

Clonidine Pretreatment Reduces the Systemic Toxicity of Intravenous Bupivacaine in Rats

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Background: Clonidine prolongs the duration of sensory and motor block induced by bupivacaine, and this association, in constant infusion by the epidural route, is used for post-operative analgesia. After a near-fatal intravenous bolus of bupivacaine in dogs, clonidine improves ventricular electrophysiologic parameters, but probably worsens bupivacaine-induced bradycardia and depression of the myocardial contractility. The current study, using a rodent animal model, evaluated the influence of clonidine pretreatment on the systemic toxic effects of bupivacaine overdose induced by a constant intravenous infusion.

Methods: Twenty Wistar male rats were anesthetized with thiopental, and controlled ventilation was started with an equal mixture of O₂ and N₂O. Electrocardiogram (ECG), electroencephalogram (EEG), and invasive arterial blood pressure were continuously recorded. Clonidine (5 µg/kg) or saline was injected intravenously in a randomized fashion. After 15 min, an intravenous infusion of bupivacaine was started at 2 mg · kg⁻¹ · min⁻¹. The time of occurrence of the bupivacaine-induced toxic events was recorded and the doses were calculated. Ten (five in each group) additional rats, pretreated according to the same protocol, were killed at the time of the first dysrhythmia, for blood sampling and plasma bupivacaine concentration measurement.

Results: Clonidine reduced heart rate and arterial blood pressure before bupivacaine infusion ($P < 0.05$). The threshold doses at the first QRS modification (11.3 ± 5.6 vs. 2.1 ± 0.9 mg/kg) and the first dysrhythmia (40.6 ± 15.3 vs. 8.48 ± 3.7 mg/kg), the increase in EEG total spectral power (33.3 ± 21.9 vs. 8.2 ± 5.1 mg/kg), the 25 and 50% reduction in baseline mean arterial pressure and heart rate, the isoelectric EEG (58.6 ± 14 vs. 22 ± 6.6 mg/kg), and the final systole (99 ± 16 vs. 51.8 ± 14.5 mg/kg) were significantly greater in the clonidine group than in the saline group ($P < 0.01$). The time between the first dysrhythmia and 50% reduction of baseline mean arterial blood pressure was not different between the groups. In the

additional series, the first dysrhythmia occurred later (10.9 ± 4.5 vs. 3.2 ± 1.0 min, $P < 0.01$) and plasma bupivacaine levels were greater (18.7 ± 8.0 vs. 7.8 ± 3.2 µg/ml, $P < 0.01$) in the clonidine group than in the saline group.

Conclusions: In this model, clonidine given prophylactically delays the toxic manifestations of bupivacaine overdose and does not accentuate the subsequent hypotension. (Key words: Anesthetics, local: bupivacaine. Heart: dysrhythmias. Sympathetic nervous system, α_2 -adrenergic agonists: clonidine.)

CLONIDINE, an imidazolin α_2 -adrenoceptor agonist, has analgesic properties.^{1,2} Stimulation of the α_2 receptors at the spinal level reinforces the central noradrenergic inhibitory control,³ helps to recruit other neurotransmitters implicated in the control of nociception (e.g., acetylcholine⁴ and adenosine⁵), and inhibits the release of substance P.⁶ Clonidine has local anesthetic properties when applied to a nerve fiber.⁷ Clonidine intensifies and prolongs analgesia from local anesthetics.⁸⁻¹⁰ For these reasons, a bupivacaine-clonidine combination has been used for epidural anesthesia and analgesia.¹¹

Recently, it has been shown that clonidine, given for the management of bupivacaine overdose, may improve ventricular electrophysiologic parameters in dogs, but probably at the cost of worsening bupivacaine-induced bradycardia and depression of myocardial contractility.¹² Although the combined toxicity of clonidine and bupivacaine has not yet been studied, a protective effect is postulated, because of the antidysrhythmic properties of the α_2 -adrenergic agonist.¹³ Using a rodent animal model of bupivacaine overdose, the current study evaluated this possible protective effect.

Materials and Methods

Approval from the Institutional Animal Care and Use Committee was obtained. In the first experiment, 20 male Wistar rats, 5 months of age, weighing 260–320 g, were used. Anesthesia was induced with diethyl ether, followed by intraperitoneal thiopental (20 ± 5 mg/kg). A tracheotomy was performed and controlled ventilation (modified Ventilog ventilator, Dräger,

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Lübeck, Germany) was started with a mixture of N₂O and O₂ at FI_{O₂} 0.5 (respiratory rate \pm 55 breaths/min). Ventilation was adjusted for an end-tidal CO₂ of approximately 4 vol percent (Datex Normocap CD 102, Helsinki, Finland). A femoral artery and vein were cannulated. Arterial blood pressure, electrocardiogram (lead II), and frontooccipital electroencephalogram were continuously recorded (Hellige Servomed electrocardiogram and pressure monitor with three-channel recorder, and OTE Biomedica electroencephalogram continuous monitor 1264, Firenze, Italy). The rats were observed for 5 min. After this period, arterial blood gases and potassium concentrations were measured (Corning blood gas analyzer and AVL 984s ionogram analyzer, Copenhagen, Denmark). A colloid (polygeline Haemaccel, Behring, Marburg, Germany, 10 \pm 2 ml/kg) was infused to compensate for blood retrieved for sample analysis and relative hypovolemia after the start of mechanical ventilation. At this time, 5 μ g/kg clonidine or saline (identical volume 2 ml/kg) was administered intravenously, in a randomized fashion, over 2 min.

Fifteen minutes later, an intravenous infusion of bupivacaine was begun at 2 mg \cdot kg⁻¹ \cdot min⁻¹ using a calibrated electronic infusion pump (Terumo, Tokyo, Japan).

The following events were recorded and the dose of bupivacaine required to produce them was calculated:

- First QRS modification (QRS mod) that consisted of an increased duration of the QRS complex.
- First dysrhythmia (DYS), defined as the first dysrhythmia accompanied by an abnormal systole on the blood pressure trace.
- Twenty-five percent reduction of basal heart rate (prebupivacaine infusion; HR-25%).
- Fifty percent reduction of basal heart rate (prebupivacaine infusion; HR-50%).
- Twenty-five percent reduction of basal mean arterial blood pressure (prebupivacaine infusion; MABP-25%).
- Fifty percent reduction of basal mean arterial blood pressure (prebupivacaine infusion; MABP-50%).
- Final systole (fSYS), defined as the absence of QRS complexes on the ECG, absence of a pressure pulse

on the arterial blood pressure trace, and absence of end-tidal CO₂ detection after 2 min.

The time between the first QRS mod and MABP-25%, and the time between DYS and MABP-25%, were also measured (QRSmod/MABP-25% and DYS/MABP-25%) to evaluate the hemodynamic consequences of the electrocardiogram disturbances.

Central nervous system (CNS) toxicity was evaluated using the quantification unit of the OTE Biomedica electroencephalogram. The EEG signal was amplified 20,000 times and compressed using a Berg Fourier analyzer (Firenze, Italy). A power-spectral analysis was performed using partially overlapping 8–9-s epochs producing power spectra with a resolution of 0.5 Hz. The values of total EEG power (0.5–32 HZ) were averaged from 1-min samples of EEG and printed. Artifacts of greater than 32-Hz frequency were directly eliminated by the system. The artifacts that were below this frequency were identified by a proportional threshold device that zeroed the tracing for 0.5 s whenever a sudden excess voltage occurred. The number of identified artifacts was visualized on the printer numeric strip.

The doses of bupivacaine required to produce isoelectric electroencephalogram (ISO EEG) were also noted.

In a second experiment, ten Wistar male rats were studied using the same protocol as previously described. They also received, in a randomized fashion, either clonidine or saline, followed by an intravenous infusion of bupivacaine. At the moment of the first dysrhythmia (DYS), the infusion of intravenous bupivacaine was stopped. Three milliliters of whole blood were withdrawn *via* the femoral arterial catheter for determination of bupivacaine concentration. Thiopental (20 mg/kg) was injected intravenously and the ventilation was stopped.

Bupivacaine concentrations in plasma were determined according to the method of Roseel *et al.*[#] Samples obtained from rats were determined with high-performance liquid chromatography and UV-detection in two different runs. Interference between clonidine and Na-thiopental was checked. Three spiked quality-control samples (10 μ g/ml) were analyzed, together with the unknown samples in each run.

Statistical analysis of variables over time was performed using one-way ANOVA with repeated measures. Further comparisons were based on Tukey's *post hoc*

[#] Roseel MT, Bogaert MG, Goossens G: Determination of bupivacaine in human plasma by capillary gaschromatography and high-performance liquid chromatography. *Spectroscopy an International Journal* 3:337–344, 1984.

least significant difference test (CSS Statistica, Statsoft, Tulsa, OK). The time required for the appearance of the different bupivacaine-induced toxic manifestations, and the calculated cumulative doses of bupivacaine at each event time, were compared using Student's *t* test. Two-tail Fisher's exact test was used for the comparison of the observed proportions. A *P* value < 0.05 was considered to be statistically significant.

Results

In the first experiment, baseline characteristics, arterial blood gases, and serum potassium levels were similar in the two groups (table 1).

Clonidine significantly reduced heart rate and mean arterial blood pressure (*P* < 0.01) before bupivacaine infusion (fig. 1). Total EEG spectral power was also reduced 15 min after clonidine administration (from $2,194 \pm 355$ to $1,381 \pm 451$, raw data *P* < 0.01 in intragroup comparison). In the saline group, no differences were noted (from $2,047 \pm 502$ to $2,091 \pm 485$).

In the saline group, the first detectable sign of bupivacaine-caused toxicity invariably consisted of the appearance of an S wave with widening of the QRS complex, which occurred after 1.05 ± 0.28 min. This S wave increased progressively in voltage. It was accompanied by the progressive disappearance of the P wave. The first dysrhythmia appeared after 4.3 ± 2.0 min. Twenty-five percent reduction of prebupivacaine heart rate occurred after 4.5 ± 1.7 min (fig. 2; table 2).

In the clonidine group, the toxic threshold doses of bupivacaine were significantly greater than in the saline group (fig. 2; table 2). Appearance and increase in amplitude of the S wave was also the first manifestation of bupivacaine toxicity. Twenty-five percent reduction of heart rate occurred before DYS (14.1 ± 11.1 min and 20.5 ± 7.1 min). This difference, however, was not statistically significant. The DYS were of the same morphology as those observed in the saline group.

Clonic manifestations were observed in only four of the rats in the saline group. An abrupt increase of the cerebral electric activity (more than 20% increase of the prebupivacaine total EEG spectral power) was demonstrated in four rats in the clonidine group and in all the rats in the saline group (*P* < 0.01), and it required 16.8 ± 11.0 min of bupivacaine infusion in the clonidine group and 4.1 ± 2.6 min in the saline group (*P* < 0.01).

Table 1. Baseline Characteristics, Blood Gases, and Serum Potassium Concentrations

	Clonidine (n = 10)	Saline (n = 10)
Weight (g)	276 ± 21	288 ± 27
pH	7.42 ± 0.04	7.43 ± 0.04
PaO ₂ (mmHg)	232 ± 33	229 ± 22
PaCO ₂ (mmHg)	32.4 ± 5.6	32.0 ± 5.6
K ⁺ (mM)	3.22 ± 0.2	3.14 ± 0.2

Reduction in mean arterial blood pressure was a late manifestation of bupivacaine toxicity in both groups (fig. 1). Clonidine pretreatment did not worsen this. This reaction took 21.6 ± 7.3 min after the first QRS modification to reach the 25% reduction in mean arterial blood pressure in the clonidine group, and 9.9 ± 2.8 min in the saline group (*P* < 0.001). The delay between the first dysrhythmia and 25% reduction in arterial blood pressure was comparable between the saline and clonidine groups (7.9 ± 4.3 min *vs.* 9.4 ± 7.9 min, *P* = 0.6).

After pretreatment and before bupivacaine infusion, hemodynamic values were significantly lower in the clonidine group. The values of 25 and 50% reduction of prebupivacaine mean arterial blood pressure and heart rate were also less in this group (fig. 1).

Hemodynamic data from the infusion of bupivacaine until the first dysrhythmia are shown in figure 3. No hypertensive reactions preceding DYS were noted in either groups.

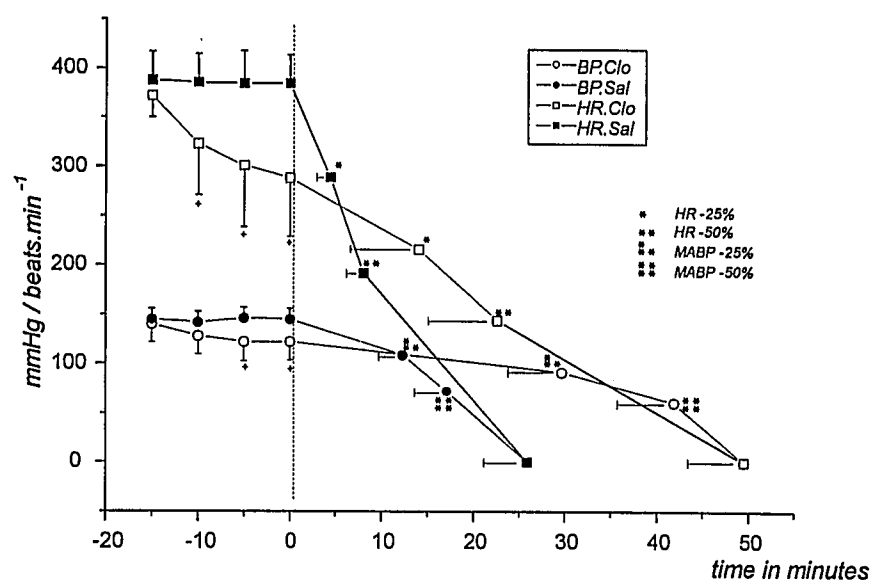
A dose of 58.6 ± 14.9 mg/kg bupivacaine in the clonidine group, *versus* 22 ± 6.4 mg/kg in the saline group, was necessary to produce isoelectric electroencephalogram (*P* < 0.001).

In the second experiment, first ventricular dysrhythmia (DYS) occurred after 10.9 ± 4.5 min in the clonidine group, *versus* 3.2 ± 1.0 min in the saline group (*P* < 0.01).

The mean plasma concentrations of bupivacaine were significantly greater in the clonidine group than in the saline group (18.74 ± 8.04 *vs.* 7.88 ± 3.2 μg/ml, *P* < 0.01). The CV of the assay was 3.6% (*n* = 6) for the quality-control samples of 10 μg/ml. For these samples, the analytical recovery was 98.5%. There was no interference between clonidine and Na-thiopental on the chromatograms.

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Fig. 1. Heart rate and mean arterial blood pressure before bupivacaine infusion (0) with reference to the chosen toxic endpoint 25 and 50% reduction of basal heart rate (HR-25% and HR-50%) and basal mean arterial blood pressure (MABP-25% and MABP-50%). Statistical analysis of heart rate and mean arterial pressure over time: $P < 0.01$ (repeated measures ANOVA). *Post hoc* comparisons, + = $P < 0.01$. Data are mean \pm SD.



Discussion

Epidural clonidine intensifies and prolongs the analgesic properties of bupivacaine.⁸⁻¹⁰ The efficacy of this association for postoperative analgesia has been demonstrated in a recent clinical investigation by Carabine *et al.*¹¹ Epidural clonidine does not induce delayed respiratory depression.¹⁴ For this reason, it may be considered as a possible alternative to the epidural opioids.

Bupivacaine intoxication, a rare, but dramatic, complication of epidural anesthesia, principally occurs after accidental intravenous bolus injection.¹⁵ Because clonidine may be administered epidurally for postoperative analgesia, it is appropriate to characterize the interaction between bupivacaine and clonidine when both are given intravenously.

Using the current model of anesthetized rats under controlled ventilation, it is possible to study many of the variables associated with local anesthetic toxicity.

Fig. 2. Doses required to produce the first QRS modification (QRS mod), increase in total EEG power (SZ), dysrhythmia (DYS), 25 and 50% reduction of the heart rate (HR-25% and HR-50%), 25 and 50% reduction of mean arterial blood pressure (MABP-25% and MABP-50%), isoelectric electroencephalogram (iso EEG), and asystole (ASYS) in the clonidine- ($n = 10$) and saline-treated ($n = 10$) rats during infusion of bupivacaine $2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Data are mean \pm SD.

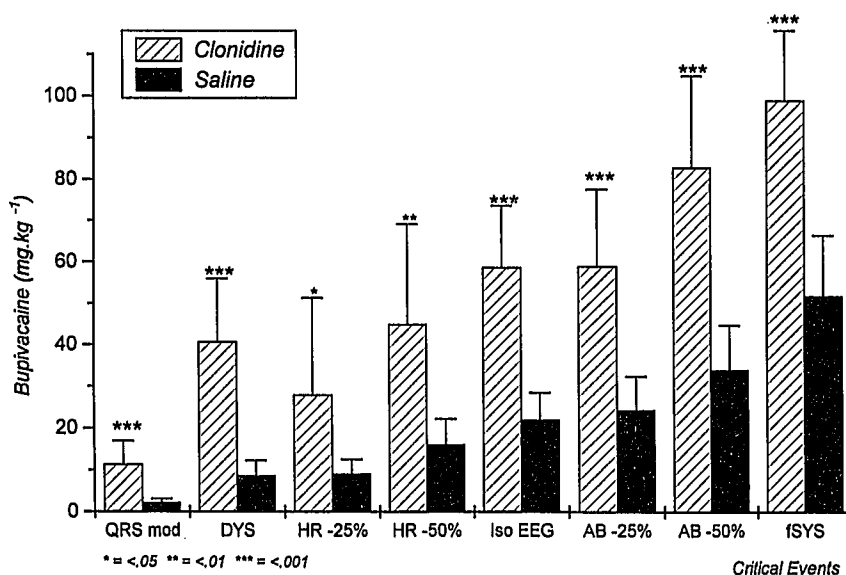


Table 2. Time to Measured End Points after Bupivacaine in Groups Receiving Clonidine or Saline

Event	Clonidine (min)	P Value	Saline (min)
QRS mod	5.7 ± 2.9	<0.001	1.0 ± 0.3
DYS	20.5 ± 7.1	<0.001	4.3 ± 2.0
HR-25%	14.1 ± 23.4	<0.05	4.5 ± 1.7
HR-50%	22.6 ± 12.2	<0.01	8.1 ± 3.1
Iso EEG	29.3 ± 7.5	<0.001	11.0 ± 3.2
AB-25%	29.7 ± 9.4	<0.001	12.3 ± 4.0
AB-50%	41.9 ± 11.1	<0.001	17.1 ± 5.5
fSYS	49.5 ± 8.4	<0.001	25.9 ± 7.3

QRS mod = first QRS modification; DYS = first dysrhythmia; HR-25% = 25% reduction of basal heart rate; HR-50% = 50% reduction of basal heart rate; Iso EEG = isoelectric electroencephalogram; AB-25% = 25% reduction of basal mean arterial blood pressure; AB-50% = 50% reduction of basal mean arterial blood pressure; fSYS = final systole.

However, because of the small blood volume of rats, blood withdrawal for measurement of drug level is a limitation. The use of a constant local anesthetic infusion allows easy observation of the progression of toxic signs.¹⁶ The threshold doses found in the saline group are compatible with our previous experience with this model.^{17,18}

Clonidine is a lipid-soluble drug with a high volume of distribution. In rats, after a single intravenous injection, clonidine rapidly enters the brain, with peak brain level occurring after 2 min, and a $t_{1/2}$ of approximately

25 min. The half-life for elimination is approximately 90 min.¹⁹

In the same animals, doses of clonidine of up to 2 $\mu\text{g}/\text{kg}$ consistently and rapidly inhibit the firing of the cells in the locus coeruleus.²⁰ Doses of 10 $\mu\text{g}/\text{kg}$ have also been reported to improve neurologic outcome after incomplete cerebral ischemia in rats.²¹ In the current experimentation, the intermediate dose of 5 $\mu\text{g}/\text{kg}$ was chosen.

Bupivacaine overdose induces cardiac toxicity,²² and directly depresses both cardiac electrophysiology and hemodynamic status. Several reports, however, indicate a participation of the CNS in this cardiac toxicity.^{23,24}

In the current experiments, the cardiac electrophysiologic manifestations of bupivacaine overdose (increased duration of the QRS complex and dysrhythmias) were of the same nature in both groups. In the clonidine group, however, they occurred significantly later than in the saline group. Clonidine pretreatment reduced heart rate and mean arterial blood pressure before bupivacaine infusion, but there was no evidence that clonidine enhanced the bradycardia and hypotension after the bupivacaine overdose. Clonidine pretreatment also reduced the incidence and, when present, delayed the onset of the bupivacaine-induced cerebral electric hyperactivity.

A pure pharmacokinetic interaction can be ruled out by the results of the second experiment. The first dysrhythmia occurred later, and at a higher plasma level

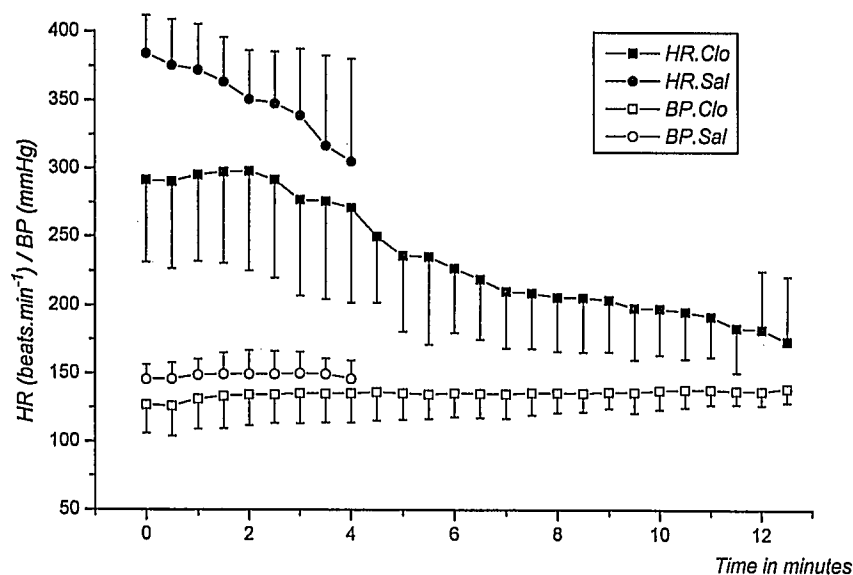


Fig. 3. Evolution of heart rate (HR) and mean arterial blood pressure (BP) in the clonidine- (Gr.1, $n = 10$) and saline-treated (Gr.2, $n = 10$) rats from the beginning of the bupivacaine infusion (0) until the first dysrhythmia.

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of bupivacaine, in the clonidine group. In mice and rats, clonidine was reported to increase plasma levels of lidocaine while slowing lidocaine metabolism.²⁵

α_2 -Adrenergic agonists have antidysrhythmogenic properties. Dexmedetomidine has been reported to increase the dysrhythmogenic threshold for epinephrine during halothane anesthesia.¹³ Alinidine prevents ventricular fibrillation after coronary occlusion.²⁶ In a recent experiment in dogs, de La Coussaye *et al.*¹² reported that clonidine improved the electrophysiologic manifestation of bupivacaine overdose by reducing increased QRS duration and HV interval. The mechanism of this antidysrhythmogenic effect is not elucidated. A central site of action is the most probable explanation. The α_2 -adrenergic agonists potently inhibit the neuronal firing rate from the locus coeruleus,²⁰ leading to a decrease in sympathetic outflow. This action may decrease the release of norepinephrine at the cardiac neuroeffector junction. If the early signs of cardiac toxicity after bupivacaine overdose are caused by an increased autonomic nervous outflow, as hypothesized by Bernards and Artu,²⁷ clonidine pretreatment may be an adequate prevention. In the current study, the interaction of clonidine with the CNS is demonstrated by the depression in EEG total spectral power before bupivacaine infusion, and by the observation that only four rats in the clonidine groups presented signs of cerebral hyperactivity after bupivacaine infusion. Delayed QRS modifications and dysrhythmias in this group may be the result of the direct myocardial toxic effects of bupivacaine.

Clonidine-induced bradycardia may be one explanation for the increased toxic threshold of bupivacaine. Bupivacaine blocks the cardiac sodium channels by combination with receptors common to quinidine²⁸ in a "fast-in, slow-out" fashion,²⁹ subject to use dependence.³⁰ A slower heart rate before bupivacaine overdose allows more time for the sodium channel to remain in the closed, or inactive, configuration, during which time the affinity of bupivacaine for the channel is reduced and bupivacaine may move away from its binding site.

In the current study, clonidine did not exacerbate the bupivacaine-induced myocardial depression, as indirectly assessed by the evolution of the arterial blood pressure. Time between the electrophysiologic disturbances and 25% decrease in mean arterial pressure is not decreased in the clonidine group. This is not in contradiction with the results found in dogs, in which

clonidine, given for treatment of near-fatal bupivacaine overdose, did not help, nor significantly precipitate, cardiac depression.¹² It is an expected result for a drug that reduced norepinephrine output given in a stress situation. Moreover, dexmedetomidine, a pure α_2 agonist, has no detectable effects on contractility, relaxation, or intracellular calcium transient in ferret ventricular myocardium.³¹

A reduction of the blood flow to the brain and the heart, the target organs for bupivacaine toxicity, consecutive to the clonidine-induced reduction in MABP, is not a likely explanation for the postponed toxic manifestation of bupivacaine overdose in this group.

At the cellular level, bupivacaine blocks the fast sodium channels,²⁸ the slow calcium channels,³² and the potassium channels.³³ Clonidine activates the potassium channels,³⁴ leading to an efflux of potassium that reduces intracellular cationic concentrations. It hyperpolarizes the excitable membrane and effectively suppresses cellular firing. Hyperpolarized cells are less excitable and, therefore, less sensitive to local anesthetics.³⁵

Bupivacaine also stimulates the production of cyclic AMP, the intracellular second messenger of epinephrine and a known dysrhythmogenic agent in human isolated lymphocytes.³⁶ Increased intracellular cyclic AMP concentrations may explain the frequent ventricular dysrhythmias after high doses of bupivacaine. It may also explain the potentiation of bupivacaine cardiotoxicity by epinephrine.³⁷ Clonidine, by stimulation of α_2 -adrenergic receptors, inhibits the adenylate cyclase and decreases the accumulation of cyclic AMP.³⁴

Pretreatment with calcium-channel entry blockers has already been reported to protect against bupivacaine cardiotoxicity in rats.³⁸ The suspected mechanisms were: calcium-channel, or even sodium-channel, blockade; reduction of cardiac irritability because of elevated catecholamine levels; and coronary vasodilatation. The protective potency of the calcium-channel blockers appeared to parallel the drug's potency for coronary vasodilatation. α_2 -Adrenergic agonists also inhibit the voltage-sensitive calcium channels,³⁴ reduce catecholamine output,³⁹ and vasodilate the coronary arteries.⁴⁰

Local anesthetics, at subtoxic doses, can act as anti-convulsant, sedative, and analgesic agents. At higher concentrations, they cause convulsions. A further increase in blood levels results in generalized depression of the CNS.⁴¹ The anticonvulsant effect of clonidine was demonstrated in different seizure models in adult

rats.^{42,43} Meanwhile, no definitive conclusion can be drawn from this observation, because all of the rats received intraperitoneal barbiturates, which protect against bupivacaine-induced convulsions.⁴⁴

The information presented above provides several possible physiologic explanations for the delayed toxic effects of bupivacaine after clonidine administration. Although no definitive explanation can be provided by the current study, our results suggest that the probable synergistic analgesic and anesthetic effects between bupivacaine and clonidine are not associated with increased toxicity. This may be another argument for the clonidine-bupivacaine association in clinical practice.

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