

The Influence of 2-Chloroprocaine on the Subsequent Analgesic Potency of Bupivacaine

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Isolated rat sciatic nerves were used to study the interaction between 2-chloroprocaine (2-CP) and bupivacaine (BP). Five nerves studied as controls were treated with 5×10^{-4} M BP and the amplitude of the compound action potential (CAP) evoked by suprathreshold stimulation was measured. This concentration of BP completely blocked nerve conduction; but, following washout with normal Krebs-Ringer solution, the CAP amplitude recovered to 50% of initial values in 50 (± 4) min with a rate of recovery of 1.7 (± 0.6) %/min. In another series of experiments, five nerves were blocked first with 5×10^{-4} M 2-CP, allowed to fully recover, and then were blocked with BP under the same conditions as the controls. Under these conditions, the half time for the recovery of CAP amplitude following BP was shortened to 25 (± 5) min, with a rate of recovery of 2.8 (± 0.3) %/min. When five nerves were exposed to a 5×10^{-4} M solution of a 2-CP metabolite, 4-amino-2-chlorobenzoic acid, no nerve blockade was produced. When these nerves subsequently were blocked with BP, recovery to 50% of initial values occurred in 22 (± 5) min, with a rate of recovery of 2.0 (± 0.2) %/min. Although pretreatment with either 2-CP or 4-amino-2-chlorobenzoic acid significantly shortened the duration of BP-induced nerve blockade, neither drug had a significant effect on the rate of recovery once the CAP amplitude returned to measurable values.

These results suggest that the metabolite of 2-CP, 4-amino-2-chlorobenzoic acid, remains in the nerve following recovery from neural blockade and interferes with the subsequent action of BP upon this nerve. (Key words: Anesthetics, local: bupivacaine, chloroprocaine. Biotransformation: metabolites; 4-amino-2-chlorobenzoic acid.)

2-CHLOROPROCAINE (2-CP) would appear to be the most appropriate drug to commence epidural anesthesia for labor pain, since its rapid onset of action will give prompt relief. Moreover, the rapid hydrolysis of 2-CP by plasma cholinesterase lessens the danger of possible toxic responses occurring from accidental intravascular injection. If labor and delivery are expected to continue for at least 2-3 h, prolongation of epidural block may be attempted with a longer-acting drug such as bupivacaine (BP). It has been our experience, however, that the use of BP following 2-CP produced blockade lasting only 30-40 min instead of the anticipated 90-120 min. A clinical

study showed a similar decrease in the efficacy of BP if preceded by 2-CP.¹ To more clearly define this interaction between 2-CP and BP, experiments were conducted *in vitro* on the isolated rat sciatic nerve.

Methods

Sciatic nerves were excised from decapitated 180-250-g male Sprague-Dawley rats. The nerves were cleaned of connective tissue and suspended in a modified Harvard Isolated Nerve Chamber containing Krebs-Ringer solution (135 mM NaCl, 2 mM CaCl₂, 5 mM KCl, 1 mM MgCl₂, 1 mM Na₂HPO₄, 15 mM NaHCO₃, 11 mM glucose bubbled with 99% O₂-5% CO₂ at room temperature, pH 7.3). The chamber was modified by dividing the interior into three separate compartments, each with an entry and exit port for exchange of solutions. At one end of the chamber a pair of platinum stimulating electrodes was used to stimulate (Grass S44 stimulator) the nerve with suprathreshold pulses of 0.1 ms duration. Compound action potentials (CAPs) were recorded extracellularly by two pairs of recording electrodes on each side of the middle compartment. The potentials were amplified (Grass P15) and displayed on a Tektronic Type RM564 storage oscilloscope. Drugs were introduced into the middle compartment and the effect on the relative amplitudes of the two CAPs was measured (CAP #2/CAP #1 = CAP Ratio). The stimulating voltage was increased until the CAP ratio became constant and maximal. This voltage then was used throughout the study with that nerve. A glass slide covered the top of the chamber to produce a seal and maintain a moist atmosphere inside. The studies were conducted at room temperature in a grounded cooper wire mesh enclosure.

Five nerves were studied as controls. The middle chamber was filled with a 5×10^{-4} M solution of BP and measurements of the CAP ratio were made at 5-min intervals. After 20 min, the middle chamber was evacuated and flushed several times with Krebs-Ringer solution. The ratio then was measured at 5-min intervals until it returned to control values. After each measurement, the chamber was flushed again with normal Krebs-Ringer solution.

A second set of five nerves initially was exposed to a 5×10^{-4} M solution of 2-CP in the middle chamber. The pH of the 2-CP solution was found to be 7.20. The 2-CP solution was removed after 20 min and the chamber

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Received from the Departments of Anesthesiology and Pharmacology, and The Jerry Lewis Neuromuscular Disease Center, Vanderbilt University School of Medicine, Nashville, Tennessee. Accepted for publication July 8, 1983. Supported in part by Grants NINCDS 12438 and NIEHS 02028.

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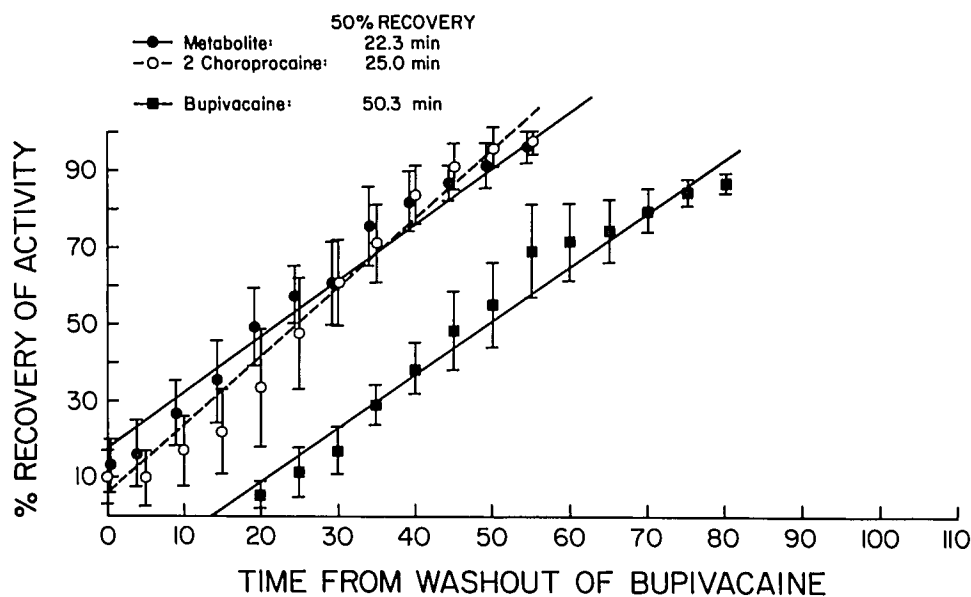


FIG. 1. The time course of recovery from bupivacaine blockade in the three groups studied (measured in minutes from the time of washout of the bupivacaine). The individual points represent the mean \pm SEM. The straight lines were constructed using linear regression analyses and were used to calculate the rates of recovery indicated in table 1.

flushed again with normal Krebs-Ringer solution. The ratio was measured at 5-min intervals until it returned to normal. When the ratio was again at preblock level, BP (5×10^{-4} M) was added to the middle chamber. The magnitude and duration of the nerve block then was measured in the same way as the control group and compared with it. Finally, a third set of five nerves was pretreated with a 5×10^{-4} M 4-amino-2-chlorobenzoic acid for 20 min. The effect of this metabolite of 2-CP on the subsequent action of BP then was determined as above.

An analysis of variance was used to compare the time with 50% recovery following washout of BP in the control, 2-CP, and metabolite groups. The same analysis was used to compare the rates of recovery in the same groups once recovery had commenced.

Results

Figure 1 shows the average recovery of nerves exposed to 5×10^{-4} M BP for 20 min. Following washout of the drug, the average time to return to 50% of the control CAP ratio ($t_{1/2}$) was 50 (± 4) min, and the rate of recovery

was 1.7 (± 0.6) %/min. Following pretreatment and recovery from 5×10^{-4} M 2-CP (20 min), the duration of subsequent BP action was reduced significantly ($t_{1/2} = 25 \pm 4$ min), and the rate of recovery was increased slightly to 2.7 (± 0.3) %/min (fig. 1). When nerves initially were exposed to the metabolite 4-amino-2-chlorobenzoic acid, which did not in itself produce nerve blockade, the duration of subsequent BP action was reduced ($t_{1/2} = 22 \pm 4$ min) and the rate of recovery was 2.0 (± 0.2) %/min (fig. 1). An analysis of variance revealed a significant effect of pretreatment with either 2-CP or 4-amino-2-chlorobenzoic acid on the duration of BP action ($P < 0.01$). None of the effects on the rate of recovery were statistically significant (table 1).

Discussion

The purpose of this study was to determine whether one could obtain experimental data that would support the clinical impression that the initial administration of 2-CP interfered with the subsequent analgesic efficacy of BP. Previous studies utilizing these drugs in combination rather than in sequence have yielded differing results. Cunningham and Kaplan² were able to significantly decrease the onset time of axillary blockade, without reducing the duration of block, by mixing the two drugs and administering them together. Cohen and Thurlow,³ however, showed that mixing the two drugs produced a block that was similar to that produced by 2-CP alone. Similar results were obtained by Galindo and Witcher,⁴ who showed that the recovery of CAP amplitude following exposure to mixtures of BP and 2-CP significantly was lengthened if the pH of the mixture was made more basic. At pH 3.6, a mixture of the two drugs produced

TABLE 1. Time in Minutes from Washout of Bupivacaine to 50% Recovery and Rate of Recovery in Percentage per Minute in Study Groups*

	Time in Minutes to 50% Recovery	Rate of Recovery Percentage per Minute
Controls	50 (± 4)	1.7 (± 0.5)
2-Chloroprocaine	25 (± 5)†	2.7 (± 0.3)
4-Amino-2-chloro Benzoic acid	22 (± 4)†	2.0 (± 0.2)

* Values are means \pm SEM.

† Significantly different from control ($P < 0.01$) by analysis of variance.

a block that recovered with the shorter time course characteristic of 2-CP. However, if the mixture was made more basic (pH 5.6), the CAP amplitude recovered with the longer time course characteristic of bupivacaine. In the present study, we show that exposure to 2-CP hastens the recovery from subsequent bupivacaine administration. It is unlikely that the effects observed in the present study are secondary to changes in pH since the preparation was washed extensively with normal Krebs-Ringer solution (pH 7.3) following each exposure to experimental solutions and the pH of the 2-CP solution in Krebs-Ringer solution was 7.2. Nevertheless, the pH dependence observed by Galindo *et al.* (1980)⁴ is interesting and suggests that the ability of 2-CP to alter the activity of bupivacaine may depend upon the pH of the chloroprocaine solution.

In this study, the duration of block produced by BP ($t_{1/2} = 50$ min) on the isolated nerve was similar to that observed in clinical practice. The recovery time was reduced significantly ($t_{1/2} = 25$ min) if the nerve was pretreated with 2-CP and allowed to recover from the 2-CP block. This result is similar to that found in the clinical situation.¹ Although the rate of recovery also appeared to be more rapid following 2-CP treatment, this effect was not statistically significant.

Since 2-CP has an ester linkage in its structure, it is

hydrolyzed by plasma cholinesterase and one metabolite produced is 4-amino-2-chlorobenzoic acid. When the nerve was pretreated with a solution of this metabolite, no nerve block was produced. However, when the nerve subsequently was blocked with BP, the pattern of recovery became very similar to that seen when pretreatment was with 2-CP (fig. 1). This suggests that the 2-CP hydrolyzed in close proximity to the nerve produces the metabolite 4-amino-2-chlorobenzoic acid, which ultimately interferes with the binding or access of BP to its site of action.

These results suggest, therefore, that this action of 2-CP is mediated by 4-amino-2-chlorobenzoic acid, a bi-product of the action of endogenous nerve cholinesterase on 2-CP.

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