ABSTRACT. Objectives. The purpose of this study was to determine the optimal configuration of an investigational, single-use, needle-free, drug system (ALGRX 3268) that delivers powdered lidocaine into the epidermis for the rapid production of local anesthesia among pediatric subjects undergoing venipuncture.

Methods. Children 3 to 18 years of age were randomly allocated to receive 1 of 3 treatments, ie, (1) placebo, (2) a system configured to deliver 0.25 mg of lidocaine, or (3) a system configured to deliver 0.5 mg of lidocaine, at the antecubital fossa 2 to 3 minutes before venipuncture. Three age groups were included, ie, 3 to 7 years, 8 to 12 years, and 13 to 18 years. Two sets of pain rating scales were used, the Faces Pain Scale-Revised for the youngest age stratum and a visual analog scale for the oldest age stratum. Children in the middle age stratum used both scales.

Results. One-hundred forty-four subjects completed the study. For all ages combined, there was a statistically significant and clinically meaningful reduction in pain scores for subjects who received 0.5 mg of lidocaine, compared with placebo. The reduction in pain after 0.25 mg of lidocaine did not achieve statistical significance.

Conclusions. Both active configurations were safe and well tolerated by pediatric subjects undergoing venipuncture at the antecubital fossa. ALGRX 3268 at 0.5 mg, administered 2 to 3 minutes before venipuncture, produced significantly lower pain scores, compared with placebo. Pediatrics 2005;115:e393–e398. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-0656; pain, venipuncture, venous cannulation, pediatric, children, lidocaine, topical anesthetic.

ABBREVIATIONS. VAS, visual analog scale; FPS-R, Faces Pain Scale-Revised.

Needle insertion for venipuncture or intravenous cannulation is a painful, frightening, distressful procedure for children.1–4 Topical anesthetics such as EMLA (AstraZeneca, Wilmington, DE; a eutectic mixture of 2.5% lidocaine and 2.5% prilocaine) and L.M.X.4 (Ferndale Laboratories, Ferndale, MI; 4% lidocaine) have been shown to provide effective local anesthesia for venipuncture and intravenous cannulation.5–9 However, a period of 30 to 90 minutes, depending on the product and the procedure, may be required between application and the onset of effect, limiting the usefulness of these products in busy health care settings and for emergency department applications.9–11

The delivery of lidocaine to the skin through iontophoresis has also been investigated among children undergoing venipuncture or intravenous catheter insertion.12,13 Iontophoretic lidocaine systems feature a controller and disposable, drug-saturated electrodes and use the application of an electric current to carry ionized lidocaine through the skin.13 Lidocaine iontophoresis has been shown to be more effective than placebo in reducing the pain of venipuncture and to be comparable to EMLA for intravenous catheter placement.12,13 However, studies indicate that lidocaine iontophoresis requires up to 15 minutes for onset of effect.14

This study was undertaken to evaluate an investigational, needle-free, single-use, prefilled, disposable system (ALGRX 3268; AlgoRx Pharmaceuticals Inc, Secaucus, NJ) capable of delivering fine, dry, powdered lidocaine into the epidermis for the rapid production (within 1–3 minutes) of local anesthesia before venipuncture. The system is placed against the skin at the site of venipuncture and is triggered simply by pressing of the actuator button (Fig 1). Pressurized, medical-grade, helium gas within the system accelerates lidocaine particles to velocities sufficient to penetrate the outer skin layers and produce local anesthesia. In this investigation, systems configured to deliver 0.25 mg or 0.5 mg of lidocaine were compared with placebo among children 2 to 3 minutes before venipuncture. The primary objective of the study was to determine the optimal configuration of ALGRX 3268 to reduce safely the pain of venipuncture at the antecubital fossa among children 3 to 18 years of age.
METHODS

Study Design

This was a single-center, randomized, double-blind, placebo-controlled, single-dose, parallel-group study among pediatric subjects who were scheduled to undergo venipuncture. Three age groups were used, ie, 3 to 7 years, 8 to 12 years, and 13 to 18 years. Within each age group, subjects were randomly allocated to receive 1 of 3 treatments, (1) placebo (system containing no lidocaine), (2) ALGRX 3268 configured to deliver 0.25 mg of lidocaine, or (3) ALGRX 3268 configured to deliver 0.5 mg of lidocaine. All 3 configurations tested, including the placebo, contained helium gas pressurized at 20 bar. The active configurations contained powdered lidocaine at a particle size of 35 μm, and the placebo contained an empty drug cassette. Treatments were administered to the antecubital fossa 2 to 3 minutes before venipuncture. The study was designed to include 48 subjects of each age group, for a total of 144 evaluable subjects. Within each age group, the distribution of placebo, 0.25 mg of lidocaine, and 0.5 mg of lidocaine was 1:1:1.

Subject Selection

Pediatric subjects, 3 to 18 years of age, who were scheduled to undergo venipuncture at the antecubital fossa were allowed to participate in the study if they had sufficient cognitive skills to identify faces depicting the extremes of pain on the Faces Pain Scale-Revised (FPS-R) (Fig 2)\textsuperscript{15,16} and/or the extremes of pain on a 10-cm visual analog scale (VAS). Obligatory written consent was required and was obtained from a parent or legal guardian for all subjects. Subjects were ineligible for study participation if (1) they had a history of allergic reactions to any local anesthetic, (2) they had any medical condition that might adversely affect the performance of the study, (3) it was deemed that venipuncture could not be accomplished cleanly, (4) they had active local infections or other skin pathologic conditions at the antecubital fossa, (5) they had tattoos, surgical scars, ports, implantable devices, or skin conditions that might interfere with treatment or skin site assessments, (6) they had undergone venipuncture at the proposed site within the prior 2 weeks (or longer, if bruising was apparent), or (7) they were uncooperative or exceptionally upset before treatment with the study medication.

Ethical Considerations

This study was conducted in accordance with good clinical practice and the ethical principles that have their origins in the Declaration of Helsinki, Title 21 of the Code of Federal Regulations, sections 50, 56, and 312, and International Conference on Harmonization Guidance Document E6 (“good clinical practice”). The study protocol and consent documents were approved by an independent ethics committee before initiation of the trial.

Procedures

Demographic data, including age, gender, race, weight, and height, were collected for all subjects. Brief medical history and physical examination results and vital signs were recorded. Children were randomly allocated to receive 1 of 3 treatments, ie, (1) placebo, (2) 0.25 mg of lidocaine, or (3) 0.5 mg of lidocaine. All personnel involved in the study were blinded with respect to study treatments. For all treatments, ALGRX 3268 was pressed firmly against the site of the antecubital fossa in which venipuncture was to occur and was triggered by pressing the actuator button. Immediately after treatment with ALGRX 3268, subjects were asked to rate the comfort of study drug administration. Venipuncture was performed at the antecubital fossa with either a 20- or 21-gauge needle and syringe or a 20- or 21-gauge “butterfly” needle, 2 to 3 minutes after use of the delivery system. Subjects were then asked to rate the pain of venipuncture. The site of treatment was assessed for signs of erythema, edema, pruritus, and hemorrhage or petechiae at 1, 30, and 60 minutes after treatment.

Measurements

Subjects in the youngest age stratum used the FPS-R to rate the pain of venipuncture. This scale consists of 6 faces depicting increasing severity of pain (Fig 2). Although the subjects did not assign a numerical score, a numerical score of 0, 2, 4, 6, 8, or 10 was assigned to each face when the data were analyzed for this report, with 0 representing the face with no pain and 10 representing the face with the most severe pain. Subjects in the oldest age stratum used a 10-cm VAS, with 0 for no pain and 10 for extreme pain, to rate the pain of venipuncture. Subjects in the middle age stratum used both rating scales to rate the pain of venipuncture.

The site of application was assessed for evidence of erythema, edema, pruritus, and hemorrhage or petechiae before treatment and 1, 30, and 60 minutes after treatment. A set of numerical

![Fig 1. ALGRX 3268.](http://www.painsourcebook.ca)

![Fig 2. FPS-R.](http://www.painsourcebook.ca) (Reproduced with permission from Pain. 2001;93:176; the scale was adapted from ref 16; administration instructions are available at: www.painsourcebook.ca.)
scales, incorporating the Draize scale for assessment of erythema and edema,\textsuperscript{17} was used to record the degree of each of these conditions, if present, at each time point (Table 1).

To evaluate the tolerability of treatment, subjects were asked to rate the comfort of the delivery system immediately after treatment and before venipuncture. Subjects in the youngest age group used the FPR-S (scored from 0 to 10) and subjects in the oldest group used the 10-cm VAS, with 0 for no discomfort and 10 for extreme discomfort. Children in the middle age group used both scales.

**Statistical Analyses**

The primary efficacy parameter was the combined treatment effect for all age groups, as measured with the FPS-R scores for the youngest age stratum, the VAS scores for the oldest age stratum, and both the FPS-R and VAS scores for the middle age stratum. Two primary comparisons were made, ie, 0.25 mg of lidocaine versus placebo and 0.5 mg of lidocaine versus placebo.

Because 2 different rating scales were used to evaluate the primary efficacy effect, a meta-analysis with Glass’s /\textsuperscript{9254} was applied to the 2 sets of scores.\textsuperscript{18} For the youngest age group, the standardized effect size was estimated from the FPS-R scores for 0.25 mg of lidocaine, compared with placebo, with an analysis of variance model. Similarly, for the oldest age group, the standardized effect size was estimated from the VAS scores for comparison. For the middle age group, the standardized effect size was estimated from both the FPS-R scores and the VAS scores for the same comparison. Combined effect sizes for all ages for 0.25 mg of lidocaine versus placebo were then estimated in 2 ways. In the first primary efficacy analysis, the combined treatment effect was estimated from the FPS-R scores for the youngest and middle age strata and the VAS scores for the oldest age stratum. In the second analysis, the combined treatment effect was estimated from the FPS-R scores for the youngest age stratum and the VAS scores for the middle and oldest age strata. The same methods were used to compare the efficacy of 0.5 mg of lidocaine versus placebo. A 2-sided test with a significance level of .05 was used for all hypothesis testing.

**RESULTS**

One-hundred forty-five subjects were randomized to treatment, and 144 subjects completed the trial. The demographic characteristics of each of the 3 treatment groups were similar (Table 2).

Results of both combined efficacy analyses are presented in Table 3. There was a statistically significant reduction in pain for subjects treated with 0.5 mg of lidocaine, compared with placebo ($P = .039$), in the combined efficacy analysis that used the VAS scores for the middle age group. The reduction in pain for subjects treated with 0.25 mg of lidocaine did not achieve statistical significance, compared with placebo ($P = .064$). When the combined efficacy analysis was performed with the FPS-R scores for the middle group, there was also a trend for the active treatments, compared with placebo, but these were not statistically significant differences (0.5 mg of lidocaine versus placebo effect size: $-0.389$, $P = .060$; 0.25 mg of lidocaine versus placebo effect size: $-0.325$, $P = .115$).

This study was not powered to detect a treatment effect within each of the 3 age groups; however, the pain scores for each age group were examined individually in a secondary efficacy analysis. The mean scores rating the pain of venipuncture for all of the age groups with the FPS-R and the VAS are presented in Table 4. For subjects 8 to 18 years of age, the pooled effect size, based on the percentage reduction in VAS pain scores with 0.5 mg of lidocaine, compared with placebo, was 47%. For subjects 3 to 12
years of age, the pooled effect size, based on the percentage reduction in FPS-R pain scores with 0.5 mg of lidocaine, compared with placebo, was 31%.

Of the 145 randomized subjects, 2 subjects experienced non-application site adverse events. One 3-year-old female subject experienced an attack of panic after treatment with placebo and was unable to complete the study. No other subjects experienced such an event, and the children were very accepting of the delivery system. A 14-year-old male subject who was a transplant recipient was hospitalized for evaluation of elevated plasma concentrations of tacrolimus, which were considered unrelated to study participation.

The mean scores for erythema tended to be higher for subjects who received active treatments, compared with placebo; however, scores were generally low for subjects of all ages (Table 5). At each assessment, the mean erythema scores were <1.0 for all ages, for both active configurations. A score of 1 indicated very slight, barely perceptible erythema. Similarly, the mean scores for hemorrhage/petechiae were higher for subjects who received active treatments, compared with placebo (Table 5). At each assessment, mean hemorrhage/petechiae scores were <1.5 for all ages, for both active configurations. A score of 1 indicated isolated petechiae up to 5 and a score of 2 indicated isolated but >5 petechiae. No subjects developed edema at any time point, and only 1 subject, who had received placebo, reported occasional pruritus at 2 time points.

The subjects’ assessment of the tolerability of treatment with this delivery system was rated with the FPS-R (scores of 0-10) for the youngest and middle age groups and the VAS (scores of 0-10 cm) for the middle and oldest age groups. Mean FPS-R scores for subjects 3 to 12 years of age were 0.44 for subjects who received 0.25 mg of lidocaine, 0.31 for subjects who received 0.5 mg of lidocaine, and 0.61 for subjects who received placebo. Mean VAS scores for subjects 8 to 18 years of age were 0.12 cm for subjects who received 0.25 mg of lidocaine, 0.32 cm for subjects who received 0.5 mg of lidocaine, and 0.35 cm for subjects who received placebo. The scores indicate that each configuration was well tolerated by all age groups.

DISCUSSION

This study demonstrated a reduction in the pain of venipuncture at the antecubital fossa among pediatric subjects, with a rapid onset of 2 to 3 minutes after administration of lidocaine, with this novel delivery system. Both active treatments reduced the pain of venipuncture, with the treatment effect of ALGRX 3268 configured to deliver 0.5 mg of lidocaine being statistically significant, compared with placebo. The reduction in pain seen with ALGRX 3268 configured to deliver 0.25 mg of lidocaine did not achieve statistical significance, compared with placebo.

For the 8- to 12-year-old group, 2 pain assessment scales, the VAS and the FPS-R, were used to assess the pain of venipuncture. A greater effect size was reported when these subjects used the VAS, compared with the FPS-R. The effect size for 0.5 mg of
Lidocaine was 72.3% with the VAS and 61.5% with the FPS-R. Although the FPS-R scores were found to be highly correlated with the VAS scores (correlation coefficient: 0.67; \( P < .0001 \)) for this age group, the combined efficacy analyses that used the VAS scores for the middle group demonstrated a statistically significant difference, whereas the analysis that used the FPS-R scores did not. The difference in pain scores was statistically significant for 0.25 mg of lidocaine vs placebo (0.382; 95% confidence interval: 0.386 to 0.786; \( P = .064 \)) and for 0.5 mg of lidocaine vs placebo (0.428; 95% confidence interval: 0.834 to 0.022; \( P = .039 \)).

### Table 3. Combined Efficacy Analyses of All Age Groups

<table>
<thead>
<tr>
<th>Pairwise Comparison</th>
<th>Effect Size</th>
<th>95% Confidence Interval</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25 mg of lidocaine vs placebo</td>
<td>-0.382</td>
<td>-0.786 to 0.022</td>
<td>.064</td>
</tr>
<tr>
<td>0.5 mg of lidocaine vs placebo</td>
<td>-0.428</td>
<td>-0.834 to 0.022</td>
<td>.039</td>
</tr>
<tr>
<td>0.25 mg of lidocaine vs 0.5 mg of lidocaine</td>
<td>0.024</td>
<td>-0.378 to 0.426</td>
<td>.908</td>
</tr>
</tbody>
</table>

### Table 4. Mean Pain Scores After Venipuncture

<table>
<thead>
<tr>
<th>Mean FPS-R scores rating pain of venipuncture (scale of 0–10)</th>
<th>0.25 mg of Lidocaine</th>
<th>0.5 mg of Lidocaine</th>
<th>Placebo</th>
<th>Effect Size of 0.5 mg of Lidocaine, %*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages 3–7 y</td>
<td>No. 16</td>
<td>16</td>
<td>16</td>
<td>-26.0</td>
</tr>
<tr>
<td>Mean</td>
<td>1.63</td>
<td>2.25</td>
<td>3.00</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>3.12</td>
<td>2.41</td>
<td>3.35</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0–10</td>
<td>0–8</td>
<td>0–10</td>
<td></td>
</tr>
<tr>
<td>Ages 8–12 y</td>
<td>No. 16</td>
<td>16</td>
<td>16</td>
<td>-61.5</td>
</tr>
<tr>
<td>Mean</td>
<td>1.00</td>
<td>0.38</td>
<td>1.13</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>1.26</td>
<td>0.81</td>
<td>1.45</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0–4</td>
<td>0–2</td>
<td>0–4</td>
<td></td>
</tr>
<tr>
<td>Ages 3–12 y</td>
<td>No. 32</td>
<td>32</td>
<td>32</td>
<td>-31.3</td>
</tr>
<tr>
<td>Mean</td>
<td>1.31</td>
<td>1.31</td>
<td>2.06</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>2.36</td>
<td>2.01</td>
<td>2.71</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0–10</td>
<td>0–8</td>
<td>0–10</td>
<td></td>
</tr>
</tbody>
</table>

### Table 5. Mean Scores for Erythema and Hemorrhage/Petechiae for All Ages

<table>
<thead>
<tr>
<th>Mean erythema scores for all ages</th>
<th>0.25 mg of Lidocaine (( N = 48 ))</th>
<th>0.5 mg of Lidocaine (( N = 48 ))</th>
<th>Placebo (( N = 49 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>( 1 ) min*</td>
<td>0.1</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>( 30 ) min</td>
<td>0.4</td>
<td>0.7</td>
<td>0.1</td>
</tr>
<tr>
<td>( 60 ) min</td>
<td>0.4</td>
<td>0.8</td>
<td>0.0</td>
</tr>
</tbody>
</table>

### Table 6. Mean Hemorrhage/Petechiae scores for all ages

<table>
<thead>
<tr>
<th>Mean hemorrhage/petechiae scores for all ages</th>
<th>0.25 mg of Lidocaine (( N = 48 ))</th>
<th>0.5 mg of Lidocaine (( N = 48 ))</th>
<th>Placebo (( N = 49 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>( 1 ) min*</td>
<td>1.3</td>
<td>1.4</td>
<td>0.0</td>
</tr>
<tr>
<td>( 30 ) min</td>
<td>1.2</td>
<td>1.2</td>
<td>0.0</td>
</tr>
<tr>
<td>( 60 ) min</td>
<td>1.0</td>
<td>1.1</td>
<td>0.0</td>
</tr>
</tbody>
</table>

* Indicates percentage reduction in pain with 0.5 mg of lidocaine, compared with placebo, calculated as \((\text{mean pain score for placebo} - \text{mean pain score for active treatment})/\text{combined SD} \times 100\).
scores reported with the 2 scales may account for the different results.

The results of studies among children with acute pain suggested the minimal, clinically significant difference in pain scores to be 1 or 2 on a VAS of 1 to 10.19,20 Slightly smaller differences were seen in this study, as expected because of the low mean scores for placebo treatment (means of 2.06 with the FPS-R for 3-12-year-old subjects and 1.12 with the VAS for 8-18-year-old subjects). Most of the subjects in this study had chronic medical conditions, and it was suspected that venipuncture in general was perceived as being less painful by these children than it would be by otherwise healthy children. Similar findings were discussed in a recent literature review in which Ramelet et al21 reported that the severity of illness was likely to affect both physiologic and behavioral pain responses that would be demonstrated normally by healthy children. Despite the generally low pain scores reported by this population, a statistically significant difference in pain was detected with treatment of 0.5 mg of lidocaine, compared with placebo.

The safety assessments indicated that both configurations of this delivery system were capable of delivering lidocaine safely. Subjects who received active treatment appeared to be more likely to develop erythema and petechiae than those who received placebo. However, the erythema was mild in all cases and the number of petechiae was small. Therefore, these findings were not considered to be clinically significant. The application of ALGRX 3268 was well tolerated by children in all age groups.

This simple, needle-free, easy-to-use, disposable, lidocaine delivery system provided for rapid onset of local anesthesia before venipuncture among pediatric subjects. ALGRX 3268 differs from other available options for the administration of lidocaine, such as topical anesthetic creams and iontophoresis, in both time of onset and ease of administration. ALGRX 3268 works within 1 to 3 minutes, in contrast to 30 to 90 minutes for currently available, topical anesthetic creams and 10 to 15 minutes for iontophoresis. Its rapid onset and ease of use should decrease the nursing time associated with topical dermal anesthetics. In addition, the rapid onset time should allow for the routine use of ALGRX 3268 in settings such as busy emergency departments, inpatient wards, and clinics, where the longer onset time for currently available, topical anesthetic products is a barrier to use.

CONCLUSIONS

ALGRX 3268 configured to deliver 0.5 mg of lidocaine can reduce the pain of venipuncture at the antecubital fossa rapidly, safely, and effectively among pediatric subjects, when administered 2 to 3 minutes before the procedure. This needle-free device was well tolerated by subjects in all age groups. The safe rapid achievement of local dermal anesthesia with this simple, needle-free system offers a reduction in the pain associated with venipuncture, as well as a reduction in the nursing time required to achieve this goal.

ACKNOWLEDGMENTS

This research was supported by AlgoRx Pharmaceuticals Inc. We gratefully acknowledge Joanna Czolnowska, RN, Grazyna Spieszko, RN, and Elzbietta Tomaszewskwa, RN, for their assistance during this study.

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Rapid, Needle-Free Delivery of Lidocaine for Reducing the Pain of Venipuncture Among Pediatric Subjects
Marek Migdal, Elzbieta Chudzynska-Pomianowska, Elizabeth Vause, Eugenia Henry and Jeffrey Lazar

*Pediatrics* 2005;115:e393
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