necessitating extra care or days in hospital. One extremely preterm neonate died after intrathoracic surgery, but this was unrelated to oxycodone administration.

One of the main limitations in our study was that the concentrations of oxycodone and its major metabolites in urine were not determined after enzymatic hydrolysis. Therefore, no information on the urinary excretion of conjugated oxycodone and metabolites was obtained. Another main limitation was the low number of blood samples in extremely preterm and preterm infants. However, it was considered unethical to take more than three samples in 24 h. The smallest subjects had body weight of just 500 g and an estimated total blood volume of between 40 and 50 ml. We did not take any blood samples from the distribution phase in preterm neonates, but focused on the elimination phase. Therefore, noncompartmental analysis likely underestimated the total AUC in preterm neonates, which leads to a slight overestimation of clearance for this patient group.

Conclusion

There is a clear trend in the maturation of oxycodone pharmacokinetics in infants that needs to be taken into account in dosing. If weight-based dosing is used, the dosing interval should be longer in preterm if repeated doses are administered. Caution is necessary in oxycodone dosing to neonates also because of the high between-subject variability. Further analysis of this and other published data are needed before any dosing recommendations can be given.

Competing Interests

There are no competing interests to declare.

Contributors

M.K., P.V., H.P., V.P.R., and H.K. designed the study. M.K., M. H., H.P., U.S. and H.K. recruited subjects and conducted the clinical project. P.V., H.H., J.H., H.P. and V.P.R. conducted the pharmacokinetic analysis. H.H. and J.H. contributed essential reagents and assayed oxycodone and metabolites concentrations. M.K., P.V., V.P.R. and H.K. analysed the data. M.K., P.V., V.P.R. and H.K. drafted the manuscript. M.K., M. H., V.P.R. and H.K. contributed equally to the study. All authors critically reviewed the manuscript drafts for the intellectual content and approved the final version for submission.

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