

Title: VERAPAMIL POTENTIATES BUPIVACAINE-INDUCED NEURAL CONDUCTION BLOCKADE

Authors: W.C.V. Parris, M.D.¹, K.E. Misulis, M.D.², J.R. Kambam, M.D.¹, J.J. Franks, M.D.¹ and W.D. Dettbarn, M.D.²

Affiliations: Departments of Anesthesiology¹ and Neurology², Vanderbilt University Medical Center, Nashville, Tennessee 37232

INTRODUCTION: The mechanism of neural conduction blockade by local anesthetics, including bupivacaine, is believed to be inhibition of sodium conductance by displacement of calcium ions. To our knowledge the effect of verapamil, a calcium channel blocker, on neural conduction blockade produced by local anesthetics has not been reported. The purpose of this study, therefore, is to determine the effect of verapamil on local anesthetic-induced conduction blockade in the rat sciatic nerve preparation.

METHODS: After obtaining appropriate institutional approval, male Sprague-Dawley rats weighing 300-350 gms were decapitated for harvest of sciatic nerves. The nerves from both sides were exposed in the lateral thigh and dissected free from surrounding connective tissue. A nerve segment of 4 to 5 cm length was placed in a dish with isotonic saline and 5% dextrose at 37° C and was bubbled with a mixture of 95% O₂ and 5% CO₂. An area in the midsection of the nerve was desheathed to facilitate entry of administered drugs. The desheathed nerve was placed in a recording chamber across five electrodes fixed at 1 cm apart and maintained at 37° C. Two electrodes were used for stimulation, two for recording, and one for grounding between the stimulating and recording electrodes. Stimuli were 0.1 ms square-wave pulses delivered by a Grass S-88 stimulator. Stimulus intensity was set 25% above the voltage at which a maximum response was recorded from the nerve. The recorded action potentials were amplified by Grass P-15 AC preamplifiers with output displayed on Tektronix oscilloscope. The amplified signal was also sent to an Apple 2E microcomputer for digital analysis. The measured parameter was peak amplitude of the compound action potential (CAP). We tested serially diluted concentrations of verapamil and arrived at a concentration (0.025%) at which the effect of conduction blockade was minimal. It is this concentration that we used to augment diluted concentration of local anesthetic. Since nerves were dissected from both sides, the left and right sides were considered as a pair. One of the pair had bupivacaine 0.125% administered first, followed by a combination of bupivacaine 0.125% - verapamil 0.025%, while the other nerve of the pair was administered verapamil 0.025% first, followed by bupivacaine 0.125% - verapamil 0.025% combination. A control recording was established and the first drug applied to the desheathed segment of nerve situated between the stimulating and recording electrodes. After 5 minutes, the segment was washed with isotonic normal saline and the bupivacaine 0.125% - verapamil 0.025% combination was added. Two minutes later, single responses and averages of 25 responses were recorded at each time point. Data were analyzed by randomized block analysis of variance and the Student-Newman-Keuls multiple comparison procedure.

RESULTS: Fig. 1a shows mean values of CAP from 5 rat sciatic nerve preparations before and after

addition of verapamil and verapamil-bupivacaine combined. Control amplitudes from this group averaged 5.50±1.50 (mean±SE) mv. Minimal depression to 4.96±1.34 mv was observed with 0.025% verapamil, in accordance with experimental design. However, bupivacaine - verapamil produced a 50% decrease in CAP to 3.00±0.98 mv, differing significantly from control and verapamil mean (p<0.01). More marked effects occurred when 7 nerve preparations were treated with bupivacaine and then with bupivacaine-verapamil (Fig. 1b). Bupivacaine reduced CAP from a control value of 3.47±0.79 to 1.70±.32 mv, p<0.01, whereas bupivacaine - verapamil caused a further reduction to 0.66±0.17, about 20% of the control value, p<0.01.

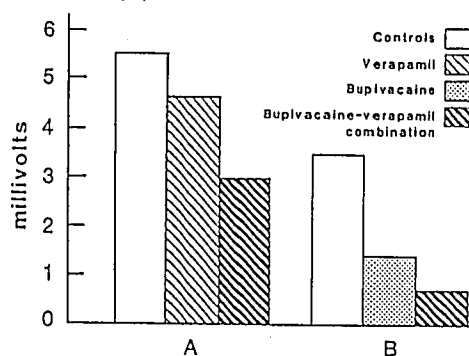


Figure 1

DISCUSSION: Verapamil effects not only the voltage dependent slow calcium channel but also the receptor activated fast channel at the nerve terminal.¹ It is possible that this latter property is utilized in potentiating local anesthetic-induced conduction blockade in the sciatic nerve preparation.

Potentiation of bupivacaine by the addition of verapamil may be of clinical value. Reduction of the dose of bupivacaine required for neural blockade should lower the risk of local anesthetic toxicity. This additive (or perhaps synergistic) action of bupivacaine and verapamil could be utilized in regional analgesia and in nerve block therapy for chronic pain patients. We found that normal strength verapamil (0.25%) alone produced significant nerve conduction blockade. Yet 0.025% verapamil significantly potentiated the conduction blockade caused by bupivacaine in the rat sciatic nerve preparation.

REFERENCE:

1. Kraynack BJ, Lawson NW, Gintautaus J. Local anesthetic effect of verapamil in vitro. *Regional Anesthesia* 1982;7:114-117.

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