Mixtures of Local Anesthetics Are No More Toxic than the Parent Drugs

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Mixtures of local anesthetics can combine the best features of both components. The authors assayed the systemic toxicity of local anesthetic mixtures given subcutaneously to mice. Convulsions regularly preceded death. The median convulsant dose (CD₅₀) of bupivacaine was one-fourth that of lidocaine, and one-seventh that of chloroprocaine. The median lethal dose (LD₅₀) of chloroprocaine was twice the CD₅₀, whereas the LD₅₀ of bupivacaine was but little greater than the CD₅₀. Hence, the more potent the agent, the greater is the chance of death from a convulsant dose of local anesthetic.

Conversion to lidocaine-equivalent doses permitted comparisons between mixtures. None of the mixtures were more convulsant or more lethal than their parent components; lidocaine-containing mixtures were significantly less lethal than the lidocaine norm. Mixing increased the distance between convulsant and lethal doses, with survival from convulsions induced by bupivacaine-containing mixtures enhanced in particular. It is concluded that local anesthetic toxicity is essentially additive. (Key words: Anesthetics, local: bupivacaine; chloroprocaine; lidocaine; mixtures of. Toxicity: convulsions; deaths.)

Mixtures of local anesthetics are used by many clinicians to combine fast onset contributed by one agent with long duration of nerve block by another agent. For instance, chloroprocaine often is mixed with bupivacaine to take advantage of the short latency of the former, and the long duration of analgesia imparted by the latter. Though large-scale clinical studies do not disclose a higher incidence of toxic reactions in patients, laboratory studies have yielded conflicting conclusions regarding the toxicity of local anesthetic mixtures.²⁻⁴

Since drug absorption following subcutaneous injection resembles in many respects conditions following infiltration anesthesia and peripheral nerve block,³ we assayed, in mice, the subcutaneous toxicity of three different local anesthetics, given singly or in combination. We found that mixtures of local anesthetics are no more toxic than when the agents are given alone; that is to say, local anesthetic toxicity is essentially additive.

Methods

A total of 369 healthy white female adult (aged 8–10 weeks) virgin Charles River mice, weighing 30 to 35 g each, were injected between 9 a.m. and 11 a.m. with local anesthetic or a mixture of local anesthetics. The mice were housed five to a cage, away from males, so as to suppress estrus.⁶ Solutions were injected with a 25-gauge needle into the subcutaneous areolar tissue of the back of the chest, after which the animal was put in a warmed cage for individual observation. We recorded time of onset of ataxia, aimless running motions, arching of tail, neck and back, convulsions, and time of recovery or death. Deaths occurring within four hours of injection were attributed to the acute effects of local anesthetic administration.⁷

We assayed a short-acting (lidocaine) and long-acting (bupivacaine) amide agent, and a brief-acting representative of the ester-class of local anesthetics (chloroprocaine). Anesthetics were donated by the respective manufacturers as sterile solutions of the hydrochloride salt in saline. In keeping with the logarithmic properties of the dose-response curve, we increased or decreased doses in geometric proportion till we bracketed the median value with four or five points for each drug. Replicate end-values of 0 per
cutaneously administered bupivacaine is a nearly four times more powerful convulsant than lidocaine, and nearly seven times more convulsant than chlorprocaine. The linearized dose-death curves for the three solitary agents are shown in figure 1; the slopes of the lines did not deviate significantly from parallelism by t test.

The lethal dose of lidocaine and chlorprocaine is about twice the convulsant dose, whereas with bupivacaine the lethal dose is just 7 per cent greater than the convulsant dose. Thus, when the lethal doses of local anesthetics given subcutaneously are compared, bupivacaine turns out to be about five times more toxic than lidocaine, and over 12 times more toxic than chlorprocaine. Said differently, if sufficient bupivacaine is given to induce convulsions, chances of recovery are slim if the animals are left untreated, whereas chances of recovery from lidocaine- or chlorprocaine-induced convulsions are good.

To facilitate interpretation of the results with mixtures, we converted mass units of drug combinations to "lidocaine equivalents" by multiplying the drug dose with the ratio of the lidocaine CD$_{50}$ (or LD$_{50}$) to the drug's CD$_{50}$ (or LD$_{50}$) (table 3). Because the log dose-convulsions and the log dose-death lines within each group did not deviate significantly from parallelism, we merely shifted with this maneuver the dose-response curves to new locations without altering their slopes.

Normalizing the median toxic values will, of course, yield the same numbers for bupivacaine and chlorprocaine as for lidocaine; therefore, only the lidocaine values are shown in table 3. Since the local anesthetics were mixed in equal proportion to their CD$_{50}$s, the equivalent convulsant doses of the components of a mixture are equal (within the constraints of rounding) in table 3. This is not so for the lethal doses, however.

In the rightmost column of table 3, the component CD$_{50}$s or LD$_{50}$s are summed to permit comparisons between mixtures. Of the three mixtures assayed here,

| Table 1. Composition of Local Anesthetic Mixtures (proportional to baseline CD$_{50}$s) |
|----------------------------------|--------|----------|---------|
|                                  | Bupivacaine (mg/ml) | Lidocaine (mg/ml) | Chlorprocaine (mg/ml) |
| Bupivacaine + lidocaine          | 2.58   | 9.66     | —       |
| Bupivacaine + chlorprocaine      | 2.81   | —        | 18.75   |
| Lidocaine + chlorprocaine        | —      | 9.19     | 16.22   |

Results

Table 2 shows the computed CD$_{50}$s and LD$_{50}$s (expressed in mg/kg with standard error) of individual local anesthetics and their mixtures. Median toxic doses for the components of the mixtures were calculated from median volumes and composition of the solutions as shown in table 1. Notable is that sub-

the lidocaine–chloroprocaine combination was the least lethal, while the bupivacaine–chloroprocaine mixture was the most toxic in that it alone did not differ significantly from the lidocaine standard. Both lidocaine-containing mixtures were significantly less lethal than lidocaine alone, as illustrated in figure 2.

Bearing on clinical practice is the much wider spread between convulsant and lethal doses of the bupivacaine-containing mixtures as opposed to bupivacaine alone. Whereas the difference between bupivacaine’s \( LD_{50} \) and \( CD_{50} \) was only 7 per cent, it was 73 per cent for the bupivacaine–chloroprocaine mixture, and 108 per cent for the bupivacaine–lidocaine mixture. Thus, convulsions from bupivacaine-containing mixtures in mice are less likely to terminate fatally than if bupivacaine were given alone.

With all doses of lidocaine and of chloroprocaine, and with doses of bupivacaine less than the \( CD_{50} \), convulsions always preceded death. (A few mice given supracoconvulsant amounts of bupivacaine died quickly without ever convulsing.) Quite consistently, the larger the convulsant dose of any of the drugs, the briefer was the latency to convulsions, and the longer convulsions in survivors lasted. This is illustrated in table 4 for a low- and a high-dose range of each drug and drug combination. Seizures from lidocaine seemed to last much longer than with the other local anesthetics. That trend was evident also with the lidocaine-containing mixtures. The bupivacaine–chloroprocaine mixture produced briefer seizures before recovery than the other mixtures, but it also caused the quickest deaths.

**Discussion**

We found that the subcutaneous \( LD_{50} \) of bupivacaine was approximately five times greater than that of lidocaine, a ratio similar to that obtained by Adams and associates who also used female mice.\(^{10}\) However, our \( LD_{50} \) values for both bupivacaine and lidocaine were approximately twice those obtained by these investigators (45 and 211 mg/kg, respectively). We have no ready explanation for the discrepancy, other than that the drugs must have been absorbed faster from their (unspecified) injection site than from the areolar tissues of the back of the chest. That assumption seems reasonable in that other investigators reported subcutaneous toxicities in mice close to our values for lidocaine (425 mg/kg)\(^{5}\) and bupivacaine

![Table 3. Median Toxicities Expressed as "Lidocaine Equivalents" (mg/kg ± SE)*](image)

<table>
<thead>
<tr>
<th></th>
<th>Bupivacaine</th>
<th>Lidocaine</th>
<th>Chloroprocaine</th>
<th>Total Drug Mass†</th>
</tr>
</thead>
<tbody>
<tr>
<td>( CD_{50} )</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>( LD_{50} )</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>( LD_{50} )</td>
<td>289.4</td>
<td>462.7</td>
<td>–</td>
<td>289.4</td>
</tr>
<tr>
<td>± 13.4</td>
<td>± 23.8</td>
<td>–</td>
<td>± 13.4</td>
<td></td>
</tr>
<tr>
<td>( LD_{50} )</td>
<td>154.0</td>
<td>381.9</td>
<td>–</td>
<td>307.2</td>
</tr>
<tr>
<td>± 9.6</td>
<td>± 15.0</td>
<td>± 10.1</td>
<td>± 19.3 (0)</td>
<td></td>
</tr>
<tr>
<td>( LD_{50} )</td>
<td>153.2</td>
<td>256.4</td>
<td>–</td>
<td>294.2</td>
</tr>
<tr>
<td>± 9.7</td>
<td>± 10.1</td>
<td>–</td>
<td>± 21.1 (0)</td>
<td></td>
</tr>
<tr>
<td>Bupivacaine + chloroprocaine</td>
<td>146.2</td>
<td>335.6</td>
<td>148.0</td>
<td>509.4</td>
</tr>
<tr>
<td>± 10.5</td>
<td>± 21.2</td>
<td>± 10.6</td>
<td>± 21.1 (0)</td>
<td></td>
</tr>
<tr>
<td>Lidocaine + chloroprocaine</td>
<td>–</td>
<td>161.9</td>
<td>161.9</td>
<td>706.3</td>
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<tr>
<td>± 11.8</td>
<td>± 25.4</td>
<td>± 11.8</td>
<td>± 23.6 (0)</td>
<td></td>
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</tbody>
</table>

* Only lidocaine values are listed, since equivalent convulsant and lethal doses of bupivacaine and chloroprocaine are the same.

† Total drug mass is the sum of the component lidocaine equivalents; † = significant, 0 = no significant difference from lidocaine value.
that the estrus cycle of the female mouse affects her response to local anesthetics. Accordingly, we housed our animals five to a cage, and away from males, to suppress estrus.\textsuperscript{6}

We observed in our mice a phenomenon described recently in dogs where a phase of aimless running motions precedes the onset of convulsions. In the dog, running motions started after an average intravenous lidocaine dose of 22.7 mg/kg, whereas convulsions required half as much again (33.7 mg/kg) of local anesthetic.\textsuperscript{14} Since these running motions superficially resemble grand mal convulsions, spuriously low CD\textsubscript{50}\textsubscript{s} may have been obtained by earlier investigators.

Hydrolysis of chloroprocaine by human serum esterases is inhibited 38 per cent by bupivacaine in vitro, suggesting that mixing bupivacaine and chloroprocaine might intensify chloroprocaine intoxication.\textsuperscript{13} Since the mouse is one of the few non-primate species to hydrolyze procaine about as well as do men,\textsuperscript{16} and since we found bupivacaine–chloroprocaine to be no more toxic than either drug alone, that hypothesis proved untenable. Nonetheless, the bupivacaine–chloroprocaine mixture was slightly more toxic than either drug mixed with lidocaine.

Our observations are based on mixtures of local anesthetics compounded in proportion to the CD\textsubscript{50}, a yardstick that represents advanced, but not necessarily irreversible, toxicity. We selected the CD\textsubscript{50} over the LD\textsubscript{50} since convulsions from local anesthetic overdosage are a familiar endpoint of severe systemic intoxication in patients given local anesthetics.\textsuperscript{17} Though we did not test it, we believe that local anes-

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thetics mixed in different proportions (e.g., lethal ratio or potency ratio) also would exhibit the property of simple additive toxicity as demonstrated here for the convulsant ratio. It is interesting to note that the subcutaneous LD₅₀ of bupivacaine in this study was about one-fifth that of lidocaine, whereas it was about two-fifth that of lidocaine when the drugs were given intraperitoneally. Even so, mixtures of bupivacaine, chloroprocaine and lidocaine given intraperitoneally still proved to be significantly less lethal (by a factor of 20 per cent) than the sum of the lethality of the two parent drugs. It appears that, regardless of differences in relative toxicities associated with different rates of absorption, the toxicity of local anesthetic mixtures is additive at most.

We conclude that mixtures of local anesthetics, administered under experimental conditions approaching those of peripheral nerve block in man, exhibit essentially additive toxicity, and thus are no more toxic than if the agents were injected singly.

We are grateful to Astra Pharmaceutical for complimentary supplies of Xylocaine, to Breon Laboratories for Marcaine, and to Pennsval Corporation for Nesacaine.

References