Pharmacokinetics of Lidocaine and Its Metabolites Following Vaginal Administration of Lidocaine Gel to Healthy Female Subjects

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Abstract

Lidocaine vaginal bioadhesive gel is being developed as a local anesthetic for use in minimally invasive outpatient gynecological procedures and was investigated in single-dose and multiple-dose studies in healthy young adult women. Lidocaine doses of 2.5%, 5%, and 10% (w/w) were administered, and parent drug and metabolites monoethylglycinexylidide and glycinexylidide were measured in plasma. Lidocaine was absorbed through vaginal tissue and into the systemic circulation in a dose-proportional manner, and there was little systemic accumulation. Plasma concentrations were 10- to 20-fold lower than concentrations obtained after administration of intravenous lidocaine used to treat arrhythmic activity, thus demonstrating a wide safety margin for a vaginal lidocaine product.

Keywords

lidocaine, vaginal, pharmacokinetics, anesthetic, absorption

Lidocaine is well established as a potent and safe anesthetic for local use for a wide variety of medical procedures including in many office practices. First introduced over 60 years ago, it is still a mainstay for rapid and safe anesthetic activity. It is relatively watersoluble in many formulations, and drug distribution into tissue is rapid, leading to only a short time before a physician or dentist can initiate a diagnostic or surgical treatment. In addition, the pharmacologic activity, blocking the transmission of sensory signals, is relatively short due to systemic absorption, metabolism, and elimination.

Lidocaine is absorbed extensively following mucosal, intramuscular, rectal, transdermal, and inhalation pathways.¹ Lidocaine is metabolized efficiently, whether by presystemic hepatic elimination or normal clearance due to systemic hepatic blood flow. When the site of administration is well vascularized, absorption can be rapid. Depending on the presentation of parent drug, 2 major metabolites, monoethylglycinexylidide (MEGX) and glycinexylidide (GX), are formed in various ratios.

Lidocaine also has antiarrhythmic properties, but plasma concentrations achieved following local administration generally can be small relative to those concentrations observed after intravenous (IV) dosing for cardiac arrhythmias. Initial lidocaine bolus doses of 50–100 mg are typically administered for arrhythmias, followed by a continuous IV infusion. Plasma concentrations of IV lidocaine used to treat cardiac arrhythmias are in the range of 1.5–5.0 µg/mL.²³

Lidocaine has been established as a safe anesthetic for local use. However, repeated administration of topical sprays can potentially lead to large cumulative doses and serum concentrations. Work by Lebedzki and colleagues demonstrated that administration of a 10% lidocaine spray solution followed by 2% to 4% liquid lidocaine doses (total doses of 480 to 720 mg) for anesthesia of the pharynx, larynx, trachea, and bronchi in patients undergoing bronchoscopy had peak mean serum concentrations of 3.6 µg/mL (range 1.9 to 7.4 µg/mL) observed within an hour of the start of diagnostic bronchoscopy procedures.⁴ In

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subsequent work, lidocaine systemic exposure administered by high-frequency nebulization was compared to spray administration to the trachea and bronchi. Nebulized lidocaine into the pulmonary vasculature resulted in approximately 60% lower lidocaine peak serum concentrations compared with the spray administration (mean concentrations: 1.4 vs 3.6 µg/mL, respectively).\(^5\)

Of note, clinical signs of overt lidocaine toxicity were not observed in either dose group (total N = 25). The authors conclude that a better safety margin is established with administration of a nebulized formulation vs a spray preparation based on peak serum concentrations.

Topical preparations, commonly creams or gels, result in effective local concentrations and fewer possibilities for clinically significant systemic adverse events. A lidocaine-containing vaginal bioadhesive gel was developed using a formulation base, polycarbophil, that can improve retention time and hydration of vaginal tissue.\(^6\) In an initial proof-of-concept study, conducted in a single site in Italy, administration of the 5% (75 mg w/w) lidocaine bioadhesive gel 5 hours prior to a challenge with vasopressin was shown objectively and subjectively to reduce intrauterine pressure, uterine contractions, perception of uterine contractions, and pain of induced dysmenorrhea as compared with placebo gel.\(^7\)

Two clinical studies were conducted to assess the safety profile of the novel vaginal formulation and the pharmacokinetics of lidocaine and its metabolites observed following systemic absorption. These studies were designed to investigate the likelihood of a vaginal preparation of lidocaine having a wide safety margin when systemic toxicity is assessed. The first study was a single-dose, placebo-controlled study in healthy adult females. The second study was performed in a multiple-dose fashion in a similar healthy adult female population. It is proposed that this lidocaine vaginal gel could provide anesthetic activity and pain relief during a minimally invasive gynecological procedure with subsequent diminished uterine contractions given the presumed multiple layer tissue penetration (unkeratinized epithelium → endometrium → myometrium).

**Methods**

**Formulation**

Lidocaine vaginal gel is a translucent, clear to slightly opalescent, bioadhesive gel for intravaginal self-administration. The gel contains 2.5%, 5%, or 10% w/w (base equivalent) lidocaine in an aqueous-based delivery system, packaged in aluminum tubes. The vehicle is comprised of polycarbophil, a bioadhesive, water swellable but water insoluble, polyacrylic acid polymer together with other nonactive ingredients including glycerin, natrosol, sorbic acid, methyl hydroxybenzoate, and purified water.

The polycarbophil has been designed to mimic mucin, the glycoprotein component of mucus, which is negatively charged and is responsible for its attachment to underlying epithelial surfaces.\(^7\) Polycarbophil is a lightly cross-linked polymer and is also a weak polyacid containing multiple carboxyl radicals (COO\(^{-}\)), which are the source of its negative charges. These acid radicals permit hydrogen bonding with the cell surface. Hydrogen bonds are generally weak, but when they are numerous, such as in the case with polycarbophil, there is a sufficiently strong affinity to the hydrogen atoms on the cell surface that may allow adhesion over an extended period of time. Being a water-insoluble polymer, the polycarbophil will stay attached to mucosal epithelial cells often until they turn over, normally up to 3 to 5 days.

A portion of the lidocaine that is present in the formulation forms an insoluble complex with the polycarbophil, although some remains in solution within the formulation. The portion in solution is available for immediate release and absorption across the vaginal mucosa. The insoluble portion is slowly released from the complex as the dissolved portion diffuses out of the formulation, resulting in the controlled-release properties of the formulation. The extended residence time of the gel vehicle at the mucosal surface permits prolonged drug release and absorption to take place.

A similarly formulated placebo dosage form was prepared. Doses of 2.5%, 5%, and 10% (w/w) lidocaine bioadhesive gel were manufactured and released following satisfactory testing within defined product specifications. In addition to providing control of both drug and impurity levels in accordance with pharmacopeia limits, other relevant specification parameters include control of gel pH, viscosity, microbiological burden, and preservative efficacy. Both the drug and placebo formulations were provided in blinded aluminum tubes.

**Study Population**

Forty-two healthy women aged between 18 and 45 years with a body weight greater than 110 pounds (50 kg) and a body mass index between 16 and 30 kg/m\(^2\) were enrolled in the first single-dose study. These women were normal healthy volunteers who met screening enrollment criteria. Study participants were enrolled in a single center, a specialized hospital clinical research unit, in Morelia, Michoacán, Mexico. Subjects in this single-dose study had a treatment period lasting 3 to 4 days (subjects admitted 12 hours prior to a 72-hour study period in the clinical research unit). The vaginal application of lidocaine gel occurred approximately 14 hours after admission to the hospital unit. Subjects were discharged on day 4. A similar female population of
42 women was enrolled in the multiple-dose study in the same clinical research unit. The treatment period lasted 8 days in the hospital (admission 1 day prior to dosing, 4 dosing days and 3 additional days of sampling). Subjects were discharged on the morning of day 8. All laboratory tests were within normal ranges. No women were pregnant, nursing, or menstruating. No prescription or over-the-counter drug use involved known CYP450 enzyme inducers. Subjects were excluded from participation if they had a history of psychiatric disorders, alcoholism (<2 years), clinically significant ECG abnormality, pelvic mass, hysterectomy, or any chronic medical condition such as hypertension or diabetes.

Study Design
Both studies were conducted in accordance with their respective protocols, all applicable Food and Drug Administration (FDA) regulations, Good Clinical Practice (GCP) standards, and adherence to applicable local regulatory requirements and laws. A properly executed written informed consent in compliance with FDA regulations and GCP guidelines was obtained from each subject prior to entering the study or performing any unusual or nonroutine procedure that involved a risk to the subject. The institutional review board that approved the protocols was Comité Científico, Comité de Ética, Fraccionamiento Mirador del Punhuato, 58249, Morelia, Michoacán, Mexico. Both studies were monitored by qualified personnel from a clinical research organization (CRO), Pharm-Olam International, Houston, Texas.

Single-Dose Study. All subjects were evaluated for general health during a physical examination with a medical history, vital signs, clinical laboratory assessment, and a 12-lead ECG. On the study day the clinical investigator administered 1.5 g of bioadhesive gel into the subject’s vagina as deeply as comfort allowed, with a plunger applicator supplied by the sponsor.

Twelve subjects in each dose group were administered the lidocaine bioadhesive gel, and 2 subjects in each group were administered the placebo gel, in a double-blind randomized manner. The dose groups were administered 2.5%, 5%, or 10% lidocaine gel, and the groups were dosed in an ascending-dose manner. The formulations delivered 37.5, 75, or 150 mg of lidocaine, respectively. All subjects were recumbent or maintained minimal movement for 2 hours after administration.

Blood samples for lidocaine and metabolite pharmacokinetic analysis were collected from subjects at baseline (0.0 hours) and 1, 2, 4, 6, 8, 12, 16, 24, 36, 48, 60, and 72 hours after administration. The blood was collected into vacutainers containing sodium EDTA as an anticoagulant. Plasma was harvested and frozen at −70°C prior to analysis of the individual plasma samples.

Multiple-Dose Study. Following a screening period, 14 subjects per dose group (2.5%, 5%, or 10% lidocaine vaginal gel) were administered lidocaine gel or placebo gel in a double-blind randomized 6:1 ratio. The lidocaine gel was administered on days 1, 2, 3, and 4 at the same time of morning as the initial dose. The dose groups were processed in an ascending-dose fashion, utilizing safety assessments for the decision to proceed to the next group. The daily doses consisted of 1.5 g of the proper formulation, administered by the investigator deeply into the subject’s vagina with the plunger applicator.

On study day 1, blood samples were taken predosing (0.0 hours) and at 1, 2, 4, 6, 8, 16, and 22.25 hours postdose. Trough blood samples were taken prior to the next 3 daily doses. Following the final administration on day 4, blood samples were collected at 1, 2, 4, 6, 8, 12, 16, 24, 36, 48, 60, and 72 hours postdose. Blood samples were collected in sodium EDTA vacutainers, and plasma was harvested for bioanalysis.

Safety
All adverse events were captured on case report forms and evaluated by the investigator. Safety and tolerability were assessed by evaluating adverse events, vital signs, physical exams, ECGs, and laboratory tests. A final physical exam was conducted prior to dismissal of all subjects.

Bioanalysis
Lidocaine, monoethylglycinexylidide (MEGX), and glycinexylidide (GX) were extracted from the plasma samples with an acetonitrile protein precipitation method and analyzed by liquid chromatography with mass spectrophotometric detection (LC-MS/MS). The standard curve ranges were 0.50 to 50 ng/mL for each of the 3 analytes. The lower limit of quantitation was 0.50 ng/mL for all assays. Prilocaine was utilized as the internal standard for the bioanalytical method. The chromatography stationary phase was a Phenomenex Aqua 3 μm, 30 mm column maintained at room temperature. The mobile phase was a gradient of 0.1% formic acid in water/0.1% formic acid in methanol. The m/z ions utilized for quantitation were 235, 207, and 179, respectively, for the 3 analytes. The interday variability was ±8.6%, and the intraday variability was ±10.8%. The method was validated to bioanalytical standards including low, middle, and high concentration quality control samples. ABC Laboratories (Columbia, Missouri) conducted the analyses.

Pharmacokinetics
The plasma concentration-time profiles of parent lidocaine and its active metabolites MEGX and GX were graphed and assessed. The pharmacokinetic
Figure 1. Mean (± SE) lidocaine plasma concentration-time profile following vaginal administration of 2.5%, 5%, and 10% lidocaine vaginal gel from the single-dose study (n = 12 for the 2.5% dose group, and n = 11 for the 5% and 10% dose groups).

Figure 2. Mean (± SE) lidocaine plasma concentration-time profiles following once-daily 10% lidocaine vaginal gel administration on day 1 and day 4 from the multiple-dose study (n = 12).

parameters, $C_{\text{max}}$, $t_{\text{max}}$, $\text{AUC}_{0-24}$, $\text{AUC}_{\infty}$, and $t_{1/2}$, were estimated via noncompartmental methods (WinNonlin version 5.2, Pharsight Corporation, Mountain View, California). The maximum concentration ($C_{\text{max}}$) and time for maximum concentration ($t_{\text{max}}$) were obtained directly from the data. The area under the
concentration-time curve (AUC<sub>∞</sub>) was determined by the linear trapezoidal rule for the single-dose study. For the multiple-dose study on day 1, AUC<sub>0-24</sub> was determined to sum the concentration-time curve through the 24-hour dosing interval (AUC<sub>0-24</sub> was actually measured to 22.25 hours). The elimination half-life (t<sub>1/2</sub>) was estimated by least-squares analysis of at least 3 terminal plasma concentrations. WinNonlin log-linear regression estimates were determined by the maximum R<sup>2</sup>. Possible accumulation in the multiple-dosing study and the dose proportionality of the treatment groups were also examined.

**Biostatistics**

The pharmacokinetic parameters are presented as means with their respective standard deviations (SD). Concentrations lower than the quantitation limit were treated as 0 and were carried through for calculation of mean values. Between-day pharmacokinetic parameters were assessed for statistically significant differences by use of a t-test. The dose proportionality of C<sub>max</sub> and AUC for the 3 doses was examined by determining the 95% confidence interval for the mean around the line of regression (CLM) for the respective parameter vs dose.

**Results**

**Study Population**

Forty-two healthy female subjects were enrolled in each of the 2 studies. All subjects completed the safety assessments, and 82 of the 84 (98%) completed the pharmacokinetic assessments; for the single-dose study, 1 subject in each of the 5% and 10% dose groups did not complete the pharmacokinetic assessments. Demographic characteristics were similar in the 2 studies. For the single-dose study, the mean ± SD age was 25 ± 6 years, and the mean ± SD weight was 58 ± 6 kg. These respective measurements were 24 ± 5 years and 59 ± 6 kg for the multiple-dose study. Vaginal pH was measured daily in the multiple-dose study, and the mean (daily) pH ranged from 4.4 to 5.4.

**Safety Assessment**

No serious adverse events were observed in either the single- or multiple-dose studies. In the single-dose study, 1 subject reported slight vaginal bleeding 30-48 hours following administration of the vaginal gel, which was described as intermenstrual bleeding. Additional adverse events reported were abdominal cramps in the subject with the vaginal bleeding and in 1 other subject; both were moderate in severity. In the multiple-dose study, 2 subjects reported mild vaginal bleeding. Two subjects reported mild dysmenorrhea (painful menses), 1 of whom also reported severe proyomenorrhea (shortened menstrual cycle). Two other subjects reported mild proyomenorrhea. Six subjects reported headaches during the study period; 4 were mild, and 2 were moderate. All of these adverse events from both studies resolved without treatment and were considered grade 1 events. There were no clinically significant findings for laboratories, ECGs, vital signs, or physical exams.

**Pharmacokinetic Assessment**

Lidocaine was effectively absorbed systemically following administration of lidocaine vaginal gel. Mean plasma concentration-time profiles of lidocaine following each of 3 single 2.5%, 5%, and 10% doses are presented in Figure 1. The plasma concentrations fall in parallel fashion with a consistent elimination half-life of approximately 10 hours following peak concentrations achieved in 6 hours. Tissue samples were not taken, so the concentration-time profile is unknown in tissue.

There is minimal accumulation for lidocaine and its sequential metabolites MEGX and GX when administered as a daily intravaginal formulation. Figures 2, 3, and 4 show the day 1 and day 4 mean concentration-time profiles for parent lidocaine, MEGX, and GX, respectively, for the 10% dose group. MEGX is formed in a rapid manner by dealkylation of the tertiary amine, and the appearance of the totally deethylated metabolite, GX, is somewhat delayed such that peak concentrations occur at 10 to 20 hours.

Key pharmacokinetic data for the single-dose study are presented in Table 1, and for the multiple-dose study in Table 2. The accuracy of the pharmacokinetic data was verified via a separate analysis utilizing SAS (Cary, North Carolina). The approximate times to maximum concentration lay in the following rank order: lidocaine (6 hours), MEGX (10 hours), and GX (18 hours). This results in the same rank order for C<sub>max</sub>, with greater concentrations for lidocaine compared to the metabolites, and for total AUC. The lidocaine C<sub>max</sub> observed for the 10% dose was 70.6 ± 39.4 ng/mL for the single-dose study and 75.7 ± 61.8 ng/mL on day 4 of the multiple-dose study. The approximate elimination half-life was most rapid for lidocaine (10 hours), followed by MEGX (12 hours) and then GX (15 hours). For each of these compounds there was minimal accumulation, given the half-life in relation to the dosing interval.

The dose proportionality of lidocaine was assessed with the single-dose pharmacokinetic data and is summarized in Figure 5a for AUC<sub>∞</sub> and Figure 5b for C<sub>max</sub>. Lidocaine displays significant pharmacokinetic linearity due to the 95% confidence intervals observed within the respective line of linearity.
Figure 3. Mean (± SE) monoethylglycinexylidide (MEGX) plasma concentration-time profiles following once-daily 10% lidocaine vaginal gel administration on day 1 and day 4 from the multiple-dose study.

Figure 4. Mean (± SE) glycinexylidide (GX) plasma concentration-time profiles following once-daily 10% lidocaine vaginal gel administration on day 1 and day 4 from the multiple-dose study.
Table 1. Single-Dose Pharmacokinetic Parameters Observed in Healthy Female Subjects After Vaginal Administration of Lidocaine

| Compound/Lidocaine Dose | \( C_{\text{max}} \) (ng/mL) | \( t_{\text{max}} \) (Hours) | AUC<sub>0-\( \infty \)</sub> (ng·h/mL) | \( t_{1/2} \) (Hours) |
|-------------------------|-----------------------------|-----------------------------|-----------------------------------|-------------------|
| **Lidocaine**           |                             |                             |                                   |                   |
| 2.5%                    | 13.6 ± 9.3                  | 6.4–12                      | 256 ± 90                          | 11.1 ± 3.9        |
| 5%                      | 35.5 ± 19.0                 | 6.2–12                      | 582 ± 258                         | 10.1 ± 4.7        |
| 10%                     | 70.6 ± 39.4                 | 6.4–12                      | 1291 ± 568                        | 9.5 ± 3.4         |
| **MEGX**                |                             |                             |                                   |                   |
| 2.5%                    | 2.16 ± 0.96                 | 12.6–16                     | 66.7 ± 16.5                       | 19.6 ± 12.2       |
| 5%                      | 4.76 ± 2.31                 | 8.4–12                      | 107 ± 46                          | 10.4 ± 4.2        |
| 10%                     | 11.1 ± 6.5                  | 8.6–12                      | 247 ± 110                         | 11.7 ± 5.2        |
| **GX**                  |                             |                             |                                   |                   |
| 2.5%                    | 0.85 ± 0.75                 | 16.12–36                    | ND                                | ND                |
| 5%                      | 2.79 ± 2.19                 | 16.6–60                     | ND                                | ND                |
| 10%                     | 5.65 ± 4.55                 | 16.12–24                    | 228 ± 159                         | 14.7 ± 5.7        |

\( AUC_{0-\infty} \): concentration-time curve extrapolated to infinity as determined by the linear trapezoidal rule; \( C_{\text{max}} \): maximum concentration; \( GX \): glycinexylylidide; MEGX, monoethylglycinexylidide; ND, not determined due to nonmeasurable concentrations; \( t_{1/2} \): elimination half-life; \( t_{\text{max}} \): time of maximum concentration.

*The 2.5% (w/w) bioadhesive gel contains 37.5 mg lidocaine. The 5% (w/w) bioadhesive gel contains 75 mg lidocaine. The 10% (w/w) bioadhesive gel contains 150 mg lidocaine. Twelve subjects were treated with lidocaine in each dose group. One subject in each of the 5% and 10% dose groups did not complete the pharmacokinetic assessments.

Discussion

A local anesthetic may be preferred for treatment of pain induced by the performance of outpatient gynecologic procedures such as IUD placement, colposcopy, endometrial or endocervical biopsy, loop electrosurgical excision procedure (LEEP), endometrial ablation, or hysteroscopy. Lidocaine has ideal properties for this indication. The bioadhesive gel formulation used in these studies contains 2.5%, 5.0%, and 10% w/w (base equivalent) lidocaine (37.5 mg, 75.0 mg, and 150 mg lidocaine, respectively) in an aqueous-based delivery system. The gel traps the lidocaine in the polymer matrix, thereby enabling the slow dissolution of the active ingredient over a sustained period of time. In order to decrease pain throughout the procedure, effective local tissue concentrations of lidocaine must be achieved. A bioadhesive vaginal gel delivery system has been shown to deliver a significantly higher ratio of endometrial to serum concentrations of progesterone (median ratio 14.1) than progesterone delivered intramuscularly (median ratio 1.2). This finding has been referred to as the “first uterine pass effect.”

Absorption into vaginal tissue can be inferred from the presence of lidocaine in the systemic circulation at the earliest 1-hour sampling time point. Once absorbed, lidocaine is metabolized sequentially to MEGX and GX by efficient metabolic processes. The only pathway for lidocaine to be present in plasma is for the soluble agent to be absorbed from the gel formulation and distribute into and through vaginal tissue. The bioavailability of lidocaine from a vaginal dose is unknown, but the formulation itself leads to a prolonged absorption phase and a time to maximum concentration of 6 hours. This also results in a longer plasma elimination half-life compared to IV administration (1.5 hours). The absorption and elimination processes are simple first-order ones, as pharmacokinetic linearity is observed within a 4-fold range of intravaginal lidocaine doses. Similar linearity is observed for the metabolites MEGX and GX. The pharmacokinetic profiles are consistent across the 2 studies and demonstrate little, if any, accumulation if lidocaine would need to be given in multiple-dose fashion on consecutive days.

Lidocaine is known to be absorbed systemically through various membranes. It is absorbed orally, although its bioavailability is limited due to first-pass metabolism. When administered at relatively high doses, intrabronchial lidocaine administration results in therapeutic serum concentrations when the drug is retained for sufficient time to allow absorption to occur. Variable and incomplete absorption was observed following an intranasal gel formulation. Low absorption was also observed following short-term intraoral administration.

Lidocaine is still prescribed for its antiarrhythmic properties and is administered as a bolus and/or IV infusion to rapidly reach therapeutic concentrations of 1.5-5 µg/mL. Because lidocaine is a potent central nervous system and cardiovascular agent, systemic safety is a potential concern following local administration. Based on these effective plasma concentrations, the peak lidocaine concentration achieved after the highest, 10% local lidocaine administration in this study...
Table 2. Multiple-Dose Pharmacokinetic Parameters Observed in Healthy Female Subjects After Vaginal Administration of Lidocaine

| Compound/Lidocaine Dose | Day  | C<sub>max</sub> (ng/mL) | t<sub>max</sub><sup>b</sup> (Hours) | AUC<sub>0-24</sub> (ng·h/mL) |
|-------------------------|------|-------------------------|-----------------------------------|----------------------------|
| Lidocaine 2.5%          | Day 1<sup>c</sup> | 16.8 ± 16.2             | 6.4–16                           | 198 ± 138                  |
|                         | Day 4  | 12.9 ± 6.3              | 6.4–24                           | 176 ± 58                   |
| 5%                      | Day 1<sup>c</sup> | 39.8 ± 28.2             | 6.2–16                           | 483 ± 294                  |
|                         | Day 4  | 25.5 ± 13.8             | 6.2–12                           | 352 ± 159                  |
| 10%                     | Day 1<sup>c</sup> | 63.3 ± 26.7             | 4.4–12                           | 781 ± 336                  |
|                         | Day 4  | 75.7 ± 61.8             | 4.4–6                            | 831 ± 364                  |
| MEGX 2.5%               | Day 1<sup>c</sup> | 6.2 ± 10.5              | 8.1–22                           | ND                         |
|                         | Day 4  | 2.1 ± 0.9               | 8.6–8                            | 34.7 ± 16.1                |
| 5%                      | Not measured on days 1 and 4 |
| 10%                     | Day 1<sup>c</sup> | 14.3 ± 7.3              | 8.6–12                           | 211 ± 106                  |
|                         | Day 4  | 18.3 ± 13.8             | 8.4–12                           | 259 ± 143                  |
| GX 2.5%                 | Day 1<sup>c</sup> | 1.8 ± 1.5               | 16.8–22                          | ND                         |
|                         | Day 4  | 1.6 ± 1.0               | 10.0–24                          | 30.4 ± 24.0                |
| 5%                      | Not measured on days 1 and 4 |
| 10%                     | Day 1<sup>b</sup> | 7.9 ± 4.0               | 16.4–22                          | ND                         |
|                         | Day 4  | 14.0 ± 10.2             | 10.0–12                          | 227 ± 148                  |

AUC<sub>0-24</sub>, plasma concentration-time curve through the 24-hour dosing interval; C<sub>max</sub>, maximum concentration; GX, glycinexylidide; MEGX, monoethylglycinexylidide; t<sub>max</sub>, time of maximum concentration. ND, not determined due to nonmeasurable concentrations.

<sup>a</sup>The 2.5% (w/w) bioadhesive gel contains 37.5 mg lidocaine. The 5% (w/w) bioadhesive gel contains 75 mg lidocaine. The 10% (w/w) bioadhesive gel contains 150 mg lidocaine. Twelve subjects were treated with lidocaine in each dose group.

<sup>b</sup>t<sub>max</sub> data are median, range

<sup>c</sup>On day 1, AUC<sub>0-24</sub> was actually measured to 22.25 hours.

Figure 5. Lidocaine single-dose (a) AUC<sub>0-24</sub> and (b) C<sub>max</sub> measurements vs dose to assess dose proportionality with the 95% confidence interval for the mean around the line of regression (CLM). The x-axis is in milligrams of lidocaine, where 37.5 mg is 2.5%, 75 mg is 5%, and 150 mg is 10% w/w lidocaine bioadhesive gel.
is still 10- to 20-fold lower than concentrations needed for antiarrhythmic therapy. With these extremely low plasma concentrations, there is a wide safety margin for lidocaine when administered as an anesthetic for vaginal use and negligible risk of systemic toxicity. This is similar to the conclusion reached when lidocaine is used for dental, dermatologic, or other purposes when rapid, short-acting anesthesia is desired.

In summary, lidocaine is effectively absorbed into vaginal tissue when administered locally in a gel formulation. Following systemic absorption, lidocaine is metabolized to MEGX and GX in a straightforward manner. Plasma concentrations of lidocaine are substantially lower than those necessary for its antiarrhythmic properties, and therefore, intravaginal lidocaine could be safely administered without concern for serious systemic adverse effects. As a result of these properties, the application of this lidocaine gel is expected to result in high endometrial/myometrial concentrations of lidocaine and relatively lower plasma concentrations, thus creating a unique safety-benefit profile for the product.

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Declaration of Conflicting Interests

Dr Bridget Martell and Elaine Richardson are employees of Juniper Pharmaceuticals, Inc. Dr Harvey Kushner is a consultant and employed by BioMedical Computer Research Institute. Dr Amy Mize is employed by ABC Laboratories, Columbia MO. Dr Philip Mayer is a private consultant.

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