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PHARMACOKINETICS AND DISPOSITION

**Ricardo de Carvalho Cavalli · Vera Lúcia Lanchote
Geraldo Duarte · Elaine Christine Moisés Dantas
Maria Fernanda Massoni de Prado
Luciana Barros de Duarte · Sérgio Pereira da Cunha**

Pharmacokinetics and transplacental transfer of lidocaine and its metabolite for perineal analgesic assistance to pregnant women

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Abstract *Background*: Obstetrical analgesia continues to be challenging to science in the search for safe and effective methods that will permit the use of these procedures allied to improved obstetrical and perinatal results.
Objective: The objective of the present study was to investigate the pharmacokinetics and the placental transfer of lidocaine and its metabolite in parturients whose pregnancies were resolved by the vaginal route under perineal analgesia.
Patients and methods: The study was conducted on 23 pregnant women who received perineal analgesia with 20 ml 2% lidocaine (400 mg) during the expulsive period of labor. Maternal venous blood samples were obtained from 0 min to 360 min after drug administration, and umbilical venous blood was obtained at delivery. Lidocaine and monoethylglycinexylidide (MEGX) were determined using high-performance liquid chromatography. The fetal/maternal ratios of the drugs were determined on the basis of maternal and fetal concentrations at delivery.
Results: Maximum lidocaine concentrations at the median times of 15 min were 3.22 μg/ml. The pharmacokinetic parameters were: half-life $t^{1/2}\alpha$ 24.0 min, area under the curve (AUC) $^{0-\infty}$ 460.2 μg/min per ml, $t^{1/2}\beta$ 180.0 min, clearance 12.2 ml/min per kg and volume distribution 3.1 l/kg. The fetal/maternal ratio for lidocaine at delivery was 0.46, with the latency time between drug administration and delivery being 11.0 min. Maximum MEGX concentrations at the median time of 90 min were 229.0 ng/ml. The $t^{1/2}$ for MEGX was 240 min, and $AUC^{0-\infty}$ was 82.4 μg min/ml.
Conclusion: Lidocaine administered by the perineal route presented a t_{max} of 15 min, significantly lower than when the drug was administered peridurally, revealing that the time between administration and the occurrence of the analgesic effect was shorter. The study demonstrated placental transfer of lidocaine at ratios of about 50% for lidocaine at the time of delivery. The MEGX placental transfer demonstrated fetal concentration higher than the maternal at the time of delivery.

Keywords Obstetrical analgesia · Perineal route · Lidocaine

R. C. Cavalli · G. Duarte · E. C. M. Dantas
M. F. M. de Prado · L. B. de Duarte · S. P. da Cunha
University Hospital,
Department of Gynecology and Obstetrics,
Faculty of Medicine of Ribeirão Preto,
University of São Paulo, Ribeirao Preto, Brazil

V. L. Lanchote
Departament of Clinical Analyses,
Toxicology and Food Sciences,
Faculty of Pharmaceutical Sciences of Ribeirão Preto,
University of São Paulo, Ribeirao Preto,
Brazil

S. P. da Cunha (✉)
Departamento de Ginecologia and Obstetrícia Av Bandeirantes,
3900, Hospital das Clínicas-8° andar,
Campus da Universidade de São Paulo,
14049-900 Ribeirão Preto, SP, Brazil
E-mail: spdcunha@fmrp.usp.br
Tel.: +55-16-6022804
Fax: +55-16-6330946

Introduction

The search for the ideal anesthetic procedure in obstetrics is one of the greatest challenges for investigators. Since chloroform was first used, countless studies have been conducted to investigate safe and effective methods of analgesia and anesthesia that will provide the best obstetrical and perinatal results, as well as comfort and safety [1].

To provide the quality analgesic–obstetrical care required today, labor and/or analgesic–surgical procedures should be conducted based on the knowledge of the physiology of pregnancy and of the physiopathology of the diseases typically occurring during this period, as

well as the domination of techniques and pharmacological knowledge about the drugs employed [2].

Many drugs are transported through the placenta by simple diffusion, with no energy expenditure, depending on the concentration gradient of the free drug and on the ratio and extension of the placental exchange barrier [3]. The inaccessibility to the placenta in situ and the principles of safety about the use of drugs for mother and fetus have limited direct studies on the human placenta.

Lidocaine has been extensively used in obstetrics, and its presence is easily detected in umbilical cord blood. However, the fetal concentration and distribution after maternal administration are more difficult to determine [4, 5]. Studies have revealed that lidocaine is fully absorbed after parenteral administration, with the absorption rate depending on several factors, such as the site of administration and the presence or absence of a vasoconstrictive agent. The plasma protein binding of lidocaine depends on the concentration of the drug in blood and on the plasma concentration of α1 acid glycoprotein, with the bound fraction decreasing with increasing drug concentration [6].

Lidocaine is mainly metabolized in the liver, where its CYP3A4- and CYP1A2-dependent de-ethylation occurs, resulting in the formation of its major metabolite monoethylglycinexylidide (MEGX) [7, 8]. Approximately 90% of administered lidocaine is excreted in the form of metabolites, and less than 10% is excreted by the renal route in an unchanged form [9]. MEGX is an active metabolite of lidocaine.

Transport of lidocaine through the placenta has been reported, but little information has been published on the pharmacokinetics of the drug in the human placenta [10]. In 1995, Ala Kokko et al. [11] reported a high rate of placental transfer of lidocaine in an in vitro cotyledon model. Studies on the pharmacokinetics of lidocaine administered by the perineal route are incomplete and have been conducted using low doses (60–80 mg).

In view of the inconsistency of the data available in the literature, the present study was conducted to investigate the pharmacokinetics and the placental transfer rate of lidocaine and of its metabolite in parturients whose pregnancies were resolved by the vaginal route under perineal analgesia.

Materials and methods

Patients and methods

The study was approved by the research ethics committee of the University Hospital, Faculty of Medicine of Ribeirão Preto, University of São Paulo (HC-FMRPUSP). All patients who participated in the study signed a term of informed consent.

The study was conducted on 23 pregnant women with no base disease admitted to the Obstetrical Center of HC-FMRPUSP who delivered a singleton term baby by the vaginal route and who were selected in an aleatory manner without randomization. The subjects received perineal analgesia with 20 ml 2% lidocaine hydrochloride (400 mg) without a vasoconstrictor (Xylestesin 2%, Cristália, São Paulo, SP, Brazil, lot 02030982) for blockade of the pudendal nerve. Maternal blood samples were obtained at 0, 5, 10, 15, 20, 30, 40, 60, 90, 120, 240 and 360 min after drug administration, and umbilical venous blood was obtained at delivery. Epidemiological data were collected using a standard protocol concerning age, parity, gestational age, use of medications, anthropometric data and ultrasonographic information about fetal and/or placental changes.

Of the 23 women, 14 received analgesia with implantation of a catheter into the epidural space during labor for administration of bupivacaine and fentanyl. However, pharmacokinetic analysis showed no difference between groups, and all patients were studied in a single group.

Determination of lidocaine and monoethylglycinaxilidide (MEGX) in plasma

Standard solutions and reagents

The stock solution of lidocaine (Wellcome, UK) was prepared in methanol (chromatography grade, EM Science, Merck, Darmstadt, Germany) at the concentration of 1 mg/ml and diluted in order to obtain solutions at concentrations of 200, 100, 70, 50, 40 and 20 μg/ml methanol. The metabolite solution (MEGX, Astra Pharmaceuticals, Södertalje, Sweden) was prepared at the concentration of 8 μg/ml methanol. The stock solution was then diluted with ethanol in order to obtain concentrations of 3.2, 1.6, 1.0, 0.8, 0.4 and 0.32 μg/ml.

Chromatographic analysis

Chromatography was carried out using a Shimadzu (Kyoto, Japan) high-performance liquid chromatography (HPLC) system, consisting of an LC-10AS pump, an SPD-10A ultraviolet detector operating at 205 nm and a C-R6A integrator. The Rheodyne injector system (Cotati, CA, USA), model 7125, was used with a 20-μl sampler. Lidocaine and its metabolite MEGX were separated on a reverse phase 250×4 mm Lichrospher 60 RP-Select B column (Merck) with 5-μm particles with a similar 4×4 mm pre-column. The mobile phase, consisting of a mixture of 25 mM phosphate buffer, pH 4.6, and acetonitrile (82:18, v/v) was used at a rate of 1 ml/min [12].

The chromatograms obtained in the sequential analysis of lidocaine and MEGX in plasma showed evidence of the absence of endogenous matrix interferents. The calibration curves constructed in the 0.5–5 μg/ml plasma range for lidocaine and in the 8–80 ng/ml plasma range for MEGX were linear and showed correlation coefficients higher than 0.99.

Sample preparation

Plasma samples (1 ml) with 50 µl of the 0.15 N hydroxide solution added were extracted with 4 ml hexane-dichloromethane (82:18, v/v) after saturation of the aqueous phase with 500 mg sodium chloride. Lidocaine and its metabolite MEGX were extracted by shaking for 45 min in a horizontal shaker at 220 ± 10 cycles/min, the material was centrifuged at 1,800*g* for 10 min and the organic extracts were concentrated at room temperature under an air current. The residues were reconstituted with 50 µl of the mobile phase, and 20 µl aliquots were analyzed by HPLC.

Pharmacokinetic analysis of lidocaine and MEGX

The kinetic disposition of lidocaine was determined using a bicompartmental model and first-order kinetics. The pharmacokinetics of MEGX were evaluated using a monocompartmental model. The compartment models were defined on the basis of the decay curves for plasma concentrations as a function of time of collection.

The areas under the curve ($AUC^{0\text{-}360}$) were determined by the trapezoid method during the period 0–360 min; total areas under curve ($AUC^{0\text{-}\infty}$) were obtained by adding $AUC^{0\text{-}360}$ to extrapolated areas derived from Ct/β, where Ct is the last quantifiable concentration. Apparent total clearance (Cl/F) of each lidocaine was derived from dose/$AUC^{0\text{-}\infty}$, and apparent volume of distribution (Vd/F) was derived from Cl/β.

The pharmacokinetic parameters for lidocaine and MEGX were calculated based on the plasma concentration versus time curves using the software Kinetica, Version 4.0, InnaPhase Corporation 2001. To assess the transplacental transfer of lidocaine and its metabolite, lidocaine and MEGX concentrations were determined in maternal plasma and in umbilical vein cord plasma at the time of delivery.

Measurements of position and dispersal were performed, and the 95% confidence interval (95% CI) and the standard error of the mean (SEM) were determined using the GraphPad InStat software.

Results

The study was conducted on 23 pregnant women, all of them normal in clinical and laboratory terms and had received prenatal care. The median age, the median gestational age, median patient weight and median body mass index are listed in Table 1.

All infants were born by vaginal delivery, and none of them had any disease. The median newborn birth weight was 3.3 kg, and median placental weight was 530 g. The newborns of the group had a fifth minute Apgar score greater than 7.

During the collection of maternal blood samples for the determination of lidocaine and MEGX concentrations, the hemodynamic parameters of the parturients were monitored by recording arterial pressure and heart rate, and both groups presented hemodynamic stability during the study. Median lidocaine concentration in maternal plasma was 0.10 µg/ml at time 0, rapidly increasing up to the 15-min time point, when it reached its maximal value of 3.22 µg/ml, followed by a slow decrease after 120 min and a final median value of 0.38 µg/ml at 360 min (Fig. 1a).

Median maternal MEGX concentration was 18.3 ng/ml at time 0, with a slow increase up to the 90 min time point, when it reached a maximum of 229.0 ng/ml, followed by a slow decrease to a median value of 86.2 ng/ml at the final time point 360 min (Fig. 1b). The pharmacokinetic data for lidocaine in parturients are presented in Table 2, and the pharmacokinetics data for MEGX in parturients are presented in Table 3.

Median latency time between drug administration and birth was 11.0 min, with a median concentration at delivery of 2.70 µg/ml in maternal plasma and 1.30 µg/ml in cord plasma, with a fetal/maternal ratio of 0.46 (Table 4).

With respect to transplacental transfer of MEGX, the median maternal concentration at delivery for group was 39.0 ng/ml, and the median for the fetus was 67.9 ng/ml, with a fetal/maternal ratio of 1.07 (Table 4).

Table 1 Demographic data for parturients

Parameter	Parturients ($n = 23$) median (P25–P75)
Age (years)	23.0 (21.5–27.5)
Gestational age (days)	278.0 (271.5–284.5)
Weight (Kg)	68.5 (61.0–76.5)
Height (m)	1.61 (1.57–1.65)
Body mass index (Kg/m^2)	26.4 (24.6–28.0)
Primigestae (%)	52.1%
Two or more pregnancies (%)	47.9%
Episiotomy (%)	
Yes	34.7%
No	65.3%
Latency: between admission and delivery (min)	311.0 (194.5–533.0)

Discussion

None of the patients included in the study presented hypotension or tachycardia associated with peripheral vasodilation after regional analgesia. Mean arterial pressure and heart rate measured during sample collection reflected hemodynamic stability in both groups.

In a study using perineal blockade with an 80 mg dose of lidocaine, Philipson et al. [13] detected a C_{max} of 0.64 µg/ml. In the present study, lidocaine was rapidly absorbed after perineal regional administration, with a C_{max} of 3.22 µg/ml for the study group (Table 2). These concentrations were considered to be elevated with respect to the toxicity of the drug, with two patients in group presenting a concentration peak above 5.0 µg/ml.

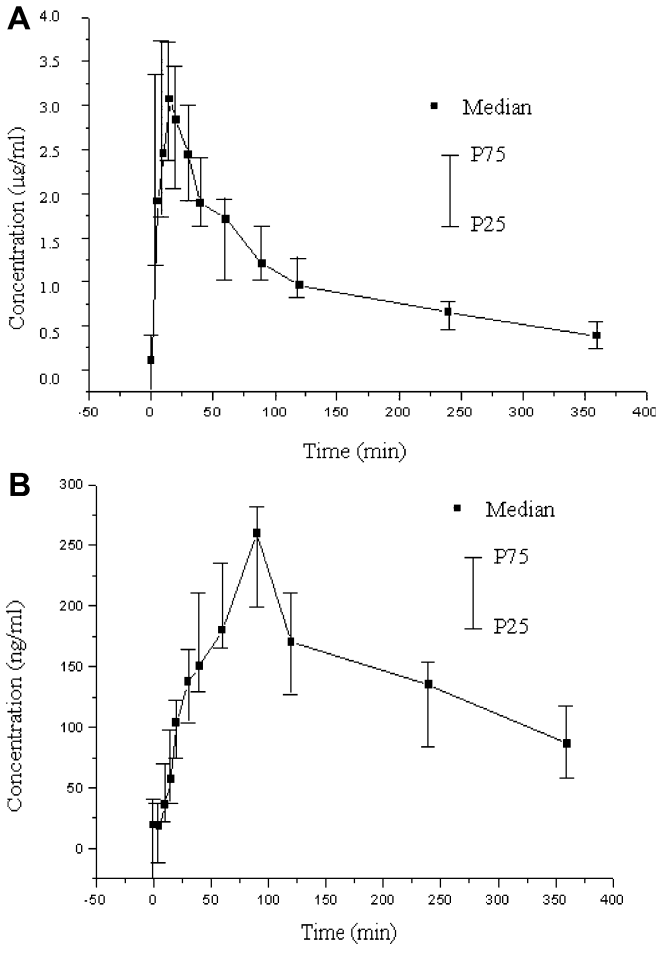

Fig. 1a,b Graphic presentation of the median (P25–P75) plasma concentrations of lidocaine (**a**) and monoethylglycinexylidide (MEGX) (**b**) in parturients ($n = 23$)

Table 2 Pharmacokinetics of lidocaine in parturients. *AUC* area under the curve. C_{max} maximum clearance, t_{max} maximum time, $t^{1/2}$ half-life, *Cl/F* apparent total clearance, *Vd/F* apparent volume of distribution

Parameter	Parturients ($n = 23$) median (P25-P75)
C_{max} (µg/ml)	3.22 (2.47–3.85)
t_{max} (min)	15.0 (10.0–20.0)
$t^{1/2}\alpha$ (min)	24.0 (20.0–30.0)
$t^{1/2}\beta$ (min)	180.0 (150.0–195.0)
$AUC^{0-\infty}$ (µg min/ml)	460.2 (407.9–498.7)
Cl/F (ml/min/kg)	12.2 (11.1–14.5)
Vd/F (l/kg)	3.1 (2.8–3.6)

Circulating plasma concentrations of the drug between 6 µg/ml and 10 µg/ml and above 10 µg/ml cause occasional and frequent toxicity, respectively [14]. Toxicity mainly manifests as ventricular arrhythmia. In 2002, Sawyer and Von Schroeder [15] reported the case of a patient who received 600 mg lidocaine intravenously for orthopedic surgery and developed temporary blindness,

Table 3 Kinetic disposition of monoethylglycinexylidide (MEGX) in parturients. *AUC* area under the curve. C_{max} maximum clearance, t_{max} maximum time, $t^{1/2}$ half-life

Parameter	Parturients ($n = 23$) median (P25–P75)
C_{max} (ng/ml)	229.0 (187.0–270.0)
t_{max} (min)	90.0 (90.0–90.0)
$t^{1/2}$ (min)	240.0 (185.0–270.0)
$AUC^{0-\infty}$ (µg min/ml)	82.4 (61.1–90.8)

Table 4 Transplacental transfer of lidocaine and monoethylglycinexylidide (MEGX) in parturients. *Latency* time elapsed between the perineal administration of the anesthetic and delivery. *F/M* fetal/maternal

Parameter	Parturients ($n = 23$) median (P25–P75)
Latency	11.0 (8.0–15.5)
Lidocaine	
Maternal concentration (µg/ml)	2.7 (2.2–3.1)
Fetal concentration (µg/ml)	1.3 (0.8–1.6)
F/M ratio	0.46 (0.32–0.59)
MEGX	
Maternal concentration (ng/ml)	39.0 (26.0–95.0)
Fetal concentration (ng/ml)	67.9 (38.0–96.0)
F/M ratio	1.07 (0.78–1.60)

with drug levels of 6.59 µg/ml. Another study [16] showed that signs and symptoms of toxicity appear in the presence of lidocaine levels of 5 µg/ml or more.

Lidocaine administered by the perineal route, an area rich in vascularization, showed rapid absorption, and the drug was detected in plasma at the first collection (5 min), with circulating levels of 1.9 µg/ml and a median time of maximum drug concentration of 15 min (Fig. 1a and Table 2). Philipson et al. [13] assessed the pharmacokinetics of a mean 80-mg dose of lidocaine administered perineally and detected the presence of the drug in plasma during the first minute after administration, with a mean t_{max} of 12 min. When assessing the $t_{max}$of lidocaine administered by other routes, the epidural one among them, Ramanathan et al. [17] and Downing et al. [18] obtained values of 34 min and 31 min, respectively, after administration of 400 mg of the drug. Thus, the present study confirms literature data concerning the rapid absorption of this drug by the perineal route compared with the epidural route, establishing a relationship between t_{max} and the occurrence of a more rapid clinical analgesic result after administration by the perineal route compared with the epidural route.

The $AUC^{0-\infty}$ was 460.2 µg min/ml for the study group (Table 2). A survey of the literature did not show any data about the $AUC^{0-\infty}$ when the drug was administered by the perineal route. For epidural administration of a mean dose of 420 mg lidocaine, Ramanathan et al. [17] detected an $AUC^{0-\infty}$ of 840 µg min/ml.

The results of the Vd/F and Cl/F represent an original contribution, since there are no literature reports about these parameters when lidocaine is administered by this route (Table 2). It should be pointed out that Vd and Cl depend on the bioavailability of lidocaine when administered by the perineal route. Bioavailability is not available for perineally administered lidocaine.

In a study in which 420 mg lidocaine was administered by the peridural route to parturients to be submitted to cesarean section, Vd/F was 0.98 l/kg and Cl/F was 6.1 ml/min per kg [13]. In turn, Nattel et al. [19], after administering lidocaine intravenously for the treatment of cardiac arrhythmia, reported a Vd of 1.1 l/kg and a Cl of 9.2 ml/min/kg.

Vd and Cl undergo changes as a function of the gravidic modifications occurring during pregnancy. In 1997, Loebstein et al. [2] reported that the Vd of some drugs may be increased by as much as 50% during pregnancy as a result of the expansion of plasma volume and of the presence of a new compartment represented by the fetus and its adnexa. The mean increase in fluid volume is 8 l, with 60% of it being distributed among the placenta, fetus and amniotic fluid and 40% among the maternal tissues [2]. In the assessment of Cl, pregnancy promotes enzymatic induction secondary to the action of progesterone, resulting in an increased elimination of the drug [20].

The elimination half-life is a parameter dependent on the Vd and Cl. In the present study, elimination half-life was 180 min for the group study (Table 2). Ramanathan et al. [17] and Downing et al. [18], using a lidocaine dose of 420 mg by the epidural route, reported elimination half-lives of 180 min and 120 min, respectively. When they administered lidocaine intravenously to adult patients, a route rarely used for pregnant women, Nattel et al. [19] reported an elimination half-life of 108 min.

There are no data in the literature about the elimination half-life of the drug when it is administered by the perineal route, and, therefore, the present data are original and at the same time agree with the information existing about the $t^{1/2}\beta$ of lidocaine when the drug is applied by other routes or to other regions of the organism. The pharmacokinetic parameters of MEGX (Table 3) are original since no reports concerning the analysis of this metabolite when lidocaine is administered by the perineal route are available in the literature.

The fetal/maternal plasma concentration ratio of lidocaine at the time of delivery was 0.46 (Table 4). These results indicate fetal plasma concentrations corresponding to 50% of the maternal concentration at the time of delivery, indicating that the drug should not be administered at doses higher than 400 mg by the perineal route. After administering lidocaine by the perineal route, Philipson et al. [13] detected a fetal/maternal ratio of 0.73, and Sakuma et al. [21] detected a ratio of 0.45. After administering lidocaine by the epidural route, Ramanathan et al. [17] detected a fetal/maternal ratio of 0.71 and Downing et al. [18] detected a ratio of 0.43. Comparison of the present data with those reported in the literature showed that perineal administration of lidocaine also results in an elevated fetal/maternal ratio, demonstrating the high rate of transplacental transfer of this drug [11, 22].

The fetal/maternal MEGX ratio at delivery was 1.07 for the study group (Table 4). Thus, higher fetal plasma concentrations of the metabolite were observed at delivery, possibly explained by the placental passage of the metabolite, by the placental metabolism of lidocaine to MEGX and by the probable immaturity of the fetus for the elimination of this metabolite through the kidneys.

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