

TITLE: BUPIVACAINE CARDIO-RESPIRATORY TOXICITY IS REDUCED BY DILTIAZEM PRETREATMENT IN RATS

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INTRODUCTION: Calcium channel blockers, widely used for hypertension, angina and supraventricular arrhythmias¹, and bupivacaine, excellent for regional anesthesia, may have important interactions. Bupivacaine can cause severe, even fatal cardio-respiratory toxicity. We studied the effect of diltiazem on 3 doses of i.v. bupivacaine.

METHODS: Ninety-two adult male Sprague Dawley rats (average weight, 300 g), randomly divided into six groups & anesthetized with intraperitoneal pentobarbital (range, 40-60 mg/kg), were monitored for respiratory rate, precordial pulsations, and with EKG lead II. A 20 μ L femoral venous sample, aspirated via a 24g catheter, was analyzed for blood gases. Either diltiazem 150 μ g/kg (250 μ g/ml) (groups I, III, V) or an equal volume of normal saline (NS, controls) (groups II, IV, VI) was given i.v. as pretreatment, followed in 3 min by 0.5% bupivacaine, 4 mg/kg (I & II), 4.5 mg/kg (III & IV), or 5 mg/kg (V & VI). At 1 min rats were tentatively classified as fatalities or survivors, and rats were observed 4 more minutes before final classification.

RESULTS: There were no differences among the six groups in weight, pentobarbital dose or venous blood gases (ANOVA). There was a statistically significant outcome difference between diltiazem (group V, 12 of 26 survived) and NS (group VI, 4 of 26

survived) pretreatment only with the 5 mg/kg bupivacaine dose ($p < 0.04$ by one-tail Fisher's exact test). One rat, a NS pretreated rat given bupivacaine 5 mg/kg, was reclassified (R). Five to 8 sec after i.v. bupivacaine, all rats had abrupt, transient bradycardia, usually 2nd degree AV block, then tachycardia. All had apnea after 5-10 sec of EKG abnormalities. Survivors resumed respirations within 10-20 sec of apnea and EKG quickly improved to sinus tachycardia with normal or slightly wide QRS. Fatalities never resumed persistent respirations (R resumed bradypneic breathing for 50 sec & died at 80 sec). Fatalities developed marked bradycardia and high grade AV block 20 to 40 sec post-bupivacaine, then bizarre, wide QRS ventricular agonal rhythms, with or without terminal asystole (delayed to 70 sec in R).

DISCUSSION: It was previously shown that verapamil protects against bupivacaine cardio-respiratory toxicity in rats². Not surprisingly, diltiazem, also a blocker of voltage-dependent calcium channels¹, also protects. Both reduce the incidence and severity of arrhythmias in this protocol. The mechanism is unknown, but may be coronary vasodilation mediated by calcium channel blockade, counteracting bupivacaine-induced coronary vasoconstriction.

IN CONCLUSION, diltiazem pretreatment reduces bupivacaine cardio-respiratory toxicity in rats. Whether it has such an effect in humans remains unknown. (Supported by the Study Center for Anesthesia Toxicology, Vanderbilt University).

REFERENCES:

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TITLE: BUPIVACAINE CARDIO-RESPIRATORY TOXICITY IS REDUCED BY VERAPAMIL PRETREATMENT IN RATS

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INTRODUCTION: Verapamil, often used for hypertension, angina & supraventricular tachyarrhythmias, and bupivacaine, excellent for regional anesthesia, may have important interactions. Bupivacaine can cause severe, even fatal cardio-respiratory toxicity. Studies of interactions of calcium entry blocking drugs with inhalational anesthetics¹ are numerous compared to those with local anesthetics^{2,3}. We therefore studied the effect of i.v. verapamil on 2 doses of i.v. bupivacaine.

METHODS: Forty two adult male Sprague Dawley rats (approx. weight, 300 g) randomly divided into six groups & anesthetized with intraperitoneal pentobarbital (range, 40-60 mg/kg) were monitored for resp. rate, precordial pulsations, and with EKG lead II. A 20 μ L femoral venous sample, aspirated via a 24g catheter, was analyzed for blood gases. Either verapamil 150 μ g/kg (250 μ g/ml) (groups I & III) or an equal volume of normal saline (NS) placebo (groups II & IV) pretreatment was given i.v. over 3 min, followed by 0.5% bupivacaine 4.25 mg/kg (groups I & II) or 4.5 mg/kg (groups III & IV). Rats maintaining adequate respirations and heart rate were classified as survivors. Rats developing apnea, cyanosis and ultimately, agonal rhythm or asystole, were fatalities. All rats that met survival criteria at 1 min were observed an additional 4 minutes before final classification.

RESULTS: There were no differences in weights, pentobarbital doses, or blood gas values among the four groups (ANOVA). There was a statistically significant outcome difference between verapamil (group III, 6 of 11 survived) and NS (group IV, 1 of 11 survived) pretreated rats only at the 4.5 mg/kg bupivacaine dose ($p < 0.02$ by Chi-square, $p < 0.03$ by Fisher's one-tail exact test). Outcomes in group I (verapamil, 7 of 10 survived) and group II (NS, 8 of 10 survived) did not differ statistically. There were no discrepancies between outcome classification at 1 & 5 min.

DISCUSSION: These results confirm previous reports that verapamil pretreatment reduces the incidence of bupivacaine cardio-respiratory toxicity⁴, and they show that verapamil pretreatment (150 μ g/kg) is not harmful to the rats, as there was no difference in fatalities between NS & verapamil pretreatment at the 4 mg/kg bupivacaine dose. This dose response study emphasizes the need to study a bupivacaine dose near LD₅₀ when checking for protective effects, as none was evident at an approximate LD₅₀ dose. Our results suggest no increased risk of bupivacaine toxicity for patients on verapamil, but they suggest possible benefit from verapamil use during bupivacaine use.

CONCLUSION: Bupivacaine toxicity is reduced by verapamil pretreatment in Sprague Dawley rats. Whether this is true in humans needs evaluation.

REFERENCES:

1. Anesthesiology 66:111-113, 1987.
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