

# Pharmacokinetics of lidocaine and its metabolite in peridural anesthesia administered to pregnant women with gestational diabetes mellitus

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## Abstract

**Background** Peridural blockade with lidocaine, bupivacaine, and fentanyl is an anesthetic procedure extensively used in obstetrics, justifying the pharmacokinetic study of these drugs during labor.

**Objective** To investigate the influence of the physiopathological changes of gestational diabetes mellitus (GDM) on the pharmacokinetics of lidocaine and its metabolite monoethylglycinexylidide (MEGX) in pregnant women subjected to peridural anesthesia.

**Patients and methods** Ten normal pregnant women (group 1) and six pregnant women with GDM (group 2) were studied, all of them at term. The patients received 200 mg 2% lidocaine hydrochloride without a vasoconstrictor by the peridural locoregional route. Maternal blood samples were collected at

predetermined times for the analysis of lidocaine and MEGX by chromatography and pharmacokinetic analysis.

**Results** The median pharmacokinetic parameters of lidocaine for groups 1 and 2 ( $P \leq 0.05$ ), respectively, were as follows: for  $C_{max}$  879.11 and 1,145.58 ng/ml,  $AUC_{0-\infty}$  256.01 and 455.95  $\mu\text{g min}^{-1} \text{ml}^{-1}$ ,  $Cl/f/kg$  10.61 and 5.64  $\text{ml min}^{-1} \text{kg}^{-1}$ , and  $Vd/f/kg$  3.26 and 2.19 L/kg. The median pharmacokinetic parameters of MEGX for groups 1 and 2 ( $P \leq 0.05$ ), respectively, were as follows: for  $C_{max}$  82.71 and 141.38 ng/ml,  $T_{max}$  44.71 and 193.14 min,  $t_{1/2\alpha}$  7.64 and 59.77 min,  $\alpha$  0.097 and 0.012/min, and  $AUC_{0-\infty}$  29.91 and 108.23  $\mu\text{g min}^{-1} \text{ml}^{-1}$ .

**Conclusion** The present data permit us to conclude that the apparent clearance of lidocaine and MEGX was reduced in diabetic patients compared to normal women, suggesting that GDM inhibits the CYP1A2/CYP3A4 isoforms responsible for the metabolism of this drug and its metabolite.

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## Introduction

Dysfunction or changes in the activity of organs and systems due to a diagnosed disease, as well as changes in the maternal organism caused by pregnancy, interfere with the pharmacokinetic processes of drug absorption, distribution, and elimination. Fetal exposure to the neonatal effects of drugs administered to the mother before delivery depends directly on the pharmacokinetics of the drug in the mother, the fetus, and the placenta [21].

Lidocaine is a local anesthetic of the amide type [25] used for anesthetic infiltration and/or regional blockade that acts by inhibiting the ion flows necessary for the conduction of impulses from pain sensation fibers [28]. Lidocaine is rapidly absorbed from the gastrointestinal tract, mucosal membranes, and injured skin and muscle, presenting immediate bioavailability when injected intravenously. Its elimination half-life is 1–2 h, but may be increased by continuous infusion or by the reduction of hepatic blood flow [25].

Approximately 90% deethylation of this anesthetic occurs in the liver depending on CYP3A4, resulting in the formation of the main active metabolite monoethylglycinexylidide (MEGX) [2, 24]. A secondary metabolic form derived from a second deethylation of MEGX is glycinaxilidide. Hydroxylation of the aromatic ring occurs by the action of CYP1A2, giving rise to 3-hydroxy-lidocaine [26, 27].

Lidocaine is a drug with a medium to high rate of hepatic extraction (0.6 to 0.8), with its clearance being influenced by changes in hepatic function or by variations in blood flow in the liver [12]. Approximately 90% of the lidocaine administered is excreted in the form of metabolites and less than 10% is excreted unchanged through the kidneys. Renal insufficiency does not affect the clearance of lidocaine but causes accumulation of its active metabolites [17, 25].

Diabetes mellitus (DM) can alter the kinetic disposition and the metabolism of drugs depending on the type and course of the disease, as well as on the drug investigated and its metabolic and excretion pathways [18, 19]. The influence of gestational DM (GDM) on the kinetic disposition and the metabolism of drugs used in clinical practice has not been investigated in depth in the literature.

This study investigates the influence of GDM on the pharmacokinetics of lidocaine and its metabolite MEGX in pregnant women subjected to peridural anesthesia.

## 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. All patients who participated in the study provided written, informed consent. It should be pointed out that the study did not interfere with the clinical conduct adopted for the patients.

The series consisted of two groups, i.e., pregnant women with no diagnosed diseases, and patients with GDM admitted to the Obstetrical Center of MATER - Maternidade do Complexo Aeroporto, or to the Obstetrical Center of the University Hospital, Faculty of Medicine of Ribeirão Preto,

University of São Paulo. All patients in the study were subjected to the 75 g, 2 h oral glucose tolerance test. The patients who had results greater than or equal to 140 mg/dL (7.8 mmol/l) in the sample of blood collected 2 h after the overload of glucose were considered to have GDM, according to criteria recommended by the World Health Organisation [1]. The diabetic group received nutritional guidance and evaluation of fasting plasma glucose and postprandial plasma glucose once a week. The patients who needed therapy with insulin or other medication for metabolic control were excluded from the study.

All parturients underwent caesarean section due to medical indication and were selected in an haphazard manner without randomization. The subjects in the two groups were not matched but had similar characteristics.

Inclusion criteria were as follows: normal pregnant women or women with GDM, term singleton pregnancy, delivery by caesarean section, and anesthetic assistance with epidural blockade. Exclusion criteria were as follows: delivery performed due to obstetrical urgency/emergency situations, presence of maternal diseases except GDM, chronic use of medications except polyvitamin supplements, altered prenatal subsidiary exams, and refusal to participate in the study or to sign the informed consent form. Criteria for discontinuation were as follows: patients who ceased participating during the study; those who needed to change the anesthetic procedure to rachianesthesia, continuous epidural or general (intravenous and/or inhalatory) anesthesia; and pregnant women who needed to receive drugs that would interfere with the pharmacokinetics of lidocaine during the surgical procedure.

Epidemiological data were collected using a standard protocol form, including age, life habits, use of medications, anthropometric data, parity, gestational age, and ultrasound information about fetal and/or placental changes.

All pregnant women underwent the anesthetic procedure with 2% lidocaine hydrochloride without a vasoconstrictor (Xylestesin, Cristália, lot 02030982) at a dose of 5 ml (100 mg) for skin. In the peridural space for the locoregional anesthesia, 2% lidocaine hydrochloride without a vasoconstrictor (Xylestesin, Cristália, lot 02030982) was injected in single dose of 10 ml (200 mg) simultaneously with 0.05 mg/ml fentanyl citrate (Fentanest, Cristália, lot 02041393) at a dose of 2 ml (0.1 mg) and 0.5% bupivacaine hydrochloride with 1:200,000 epinephrine (Neocaína, Cristália, lot 53200809) at the dose of 15 ml (75 mg).

Before the administration of the anesthetic drugs, a maternal blood sample was collected for hematologic and biochemical laboratory tests in order to detect possible undiagnosed diseases. Serial blood samples were collected for the determination of lidocaine and MEGX concentrations at 1, 5, 15, 30, 45, and 60 min and at 2, 4, 6, 8, 10, 12, and 14 h after drug administration.

**Table 1** Median values and 25th and 75th percentiles of the maternal demographic data

Parameters	Control group	Diabetic group
Age (years)	28.50 (22.5–32.00)	34.00* (30.00–37.00)
Gestational age (days)	271.50 (266.50–286.00)	270.50 (266.50–272.50)
Weight (kg)	69.25 (66.55–77.65)	81.55* (75.00–90.15)
Height (m)	1.61 (1.54–1.66)	1.58 (1.54–1.61)
Body mass index (kg/m <sup>2</sup> )	27.20 (24.20–30.10)	31.86* (31.20–35.70)

\* $P < 0.05$ 

### Determination of lidocaine and MEGX

A stock lidocaine solution was prepared in methanol (chromatography grade, EM Science, Merck, Darmstadt, Germany) at a concentration of 1 mg/ml and diluted to working solutions at concentrations of 200, 100, 70, 50, 40, and 20 µg/ml methanol. The stock solution of MEGX (Astra Pharmaceuticals, Södertälje, Sweden) was prepared at a concentration of 8 µg/ml methanol and diluted to concentrations of 3.2, 1.6, 1.0, 0.8, 0.4, and 0.32 µg/ml.

Sodium chloride (analytical grade), sodium hydroxide (analytical grade), hexane (chromatography grade), and dichloromethane (chromatography grade), used in the extraction process, were from Merck.

### Chromatographic analysis of lidocaine and MEGX in plasma

Lidocaine and MEGX were separated from the endogenous constituents of plasma on a reverse-phase 250×4 mm Lichrospher 60 RP-Select B column (Merck) with 5-µm particles, with a similar 4×4 mm precolumn. The mobile phase, consisting of a mixture of 25 mM phosphate buffer, pH 4.5, and acetonitrile (82:18, v/v), was used at a rate of 1 ml/min.

Fifty microliters of the 0.15 N sodium hydroxide solution was added to 1-ml plasma samples, which were then extracted with 4 ml hexane-dichloromethane (82:18, v/v) after saturation of the aqueous phase with 500 mg sodium chloride. Lidocaine and MEGX were extracted by shaking at 220±10 cycles/min for 45 min in a horizontal shaker, followed by centrifugation at 1,800 rpm for 10 min, and concentration of the organic extracts at room temperature. Then, 20-µl aliquots were analyzed by high performance liquid chromatography (HPLC).

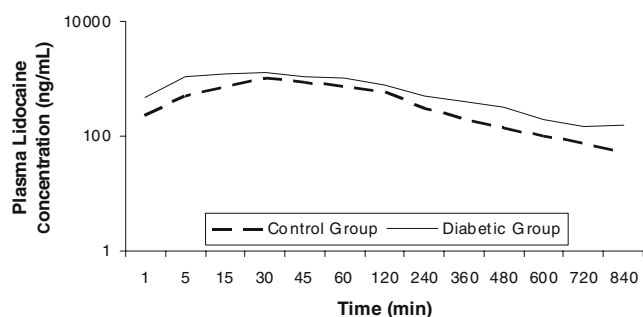
The HPLC system (Shimadzu, Kyoto, Japan) used for chromatographic analysis consisted of an LC-10AS pump, an SPD-10A ultraviolet detector operating at 205 nm, and a C-R6A integrator. The Rheodyne injection system (Cotati, CA, USA), model 7125, was used with a 20-µl sampler.

For the construction of the calibration curves, 1-ml aliquots of blank plasma obtained from healthy volunteers receiving no medications for the last 10 days were enriched with 25 µl each of the standard solutions of lidocaine (0.5–5.0 µg/ml) and MEGX (8–80 ng/ml) and subjected to the extraction and chromatography procedures described above. Linear regression equations and correlation coefficients were calculated on the basis of the ratios of the peak areas obtained (standard/internal standard) as a function of plasma concentration. The calibration curves for lidocaine and MEGX had the following linear regression equations, respectively:  $1,911.71 + 41,527.46x$  (coefficient of determination=0.99718) and  $7.8185 + 44.4046x$  (coefficient of determination=0.99771).

The recovery of plasma lidocaine and MEGX was determined by comparing the height of the peaks obtained after plasma extraction with the height of the peaks obtained after direct injection of the standard solution. Recovery was evaluated in triplicate at concentrations of 5, 1, and 0.5 µg/ml plasma for lidocaine and of 80, 20, and 8 ng/ml plasma for MEGX. Linearity was evaluated by analysis of plasma samples enriched with increasing concentrations of standard solutions compared to those used for the construction of the calibration curve. Samples enriched with concentrations up to 20 µg/ml plasma (0.5–20.0 µg/ml) for lidocaine and 640 ng/ml plasma (8.0–640.0 ng/ml) for MEGX were evaluated. Precision and accuracy were determined by analysis of plasma samples enriched with lidocaine (0.4 and 2.8 µg/ml) and MEGX (8 and 45 ng/ml). Plasma samples were analyzed in replicate ( $n=10$ ), using a single calibration curve for the intra-assay evaluation and in duplicate for 5 consecutive days for the interassay evaluations. The coefficients of variation obtained in the study of intra- and interassay precision for low and high lidocaine and MEGX concentrations were lower than 15%.

### Pharmacokinetic analysis of lidocaine and MEGX

The pharmacokinetic parameters of lidocaine and MEGX were obtained using the WinNonlin version 4.0 software (Pharsight, Mountain View, CA, USA).



**Fig. 1** Comparison of the median plasma concentrations of lidocaine (ng/ml) versus time (min) in the control and diabetic groups

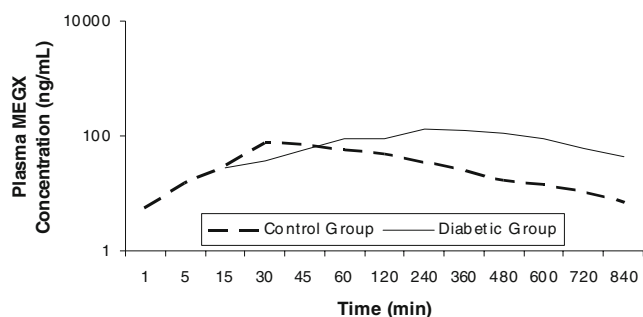
### Statistical analysis

The GraphPad Prism 3 software was used to calculate the measures of position and dispersal of each variable and to carry out the statistical analysis for comparison of normal and GDM pregnant women, with the level of significance set at 5%.

### Results

The study was conducted on 10 parturients with no base disease (group 1) and on six parturients with GDM (group 2). The median and 25th and 75th percentiles for maternal age, gestational age, body weight, height, and body mass index (BMI) are listed in Table 1. The laboratory tests carried out for functional evaluation of the hematologic, renal, hepatic, and endocrine systems/organs did not reveal important changes, except for glucose metabolism in the diabetic group. The median glycated hemoglobin (HBA1c) was 4.70 in the control group and 6.40 in the diabetic group ( $P < 0.05$ ). In addition, elevated plasma albumin and  $\alpha_1$ -acid glycoprotein ( $P < 0.05$ ) were observed in the diabetic group when compared to control group.

During the period of blood sample collection for the determination of lidocaine and MEGX concentrations in maternal plasma, maternal systolic and diastolic arterial



**Fig. 2** Comparison of the median plasma concentrations of MEGX (ng/ml) versus time (min) in the control and diabetic groups

pressure and heart rate were monitored, demonstrating hemodynamic stability throughout the study.

The median plasma concentrations as a function of time of collection are given in Figs. 1 and 2. The ratios of lidocaine and MEGX concentrations (lidocaine/MEGX ratio) at 15 and 30 min were significantly higher in diabetic patients compared to normal women (58.34 versus 23.21 at 15 min and 37.52 versus 15.80 at 30 min). The pharmacokinetic parameters of lidocaine and MEGX are presented in Tables 2 and 3.

### Discussion

The patient groups studied differed in some clinical data. Diabetic women were older than controls and their weight and BMI were also higher than those of control women, characteristics usually observed in patients with GDM.

Anthropometric data may influence the pharmacokinetics of drugs [10]. However, the anthropometric characteristics of the patients under study were within limits considered to be acceptable during pregnancy. In addition, the drug used has high bioavailability, rapidly passing into the blood stream from the site of administration, being then rapidly distributed and redistributed from striated muscle and adipose tissue [25]. Braid and Scott [4] demonstrated a poor correlation between maximum lidocaine concentration and BMI in a population of nonpregnant women. Downing et al. [7], in a study of pregnant women, also observed no correlation between maximum lidocaine concentration and BMI. Thus, these factors are considered not to directly affect the data obtained, minimizing the possibility of group differences in the pharmacokinetic data.

Drugs injected into the peridural space, in addition to acting on their local sites of action causing neural blockade, may pass through the paravertebral holes and be absorbed by blood and lymph capillaries [3]. The rich vascularization of the epidural space permits rapid absorption of lidocaine administered by this route and detection of the drug in plasma as early as in the first blood sample collected, with median circulating levels of 227.75 and 460 ng/ml in the control and diabetic groups, respectively. GDM did not interfere with the passage of lidocaine from the epidural space to the blood stream.

Analysis of lidocaine showed a monocompartmental pattern. The curves did not demonstrate the phase of systemic absorption of the drug, probably due to the high capacity of lidocaine to cross the cell membranes of blood capillaries in the epidural vascular plexus. This absorptive capacity is provided by the increased pressure in the peridural and cerebrovascular fluid space caused by the difficulty in venous return during the final phase of pregnancy.

**Table 2** Median values and 25th and 75th percentiles of the pharmacokinetic parameters of lidocaine in maternal plasma

Parameter	Control group	Diabetic group
C <sub>max</sub> (ng/ml)	879.11 (779.59–1,064.37)	1,145.58* (977.57–1,792.82)
t <sub>1/2β</sub> (min)	202.09 (168.12–236.49)	272.16 (199.90–297.59)
β (min <sup>-1</sup> )	0.0034 (0.0029–0.0041)	0.0025 (0.0023–0.0034)
AUC <sub>0–∞</sub> (μg min <sup>-1</sup> ml <sup>-1</sup> )	256.01 (238.37–308.07)	455.95* (333.48–661.13)
Cl/f (ml/min)	781.43 (650.67–839.08)	438.86* (321.89–605.85)
Cl/f/kg (ml min <sup>-1</sup> kg <sup>-1</sup> )	10.61 (9.19–12.82)	5.64* (3.98–6.96)
Vd/f (L)	227.93 (188.74–256.55)	174.62* (112.69–204.69)
Vd/f/kg (L/kg)	3.26 (2.44–3.93)	2.19* (1.49–2.27)

\**P*<0.005

The data obtained here for the control group are comparable to those reported in the literature regarding proportionality in terms of dose and route of administration. However, there are no data in the literature regarding the pharmacokinetics of lidocaine and MEGX in diabetic pregnant women, with the results obtained in the present study thus being original.

In the present study, median C<sub>max</sub> was 0.88 and 1.15 μg/ml (*P*<0.05) for the control and diabetic groups, respectively. These plasma concentrations did not reach systemic therapeutic levels and are considered to be safe in terms of toxicity [28]. Among nonpregnant women, plasma concentrations of 1.5–6 μg/ml are considered to be therapeutic for systemic effects and plasma concentrations of 6–10 μg/ml are considered to be occasionally toxic, while plasma concentrations > 10 μg/ml are considered to be frequently toxic [9]. Ramanathan et al. [20] detected a C<sub>max</sub> of 2.8 μg/ml in normal pregnant women submitted to peridural anesthesia with 400 mg lidocaine. In a study on pregnant women without base diseases receiving 2% lidocaine by the peridural route at a mean dose of 6.1 mg/kg (130 mg), a C<sub>max</sub> of 6.4 μg/ml was observed, reaching values with a toxic potential in two patients, although without maternal or fetal repercussions [7]. In a study on 23 normal pregnant women who underwent vaginal delivery at term under perineal anesthetic blockade with lidocaine, Cavalli et al. [5] reported a maximum concentration of 3.22 μg/ml at 15 min.

The area under the curve (AUC<sub>0–∞</sub>) determines the plasma concentration of the drug as a function of time after the administration of a single dose. In a literature review, Little [14] reported a tendency toward a reduction in the AUC<sub>0–∞</sub> during pregnancy. In the present study, the median values of the AUC<sub>0–∞</sub> were 256.01 and 455.95 μg min<sup>-1</sup> ml<sup>-1</sup> (*P*<0.05) in the control and diabetic groups, respectively, after epidural administration of 200 mg lidocaine. The area under the curve was 840 μg min<sup>-1</sup> ml<sup>-1</sup> in a study with peridural administration of a mean dose of 420 mg lidocaine [20] and 460.2 μg min<sup>-1</sup> ml<sup>-1</sup> when 400 mg lidocaine was administered via perineal blockade [5].

Distribution volume (Vd/f) and clearance (Cl/f) are pharmacokinetic parameters that depend on the dose and bioavailability of lidocaine. In turn, bioavailability depends on the route of administration. Vd/f and Cl/f also undergo changes as a function of the gravidic modifications occurring during pregnancy.

Elevated free fatty acids and glycosylation of plasma protein in diabetes mellitus may affect the extent of binding of drugs. In addition, extra- and intracellular volumes are elevated in experimental diabetes mellitus. Hence, the volume of distribution of drugs may be altered in the diabetic state [8]. Lidocaine plasma protein binding is approximately 66% [25]. In the present study, we observed elevated plasma albumin and α<sub>1</sub>-acid glycoprotein (*P*<0.05) in the diabetic group when compared to control group. The median Vd/f of lidocaine was 3.26 and 2.19 L/

**Table 3** Median values and 25th and 75th percentiles of the pharmacokinetic parameters of MEGX in maternal plasma

Parameter	Control group	Diabetic group
C <sub>max</sub> (ng/ml)	82.71 (54.04–92.15)	141.38* (107.65–183.14)
T <sub>max</sub> (min)	44.71 (20.07–55.74)	193.15* (178.78–257.01)
t <sub>1/2α</sub> (min)	7.64 (3.15–10.02)	59.77* (38.38–94.22)
α (min <sup>-1</sup> )	0.097 (0.069–0.220)	0.012* (0.008–0.018)
t <sub>1/2β</sub> (min)	247.28 (217.65–348.04)	492.20 (244.64–925.04)
β (min <sup>-1</sup> )	0.0028 (0.0021–0.0032)	0.0016 (0.0007–0.0030)
AUC <sub>0–∞</sub> (μg min <sup>-1</sup> ml <sup>-1</sup> )	29.91 (21.75–51.49)	108.23* (83.14–270.34)

\**P*<0.005

kg ( $P < 0.05$ ) in the normal and diabetic patients, respectively. Among nonpregnant women, the reference value for  $V_d/f$  is  $1.1 \pm 0.4$  L/kg [9]. Downing et al. [7] reported a  $V_d/f$  of 0.98 L/kg for normal pregnant women receiving lidocaine by the epidural route. When lidocaine was administered intravenously in a study on patients under treatment for cardiac arrhythmia, a  $V_d/f$  of 1.1 L/kg was obtained [16]. In turn, when lidocaine was administered by the perineal route to normal pregnant women, its distribution volume was 3.1 L/kg [5].

In the present study, the median  $Cl/f$  value for lidocaine was 10.61 and 5.64  $\text{ml min}^{-1} \text{kg}^{-1}$  ( $P < 0.05$ ) for normal and diabetic pregnant women, respectively. Among nonpregnant women, the standard normal value for clearance is  $9.2 \pm 2.4$   $\text{ml min}^{-1} \text{kg}^{-1}$  [9]. Downing et al. [7] detected a  $Cl/f$  of 6.1  $\text{ml min}^{-1} \text{kg}^{-1}$  when lidocaine was administered epidurally to normal pregnant women. According to Nattel et al. [16],  $Cl/f$  was 9.2  $\text{ml min}^{-1} \text{kg}^{-1}$  when the drug was injected intravenously in nonpregnant women. In turn, Cavalli et al. [5] obtained a clearance of 12.2  $\text{ml min}^{-1} \text{kg}^{-1}$  when the drug was administered by the perineal route to normal pregnant women.

The rightward shift for the plasma concentration versus time curve for MEGX in the diabetic women compared to the normal women and the plasma concentration ratios of lidocaine to MEGX, which were significantly higher in diabetic patients compared to normal women (58.34 versus 23.21 at 15 min and 37.52 versus 15.80 at 30 min), suggest that GDM inhibits the metabolism of lidocaine to MEGX, explaining the apparent reduction in the clearance of lidocaine.

The elimination half-life of drugs is also indirectly dependent on the bioavailability of the drug and the route of administration. In the present study, the median  $t_{1/2\beta}$  value of lidocaine was 202.09 min for the control group and 272.16 min for the diabetic group ( $P > 0.05$ ), higher than the value reported in the literature for a nonpregnant population, which was  $1.8 \pm 0.4$  h for single intravenous infusions [9]. Using the same route of administration as in the present study, Ramanathan et al. [20] detected a  $t_{1/2\beta}$  of 180 min in a group of pregnant women with no diagnosed diseases. Later, Downing et al. [7] reported a  $t_{1/2\beta}$  of 113.9 min for the drug also administered by the peridural route. The value reported for the perineal route in normal pregnant women was 180.0 min [5]. In a population of adult nonpregnant women, Nattel et al. [16] detected a  $t_{1/2\beta}$  of  $108 \pm 24$  min when the drug was administered intravenously. This difference between the pregnant and nonpregnant population is expected since during pregnancy there is an increase in drug distribution and elimination, with a consequent increase in  $t_{1/2\beta}$  for most drugs [14].

The model of MEGX analysis was bicompartmental, and the parameters analyzed were  $C_{\text{max}}$ ,  $T_{\text{max}}$ ,  $t_{1/2\alpha}$ ,  $t_{1/2\beta}$ , and

$AUC_{0-\infty}$ , with the following respective results for the control and diabetic women: 82.71 and 141.38 ng/ml, 44.71 and 193.15 min, 7.64 and 59.77 min, 247.28 and 492.20 min and 29.91 and 108.23  $\mu\text{g min}^{-1} \text{ml}^{-1}$ . The difference between normal and diabetic women was statistically significant, except for the elimination half-life. In a study in which lidocaine was administered by the perineal route to normal pregnant women, Cavalli et al. [5] reported the following results regarding MEGX:  $C_{\text{max}}$  229.0 ng/ml,  $AUC_{0-\infty}$  240 min, and  $AUC_{0-\infty}$  82.4  $\mu\text{g min}^{-1} \text{ml}^{-1}$ .

$C_{\text{max}}$  and  $AUC_{0-\infty}$  were lower in MEGX compared to lidocaine because this is a metabolite of the drug. On the other hand,  $t_{1/2\beta}$  was higher in diabetic women. The present data also demonstrate a greater area under the curve for plasma concentration versus time in the diabetic group than in normal women, for both lidocaine and MEGX (an increase of 78.10 and 261.85%, respectively). These data, taken together with the rightward shift in the plasma concentration versus time curve of MEGX in diabetic women, suggest that the metabolism of lidocaine to MEGX is affected by GDM, with a partial blockade of the biotransformation of the original drug. On the other hand, there was MEGX accumulation in the diabetic group compared to control, also suggesting inhibition of MEGX metabolism into secondary forms.

Analysis of the data as a whole reveals an important effect of GDM on the pharmacokinetics of lidocaine. To understand this effect, it should be remembered that during pregnancy the hepatic metabolism of drugs may be increased, reduced, or unchanged depending on the drug and on its metabolic pathway, with a consequent alteration of the clearance of the drug under study. Also, the CYP enzymatic system, which consists of a multigene enzyme superfamily, is responsible for the hepatic metabolism of various drugs, among them lidocaine. The CYP3A4 isoenzyme has been primarily reported to be responsible for lidocaine deethylation and has a small action on the hydroxylation of the drug, resulting in the formation of MEGX [2, 24]. In an in vitro study, Wang et al. [27] determined that CYP1A2 is the main isoform involved in the metabolic process of lidocaine deethylation when the drug is present at low concentrations (5  $\mu\text{M}$ , which corresponds to the lowest therapeutic plasma concentration) and of lidocaine hydroxylation, regardless of its concentrations.

CYP3A4 activity can be changed by endogenous factors such as hepatic alterations and metabolic diseases or by exogenous factors such as the administration of drugs [13, 29]. These factors, except GDM, were evaluated and were found not to be present in the study, so that they could not affect the pharmacokinetics of lidocaine and of MEGX or alter the results obtained.

Clinical and experimental studies have shown that DM may result in changes in the activity of various enzymes, among them the cytochrome P450 (CYP) system, modifying the expression of its isoforms by suppressing or activating them, with consequent changes in the metabolism of drugs depending on the function of this system [6, 15, 22].

Experimental studies have confirmed the influence of diabetes mellitus induced in rats on the suppression of the expression of various isoforms of the CYP system mainly through the action of glucagon and of its second messenger cyclic AMP and on the down-regulation of these enzymes [11]. It has been postulated that insulin has a contrary effect regarding the regulation of these isoenzymes, normalizing the actions suppressed or stimulated by decompensated diabetes or by the action of glucagon [23, 30, 31]. A study on nonpregnant hypertensive women with type 2 diabetes using lidocaine as a marker drug of *in vivo* CYP3A4 activity demonstrated that type 2 diabetes inhibits the CYP3A4 enzymatic system, with a consequent reduction in lidocaine clearance [15].

Thus, the present data suggest that lidocaine metabolism to MEGX is partially inhibited by the influence of GDM on its enzymatic system, causing a reduction in clearance. In addition, inhibition of lidocaine hydroxylation to 3-hydroxylidocaine, a process that depends on CYP1A2, also probably occurred, with a consequent accumulation of lidocaine in the diabetic group. Another point to be raised is that the formation of other metabolites from MEGX (not evaluated in the present study) was also inhibited by GDM, thus causing MEGX accumulation in these patients. The present data indicate the need for further studies in order to clarify the effect of GDM on other substrates dependent on CYP3A4/CYP1A2 and on other isoforms of the CYP system.

## Conclusions

On the basis of the data obtained and analyzed in the present study, we conclude that (1) lidocaine passes rapidly from the epidural space to the bloodstream, being detected in maternal plasma 1 min after administration, (2) epidural administration of 200 mg lidocaine causes maximum plasma concentrations that do not reach a therapeutic concentration, being safe in terms of toxicity in normal and diabetic pregnant women, (3) the apparent distribution volume of lidocaine administered by the epidural route to diabetic pregnant women was reduced compared to normal pregnant women, and (4) the reduction in the apparent clearance of lidocaine in the diabetic group compared to control suggests that GDM inhibits the enzymatic isoforms CYP1A2/CYP3A4 that are responsible for the metabolism of this drug.

## References

- Alberti KGMM, Zimmet PZ (1998) Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. *Diabet Med* 15:539–553
- Bargetzi MJ, Aoyama T, Gonzalez FJ, Meyer UA (1989) Lidocaine metabolism in human liver microsomes by cytochrome P450III<sub>A4</sub>. *Clin Pharmacol Therap* 46:521–527
- Bernards CM (2001) Epidural and spinal anesthesia. In: Barash PG, Cullen BF, Stoelting RK (eds) *Clinical anesthesia*, 4th edn. Lippincott Williams & Wilkins, Philadelphia, pp 1–43
- Braid DP, Scott DB (1966) Dosage of lignocaine in epidural block in relation to toxicity. *Br J Anaesth* 38:596–602
- Cavalli RC, Lanchote VL, Duarte G, Moisés ECD, Prado MFM, Duarte LB, Cunha SP (2004) Pharmacokinetics and transplacental transfer of lidocaine and its metabolite for perineal analgesic assistance to pregnant women. *Eur J Clin Pharmacol* 60:569–574
- Cheng PY, Morgan ET (2001) Hepatic cytochrome P450 regulation in disease states. *Curr Drug Metab* 2:165–183
- Downing JW, Johnson HV, Gonzalez HF, Arney TL, Herman NL, Johnson RF (1997) The pharmacokinetics of epidural lidocaine and bupivacaine during cesarean section. *Anesth Analg* 84:527–532
- Emami J, Passutto FM, Jamali F (1998) Effect of experimental diabetes mellitus and arthritis on the pharmacokinetics of hydroxychloroquine enantiomers in rats 15(6):897–903
- Gilman GA, Hardman JG, Limbird LE (2001) *Goodman and Gilman's the pharmacological basis of therapeutics*, 10th edn. McGraw-Hill, New York
- Hodgkinson R, Husain FJ (1980) Obesity and cephalad spread of analgesia following epidural administration of bupivacaine for cesarean section. *Anesth Analg* 59:89–92
- Iber H, Li-Masters T, Chen Q, Yu S, Morgan ET (2001) Regulation of hepatic cytochrome P450 2C11 via cAMP: implications for down-regulation in diabetes, fasting and inflammation. *J Pharmacol Exp Therap* 297:174–180
- Isohanni MH, Neuronen PJ, Palkama VJ, Olkkola KT (1998) Effect of erythromycin and itraconazole on the pharmacokinetics of intravenous lignocaine. *Eur J Clin Pharmacol* 54:561–565
- Kivisto KT, Kroemer HK (1997) Use of probe drugs as predictors of drug metabolism in humans. *J Clin Pharmacol* 37(1 Suppl): S40–S48
- Little BB (1999) Pharmacokinetics during pregnancy: evidence-based maternal dose formulation. *Obstet Gynecol* 93:858–868
- Marques MP, Coelho EB, Dos Santos NA, Geleilate TJ, Lanchote VL (2002) Dynamic and kinetic disposition of nisoldipine enantiomers in hypertensive patients presenting with type-2 diabetes mellitus. *Eur J Clin Pharmacol* 58:607–614
- Nattel S, Gagne G, Pineau M (1987) The pharmacokinetics of lignocaine and b-adrenoreceptor antagonists in patients with acute myocardial infarction. *Clinl Pharmacokinet* 13:293–316
- Orlando R, Piccoli P, De Martin S, Padrini R, Palatini P (2003) Effect of the CYP3A4 inhibitor erythromycin on the pharmacokinetics of lignocaine and its pharmacologically active metabolites in subjects with normal and impaired liver function. *Br J Clin Pharmacol* 55:86–93
- Preston RA, Chung M, Gaffney M, Alonso A, Baltodano NM, Epstein M (2001) Comparative pharmacokinetics and pharmacodynamics of amlodipine in hypertensive patients with and without type II diabetes mellitus. *J Clin Pharmacol* 41:1215–1224
- Preston RA, Epstein M (1999) Effects of diabetes on cardiovascular drug metabolism. *Emerging clinical implications. Diabetes Care* 22:982–988

20. Ramanathan J, Bottorff M, Jeter JN, Khalil M, Sibai BM (1986) The pharmacokinetics and maternal and neonatal effects of epidural lidocaine in preeclampsia. *Anesth Analg* 65:120–126
21. Reynolds F, Taylor C (1970) Maternal and neonatal blood concentrations of bupivacaine: a comparison with lignocaine during continuous epidural analgesia. *Anesthesia* 25:14–23
22. Schenkman JB (1991) Induction of diabetes and evaluation of diabetic state on P450 expression. *Methods Enzymol* 206:325–331
23. Shimojo N (1994) Cytochrome P450 changes in rats with streptozotocin-induced diabetes. *Int J Biochem* 26:1261–1268
24. Sotaniemi EA, Rautio A, Bäckström M, Arvela P, Pelkonen O (1995) CYP3A4 and CYP2A6 activities marked by the metabolism of lignocaine and coumarin in patients with liver and kidney diseases and epileptic patients. *Br J Clin Pharmacol* 39:71–76
25. Sweetman SC (2002) *Martindale: the complete drug reference*, 33rd edn. Pharmaceutical Press, London
26. Wang JS, Backman JT, Wen X, Taavitsainen P, Neuvonen PJ, Kivisto KT (1995) Fluvoxamine is a more potent inhibitor of lidocaine metabolism than ketoconazole and erythromycin in vitro. *Pharmacol Toxicol* 85:201–205
27. Wang JS, Backman JT, Taavitsainen P, Neuvonen PJ, Kivisto KT (2000) Involvement of CYP1A2 and CYP3A4 in lidocaine n-deethylation and 3-hydroxylation in humans. *Drug Metab Disp* 25:959–965
28. Wildsmith JA, Strichartz C (1984) Local anaesthetic drugs - an historical perspective. *Br J Anaesth* 56:937–939
29. Wildt SN, Kearns GL, Leeder JS, Van den Anker JN (1999) Cytochrome P450 3A. Ontogeny and drug disposition. *Clin Pharmacokinet* 37:485–505
30. Woodcroft KJ, Novak RF (1999) Insulin differentially affects xenobiotic-enhanced, cytochrome P-450 (CYP)2E1, CYP2B, CYP3A, and CYP4A expression in primary cultured rat hepatocytes. *J Pharmacol Exp Therap* 289:1121–1127
31. Woodcroft KJ, Novak RF (1999) The role of phosphatidylinositol 3-kinase, Src kinase, and protein kinase A signaling pathways in insulin and glucagon regulation of CYP2E1 expression. *Biochem Biophys Res Comm* 266:304–307