Tetracaine versus lidocaine-prilocaine for preventing venipuncture-induced pain in children

H.J.M. van Kan, A.C.G. Egberts, W.P.M. Rijnvos, N. ter Pelkwiik, and A. W. Lenderink

Abstract: The efficacy of tetracaine cream versus that of lidocaine-prilocaine cream for the prevention of pain in children undergoing venipuncture was studied.

Hospital inpatients 1–15 years of age received, on the back of each hand, a 30-minute application of tetracaine 4% cream or a 60-minute application of lidocaine-prilocaine cream (EMLA, Astra) before undergoing scheduled venipuncture. The phlebotomists in this open, randomized trial evaluated the efficacy of the cream at the moment of venipuncture as adequate, inadequate, or inconclusive. Blood samples were taken immediately after venipuncture from 10 patients one to five years of age to measure the serum concentrations of tetracaine and its metabolite, N-butyl-p-aminobenzoic acid.

Lidocaine-prilocaine cream was significantly more efficacious in preventing pain than tetracaine 4% cream (97% of the former group [n = 32] had adequate pain relief, compared with 76% of the latter [n = 34]). The only adverse effects observed were mild local erythema in the tetracaine group and local skin blanching in the lidocaine-prilocaine group. No tetracaine could be detected in serum, and the serum concentrations of N-butyl-p-aminobenzoic acid ranged from 0 to 1.8 mg/L.

Statistically, lidocaine-prilocaine cream was more efficacious than tetracaine 4% cream, but the difference is of minor clinical significance and is outweighed by the practical advantages of tetracaine 4% cream, namely the shorter application time, vasodilation and lower cost.

Index terms: Anesthetics, local; Blood levels; N-butyl-p-aminobenzoic acid; Creams; Drug comparisons; Injections; Lidocaine; Pain; Pediatrics; Phlebotomy; Prilocaine; Tetracaine; Topical preparations; Toxicity

Am J Health-Syst Pharm. 1997; 54:388-92

Percutaneous local anesthesia is of particular value in pediatric practice. Stress can make relatively minor procedures like venipuncture and catheter insertion more difficult for both health care provider and child. Since infiltration of local anesthetics is painful in itself, a topical preparation allowing the anesthetic drug to penetrate the skin and reach the underlying nociceptors is preferable. The ideal formulation should provide rapid, deep, and relatively prolonged anesthesia with minimal adverse effects.

Although research in this area has been ongoing for almost 40 years, the first effective formulation (EMLA, Astra) was introduced only several years ago. The main research problem was developing a formulation allowing sufficient anesthetic drug to penetrate intact skin in a short period. The stratum corneum can be an effective barrier to drug absorption. To achieve adequate anesthesia, aspects of both the local anesthetic drug and the formulation are relevant. EMLA is a hydrophilic cream that contains a eutectic mixture of the local anesthetics lidocaine 2.5% and prilocaine 2.5% in a suitable base.

The efficacy of the lidocaine-prilocaine cream in preventing pain has been well demonstrated for procedures like venipuncture and removal of molluscum contagiosum lesions. The product, however, has some disadvantages: (1) It takes 60 minutes under...
an occlusive dressing to provide adequate analgesia, (2) application of lidocaine-prilocaine cream often results in vasoconstriction, which can make venipuncture more difficult, and (3) widespread use of EMLA is costly in the Netherlands (equivalent to approximately U.S. $2.50 per application).

Recent experiments in vitro and in vivo have shown that tetracaine 4% in a suitable formulation might be an alternative. These studies suggest that a tetracaine-containing formulation may provide analgesia with a faster onset, a longer duration of action, and a venodilating effect. Furthermore, such a formulation can be easily compounded at low cost (approximately $1.20 per application). However, no randomized comparative studies in children have, until now, been published.

We studied the efficacy of a tetracaine 4% cream versus that of lidocaine-prilocaine cream for the prevention of pain in children undergoing venipuncture, and examined the systemic absorption of tetracaine.

**Methods**

**Design.** A double-blind study was not feasible because of a visible difference in local adverse effects between lidocaine-prilocaine (skin blanching caused by vasoconstriction) and tetracaine (mild erythema caused by vasodilation). Also, the amounts of cream to be applied were different. Therefore an open randomized design was chosen. To obtain similar age distributions in the two groups, three age categories were defined: 1–5, 6–10, and 11–15 years. At least 20 subjects were to be included in each group. Patients were stratified by age and then randomly assigned to receive lidocaine–prilocaine (EMLA) or tetracaine 4% cream. The study was approved by the medical ethics committee of the hospital.

**Subjects.** Candidates for the study were children 1–15 years of age who were admitted to the pediatric ward and had to undergo a first venipuncture for blood collection or placement of an indwelling catheter. Children with a known hypersensitivity to local anesthetic drugs or with nonintact skin at the application site were excluded. Written informed consent was required for subject inclusion and had to be given by one of the parents (or by the children themselves if they were older than 12).

**Medication.** Lidocaine–prilocaine cream was purchased from Astra (Rijswijk, Netherlands). Tetracaine 4% cream was compounded by the hospital’s pharmacy. Ingredients of this cream were tetracaine base 4 g (Sigma Chemical Company, St. Louis, MO), sorbitan olate 0.2 mL, polysorbate 80 0.2 mL, arachis oil 10 g (OPG Pharma, Utrecht, Netherlands), and carbomer 934P 1% gel 86 g (compounded by the pharmacy). The pH of the tetracaine cream was 7.0.

Approximately 2.5 g of lidocaine-prilocaine cream was applied to the back of each hand in subjects in that group and covered with an occlusive dressing (Tegaderm, 6 × 7 cm, 3M, Zoeterwoude, Netherlands) for 60 minutes, as is recommended by the manufacturer. Alternatively, tetracaine 4% cream 1 g was applied to each hand in the same way, but for only 30 minutes. Both hands received cream to enable multiple puncture attempts, if necessary. Before venipuncture, the occlusive dressing and the cream residue were removed. Needles of various sizes were used as necessary; this is routine practice on the pediatric ward.

The subjects were treated between January and November 1994.

**Study variables.** At the moment of venipuncture, the phlebotomist judged the effect of the cream as adequate, inadequate, or inconclusive. The number of phlebotomists was limited to seven; each had had routine experience in pediatric venipuncture. The number of attempts needed for successful venipuncture, the times of cream application and removal, and the age, sex, and body weight of each subject were recorded.

To determine the extent of systemic absorption of tetracaine, blood samples were taken from the first 10 subjects ages one to five years in the tetracaine group. This age category was chosen because it represents the highest expected systemic absorption of tetracaine.

Blood sampling was done immediately after venipuncture. The first blood drops after venipuncture were discarded to avoid contamination with the cream. The blood samples were collected in glass tubes containing 50 mg of sodium pyrosulfite and 20 mg of sodium hydroxide (freeze-dried). The serum was stored at −70 °C. Sample collection and storage were completed within 15 minutes after venipuncture to prevent degradation of tetracaine.

**Analysis of serum samples.** The serum samples were first treated by a solid-phase extraction procedure. A solid-phase cartridge (Sep-Pak Vac tC18, 3 mL; Waters, Etten-Leur, Netherlands) was used for each sample. Each cartridge was washed twice with methanol 2 mL (E. Merck, Amsterdam, Netherlands) and twice with water 2 mL. Next, 1 mL of serum and 250 µL of the internal standard solution, desmethyldiazepam (Roche, Mijdrecht, Netherlands) 10 mg/L in water, were passed through the cartridge under mild vacuum. The cartridge was washed twice with water 2.5 mL and dried by centrifugation at 4000 rpm. Diethyl ether 3 mL (OPG Pharma) and then 3 mL of methanol were passed through, and the eluate was dried under nitrogen gas flow at 40 °C.

The residue was reconstituted with 100 µL of eluant for a reverse-phase, high-performance liquid chromatography system (Merck/Hitachi HPLC with L-3000 diode-array detector and L-6200 gradient pump, isocratic mode, E. Merck). The eluant used in the system was prepared by adding 470 mL of acetonitrile to a mixture consisting of 530 mL of water, 300 µL of...
phosphoric acid 85%, and 146 µL of triethylamine adjusted to pH 3.30 with 10 M potassium hydroxide. The column was a LiChrospher 100 RP-18, end-capped, 5 µm column (LiChroCART 125-4, E. Merck); the flow rate was 0.6 mL/min. Twenty microliters of the reconstituted residue was injected into the system. Ultraviolet light detection took place at 310 nm (monitor wavelength).

Reference samples of tetracaine and its metabolite, N-butyl-p-aminobenzoic acid (Aldrich, Milwaukee, WI), were analyzed as described above. All reagents were purchased from E. Merck. The solvents were of analytical grade. The procedures for measuring tetracaine and its metabolite were validated and executed in accordance with good laboratory practice.

The between-day and within-day coefficients of variation (n = 6) were 3.3% and 5.9%, respectively, for tetracaine, and 3.0% and 5.1% for N-butyl-p-aminobenzoic acid. The detection limit was 0.05 mg/L for both tetracaine and N-butyl-p-aminobenzoic acid.

**Statistical analysis.** The lidocaine-prilocaine cream was estimated to be effective in 95% of patients. To detect a 20% difference in efficacy with a power of 80%, at least 68 evaluable subjects were needed.

The continuous variables age and body weight were analyzed with the Mann-Whitney rank-sum test because of the skewed distribution. The same test was used for analyzing differences in performance scores. The categorical variable sex was tested with the chi-square test with continuity correction. Fisher’s exact test (two sided) was used to test differences in the number of children needing two attempts at successful venipuncture.

A priori level of significance of 0.05 (two sided) was used to test differences in the number of subjects (lidocaine–prilocaine, n = 32; and tetracaine, n = 34) were evaluable. Demographic data on these children are shown in Table 1; there were no significant differences between the two groups.

The phlebotomists indicated adequate, inadequate, or inconclusive performance for tetracaine 4% cream in 76%, 15%, and 9% of the children in that group, respectively. For lidocaine–prilocaine cream, these figures were 97%, 3%, and 0%. The percentage of evaluations that were adequate was significantly higher in the lidocaine-prilocaine group (p = 0.02).

In five patients in the lidocaine-prilocaine group, two attempts were needed for successful venipuncture, whereas in the tetracaine group this occurred for only one subject. The difference was not significant (p = 0.10).

Apart from mild erythema at the site of application of tetracaine cream and local skin blanching in the lidocaine–prilocaine group, no adverse effects were reported. The observed skin reactions lasted for several hours after removal of either cream.

Tetracaine was not detectable in the serum of any of the 10 subjects in the lowest age category (one to five years) (Table 2). N-butyl-p-aminobenzoic acid was detectable in seven of these subjects.

**Discussion**

Our study confirms the efficacy of a tetracaine 4% cream in preventing pain in children undergoing venipuncture. Our results are in line with the reported 80% efficacy of a tetracaine 4% formulation in two open trials in children.7,8 The lidocaine-prilocaine cream was more efficacious than the tetracaine 4% cream. We consider the difference in efficacy, although statistically significant, to be of minor clinical importance. Tetracaine 4% cream remains the preparation of choice in our hospital because of its practical advantages over lidocaine-prilocaine cream (i.e., shorter application time, vasodilation, and lower cost).

Our study has several limitations. First, we did not use a standardized rating scale for pain assessment. Although several scales for rating pain in children are available, we used a simple dichotomous rating system. Second, the number of children in the lowest age category (one to five years) was small, and the results may not be generalizable to older children.

### Table 1. Demographic Characteristics of Study Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lidocaine–Prilocaine (n = 32)</th>
<th>Tetracaine (n = 34)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (% girls)</td>
<td>16 (50)</td>
<td>10 (29)</td>
<td>0.14a</td>
</tr>
<tr>
<td>Median age in years (range)</td>
<td>8 (1–15)</td>
<td>6 (1–15)</td>
<td>0.36b</td>
</tr>
<tr>
<td>Median body weight in kg (range)</td>
<td>26.5 (9.3–74.0)</td>
<td>23.5 (9.1–74.0)c</td>
<td>0.83c</td>
</tr>
</tbody>
</table>

aChi-square test with continuity correction and 1 degree of freedom (two sided).
bMann-Whitney rank-sum test (two sided).
cValue missing for one subject.

### Table 2. Serum Concentrations of Tetracaine and N-Butyl-p-aminobenzoic Acid at Time of Venipuncture

<table>
<thead>
<tr>
<th>Subject</th>
<th>Tetracaine Concentration (mg/L)</th>
<th>N-Butyl-p-aminobenzoic Acid Concentration (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.05</td>
<td>0.48</td>
</tr>
<tr>
<td>B</td>
<td>0.05</td>
<td>0.76</td>
</tr>
<tr>
<td>C</td>
<td>0.05</td>
<td>0.06</td>
</tr>
<tr>
<td>D</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>E</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>F</td>
<td>0.05</td>
<td>0.91</td>
</tr>
<tr>
<td>G</td>
<td>0.05</td>
<td>1.80</td>
</tr>
<tr>
<td>H</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>I</td>
<td>0.05</td>
<td>0.08</td>
</tr>
<tr>
<td>J</td>
<td>0.05</td>
<td>0.39</td>
</tr>
</tbody>
</table>
available, no single uniform scale was found suitable for the wide age range (1–15 years) of the children we enrolled. We chose to have the phlebotomists assess pain in a simple, clinically relevant way. Venipuncture is a relatively brief procedure in which the patient may basically show a pain reaction or not. Second, it was impossible to perform a correct double-blind comparison. The amounts of cream to be applied, as well as the application durations, differed between the two products. The amounts of the creams could not be equalized without affecting the concentrations of the active ingredients and therefore efficacy. Furthermore, the objective of our study was to compare the advised one-hour application time for lidocaine–prilocaine cream with a shorter application time for tetracaine. Reduction of application time is seen as a clear advantage in daily clinical practice. Similar investigations comparing the two creams were in fact incorrectly called double-blind. This problem might have been solved by including a placebo cream with various application times, but this was considered unethical.

Some studies have shown a time-dependent efficacy of topical tetracaine preparations, indicating that our goal of reducing the application time to 30 minutes may have been too optimistic. One such trial compared lidocaine–prilocaine cream (EMLA) and a tetracaine 5% formulation in 120 gynecological patients. Both creams were applied for either 30 or 60 minutes. Although in this study there were no significant differences in efficacy, the results suggested that the efficacy of tetracaine could be improved by using a 60-minute application time instead of 30 minutes. Woolfson et al. observed a significant time dependence of the efficacy of tetracaine 4% cream; efficacy was maximal (89%) after 41–60 minutes. One could propose an application time of at least 45 minutes instead of 30 minutes to help ensure optimum efficacy of tetracaine 4% cream. However, in our hospital 30 minutes for tetracaine 4% cream instead of the recommended 60 minutes for lidocaine–prilocaine cream is considered to provide such a substantial practical advantage that no change is considered necessary.

We used a tetracaine 4% cream formulation similar to that reported by McCafferty et al. Miller et al. found that a combination of tetracaine base and salt was most efficacious when applied as a solution on a dermal patch. It is unknown whether these results can be extrapolated to a cream.

Observations repeatedly described in the literature, that application of lidocaine–prilocaine cream leads to local vasoconstriction, and that tetracaine 4% cream has the opposite effect, were confirmed in our study. This is possibly why a difference (although not a significant one) was found in the number of patients for whom two attempts were needed for successful venipuncture. Venous access may be facilitated when tetracaine preparations are used.

The only adverse effects observed were mild local erythema for several hours for tetracaine 4% cream and local skin blanching for lidocaine–prilocaine cream. The local erythema was presumably caused by the vasodilating effect of tetracaine.

We were not able to detect tetracaine in the blood. Mazumdar et al. and Small et al. reported the same results after application to adult skin of the maximum recommended dose of tetracaine (2 g of a 5% cream). Some have questioned the safety of topically applied tetracaine, along with that of other ester-type local anesthetics. Reported cases of toxicity occurred, however, after application to mucous membranes instead of intact skin. Systemic absorption of tetracaine when applied to intact skin is much lower and slower than when applied to mucous membranes. Tetracaine is hydrolyzed to N-buty1-p-aminobenzoic acid by nonspecific tissue esterases in the dermis. This cutaneous metabolism further decreases the potential for toxicity of dermally applied tetracaine. The combination of drug retention in, and subsequent slow release from, the stratum corneum, together with the action of nonspecific esterases in the skin, probably accounts for the lack of systemic toxicity. No data are available on the systemic toxicity, if any, of N-buty1-p-aminobenzoic acid. In theory, toxicity after substantial absorption of tetracaine may result from CNS effects (yawning, dizziness, nausea), depression of the cardiovascular system (hypotension, bradycardia), and hypersensitivity. Large numbers of patients would be needed to determine the frequency and severity of potential idiosyncratic toxic effects. Care should be taken, however, whenever applying tetracaine to broken skin or mucous membranes.

**Conclusion**

Tetracaine 4% cream is a valuable alternative to lidocaine–prilocaine cream for the prevention of pain during venipuncture in children. Further research is needed to demonstrate its efficacy and safety in children younger than one year, as well as its value for other indications.

**References**

6. Small J, Wallace RG, Millar R et al. Pain-free cutting of split...
Reports Tetracaine versus lidocaine-prilocaine