



This article continues the theme of the September 2003 *Journal: Managing Medical and Behavioral Changes in Children*.

# Serum Mepivacaine Concentrations After Intraoral Injection in Young Children

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## A B S T R A C T

The authors measured plasma concentrations of mepivacaine in 36 children from the ages of 2 to 5 years who received dental care under light general anesthesia. The subjects were randomly assigned to receive either 2 percent mepivacaine hydrochloride with 1:20,000 levonordefrin or 3 percent mepivacaine hydrochloride without vasoconstrictor. The volume of anesthetic injected depended on the planned procedures for each patient. Blood samples (3 mL) were drawn from an intravenous line before and 5, 10, 20, 30, 45, and 60 minutes after mepivacaine injection. The serum was collected and analyzed by gas-liquid chromatography. Mean serum concentrations, normalized to a dose of 1 mg/kg body weight, reached a peak of  $0.67 \pm 0.42$   $\mu\text{g/mL}$  (mean  $\pm$  SD) after 3 percent mepivacaine and  $0.63 \pm 0.21$   $\mu\text{g/mL}$  after 2 percent mepivacaine with levonordefrin. Levonordefrin had no significant effect on the plasma concentrations. However, because of the higher concentration of mepivacaine in the 3 percent formulation, it was potentially 1.5 times as toxic ( $P < 0.002$ ) on a volume basis. Statistical analysis also suggested that the maximum recommended dose of 3 mg/lb could result in potentially toxic blood concentrations in a small percentage of pediatric patients. The authors conclude that 3 percent mepivacaine should not be used when relatively large volumes of local anesthetic must be administered to small children and recommend that the maximum dose of mepivacaine not exceed 5 mg/kg.

Mepivacaine (Carbocaine, Polocaine, Scandonest, etc.), introduced clinically in 1955, is widely used by dentists for intraoral anesthesia. As a 2 percent hydrochloride solution with 1:20,000 levonordefrin, mepivacaine is similar in onset, duration, efficacy, and safety to the more commonly used formulation of 2 percent lidocaine HCl with 1:100,000 epinephrine.<sup>1-3</sup> As a 3 percent HCl solution without vasoconstrictor, mepivacaine combines high efficacy with a relatively short duration of pulpal anesthesia, at least after maxillary supraperiosteal injection.<sup>4</sup> The 3 percent formulation is often preferred by general dentists for use in young children, presumably because of a per-

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ceived reduced risk of postoperative lip, tongue, and cheek biting.<sup>5,6</sup>

Significant toxic reactions, including fatalities, have been reported in children given 3 percent mepivacaine.<sup>7-9</sup> Early signs of toxicity, usually excitatory in nature, develop in humans when the plasma concentration exceeds 5 µg/mL.<sup>10</sup> Seizures may occur when plasma concentrations reach 6 to 10 µg/mL.<sup>11</sup> A massive overdose can result in respiratory and cardiac arrest. One such report described a 16.4-kg, 5-year-old patient receiving an unknown concentration of nitrous oxide who was administered five cartridges (9 mL) of 3 percent mepivacaine in less than five minutes.<sup>7</sup> The patient began seizing shortly thereafter and suffered cardiopulmonary arrest. The child was resuscitated but died four days later from anoxic brain injury secondary to cardiopulmonary arrest.

Clinicians depend on maximum dosage guidelines for determining safe quantities of local anesthetic for their patients. For mepivacaine, the maximum recommended dosage is 6.6 mg/kg, or 3 mg/lb, up to a total dose of 400 mg.<sup>12</sup> Unfortunately, with no published data on blood concentrations of mepivacaine after intraoral injection in young children, it is not firmly established if these recommendations are appropriate. An additional concern regarding safety in children is that general dentists are more likely to exceed maximum recommended dosages of local anesthetic in patients weighing less than 20 kg.<sup>6</sup> Finally, a nationwide survey of pediatric dentists revealed that only half of these practitioners used exact body weight to determine anesthetic dosage.<sup>13</sup>

In this study, the authors determined the serum concentrations of mepivacaine in young children when the local anesthetic was administered

as a 3 percent solution without vasoconstrictor or as a 2 percent solution with 1:20,000 levonordefrin. The study's purpose was to help verify maximum dosage limits for mepivacaine in children and ultimately increase the safety of local anesthetics in dentistry.

### Methods

This study, approved by the UCLA Human Subjects Protection Committee, enrolled 36 healthy children from the ages of 2 to 5 years who were scheduled to receive full-mouth rehabilitation

thetia was maintained with propofol (Diprivan) infused as needed.

Each patient was randomly assigned before treatment to receive intraoral injection of either 2 percent mepivacaine HCl with 1:20,000 levonordefrin (Polocaine with Levonordefrin) or 3 percent mepivacaine HCl (Polocaine). The operator was informed of the manufacturer's recommended maximum dose of mepivacaine (3 mg/lb) and of the randomly assigned formulation to be administered to the patient. The volume of anesthetic injected depended on the planned procedures as determined by the operator. All mepivacaine injections were given at the beginning of treatment over a three-minute period using preweighed cartridges. Two percent lidocaine HCl with 1:100,000 epinephrine (Xylocaine with epinephrine) was used if additional local anesthetic was needed intraoperatively. All dispensed mepivacaine anesthetic cartridges were retrieved immediately after treatment. Used cartridges were weighed to determine the injected dose.

Blood samples (3 mL) were drawn before and at 5, 10, 20, 30, 45, and 60 minutes after mepivacaine injection. If the dental treatment was finished before 60 minutes, blood collection ceased when the IV line was removed during the recovery period. The blood samples were drawn through the IV line, which was equipped with a stopcock. Saline dilution was minimized by turning off the IV drip approximately 15 seconds before blood sampling and then withdrawing 3 mL of blood before obtaining each sample.

The blood was allowed to clot and then centrifuged at 2000 g for 10 minutes. The serum was collected and stored at -20 degrees Celsius for subsequent analysis. The serum concentra-

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under light general anesthesia at the University of California at Los Angeles Pediatric Dental Clinic. After parental informed consent was obtained for acquiring blood samples, the following characteristics were recorded for each patient: weight, sex, age, and ethnicity. Deep sedation was then introduced with an intramuscular injection of 2.5 mg/kg ketamine HCl (Ketalar), 0.1 mg/kg midazolam HCl (Versed), and 6 to 8 µg/kg glycopyrrolate (Robinul). Intravenous access was obtained with a 20-gauge catheter (Angiocath) once the child was sedated. Light general anes-

tions of mepivacaine were determined by gas chromatography essentially according to the method of Zylber-Katz and colleagues.<sup>14</sup>

Mepivacaine was extracted into 3 mL of n-hexane from 0.5-mL serum samples diluted with 0.5 mL of triple distilled water to which 0.1 mL of 4 N NaOH was added to convert the local anesthetic to the free base form. Cyclizine (1 µg) was also added as an internal standard. The samples were gently shaken (one minute) and centrifuged (2000 g, 10 minutes). The top organic phase was removed and gently shaken (one minute) with 0.5 mL 4 N HCl and centrifuged again (2000 g, five minutes). The samples were stored in tightly capped centrifuge tubes in an ice bath for injection into the gas chromatograph. All chemicals were obtained from Sigma (St. Louis, Mo.).

For drug measurement, 1 µL of the lower aqueous phase was withdrawn with a 10-µL microsyringe (Hewlett Packard, Co., Palo Alto, Calif.) and injected into a gas chromatograph (Hewlett Packard Model 6890). A 30-m (0.32-mm inner diameter, 0.25-µm film thickness) cross-linked 5 percent-diphenylene-95 percent-dimethylsiloxane copolymer capillary column (Hewlett Packard Model HP-5) was used. The oven was programmed to escalate in temperature from 75 degrees Celsius to 175 degrees Celsius at a rate of 50° C/min, with a hold time of 1 minute at 175 degrees Celsius, and from 175 degrees Celsius to 250 degrees Celsius at a rate of 25° C/min, with a hold time of 2.5 minutes at the final temperature. Helium was the carrier gas. The temperatures of the injection port and detector were 310 degrees Celsius and 325 degrees Celsius, respectively. Peak areas were recorded as measured by the HP 6890 Series

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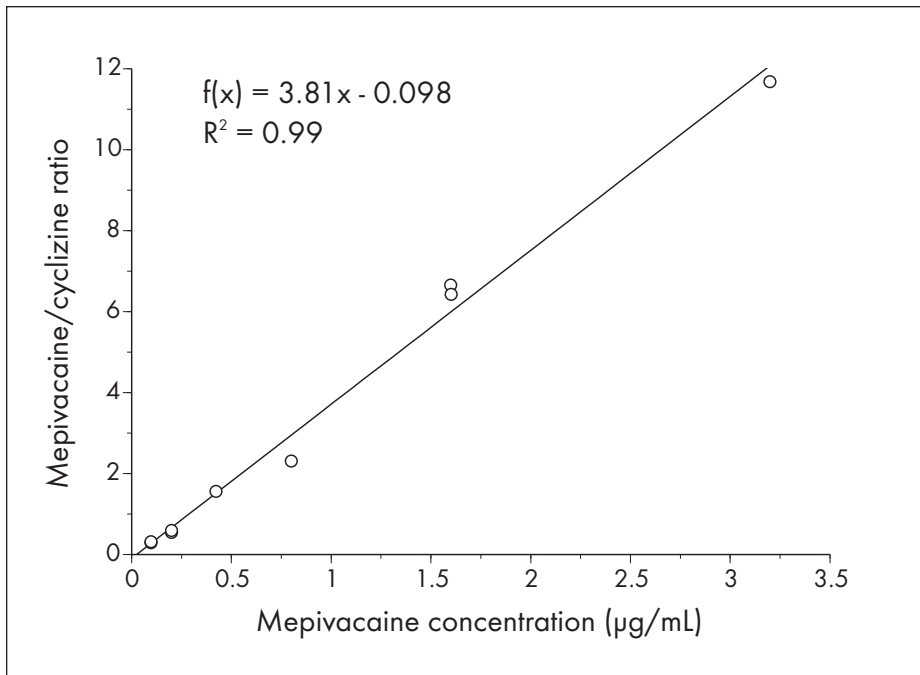


Figure 1. Standard mepivacaine analysis curve prepared by adding cyclizine (1 µg) and mepivacaine (0-1.6 µg) to drug-free serum samples.

Integrator. Each measurement was made in triplicate, with the mean value used for analysis.

Drug-free serum was analyzed to determine that no extraneous peaks were detected that could possibly interfere with the mepivacaine and cyclizine peaks. To ensure that peaks from the other therapeutic agents used would not interfere with those of mepivacaine and cyclizine, ketamine, midazolam, propofol, and lidocaine with epinephrine were added to drug-free serum and analyzed. Standard curves were constructed from controls containing 0, 0.1, 0.2, 0.4, 0.8, and 1.6 µg mepivacaine added to the drug-free serum to permit calculation of unknown mepivacaine concentrations (Figure 1).

An analysis of variance with repeated measures was used to compare the serum concentrations of mepivacaine for the two drug treatments over

time. Student's t-test was used to compare patient characteristics, mepivacaine dosages and volumes, peak serum concentrations, and times to peak concentration. Linear regression forced through the origin was used to correlate the injected dose with the peak concentration of mepivacaine. All statistical analyses were performed using Systat, version 5.2 for Macintosh (SPSS, Inc., Chicago).

## Results

The results of one subject could not be used because of a failure to record the body weight. Descriptive data from the remaining 35 subjects, as listed in Table 1, demonstrate that the randomization method resulted in two similar test groups. Overall, the body weight ranged from 11 to 24 kg, with a mean ( $\pm$  SD) weight of  $17.3 \pm 4.3$  kg. The age of the subjects ranged from 25 to 67

months, with a mean age of  $47 \pm 12$  months. The study population was ethnically diverse, including 46 percent Hispanic, 43 percent Caucasian, and 11 percent African-American children. No toxic reactions to the local anesthetic were observed, nor were there any adverse effects from the dental treatments or anesthetic agents.

The sedative and anesthetic agents did not interfere with mepivacaine measurements in our study, which is in accordance with the findings of others.<sup>15</sup> In addition, there was no independent effect of age or race on the results.

Figure 2 illustrates the injected dose of mepivacaine for the each study patient. The mean injected dose for 3 percent mepivacaine was  $4.42 \pm 1.38$  mg/kg. This value was almost exactly 50 percent (49.3 percent) higher than the  $2.96 \pm 1.13$  mg/kg mean for 2 percent mepivacaine with levonordefrin. This difference indicates that the injected volumes for the two anesthetic formulations were essentially identical.

Figure 3 shows the mean serum mepivacaine concentrations versus time after local anesthetic injection for 31 subjects. (Data from four subjects were lost during sample preparation. Only insignificant changes would have resulted from their exclusion in Table 1 and the mean dosing data.) The values are normalized to an injection dose of 1 mg/kg. The 3 percent formulation resulted in slightly higher mean serum concentrations from 10 to 45 minutes after injection. These differences were not statistically significant overall or at any time period. The normalized peak serum concentration was reached with both formulations at 30 minutes. The normalized mean peak concentration without respect to time (not shown in Figure 3) was 8 percent higher in the 3 percent mepivacaine group ( $0.67 \pm$

0.42 µg/mL versus 0.63 ± 0.21 µg/mL). All of the differences between the two formulations could be attributed to a single subject whose concentrations were more than three standard deviations above the mean. Excluding this subject would result in a mean of 0.58 ± 0.18 µg/mL for the peak mepivacaine concentration in the 3 percent mepivacaine group.

The peak serum concentration for each patient is plotted in **Figure 4** as a function of the injected dose. Because there was no significant difference between the normalized peak serum concentrations for the two formulations, data for the two test groups were combined. The outlier (indicated by an asterisk) was omitted from the linear re-

Table 1

**Subject Data by Treatment Group**

	3% mepivacaine	2% mepivacaine + levonordefrin
Age (mo)	47 ± 13*	47 ± 12*
Weight (kg)	16.7 ± 3.7*	18.1 ± 5.0*
Race (His/Cauc/Af-Am)	8/9/3†	

\*Mean ± SD  
 †Numbers of Hispanic/Caucasian/African-American children enrolled

gression calculation based on the assumption that some of the drug was injected intravascularly or a mistake occurred in recording the injected volume of anesthetic.

**Discussion**

The mean peak serum concentrations described here for children are similar to those reported previously by Goebel and colleagues for adults after intraoral injection (0.69 µg/mL for 3

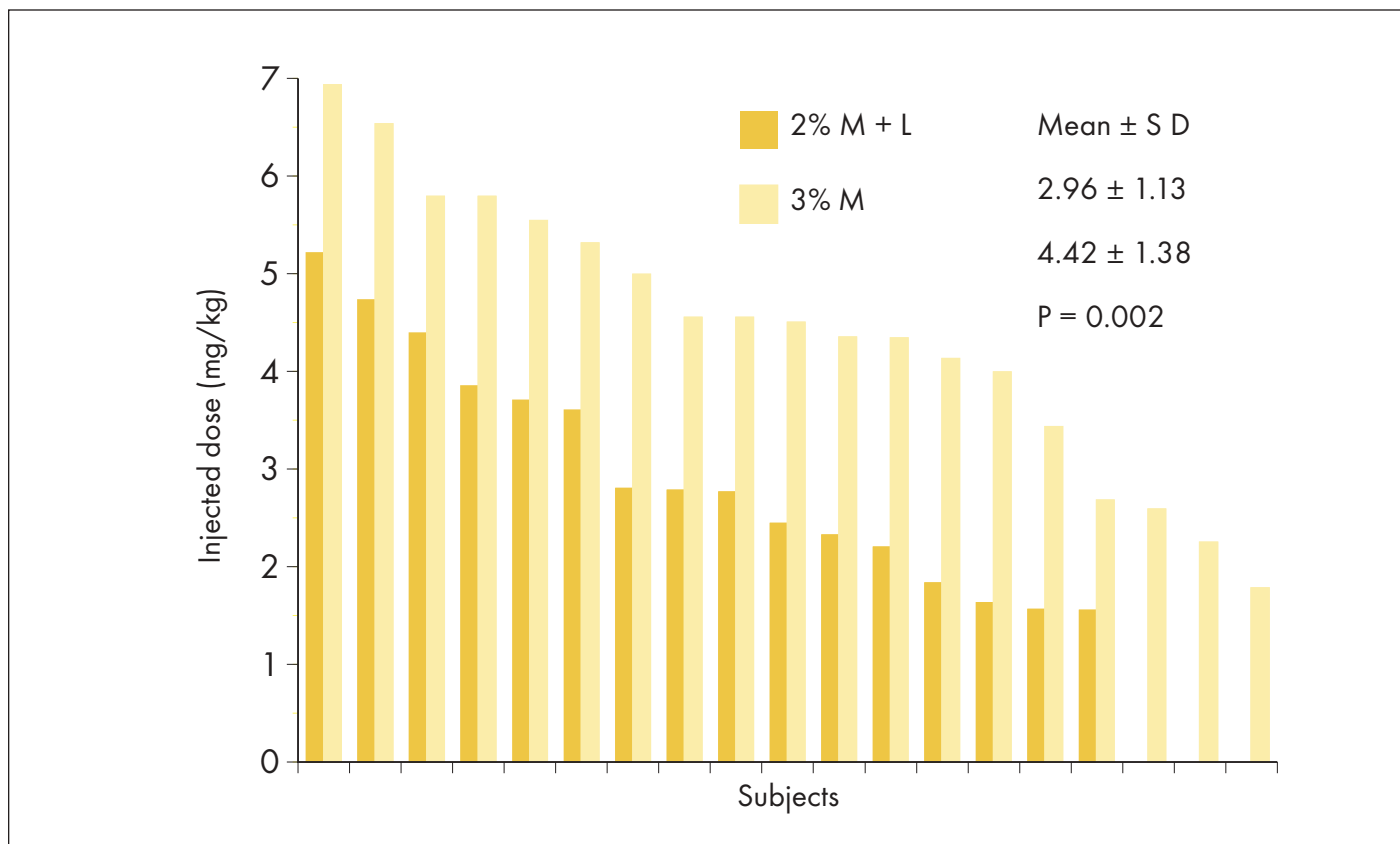


Figure 2. Injected dose of mepivacaine by body weight. Each bar represents a single subject.

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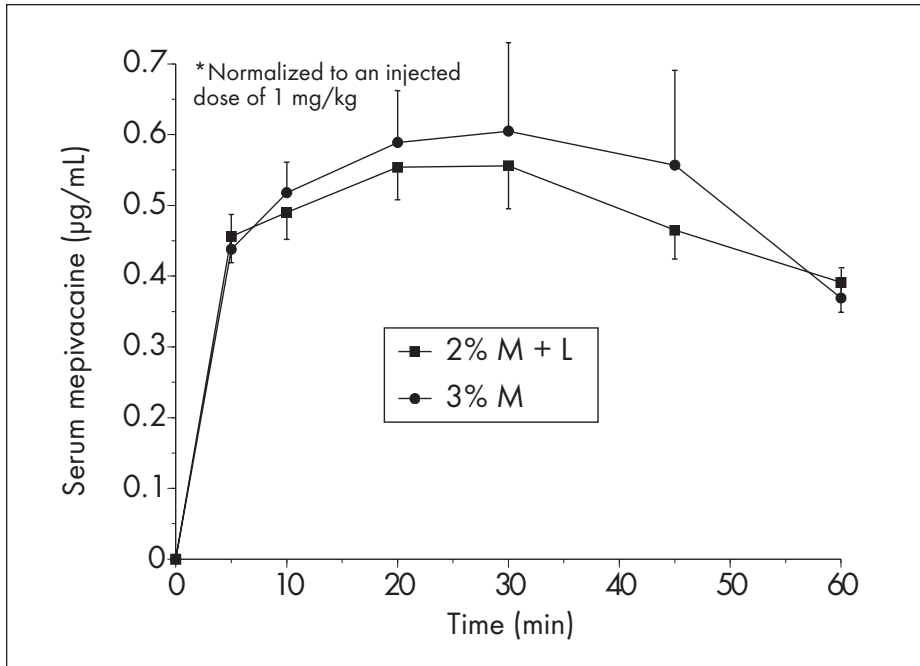


Figure 3. Serum mepivacaine concentrations normalized to an injected dose of 1 mg/kg. Bars indicate the standard errors. M = mepivacaine; L = levonordefrin

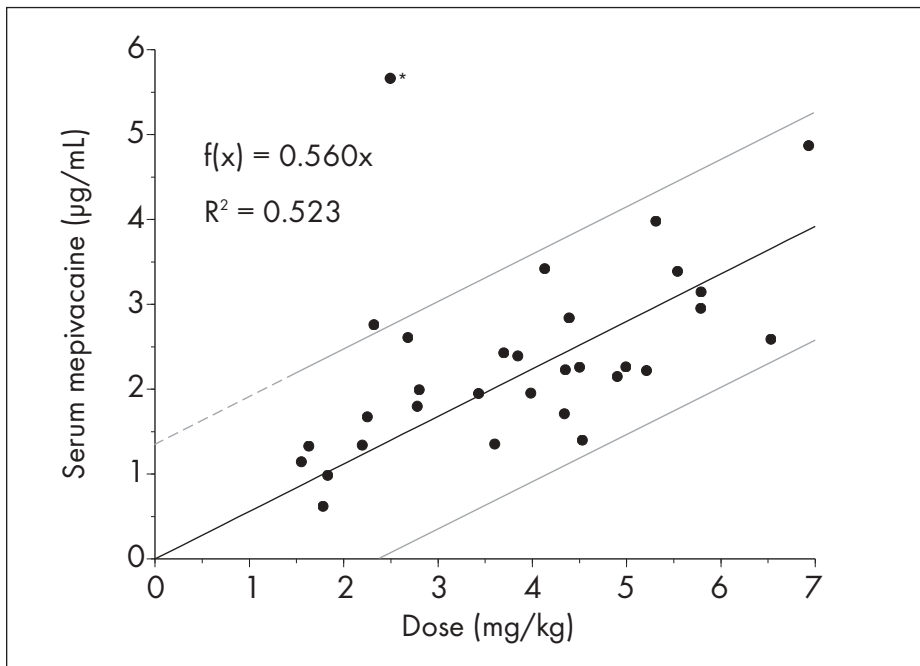


Figure 4. Linear regression of the pooled peak serum concentrations. Each point represents a single subject. A single outlier, not used in the regression analysis, is indicated by an asterisk (\*). The 95 percent prediction limits are indicated by lines above and below the regression line

percent mepivacaine and 0.62 µg/mL for 2 percent mepivacaine with 1:20,000 levonordefrin when normalized to a 1 mg/kg injected dose of mepivacaine).<sup>16,17</sup> As with this study, they found no significant influence of levonordefrin on peak mepivacaine concentrations, which also occurred 30 minutes after injection.

The regression equation shown in **Figure 4** indicates that a dose of 1 mg/kg will, on average, result in a peak serum concentration of 0.56 µg/mL. For a maximum recommended dose of 6.6 mg/kg (3 mg/lb), this relationship would yield a mean concentration of 3.7 µg/mL, a relatively high but safe value. However, the 95 percent prediction limits for the regression equation indicate that 2.5 percent of children would achieve a peak serum concentration of at least 5 µg/mL, the maximum “safe” concentration. Using the pooled mean of 0.60 µg/mL calculated from the measured peak serum concentrations normalized to an injection dose of 1 mg/kg, and the pooled standard deviation of 0.19 µg/mL (both values excluding the outlier), the authors can also estimate that 2.5 percent of the population would have a serum concentration of at least 5 µg/mL at an injection dose of only 5.1 mg/kg. These two methods of estimation use different statistical assumptions. Regression analysis assumes that the residual errors are normally distributed, whereas the normalized data calculation assumes that the serum concentrations themselves are normally distributed once they have been normalized to an injection dose of 1 mg/kg. Although the assumption underlying the linear regression has a slightly better fit with the data, neither assumption could be rejected at the  $P = 0.1$  level of confidence; and

caution dictates using the more conservative estimate of risk. Therefore, to ensure that the vast majority of patients will have a peak serum concentration below 5 µg/mL, the injected dose should not exceed 5 mg/kg.

The single outlier in this study deserves special comment. Although a laboratory error of some kind could have occurred, the fact that the subject's mepivacaine concentration was high at all times after baseline and that other samples assayed at the same time were within normal limits suggests that the measurements were accurate. A possible mistake more consistent with the measured data is that the injected dose was underestimated because one or more used cartridges were either not weighed accurately or not weighed at all. Subsequent review of the patient's chart, however, revealed no evidence in support of a larger dose being given. It is also possible that some of the drug was injected intravascularly by mistake. A misadventure of this kind should normally have resulted in a high peak serum concentration occurring almost immediately after injection. Since the first sample was taken five minutes after injection, there may have been sufficient time for the drug to be distributed such that the five-minute value was not high compared to later measurements. A final, disturbing possibility is that the outlier represents a truly idiopathic response to injected mepivacaine. Other investigators have also reported individual subjects with unusually high serum concentrations of mepivacaine.<sup>18,19</sup> As in this study, no adverse event occurred despite these "toxic" values.

Local anesthetics are often not administered according to concentration or dose but rather according to the volumes normally used for particular

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injection techniques. For example, when administering an inferior alveolar nerve block, many dentists will inject one cartridge regardless of the type or strength of anesthetic used or even the size of the patient.<sup>6</sup> These tendencies compound the risk of local anesthetic overdose when 3 percent mepivacaine is used in lieu of a 2 percent local anesthetic formulation with vasoconstrictor simply because 50 percent more local anesthetic is given. Young children with low body weights are at special risk for receiving relatively large amounts of local anesthetic. Since the primary reason dentists cite for selecting 3 percent mepivacaine over less concentrated local anesthetics — that being reduced cheek, lip, and tongue biting — is debatable and unproved, the increased toxic potential of the formulation should limit its routine use.<sup>5</sup>

Finally, accidental intravascular injection of the local anesthetic must

be considered. In dentistry, the use of local anesthetic cartridges with a limited volume of solution greatly reduces this risk in adults. But very small children are not protected by this volume limitation because the content of one cartridge may be sufficient to cause systemic toxicity. One way to avoid intravascular deposition of local anesthetics is to limit the use of nerve blocks and use supraperiosteal injections whenever possible. Several reports have shown that infiltration in the pediatric mandible is as effective as the inferior alveolar nerve block when simple dental procedures are performed.<sup>20,21</sup>

## Conclusion

Because levonordefrin does not significantly affect the peak serum concentration of mepivacaine after intraoral injection, the 3 percent formulation is potentially 1.5 times as toxic as the 2 percent formulation when given in the same volume. Therefore, the authors believe that 3 percent mepivacaine should not be used when relatively large volumes of local anesthetic must be administered to small children and that the dosage of mepivacaine with or without vasoconstrictor should not exceed 5 mg/kg. **CDA**

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