Nicardipine reduces the cardio-respiratory toxicity of intravenously administered bupivacaine in rats

Fumiko Matsuda MD, Wesley W. Kinney MD,
William Wright BS, J. Reddy Kambam MD

The purpose of our study was to examine the effect of intravenous (IV) nicardipine pretreatment ($30 \mu\text{g} \cdot \text{kg}^{-1}$), given three minutes before an IV bolus of bupivacaine to determine its effect on the incidence of fatal bupivacaine cardio-respiratory toxicity in adult male Sprague Dawley rats anaesthetized with intraperitoneal pentobarbital. Fifty rats were divided into four groups. Groups I and II ($n = 10$ each) received $3.5 \text{ mg} \cdot \text{kg}^{-1}$ 0.5 per cent bupivacaine and Groups III and IV ($n = 15$ each) received $5.0 \text{ mg} \cdot \text{kg}^{-1}$ 0.5 per cent bupivacaine. Groups I and III received pretreatment with normal saline before bupivacaine, whereas Groups II and IV were given pretreatment with nicardipine, $30 \text{ mg} \cdot \text{kg}^{-1}$. There was no difference in the incidence of survival between the nicardipine pretreatment group and the saline placebo pretreatment group given $3.5 \text{ mg} \cdot \text{kg}^{-1}$ 0.5 per cent bupivacaine (no fatalities in either group). However, there was significant protection by nicardipine pretreatment in the group given $5 \text{ mg} \cdot \text{kg}^{-1}$ 0.5 per cent bupivacaine (13 of 15 survived, compared with only 4 of 15 in the saline pretreatment group, $P < 0.001$). In conclusion, our data demonstrate that in rats given 0.5 per cent bupivacaine, $5 \text{ mg} \cdot \text{kg}^{-1}$ nicardipine pretreatment protected against fatal cardio-respiratory toxicity.

Le but de notre étude était d'examiner les effets d'un pré-traitement intraveineux à la nicardipine ($30 \mu\text{g} \cdot \text{kg}^{-1}$), administré trois minutes avant un bolus intraveineux de bupivacaine

Key words

ANAESTHETICS, LOCAL: bupivacaine toxicity;
PHARMACOLOGY: calcium channel blockers, nicardipine;
TOXICITY: local anaesthetics.

From the Department of Anesthesiology, Vanderbilt University School of Medicine, Nashville, TN, USA, 37232-2125.

Supported by the Study Center for Anesthesia Toxicology, Vanderbilt University. Nicardipine was donated by Yamaguchi Pharmaceutical Co., Ltd., Tokyo, Japan.

Address correspondence to: Dr. W.W. Kinney, Department of Anesthesiology, VUH 3255, Nashville, TN, USA, 37232-2125.

afin de déterminer les effets sur l'incidence de la toxicité cardio-respiratoire de la bupivacaine chez les rats adultes mâles Sprague Dawley anesthésiés avec du pentobarbital intrapéritonéal. Cinquante rats ont été divisés en quatre groupes. Le groupe I et II ont reçu $3,5 \text{ mg} \cdot \text{kg}^{-1}$ 0,5 pour cent bupivacaine, groupe III et IV ($n = 15$ chaque) ont reçu $5,0 \text{ mg} \cdot \text{kg}^{-1}$ 0,5 pour cent de bupivacaine, le groupe I et III ont reçu un pré-traitement physiologique avant la bupivacaine alors que le groupe II et IV ont été pré-traités avec de la nicardipine $30 \text{ mg} \cdot \text{kg}^{-1}$. Il n'y avait aucune différence dans l'incidence de survie entre le groupe pré-traité à la nicardipine et le groupe traité au physiologique placebo et a reçu $3,5 \text{ mg} \cdot \text{kg}^{-1}$ 0,5 pour cent de bupivacaine (aucun décès dans aucun des groupes). Cependant, il y avait une protection significative dans le traitement à la nicardipine dans le groupe qui ont reçu $5 \text{ mg} \cdot \text{kg}^{-1}$ 0.5 pour cent de bupivacaine (13 des 15 ont survécus comparativement à 4/15 dans le groupe pré-traité au physiologique, $P < 0,001$). En conclusion, nos données démontrent que les rats ayant reçus 0.5 pour cent de bupivacaine, $5 \text{ mg} \cdot \text{kg}^{-1}$ de nicardipine en pré-traitement ont été protégés contre une toxicité fatale cardio-respiratoire.

Bupivacaine, an amide local anaesthetic, is widely used because of its excellent anaesthetic properties, including high potency, dense sensory blockade for a given degree of motor blockade, and long duration of action. However, bupivacaine is probably more cardiotoxic than any other local anaesthetic in clinical use today.¹⁻³

Calcium channel antagonists are frequently used in the treatment of angina pectoris, hypertension, and cardiac dysrhythmias, both chronically and acutely in the perioperative period. Other investigators have previously shown that bupivacaine inhibits both fast sodium-dependent channels and slow calcium-dependent channels.^{3,4} Many patients undergoing surgery with bupivacaine regional anaesthesia will already be taking calcium channel entry blockers, and/or will receive them perioperatively, and thus there is considerable potential for drug interactions

between these drugs. Drug interactions are probably more common than is usually appreciated, and may be either harmful to the patient, especially if not recognized early, or beneficial, if they can be utilized to increase a desired effect.⁵ In the presence of calcium channel blockers, bupivacaine may be more cardiotoxic,⁶ although this issue is unsettled, as other studies suggest that some calcium channel blockers may reduce bupivacaine cardiotoxicity.⁷

Nicardipine, a new dihydropyridine calcium channel antagonist structurally related to nifedipine, has been shown to reduce systemic vascular resistance and to produce potent coronary vasodilatation without negative inotropic effect.⁸ We have previously shown that pretreatment with verapamil protects against the cardio-respiratory toxicity due to bolus IV bupivacaine in adult male Sprague Dawley rats.⁷ The purpose of the present study was to investigate the effect of nicardipine pretreatment on bupivacaine's cardio-respiratory toxicity.

Methods

Our Institution's Animal Care Committee guidelines were followed throughout the study. The protocol was essentially identical to that which we have previously reported.⁷ Fifty adult male Sprague Dawley rats weighing approximately 300 g were randomly divided into four groups and anaesthetized with intraperitoneal pentobarbital 40 mg · kg⁻¹ (initial dose) until they were unresponsive to a painful stimulus (pinching skin with a forceps). Lead II of the ECG was monitored with a Hewlett-Packard monitor, precordial pulsations were observed through an illuminated magnifying lens, and respiratory rate was monitored. After cutdown, a femoral vein was cannulated with a 24-gauge IV catheter, and 20 µl was taken for blood gas analysis in a Corning 168 analyzer. Saline, 0.5 ml IV, was given after venous blood sampling.

Our preliminary dose response experiments in Sprague Dawley rats had shown that 5 mg · kg⁻¹, 0.5 per cent bupivacaine was fatal in about 90 per cent of the rats (LD₉₀), and that 3.5 mg · kg⁻¹ was fatal in fewer than ten

per cent. Based on these preliminary results with 0.5 per cent bupivacaine, 3.5 mg · kg⁻¹ and 5 mg · kg⁻¹ were chosen as the doses for the study of cardio-respiratory toxicity.

Groups I and II received 3.5 mg · kg⁻¹, 0.5 per cent bupivacaine IV, and Groups III and IV received 5 mg · kg⁻¹. Groups I and III were given pretreatment with normal saline (NS) placebo IV (a volume equal to the volume of nicardipine they would have received had they been in a nicardipine group), whereas Groups II and IV were given pretreatment with nicardipine 30 µg · kg⁻¹ (50 µg · ml⁻¹ in NS), a dose that has been recommended for human patients.⁸ Pretreatment was given slowly over two minutes. One minute following completion of pretreatment, i.e., three minutes after beginning pretreatment, all rats were given either 3.5 mg · kg⁻¹ (Groups I and II) or 5 mg · kg⁻¹ (Groups III and IV), 0.5 per cent bupivacaine as a rapid IV bolus injection (in ≤2 sec). Studies were performed between 9 a.m. and 12 noon. Rats were neither ventilated nor oxygenated, in order to simulate a frequent clinical scenario at the onset of bupivacaine cardio-respiratory toxicity, namely that the patient is apnoeic.

Five minutes after bupivacaine injection, rats were classified as fatalities or survivors.⁷ Rats that maintained adequate respiration and heart rate and did not develop cyanosis were classified as survivors. Rats that developed apnoea, cyanosis and ultimately, agonal rhythm or asystole, were classified as fatalities.

Data on body weights, pentobarbital doses, and blood gas analyses were compared using analysis of variance (ANOVA). Incidences of survival and fatality were compared using Chi-square analysis with Yates' correction. *P* values <0.05 were considered statistically significant.

Results

There were no differences in the body weights, pentobarbital doses or blood gas results among the four groups (ANOVA) (see Baseline Data, Table I). Outcome data are

TABLE I Baseline data*

	<i>Bupivacaine 3.5 mg · kg⁻¹</i>		<i>Bupivacaine 5 mg · kg⁻¹</i>	
	<i>Group I (n = 10)</i>	<i>Group II (n = 10)</i>	<i>Group III (n = 15)</i>	<i>Group IV (n = 15)</i>
Weight, g	289.53 ± 20.12	275.40 ± 16.73	293.20 ± 13.25	303.75 ± 18.11
Pentobarbital, mg · kg ⁻¹	40 ± 0	44 ± 12	45.33 ± 13.60	48 ± 21.66
pH	7.43 ± 0.04	7.43 ± 0.04	7.42 ± 0.06	7.39 ± 0.03
PCO ₂ , mmHg	49.86 ± 4.17	49.27 ± 4.42	51.67 ± 10.15	48.11 ± 6.66
PO ₂ , mmHg	44.35 ± 9.07	43.01 ± 6.73	55.11 ± 8.29	56.00 ± 8.29
BE, meq · L ⁻¹	6.02 ± 4.80	3.88 ± 3.39	7.32 ± 3.22	7.65 ± 2.68

*The mean (±SEM) baseline venous blood gas tensions, weights and pentobarbital doses are shown. *P* > 0.05 for all groups (ANOVA).

TABLE II Outcome data*

	<i>Bupivacaine 3.5 mg · kg⁻¹</i>		<i>Bupivacaine 5 mg · kg⁻¹</i>	
	<i>Group I (n = 10)</i>	<i>Group II (n = 10)</i>	<i>Group III (n = 15)</i>	<i>Group IV (n = 15)</i>
Nicardipine pretreatment, $\mu\text{g} \cdot \text{kg}^{-1}$	0	30	0	30
Survival: proportion	10/10	10/10	4/15	13/15
Survival: incidence	100%	100%	27%	87%

summarized in Table II. All rats receiving low-dose bupivacaine (Groups I and II) survived (ten of ten in both groups). For the rats given high-dose bupivacaine, 5 $\text{mg} \cdot \text{kg}^{-1}$, there was a statistically significant greater survival in the group receiving nicardipine pretreatment (13 of 15 in Group IV, 87 per cent), compared with rats receiving NS placebo (four of 15 in Group III, 27 per cent) ($P < 0.001$).

Rats given low-dose bupivacaine had no significant changes in respiration or cardiac rhythm; two such rats had transient, spontaneously resolving apnoea (< 5 sec). All rats given high-dose bupivacaine became apnoeic approximately eight to 14 seconds after bupivacaine injection, followed shortly afterwards (within 2–5 sec) by the onset of cardiac arrhythmias. Typically, these consisted of fleeting sinus tachycardia, which ushered in brief second or third degree atrioventricular block, followed either by reversion to sinus tachycardia with resumption of adequate respirations (in the survivors), or progression to (brief) complete heart block and then, promptly, asystole, associated with persistent apnoea (in the fatalities). Surviving rats spontaneously resumed respiration within about ten seconds, never developed cyanosis, and continuously maintained precordial pulsations. On the contrary, fatalities became deeply cyanotic, never resumed respiration, lost precordial pulsations, and developed slow agonal rhythms and/or asystole within 40–45 sec of receiving bupivacaine.

Discussion

When bupivacaine is given intravascularly, it probably causes the most cardio-respiratory toxicity of all local anaesthetics. Because of this the US Food and Drug Administration withdrew the 0.75 per cent concentration of bupivacaine from use in obstetrical anaesthesia in 1984.⁹ However, bupivacaine is still used extensively for epidural anaesthesia because of its unique, superior properties of long duration of action, high potency, and relatively less motor blockade for a given degree of sensory block.¹⁰

The mechanism of bupivacaine cardio-respiratory toxicity is not clear, nor does the present study establish the mechanism. Clerkson¹¹ explained the mechanism of

bupivacaine cardiotoxicity with the modulated receptor hypothesis put forward by Hille,¹² proposing that bupivacaine blocks cardiac sodium channels in a time- and voltage-dependent fashion. Relative to sodium, bupivacaine has an enhanced affinity for inactive myocardial sodium channels, thereby reducing sodium conductance and blocking the maximum upstroke velocity of the myocardial action potential (V_{max}). Furthermore, diastolic recovery from channel blockade is relatively slow for bupivacaine, compared with lidocaine. With respect to their properties relative to myocardial sodium channels, lidocaine is a "fast-in, fast-out" drug, whereas bupivacaine is a "fast-in, slow-out" drug. Thus, bupivacaine is felt to display prolonged cardiotoxicity clinically, including pronounced atrioventricular conduction disturbances and ventricular arrhythmias, because of the long time constant for its myocardial sodium channel blockade.

At high blood concentrations, bupivacaine is known to increase systemic and pulmonary vascular resistance in dogs¹³ and sheep,^{14,15} and it has also been speculated that it may cause coronary vasoconstriction in guinea pigs,¹⁶ or reduced coronary perfusion without coronary vasoconstriction.¹⁶ Nicardipine is a potent coronary and systemic arterial vasodilator that lacks a pronounced inotropic effect.⁸ The dose of nicardipine used, 30 $\mu\text{g} \cdot \text{kg}^{-1}$ IV, is enough to dilate coronary arteries. Since bupivacaine increases systemic and pulmonary vascular resistance, and may cause coronary vasoconstriction as well, perhaps nicardipine's potent vasodilatory properties explain its protective effect against bupivacaine cardio-respiratory toxicity.

Calcium channel entry blocking drugs are also known to possess sodium channel blocking properties when given in doses higher than those usually employed clinically.¹⁷ It seems likely that the protective effects against bupivacaine cardio-respiratory toxicity which we have reported for pretreatment with verapamil,⁷ and now nicardipine, are due mainly to the antagonism by these agents of the pathophysiological effects of IV bupivacaine. Whether these protective effects are mediated via calcium or sodium channels, both or neither, is uncertain. This desirable property may be common to many, if not all, calcium channel antagonists. Each

calcium channel entry blocker would appear to have a different potency in this regard, with the protective potency appearing to parallel the drug's potency for coronary vasodilation. Nicardipine has the most potent protective effect of the agents studied. Nifedipine's potency is greater than that of diltiazem and verapamil, which do not appear to differ greatly from one another. In addition, calcium channel antagonists reduce cardiac irritability due to elevated catecholamine levels,¹⁸ and this may contribute to their protective effects whenever catecholamine levels are elevated, whether endogenously or exogenously.

We agree with recommendations for the cautious use of calcium channel blockers during general or inhalational anaesthesia.¹⁹ Our results suggest no increased risk of bupivacaine cardio-respiratory toxicity for patients already receiving nicardipine; rather, they suggest a protective benefit from prophylactic or therapeutic use of nicardipine with bupivacaine regional anaesthesia techniques.

In conclusion, our results demonstrate that pretreatment with IV nicardipine, 30 $\mu\text{g}\cdot\text{kg}^{-1}$, reduced the incidence of fatal cardio-respiratory toxicity due to 0.5 per cent bupivacaine, 5 $\text{mg}\cdot\text{kg}^{-1}$ IV, in adult male Sprague Dawley rats. The mechanism of this protective effect is unknown. Whether this protective effect will hold true in humans awaits further study.

References

- 1 Albright GA. Cardiac arrest following regional anesthetic with etidocaine or bupivacaine. *Anesthesiology* 1979; 51: 285–7.
- 2 Edde RR, Deutsch S. Cardiac arrest after interscalene brachial plexus block. *Anesth Analg* 1977; 56: 446–7.
- 3 Moller RA, Covino BG. Cardiac electrophysiologic effect of lidocaine and bupivacaine. *Anesth Analg* 1988; 67: 107–4.
- 4 Eledjam JJ, dela Coussaye JE, Bassoul B, Burgada J. Mechanism of the cardiotoxicity of bupivacaine. *Ann Fr Anesth Reanim* 1988; 7: 204–10.
- 5 Stanley TH. Foreword In: Smith NT (Ed.). *Drug Interactions in Anesthesia*, Philadelphia; Lea & Feiberger 1986; vii–viii.
- 6 Rosenblatt RM, Weaver JM, Wang Y, Tallman RD. Verapamil potentiates the toxicity of local anesthetics. *Anesth Analg* 1984; 63: A269.
- 7 Kinney WW, Kambam JR, Matsuda F, Wright W, Holaday D. Bupivacaine cardiotoxicity is reduced by verapamil pretreatment in rats. *Anesthesiology* 1989; 71: A1145.
- 8 Kaplan JA. Nicardipine, a new intravenous calcium antagonist: a review of its pharmacology, pharmacokinetics and perioperative applications. *Journal of Cardiothoracic Anesthesia* 1989; 3: 344–55.
- 9 Writer WDR, Davies JM, Strunin L. Trial by media. The bupivacaine story. *Can Anaesth Soc J* 1984; 31: 1–4.
- 10 Abboud TK, Khoo SS, Miller F, Doan T, Henriksen EH. Maternal, fetal and neonatal responses after epidural anesthesia with bupivacaine, 2-chloroprocaine or lidocaine. *Anesth Analg* 1982; 61: 638–44.
- 11 Clerkson CW, Hondeghem LM. Mechanism of 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.
- 12 Hille B. Local anesthetics. Hydrophilic and hydrophobic pathways for the drug-receptor reaction. *J Gen Physiol* 1977; 69: 497–515.
- 13 Liu P, Feldman HS, Covino BM, Giasi R, Covino BG. Acute cardiovascular toxicity of intravenous amide local anesthetics in anesthetized ventilated dogs. *Anesth Analg* 1988; 67: 107–14.
- 14 Kotelko DM, Shnider SM, Dailey PA *et al.* Bupivacaine induced cardiac arrhythmias in sheep. *Anesthesiology* 1984; 60: 10–8.
- 15 Rosen MA, Thigpen JW, Shnider SM, Foutz SE, Levinson G, Koike M. Bupivacaine induced cardiotoxicity in hypoxic and acidotic sheep. *Anesth Analg* 1985; 64: 1089–96.
- 16 Tanz RD, Heeskett T, Loehing RW *et al.* Comparative cardiotoxicity of bupivacaine in the isolated mammalian heart. *Anesth Analg* 1984; 63: 549–56.
- 17 Kapur P. Calcium Channel Blockers. *Advances in Anesthesia* 1985; 2: 167–205.
- 18 Atwal KS, O'Reilly BC, Ruby EP. Substituted 1,2,3,4-tetrahydroaminoaphthols: antihypertensive agents, calcium channel blockers, and adrenergic receptor blockers with catecholamine-depleting effects. *J Med Chem* 1987; 30: 627–35.
- 19 Merin RG. Calcium channel blocking drugs and anesthetics: is the drug interaction beneficial or detrimental? *Anesthesiology* 1987; 66: 111–3.