A681

TITLE: EPINEPHRINE INCREASES BUPIVACAINE TOXICITY IN RATS

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INTRODUCTION: Bupivacaine (BUP) is frequently used for regional anesthesia. Epinephrine (EPI) is added to local anesthetics (LA) to prevent rapid vascular absorption and/or prolong local anesthetic duration of action, and is believed to antagonize local anesthetic-induced cardiovascular depression[1]. EPI, 1:200,000, (5 μg/ml = EPI 5) increases BUP toxicity in rats[1]. Here we report a dose response study of 3 doses of EPI added to BUP.

METHODS: Institutional Animal Care Committee guidelines were followed. Adult male Sprague Dawley rats, divided randomly into 4 groups of 10, were studied under intraperitoneal pentobarbital anesthesia (40-80 mg/kg). Lead II of the EKG was monitored and a femoral venous catheter was placed. Groups II-IV got i.v. BUP 0.5%, 4 mg/kg, to which EPI had been added as follows: 5 μg/ml (EPI 5, group II), 2.5 μg/ml (EPI 2.5, group III), or 2 μg/ml (EPI 2, group IV). An equivalent volume of normal saline placebo (NS) with EPI 5 was given i.v. to group I to assess for toxicity due to the highest dose of EPI alone. Rats maintaining adequate respirations, heart rate with precordial pulsations, and not developing cyanosis, were survivors. Rats developing apnea, cyanosis and ultimately, electromechanical dissociation, agonal rhythm, asystole or ventricular fibrillation with loss of precordial pulsations, were fatalities. Classification was 5 min after BUP-EPI or NS-EPI placebo injection.

RESULTS: Neither weights nor pentobarbital doses differed statistically among groups (ANOVA). One out of 10 (10%) rats in group I, 8/10 (80%) in groups II & III, and 9/10 (90%) in group IV, died ($P<0.007$, Chi-square analysis with Yate's correction).

DISCUSSION: BUP is probably the most cardiotoxic LA in clinical use if accidentally injected i.v. Our results agree with previous findings[1] that BUP with EPI is more toxic than plain BUP. We found this to be true even in group IV, with the BUP concentration reduced to 2 μg/ml (BUP with EPI 2).

BUP toxicity may involve both fast (sodium dependent) and/or slow (calcium dependent) cardiac channels[2,3]. By phosphorylation of the calcium channel via cAMP-dependent kinases, EPI increases the number of open calcium channels available for BUP entry[4], and possibly thereby increases BUP toxicity. Also, BUP increases systemic and pulmonary vascular resistance[5]. Thus, EPI may promote BUP toxicity by further increasing these vascular resistances, especially if it also causes coronary vasoconstriction.

IN CONCLUSION, added epinephrine, 2-5 μg/ml, increases toxicity of i.v. bupivacaine in rats.

REFERENCES:
1. Anesth Analg 70:543-5, 1990
2. Ann Fr Anesth Reanim 7:204-10, 1988
3. Anesth Analg 67:107-114, 1988
4. Nature 301:569-74, 1983
5. Anesth Analg 61:317-22(1982)

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A682

TITLE: STIMULATION OF CYCLIC AMP PRODUCTION BY BUPIVACAINE: A POSSIBLE MECHANISM OF LOCAL ANESTHETIC CARDIOVASCULAR TOXICITY

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Introduction: Cardiac arrest in animals occurs after lower doses of bupivacaine (B) if given with epinephrine (E).[1,2] We tested whether B might alter the ability of E to stimulate the production of cyclic AMP, the intracellular 2nd messenger of (E) and a known arrhythmogenic agent.[3,4]
Methods: After IRB approval, 20 ml of venous blood was withdrawn from consenting subjects. Isolated lymphocytes were incubated with 50 μM isobutylmethylxanthine (to inhibit cyclic AMP breakdown), radiolabelled ATP, and the appropriate B concentration. After 10 min, the reaction was quenched. Cyclic AMP was determined by radioimmunoassay. Results from 15 assays were assessed by analysis of variance and generalized linear model technique. $P<.05$ was considered significant.
Results: E produced significant concentration-dependent increases in cyclic AMP. At concentrations above 10 μg/ml, B significantly increased cyclic AMP formation compared to the basal rate (Figure). When coadministered, E 10^{-7}M significantly increased the cyclic AMP response to B (Figure).
Discussion: Our data demonstrate that B alone or with E increases cyclic AMP production in human lymphocytes. Lymphocytes have ß-adrenergic receptors which bind agonists and couple with adenylyl cyclase in an identical manner to myocardial ß receptors.[5] Thus, we believe that our results predict the response of heart cells to B and E.

Increased cyclic AMP production may well underlie the increased blood pressure and heart rate commonly seen early during B intoxication in experimental animals and patients. Finally, increased intracellular cyclic AMP concentrations may explain the potentiation of B cardiotoxicity by E, and the frequent production of ventricular arrhythmias by high concentrations of B.

References:
1. Bernards CM et al: Anesthesiology 71:711-7, 1989
2. Kambam JR et al: Anesth Analg 70:543-5, 1990
3. Podzuweit T et al: Lancet 1:341-2, 1976
4. Huang XD, Wong TM: Clin Exp Pharmacol Physiol 16:751-7, 1989
5. Brodde O-E et al: Eur Heart J 10B:2-10, 1989