Milrinone is superior to epinephrine as treatment of myocardial depression due to ropivacaine in pigs

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Purpose: To determine whether milrinone is more effective than epinephrine in the resuscitation of ropivacaine induced cardiotoxicity in pigs.

Methods: Arterial, pulmonary, and LVdP/dt catheters were placed in 12 anesthetized, intubated and mechanically ventilated pigs. They received ropivacaine *iv* to cardiovascular toxicity: 50% decrease in LVdP/dt, cardiac output and mean arterial pressure (MAP). Group I (n=6) was treated with 100 $\mu\text{g}\cdot\text{kg}^{-1}$ milrinone *iv*, and Group II (n=6) received 0.5 mg epinephrine *iv*. Resuscitation was successful if cardiac output returned to baseline, and MAP reached 80% of baseline.

Results: After ropivacaine, MAP decreased from 88 ± 7 to 49 ± 8 mmHg ($P < 0.05$), CO decreased from 2.8 ± 0.4 to 1.2 ± 0.2 L $\cdot\text{min}^{-1}$ ($P < .05$), HR decreased from 103 ± 8 to 74 ± 7 beats $\cdot\text{min}^{-1}$ ($P < 0.05$) and LVdP/dt decreased from 1950 ± 130 to 755 ± 125 mmHg ($P < 0.05$). The LV EDP increased from 5 ± 1 to 8 ± 1 mmHg ($P < 0.05$) and SVR from 2317 to 3000 ± 120 dynes $\cdot\text{sec}^{-1}\cdot\text{cm}^{-5}$. Electrocardiogram changes included increases in the QTU interval and QRS duration. In all animals, milrinone restored MAP, CO, SV, HR, and dP/dt to baseline and no animal developed arrhythmias. In contrast, epinephrine produced severe hypertension and tachycardia. There was no improvement in CO or SV, and SVR increased. Epinephrine caused A-V dissociation and ventricular arrhythmias in three animals.

Conclusion: Milrinone, was more successful than epinephrine in resuscitating anesthetized pigs from ropivacaine-induced cardiovascular toxicity.

Objectif : Déterminer si la milrinone est plus efficace que l'épinéphrine au moment de réanimer des porcs victimes d'une cardiotoxicité induite par la ropivacaïne.

Méthode : Des cathéters artériels, pulmonaires et ventriculaires gauches (dP/dtVG) ont été mis en place chez 12 porcs anesthésiés, intubés et sous ventilation mécanique. Ils ont reçu de la ropivacaïne *iv* qui a provoqué la cardiotoxicité manifestée par : une baisse de 50 % dP/dtVG, du débit cardiaque (DC) et de la pression artérielle moyenne (PAM). Le groupe I (n=6) a été traité avec 100 $\mu\text{g}\cdot\text{kg}^{-1}$ de milrinone *iv* et le groupe II (n=6) avec 0,5 mg d'épinéphrine *iv*. La réanimation était réussie lorsque le DC revenait aux valeurs de base et que la PAM atteignait 80 % des valeurs de base.

Résultats : Après l'administration de la ropivacaïne, la PAM a chuté de 88 ± 7 à 49 ± 8 mmHg ($P < 0,05$), le DC de $2,8 \pm 0,4$ à $1,2 \pm 0,2$ L $\cdot\text{min}^{-1}$ ($P < 0,05$), la FC de 103 ± 8 to 74 ± 7 battements $\cdot\text{min}^{-1}$ ($P < 0,05$) et dP/dtVG de 1950 ± 130 à 755 ± 125 mmHg ($P < 0,05$). La pression télédiastolique du VG a augmenté, passant de 5 ± 1 à 8 ± 1 mmHg ($P < 0,05$) et la résistance vasculaire périphérique (RVP) de 2317 à 3000 ± 120 dynes $\cdot\text{s}^{-1}\cdot\text{cm}^{-5}$. Les changements à l'électrocardiogramme comprenaient des augmentations de l'intervalle QTU et de la durée de QRS. Chez tous les animaux, la milrinone a ramené la PAM, le DC, le débit systolique (DS), la FC et dP/dt aux valeurs de base et aucun animal n'a présenté d'arythmie. Par ailleurs, l'épinéphrine a produit une sévère hypertension et de la tachycardie. Il n'y a pas eu d'amélioration du DC ou du DS et la RVP a augmenté. L'épinéphrine a aussi causé une dissociation AV et des arythmies ventriculaires chez trois animaux.

Conclusion : La milrinone a été plus efficace que l'épinéphrine pour la réanimation de porcs anesthésiés qui ont subi une cardiotoxicité provoquée par de la ropivacaïne.

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WE investigated the effectiveness of milrinone in the resuscitation of anesthetized pigs given ropivacaine intravenously. Milrinone is a selective cAMP phosphodiesterase inhibitor, which enhances cardiac contractility and increases cardiac output.

We studied ropivacaine because it is a relatively new local anesthetic that may replace bupivacaine in the future due to its reduced toxicity. Clinical experience regarding its cardiotoxicity and treatment is very limited.

The purpose of this study was to determine whether the administration of milrinone is superior to epinephrine in resuscitation of ropivacaine induced cardiotoxicity in pigs.

Methods

After approval of the protocol by the Institutional Animal Investigation Committee, Yorkshire albino pigs weighing 25-30 kg were anesthetized with 30 mg·kg⁻¹ pentobarbital *iv* and anesthesia was maintained with pentobarbital infusion at 4 mg·kg⁻¹·hr⁻¹. Tracheal intubation was performed and then mechanical ventilation instituted to maintain the arterial blood gases at pH 7.35 ± 0.01 and the PaCO₂ at 35 to 40 mmHg. A heating lamp maintained the esophageal temperature between 37°C and 39°C.

Normovolemia was maintained by infusing lactated Ringer's solution via an intravenous cannula at the rate of 4 mL·kg⁻¹·hr⁻¹. A 14-gauge polyurethane cannula was inserted into the femoral artery to measure aortic pressure and to obtain intermittent arterial blood gas and electrolyte measurements. A thermidilution pulmonary catheter was placed in the pulmonary artery via the femoral vein. A left-sided thoracotomy was performed and the pericardium excised. A Millar (Millar Instruments, Houston, Texas) microtipped pressure transducer was inserted into the left ventricle by way of the left atrial appendage to measure end-diastolic pressure and the first derivative of left ventricular pressure (LVdP/dt).

Measurements

The following variables were recorded - heart rate, systolic, diastolic and mean arterial pressure, right atrial pressure, mean pulmonary artery pressure and pulmonary artery capillary wedge pressure. Left ventricular systolic and diastolic pressure and LVdP/dt were measured and recorded. Cardiac output was measured in triplicate by thermidilution. An electrocardiograph (ECG) was continuously monitored and results were examined for arrhythmias, conduction defects, and ST Segment changes.

Experimental protocol

After the 30 min stabilization period, hemodynamic measurements were obtained. Ropivacaine 0.5% was administered by a syringe infusion pump, (2 mg·kg⁻¹·min⁻¹) until there was a 50% decrease in LVdP/dt, cardiac output and MAP.

At the same time, to mimic the respiratory conditions after clinical seizures which often render patients apneic, the animals were made apneic for 90 sec by disconnecting the ventilator from the endotracheal tube. After 90 sec apnea, ABG tensions were measured, and the lungs were ventilated with oxygen 100%. Animals were then randomized to one of two groups. The animals in Group I (n=6) were treated with 100 µg·kg⁻¹ milrinone *iv*. If there was no improvement after five minutes, milrinone was repeated. Those in Group II (n=6) received 0.5 mg epinephrine, and the dose was repeated if there was no improvement after five minutes. The animals were considered to have been successfully resuscitated if the cardiac outputs improved to baseline, and the mean arterial pressure reached 80% of the baseline value.

Statistical Analyses were performed using two way repeated measure ANOVA. $P < 0.05$ was considered statistically significant.

Results

The hemodynamic data obtained during the control period, ropivacaine infusion and therapeutic intervention with either milrinone (Group I) or epinephrine (Group II) are shown in Tables I and II.

No animal received more than one dose of the study drug.

Compared with base line, ropivacaine infusion (average dose 7.2 ± 0.5 mg·kg⁻¹) caused, in both groups, decreases in MAP, cardiac output, stroke volume, heart rate, LVdP/dt and increases in LVEDP and SVR ($P < 0.05$). The electrocardiographic changes included increases of the QT interval and QRS duration. The duration of QRS and QT interval increased in both groups following injection of ropivacaine. In Group I, the QRS interval increased from control 50 ± 4 to 66 ± 7 msec. The QT interval increased from control 210 ± 8 to 281 ± 10 msec. In Group II QRS interval increased from control 52 ± 5 to 67 ± 4 msec and the QT interval from control 212 ± 6 to 283 ± 9 msec. Despite electrophysiologic changes induced by ropivacaine, no spontaneous arrhythmias occurred in any animal.

In all animals, administration of milrinone (average dose 100 µg·kg⁻¹) rapidly restored MAP, cardiac output, stroke volume, heart rate and LVdP/dt to baseline. SVR and LVEDP decreased (Table I). No animal

TABLE I

Parameters	Baseline	After Ropivacaine		After Milrinone		
		1 min	3 min	1 min	3 min	5 min
HR bpm	103 ± 8	81 ± 9	74 ± 7*	98 ± 9†	108 ± 7†	111 ± 8†
MAP mmHg	88 ± 7	72 ± 5*	49 ± 8*	76 ± 6†	83 ± 5*	88 ± 6†
CO L·min ⁻¹	2.8 ± 0.4	1.3 ± 0.2*	1.2 ± 0.2*	2.6 ± 0.3	2.9 ± 0.4†	2.9 ± 0.6†
SV ml·beat ⁻¹	27 ± 2	16 ± 2*	16.0 ± 3*	26 ± 2†	28 ± 1†	27 ± 2†
LVdP/dt mmHg	1950 ± 130	780 ± 120*	755 ± 125*	1750 ± 140†	2050 ± 130†	2100 ± 90†
LVEDP mmHg	5 ± 1	7 ± 1*	8 ± 1*	6 ± 1†	6 ± 1†	6 ± 1†
SVR dyne·sec ⁻¹	2317 ± 120	4123 ± 130*	3000 ± 120	2184 ± 95	2289 ± 125	2344 ± 105

Mean ± SP

*P < 0.05 vs baseline†*P* < 0.05 vs after ropivacaine (3 min)

TABLE II

Parameters	Baseline	After Ropivacaine		After Epinephrine		
		1 min	3 min	1 min	3 min	5 min
HR bpm	106 ± 6	84 ± 7	76 ± 8*	163 ± 21†	175 ± 18†	173 ± 21†
MAP mmHg	92 ± 7	78 ± 5	57 ± 8*	140 ± 16†	155 ± 13†	131 ± 15†
CO L·min ⁻¹	3.1 ± 0.6	1.1 ± 0.1*	1.0 ± 0.2*	1.4 ± 0.3*	1.9 ± 0.2*	2.1 ± 0.9*†
SV ml·beat ⁻¹	30 ± 2	13.1 ± 1*	13.2 ± 3*	8.5 ± 3*†	10.8 ± 2*	12.1 ± 3*
LvdP/dt mmHg	1820 ± 110	760 ± 130*	745 ± 90*	1650 ± 130†	1950 ± 120†	1970 ± 130†
LVEDP mmHg	4 ± 1	7 ± 1*	8 ± 0.5*	7.1†	7 ± 1†	6 ± 1
SVR dyn·sec	2175 ± 130	5309 ± 125*	4320 ± 130*	7657 ± 135*†	6231 ± 100*†	4761 ± 125*

Mean ± SD

*P < 0.05 vs baseline†*P* < 0.05 vs after ropivacaine (3 min)

developed serious cardiac arrhythmias, but there was no improvement in QT and QRS duration.

In contrast to milrinone, administration of 0.5 mg epinephrine *iv* precipitated severe hypertension and tachycardia. Although LVdP/dt increased, there was no improvement in cardiac output or stroke volume, and the SVR increased. Epinephrine induced A-V dissociation and ventricular arrhythmias in three animals. One pig demonstrated ventricular tachycardia that degenerated to terminal ventricular fibrillation. Arterial PO₂, PCO₂ and pH did not change significantly during the experiment in either group, except during the short period of apnea.

All animals in both groups, except the animal which developed ventricular fibrillation, had stable blood pressure 30 min after treatment without need for additional pharmacologic support.

Discussion

Ropivacaine (Naropin®, ASTRA Pharmaceutical, Sweden) is a new amide local anesthetic that is structurally similar to bupivacaine and has similar local anesthetic therapeutic effects. Although ropivacaine

has been reported to have less cardiotoxicity than bupivacaine, cardiovascular complications may still occur after inadvertent intravenous administration or following absorption.^{1,2}

There has been much interest in the untoward cardiovascular effects of potent long acting anesthetics.³⁻⁶ However, few detailed studies have determined whether animals could be successfully resuscitated.⁷ Feldman *et al.*⁷ studied the treatment of acute cardiovascular toxicity from bupivacaine and ropivacaine in dogs. Treatment included increasing doses of 0.5 mg epinephrine, bretylium, direct current cardioversion, and cardiac massage. In that study, there was still a high mortality rate, although it was less in the ropivacaine group. Several dogs in the ropivacaine group developed ventricular fibrillation after epinephrine administration. In conclusion, these authors suggested that other inotropes or vasopressor drugs may be preferable to epinephrine for cardiovascular resuscitation from local anesthetic toxicity.

Butterworth *et al.*⁸ demonstrated *in vitro* that bupivacaine inhibit both basal and epinephrine stimulated cAMP production. They postulated that local

anesthetic inhibition of cAMP involves beta-receptors in the myocardium, contributing to the difficulty of resuscitation following induced cardiovascular toxicity. In this study, a high dose of epinephrine was unsuccessful in increasing cAMP production in the presence of bupivacaine toxicity.

Milrinone^{9,10} is a selective cAMP phosphodiesterase inhibitor. It increases the intracellular concentration of cAMP in the heart by preventing its breakdown, and acts independently of beta adrenergic receptors. Milrinone improves myocardial contractility, increases cardiac output and produces peripheral vasodilatation. All these attributes suggest that milrinone could be a better choice than epinephrine in the treatment of cardiovascular toxicity induced by ropivacaine.

In our study, the infusion of ropivacaine resulted in severe and sustained hypotension, and decreases in LVdP/dt and cardiac output, indicating myocardial depression. However, in contrast to bupivacaine, ropivacaine did not induce cardiac arrhythmias. Similar findings were reported by Santos *et al.*¹¹ in sheep although no attempts were made to resuscitate animals.

In our study, milrinone reversed myocardial depression induced by ropivacaine. Mean arterial pressure, cardiac output, stroke volume, LVdP/dt and LVEDP returned to baseline in all animals within two to three minutes. Milrinone did not produce tachycardia, hypertension, or cardiac arrhythmias. In contrast to milrinone, epinephrine induced severe tachycardia, hypertension and arrhythmias, and failed to improve myocardial function, although LVdP/dt did increase.

We did not attempt to establish dose-response relationships with either milrinone or epinephrine. Rather, the intent was to use these drugs to establish whether cardiotoxicity induced by ropivacaine could be reversed. A limitation of our study is that pregnant animals were not used and, therefore, the results cannot be extrapolated to the pregnant human patients.

It is possible that in awake animals hypoxia and acidosis due to grand mal seizure may exacerbate the cardiovascular toxicity of ropivacaine. We attempted to reproduce the respiratory effect of a seizure by making the animals apneic for 90 sec at the start of the ropivacaine injection. After the 90 sec apnea, the lungs were ventilated with oxygen 100%. These experimental conditions are similar to the clinical situations that occur during a seizure, when patients become apneic and are ventilated with oxygen. Most of our animals were hypoxic following the apnea but they improved immediately after ventilation.⁷

During our experiment, fluids were given in amounts adequate to maintain right-atrial pressure between 4 and 10 mm Hg. It is possible that had we

not monitored the right atrial pressure constantly, we might not have given an adequate amount of fluid. The success of our resuscitation might have been diminished if the animals were allowed to become hypovolemic. General anesthesia may have altered the toxic profile of the local anesthetic drugs. For example, ventricular arrhythmias, which have been reported in humans and conscious animals occur less frequently, in anesthetized dogs which had received large doses of bupivacaine *iv*. In addition, the cardiovascular depression produced by ropivacaine is less marked than that produced by bupivacaine and, therefore, may be more easily managed.⁷

In summary, milrinone, was more successful in resuscitating anesthetized pigs with cardiovascular toxicity induced by ropivacaine. The general anesthetic may have had a protective effect against the stimulation of the sympathetic nervous system.

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