TITLE: THE INFLUENCE OF A 2-CHLOROPROCAINE METABOLITE ON THE CARDIOTOXIC EFFECTS OF BUPIVACAINE

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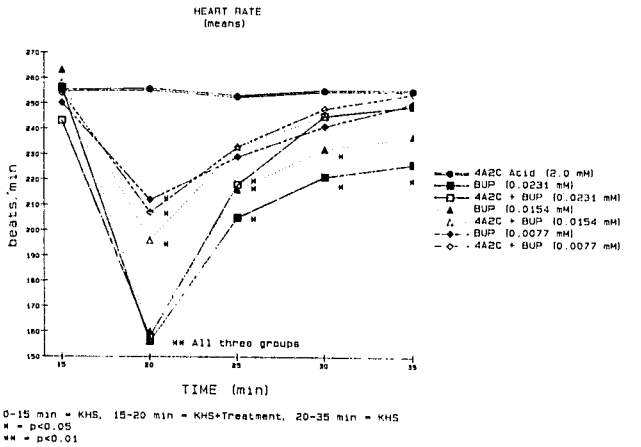
Purpose. It has recently become apparent that bupivacaine (BUP) is significantly more cardiotoxic than other local anesthetics.(1) Hodgkinson reported that the use of 2-chloroprocaine interfered with the subsequent local anesthetic activity of BUP.(2) This interaction was reproduced in a laboratory study using 4-amino-2-chlorobenzoic acid (4A2C), a 2-chloroprocaine metabolite.(3) The present study examined the effects of 4A2C on the cardiotoxic effects of BUP in the isolated rat heart using a Langendorff apparatus.

Methods. Forty-six adult male Sprague-Dawley rats (400-600g) were anesthetized with ether. The heart was excised and perfused with Krebs-Henseleit solution (KHS), aerated with 95% O_2 and 5% CO_2, and maintained at 37°C, on a modified Langendorff apparatus. ECG electrodes were attached and a balloon catheter inserted in the left ventricle providing a tracing from which heart rate, left ventricular pressures and dP/dt were measured. Coronary perfusion pressure and flow were also measured. After an equilibration period, hearts were perfused with 4A2C (2.0mM), BUP (0.0231, 0.0154, 0.0077mM), or combinations of these two compounds. The test solution was then perfused for five minutes followed by reperfusion with KHS alone for fifteen minutes to examine reversibility of drug effects. The data was analyzed using Student's t-test. A p value less than 0.05 was considered significant.

Results. There was no significant change ($p>0.05$) from measured baseline values in the hearts receiving KHS with 2.0mM 4A2C. All six BUP solutions significantly decreased the heart rate during their exposure (Fig. I). All hearts except the high dose BUP returned to baseline rate within 15 minutes following termination of the BUP. There were no significant changes in left ventricular systolic pressure except for the 0.0231mM BUP group which dramatically depressed the heart. All three concentrations of BUP alone significantly decreased dP/dt, and simultaneous perfusion with 4A2C protected them from this effect (Fig II). All contractile parameters returned to baseline values within five minutes after reperfusion with normal KHS.

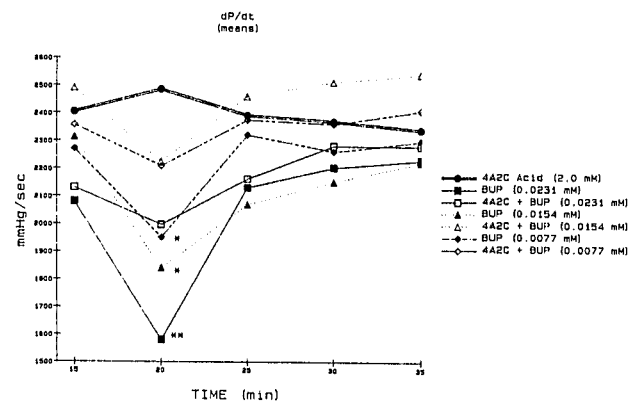
Discussion. From previous studies (2-3) it was concluded that 4A2C, a metabolite of the local anesthetic 2-chloroprocaine, competes with BUP for receptor sites in nerve tissue. This study was undertaken to investigate whether the same phenomenon could be observed with respect to cardiac receptors where local anesthetics are also known to have a depressant effect. A significant protection was afforded by 4A2C against changes in dP/dt and heart rate produced by 0.0231mM BUP. Although there was trend towards antagonism by 4A2C in the lower concentrations of BUP, these changes did not reach statistical significance. Currently, we are looking at the levels of BUP extracted from the heart muscle to see if this effect may be due to a reduction in the amount of BUP present in the myocardial tissue. Thus, it could be possible that the protection provided by 4A2C may be competitive as was seen in neuronal conduction.

FIGURE 1



0-15 min = KHS, 15-20 min = KHS+Treatment, 20-35 min = KHS
* = p<0.05
** = p<0.01

FIGURE 2



0-15 min = KHS, 15-20 min = KHS+Treatment, 20-35 min = KHS
* = p<0.05
** = p<0.01

References.

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2. Hodgkinson R, Husain FJ, Bluhm C: Reduced effectiveness of bupivacaine 0.5% to relieve labor pain after prior injection of chloroprocaine 2%. Anesthesiology 57:3A201, 1982.
3. Corke BC, Carlson CG, Dettbarn WD: The influence of 2-Chloroprocaine on the subsequent analgesic potency of bupivacaine. Anesthesiology 60:25-27, 1984.