Anesthesiology
V 75, No 3A, Sep 1991

POSTER SESSION VIII

A765

TITLE: PROLONGED SCIATIC NERVE BLOCKADE USING SUSTAINED RELEASE OF BUPIVACAINE FROM A BIODEGRADABLE POLYMER MATRIX

Authors: D. B. Masters, PhD, C.B. Berde, MD, PhD, S. Dutta, BA, R. Langer, PhD
Affiliations: Department of Anesthesia, Children's Hospital, Boston, MA 02115 & Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139

Introduction

Biodegradable polyanhydride polymers (PP) have been shown to be an effective vehicle for sustained release of medications in humans and animals for weeks to months[1]. Application of a timed-release local anesthetic (LA) preparation adjacent to nerves could potentially be a useful alternative to catheter infusions or neurolytic blocks for providing prolonged regional analgesia. *In vitro* studies showed that sustained release of a LA from PP was feasible[2]. The aim of this study was to measure motor and sensory blockade of the rat sciatic nerve *in vivo* using bupivacaine (B)-impregnated PP implants.

Methods

1,3 bis(p-carboxyphenoxy) propane-sebasic acid anhydride copolymers (20:80) were synthesized as described previously[1], and B-HCl was incorporated by hot melt molding in 20% weight ratios in 50 mg pellets. Seven anesthetized rats received implants of 20% B pellets (300 mg total) under direct vision adjacent to the sciatic nerve on one side with an equal mass of sham pellets implanted along the contralateral nerve. Each day, we recorded motor blockade, using a 4-point scale, and latency of withdrawal following application of the foot to a 56 °C surface. A group of 5 similarly treated rats received indwelling central venous cannulae, and blood samples were obtained for bupivacaine assay by HPLC. Data were analyzed using repeated measures ANOVA, post-hoc paired t-tests, and Wilcoxon rank-sum tests.

Results

In vitro studies from the same preparation used *in vivo* showed B release from PP over 6-8 days. Motor blockade lasted at least 2 days (Figure 2) in all animals in the B-treated side; control sides showed no motor blockade. In comparison to the control side, the B-treated side showed significantly longer hot-plate latencies for 3 days ($p<0.05$, Figure 3). Plasma B levels at 1, 4, 24, 48, 72 and 96 hrs post-implant were all < 0.1 µg/ml.

Discussion

Three day reversible blockade of the rat sciatic nerve *in vivo* can be produced using B-PP matrices. Plasma levels were well below those associated with toxicity. B-PP matrices may be a convenient method for prolonged reversible regional blockade.

References

1. J. Biomed. Mat. Res. 19: 941-955, 1985.
2. Anesthesiology 73:A776, 1990.

Fig 1 Motor Blockade

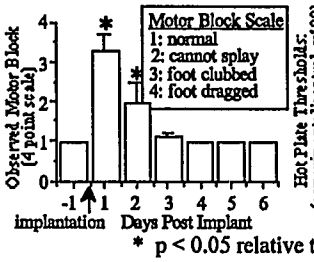
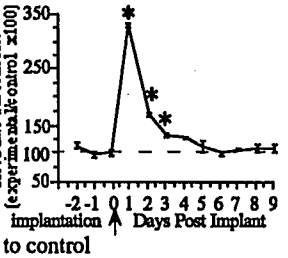


Fig 2 Sensory Blockade



* $p < 0.05$ relative to control

A766

TITLE: NICARDIPINE REDUCES TOXICITY FROM I.V. BUPIVACAINE WITH EPINEPHRINE IN RATS

AUTHORS: WW Kinney MD, JL Horn MD, SA Hyman MD, C Skelley RN, PM Kinney RN
AFFILIATION: Anesthesiology Dept, Vanderbilt Medical School, Nashville, TN, USA 37232-2125

INTRODUCTION: Nicardipine[1] (NIC), verapamil[2] and diltiazem[3] pretreatment protect against i.v. bupivacaine (BUP) in Sprague Dawley rats, but addition of epinephrine (EPI) to the BUP eliminates verapamil's protection[4]. We studied NIC effects on toxicity of i.v. 0.5% BUP with EPI.

METHODS: Institutional Animal Care Committee guidelines were followed. Adult male Sprague Dawley rats were divided randomly into 6 groups and studied under intraperitoneal pentobarbital anesthesia (50-100 mg/kg). EKG lead II was monitored. A femoral v. catheter was placed and either NIC 30 µg/kg, 50 µg/ml, (groups II, IV & VI) or an equivalent volume of saline placebo (NS, in groups I, III & V), pretreatment was given i.v. Three min later, one of the 3 following solutions was given: 3.75 mg/kg of 0.5% bupivacaine + either EPI 1:200,000 (EPI 5, 5 µg/ml, groups I & II), or EPI 1:500,000 (EPI 2, 2 µg/ml, groups III & IV), or 4 mg/kg of 0.5% BUP + EPI 2 (groups V & VI). Rats maintaining adequate respirations, heart rate with precordial pulsations, and not developing cyanosis, were survivors. Those developing apnea, cyanosis and ultimately, electromechanical dissociation, agonal rhythm, asystole, or ventricular fibrillation with loss of precordial pulsations, were fatalities. Classification was 5 minutes after BUP-EPI.

RESULTS: Neither weights nor pentobarbital doses differed among groups ($p>0.05$ by ANOVA). Survival was statistically significantly greater in NIC-pretreated groups II & IV (11/16 survived in each) compared to their matched NS controls (4/11, in both groups I & III) ($P<0.001$), and also in NIC, group VI (9/13) compared to NS, group V (2/13 survived) ($P<0.02$). Outcome P values are by Chi-square analysis with Yates' correction.

DISCUSSION: NIC protects against toxicity due to plain BUP[1] to the greatest degree of all the calcium channel blockers (CCBs) reported on[1-4]. NIC also reduces fatalities from i.v. BUP even when EPI 2-5 µg/ml is added. Adding EPI to the BUP largely or totally eliminates protection by the other CCBs. BUP cardiotoxicity may involve coronary arterial spasm[5]. If so, NIC's greater protection may be due to its relatively more potent coronary artery vasodilation.

IN CONCLUSION, 30 µg/kg i.v. nicardipine pretreatment signficantly reduces fatal toxicity due to 0.5 % BUP with added EPI, 2-5 µg/ml, in rats.

REFERENCES

1. C J Anaesth 37: 920-3, 1990
2. Anesthesiology 71: A1145, 1989
3. Anesthesiology 73: A811, 1990
4. Kinney W et al: Proceedings Soc CV Anesthesia, 1989
5. Albright GA, Report to FDA, 1983

Supported by the Study Center for Anesthesia Toxicology, Vanderbilt University Medical Center, Nashville, TN, USA 37232-2125