Acta Anaesthesiol Scand 2009; ■■: 1–7
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ACTA ANAESTHESIOLOGICA SCANDINAVICA
doi: 10.1111/j.1399-6576.2009.02135.x

Pharmacokinetics after an intravenous single dose of the opioid ketobemidone in children

S. Lundeberg[1], N. Stephanson[2], P. Lafolie[3], G. L. Olsson[1], C.-O. Stiller[2] and S. Eksborg[4]
[1]*Department of Pediatric Anesthesia and Intensive Care, Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden,* [2]*Department of Medicine, Clinical Pharmacology Unit, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden,* [3]*Karolinska Trial Alliance, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden and* [4]*Karolinska Pharmacy and Pediatric Cancer Research Unit, Department of Woman and Child Health, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden*

Background: Ketobemidone is often used as an alternative to morphine in children in the Scandinavian countries. The aim of this clinical trial was to explore the pharmacokinetics of ketobemidone in children because these properties have not been reported previously.
Methods: Thirty children, newborn to 10 years, scheduled for elective surgery were included in the trial. Ketobemidone hydrochloride was administered as a single intravenous bolus dose and ketobemidone and norketobemidone concentrations were measured by LC-MS over 8 h. Pharmacokinetic parameters were determined using compartmental methods.
Results: Six children were excluded from pharmacokinetic analysis because of incomplete blood sampling. The values of ketobemidone clearance (l/h/kg) given as median (range) were 0.84 (0.29–3.0) in Group A (0–90 days), 0.89 (0.55–1.35) in Group B (1–2.5 years) and 0.74 (0.50–0.99) in Group C (7–10 years). The corresponding values for apparent volume of distribution (l/kg) were 4.4 (3.7–6.9) (Group A), 2.6 (2.0–5.6) (Group B) and 3.9 (2.7–5.0 (Group C), and for elimination half-life (h) 3.0 (1.4–8.9) (Group A), 2.0 (1.2–4.7) (Group B) and 3.7 (2.4–6.9) (Group C), respectively. In the two neonates the elimination half-life was almost 9 h. The metabolite norketobemidone did not reach levels above the limit of quantification (0.07 ng/ml) in any of the patients.
Conclusion: The pharmacokinetic parameters of ketobemidone in children older than 1 month appear to be similar to those in adults. Because of the large interindividual variability of the pharmacokinetics in neonates, further studies especially in this age group are warranted.

Accepted for publication 3 September 2009

Opioids are a first-line analgesic in the treatment of moderate to severe nociceptive pain in adults and are increasingly being used in the pediatric population. Ketobemidone has been used in the Scandinavian countries for more than 50 years in both adults and children. However, documentation on its use in children remains sparse. In a previous study, we have demonstrated that ketobemidone administered to children via a patient-controlled analgesia pump provides effective pain relief similar to that from morphine.[1] Ketobemidone, a phenylpiperidine structurally related to meperidine, is a full agonist at the μ opioid-receptor (MOR). The affinity of ketobemidone for the δ and κ opioid receptors is 20- and 100-fold lower, respectively, than for the MOR.[2] In addition, ketobemidone has been shown to inhibit the excitatory effect of NMDA receptor agonists to a considerable extent,[3,4] an effect that might also contribute to analgesia in certain pain conditions.

The pharmacokinetic effects of intravenous, oral and rectal administrations of ketobemidone have been studied in adults.[5–8] Ketobemidone is generally considered to lack pharmacologically active metabolites, an advantage in patients with renal insufficiency or immature renal function. Norketobemidone, the major metabolite in adults,[9] is considered to be inactive.

The dosage of ketobemidone in children and infants is largely based on clinical experience, because data on its pharmacokinetic properties in children are not available. It has been shown that the metabolic capacity varies from birth up to adolescence.[10]

This study aimed to investigate the pharmacokinetic profile of intravenous ketobemidone in newborns and children up to 10 years of age.

Methods

This pharmacokinetic study was approved by the regional research ethics committee in Stockholm at the Karolinska Institutet as well as by the Swedish Medical Product Agency. Good Clinical Practice standards, which include regular monitoring of all procedures and protocols, were followed. Parental consent was required for participation and the older children were also informed about the study.

Participants

Children aged from full term neonates up to 10 years of age, scheduled for surgery at Astrid Lindgren Children's Hospital in Stockholm-Solna, were enrolled in the trial between September 2007 and April 2008. The exclusion criteria were: American Society of Anesthesiologists (ASA) physical status III and IV or known hepatic disorder. Thirty-one children were screened for participation and thirty participated. The data from six of the children were excluded from pharmacokinetic analysis because of technical problems with blood sampling. Thus, data from 24 children aged from newborn to 10 years were used for pharmacokinetic modelling. In children up to 3 months of age, conditions within the gastrointestinal system such as atresia were the major reason for surgery. In children over 1 year, typical surgical procedures included cleft palate repair, osteotomy, re-implantation of ureters, pyeloplasty and abdominal hernia repair. The body surface area (BSA) was calculated from the body weight (BW) using the Boyd self-adjusting formula.[11]

Study design and protocol

The academically initiated study was conducted as a single-center open trial. All children were given general anesthesia according to usual clinical routines. The induction of anesthesia was by intravenous barbiturates (Sodium Thiopental) in 19 patients, and the dosage ranged from 4 to 9 mg/kg (mean 6 mg/kg). One patient received propofol 6 mg/kg. Inhaled sevoflurane was used for induction in the remaining patients. The trachea was intubated and patients were mechanically ventilated during surgery. Anesthesia was maintained with sevoflurane and intermittent doses of fentanyl. Intravenous cannulae were inserted as part of the anesthesia care, and subsequently used for blood sampling ($n = 29$). In one 3-day-old patient, samples were taken from an arterial cannula that was inserted for peri-operative monitoring. A single bolus dose of either 0.05 or 0.1 mg/kg ketobemidone (1 mg/ml) was administered intravenously before surgery: the lower dose for neonates up to 90 days of age (Group A) and the higher dose in children over 1 year old (Group B; 1–2.5 and Group C; 7–10 years). The intravenous dose of ketobemidone was based on current clinical practice at Astrid Lindgren Children's Hospital. In the youngest age group, a lower dose of ketobemidone was used, in accordance with data showing reduced opioid dose requirements and an increased susceptibility to respiratory depression in neonates.

No dose of ketobemidone other than the study dose of ketobemidone hydrochloride was permitted until the end of the study period, i.e. 8 h after the bolus injection. If additional opioid analgesia was considered necessary, either intra-operative fentanyl or post-operative morphine was given according to our established protocols for pain assessment and the administration of rescue analgesia.

Sampling

Blood samples (1.5 ml) were collected 0.5, 1, 2, 4, 6 and 8 h after administration of a single intravenous dose of ketobemidone. In Group A, sampling at 1 h was omitted to reduce the total amount of blood taken from the patient. Blood samples were kept on ice and centrifuged within 1 h. Plasma was separated and kept frozen at $-80\ ^{\circ}C$ until analysis.

Chemicals

The reference material ketobemidone and norketobemidone were obtained from Lundbeck A/S (Copenhagen, Denmark) and the internal standard ketobemidone-$^{2}H_4$ was a gift from Prof. Ulf Bondesson (Swedish University of Agricultural Sciences, Uppsala, Sweden). The stock solutions of ketobemidone, norketobemidone and ketobemidone-$^{2}H_4$ were prepared in water at a concentration of 100 μg/ml, which were stored at $-20\ ^{\circ}C$. A working solution of ketobemidone-$^{2}H_4$ was prepared at a concentration of 2 μg/ml by dilution with water. Acetonitrile and methanol were obtained from JT Baker/Mallinckrodt Baker B.V. (Deventer, the Netherlands) and formic acid from Merck GmbH (Darmstadt, Germany). All other chemicals were of analytical grade and ultra-pure water ($>18\ M\Omega/cm$) was used.

Sample preparation procedure

A 200 µl aliquot of plasma was mixed with 50 µl (100 ng) of ketobemidone-$^2H_4$ (internal standard) working solution and 350 µl of acetonitrile in a glass testtube. The sample was shaken vigorously for 1 min and centrifuged at 1000 × *g* for 5 min. An aliquot of 250 µl of the resulting supernatant was transferred to a separate glass test-tube and evaporated to dryness under a nitrogen stream at 40 °C. The residue was dissolved in 100 µl of ultra-pure water and transferred to a glass auto-sampler vial.

LC-MS analysis

A volume of 10 µl was injected into an Agilent 1100 MSD liquid chromatography – mass spectrometry system (Agilent Technologies, Santa Clara, CA). The system was equipped with an electrospray interface, a dual LC pump, degasser, column thermostat and an auto-sampler. A separation column 50 mm × 2.1 mm, particle size 3 µm (Hypersil Gold, Thermo Electron Corporation, Essex, UK) was used. The mobile phase (A) consisted of 10 mmol/l formic acid with 2% of both methanol and acetonitrile (A), and the mobile phase (B) consisted of 10 mmol/l formic acid with 30% of both methanol and acetonitrile. The flow rate was 250 µl/min. The following gradient elution was used: at a time 0 min 5% B was held for 1 min, increased to 100% B at 6.5 min and held at 100% for 1.5 min and switched back to the initial conditions in 0.01 min. Before injection of the next sample, the column was allowed to re-equilibrate for 4 min.

The instrument operated in the positive SIM mode with a fragmenter voltage of 70 V for *m/z* 248.2 (ketobemidone), *m/z* 234.2 (norketobemidone) and *m/z* 252.2 (ketobemidone-$^2H_4$). The dwell time was 192 ms, drying gas flow was 10 l/min, drying gas temperature 350 °C, the nebulizer gas pressure 330 kPa and capillary voltage was 3000 V.

Quantification

The analytical method used an initial protein precipitation with acetonitrile, followed by evaporation, dissolving the residue in water and the subsequent direct injection of the extract into the LC-MS system. The recovery of ketobemidone in the sample preparation was >95%. Calibrator samples were prepared in calf serum from stock solutions. The concentrations ranged from 15 to 3000 ng/ml for ketobemidone and norketobemidone. The prepared calibrators were stored at −20 °C. Quantification was achieved by using peak area ratios between the analyte and the internal standard. Calibration graphs were constructed using linear regression. The limit of quantification was 0.1 ng/ml and the calibrated range was up to 1000 ng/ml for both ketobemidone and norketobemidone.

At concentrations of 0.5 and 10 ng/ml, the intra- and inter-assay CV for ketobemidone were <12% and <10%, respectively. The analytical procedure was documented according to CLSI guidelines.[12]

Pharmacokinetic evaluation

Pharmacokinetic analysis was performed with GraphPad Prism, version 5.02. (Graph Pad Software Inc., CA). The one-compartment model (i.e., mono-exponential decay) was used for the evaluation of the pharmacokinetics. The reciprocal concentrations were used as weights for the iterative procedure. The area under the plasma concentration time curves (AUC, expressed in ng h/ml) were estimated by numeric integration using constants from the curve-fitting procedure, and the half-lives ($t_{1/2}$, expressed in hours) were estimated as ln 2/β, where β is the elimination rate constant. Plasma clearance (Cl, expressed in l/h/kg) was derived from Dose/(AUC · BW) and the apparent volume of distribution V_z (expressed in l/kg) from Cl/β. Values below the limit of quantification were not included in the pharmacokinetic analysis.

Statistical analysis

The aim of the present pilot study was to describe the pharmacokinetics of ketobemidone in pediatric patients with special attention to age-related differences. Because no previous data on the pharmacokinetic profile of ketobemidone in children were available, we could not perform a power analysis in advance.

The Mann–Whitney *U*-test was used for comparison of the elimination half-lives in the present pediatric population with individual data from adult patients available in the publications of Bondesson et al.[7] and Andersson et al.[8] The Spearman Rank Correlation test was performed to evaluate the relation between age of the patients and the dose-normalized AUC (area under the plasma concentration time curve) values (AUC/mg/kg and AUC/mg/m^2, respectively). Data from the two youngest patients were excluded in these evaluations as well as in the comparisons with data from adult patients because the pharmacoki-

netics deviated significantly in these very young patients compared with the rest of the pediatric patient population studied.

Results

Baseline characteristics

The baseline characteristics of the children are presented in Table 1.

Pharmacokinetic analysis

The plasma concentration–time curves after intravenous administration for each age group as well as each individual concentration are presented in Fig. 1.

Graphic presentation of elimination half-life, apparent volume of distribution and area under the curve (AUC) normalized for dose in mg/kg and mg/m^2, respectively, are shown in Fig. 2. In the two youngest children in Group A ketobemidone showed deviating pharmacokinetic behavior and these data were not included in the statistical evaluations.

The pharmacokinetic parameters of ketobemidone obtained after a single intravenous dose are listed in Table 2.

The area under the BSA-normalized AUC values (AUC/mg/m^2) ranged between 19 and 243 mg/m^2. Plasma clearance (Cl) ranged from 0.29 to 3.0 l/h/kg taking all patients into consideration. The apparent volume of distribution (V_z) ranged from 2 to 7 l/kg. The median clearance and apparent volume of distribution in children over 1 month of age were 0.85 l/h/kg and 3.7 l/kg, respectively. Detailed information for each group of patients is presented in Table 2.

The elimination half-lives of ketobemidone in children older than 1 month did not differ from the data obtained from adults [7,8] ($P = 0.43$).

The BW-normalized AUC values (AUC/mg/kg) showed a somewhat higher variability than BSA-normalized AUC values (AUC/mg/m^2), the coefficients of variation being 36.5% and 33.4%, respectively. More importantly, AUC/mg/kg increased with increasing age ($P = 0.0214$), while AUC/mg/m^2 was unaffected by the age of the patients ($P = 0.5663$).

Samples from all patients in Groups B and C and for three patients in Group A (4 and 5 days old) were analyzed for norketobemidone. However, the concentrations were below the detection limit (0.07 ng/ml) in all the plasma samples investigated.

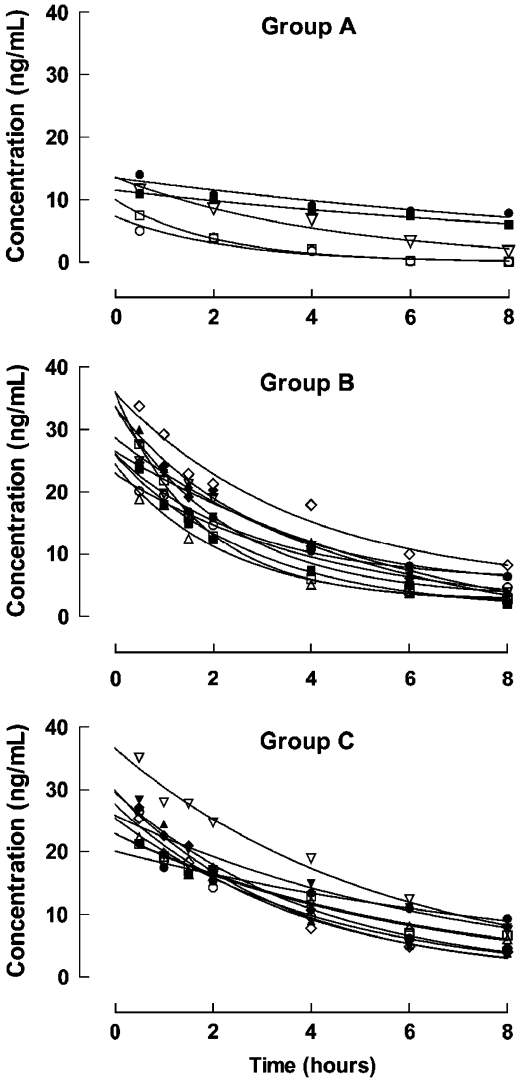

Fig. 1. Concentration of ketobemidone (ng/ml) during the first 8 h after an intravenous injection of a single bolus dose 0.05 mg/kg (Group A) to 0.1 mg/kg (Groups B and C). Group A represents (0–90 days), Group B (1–2.5 years) and Group C (7–10 years), respectively. Each individual concentration–time measurement is indicated. The lines illustrate fitted curves in the pharmacokinetic modelling for each individual.

Table 1

Patient characteristics in the three study groups.

Parameter	Group A 0–90 days ($n = 5$)	Group B 1–2.5 years ($n = 10$)	Group C 7–10 years ($n = 9$)
Male/female (n)	2/3	5/5	8/1
Age (days/months)	30 (4–63)	19 (12–25)	112.2 (85–127)
Weight (kg)	4.2 (3–5.7)	11.7 (9.8–14)	29.7 (23–38)

Values are expressed as median and (range).

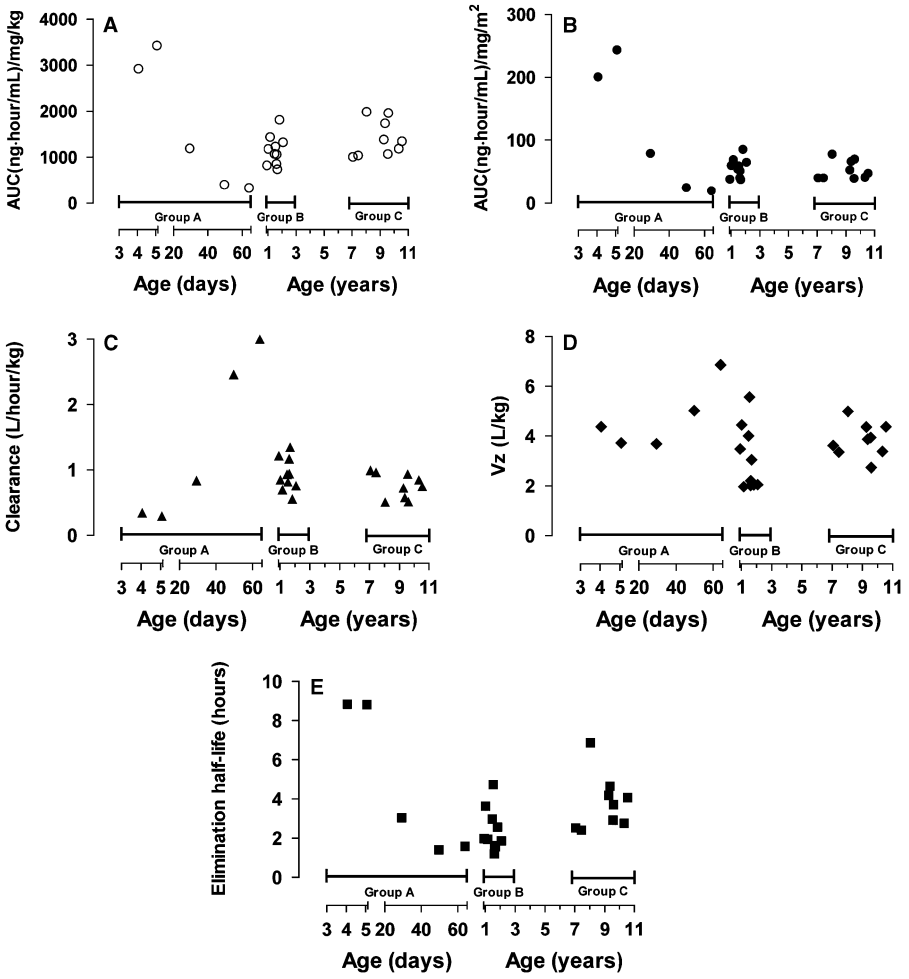

Fig. 2. Individual area under the curve normalized for ketobemidone dose [AUC(ng h/ml)/mg/kg, and AUC(ng h/ml)/mg/m^2, respectively] (A, B), clearance (l/h/kg) (C), apparent volume of distribution (l/kg) (D) and elimination half-lives (h) (E) for all children participating. The three age groups are indicated in the figure.

Table 2

Pharmacokinetics of plasma ketobemidone after an intravenous dose in the three study groups.

Parameter	Group A 0–90 days ($n = 5$)	Group B 1–2.5 years ($n = 10$)	Group C 7–10 years ($n = 9$)
$t_{1/2}$ (h)	3.0	2.0	3.7
Range	1.4–8.9	1.2–4.7	2.4–6.9
Cl (l/h/kg)	0.84	0.89	0.74
Range	0.29–3.0	0.55–1.35	0.5–0.99
AUC (mg/m^2)	79.3	57.0	47.9
Range	19.8–243.4	37.7–85.5	39.6–78.1
AUC (mg/kg)	1191	1125	1344
Range	333–3422	741–1813	1008–1987
V_z (l/kg)	4.4	2.6	3.9
Range	3.7–6.9	2.0–5.6	2.7–5.0

Values are expressed as median and interval. $t_{1/2}$, elimination half-life; Cl, clearance; AUC (expressed in ng h/ml), area under the plasma concentration time; V_z, apparent volume of distribution.

Discussion

To the best of our knowledge, the present study is the first to describe the pharmacokinetics of ketobemidone in infants and children. Considering the long time use of this drug in the pediatric population in Scandinavia, this may seem surprising. Fortunately, it has been possible to statistically compare our ketobemidone pharmacokinetic data in infants and children with previously published

individual pharmacokinetic data from adult patients.[7,8] Our results show that the elimination half-life of 2.7 h (median value) in children older than 1 month is within the same range as for adults according to studies in adult patients (2.6 h; median value).[6,7] However, in the two youngest children, aged 3 and 4 days, the elimination half-lives were considerably longer, Fig. 2. Most likely, the prolonged elimination half-life could be explained by a reduced clearance in the youngest individuals. This hypothesis is currently being tested in a larger group of neonates and we plan to publish our results in the near future. The apparent volume of distribution for the children ranged from 2 to 7 l/kg, which is similar to the adult population.[6,8]

Data were divided into three age ranges (0–90 days; 1–2.5 years; and 7–10 years) based on known metabolic differences. The one-compartment modelling was used for each individual and the fitting was applicable in all age groups, Fig. 1.

Newborns show a tendency towards a longer terminal half-life and higher values of dose-normalized AUC. A faster elimination during the first month of life is considered to be a sign of maturation of metabolic pathways. Two children, aged 49 days and 63 days, respectively, displayed a rather rapid metabolism of ketobemidone, suggesting that a dose of 0.1 mg/kg may be insufficient in some infants. However, other infants displayed a prolonged half-life, which carries the risk of accumulation of ketobemidone upon repeated administration. These findings are similar to the increased variability in the pharmacokinetic profile of morphine that has also been observed during infancy.[13–15]

When compared with the older children, we observed a trend towards a shorter elimination half-life of ketobemidone in the children aged one to two and a half years, a finding that is in accordance with an increased metabolic capacity during this period of life.[10]

We failed to detect norketobemidone, the major metabolite of ketobemidone with an affinity to MOR[16] in plasma. Thus, a rapid formation of norketobemidone may not be the explanation for the fast metabolism of ketobemidone in the children of the younger age group.

Ketobemidone is a substrate for cytochrome P450 enzymes (CYP), CYP2C9 and CYP3A4.[17]

Furthermore, the liver cytochrome 450 exists in a fetal form (CYP3A7) and transforms into CYP3A4 during the neonatal period.[18] Decreased expression of CYP3A4 could, to some extent, explain the slower metabolic rate of ketobemidone and contribute to greater interindividual variability. The full metabolic capacity for many substances may be observed around 3–6 months of age.[10] Because barbiturates, other opioids and propofol were used during anesthesia, it is possible that these agents could have influenced the pharmacokinetic results in this study,[19] but this was not assessed in the present pilot study.

Pharmacokinetics studies in children have limitations, especially in neonates, as it is essential to minimize the blood volume removed and frequency of sampling. In order to limit the trauma of inserting additional catheters for monitoring plasma levels, we used catheters that had been placed for routine care. In one patient, blood was sampled from an arterial line. Because the sampling started during the elimination phase, we presumed an equilibrium between arterial and venous blood. As pediatric studies cannot be ethically performed in healthy volunteers, blood samples can only be obtained in children scheduled for an elective surgical procedure with indwelling catheters. However, these data may be influenced by confounding factors such as interactions with other drugs administered during the course of anesthesia, perioperative cardiovascular changes and blood loss.

In adults, ketobemidone pharmacokinetics is often best fitted in a two-compartment model. A one-compartment model was used in the present study because we were not able to take blood samples from the patients during the distribution phase, i.e. during the first 30 min following drug administration. This is a major limitation in this study. Calculations on pharmacokinetic data in adults[6,7] indicate that the elimination phase accounts for approximate 80% of the total AUC. The small number of patients under 90 days of age makes it difficult to evaluate the pharmacokinetic profile in this specific age group. However, the presented data suggest that the kinetic profile in newborns and infants warrants further study.

Dosing strategies for pediatric patients have been debated extensively for decades.[20] Many reference textbooks recommend calculation of drug dosages for children according to BSA. This procedure has mostly been adopted for the dosing of anti neoplastic drugs, but only rarely for other types of drugs. Mosteller[21] presented a simplified formula for estimation of BSA from routine clinical measures of height and BW. It should be noted that BSA can be estimated from the BW alone when values of

height are lacking.[11] Our results show that AUC normalized for milligram per BW increased with increasing age. Therefore, the systemic drug exposure (AUC) to ketobemidone will decrease with decreasing age when dosage is based on BW. In contrast, dosage based on BSA is likely to provide a more predictable systemic drug exposure, independent of age. We have previously presented similar results for etoposide and acyclovir.[22,23]

In conclusion, this is the first study to explore the pharmacokinetics of ketobemidone in children. The pharmacokinetic parameters of ketobemidone in children older than 1 month appear to be similar to those in adults. Dosing adjusted to BSA might be more appropriate than according to BW after the neonatal period. Because of the large interindividual variability of the pharmacokinetics in neonates, further studies especially in this age group are warranted.

Acknowledgements

This study was supported by the Karolinska University Hospital and the Karolinska Institutet. This study did not obtain financial support from any external foundation. The authors have no conflicts of interest that are directly related to the content of this study.

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Address:
Stefan Lundeberg
Department of Pediatric Anesthesia and Intensive Care
Astrid Lindgren Children's Hospital
Karolinska University Hospital
SE-171 76 Stockholm
Sweden
e-mail: stefan.lundeberg@karolinska.se