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Pharmacokinetics after a single intravenous dose of the opioid ketobemidone in neonates

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Background: Ketobemidone is often used as an alternative to morphine in children in the Scandinavian countries. In an earlier study, we have examined the pharmacokinetic properties in children in different age groups but have not focused on neonates. The aim of this clinical trial was to explore the pharmacokinetics of ketobemidone in neonates.
Methods: Fifteen full-term neonates (eight females) from 37 gestational weeks at birth and scheduled for elective surgery were included in the trial. Their median age was 3 days (range 1–18 days). Ketobemidone hydrochloride was administered as a single intravenous bolus dose, and ketobemidone concentrations were measured by liquid chromatography-mass spectrometry over 10 h. Pharmacokinetic parameters were calculated with standard compartmental methods.
Results: The median (range) values for ketobemidone clearance, apparent volume of distribution, volume of central compartment, distribution half-life and elimination half-life were 0.46 (0.23–0.84) l/h/kg, 4.64 (3.50–7.31) l/kg, 1.71 (0.16–3.47) l/kg, 2.85 (1.04–10.78) min and 7.26 (3.5–11.3) h.
Conclusion: Compared with our previous study in children older than 1 year of age, the elimination of ketobemidone appeared to be slower in full-term neonates. Despite a low pharmacokinetic variability of ketobemidone as observed in the present neonatal patient population, we recommend individualizing the dose of ketobemidone based on observations of analgesic efficacy.

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Ketobemidone, a phenylpiperidine structurally related to meperidine, is a full agonist at the mu opioid-receptor and with a considerably lower affinity for the delta and kappa opioid receptors.[1] Ketobemidone has been demonstrated to inhibit the excitatory effect of N-methyl-D-aspartate receptor agonists.[2,3] Whereas morphine breakdown results in excitatory metabolites, the main ketobemidone metabolite, norketobemidone, has only been detected in urine samples in adults and has not reached detectable levels in plasma in either adults or children.[4,5] In children, ketobemidone has a potency and pain relief effect comparable with morphine when administered via a patient-controlled analgesia pump.[6]

The pharmacokinetic profile of intravenous, oral and rectal administrations of ketobemidone has been studied in adults.[7–10] A recent study showed that the pharmacokinetic profile of ketobemidone in children over 1 year of age was similar to that of adults.[5] The clearance of many drugs is known to be reduced in the neonatal period, gradually increasing up to adolescence.[11]

The aim of the present study was to extend our knowledge regarding the pharmacokinetic profile of intravenous ketobemidone in full-term neonates.

Methods

The study was approved by the regional research ethics committee at the Karolinska Institutet, Stockholm (2009/1648-32) as well as by the Swedish Medical Product Agency (Eu 2008–008012-98/151:2009/65671). Good clinical practice standards, which include systematic monitoring of all events and protocols, were followed. Parental consent was mandatory for participation.

Participants

Neonates over 37 gestational weeks, scheduled for surgery at Astrid Lindgren Children's Hospital in

Stockholm, were enrolled in the study between 2010 and 2011. Exclusion criteria included: gestational age less than 37 weeks, American Society of Anesthesiologists physical status III and IV, or known hepatic disorder. Fifteen neonates were screened for participation, and all were included. The body surface area (BSA) was calculated from the body weight (BW) using the Boyd self-adjusting formula.[12]

Study design and protocol

We used a single-center open study design. General anesthesia was given according to usual clinical routines. After the induction of anesthesia, the trachea was intubated, and patients were mechanically ventilated during surgery. Anesthesia was maintained with sevoflurane and intermittent doses of fentanyl. An intravenous or arterial cannula was inserted as part of the anesthesia care and subsequently used for blood sampling. A single bolus dose of 0.05 mg/kg ketobemidone hydrochloride (0.1 mg/ml) was administered intravenously prior to surgery. The bolus dose was administered manually over a period of 5 s. The intravenous dose of ketobemidone was based on present clinical practice at our department.

No dose of ketobemidone other than the study dose of ketobemidone hydrochloride was permitted until the end of the study period, i.e., 10 h after the bolus injection. If supplementary opioid analgesia was required, either intraoperative fentanyl or postoperative morphine was given according to our established protocols.

Sampling

Blood samples (1.5 ml) were collected 5, 10 and 20 min, and 2, 6 and 10 h after the administration of a single intravenous dose of ketobemidone. Blood samples were kept on ice and centrifuged within 1 h. Plasma was separated and kept frozen at –20°C until analyzed.

Quantification of ketobemidone

Ketobemidone was analyzed by liquid chromatography-mass spectrometry using a previously published method albeit with minor modifications.[5] The limit of quantification was 0.1 ng/ml, and the calibrated range was up to 100 ng/ml for ketobemidone. The recovery of ketobemidone in the sample preparation was > 95%. The intra- and inter-assay coefficients of variation (CV) for ketobemidone were less than 10% respectively at concentrations of 0.5 ng/ml and 10 ng/ml.

Pharmacokinetic evaluation

Pharmacokinetic analysis was performed using pharmacokinetic modeling performed by the WinNonlin program Standard Edition version 1.5 (Pharsight Corporation, Mountain View, CA, USA). The two compartment model was used for the evaluation of the pharmacokinetics. The optimal pharmacokinetic model was established by visual inspection of the fitted serum concentration vs. time curves and from the weighted squared residuals by using the F-ratio test.[13] The bias and precision of the pharmacokinetic fits were evaluated according to Sheiner and Beal.[14] The reciprocal concentrations were used as weights for the iterative procedure. Area under the plasma ketobemidone concentration-time curve (AUC) was calculated from the fitted zero-time intercepts and exponential rate constants of a two-exponential function. AUC is presented from zero to infinity. Plasma clearance (Cl, expressed in l/hour/kg) was derived from dose/(AUC·BW) and apparent volume of distribution (Vz) (expressed in l/kg) from Cl/β.

Statistical analysis

The aim of the present study was to describe the pharmacokinetics of ketobemidone in neonatal patients. Because limited data on the pharmacokinetic profile of ketobemidone in neonates was available, we could not perform a power analysis in advance.

The Mann–Whitney *U*-test was used for comparison of the derived pharmacokinetic parameters in the present neonatal population with previously published data from children aged > 1 year[5] and for the comparison of derived pharmacokinetic parameters after venous and arterial sampling. The Spearman Rank Correlation test was used to evaluate the possible relationship between age of the patients and the derived pharmacokinetic parameters.

Results

Baseline characteristics

The baseline characteristics of the children are presented in Table 1. Their median age was 3 days (range 1–18 days). The most common diagnosis was anal atresia followed by esophageal atresia. An arterial cannula was used in six patients for blood sampling and an intravenous cannula in nine patients. Anesthesia was induced by thiopental in 12 patients. One patient received propofol. Two patients were already on a ventilator pre-operatively.

Table 1

Patient characteristics: age at procedure, diagnosis and length of surgery for each neonate.

Patient	Gender (m/f)	Weight (kg)	Gestational age at birth (weeks)	Age at procedure (days)	Diagnosis	Length of surgery (h)	Sampling site (a/v)
1	f	3.5	38	1	Anal atresia	2	Venous
2	f	4	41	1	Anal atresia	1	Arterial
3	m	3.1	37 + 2	15	Esophageal atresia	5	Arterial
4	m	3	37 + 4	2	Esophageal atresia	2.3	Arterial
5	f	3.3	38 + 6	4	Diaphragmatic hernia	1.3	Arterial
6	m	3.5	39 + 5	2	Esophageal atresia	2.1	Arterial
7	m	3.7	38 + 6	2	Anal atresia	0.9	Venous
8	f	3.7	40 + 6	3	Anal atresia	2	Venous
9	f	3	41 + 3	6	Sternal cleft	1.2	Venous
10	m	4.3	40	2	Anal atresia	0.3	Venous
11	m	4	40	18	Pylorus stenosis	0.7	Venous
12	f	3.3	39 + 4	9	Esophageal fistula	2.1	Arterial
13	f	4.1	40 + 4	1	Anal atresia	0.9	Venous
14	f	3.9	40 + 2	6	Anal atresia	1	Venous
15	m	3.2	40 + 6	5	Anal atresia	0.8	Venous
	7m/8f						6a/9v
Median (range)		3.5 (3–4.3)	40 (37 + 2–41 + 3)	3 (1–18)		1.2 (0.3–5)	

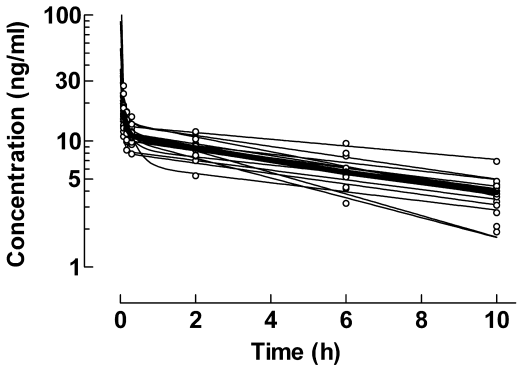

Fig. 1. The concentration of ketobemidone during the first 10 h after intravenous injection of a single bolus dose. Each individual concentration-time measurement is indicated. The lines illustrate fitted curves in the pharmacokinetic modeling for each individual. Mean is indicated as a thick line.

Pharmacokinetic analysis

The plasma concentration-time curves after intravenous administration for each individual concentration are presented in Fig. 1.

The pharmacokinetics of ketobemidone were best described by the two compartment model in all patients. The bias (percentage of mean prediction error, MPE%) and precision (percentage of root mean squared prediction error, RMSE%) were 0.059% and 6.97%, respectively, as evaluated from a plot of predicted vs. observed concentrations from all concentration data ($n = 90$).

Graphic presentation of distribution half-life, elimination half-life, apparent Vz, volume of central compartment (Vc), clearance and AUC normalized for dose expressed in mg/kg and mg/m^2, respectively, are shown in Fig. 2.

Median values of clearance, apparent Vz, Vc, distribution half-life and elimination half-life were 0.46 l/hour/kg, 4.64 l/kg, 1.71 l/kg, 0.047 h and 7.26 h, respectively. Plasma clearance (Cl) ranged from 0.23 to 0.84 l/h/kg taking all patients into consideration. The apparent Vz ranged from 3.50 to 7.31 l/kg and the Vc from 0.16 to 3.47 l/kg. Distribution half-life and elimination half-life ranged from 1.04 to 10.78 min and 3.52 to 11.27 h, respectively.

The area under the BSA normalized AUC values (AUC/mg/m^2) ranged between 79 and 301 (ng·hour/ml)/mg/m^2. AUC normalized for the dose calculated per BW and AUC normalized for the dose calculated per BSA had almost the same variability (33.6% and 33.9%, respectively). The extrapolated value of AUC was 36%. Detailed information is presented in Fig. 2. There was no significant difference between the arterial and venous sampling group in any calculated parameter.

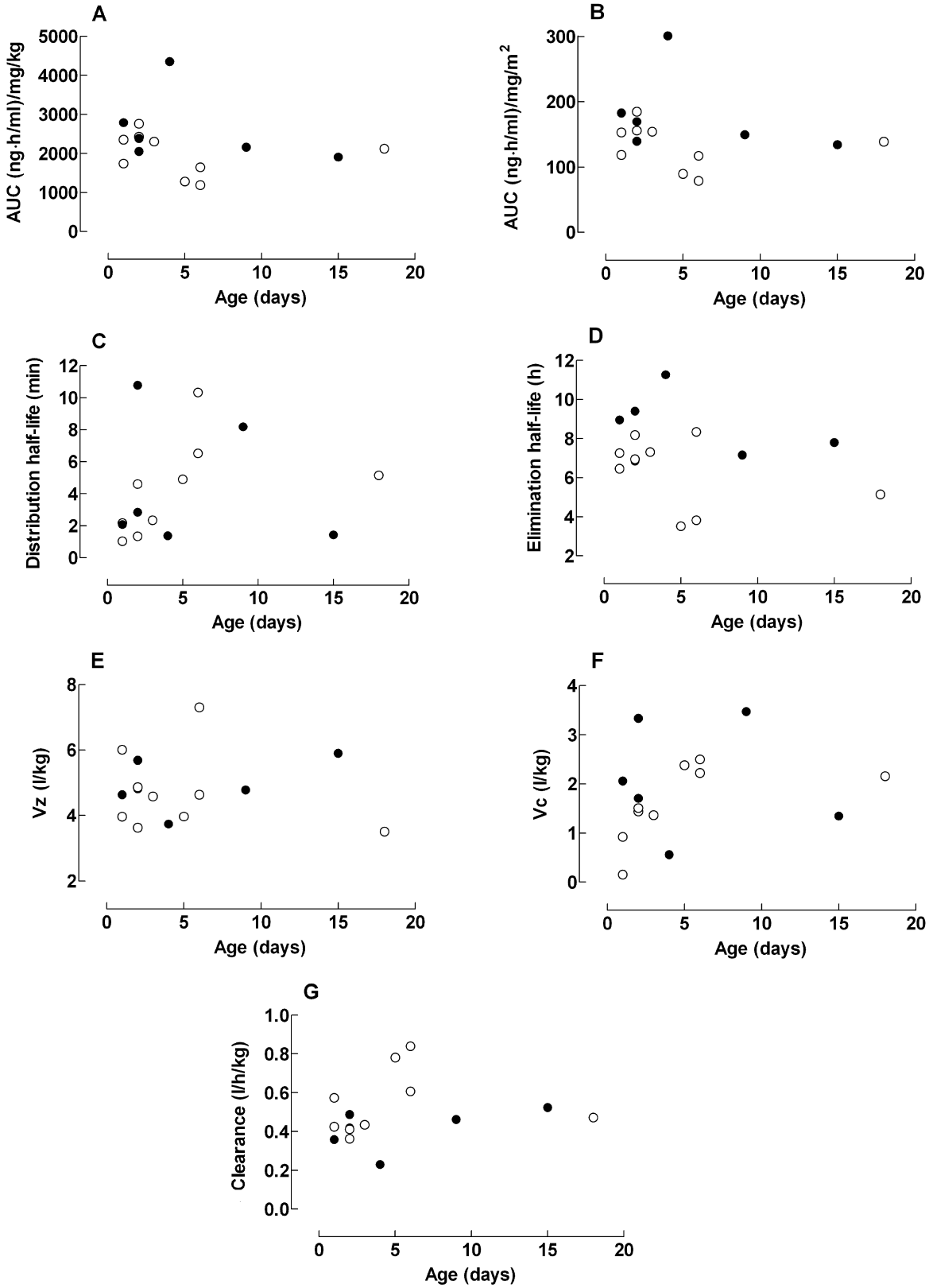

Fig. 2. Ketobemidone area under the curve (AUC) normalized for dose calculated per body weight (A), ketobemidone AUC normalized for dose calculated per body surface area (B), distribution half-life (C), elimination half-life (D), apparent volume of distribution (Vz) (E), volume of central compartment (Vc) (F) and ketobemidone clearance (G) related to age in 15 full-term neonates after an intravenous dose of 0.05 mg/kg of ketobemidone. Open circles represent venous sampling and filled circles arterial sampling.

There was no correlation between age and any of the pharmacokinetic parameters.

The values for AUC normalized for the dose calculated per BW or surface area, Vz and elimination half-life were significantly ($P < 0.0001$) higher and that of Cl lower ($P < 0.0001$) than in children over 1 year of age.[5]

Discussion

Our results show that neonates have a significantly longer elimination half-life time compared with the older children in our previous study. This is most likely attributable to reduced metabolism in the neonatal population.

These findings are similar to the increased variability in the pharmacokinetic profile of morphine and oxycodone that have been observed during infancy.[15–18] A prolonged half-life in neonates carries the risk of high concentration of the particular drug with repeated administration, which should be considered in the clinical situation. The apparent Vz for the neonates ranged from 3.5 to 7.3 l/kg, which appears to be higher than in older children[5] and the adult population.[8,10]

Ketobemidone is a substrate for cytochrome P450 enzymes (CYP), CYP2C9 and CYP3A4.[19] Moreover, the liver cytochrome 450 is present in a fetal form (CYP3A7) and shifts into CYP3A4 during the neonatal period.[20] A lower metabolic rate for ketobemidone in the neonates in our study could to some extent be explained by a decreased expression of CYP3A4. Complete metabolic capacity for many substances may be reached first around 3–6 months of age.[11]

Opioids are often used in the management of moderate-to-severe nociceptive pain. Morphine is still the most commonly used opioid in the treatment of nociceptive pain. The main metabolites of morphine are the analgesic morphine-6-glucuronide and morphine-3-glucuronide (M3G) that lacks analgesic effect.[21] In neonates, M3G is the predominant metabolite.[14] One of the major metabolites of ketobemidone with affinity to the mu opioid-receptor, norketobemidone, has not reached detectable levels in plasma in children and adults. We did not detect norketobemidone in our previous study, and norketobemidone quantification was not included in the present study. The apparent lack of active metabolites of ketobemidone in plasma might be an advantage in neonates, especially during prolonged use.

The present study is the first to examine the pharmacokinetics of ketobemidone in neonates. Blood samples were taken during the distribution as well as during the elimination phase, which extends our earlier study in children. The two compartment modeling was used for each individual, and the quality of the fit was good as stated by the analysis of bias and precision according to Sheiner and Beal.[14]

Pharmacokinetic trials in children, and neonates especially, have limitations. It is important to minimize the blood volume removed, the rate of sampling and the procedural trauma inflicted.[22] As pediatric studies cannot be ethically performed in healthy volunteers, blood samples can only be obtained in children scheduled for surgical procedures with indwelling catheters inserted at the time of surgery. Results from plasma analysis may therefore be influenced by confounding factors such as interactions with other drugs administered during the course of anesthesia, perioperative cardiac output, distribution of blood and blood loss. Barbiturates are known to induce enzyme systems like CYP. The effect could be an increase of the metabolism of ketobemidone. Local anesthetics and fentanyl are both metabolized via the CYP system and may in theory decrease metabolism of ketobemidone. Morphine is not metabolized via CYP and should therefore not alter the metabolism of ketobemidone. In the actual clinical situation, more than one drug, including barbiturates and other opioids, is often used, and it is more speculation to wonder if metabolism is altered in some way.[23]

The use of both arterial and venous blood sampling is not optimal but was used in this study from a clinical point of view to secure blood sampling up to 10 h. There were however no significant difference when the two groups were compared with regard to calculated pharmacokinetic parameters, including the distribution phase. The short distribution time has a high degree of uncertainness with a coefficient variation of 62%. The extrapolated AUC was 36%. A longer sampling period than 10 h would be preferable, but in the clinical situation, both sampling volume and study time are limitations. The precision (CV) in the individual AUC values was 11.0% indicating a good model accuracy.

Dosing strategies for pediatric patients have been debated extensively for decades. Many reference textbooks recommend calculation of drug dosages for children according to BSA. This procedure has mostly been adopted for the dosing of antineoplastic drugs but only rarely for other types of drugs. The results of the present pharmacokinetic study indicate that dosing of ketobemidone based on BW results in low interindividual variability in sys-

temic drug exposure compared with dosing based on BSA in infants aged 1–18 days. The dose of ketobemidone administered in this study was based on clinical experience. The analgesic effect can however differ between individuals to a large extent. Dosing recommendations can therefore not be made solely based on pharmacokinetic knowledge. Our results indicate that caution for overdosing has to be kept in mind in prolonged use of ketobemidone.

In conclusion, this is the first study to explore the pharmacokinetics of ketobemidone in neonates. A lower clearance could be demonstrated compared with children after the neonatal period. Most likely, the prolonged elimination half-life could be explained by a reduced metabolic capacity in the neonatal population. The knowledge of the pharmacokinetics of ketobemidone in the neonatal period is important in order to reduce the risk of overdosing or underdosing. Ketobemidone, like all opioids, should be titrated individually.

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Conflics of interest: The authors have no conflicts of interest that are directly related to the content of this study.

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