Electrophysiologic cardiac effects of the new local anesthetic IQB-9302 and of bupivacaine in the anesthetised dog

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Background: Local anesthetics are not free from potentially fatal complications. Therefore every new local anesthetic should be tested to demonstrate a lower, or at least similar, degree of toxicity over clinically used analogs. Most toxic effects from local anesthetics affect the cardiac electrophysiologic function, so the aim of this study was to characterize the electrophysiologic effects of a new long-acting local anesthetic (IQB-9302, Ciprocaine), and compare them with those of bupivacaine in the anesthetized dog.

Methods: Eight Beagle dogs received three increasing infusion doses of either IQB-9302 or bupivacaine. Under isoflurane anesthesia, dogs were instrumented to monitor cardiovascular (cardiac output, arterial and venous blood pressures) and cardiac electrophysiologic data (sinus and atrioventricular (AV) node function, atrial, nodal and ventricular conduction times, and refractoriness).

Results: Only the highest dose of both drugs induced hemodynamic or electrophysiologic alterations: cardiac output and heart rate were reduced while blood pressures remained unchanged. Atrial and intranodal conduction times and atrial refractoriness increased similarly with both anesthetics, but to a slightly lesser extent with IQB-9302. Significant increases in His-Purkinje and intraventricular conduction times were the most severe noxious effects and occurred only with large doses of either drug. IQB-9302 was slightly less toxic than bupivacaine and, unlike this latter drug, potentially fatal arrhythmias were not induced.

Conclusion: IQB-9302 has hemodynamic and cardiac electrophysiologic effects similar to those caused by bupivacaine. Nevertheless, slightly less toxic effects were derived from IQB-9302 administration than with bupivacaine, and, unlike the latter, the former might be less proarrhytmogenic. The new long-acting local anesthetic IQB-9302 may offer clinical advantages compared with bupivacaine.

IQB-9302 [1-methylcyclopropyl-N-(2,6-dymethylphenyl)-2 piperidinecarboxamide, Ciprocaine; Instituto Químico-Biológico, Madrid, Spain] is a new local anesthetic closely related to bupivacaine. When given by the epidural route in the dog, IQB-9302 is slightly more potent than bupivacaine and produces a longer-lasting blockade (1). Sensorial block times induced by IQB-9302 are very similar but bupivacaine can produce a longer motor block. This feature is clinically relevant. Administration of local anesthetics runs the potential risk of intravascular injection, inducing life-threatening central nervous system and cardiovascular toxicity (2).

The aim of this study was to characterize the electrophysiologic cardiac effects of IQB-9302 in comparison with those of bupivacaine in dogs in an attempt to evaluate whether this newer drug produces less cardiotoxic effects than does bupivacaine.

Materials and methods

This study was conducted to show the electrophysiologic cardiac effects of IQB-9302 compared with bupivacaine in anesthetized dogs. Other indirect measures of cardiovascular toxicity were included but no attempt was made to determine their effects on either cardiac inotropy or the brain. The study was conducted after institutional approval of the animal experimentation. Eight adult female Beagle dogs weighing 14–16 kg and aged 12 months old (Isoquimen C, Barcelona, Spain) were used. Dogs were studied twice at intervals of at least 8 days (range: 8–14 days), and given IQB-9302 (1-methylcyclopropyl-N-(2,6-dymethylphenyl)-2 piperidinecarboxamide) or bupivacaine (Svedocain®, Inibsa, Barcelona, Spain). Within each experiment each dog received three increasing doses of the same drug. Bupivacaine and IQB-9302 were used at a concentration of

0.75% (bupivacaine: 26.00 mmol l^{-1}; IQB-9302: 23.23 mmol l^{-1}).

Dogs were fasted for 12 h for solids but had free access to water. They were preoxygenated by means of a facemask with a mixture of oxygen (2 l min^{-1}) and nitrous oxide (4 l min^{-1}). Isoflurane was then administered at 0.5% volume intervals (Forane, Abbott Laboratories, Madrid, Spain) until the anesthetic level was sufficient (2–2.5%) to allow endotracheal intubation and catheter placement. Once endotracheal intubation was performed, nitrous oxide administration was discontinued and mechanical ventilation was initiated to maintain normocarbia (35–45 mmHg; Penlon, Nuffield Series 200; 3, 4).

Continuous capnography, oximetry and isoflurane concentration from exhaled gases and pulse oximetry (Capnomac Ultima, Datex-Ohmeda, Helsinki, Finland), as well as ECG and blood pressures (Cardiocap II, Datex-Ohmeda, Helsinki, Finland) were monitored. A pulse oximetry sensor was placed on the tongue of the animals. Body temperature was maintained by means of a circulating water warming blanket (Term-o-Rite), and monitored with a probe placed in the esophagus.

Once intravascular catheters were placed (see below), anesthesia was maintained at 1.3x. Minimum alveolar concentration of isoflurane in the dog (MAC= 1.28% and anesthesia=1.7% volume) with a stabilization period of 20 min (alveolar to inspired ratio: Fa/Fi>0.98). Individual MAC values for isoflurane were not determined. Fluid maintenance was given with a saline solution at 2–3 ml kg^{-1}h^{-1}.

The skin area over the jugular and femoral veins was clipped and scrubbed with antiseptic solution (chlorhexidine 0.5% solution, Hibitane). A small cut in the skin was performed to place introducers in the right jugular vein (Input-PS 5F, Medtronic AVE, Santa Rosa, CA, USA), the right femoral artery (4F), the right femoral vein (6F) and the left femoral vein (4F and 6F) (Table 1). Although all procedures were performed under sterile conditions, the antibiotic cephazolin (30 mg kg^{-1}) was given immediately before

the study, and daily care of the incision sites was performed on the following days. No signs of infection or discomfort were noted in any dog.

The catheter inserted in the femoral artery was connected to a disposable transducer (Sorenson Transpac, Abbott, IL, USA) and to the cardiovascular monitor to measure blood pressure. Radioscopic imaging was employed to insert the remaining catheters. The 5F thermodilution catheter (Swan-Ganz, Arrow Balloon Thermodilution catheter) was inserted into the jugular vein and the tip located in the pulmonary artery. A 6F tetrapolar electrode catheter (5 mm 100 cm^{-1}, Boston EP Technologist, Explorer St, Boston, MA, USA) was inserted into the left femoral vein and the tip advanced to the right atrium for stimulation and recording purposes. A second hexapolar electrode catheter (J-Josephson Type, 2 mm 100 cm^{-1}, Cordis, NJ, USA) was introduced into the right femoral vein and advanced to the right heart to record the His electrogram. Finally, a third 4F tetrapolar electrode catheter (J-Josephson Type, 2 m/1 cm/80 cm, Bard, NJ, USA) was inserted and advanced to the right ventricle apex through the left femoral vein. All catheters were prerinsed with 1% heparinized solution.

Dogs were randomly given three increasing doses of a local anesthetic (bupivacaine or IQB-9302: 5 μg kg^{-1}min^{-1}; 25 μg kg^{-1}min^{-1}; 100 μg kg^{-1}min^{-1}) administered continuously with a syringe pump (infusion pump model 22, Harvard Apparatus, MA, USA) with an initial loading bolus at doses of 0.1 mg kg^{-1}, 0.2 mg kg^{-1} and 0.4 mg kg^{-1}, respectively, over a 10-h period. Higher doses were not selected because they produced severe cardiac toxicity in a preliminary study, thus preventing the electrophysiologic study. The molecular weight of IQB-9302 is 323 (C_{18}, H_{26}, N_2, O, HCl) and that of bupivacaine 325 (C_{18}, H_{28}, N_2, O, HCl); so the difference in the molar concentration between the drugs is negligible. Drugs were diluted to 0.75% and given intravenously in the right jugular vein.

Baseline values were recorded just before administering the first anesthetic bolus dose. Then a continuous infusion was started and 3 min later data were

Table 1

Relation of used catheters and routes.

Route	Catheter size		Purpose
Right jugular vein	5F (Swan Ganz)	Cardiac output	
Left femoral vein		4F (tetrapolar elect)	Ventricle recording
		6F (tetrapolar elect)	Right atrium recording and stimulation
Right femoral vein	6F (Hexapolar elect)	His recording	
Right femoral artery	4F	Blood pressure	

recorded again before the next bolus of anesthetic. Two increasing bolus doses followed by their corresponding continuous infusion were subsequently given and data were recorded as previously indicated. The total infusion time for each dose was 30 min plus the time necessary to record all the studied variables.

The following hemodynamic variables were measured: systemic arterial and pulmonary artery blood pressures; and central venous pressure and pulmonary capillary wedge pressure, which were monitored by means of an arterial catheter (systemic arterial pressure) and the Swan Ganz catheter (pulmonary artery, central venous, and pulmonary capillary wedge pressures). The thermodilution catheter was also employed to determine cardiac output (9520 A Cardiac Output Computer, American Edwards Laboratories, Irvine, CA, USA) as the average of four consecutive measurements. All hemodynamic data were recorded at baseline, and at 5 and 30 min after the administration of the loading doses.

Endocavitary atrial, His and ventricular electrograms signals were amplified and filtered (DAM 70 and DAM 50 amplifiers, World Precision Instruments, Sarasota, FL) to record the cardiac electrophysiologic data. A lead II surface ECG was also simultaneously recorded. A computerized data-lodger system (PC-Laboratory, Chart for Windows, AD Instruments Inc., Hastings, UK) was employed, and intervals were measured by the manual application of screen callipers. All electrophysiologic data were recorded at baseline and after 30 min of every stage of continuous drug infusion.

Before recording baseline data the electrical stimulus intensity threshold sufficient to provoke depolarization in the right atrium and ventricle was determined in order to perform programed electrical stimulation studies. A programmable stimulator was employed for pacing maneuvers (model 5325, Medtronic, Minneapolis, MN). The stimulation intensity was twice that of the diastolic threshold, and its duration was 3 ms.

Conduction times and ECG intervals

The following electrophysiologic measurements were recorded in milliseconds: the P-R interval, measured at the surface ECG from the onset of the P wave to the onset of the Q wave of the QRS complex; the P-A interval, measured from the onset of the electrocardiogram lead II P wave to the onset of the atrial depolarization, measured from the His bundle catheter (intra-atrial conduction time); the AH interval, measured from the onset of atrial depolarization at the His catheter to the His bundle electrogram (AV node conduction time); the

ventricular conduction (HV) interval, measured from the His bundle electrogram to the QRS onset in lead II (His-Purkinje conduction time); and the QRS duration (intraventricular conduction time) and the Q-T interval corrected by heart rate ($QT/\sqrt{HR}$, Bazett formula), which reflects ventricular refractoriness. As the main toxic action of local anesthetics belongs to ventricular conduction, the main variable employed to demonstrate the difference in their relative toxic action of both anesthetics is the HV time.

Conduction times after pacing

Because local anesthetics slow ventricular conduction in a rate-dependent manner (the faster rate paced, the greater the block), conduction time data was measured not only in the referred basal status but after pacing nine atrial stimuli at a cycle length of 300 ms (200 beats min^{-1}) and after pacing at 250 ms (240 beats min^{-1}). Thus the following extra variables were analyzed with every dose of the study drug: AH_{250}, AH_{300}, HV_{250}, HV_{300}, QRS_{250}, QRS_{300}, and the interval between the stimulus spike and atrial depolarization at the His catheter (St-A$_{250}$, St-A$_{300}$).

Sinus node function

In addition to HR measurement (RR in ms) the sinus activity was measured by the corrected sinus recovery time (CSRT). Suppression of sinus node pacemaker activity by driving the atrial at rapid rates (overdrive suppression) is a standard measure of sinus node function. In this study of drug toxicity, the longer it takes the sinus node to recover a spontaneous activity, corrected by the basal RR, the bigger the possible toxic effect at this level. The CSRT was assessed as the time needed by the sinus node to recover a spontaneous atrial rhythm after 30 s of atrial rapid stimulation at a cycle length of 250 ms and at 300 ms minus the previous sinus cycle length.

Atrioventricular node function

In addition to the surface PR and the local AH interval, it was specifically studied recording the Wenckebach Point. Atrial pacing was performed with progressive shortening of the cycle length to a cycle at which an AV second-degree type I (Wenckebach) block developed. The paced atrium cycle length at which AV blocks develop reflects the Wenckebach Point. When decreasing it indicates a deterioration in the AV node conduction properties.

Refractoriness

The refractory period reflects the minimum time needed for the cardiac tissue to reactivate after an ini-

tial depolarization. The atrial refractory period was determined with a drive of eight consecutive stimuli applied at the right atrium, at a cycle length of 250 ms, followed by an extra stimulus with a progressively decreasing coupling interval, until an atrial response was no longer elicited. The ventricular refractory period was assessed in a similar way, pacing at the right ventricular apex.

For the determination of blood gases and pH, venous samples were taken at baseline and 30 min after starting the three continuous doses of anesthetic (Statnova Profile, Nova Biomedical, Waltham, MA).

Results are expressed as the mean ± SD. Although both the anesthetics were tested in the same dogs to minimize individual differences the measured values varied slightly, and therefore data were compared by employing the percentage of variation with respect to baseline values. The HV interval was selected as the main variable because of its clinical importance when demonstrating the toxicity of a local anesthetic. Therefore, the estimated number of animals necessary to demonstrate the hypothesis of differences between the tested drug (IQB-9302) and the control drug (bupivacaine) was based on the variability of this parameter. This estimate was assessed with the statistical computer program 'nQuery advisor' (Statistical Solutions, Saugus, MA, USA), which gave an n-value of eight dogs. The effects of each local anesthetic were tested using the two-way analysis of variance (drug and dose) to determine the presence of cardiotoxic effects, and whether or not these were dose-dependent. The Fisher LSD post-hoc test was employed to compare individual groups with baseline values. The chi-square test was employed to compare qualitative data within the studied groups. A $P<0.05$ indicated statistical significance. Results were analyzed using the Statview computer program (Abacus Concepts, Berkeley, CA)

Results

Mean infusion times of both drugs were 49 ± 6 min, 49 ± 7 min, and 69 ± 17 min with the low, medium and high doses of bupivacaine, respectively, and 54 ± 5 min, 56 ± 11 min, and 66 ± 16 min, respectively, with IQB-9302. The two lower doses of IQB-9302 and bupivacaine barely affected the measured hemodynamic and electrophysiologic variables and no significant differences were found with baseline values. No differences were found comparing the effects at the same dose of both drugs. Hemodynamic and electrophysiologic alterations were first observed at the highest dose (100 μg kg^{-1}min^{-1}), and only the results at this dose are fully reported and compared with basal status.

Cardiac output decreased with both drugs following the highest dose (bupivacaine: baseline, 2.3 ± 0.4 1 m^{-1}; dose 3 bolus, 1.8 ± 0.2 1 m^{-1}; dose 3 infusion, 1.6 ± 0.2 1 m^{-1}; and IQB-9302: baseline, 2.0 ± 0.3 1 m^{-1}; dose 3 bolus, 1.6 ± 0.2 1 m^{-1}; dose 3 infusion, 1.5 ± 0.2 1 m^{-1}). Heart rate decreased following the infusion of the highest dose (dose 3 infusion) of bupivacaine (baseline, 114 ± 13 b.p.m.; dose 3 infusion, 96 ± 14 b.p.m.). Systemic arterial and pulmonary artery blood pressures and central venous pressure were not modified. Within the electrophysiologic study, some data requiring atrial pacing, especially at high rates, could not be fully recorded in some cases because atrial blocks or capture failures developed. When pacing, AV block at the nodal level was also observed in a few occasions, especially at the highest rate (240 b.p.m.). No differences in the occurrence of these toxic effects were observed between bupivacaine and IQB-9302 (chi-square test).

At surface ECG before pacing we found that the PR interval had increased with both drugs but only reached statistical significance when bupivacaine was administered. This increase was lost when adjusting the PR interval with the simultaneous RR. The QRS duration was similarly and significantly augmented by both anesthetics whereas the QT interval corrected by the HR was not modified. (Table 2)

Conduction times

Overall conduction times were increased by both local anesthetics after the high dose infusion. While these increases reached a statistically significant difference compared with baseline values with either drug, no significant differences could usually be found when comparing the two drugs.

Intra-atrial conduction

The PA interval was not modified at a spontaneous HR, but the St-A value (following programed electrical stimulation) was increased by more than 50% with IQB-9302 and by 100% with bupivacaine, reflecting a rate-dependent conduction delay. Bupivacaine significantly increased the St-A interval at a cycle length of 300 and 250 ms, whereas IQB-9302 induced the same increase with a cycle length of 250 ms ($P<0.05$) (Table 3).

Intranodal conduction

The AH intervals were increased with either anesthetic at spontaneous (AH) and stimulated (AH $_{250}$ and AH $_{300}$) HR. Significant increases of the spontaneous AH interval were observed after bupivacaine. This increment was lost when adjusting the AH inter-

val with the simultaneous RR. The AH interval at a cycle length of 250 and 300 ms was increased by both anesthetics, again reflecting a rate-dependent conduction delay (significant at 300 ms; Table 3).

His bundle and intraventricular conduction

IQB-9302 and bupivacaine significantly increased the HV interval and QRS duration at spontaneous and stimulated HR. Bupivacaine always induced a higher increase of His bundle, and intraventricular conduction times and significant differences between both anesthetics were observed with atrial pacing at a cycle length of 300 ms (Figs 1,2).

Sinus node function

In addition to the effect at the HR previously described, the CSRT was increased by both anesthetics. This effect was observed at both stimulation cycle lengths (250 and 300 ms). It only reached statistical significance, compared with baseline values, following IQB-9302 ($P < 0.05$) (Table 4).

Atrioventricular node function

Apart from the described effects at the PR and AH times, the Wenckebach Point was also modified. Both anesthetics reduced the Wenckebach Point, being significant only with bupivacaine (Table 4).

Table 2

Surface lead II ECG data.

Anesthetic	ms	Baseline	Dose 1	Dose 2	Dose 3
Bupivacaine	RR	544 ± 50	558 ± 70	545 ± 57	$631 \pm 76*$
	P-R interval	98 ± 14	99 ± 15	95 ± 9	$122 \pm 22*$
	P-R/RR	0.2 ± 0.2	0.2 ± 0.3	0.2 ± 0.3	0.2 ± 0.4
	QRS duration	58 ± 2	58 ± 2	58 ± 2	$66 \pm 7*$
	Q-Tc	349 ± 27	356 ± 21	349 ± 29	360 ± 31
IQB-9302	RR	561 ± 40	536 ± 47	553 ± 54	620 ± 92
	P-R	107 ± 14	97 ± 12	103 ± 18	115 ± 14
	P-R/RR	0.2 ± 0.3	0.2 ± 0.3	0.2 ± 0.3	0.2 ± 0.4
	QRS duration	57 ± 2	57 ± 2	58 ± 2	$63 \pm 2*$
	Q-Tc	338 ± 16	346 ± 20	341 ± 26	348 ± 25

Dogs were given three boluses (dose 1: 0.1 μg kg^{-1}; dose 2: 0.2 μg kg^{-1}; and dose 3: 0.2 μg kg^{-1}), followed by three continuous infusions (5, 25 and 100 μg kg^{-1} min^{-1}, respectively) of either bupivacaine or IQB-9302.
RR, heart rate measurement; PR, ; QRS, ; QTc, QT interval corrected by heart rate.
*Significantly different from baseline ($P < 0.05$).
Mean $\pm$ SD; n-value is always 8.

Table 3

Atrial and intranodal conduction times.

Anesthetic	ms	Baseline	Dose 1	Dose 2	Dose 3
Bupivacaine	P-A interval	26 ± 3	24 ± 2	22 ± 5	25 ± 8
	St-A$_{300}$ interval	29 ± 5	31 ± 7	32 ± 7	$58 \pm 14*(n=4)$
	St-A$_{250}$ interval	29 ± 5	31 ± 7	34 ± 9	$51 \pm 6*$
	A-H interval	68 ± 13	68 ± 13	71 ± 12	$88 \pm 19*$
	A-H/RR	0.12 ± 0.02	0.12 ± 0.03	0.13 ± 0.03	0.14 ± 0.03
	A-H$_{300}$ interval	85 ± 23	84 ± 19	85 ± 16	$123 \pm 26*$
	A-H$_{250}$ interval	111 ± 36	111 ± 37	112 ± 42	$147 \pm 19 (n=4)$
	P-A interval	27 ± 3	24 ± 4	22 ± 4	25 ± 7
IQB-9302	St-A$_{300}$ interval	33 ± 13	36 ± 8	34 ± 6	$47 \pm 23 (n=6)$
	St-A$_{250}$ interval	33 ± 14	35 ± 9	35 ± 7	$50 \pm 13*$
	A-H interval	71 ± 15	66 ± 11	71 ± 14	87 ± 45
	A-H/RR	0.13 ± 0.02	0.12 ± 0.03	0.13 ± 0.03	0.14 ± 0.08
	A-H$_{300}$ interval	96 ± 29	84 ± 16	93 ± 20	$128 \pm 40*$
	A-H$_{250}$ interval	118 ± 46	114 ± 39	120 ± 41	$146 \pm 49 (n=6)$

Dogs were given three boluses (dose 1: 0.1 μg kg^{-1}; dose 2: 0.2 μg kg^{-1}; and dose 3: 0.2 μg kg^{-1}) followed by three continuous infusions (5, 25 and 100 μg kg^{-1} min^{-1}, respectively) of either bupivacaine or IQB-9302.
PA, ; AH, ; RR, heart rate measurement.
St-A, stimulus to A interval; A-H$_{300}$, A-H interval at 300 ms cycle length; A-H$_{250,}$, A-H interval at 250 ms cycle length.
Unless indicated, n= 8. Mean $\pm$ SD.
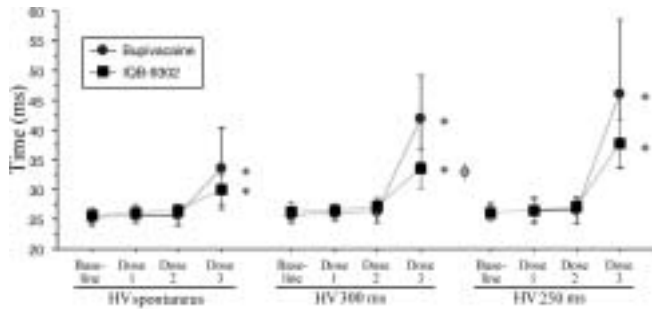*Significantly different from baseline ($P < 0.05$).

Fig. 1. Ventricular conduction (HR) interval: spontaneous (above, mean ± SD) and stimulated (HV 300 ms and HV 250 ms, below) at three increasing doses of either bupivacaine or IQB-9302. *Significantly different from baseline (P<0.05). †Significantly different from the same dose of bupivacaine (P<0.05).
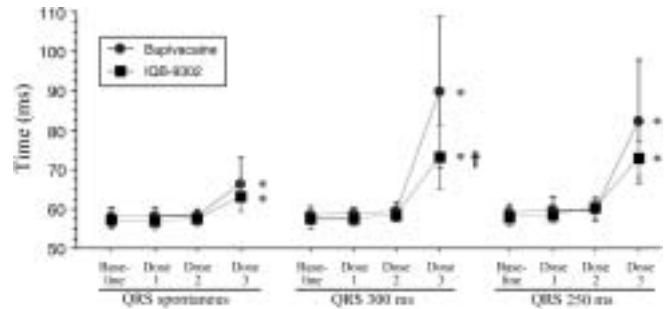

Fig. 2. QRS (QRS complex) duration: spontaneous (above, mean ± SD) and after atrial pacing (QRS 300 ms and QRS 250 ms, below) at three increasing doses of either bupivacaine or IQB-9302. *Significantly different from baseline (P<0.05). †Significantly different from the same dose of bupivacaine (P<0.05).

Refractoriness

Refractory times, pacing at a cycle length of 250 ms, were increased significantly by both drugs; the atrial refractory period augmented by 41% and 67%, respectively, following bupivacaine and IQB-9302, whereas the ventricular refractory period was increased by 11% and 12%, respectively (Table 4).

Arrhythmias

At the highest dose the auricular diastolic threshold increased in three dogs receiving IQB-9302 and five dogs receiving bupivacaine (non-significant). Four dogs presented a Wenckebach type intra-atrial block when pacing at the atrial level with either drug. No spontaneous atrioventricular block was observed with either drug; these only occurred in a few cases when pacing, mainly at 250 ms, and were located at the AV node, without statistical differences between both drugs. When pacing for ventricular refractoriness, short runs of non-sustained ventricular tachycardia appeared in three dogs receiving bupivacaine but in none receiving IQB-9302 (P<0.05).

The carbon dioxide and oxygen values were within the normal range. Analysis of blood gases and pH showed no differences between either anesthetic at the same dose level or when compared with baseline values. The isoflurane end-tidal concentration was 1.76% ± 0.19% and 1.77% ± 0.19% for IQB-9302 and bupivacaine, respectively.

Discussion

The new long-acting local anesthetic IQB-9302 produces hemodynamic and cardiac electrophysiologic actions similar to those produced by bupivacaine. These effects are dose-dependent and were only de-

Table 4

Sinus and atrioventricular node function and atrial and ventricular refractoriness.

Anesthetic		Baseline	Dose 1	Dose 2	Dose 3
Bupivacaine	$CSRT_{300}$ (ms)	80 ± 49	82 ± 61	135 ± 142	146 ± 46 (n=7)
	$CSRT_{250}$ (ms)	74 ± 61	80 ± 45	98 ± 67	123 ± 60 (n=5)
	Wenckebach Point (b.p.m.)	283 ± 46	272 ± 48	273 ± 44	200 ± 41*
	ARP_{250} (ms)	110 ± 11	109 ± 18	110 ± 21	156 ± 31*
	VRP_{250} (ms)	145 ± 8	146 ± 9	148 ± 7	161 ± 11*
IQB-9302	$CSRT_{300}$ (ms)	58 ± 104	87 ± 83	125 ± 111	165 ± 97*
	$CSRT_{250}$ (ms)	39 ± 79	60 ± 60	82 ± 68	196 ± 144*(n=7)
	Wenckebach Point (b.p.m.)	272 ± 64	268 ± 58	261 ± 65	220 ± 48
	ARP_{250} (ms)	103 ± 10	106 ± 9	118 ± 26	173 ± 34*
VRP_{250} (ms)		141 ± 10	141 ± 6	148 ± 14	158 ± 9*

Dogs were given three boluses (dose 1: 0.1 µg kg^{-1}; dose 2: 0.2 µg kg^{-1}; and dose 3: 0.2 µg kg^{-1}) followed by three continuous infusions (5, 25 and 100 µg kg^{-1} min^{-1}, respectively) of either bupivacaine or IQB-9302.
CSRT, corrected sinus recovery time; ARP$_{250}$, atrial refractory period at cycle length of 250 ms; VRP$_{250}$, ventricular refractory period at cycle length of 250 ms.
Unless indicated, n=8. Mean ± SD.
*Significantly different from baseline (P<0.05).

tectable when the largest doses of both drugs were employed. Reduction in cardiac output with minor changes in blood pressure was probably a result of reduced ventricular inotropy (5). The cardiotoxicity of bupivacaine and IQB-9302 mainly affects the electrophysiologic values reflecting His-Purkinje and intraventricular electrical conduction (HV and QRS duration) (6).

The local absorption of injected local anesthetics from the injection site can increase plasma concentrations to levels that may have toxic effects on the heart (7). Rapid peak plasma levels may also occur from an inadvertent injection of the anesthetics directly into the blood stream. Levels between 2.5 and $4\,\mu g\,ml^{-1}$ are reported to elicit early subjective central nervous system (CNS) symptoms of bupivacaine toxicity. Mean peak plasma concentrations between 2.3 and $3.3\,\mu g\,ml^{-1}$ have been reported after lumbar epidural, bilateral intercostal and axilary plexus block (8, 9). In dogs, toxic doses of bupivacaine producing cardiovascular and cardiac electrophysiologic changes were correlated with plasma concentrations above 2.4 $\mu g\,ml^{-1}$ (5). The same dose was employed in this study with similar results on cardiac function.

The potential for cardiovascular toxicity with local anesthetics is explained by sodium channel blockade, not only in the nerve cell membranes but also in other excitable tissues, such as the heart (10, 11). Both direct and indirect cardiac effects may count for this action; direct blockade of sodium channels, as well as blockade of potassium and calcium channels, delays conduction and prolongs QRS. IQB-9302 causes a lesser degree of inhibition of potassium channels (Kv1.5; 12), which are involved in the control of cardiac repolarization (13), compared with bupivacaine.

A blockade of sympathetic cardiac innervation (14) as well as their effects on the cardiovascular center in the brain stem are among the indirect effects on the heart (11, 15). Longer-acting local anesthetics like bupivacaine have a greater risk of toxicity (16). Cardiotoxicity induced by bupivacaine is characterized by the appearance of cardiac arrhythmias, including ventricular tachycardia and ventricular negative inotropy (17). This latter effect was only indicated in this study by its indirect effects on blood pressure and cardiac output. Furthermore, the increased HR produced by atrial pacing intensifies the cardiac sodium channel blockage induced by drugs like bupivacaine (11, 18).

The QRS duration and HV interval are measurements of intraventricular and His-Purkinje conduction velocities, respectively (6). Local anesthetics slow ventricular conduction by increasing both parameters, and to a greater extent with rapid atrial pacing (rate-

dependency) (5). This favors the re-entry phenomena (19), which may provoke serious ventricular arrhythmias. Slowing of ventricular conduction velocities under atrial pacing induced by IQB-9302 was less marked than with bupivacaine, which should provide a wider safety margin. In fact, only bupivacaine induced non-sustained ventricular tachyarrhythmias when ventricular pacing.

To reduce drug interaction (20), only isoflurane was given. Isoflurane alone can produce various cardiovascular effects (21, 22) as well as modify those produced by bupivacaine. Isoflurane (23) and sevoflurane (24) interact with bupivacaine and similarly attenuate its cardiac toxicity, but may potentiate its negative effects on cardiac contractility (25). Propofol reduces the systemic toxicity of bupivacaine even more than the two former drugs (26). Using regional anesthesia as an adjunct, general anesthesia can be maintained with either volatile or intravenous anesthetics, and therefore the conditions of the present experiment may mimic the clinical setting. Results may differ if animals are not previously medicated but the electrophysiologic study we performed would have not been possible, with the experimental design used, in conscious animals for practical reasons. Nevertheless, it should be emphasized that the conditions of the study do not match all situations found in the clinical setting, i.e. accidental bolus injection in a patient without general anesthesia. Halothane has been shown to not modify bupivacaine-induced slowing of ventricular conduction, while it does slightly lengthen ventricular refractoriness and significantly decreases cardiac inotropy. A potentially more severe toxic effect from halogenated anesthetics is derived from their effects on the hepatic clearance reduction of local anesthetics (27).

A previous study from our laboratory showed that epidurally administered IQB-9302 is at least as potent as bupivacaine, but has a higher sensorial to motor block ratio (1) with a potential clinical benefit, i.e. patient well-being and reduced hospital stay.

Conclusion

IQB-9302 causes dose-dependent hemodynamic and cardiac electrophysiologic effects that are similar to those produced by bupivacaine. The main toxic alterations observed affected His-Purkinje and intraventricular conduction times and, to a lesser extent, the sinus and atrioventricular nodes. IQB-9302 caused lower toxicity than bupivacaine, without inducing potentially fatal arrhythmias. This reduced toxicity may provide a wider safety margin compared with

bupivacaine. Nevertheless, further studies are needed to demonstrate whether IQB-9302 has less cardio-vascular toxic effects than other recently introduced local anesthetics, such as levobupivacaine or ropivacaine.

Acknowledgement

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