Comparison of Five Commonly-Available, Lidocaine-Containing Topical Anesthetics and Their Effect on Serum Levels of Lidocaine and Its Metabolite Monoethylglycinexylidide (MEGX)

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Abstract

Background: Topical anesthetics are commonly applied for a variety of indications. Several lidocaine-containing topical anesthetics are available for purchase over the counter (OTC). Recently, the authors’ group has shown that there is great interindividual discrepancy in the manner in which lidocaine is absorbed and metabolized for even a single OTC product.

Objectives: The authors compare five commonly-available lidocaine preparations and their levels of absorption when applied to the face. Three of the preparations are available OTC; two require prescriptions and were compounded in a pharmacy.

Methods: Twenty-five subjects enrolled in this Institutional Review Board–approved study were randomly assigned to one of five groups. The five topical anesthetics were LMX-4 (4% lidocaine; Biopelle/Ferndale Laboratories, Ferndale, Michigan), Topicaine (4% lidocaine; Ebsa Laboratories, Jupiter, Florida), 2.5% lidocaine/2.5% prilocaine (generic EMLA preparation; High Tech Pharmaceuticals, Amityville, New York), LET (4% lidocaine, 1:2000 epinephrine, and 0.5% tetracaine), and BLT (20% benzocaine, 6% lidocaine, and 4% tetracaine). After a patch test for adverse reactions, the topical anesthetic was applied to each patient’s face and neck and covered with an occlusive dressing for 60 minutes. Blood was drawn at 90, 120, 150, 240, and 480 minutes to measure serum levels of lidocaine and monoethylglycinexylidide (MEGX).

Results: The average age of the 17 women and eight men included in the study was 26 years (range, 22-62 years), and the average weight was 70.9 kg (range, 46.4-96.4 kg). The OTC preparations had the highest serum lidocaine and MEGX levels. Topicaine had the greatest serum levels of individual lidocaine absorption (0.808 µg/mL), followed by generic EMLA (0.72 µg/mL), LMX-4 (0.44 µg/mL), BLT (0.17 µg/mL), and LET (0.13 µg/mL). On average, Topicaine had the highest serum lidocaine and MEGX levels: 0.438 µg/mL and 0.0678 µg/mL, respectively. There were significant interindividual differences between the serum levels of MEGX and lidocaine in all groups except LET (P < .0001). There were significant differences between the 4% lidocaine-containing preparations (P = .0439); the 2.5% preparation had a greater absorption than the 4% lidocaine-containing preparation and the 6% lidocaine preparation (P = .0016). There were three adverse reactions in patients who received OTC preparations, one of which resulted in postinflammatory hyperpigmentation.

Conclusions: This study demonstrates that although topical anesthetics are considered safe, some individuals have unpredictably high absorption levels. This study also demonstrates that the concentration of lidocaine, the formulation of the drug, and the individual patient all have significant effects on serum levels of lidocaine. The authors recommend that even OTC topical anesthetics be used under the supervision of a healthcare professional to avoid adverse toxic effects and, in rare cases, death.

Level of Evidence: 2

Keywords
research, lidocaine, serum, anesthetic, topical, MEGX

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with unsupervised application of the drug by the patient. OTC products tend to have vague instructions on how much to apply, over what area, and with what frequency. It is therefore imperative that the systemic absorption profiles of these drugs be properly investigated.

It has always been assumed that these topical anesthetic delivery systems are safe. There are several studies in the literature attesting to the safety when these agents are used in areas such as the arms, legs, or abdomen. However, recently our group has shown that there are great interindividual differences in the manner in which lidocaine is absorbed and metabolized for just one of the OTC products that contains lidocaine. Unfortunately, there are numerous lidocaine-containing topical anesthetic products commonly used on the face for a number of different procedures. The skin on the face is different from the skin elsewhere on the body in that it has a greater vascular supply and a stronger density of glandular structures. To date, there is a paucity of data examining the safety of these OTC products when applied to the face.

This study evaluates five common topical anesthetics, three of which are available OTC and two of which are compounded (Table 1). We compared the absorption of a fixed amount of each drug applied to the face by measuring the serum levels of lidocaine and its active metabolite, monoethylglycinexylidide (MEGX). In this way, we hope to provide more information on the safety profile for these drugs for treatment of the facial skin.

### METHODS

Twenty-five healthy subjects were consented and screened in accordance with Title 45 Code of Federal Regulations, Part 46, Protection of Human Subjects (45 CFR part 46) for participation in this UT Southwestern Medical Center Institutional Review Board (IRB) study. Each enrolled participant was subject to a patch test for drug sensitivity before inclusion into the next phase of the study. The patch test consisted of a 1-cm application of each of the study drugs to the forearm with an occlusive dressing for 10 minutes. Any subjects with adverse skin reactions such as erythema or welting were excluded at this point.

The remaining subjects were randomly assigned to one of five treatment groups, with five patients in each group:

- **Group A**: 30 g Topicaine (active ingredient 4% lidocaine; Esba Laboratories, Jupiter, Florida)—nonprescription, OTC
- **Group B**: 30 g eutectic mixture of 2.5% lidocaine, 2.5% prilocaine (generic form of EMLA; High Tech Pharmaceutical, Amityville, New York)—nonprescription, OTC
- **Group C**: 30 g LMX-4 (active ingredient 4% lidocaine; Ferndale Laboratories, Ferndale, Michigan)—nonprescription, OTC
- **Group D**: 30 g LET (4% lidocaine, 1:2000 epinephrine, and 0.5% tetracaine)—prescription required, compounded in pharmacy
- **Group E**: 30 g BLT (20% benzocaine, 6% lidocaine, and 4% tetracaine)—prescription required, compounded in pharmacy

Each subject received 30 g of the assigned drug applied to the face and neck area (Figure 1). The area was then covered immediately with an occlusive dressing and left for 60 minutes (Figure 2). Vital signs (electrocardiogram [ECG], blood pressure, heart rate, and O₂ saturations) were measured for the duration of the 60 minutes during which

### Table 1. Comparison Between the Five Different Local Anesthetics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Composition</th>
<th>Recommended Doses</th>
<th>Metabolized</th>
<th>Patient Instruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMX 4</td>
<td>4% lidocaine Liposomal carrier</td>
<td>Apply externally to the affected area up to three to four times a day.</td>
<td>Liver</td>
<td>For use on adults and children two years and older. Children younger than two years—ask a doctor. May be applied under occlusive dressing.</td>
</tr>
<tr>
<td>Generic form of EMLA</td>
<td>2.5% lidocaine and 2.5% prilocaine eutectic mixture (oil in water)</td>
<td>See data sheet31 (instructions given depending on clinical scenario).</td>
<td>Liver</td>
<td>See data sheet31 (instructions given depending on clinical scenario).</td>
</tr>
<tr>
<td>Topicaine</td>
<td>4% lidocaine Amide Translucent microemulsion gel</td>
<td>Adults and children older than two years. Apply externally to affected area up to three to four times per day.</td>
<td>Liver</td>
<td>Apply a moderately thick layer to the affected area (approximately 1/8 inch thick). Allow time for numbness to develop. Best results obtained 20 minutes to one hour following application.</td>
</tr>
<tr>
<td>LET</td>
<td>4% lidocaine, 1:2000 epinephrine, 0.5% tetracaine Gel, Methylcellulose base</td>
<td>NA</td>
<td>Liver (lidocaine) Plasma (tetracaine)</td>
<td>Apply under direction of prescribing health professional.</td>
</tr>
<tr>
<td>BLT</td>
<td>20% benzocaine, 6% lidocaine, 4% tetracaine Emollient base</td>
<td>NA</td>
<td>Liver (lidocaine) Plasma (benzocaine, tetracaine)</td>
<td>Apply under direction of prescribing health professional.</td>
</tr>
</tbody>
</table>

NA, not available.
the study drug was applied to the face/neck. At 60 minutes, the study drug was removed and the subjects were asked to cleanse their face with Cetaphil (Galderma Laboratories, Fort Worth, Texas) skin cleanser. Blood samples were taken via an intravenous catheter that was left in place for the duration of the study. Time intervals of the blood samples were 90, 120, 150, 240, and 480 minutes. Any AE relating to the procedure were recorded.

Blood Sample Procurement and Analysis
Whole blood samples (approximately 15 mL of blood) were collected in ethylenediaminetetraacetic acid (EDTA)-containing vials. The blood samples were immediately centrifuged (3000 rpm for 10 minutes at 4°C) and stored at −80°C until analyzed. The Department of Clinical Chemistry, George-August University (Goettingen, Germany) analyzed lidocaine and MEGX in plasma using a previously-described technique.7

Statistical Analysis
The serum concentration-time courses of lidocaine and MEGX were characterized with Microsoft Excel (Microsoft Corp., Redmond, Washington). A repeated-measures analysis of variance (ANOVA) test for nonparametric data was used to analyze differences between the groups. Associations with \( P < .05 \) were considered statistically significant.

RESULTS
All 25 subjects completed the study. Seventeen women and eight men were included in the study, with an average patient age of 26 years (range, 22-62 years) and average weight of 70.9 kg (range, 46.4-96.4 kg). All patients described numbness of the face and neck after 60 minutes, although time to anesthesia and depth of anesthesia were not formally assessed. The patient demographics are shown in Table 2.

Table 2. Patient Demographics

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>25</td>
</tr>
<tr>
<td>Age, y (range)</td>
<td>26 (22-62)</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>8/17</td>
</tr>
<tr>
<td>Weight, kg (range)</td>
<td>70.9 (46.4-96.2)</td>
</tr>
</tbody>
</table>

Figure 1. Topical lidocaine-containing cream is applied to the face and neck.

Figure 2. An occlusive dressing is placed over the face for 60 minutes’ duration while the subject’s cardiac status is monitored.
Drug Absorption

OTC preparations showed the highest serum lidocaine and MEGX levels. Topicaine had the greatest serum levels of lidocaine absorption (0.808 µg/mL) for an individual, followed by generic EMLA (0.72 µg/mL), LMX-4 (0.44 µg/mL), BLT (0.17 µg/mL), and LET (0.13 µg/mL). On average, Topicaine had the highest serum lidocaine and MEGX levels (0.438 µg/mL and 0.0678 µg/mL, respectively).

There were significant differences across the time points between the serum levels of lidocaine ($P = .0002$) and MEGX ($P = .0045$) in all five groups (Figures 3 and 4). LET had the least absorption of all five study drugs; in fact, four of five patients in this group had no detectable levels of lidocaine or MEGX in their serum. When averaged across each group for all study drugs, there were still detectable levels of lidocaine and MEGX in the serum of participants at eight hours. Table 3 summarizes the different groups and the average peak serum levels of lidocaine and MEGX.

Interindividual Variation Within the Groups

Interindividual variation was shown in each group except for LET. Topicaine ($P < .0001$), generic EMLA ($P < .0001$), LMX-4 ($P < .0001$), and BLT ($P < .0001$) all showed significant differences between the serum levels of MEGX and lidocaine combined in their respective groups.

Differences Between 4% Lidocaine-Containing Preparations (Figure 5)

Topicaine had the greatest serum absorption (0.491 µg/mL), followed by LMX-4 (0.336 µg/mL) and LET (0.038 µg/mL). The differences between these three groups were statistically significant ($P = .0439$).

Differences Between Preparations Containing Differing Lidocaine Concentrations (Figure 6)

The 2.5% lidocaine-containing preparation had greater absorption with a peak combined serum level of 0.4384 µg/mL compared with 0.276 µg/mL for the 4% lidocaine-containing preparations and 0.1482 µg/mL for the 6% lidocaine-containing preparation, which had the least absorption. The differences between the different lidocaine concentrations were statistically significant ($P = .0016$).

Adverse Skin Reactions

Two participants developed minor adverse reactions of erythema within the first four hours, with scaling and prolonged erythema at 48 hours—one in the Topicaine...
(4% lidocaine) group and one in the EMLA group (2.5% lidocaine). All skin reactions resolved within seven days. One subject (Fitzpatrick V) in the Topicaine group developed a more severe skin reaction that resulted in postinflammatory hyperpigmentation over the cheeks and dorsum of the nose (Figure 7). This resolved with conservative care.

**DISCUSSION**

The ideal topical anesthetic would have high efficacy with minimal systemic absorption. These agents are used for a variety of applications, ranging from venipuncture in children, to skin graft harvesting, to laser treatments such as facial rejuvenation and hair removal in adults. They are commonly available, and some can be purchased OTC. Although these topical lidocaine-containing compounds are considered safe, they have been poorly studied. There is some systemic absorption of lidocaine, and in rare cases, this has led to severe cardiac and neurological side effects (and, in extreme cases, death). This study has quantified the systemic absorption of five different lidocaine-containing topical anesthetics, three of which are available without prescription, and has shown that four of the five (with the exception of LET) are associated with considerable systemic absorption.

Local anesthetics (LA) can be split into two classes: amides (eg, lidocaine, prilocaine) and esters (eg, benzocaine and tetracaine). The basic chemical structure of local anesthetics consists of a lipophilic group and intermediate bond (which is either an ester or an amide) and a hydrophilic group. All local anesthetics are weak bases; inflammation causes an acidic environment that in turn causes more of the LA to be ionized, leading to a slower onset of action. Amides are metabolized in the liver by the P450 cytochrome pathway more slowly than esters, which are metabolized in the plasma by cholinesterases. Both are excreted through the kidneys. Therefore, because they

Table 3. Average and Peak Combined Serum Levels for the Five Different Topical Anesthetic Preparations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Peak Levels, µg/mL</th>
<th>Average Levels, µg/mL</th>
<th>Time, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topicaine (4% lidocaine)</td>
<td>0.808</td>
<td>0.4996</td>
<td>90/120</td>
</tr>
<tr>
<td>Generic EMLA (2% lidocaine + 2% prilocaine)</td>
<td>0.779</td>
<td>0.4384</td>
<td>90/90</td>
</tr>
<tr>
<td>LMX-4 (4% lidocaine)</td>
<td>0.477</td>
<td>0.3359</td>
<td>150/120</td>
</tr>
<tr>
<td>BLT (20% benzocaine, 6% lidocaine, 4% tetracaine)</td>
<td>0.178</td>
<td>0.1482</td>
<td>90/90</td>
</tr>
<tr>
<td>LET (4% lidocaine, 1:2000 epinephrine, 0.5% tetracaine)</td>
<td>0.188</td>
<td>0.0376</td>
<td>240/240</td>
</tr>
</tbody>
</table>

*aIndividual within the group.
*bFirst reading is peak time for individual; second reading is peak time for the group average.
are metabolized more slowly, amides can be more toxic than esters. Lidocaine (amide) has a relative potency of four, whereas tetracaine (ester) has a relative potency of 10. Prilocaine is less toxic than lidocaine for a given dose because it has a lesser vasodilatory effect and is metabolized faster, so doses of >8 mg/kg can lead to toxic
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LA products bound to proteins have a longer duration of action, and those in the nonionized form lead to a more rapid onset of action. The higher the pH, the longer-acting the LA: lidocaine (pH 7.6-7.8) has a faster onset than tetracaine (pH 8.1-8.9). Both amide- and ester-type LA work by binding to receptors on Na⁺ channels and reducing the uptake of Na⁺ ions into the nerve, thus preventing depolarization and therefore also preventing conduction of the nerve impulse.

Many clinicians use a combination of local anesthetics. Indeed, three of the five drugs that were used in this study contain more than one type of local anesthetic. The effect of the different anesthetics is additive. For each drug, there is a safe limit in mg/kg that should be administered to the patient, and this is a guideline to which clinicians should always adhere.

**OTC Topical Anesthetics Have Greater Absorption Than Prescription Anesthetics**

Our results showed that the OTC products were associated with greater levels of lidocaine in the bloodstream than the prescription preparations. The literature relating to lidocaine toxicity is largely centered on its intravenous use for cardiac arrhythmias. Clinical symptoms of lidocaine toxicity include lightheadedness, paraesthesia, nausea, and vomiting, which can progress to seizures, arrhythmias, and cardiorespiratory depression.3,4,18,19 Toxic levels of lidocaine are said to occur with serum levels above 5 µg/mL, with central nervous system disturbance such as seizures occurring at levels greater than 8 µg/mL.20 Although the observed levels did not exceed 1 µg/mL (the lower limit of therapeutic intravenous lidocaine therapy for arrhythmias), it is still a sobering thought that, for example, one individual with topicalaine applied to the face had serum levels in excess of 0.8 µg/mL. The doses that were used in this study and the application of occlusive dressings were all within the manufacturer guidelines.

Allergy rarely occurs with amides but can occur with esters such as benzocaine because, when metabolized, it forms p-aminobenzoic acid (PABA), which has been associated with allergic reactions.21 In addition, benzocaine can cause methemoglobinemia, as can lidocaine and prilocaine,14 which can be potentially fatal, particularly in the pediatric population.22,23 All adverse skin effects were seen with the OTC products. Interestingly, some studies have shown that Topicaine and EMLA can be used under occlusion with “mild and transient” AE.5 These studies were performed on the legs and forearm—not on the face, as with our study. Other studies support our findings, particularly with EMLA, showing that it can cause minor skin irritations.24 The composition of Topicaine contains alcohol; a hypersensitivity to this could be the cause of the more severe postinflammatory hyperpigmentation reaction that one patient experienced. It has already been shown that the prilocaine component of generic topical anesthetic, which resembles the same composition as EMLA, can cause contact sensitivity.5 We had one adverse skin reaction in this group. For these reasons, our study highlights the need for caution with unsupervised patient use of these drugs. Even when a test patch is offered, as in this study, skin reactions may not be evident until the drug is actually applied to the face.

**Interindividual Variability**

This study compared five different lidocaine-containing topical anesthetics and demonstrated that absorption of the drug through the facial skin varies from individual to individual. This has previously been demonstrated by our group in topical anesthetic and liposuction studies.7,25 It has also been shown in other studies examining the use of local anesthetics in breast augmentation.26 The significance of this is that one cannot predict the amount of drug a patient will absorb. Lidocaine is metabolized in the liver via the P450 cytochrome pathway, and its breakdown products, including MEGX, are excreted via the kidneys. As a result, patients who have liver or kidney problems will have a reduced capacity for lidocaine metabolism and therefore will have greater circulating levels of the drug. In addition, patients who have broken areas on the skin prior to drug application will also have greater absorption of the drug, as the barrier to drug absorption is the stratum corneum (the outermost layer of the skin).

**Drug-Delivery Vehicle Influences Drug Absorption**

The results of this study highlighted the effect of the drug-delivery vehicle on the absorption through the skin. Three of the tested products contained 4% lidocaine, and all three had differing absorption profiles. One of the drugs had an alcohol-based composition, the second was a liposomal drug-delivery system, and the third was an emollient-based product. Alcohols act as skin penetration enhancers by removing lipid from the stratum corneum and therefore increasing its permeability.27 Liposomes...
facilitate drug penetration through the skin because they are lipid bilayer constructs that encapsulate a drug, and emollients are lipid-based.\textsuperscript{28} In both of these cases, the lipophilic nature of the drug-delivery system enhances penetration through the stratum corneum.\textsuperscript{29} What was interesting to note is that the 2.5% lidocaine-containing formula had the greatest absorption when compared with the 4% and 6% lidocaine-containing products. This is because the drug exists in a eutectic mixture with 2.5% prilocaine. The significance of this is that the active ingredients (ie, lidocaine and prilocaine) exist as an oil-in-water mixture with a lower melting point of 18°C. This means that at room temperature, lidocaine and prilocaine exist as a liquid rather than a solid, and absorption is therefore enhanced. This is further facilitated by the addition of an occlusive dressing. LET had the least absorption of all five drugs, with only one participant in this group having any detectable levels in the bloodstream. This is probably attributable to the fact that this drug contains epinephrine, which is a known vasoconstrictor. The benefit of this is that the drug is confined to the epidermis/dermis and is not typically absorbed systemically.

### Compounded Drugs

Two of the local anesthetic mixtures in this study were compounded in the pharmacy. Recently, the US Food and Drug Administration (FDA) has issued warnings to five companies with regard to their practice of mass-producing compounded products.\textsuperscript{30,31} Compounded products should be prescribed specifically for the patient and should not, therefore, be mass-produced. Compounded drugs are not FDA-approved and often have higher concentrations of active ingredients than OTC products. These drugs should be administered under the guidance of a healthcare professional, who can give the patient clear instructions for use. Fatalities related to compounded products have been secondary to unsupervised use, as they are not packaged with the usual patient inserts/written instructions, as OTC local anesthetics are.

### Recommendations and Future Directions

This study and previous studies by this group have demonstrated that although topical anesthetics are safe, there can be considerable systemic absorption of lidocaine-containing topical anesthetics. In particular, it is difficult to predict those patients who may be “sensitive” to topical applications, resulting in high circulating serum levels of lidocaine. We would therefore advise patient and physician caution, particularly with OTC lidocaine preparations, which our results showed to have the greatest systemic absorptions.

This study focused on lidocaine and its metabolites because the drug has well-documented guidelines for toxicity and the serum drug levels at which symptoms occur. It is also the most potent of the active drugs in the topical anesthetics. Esters such as benzocaine and tetracaine are less well-researched in the literature but have less potency than amides due to their method of metabolism.\textsuperscript{15} What can be said is that combinations of drugs will have an additive effect. For future studies, levels of benzocaine, tetracaine, and prilocaine could be measured in the serum to give an indication of their relative contribution.

Occlusive dressings enhance penetration of the drug, and the length of time over which the occlusive dressing is applied will influence drug absorption. Added to this, participants in all study groups still had detectable levels of lidocaine and MEGX in their serum at eight hours, which has ramifications for repeat applications. Ideally, these drugs should be used under the supervision of a healthcare professional, so that patients do not apply large amounts of the drug to large surface areas under occlusive dressings, all factors that result in enhanced absorption. Although these products are packaged with instructions on maximum recommended surface areas for application, maximum dosage, and the need for occlusion, it is still prudent for the healthcare professional to be familiar with warning signs of lidocaine toxicity. Systemic drug absorption following topical application will be influenced by several factors, but again, our study demonstrates that it is also dependent on individual patient physiology. Skin of the face would most likely have an increased absorption profile compared with skin on the leg or abdomen. Further studies would need to be carried out to compare these areas before recommendations can be made on specific drugs and their doses.

It is well known that disruption of the stratum corneum leads to enhanced drug absorption. Several clinical studies show that disruption of the stratum corneum by laser pretreatment, followed by topical application of anesthetic, can lead to a faster onset of anesthesia.\textsuperscript{12,32,33} We have already conducted preclinical studies in an animal model showing that laser pretreatment leads to increased systemic absorption of topically-applied lidocaine (data not yet published). Our next step is to examine the safety profile of laser pretreatment as a method to facilitate faster anesthesia in a clinical model, for procedures such as laser facial resurfacing.

### CONCLUSIONS

Topical anesthetics are safe, but systemic absorption in some individuals can reach unpredictably high levels. The type of drug-delivery system, occlusive dressings, and individual patient factors such as liver function can affect systemic absorption, metabolism, and excretion of lidocaine. Our data show that OTC products have the greatest level of systemic absorption and can persist in the bloodstream at eight hours postapplication. Therefore, we recommend that topical anesthetics—even OTC formulations—be used under the supervision of a healthcare professional to avoid adverse toxic effects and, in rare cases, death.

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REFERENCES


