Effect of 4% Topical Lidocaine Applied to the Face on the Serum Levels of Lidocaine and Its Metabolite, Monoethylglycinexylidide

Georgette Oni, MBChB, MRCS; Spencer Brown, PhD; Clint Burrus, BA; Lorin Grant, BA; Jeff Watkins, BA; Matthew Kenkel; Fritz Barton Jr., MD; and Jeffrey Kenkel, MD

Abstract

Background: Topical lidocaine is a common form of anesthesia for a wealth of procedures across a large number of disciplines, including laser treatments. Preparations can be purchased over the counter with no prescription necessary. It is considered a safer and more acceptable form of anesthetic than hypodermic injections; however, there have been reports of fatalities following its application. Above certain serum lidocaine concentrations, patients may experience effects of toxicity such as lightheadedness and paraesthesia; these effects can progress to seizures and cardiorespiratory depression, which can ultimately lead to death. The active metabolite of lidocaine, monoethylglycinexylidide (MEGX), can be almost as potent as lidocaine in terms of toxicity.

Objectives: The authors examine the levels of both lidocaine and MEGX in blood serum after application of topical lidocaine.

Methods: Twenty-five healthy volunteers were assigned to one of four groups (A, B, C, D). Group A had 2.5 g of 4% lidocaine topical anesthetic cream applied to the face for one hour without occlusion, Group B had 5 g applied to the face for one half-hour without occlusion, Group C had 5 g applied to the face for one hour without occlusion, and Group D had 5 g applied to the face for one hour with occlusion. To evaluate serum concentrations, blood was drawn every 30 minutes for four hours.

Results: Group D showed the highest serum levels of lidocaine and MEGX, a three-fold increase compared with group C, which received the same dose (5 g topical 4% lidocaine) but without occlusion. In group D, peak serum levels occurred at 90 minutes for serum lidocaine, which was also the fastest of the four groups. Serum MEGX levels peaked much later than serum lidocaine levels, at 210 minutes. Individual serum levels did not exceed 0.6 µg/mL. Across the groups, there was significant interindividual variation in both lidocaine and MEGX serum levels (P = .061). Applications of 5 g of 4% lidocaine resulted in higher serum concentration of both lidocaine and MEGX. When comparing group A to group C, doubling the dose of 4% lidocaine from 2.5 g to 5 g resulted in double the serum levels of MEGX and a 50% increase in the serum lidocaine levels (P = .021). When comparing groups C and D, the addition of an occlusive dressing resulted in a tripling of the serum lidocaine levels and a doubling of the serum MEGX levels, both of which were statistically significant (P < .001). When comparing all four groups, there were significant differences between the combined serum concentrations of lidocaine and MEGX (P < .001).

Conclusions: Topical lidocaine preparations are increasingly being employed to provide a patient-friendly form of noninvasive analgesia for a multitude of procedures. Some preparations are available over the counter for unsupervised patient application. Our study has demonstrated significant interindividual variability for a given dose, especially when occlusion is applied. There have been fatalities resulting from topical lidocaine application, and our study suggests that this is the result of the unpredictability of lidocaine metabolism between individuals. Therefore, we recommend that caution be exercised with topical lidocaine preparations, in particular when applied in conjunction with occlusive dressings.

Keywords

Topical anesthetics, lidocaine, monoethylglycinexylidide, lidocaine toxicity

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Topical lidocaine is employed across a large number of disciplines for a wealth of procedures, ranging from venipuncture to laser treatments to split skin grafting, just to name a few. Its use is well tolerated, as it is noninvasive and can be relatively effective in providing analgesia. It is considered a safer and more acceptable form of anesthetic than hypodermic injections; however, there have been reports of hospital admissions and fatalities following its application.
It is well known that when serum lidocaine concentrations reach a certain level, patients begin to experience effects of toxicity, such as lightheadedness, paraesthesia, nausea, and vomiting. These symptoms can progress to seizures and cardiorespiratory depression,4-7 which can ultimately lead to death.8 The active metabolite of lidocaine, monoethylglycinexylidide (MEGX), can be almost as potent as lidocaine in terms of toxicity, but there are few studies in the literature that examine serum MEGX concentrations.

In this study, the authors examine the metabolism of lidocaine through facial skin, including particular reference to changes in serum levels of both lidocaine and MEGX, with the goal of increasing patient safety.

METHODS

After the study was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center, subjects were evaluated and considered for inclusion in the study. The inclusion criteria required that subjects be between the ages of 18 and 65. Exclusion criteria for this study were pregnancy, known allergy to lidocaine or known adverse reactions to local anesthetics of the amide type, and current treatment with medication for a heart rhythm disorder.

In total, 25 healthy subjects were enrolled in the study. The patients were randomized into four experimental groups (A, B, C, and D). The topical anesthetic used for the study was 4% lidocaine topical anesthetic cream (LMX 4, Ferndale Laboratories, Inc., Ferndale, MI, USA). Regardless of the group to which they were assigned, each patient received lidocaine applied to the main and anterior portions of the face and neck. The surface area of each patient’s face and neck (Figure 1) was quantified with Mirror 3D photography and Rhinoceros 3D NURBS modeling (version 4.0, McNeel, Seattle, WA, USA). Group A was randomized to receive 2.5 g of the preparation applied to the face with one hour of exposure and no occlusive dressing. Group B was randomized to receive 5 g of the preparation with 30 minutes exposure and no occlusive dressing. Group C was randomized to receive 5 g of the preparation with one hour of exposure and no occlusive dressing. Group D was randomized to receive 2.5 g of the preparation with one hour of exposure with an occlusive dressing.

Specimen Procurement

Whole blood samples (approximately 15 mL of blood) were collected in vials containing ethylenediaminetetraacetic acid (EDTA). The samples were obtained via an intravenous line left in place for the course of the study at zero (baseline), 30, 60, 90, 120, 150, 180, 210, and 240 minutes. The blood samples were immediately centrifuged at 3000 rpm for 10 minutes at 4°C and stored at −80°C until analyzed.

The serum samples were sent to the Department of Clinical Chemistry at George-August University (Goettingen, Germany) for analysis of lidocaine and MEGX levels in the plasma with a previously described technique.9 The plasma concentration and time courses of lidocaine and MEGX were charted with Microsoft Excel (Version 5.1.2600, 2006, Microsoft Corporation, Redmond, WA, USA). A Kruskal-Wallis test for nonparametric data was administered to analyze the differences within and between the groups, and a Mann-Whitney two-tailed test was employed to compare the mean values with a 95% confidence interval (CI). Associations with P < .05 were considered statistically significant.

RESULTS

Twenty-five subjects, 14 men and 11 women, were enrolled in the study. The patients had a mean age of 28.4 years (range, 22-46 years); their average weight was 165.66 lbs (range, 115.94-262.9 lbs). The average facial surface area from the 3D face/neck imaging was 500 cm² (range, 406-599 cm²).

Group A: 2.5 g Topical 4% Lidocaine, One Hour Exposure, No Occlusion

Patients in Group A had the lowest dose of lidocaine applied. Mean serum levels of lidocaine peaked at 120 minutes, but serum MEGX levels continued to rise at 240 minutes. The serum levels of lidocaine or MEGX did not exceed 0.25 µg/mL at any time, either in isolation or when combined. There were threefold differences between the serum levels of individual subjects within this group for both serum lidocaine (P = .003) and serum MEGX (P = .034), as well as for both combined (P = .025). One patient in this group described flushing and perioral tingling.

Group B: 5 g Topical Lidocaine, Half-hour Exposure, No Occlusion

Peak levels of serum lidocaine in Group B occurred at 120 minutes, whereas serum MEGX levels continued to rise at the conclusion of the study (Table 1). Serum levels of lidocaine and MEGX did not exceed 0.25 µg/mL at any point. There was a threefold difference in serum MEGX levels (P = .282) and twofold difference in serum lidocaine levels (P = .029) among the individuals within this group. There was a statistically significant difference when combining serum lidocaine and MEGX levels within the group (P = .047).

Group C: 5 g Topical Lidocaine, One Hour Exposure, No Occlusion

Peak serum levels of lidocaine occurred at 150 minutes, whereas peak levels of serum MEGX occurred at 210 minutes (Table 1). After 120 minutes, mean serum levels of
both lidocaine and MEGX in this group rose at a faster rate than in Group B. There were significant differences between individuals within the group for serum lidocaine ($P < .001$), serum MEGX ($P = .041$), and both combined ($P = .015$). The combined serum levels of both lidocaine and MEGX did not exceed 0.25 µg/mL at any time point.

**Group D: 5 g Topical Lidocaine, One Hour Exposure, With Occlusion**

Patients in Group D demonstrated the highest serum levels of lidocaine and MEGX, a threefold difference for the same dose without occlusion (Figure 2). Peak serum levels occurred at 90 minutes for serum lidocaine, which was also the fastest of the four groups. Serum MEGX levels peaked at 210 minutes. Individual serum levels did not exceed 0.6 µg/mL. There was significant interindividual variation (Figure 3) in MEGX serum levels ($P = .008$), lidocaine ($P < .001$) levels, and for both combined ($P < .001$).

### Comparing the Groups

Across all four groups, serum lidocaine levels appeared to peak and then fall (Table 2). This peak occurred fastest in Group D, where an occlusive dressing was applied. This finding was in contrast to MEGX, the levels of which continued to increase in Groups A and B at the conclusion of the study. Serum MEGX levels began to fall in Groups C and D after 210 minutes. Peak serum levels of lidocaine and MEGX combined in Group D approached 0.60 µg/mL in one individual, although the mean for that group was 0.3 µg/mL. The therapeutic range for intravenous administration when treating dysrhythmias is 1.0-5.0 µg/mL. The greater applications of 4% lidocaine (5 g) resulted in higher serum concentration of both lidocaine and MEGX. This was also the case when exposure time was increased. Comparing Groups A and C, doubling the dose of 4% lidocaine from 2.5 to 5 g resulted in double the serum levels of MEGX and a 50% increase in the serum lidocaine levels ($P = .021$). When comparing Groups C

<table>
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<th>Group</th>
<th>Serum Lidocaine (µg/mL)</th>
<th>Time (min)</th>
<th>Serum MEGX (µg/mL)</th>
<th>Time (min)</th>
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<tr>
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<td>0.012</td>
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<tr>
<td>D&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.28</td>
<td>90</td>
<td>0.033</td>
<td>150</td>
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</tbody>
</table>

Abbreviations: MEGX, monoethylglycinexylidide.

<sup>a</sup>Group A: 2.5 g topical lidocaine, one hour, no occlusion.
<sup>b</sup>Group B: 5 g topical lidocaine, one half-hour, no occlusion.
<sup>c</sup>Group C: 5 g topical lidocaine, one hour, no occlusion.
<sup>d</sup>Group D: 5 g topical lidocaine, one hour, with occlusion.
and D, the addition of an occlusive dressing resulted in a tripling of the serum lidocaine levels and a doubling of the serum MEGX levels; both were statistically significant ($P < .001$). When comparing all four groups (Figure 4), there were significant differences between the combined serum concentrations of lidocaine and MEGX ($P < .001$).

### DISCUSSION

Topical lidocaine is a patient-friendly, noninvasive method of providing good analgesia for a variety of interventions, ranging from venipuncture to facial resurfacing. It is available to the patient over the counter without prescription, but unfortunately, there have been reported deaths following its application. This study has shown that, at specific doses applied over a certain surface area for a given length of time, serum lidocaine is within accepted safe limits. However, it has also shown that there is significant interindividual variability in the amount of lidocaine that is absorbed through the skin (and therefore, subsequent levels found in the blood), and that absorption is not necessarily related to dose or exposure. In some subjects, serum levels were double or triple those of other patients within the same group. All subjects were fit and well, with no medical history of note, so it was not possible to predict who would be “sensitive” to the topical lidocaine. These findings have important ramifications for unsupervised patient application, particularly in conjunction with occlusive dressings.

This interindividual variability has previously been described in liposuction, transmucosal lidocaine patches, breast augmentation, and transverse abdominis plane (TAP) block when a solution of lidocaine is infiltrated subdermally. $^{10,14}$ Kenkel et al examined five subjects undergoing liposuction who had lidocaine administered in their tumescent fluid. $^9$ They found that there was a large variation in the amount of lidocaine absorbed, as well as in the subsequent serum lidocaine and MEGX levels between their subjects. A study by Rygnestad et al yielded similar conclusions when 10 patients undergoing breast augmentation were given a mixture of xylocaine and adrenaline 5 mg/mL infiltrated into the subcutaneous and glandular tissue. $^{11,12}$

The rate of lidocaine metabolism can be affected by numerous factors, including hepatic function, $^{15}$ levels of plasma protein (which can be related to age), $^{16}$ renal failure, $^{17}$ cardiac failure, drugs such as antibiotics $^{18}$ and anti-depressants, $^{19}$ hypercapnia, or hypoxia. $^{20}$ Furthermore, lidocaine may also be metabolized in the skin, further affecting circulating serum levels. Rosléd et al confirmed that topically applied lidocaine is metabolized by enzymes (including cytochrome P450) in the skin, albeit at a much lower concentration than in the liver. $^{21}$ Their study also demonstrated that the level of MEGX expression varied...
within their experimental group and concluded that this finding was a result of differing individual concentrations of enzyme expression in the skin.

Our study has illustrated that there can be significant differences between individuals within each group irrespective of the applied dose of topical lidocaine. This finding may be attributable to enzymatic liver function or, indeed, saturation of the enzyme at the level of the skin. Further work should be done to ascertain which factor contributes more to lidocaine metabolism and subsequent blood serum circulating levels.

Therapeutic ranges for lidocaine are determined by the drug’s effective treatment of symptomatic dysrhythmias. The lowest serum concentration considered therapeutic is 1 µg/mL. One subject in Group D of our study had combined lidocaine and MEGX serum levels of 0.55 µg/mL, which occurred with an occlusive dressing, but the subject was asymptomatic; another subject in Group A (to which the low dose of lidocaine was applied) had serum levels of less than 0.1 µg/mL, but the subject described flushing and perioral tingling. The safe, therapeutic range for lidocaine as a topical analgesic has never been determined.

A review of the literature shows a paucity of data in the area of topical lidocaine and serum levels of metabolites after its application. Ogden et al examined the serum levels of lidocaine and tetracaine after an application of a 7% lidocaine and 7% tetracaine peel in adults. The authors found undetectable levels of lidocaine and tetracaine in the blood, but they did not look specifically at MEGX levels and subsequently concluded that the peel was safe. Our results demonstrate that serum lidocaine levels can peak before MEGX levels and that MEGX levels continue to rise even when lidocaine levels are falling, especially when occlusive dressings are applied. MEGX is an active, potent metabolite of lidocaine and therefore should be added to lidocaine to determine peak serum concentrations. There are many reports of studies evaluating serum concentrations of lidocaine only, but it is important to understand that failure to add the active metabolite may yield inaccurate total serum concentrations and therefore toxic effects.

Nestor et al analyzed the absorption of different quantities of topical lidocaine on the face, abdomen, and thigh with occlusive dressings in eight subjects. Although there were no actual documented data, the authors stated that blood results were less than the detectable limit of their analyzer (0.5 µg/mL) and concluded that topical lidocaine was safe for cutaneous procedures. However, blood samples were taken from their subjects at an interval of one, two, six, and 24 hours. Our study shows that peak levels of serum lidocaine occur in the blood at around 90 minutes with occlusion and that these levels were significantly different than if no occlusion were applied.

In two of the groups, MEGX levels continued to rise at 240 minutes; therefore, it would have been desirable to extend the time period to determine the point at which MEGX levels would become undetectable. The rate of topical lidocaine absorption, in addition to the concentration applied, is related to surface area. All of our subjects were treated in a similar facial area, but it would also have been interesting to see whether there was an increase in serum levels if the surface area was increased for a given concentration. Furthermore, we did not document any posttreatment symptoms experienced by our patients; further studies in this area would help to compile a toxicity profile for topical lidocaine. There are a large number of topical anesthetic preparations available, and there has been no comparative study documenting lidocaine levels in the blood with each type; rather, their safety has simply been assumed.

In summary, we would recommend future study of the effect of surface area in relation to the concentration of lidocaine applied with and without occlusive dressings, comparisons between the different topical anesthetic preparations and their absorption through skin, the effect on serum concentrations of reapplication of the topical lidocaine over a given time periods, and the effect on serum levels of lidocaine/MEGX when the stratum corneum is disrupted (for example, following pretreatment of the skin with an ablative laser).

**CONCLUSIONS**

Topical lidocaine preparations are increasingly being utilized as a patient-friendly form of noninvasive analgesia for a multitude of procedures. Some preparations are available over the counter for unsupervised patient application. Our study suggests that the unpredictability of lidocaine metabolism between individuals may be responsible for the reports of untoward effects with lidocaine application, both in the clinical setting and by individuals at home. Our data document the variability of lidocaine and MEGX serum levels in the blood after topical facial application of 4% lidocaine over varying time periods, with and without occlusion. A more comprehensive body of toxicity studies is needed before we can categorically determine that topical lidocaine is truly safe and the limits to which that safety applies.

**Disclosures**

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REFERENCES


