Alkalinization and Precipitation Characteristics of 0.2% Ropivacaine

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Background and Objectives: Alkalinization of local anesthetics has been used to increase the speed of onset of nerve blocks. However, alkalinization of local anesthetic solutions may cause precipitation, thereby decreasing bioavailability and anesthetic activity. Alkalinization of ropivacaine has not been described. This laboratory study assessed the alkalinization and precipitation characteristics of ropivacaine.

Methods: Aliquots (2 mL) of commercially available ropivacaine (Naropin, 0.2%; Astra Pharmaceutical, Westborough, MA) were alkalinized with increasing amounts (0.01, 0.02, 0.04 mL) of sodium bicarbonate (8.4%) and immediately monitored for pH change and onset of visible precipitation at room temperature. We then alkalinized ropivacaine with sodium bicarbonate and measured the amount of precipitate that accumulated after various incubation times.

Results: The pH of ropivacaine increases with the addition of small amounts of bicarbonate. The calculated percentage of nonionized ropivacaine increased from 0.3% to greater than 30% with alkalinization from pH of 5.51 to 7.63. Drug loss to precipitation increased with higher doses of bicarbonate, reaching 25% to 30% of the total ropivacaine. Even with a low dose of bicarbonate (0.1 mL bicarbonate/20 mL ropivacaine), precipitation increased with time of incubation, reaching a plateau at 20 minutes.

Conclusions: A laboratory evaluation that establishes the alkalinization characteristics of ropivacaine is a prerequisite for designing a clinical study of alkalinized ropivacaine. In our experiment, low doses of bicarbonate produced significant increases in the proportion of nonionized ropivacaine with only modest precipitation. There would be a low likelihood of substantial drug precipitation if the mixture was administered within 5 to 10 minutes after alkalinization. These results indicate that alkalinized ropivacaine should not be used for infusions and that ropivacaine should not be alkalinized until just before use. *Reg Anesth Pain Med 2000;25:518-521.*

Key Words: Ropivacaine, Local anesthetics, Alkalinization, pH adjustment.

Alkalinization of local anesthetics has been used to increase the speed of onset of epidural anesthesia and major nerve blocks,[1-5] with some reports also claiming that alkalinization prolongs the duration of a block.[1-3]

Local anesthetics are weak bases that are supplied in acidic solution for solubility. Thus, a higher pH can increase the proportion of the lipid soluble, nonionized, form of the local anesthetic. The nonionized form of the drug is believed to more rapidly cross the perineural and nerve cell membranes to its site of action. However, alkalinization of a local anesthetic solution may cause precipitation,[5] which would decrease bioavailability of the drug and hinder activity. Previous studies have examined alkalinization of commonly used local anesthetics and described their tendency to precipitate.[1-6]

Ropivacaine is an enantiomerically pure (S-enantiomer), long-acting, local anesthetic in the amide class. It has been reported that compared with bupivacaine, ropivacaine has less effect on motor fibers (AB fibers), whereas the blocking effects on sensory fibers (C, A-delta) are similar.[7-9] Another advantage cited for ropivacaine is that it has less cardiotoxicity than bupivacaine.[10,11] Given these benefits, ropivacaine is being used with increasing frequency for surgery, obstetrics, postoperative pain treatment, and even chronic pain therapy.[12-15]

There are no studies in the literature detailing the pH and precipitation characteristics of this new local anesthetic. We sought to do so in a series of laboratory experiments. A laboratory study to obtain this information is necessary before undertaking a clinical evaluation of alkalinized ropivacaine.

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The goal of this experiment was to define the alkalinization characteristics of ropivacaine. We chose to study a dilute ropivacaine solution (0.2%) that is used for pain relief, particularly in the obstetric setting.

Using commercially packaged ropivacaine and sodium bicarbonate solutions, we defined the amount of sodium bicarbonate required to reach physiologic pH, calculated the percentage of the nonionized form of the local anesthetic, and measured the time to formation of visible precipitate after alkalinization. We also quantitated the fraction of ropivacaine lost to precipitation after alkalinization at time intervals from 10 minutes to up to 1 hour.

Using these data from the laboratory experiment, we determined that an optimal amount of sodium bicarbonate to add would be 0.1 mL of 8.4% sodium bicarbonate to 20 mL of ropivacaine. This ratio provides for the highest amount of nonionized local anesthetic while minimizing the amount of precipitated drug. It also generates a "titratable" dose of sodium bicarbonate that the clinician can add through a tuberculin syringe.

Materials and Methods

The ropivacaine (Naropin, 0.2%) used in the experiments was a commercially available preparation from Astra Pharmaceutical (Westborough, MA). Sodium bicarbonate 8.4% (wt/vol), (1 mEq/mL), also manufactured by Astra, was the alkalinizing agent used in the study.

pH Studies

Aliquots (2 mL) (n = 18) of ropivacaine were alkalinized with sodium bicarbonate (0.01, 0.02, 0.04 mL). The bicarbonate solution was added with a micropipette (Pipetman; Rainin Instruments, Woburn, MA) to the local anesthetic in a plain glass tube. The resulting mixture was immediately monitored for pH change and onset of visible precipitation at room temperature. Sample pH was measured using a PHM 84 Research pH meter calibrated to a pH of 7.000 with a certified buffer standard from Fisher Scientific (Fair Lawn, NJ). The precipitation data are recorded as time, in minutes, to onset of visible precipitation after alkalinization of the local anesthetic.

The pKa is the pH at which the amount of ionized and nonionized drug is equal. The pKa of ropivacaine is 8.1.[7] Given this pKa, the predicted percentages of nonionized ropivacaine at different pH values were derived using the Henderson-Hasselbalch equation (Eq 1).

$$\text{pH} = \text{pKa} + \log(\text{base}/\text{acid}) \quad (1)$$

Precipitation Studies

The second part of the study measured the fraction of ropivacaine lost to precipitation after alkalinization. A gravimetric technique was used. Aliquots of sodium bicarbonate (0.025, 0.05, 0.1 mL) were pipetted into plain glass tubes with ropivacaine (5 mL). In this way, the samples had an equivalent ratio of base to local anesthetic as in the pH studies. The samples were vortexed for 5 seconds to ensure proper mixing and incubated for 10 minutes at room temperature. To collect the precipitate, samples were filtered through preweighed GF/F filters (Whatman Glass microfiber filters, 2.5 cm with pore size of 0.7 μm; Whatman, Clifton, NJ) using a Millipore suction apparatus (Millipore Corp, Bedford, MA) and wall suction. The tubes were washed twice with a solution of 5 mL of Normal Saline (0.9% Sodium Chloride; Abbott Laboratory, North Chicago, IL) alkalinized to the same pH used to precipitate the local anesthetic.

The filters were dried on a warming plate and weighed again on the scale. The difference in the weights was used to assess the amount of precipitate. The control for the experiment was ropivacaine without any bicarbonate added; control filters were washed with normal saline. The control values were subtracted from the experimental trials to determine the amount of precipitate produced with alkalinization. For weight measurement we used a Mettler AE 163 balance (Mettler Instrument Corp, Hightstown, NJ) calibrated to 0 to 30 mg with an accuracy of 0.01 mg.

The precipitate that would be produced over time was studied by mixing 5 mL of ropivacaine with 0.025 mL of bicarbonate as described above. Samples were incubated at room temperature for 10, 20, 40, and 60 minutes, respectively. Formation of precipitate was determined as described above.

Results

pH Studies

The pH of untreated aliquots of commercially packaged ropivacaine (0.02%) averaged 5.51. The pH of the ropivacaine solution readily increased in a dose-dependent fashion with the addition of small amounts of sodium bicarbonate (Table 1). Precipitation was observed at 8 to 10 minutes in the trials using 0.010 mL of sodium bicarbonate in 2 mL ropivacaine and at earlier times with higher bicarbonate doses. As seen in Table 1, the predicted percentage of the nonionized form of the ropivacaine increases from 0.3% to greater than 30% with alkalinization.

Table 1. Alkalinization and Precipitation Characteristics of Ropivacaine (0.2%)

Bicarbonate (mL/5 mL ropivacaine) (n = 18)	pH ± SD	Time (min) to Precipitation	Percent Base (nonionized ropivacaine)
0.000	5.51 ± 0.09	∞	0.3
0.025	7.37 ± 0.10	8-10	18.6
0.050	7.54 ± 0.06	4-5	27.5
0.100	7.63 ± 0.07	2-3	33.8

NOTE. Results of adding increasing amounts of sodium bicarbonate (column 1) to 5 mL of ropivacaine. Columns 2 and 3 list the observed pH (±SD) and time of onset of visible precipitation of the ropivacaine/bicarbonate mixture. Column 4 is the predicted percentage of the nonionized form of the local anesthetic in solution using the Henderson-Hasselbalch equation (n = 18).

Precipitation Studies

The quantity of precipitate collected by filtering increased with increasing doses of sodium bicarbonate. As illustrated in Fig 1, the amount of precipitate increases from less than 0.5 mg to around 2.5 mg with increasing doses of bicarbonate. Because samples contained 10 mg of local anesthetic (5 mL of ropivacaine, 0.2%), up to one quarter of the total drug is precipitated, depending on the amount of bicarbonate added.

The effect of incubation time on the formation of precipitate of alkalinized ropivacaine was shown in the second part of the precipitation studies. The formation of precipitate, determined after 10, 20, 40, and 60 minutes of incubation, initially increased with time and then leveled off (Fig 2).

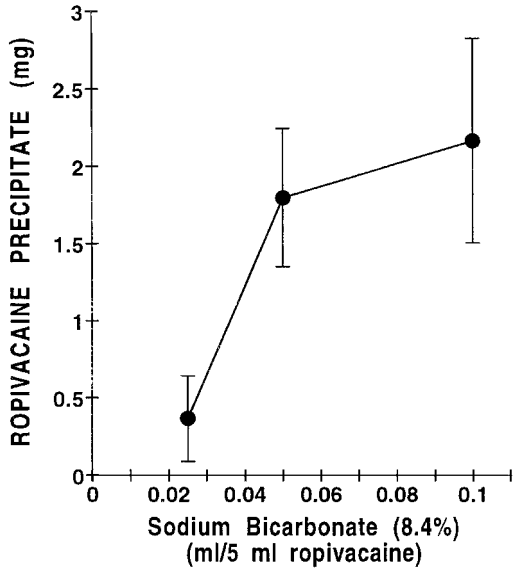

Fig 1. Precipitation increases in proportion to the amount of sodium bicarbonate added to ropivacaine (0.2%). Aliquots of ropivacaine alkalinized at room temperature with sodium bicarbonate were filtered and assayed for the amount of precipitate (mean ± SD, n = 6).

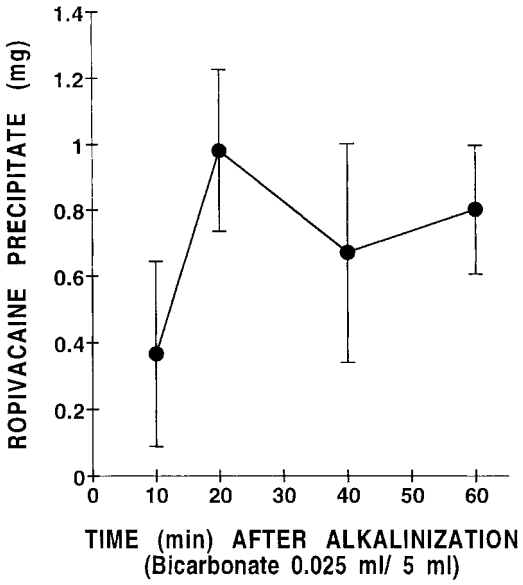

Fig 2. Precipitation of ropivacaine (0.2%) as a function of time after alkalinization with sodium bicarbonate. Aliquots of ropivacaine alkalinized at room temperature with sodium bicarbonate (0.025 mL/5 mL of ropivacaine) were filtered and assayed for the amount of precipitate after incubation times of 10, 20, 40, and 60 minutes, respectively (mean ± SD, n = 7).

Discussion

The possible clinical application of increasing the proportion of nonionized ropivacaine in anesthetic solutions was the impetus for this study. The pH values of the ropivacaine before pH adjustments are similar to reported values of other commercially available local anesthetics. The ability to adjust the pH of ropivacaine with small amounts of sodium bicarbonate make the alkalinizing profile similar to that of bupivacaine, as previously described.[6]

The pKa of ropivacaine is 8.1.[7] This study shows that small amounts of sodium bicarbonate alkalinize the commercially packaged local anesthetic close to the pKa. The proportion of drug in the basic (nonionized) form is predicted to increase from less than 1% to greater than 30%, depending on the pH as derived by the Henderson-Hasselbalch equation. It would be expected that an increased proportion of nonionized ropivacaine should hasten the onset of clinical nerve block.

This study also shows that precipitation of ropivacaine occurs in a dose-dependent fashion with the addition of sodium bicarbonate. With increasing amounts of bicarbonate, the amount of precipitation can increase to 25% to 30% of the local anesthetic. This may be of concern for clinicians using the alkalinized local anesthetic because precipitation would likely decrease bioavailability of the drug.

The findings suggest that a low dose of bicarbon-

ate (0.1 mL bicarbonate/20 mL of ropivacaine 0.2%) would produce a significant increase in the proportion of nonionized local anesthetic with a modest amount of precipitation. However, the study also shows that the amount of precipitation increases with time, even with this dose of bicarbonate. Though not directly evaluated in our study, it would be predicted that more concentrated solutions of ropivacaine (i.e., 0.75%) would precipitate more quickly under these conditions.

Based on our findings, we suggest that there would be low likelihood of substantial drug precipitation if the ropivacaine (0.2%) is administered within 5 to 10 minutes of alkalinization. This information is of potential significance for anesthesiologists who would choose alkalinized solutions of this local anesthetic for clinical nerve block. In particular, the results indicate that alkalinized ropivacaine should not be used for infusions. Also, if placing catheters or needles for clinical nerve block is likely to be difficult and time consuming, we suggest that the ropivacaine should not be alkalinized until just before it is administered. Lastly, the information generated in this laboratory study is a prerequisite for designing clinical evaluations on the utility of alkalinizing ropivacaine.

Using the data from the laboratory experiment, we determined that an optimal amount of sodium bicarbonate to add would be 0.1 mL of 8.4% sodium bicarbonate to 20 mL of ropivacaine. This ratio provided for the highest amount of nonionized local anesthetic while minimizing the amount of precipitated drug. If lower amounts of sodium bicarbonate were used, not only would the percentage of nonionized local anesthetic be less than 15%, but the resultant pH of the local anesthetic would be lower than the normal human range.

In summary, alkalinization of ropivacaine can be achieved with low doses of bicarbonate. However, the clinician must balance the potential benefit of hastening the onset of nerve block with the concern of losing bioavailability of the drug through precipitation.

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