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Chemical Stability of Bupivacaine in pH-adjusted Solutions

Laurence Bonhomme, B.S.,* Dan Benhamou, M.D., † Magid Jebri, M.D., ‡ Philippe Bourget, B.S., § Hélène Martre, B.S., § Eric Postaire, Ph.D., ¶ Nicole Preaux, Ph.D. ¶

Recent clinical studies have suggested that alkalization of bupivacaine may shorten the time to onset and lengthen its duration of action. However, addition of sodium bicarbonate to commercially manufactured bupivacaine can rapidly produce precipitation. This study was performed to study the stability and precipitation of bupivacaine solutions 0.25% and 0.50% with and without epinephrine 1:200,000 after alkalization. The results indicate that alkalization does not increase precipitation above recommended limits and that the concentration of bupivacaine in solutions is maintained at least 6 h after alkalization. (Key words: Acid-base equilibrium; pH. Anesthetics, local: alkalization, Bupivacaine.)

Bupivacaine hydrochloride is commercially available in slightly acidic solutions, with a pH between 3.3 and 5.1,2 With a pKa of 8.1,3 most of the drug is in the ionized, hydrophobic form. To increase the unionized, lipophilic form of bupivacaine, the pH of the solutions can be increased by addition of sodium bicarbonate (NaHCO3). Several recent clinical studies have shown that alkalization of bupivacaine results in a more rapid onset of analgesia and an increased duration of action.4-6 dotdotdot However, unlike lidocaine, alkalization of bupivacaine to pH greater than 7.0 results in precipitation, thus limiting the feasibility of increasing the pH.7 dotdotdot This study was designed to define the stability of bupivacaine in pH-adjusted solutions.

Materials and Methods

Three different commercial solutions of bupivacaine were studied: 0.25%, 0.5% with 1:200,000 epinephrine, and 0.5% without epinephrine (R. Bellon, France). pH was measured in ten bottles (20 ml) of each of five lots of each solution type with a pH meter (pHm 82, standard pH meter, Radiometer Copenhagen, sensitivity 0.01 pH unit) calibrated before each measurement with known standard solutions of pH 4 and 7. However, all of the subsequent studies and the results reported in the tables relate to analyses performed on bottles from the first lot. Local anesthetic solutions were titrated with 1.4% sodium bicarbonate to obtain a pH of 7.0. The bupivacaine solutions thus alkalized were tested before and at 1 min, 1 h, and 6 h after alkalization by the following methods: 1) optical microscopy (phase contrast) after centrifugation (5,000 RPM) for visual evidence of precipitation; 2) particle count that indicates the precipitation of bupivacaine-base8 performed using a counter Hiac Roysco® (Pacific Scientific) after separation in several channels (each accepting a maximal particle size of 2, 5, 10, 25, and 50 microns diameter) and comparison with recommended values for injectable products; 3) ultraviolet spectrophotometry (spectrophotometer 100-80A, Hitachi®) com-

<p>| Table 1. pH of lot number 1 Bupivacaine (Mean ± SD) before and after Addition of Bicarbonate |
|---------------------------------|----------------|----------------|</p>
<table>
<thead>
<tr>
<th>Initial pH</th>
<th>Final pH</th>
<th>Volume of 1.4% NaHCO3</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25% Bupivacaine</td>
<td>5.42 ± 0.03</td>
<td>7.01 ± 0.02</td>
</tr>
<tr>
<td>0.5% Bupivacaine</td>
<td>5.38 ± 0.05</td>
<td>6.87 ± 0.01</td>
</tr>
<tr>
<td>0.5% Bupivacaine, 1/200,000 epinephrine</td>
<td>4.80 ± 0.04</td>
<td>6.68 ± 0.01</td>
</tr>
</tbody>
</table>

<p>| Table 2. Bupivacaine Concentrations (Mean ± SD) before and after Addition of Sodium Bicarbonate |
|---------------------------------|----------------|----------------|</p>
<table>
<thead>
<tr>
<th>Time</th>
<th>0.5% Bupivacaine (mg/ml)</th>
<th>0.5% Bupivacaine, 1/200,000 Epinephrine (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>4.85 ± 0.1</td>
<td>4.65 ± 0.1</td>
</tr>
<tr>
<td>1 min</td>
<td>5.01 ± 0.1</td>
<td>4.54 ± 0.05</td>
</tr>
<tr>
<td>2 h</td>
<td>5.20 ± 0.26</td>
<td>4.61 ± 0.09</td>
</tr>
<tr>
<td>6 h</td>
<td>4.97 ± 0.14</td>
<td>4.61 ± 0.09</td>
</tr>
</tbody>
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* Resident, Pharmacy.
† Assistant Professor of Anesthesiology.
‡ Resident, Anesthesiology.
§ Hospital Pharmacist.
Receives from the Laboratory of Pharmacy and Toxicology and the Department of Anesthesiology, Université Paris-Sud, Hôpital Antoine Béclère, Clamart, and the control Central Laboratory of Pharmacy, Paris, France. Accepted for publication June 22, 1988. Presented in part at the American Society of Anesthesiologists Meeting, Atlanta, Georgia, October, 1987.
Address reprint requests to Dr Benhamou: Department of Anesthesiology, Hôpital Antoine Béclère, 157 Rue de la Porte de Trivaux 92141, Clamart, France.

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paring the absorption peaks at wavelengths between 230 and 350 nm after dilution at 0.04% in hydrochloric acid (HCl) 0.01 N; and 4) thin layer chromatography (support: kieselgel pH-adjusted Bupivacaine 60 P254; solvent strong ammonia solution: methanol 1.5/100; time of runs: 30 min; examination under UV light 254 nm and revelation with iodoplatinate spray) allowing comparison of RF values between commercial and pH-adjusted solutions.

Measurement of bupivacaine concentration (0.5% with epinephrine and without epinephrine) was performed by gas chromatography (Varian® 1400, Aerograph), using aliquots of 100 µl. The internal standard (prilocaine 1 mg/ml in water) was mixed in an equimolar solution with bupivacaine. Extraction in diethyl ether was followed by evaporation with dry nitrogen. The residue of prilocaine and bupivacaine thus obtained was mixed with methanol, and 3 µl of this mixture was injected on a 2 m x 2 mm 1D glass column (Chrompack®) fitted with 3% OV225 on 80-100 mesh chromosorb wax, DMCS equipped with a flame ionization detector. Bupivacaine concentration was measured using a Shimadzu® CR6A recorder-integrator before and 1 min, 2 h, and 6 h after alkalization.

Values obtained for particle counts and for bupivacaine concentrations were analyzed statistically using one-way analysis of variance followed by Student’s t test when necessary. P < 0.05 was considered statistically significant.

Results

The pH values of the three solutions of the first lot before and after alkalization and the volumes of 1.4% sodium bicarbonate necessary to obtain a pH close to 7.0 are shown in table 1. The pH values of all lots of the solutions of 0.25% bupivacaine ranged from 5.42 to 6.06, of 0.5% bupivacaine from 5.38 to 5.82, and of 0.5% bupivacaine with epinephrine from 3.35 to 4.80. The pH of alkalized solutions remained unchanged for 24 h.

Amounts of bicarbonate added to each solution type were 0.1 mEq, 0.1 mEq, and 0.25 mEq, respectively, for 0.25%, 0.5%, and 0.5% bupivacaine with epinephrine. After pH adjustment, solutions remained clear and optical microscopy after centrifugation revealed only rare crystals in the alkalized solutions. UV spectrophotometry revealed that commercial and alkalized bupivacaine had two identical absorption peaks (261 and 270 nm). Thin layer chromatography revealed only one spot with a similar RF value (0.71) before and after pH adjustment. Alkalization did not modify bupivacaine concentrations that remained stable for 6 h (table 2). The particle count (table 3) indicated that before alkalization, plain solutions of 0.5% bupivacaine had fewer 10 µ particles than either 0.25% or 0.5% solutions with epinephrine 1:200,000 (P < 0.05). Alkalization of the three solutions produced precipitation that was detected by increased particle
counts of 10 and 25 μ diameter. This precipitation occurred immediately after addition of bicarbonate and persisted for at least 6 h. However, even after alkalination, the particle count still met the USP requirements for small volume injections.1

Discussion

The present study demonstrates that bupivacaine solutions are stable and do not contain excessive particulate matter after pH adjustment. Additionally, we found that commercially manufactured solutions of bupivacaine have a wide range of pH from one lot to another. These results are in agreement with those of MacMorland et al.4 who reported that the standard error of the mean pH of 0.25% bupivacaine solutions was 1 unit. These variations should be taken into account when interpreting the results of studies examining the efficacy of bupivacaine solutions. Moreover, the increase in pH that occurs after addition of a standard amount of sodium bicarbonate will vary, depending on the initial pH of the solution. Thus, we believe that measurement of pH is necessary before clinical trials with alkalized bupivacaine are performed.

Unlike previous clinical studies,4-6 we used 1.4% sodium bicarbonate in the present study because the recommended volume of 8.4% sodium bicarbonate (0.1 ml/20 ml plain bupivacaine) is too small to be precisely used in clinical practice with a high degree of accuracy. Indeed, volumes greater than 0.1 ml of 8.4% sodium bicarbonate added to 0.5% bupivacaine without epinephrine result in immediate precipitation7 of bupivacaine base.8 On the other hand, while more dilute solutions of bicarbonate are easier to administer, they can result in excessive dilution of the local anesthetic solution. In fact, the volume of 1.4% sodium bicarbonate that we added is still very small and only leads to a dilution of 1.03 and 1.075% with 0.6 and 1.5 ml, respectively. We have found that it is impossible to increase pH over the final values reported in Table 1, since precipitation occurs as pH is greater than 7.0. This inability to increase the pH of bupivacaine above 7.0 limits the increase in the unionized form of the drug and might at least partially explain the lack of efficacy of alkalization reported by some investigators.9

In summary, alkalization of bupivacaine solutions with 1.4% sodium bicarbonate causes an increase in pH values close to the physiological pH with precipitation of bupivacaine base not exceeding recommended values and without changing the concentrations of the solutions. The stability of these pH-adjusted solutions over time allows use of these solutions for at least 6 h following alkalization.

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References