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Mixtures of Local Anesthetics: Bupivacaine-Chloroprocaine

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Experiments were performed in a rat sciatic nerve preparation to determine the characteristics of nerve blocks produced by a combination of commercially available solutions of bupivacaine and chloroprocaine. A mixture of equal parts of commercially available chloroprocaine 2% and bupivacaine 0.5% resulted in a nerve blockade with characteristics of a chloroprocaine block. Changing the pH value of this mixture from 3.60 to 5.56 changed these characteristics to a blockade resembling that produced by bupivacaine. It is concluded that the nerve blockades obtained by mixing commercially available solutions of local anesthetics are unpredictable and may depend on a number of factors which include not only the types of drugs but the pH of the mixture.

Key Words: ANESTHETICS, Local: bupivacaine; ANESTHETICS, Local: chloroprocaine.

THE MIXTURE of an anesthetic of short duration and rapid onset, such as chloroprocaine, with one of long duration but slow onset, such as bupivacaine, is said to induce a nerve block having the best characteristics of the individual agents.[1] Our clinical experience, however, does not confirm this belief.[2] Mixing anesthetic solutions, commercially prepared to be used as individual agents, may alter the ideal pH for one or both drugs. Anesthetics may also compete for receptor sites,[3] with one agent dominating the ensuing block.

The objective of this work was to determine, under laboratory conditions, the characteristics of nerve blocks produced by commercially available solutions of chloroprocaine and bupivacaine alone and in combination.

Methods

Thirty-six experiments were performed using rat sciatic nerve preparations. Rats (250 mg) were anesthetized with intraperitoneal pentobarbital (30 mg/kg), paralyzed with intramuscular gallamine triethiodide (Flaxedil, 5 to 10 mg) and ventilated with a small animal respirator (Harvard). Both sciatic nerves were dissected with special care to preserve their blood supply. Temperature of the preparation was maintained at 35 ± 1 C. Electrical stimulation was performed using square wave pulses of 0.1-msec duration and suprathreshold voltage at a frequency of 5 Hz (Grass S88 stimulator). Recording was made distally using platinum electrodes 5 mm apart. Compound action potentials were amplified and displayed on a two-channel memory oscilloscope for measurements and permanent photographic record.

The nerves were crushed between recording electrodes to obtain monophasic action potentials and near the spinal cord to avoid reflex stimulation.

The anesthetic solutions (0.5 ml) were applied to a 3-mm segment of the sciatic nerve, wrapped with tissue paper, for a period of 10 minutes followed by washout with warm Ringer's solution pH 7.2 to 7.4.[4] Two different anesthetic solutions were applied to each pair of nerves in any given experiment. Changes in the amplitude of the nerve action potential, as measured on a Tektronix 565 oscilloscope, were used to determine the effects of solutions of chloroprocaine

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1% (Nesacaine, Pennwalt, pH 3.56), bupivacaine 0.25% (Marcaine, Winthrop, pH 5.60, or bupivacaine (Abbott), pH 6.11), a mixture of equal parts of Nesacaine 2% and Marcaine 0.5% (pH 3.60), and equal parts of Nesacaine 2% and Marcaine 0.5% with sodium bicarbonate added to obtain a pH of 5.56. The results were plotted as percentage depression vs time; separate regressions for each experiment were run during the first 30 minutes of the recovery period.[5] These regressions were averaged within each treatment group to obtain a common slope; the groups' slopes were compared by analysis of covariance (Figure).

Results

Changes in amplitude of the nerve action potential observed with the combination of commercially available chloroprocaine-bupivacaine resembled that obtained with chloroprocaine alone (Table). The long duration block characteristic of bupivacaine was not apparent when mixtures of the two drugs as commercially provided were studied (Figure). Changing the pH value of the mixture from 3.60 to 5.56, however, slowed the rate of recovery (Figure) to the extent that the rate of recovery then resembled that observed after application of bupivacaine alone.

Discussion

Combining commercially available anesthetic solutions may not result in the theoretical advantages suggested by single drug effects, since local anesthetics differ in their physicochemical characteristics, possible mechanisms and sites of action, as well as

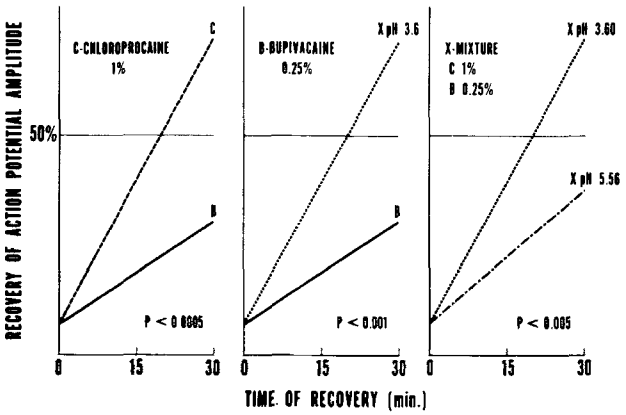

FIGURE. Normalized regression analysis of the rate of recovery of the sciatic nerve action potential. This rate was significantly faster following 10 minutes of application of commercially available chloroprocaine 1% (C) or the mixture of chloroprocaine 1% and bupivacaine 0.25% (X) at pH 3.60, than it was following application of bupivacaine 0.25% (B) alone or in combination with chloroprocaine 1% but with a pH of 5.56.

TABLE

Depression of Compound Nerve Action Potential by Various Anesthetic Solutions

Drug	No. of experiments	% depression of action potential 10 min after administration*
Chloroprocaine 1%	9	64 ± 4
Bupivacaine 0.25%	8	44 ± 7
Mixture, pH 3.60	12	66 ± 5
Mixture, pH 5.56	7	51 ± 7

* Means ± standard error.

the pH value of the solution as provided by the manufacturer. A given pH value in an anesthetic mixture of two drugs may favor the active form (base or cationic) of one of the anesthetics, thus preventing the other from occupying the active sites. Under these circumstances, results obtained by the mixture may be dominated by one of the drugs. However, early clinical observations supported the use of local anesthetic mixtures despite lack of concrete evidence in their favor.[6] In experimental observations, using the response to painful stimuli during epidural anesthesia in dogs, Defalque and Stoelting[7] found reason to doubt the theoretical advantages of mixing tetracaine with procaine or lidocaine under certain circumstances. In the present work we have developed a neurophysiologic preparation for in vivo testing of local anesthetic mixtures in a mammalian nerve. Results indicate that the pH value of mixtures of local anesthetics is an important factor in determining how the mixtures act. When commercially available solutions of chloroprocaine and bupivacaine are mixed to obtain anesthesia with rapid onset and long duration, pH value must be increased if the mixture is not to act like chloroprocaine.

The importance of the pH change in mixtures of chloroprocaine and bupivacaine may be related to the relative proportion between the base and the cationic form of the anesthetics at the site of injection as determined by their pKa values (bupivacaine 8.1, chloroprocaine 9). The available base of bupivacaine at pH 3.60, or in the mixture of the two commercial solutions, is one hundredth of that available at the pH 5.60 of the 0.25% solution. However, the available base of chloroprocaine remains the same since the pH value of both the mixture (3.60) and its commercial solution (3.56) are so similar.

We conclude that the characteristics of nerve blocks obtained using these commercial mixtures are unpredictable and depend on the types of drugs, and the final pH value of the solution.

Since the completion of our work, two clinical

reports[8, 9] have confirmed our earlier observations[2] and present support for the clinical relevance of our data.

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Cardiac Complications in Surgical Patients with Bifascicular Block

Ninety-eight patients with ECG evidence of bifascicular block who had undergone general anesthesia and surgery were followed. The His bundle electrogram was recorded in all patients prior to the surgery. On the basis of electrophysiologic studies, patients were divided into two groups: normal H-V group (47 patients) and prolonged H-V group (51 patients). The prolonged H-V group presented a significantly greater incidence of organic heart disease and cardiac symptoms. Correspondingly, there was a significantly higher incidence of cardiac complications during and following operations in patients with prolonged H-V interval, but none of the patients developed complete heart block. Ventricular fibrillation, rather than complete heart block, was the cause of sudden cardiac death in three patients who had a prolonged H-V interval and severe organic heart disease. The authors suggest that patients with bifascicular block, undergoing anesthesia and surgery, even in the presence of presumable risk factors, do not require prophylactic pacing. The H-V duration represents a more accurate predictor of major cardiac intraoperative and postoperative complications than the surface recordings, but only in patients with symptomatic heart disease. These data support the concept that high-risk patients can be identified clinically and that preoperative determination of H-V intervals is not necessary. *(Bellocci F, Santarelli P, Di Gennaro M, et al: The risk of cardiac complications in surgical patients with bifascicular block: a clinical and electrophysiologic study in 98 patients. Chest 77:343-348, 1980)*