Propranolol pretreatment reduces cardio-respiratory toxicity due to plain, but not epinephrine-containing, intravenous bupivacaine in rats

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The purpose of this study was to evaluate the effects of pretreatment with propranolol on the cardio-respiratory toxicity of bupivacaine, either plain or with epinephrine 1:200,000 ($5 \mu\text{g} \cdot \text{mL}^{-1}$) added. Adult male Sprague Dawley rats, anaesthetized with intraperitoneal pentobarbital, were divided into four groups. Groups I and III were pretreated with iv propranolol $150 \mu\text{g} \cdot \text{kg}^{-1}$, and Groups II and IV received iv NS as a placebo. Three minutes later, rats in Groups I and II received plain 0.5% bupivacaine, $4 \text{ mg} \cdot \text{kg}^{-1}$, and Groups III and IV received $4 \text{ mg} \cdot \text{kg}^{-1}$ of 0.5% bupivacaine with epinephrine, $5 \mu\text{g} \cdot \text{mL}^{-1}$ iv. Five of eight rats pretreated with propranolol survived (Group I), compared with uniform fatality with NS pretreatment (Group II) ($P < 0.05$). Addition of epinephrine to the bupivacaine eliminated the protective effect of propranolol. All rats pretreated with propranolol (Group III) or NS (Group IV) died when given bupivacaine with epinephrine. In conclusion, acute propranolol pretreatment reduced the fatal cardiotoxicity due to

iv bupivacaine in male Sprague Dawley rats, but the addition of epinephrine $5 \mu\text{g} \cdot \text{mL}^{-1}$ to bupivacaine eliminated the protective effect of propranolol.

Le but de cette étude était d'évaluer les effets d'un traitement préalable au propranolol sur la toxicité cardiorespiratoire de la bupivacaine simple ou associée à l'épinéphrine 1:200,000 ($5 \mu\text{g} \cdot \text{mL}^{-1}$). Des rats adultes mâles Sprague Dawley, anesthésiés par du pentobarbital intrapéritonéal, furent divisés en quatre groupes. Les groupes I et III furent traités au préalable avec du propranolol iv $150 \mu\text{g} \cdot \text{kg}^{-1}$ et, et le groupe II et IV ont reçu une injection intraveineuse d'une solution physiologique comme placebo. Trois minutes plus tard, les rats du groupe I et II ont reçu de la bupivacaine 0.5%, $4 \text{ mg} \cdot \text{kg}^{-1}$ et le groupe III et IV ont reçu $4 \text{ mg} \cdot \text{kg}^{-1}$ de 0.5% de bupivacaine associé à $5 \mu\text{g} \cdot \text{mL}^{-1}$ iv. Cinq des huit rats traités au préalable avec le propranolol ont survécu (groupe I), comparativement à une mortalité certaine avec le traitement au préalable à la solution physiologique (groupe II) ($P < 0.005$). L'addition de l'épinéphrine à la bupivacaine a éliminé les effets protecteurs du propranolol. Tous les rats traités au préalable au propranolol (groupe III) ou au soluté physiologique (groupe IV) sont morts lorsqu'ils ont reçu de la bupivacaine avec épinéphrine. En conclusion, le traitement aiguë au préalable au propranolol a réduit la mortalité cardiothoxique due à la bupivacaine iv chez les rats mâles Sprague Dawley mais l'addition d'épinéphrine $5 \mu\text{g} \cdot \text{mL}^{-1}$ à la bupivacaine a éliminé l'effet protecteur du propranolol.

Key words

ANAESTHETICS, LOCAL: bupivacaine;

PHARMACOLOGY: beta adrenergic blockers, propranolol;

TOXICITY: local anaesthetics.

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Beta adrenergic blocking drugs are widely used in the management of patients with cardiovascular disease, including hypertension, angina pectoris, and occasionally for supraventricular arrhythmia.¹ When these patients need surgery, regional anaesthesia is often considered.

Bupivacaine is frequently used for local and regional

TABLE Outcome data

	0.5% Bupivacaine 4 mg · kg ⁻¹			
	Plain		+ epinephrine 5 µg · ml ⁻¹	
	Group I	Group II	Group III	Group IV
Propranolol pretreatment, µg · ml ⁻¹	150	0	150	0
Survival (n)	5/8*	0/8	0/8	0/8
Survival (%)	62.5%	0	0	0

* $P < 0.05$ (Group I vs Group II).

anaesthesia techniques in surgical and obstetrical patients because of its excellent anaesthetic properties. Nevertheless, bupivacaine can cause marked, often fatal, cardiotoxicity^{2,3} if a sufficient amount is absorbed from vessels adjacent to the site of deposition or if it is injected accidentally intravenously.

Drug interactions are probably more common than usually appreciated, and may be either manipulated to the patient's benefit, or may be potentially life-threatening if not anticipated and managed safely.⁴ Myocardial depression due to propranolol is known to be additive to that caused by halothane,^{5,6} enflurane⁷ and isoflurane.^{8,9} Therefore it was hypothesized that propranolol's negative inotropic effect might similarly potentiate the cardiotoxicity due to myocardial depression from bupivacaine accidentally given *iv*, and that the positive inotropic effect of epinephrine would decrease the cardiotoxicity.¹⁰

The purpose of this study was to investigate the effect of acute *iv* propranolol pretreatment on cardio-respiratory toxicity due to either plain bupivacaine or bupivacaine with epinephrine.

Methods

Our Institution's Animal Care Committee guidelines were followed throughout this study of 32 adult male Sprague Dawley rats. Anaesthesia was achieved with intraperitoneal sodium pentobarbital. Lead II of the ECG was monitored and video recorded. A femoral vein was cannulated with a 24-gauge catheter, a 20 µl venous sample was taken for analysis of venous blood gases in a Corning 168 analyzer, and the catheter was flushed with 0.5 ml normal saline (NS). Pilot studies had previously shown that the LD₅₀ dose of bupivacaine was 4.0 mg · kg⁻¹, and that at 3.5 mg · kg⁻¹ (approximate LD₅₀), propranolol pretreatment had no effect on bupivacaine cardio-respiratory toxicity. Therefore a dose of 4 mg · kg⁻¹ was chosen to detect any protective effect of propranolol pretreatment.

Group I and III rats received 150 µg · kg⁻¹ propranolol (250 µg · ml⁻¹ in NS) *iv* pretreatment, while Groups II and IV received a similar volume of NS. Three minutes later,

4 mg · kg⁻¹ of bupivacaine plain (Groups I and II), or with epinephrine 5 µg · ml⁻¹ (Groups III and IV), was given *iv*.

Rats were observed for apnoea, arrhythmias, and precordial pulsations. One minute after bupivacaine administration, rats were classified as either a survivor or a fatality. Survivors were sacrificed with an additional dose of bupivacaine. Outcome data were analyzed using two-tailed Fisher's exact test and Chi-square analysis. Student's *t* test was used for comparison of Group I with II and Group III with IV. $P < 0.05$ was considered statistically significant.

Results

There were no statistically significant differences between Groups I and III or between Groups II and IV with respect to weight, pentobarbital doses or venous blood gas analysis. Five of eight rats in Group I survived, whereas all rats in group II died ($P < 0.05$). All rats in Groups III and IV died (see Table). Group I survivors had brief apnoea (<14 sec), and simultaneously, or immediately afterwards, had transient increases in heart rate, with or without minimal transient widening of the QRS complex, and uninterrupted precordial pulsations. There was prompt resumption of rate and depth of respirations similar to their baseline. Groups I and II fatalities first became apnoeic, then had slight increases in heart rate, followed by minimal broadening of the QRS complex and/or transient 2:1 atrioventricular blockade, prior to resumption of sinus rhythm with persistent apnoea and death in electromechanical dissociation. Group III and IV fatalities developed apnoea, followed promptly either by asystole, complete heart block, or bizarre wide-QRS ventricular arrhythmias, with deep cyanosis and loss of precordial pulsations. Ventricular fibrillation developed only in NS pretreated rats given bupivacaine with epinephrine (Group IV).

Discussion

The protective effect of acute propranolol pretreatment against cardio-respiratory toxicity due to plain bupivacaine was somewhat unexpected, since propranolol is

known to have myocardial depressant effects. Despite its β -adrenergic myocardial stimulant effects, epinephrine, when added to bupivacaine, eliminated the protective effect of propranolol pretreatment. In previous studies we found verapamil to be protective against the cardio-respiratory toxicity due to plain bupivacaine, but not against the cardio-respiratory toxicity due to bupivacaine to which epinephrine $5 \mu\text{g} \cdot \text{ml}^{-1}$ had been added.^{11,12} The mechanism(s) of these protective effects remains undetermined.

Beta adrenergic blockers are known to reduce arrhythmias dependent on catecholamine stimulation, and this is perhaps related to a reduction of β -2 mediated hypokalaemia.^{13,14} Whether hypokalaemia occurs at the onset of bupivacaine cardio-respiratory toxicity and is preventable by β -blockade is unknown, but needs clarification, as this may be a mechanism of propranolol's protective effect. It is noteworthy that rats receiving plain bupivacaine did not exhibit the bizarre, markedly widened QRS complexes seen in rats receiving bupivacaine with epinephrine. Furthermore, the only instances of ventricular fibrillation occurred in NS pretreated rats receiving bupivacaine with epinephrine, consistent with the arrhythmogenic properties of epinephrine. Propranolol may protect against plain bupivacaine toxicity due to its antiarrhythmic properties. Since the addition of epinephrine completely eliminated the protective effect of propranolol pretreatment, evidently any expected beneficial effect due to epinephrine's positive inotropy¹⁰ is more than overcome by the potential additive arrhythmogenicity of epinephrine with that of bupivacaine. This is consistent with our previous report:¹² Whereas nine of ten rats given $4 \text{ mg} \cdot \text{kg}^{-1}$ 0.5% bupivacaine with $5 \mu\text{g} \cdot \text{ml}^{-1}$ epinephrine added died, most with ventricular arrhythmias, epinephrine alone was shown to be nontoxic, as none of the ten rats given only an equivalent volume of NS with epinephrine, $5 \mu\text{g} \cdot \text{ml}^{-1}$, died. Our previous¹² and current results suggest that addition of epinephrine offers no additional safety margin in case of accidental *iv* administration of bupivacaine. We suspect that the addition of epinephrine may increase bupivacaine cardiotoxicity in humans, as it does in rats^{12,15} if the local anaesthetic is injected *iv*.

The mechanism(s) of bupivacaine toxicity is uncertain. By blocking fast sodium channels, bupivacaine exerts its local anaesthetic action. Bupivacaine also blocks "fast response" cardiac structures, specifically the maximum upstroke velocity of the myocardial action potential (V_{max}) of phase 0 of the action potential, thus depressing myocardial contractility.¹⁶ It also blocks "slow response" cardiac structures, thus exerting calcium channel blocking properties, specifically on specialized cardiac conduction tissue, thus depressing AV conduction.¹⁶ Bupivacaine cardiotoxicity could occur via either or both of these

mechanisms. The membrane-stabilizing properties of propranolol may modify bupivacaine cardiotoxicity. Toxic doses of bupivacaine may have coronary artery vasoconstrictive properties in guinea pigs.¹⁷ Perhaps propranolol's negative chronotropic effect increases tolerance for bupivacaine-induced coronary vasoconstriction, because of reduced compromise of coronary perfusion due to less relative shortening of diastolic time than would occur at a higher heart rate in the absence of propranolol pretreatment.

We recommend cautious use of propranolol in patients during general or regional anaesthesia. However, our results suggest no increased risk of bupivacaine cardio-respiratory toxicity in patients already taking propranolol. In fact, they raise the possibility of a prophylactic role for propranolol which warrants further investigation.

In conclusion, in adult male Sprague Dawley rats, propranolol pretreatment reduced fatal cardio-respiratory toxicity due to plain bupivacaine, but not due to bupivacaine with epinephrine added.

References

- 1 Wilkowski DAW, Lunn JJ. Preoperative evaluation. In: Tarhan S (Ed.). Cardiovascular Anesthesia and Post-operative Care, 2nd ed. Chicago: Yearbook Medical Publishers 1989; 7-8.
- 2 Albright GA. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. *Anesthesiology* 1979; 51: 285-7.
- 3 Liu P, Feldman HS, Covino BM, Giasis R, Covino BG. Acute cardiovascular toxicity of intravenous amide local anesthetics in anesthetized, ventilated dogs. *Anesth Analg* 1982; 61: 317-22.
- 4 Stanley TH. Foreword, Drug Interactions in Anesthesia, 2nd ed. Smith NT, Corbascio AN (Eds.). Philadelphia, Lea & Feiberger 1986; vii-viii.
- 5 Roberts JG, Foex P, Clarke JNS, Bennett MJ. Haemodynamic interactions of high dose propranolol pretreatment and anaesthesia in the dog. 1: Halothane dose-response studies. *Br J Anaesth* 1976; 48: 315-25.
- 6 Kopriva CJ, Brown ACD, Pappas G. Hemodynamics during general anesthesia in patients receiving propranolol. *Anesthesiology* 1978; 48: 28-33.
- 7 Horan BF, Prys-Roberts C, Hamilton WK, Roberts JG. Haemodynamic responses to enflurane and hypovolaemia in the dog and their modification by propranolol. *Br J Anaesth* 1977; 49: 1189-97.
- 8 Philbin DM, Lowenstein E. Lack of beta adrenergic activity in the dog: a comparison of circulatory effects of halothane and isoflurane after propranolol administration. *Br J Anaesth* 1976; 48: 1165-70.
- 9 Horan BF, Prys-Roberts C, Roberts JG, Bennett MJ, Foex P. Haemodynamic responses to isoflurane anaesthesia

- and hypovolaemia in the dog, and their modification by propranolol. *Br J Anaesth* 1977; 49: 1179-87.
- 10 Moore DC. Systemic toxicity of local anesthetic drugs. *Seminars in Anesthesia* 1983; 2: 62-74.
 - 11 Kinney WW, Kambam JR, Matsuda F, Wright W, Holaday D. Bupivacaine cardiotoxicity is reduced by verapamil pretreatment. *Anesthesiology* 1989; 71: A1145.
 - 12 Kinney WW, Kambam JR, Matsuda F, Wright W, Holaday D. Epinephrine-containing bupivacaine cardiotoxicity is not reduced by verapamil pretreatment in rats. Proceedings of the Society of Cardiovascular Anesthesiologists, 11th Annual Meeting, Seattle WA, April 1989; 174.
 - 13 Brown MJ, Brown DC, Murphy MB. Hypokalemia from beta-2 receptor stimulation by circulating epinephrine. *N Engl J Med* 1983; 309: 1414-9.
 - 14 Nordehaug JE. Malignant arrhythmia in relation to serum potassium in acute myocardial infarction. *Am J Cardiol* 1985; 56: 20d-23d.
 - 15 Kambam J, Kinney W, Matsuda F, Wright W, Holaday D. Epinephrine and phenylephrine increase cardio-respiratory toxicity of intravenously administered bupivacaine in rats. *Anesth Analg* 1990; 543-5.
 - 16 Clarkson CW, Hondeghem LM. Mechanism for bupivacaine depression of cardiac conduction: fast block of sodium channels during the action potential with slow recovery from block during diastole. *Anesthesiology* 1985; 62: 396-405.
 - 17 Tanz RD, Heskett T, Loehning PW, Fairfax CA. Comparative cardiotoxicity of bupivacaine and lidocaine in the isolated mammalian heart. *Anesth Analg* 1984; 63: 549-56.