TITLE: ACUTE TOXICITY OF BUPIVACAINE AND DESBUTYLBUPIVACAINE IN THE RAT

AUTHORS: P.H. Rosenberg, M.D., Ph.D. and J.E. Heavner, D.V.M., Ph.D.
AFFILIATION: Departments of Anesthesiology, TTUHSC Lubbock, TX 79430, and University of Helsinki, SF-00130 Helsinki, Finland

Desbutylbupivacaine (DBB) is the major metabolite of bupivacaine (BUPI). During long-term intermittent administration of BUPI there is considerable accumulation of DBB in the blood.[1] DBB has been reported to be 1/8 times as toxic as BUPI in mice.[2] Using a rat model recently developed for the study of local anesthetic toxicity,[3] we investigated the acute central nervous system (CNS) and cardiovascular (CV) toxicity of BUPI and DBB.

After approval from the Animal Care and Use Committee, we studied 26 Sprague-Dawley male rats (250-300 g). Under halothane anesthesia, fronto-occipital EEG and EKG electrodes were placed, tracheostomy performed, and femoral artery (blood pressure recording) and vena cava (test drug infusion) were cannulated. After a 30 min stabilization period (0.5% halothane in 70% N_2O/30% O_2, pancuronium 0.1 mg/kg) with controlled ventilation monitored by arterial blood-gas analyses, infusion of 0.5% BUPI, 2 mg/kg/min (N=10) or 1% DBB, 4 mg/kg/min (N=10), or a combination of 0.5% BUPI (2 mg/kg/min) and 0.15% DBB (0.67 mg/kg/min) (N=6) was started. Predefined toxic end-points were: 1. first dysrhythmia (DYS), 2. first seizure activity on EEG (SZ), 3. isoelectric EEG (ISO EEG) and 4. asystole (ASYS). Statistical analyses: ANOVA and Newman-Keuls' test.

The mean (± SD) doses of BUPI producing CV toxicity were approximately 50% of those of DBB($P<0.01$) (table). Seizure activity was observed in only one DBB rat, while all BUPI rats developed seizures, which always occurred earlier than dysrhythmias. Arterial blood pressure was well maintained until ISO EEG) and near-ASYS. DBB potentiated the CV toxicity of BUPI ($P<0.05$), while the EEG parameters were not significantly altered by the combined infusion in comparison to BUPI alone.

	DYS	SZ	ISO EEG	ASYS
BUPI (mg/kg)	12.4±8.5	5.2±1.4	13.4±5.9	24.±7.7
DBB (mg/kg)	24.0±8.2	-	37.6±8.8	47.8±10
Combination				
-BUPI (mg/kg)	4.6±2.3	6.0±1.4	10.9±.3	16.0±4.2
-DBB (mg/kg)	1.4±0.7	1.8±0.4	3.3±1.0	4.9±1.3

In this experimental model, DBB was about 1/2, instead of 1/8,[2] as toxic as BUPI when DYS and ASYS were the CV toxic end-points. DBB clearly potentiated the dysrhythmogenic activity, but not the CNS toxicity (SZ, ISO EEG) of BUPI. This study contradicts the belief that DBB is relatively non-toxic.[1] Interestingly, DBB is a metabolite also of mepivacaine and probably of ropivacaine.

DBB was a gift from Sterling Winthrop.

References
1.Anaesthesia 25:14-23, 1970.
2.Acta Pharmacol Toxicol 2:213-223, 1965.
3.Reg Anesth 15 (Suppl. 1S):S31, 1990.

A818

TITLE: DEMOGRAPHIC FACTORS INFLUENCING THE PCA MORPHINE REQUIREMENT

AUTHORS: R.K. Parker, D.O., F. Perry, Ph.D., B. Holtmann, M.D., P.F. White, Ph.D., M.D.
AFFILIATION: Department of Anesthesiology, Washington University, St. Louis, MO 63110

Many factors have been alleged to influence the postoperative analgesic requirement. Previous studies have involved retrospective analyses of patients undergoing a wide variety of surgical procedures utilizing different anesthetic techniques. In this prospective study, we evaluated the morphine requirement using a patient-controlled analgesia (PCA) delivery system for pain control after total abdominal hysterectomy (TAH).

101 consenting ASA I-II adult women undergoing TAH were studied according to an IRB-approved protocol. All patients received the same general anesthetic technique. In the recovery room, patients received morphine sulfate, 1-2 mg iv bolus doses as needed, to achieve adequate pain relief. Prior to discharge from the recovery room, an Abbott 4100 PCA infuser was connected to the patients intravenous catheter. The PCA device was programmed to deliver morphine 2 mg iv bolus doses "on demand" with a 10 min lockout interval. Postoperative assessments included morphine usage (mg/h), pain and sedation analog scales (q8h), and side effects. Data were analyzed using linear regression analysis and correlation, with $p<0.05$ considered statistically significant.

The demographic factors which were evaluated are summarized in table 1. There was an age-related decrease in the amount of morphine required during the first 24 h after surgery. Similarly, ASA physical status II patients required less morphine than ASA-PS I patients during the first and second postoperative days. Finally, race appeared to influence morphine usage, with black patients requiring less opioid medication than their caucasian counterparts. Neither the patient's body weight, duration of operation, nor history of previous abdominal surgery correlated with their opioid usage. Surprisingly, chronic preoperative use of oral analgesics, beta-blockers or clonidine did not influence the postoperative morphine requirement.

We conclude that age, race and physical status appear to influence the postoperative morphine requirement after TAH. However, the marked variability which existed among patients in their requirement for opioid analgesics is probably related to non-demographic factors.

Table 1: Correlations (r) between demographic factors and morphine usage at 0-24h and 24-48h after surgery

Factors	0 - 24h	24 - 48h
Age	-0.26*	-0.12
Weight	-0.06	+0.06
Race	-0.23*	+0.01
ASA physical status	-0.26*	-0.24*
Analgesic use	+0.07	+0.02
Prior intrabdominal surgery	+0.11	+0.08
Duration of surgery	-0.15	+0.07
Beta-blockers	-0.05	+0.10
Clonidine	0.00	0.00

*Significant correlation, $p<0.05$ with $r>0.22$ for 2-tailed test of $r>0$

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/73/3A/NA/666381/0000542-199009001-00817.pdf by guest on 17 April 2024