Ulnar Nerve Block Induced by the New Local Anesthetic IQB-9302 in Healthy Volunteers: A Comparison with Bupivacaine

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We evaluated the duration of sensory anesthesia after blockade of the ulnar nerve of IQB-9302, a new local amide anesthetic, compared with bupivacaine. A double-blinded, randomized, cross-over study in 12 healthy volunteers aged 18 to 35 yr was performed. Three milliliters of 0.25% IQB-9302 was administered in one wrist and bupivacaine in the other. A week later, the blocks were repeated with a concentration of 0.5%. These concentrations were chosen because they seemed to be equipotent in previous studies. The duration of sensory anesthesia was the main variable measured; secondary outcomes were motor block, time to onset, and time to recovery from block. The duration of sen- sory block was similar for IQB-9302 and bupivacaine at a concentration of 0.25%; median and range: 409 min (0–800 min) for IQB-9302 and 258 min (0–665 min) for bupivacaine (95% confidence interval for the difference from −47 to 545, $P = 0.82$, Wilcoxon's test). The results with 0.5% were: 525 min (440–735 min) and 690 min (365–1098 min), respectively ($P = 0.026$). There were no significant differences in the other variables measured. No important adverse reactions were seen. We con- clude that IQB-9302 is an effective new local anesthetic for blockade of ulnar nerve at the concentrations tested.

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Drugs with local anesthetic activity can be catego- rized in two different chemical groups, ester and amide (1,2). To improve the tissue distribution and fixation of the anesthetic molecule, a series of amide anesthetic derivatives bearing a cyclopropyl group linked to the side chain were designed. This low-molecular-weight alkyl group maintains the steric and lipophilic properties of the most potent amide anesthetics, such as bupivacaine, and provides resis- tance to enzymatic metabolization prolonging the du- ration of action. From this series, IQB-9302 (Fig. 1) was selected because of its long duration of action and relatively low toxicity as revealed by the preliminary pharmacologic screening (3). Because of the presence of an asymmetric carbon atom, IQB-9302 is a mixture of two stereoisomers, L(−)-IQB-9302 and D-(+)-IQB- 9302. No significant differences were shown in the respective activity of L and racemic IQB-9302. D-(+)- IQB-9302 was the less potent of the test compounds (3). The pK for IQB-9302 is 7.9 compared with 8.1 for bupivacaine.

The anesthetic effects of IQB-9302 were studied by three standard tests: infiltration anesthesia in the guinea pig, palpebral anesthesia in the rabbit and guinea pig, and sciatic nerve block in the rat. In these preliminary experiments, IQB-9302 exhibited the best therapeutic index of all local anesthetics to date, approximately twice that of lidocaine, mepi- vacaine, and bupivacaine, which are the most used drugs today (4).

Our primary objective was to compare the dura- tion of sensory anesthesia after blockade of the ul- nar nerve of the test product (IQB-9302) with the reference product (bupivacaine). The secondary ob- jectives were measurement of the following: 1) onset of sensory block and motor block, 2) duration of motor block, 3) skin temperature of the anesthetized
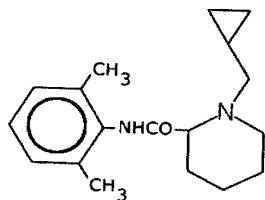
Figure 1. Chemical structure of IQB-9302.

area, and 4) incidence of adverse events. This is one of the phase I studies required for the clinical evaluation of a new local anesthetic drug included in the Food and Drug Administration guidelines, which represent generally acceptable principles for arriving at valid conclusions concerning safety and effectiveness of new drugs (5).

Methods

This protocol was performed following the Spanish law on clinical trials and approved by the Ethics Committee for Clinical Research of the Hospital Universitario de La Princesa. All participants gave written consent. Subjects recruited from the medical school and community were included in the study if they were nonsmoking males, aged 18–35 yr, and considered healthy after clinical history, physical examination, 12-lead electrocardiogram, urinalysis, hematology, and blood chemistry analysis.

We performed a double-blinded, randomized, four-sequence, cross-over study. Volunteers were allocated to one of the following four treatment sequences: 1 = abAB, 2 = abBA, 3 = baBA, and 4 = baAB (A and B representing the different treatments IQB-9302 and bupivacaine, and a and b the two doses); the volunteers were distributed into groups of four by block randomization. Laboratorios Inibsa provided the two drugs. The ulnar block was performed first in the left wrist and then in the right one, with each dose in two different sessions.

Participants did not take ethanol, caffeine, tea, or cola-containing beverages at least 48 h before each study. In addition, they took no prescription drug for 2 mo before the beginning of the study, and no prescription or other drugs were taken for the duration of the study. The participants fasted from 10 h before until 5 h after the first nerve block. During the first 5 h before eating, the subjects were confined to bed. The dietary regimen was similar for all subjects in both trial periods.

IQB-9302 and bupivacaine were administered by infiltration near the cubital nerve at concentrations of 0.25% and 0.5% (w/v) in two separate sessions, with a 1-wk washout period. A blunted retrobulbar 25-gauge needle was inserted on the ulnar side of the ulnar artery and advanced between it and the

flexor carpi ulnaris to the level of the ulnar styloid. When a paresthesia was elicited, the needle was retracted 1–2 mm. Three milliliters of one of the two solutions (test and comparative standard) was injected in the left wrist. One and a half hours later, the ulnar block was performed in the right wrist with the second solution. On the second day, after a 1-wk washout period, 3 mL of the larger concentration of both drugs (0.5%) was injected, and the same procedures were followed. Each block was performed by the same anesthesiologist who was blinded to the solution being used. The subject and the investigator who assessed the block were also blinded to the treatment. The trial periods were conducted with the smallest concentration (0.25%) followed a week later with the larger concentration (0.5%).

The following variables were evaluated: duration of sensory block (main variable), duration of motor block, onset and time of recovery of sensory and motor blocks, and skin temperature of the anesthetized area, and adverse effects.

Sensory block was evaluated by pricking the anesthetized area in three different places, in the ulnar palm region and the fifth finger with a sharp needle. Complete sensory block was considered when the subject did not feel pain from the prick. Motor block was measured by the capacity of the volunteer to oppose the thumb and little finger; complete motor block was considered when the subject could not make this movement. Skin temperature of the anesthetized area was also measured with an instantaneous thermometer included in the neurostimulator Tof-Guard INMT to evaluate the autonomic nervous system block.

Measurements were made at the following times after injection of the drug: 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 12, and 15 min, 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5 h, and then every 30 min until recovery of motor and sensory function.

Adverse clinical events were recorded by using an open question (Have you noted anything?) during the study. Blood pressure and heart rate were monitored at baseline (preblock), 15 min, 2, 4, 6, and 8 h, and then each 2 h until recovery of motor and sensory functions. A 12-lead electrocardiogram (PR and QTc intervals) was recorded at baseline time and 2 h after each block.

We decided to include 12 volunteers inasmuch as this was an exploratory dose-finding study, and this is the sample size used in published studies (6,7). All variables were analyzed for each drug and dose by Wilcoxon's matched-pairs test by using SPSS Version 10.0 for Windows (SPSS, Chicago, IL). A P value $\geq$ 0.05 was considered a significant difference. Data were expressed as median and range (minimal and maximal values) because of their high variability.
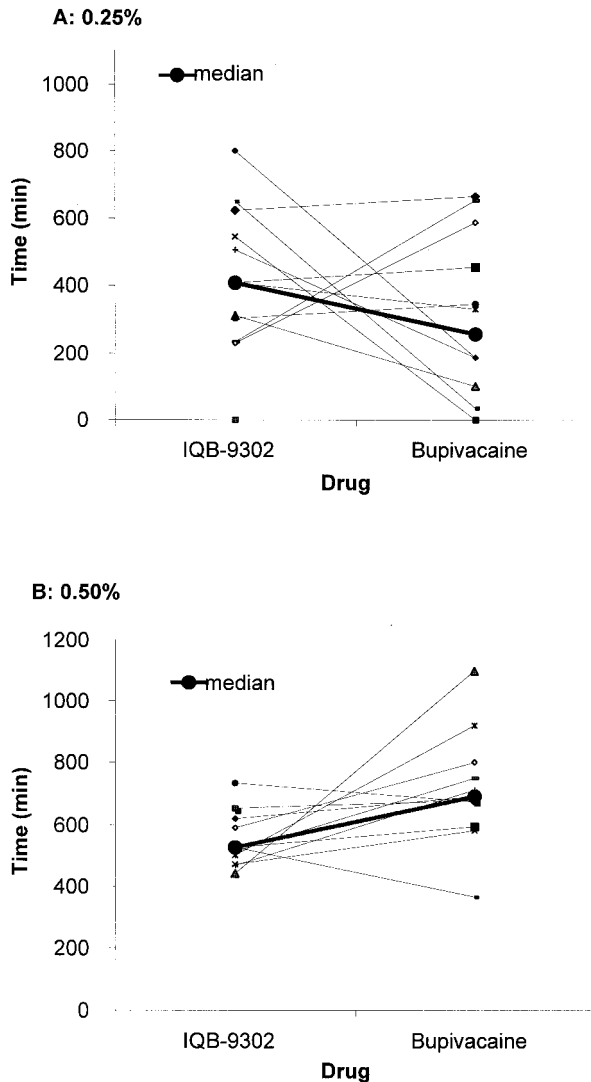
Figure 2. A comparison of the duration of complete ulnar sensory block induced by IQB-9302 and bupivacaine at the concentrations of 0.25% (A) and 0.50% (B).

Table 1. Duration of Sensory and Motor Ulnar Block Induced by IQB-9302 and Bupivacaine

Dose	IQB-9302	Bupivacaine	P Value*
Sensory block			
0.25%	409 (0–800)	258 (0–665)	0.826
0.50%	525 (440–735)	690 (365–1098)	0.026
P value†	0.016	0.010	
Motor block			
0.25%	285 (0–680)	0 (0–755)	0.515
0.50%	510 (210–732)	675 (150–1030)	0.110
P value‡	0.014	0.021	

Data are median (range) of the duration in minutes of the sensory or motor block.

* Comparing IQB-9302 and bupivacaine.
†‡ Comparing 0.25% and 0.50% doses.

Results

Twelve healthy volunteers, aged between 18 and 31 yr (mean 24 yr) and weighing between 64 and 85 kg (mean 69 kg), were included in the study. Subject number 1 was excluded before the second trial, so he only received the smaller dose of the medication. The investigators decided not to administer the larger dose because this subject presented slight paresthesias in one hand after the smaller dose. Data from 46 blocks (24 with the 0.25% concentration and 22 with the 0.5%) were included in the statistical analyses.

At the small concentration (0.25%), complete sensory block was achieved in 11 of 12 volunteers after IQB-9302, and in 10 of 12 volunteers after bupivacaine (Fig. 2). The duration of sensory block was similar for IQB-9302 and bupivacaine at a concentration of 0.25%; median and range: 409 min (0–800 min) for IQB-9302

and 258 min (0–665 min) for bupivacaine (95% confidence interval [CI] for the difference from −47 to 545, $P = 0.82$, Wilcoxon's test). Motor block was achieved in 7 volunteers with IQB-9302 and in 5 volunteers after bupivacaine. The duration and onset of motor were similar for both drugs (Tables 1 and 2). An increase in skin temperature, revealing blockade of the autonomic nervous system, was observed after the administration of both drugs. A decrease in skin temperature was observed just after the IQB-9302 injection (Fig. 3).

At the larger concentration (0.5%), complete sensory block was achieved in all 11 subjects treated with IQB-9302 and bupivacaine (Fig. 2). Complete motor block was also achieved in all subjects. The duration of sensory block was shorter for IQB-9302 than for bupivacaine (95% CI for the difference from −658 to −25 min, $P = 0.026$) (Table 1), but the onset of sensory anesthesia was similar (95% CI for the difference from −15 to 18 min) (Table 2). The duration of motor block was similar for both drugs (Table 1); there were no differences as regards the onset of motor block. There were no differences for any of the secondary variables between both drugs (Table 2).

There were no important adverse reactions. One subject was excluded from the study because he reported slight paresthesias in the hand after 0.25% IQB-9302 injection. This adverse reaction was probably related to the technique, because this subject had a severe paresthesia before the drug was infused. The duration of paresthesias was about a month, disappearing spontaneously. The subject did not need any medical treatment and continued normal daily activities. Another volunteer reported slight paresthesias in the right hand; in this case, the technique took longer than usual because it was difficult to elicit paresthesia. The drug used was 0.5% IQB-9302 and the duration of paresthesias was only 2 days. Two volunteers had pain in the wrist after the administration of IQB-9302 and one after bupivacaine. One subject had itching in the fifth finger after bupivacaine injection. Both formulations were well tolerated, and no significant changes were found in biochemical or hematologic variables.

Table 2. Secondary Variables Concerning the Sensory and Motor Ulnar Block Induced by IQB-9302 and Bupivacaine
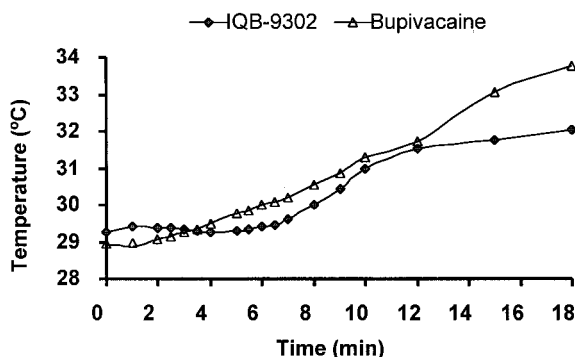
	IQB-9302	Bupivacaine
Dose 0.25%		
Time to onset of sensory block	20 (5–40) *n* = 11	25 (6–60) *n* = 10
Time to onset of motor block	30 (18–90) *n* = 7	35 (25–60) *n* = 5
Time to recovery of sensory function	180 (60–240) *n* = 11	135 (90–300) *n* = 10
Time to recovery of motor function	90 (60–210) *n* = 7	60 (60–90) *n* = 5
Dose 0.50% *n* = 11		
Time to onset of sensory block	15 (9–40)	10 (1–30)
Time to onset of motor block	30 (18–120)	20 (6–90)
Time to recovery of sensory function	120 (90–240)	90 (60–150)
Time to recovery of motor function	90 (60–180)	90 (60–240)

Data are medians (range) of the number of subjects indicated as "*n*" for each variable in minutes. There were no statistical differences noted.

A: 0.25%
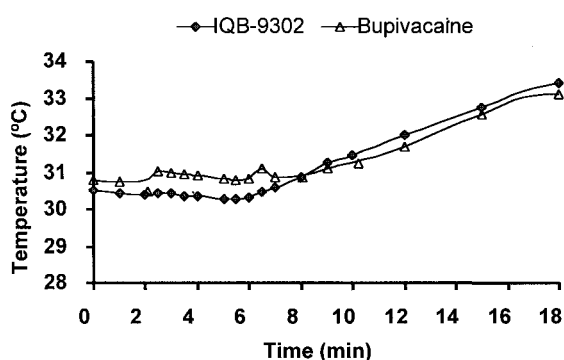
B: 0.50%

Figure 3. Changes in skin temperature induced by the administration of IQB-9302 and bupivacaine at 0.25% (A) and 0.50% (B). There were no statistical differences noted.

Discussion

Bilateral ulnar nerve blocks on volunteers have been studied by different investigators to assess the blocking characteristics of different local anesthetics. The results from different test series performed at different times led to the conclusion that results of blocks using different test solutions may be compared even if a common reference drug was not included in the study. Furthermore, only 10 to 12 volunteers had to be tested in each series to demonstrate significant differences between commonly used local anesthetics (8). The duration of action of bupivacaine is approximately 2 to 3 times longer than lidocaine or mepivacaine, and 20% to 25% longer than tetracaine (9). In recommended doses, bupivacaine produces complete sensory block; however, the effect on motor functions differs among the three concentrations (0.25%, 0.5%, and 0.75%). The 0.25% concentration produces incomplete motor block when used for caudal epidural or peripheral nerve block.

The results from different studies show that bupivacaine 0.25% and etidocaine 0.5% produced the longest minor nerve blocks compared with procaine, lidocaine, prilocaine, and mepivacaine (8), and very similar to ropivacaine (450–550 minutes) (10,11). The duration of action in ulnar blocks was roughly the same as digital blocks, axillary blocks, and caudal blocks (approximately 500, 450, 550, and 460 minutes, respectively, with bupivacaine 0.25%) (8). It is well described that the duration of anesthetic activity for minor nerve block in general is between 180 and 360 minutes (12), and the onset of anesthesia is between 4 and 11 minutes (7,8,12). In a comparative study between etidocaine and bupivacaine in ulnar nerve block (13), the onset and duration of analgesia were 7.9 ± 7.2 and 576 ± 90 minutes, respectively, for bupivacaine 0.25%, and 7.7 ± 4.3 and 758 ± 226 minutes for bupivacaine 0.5%.

In our study, it is difficult to find statistically significant differences between the efficacy of the two drugs in ulnar block. This may be attributable to the large variability in the technique used to induce nerve blockade. The results for bupivacaine are similar to those found in the literature, although interindividual variability values are larger than those previously reported (17%–27%) (4,6). The coefficient of variation in our study was 84% and 59% for the 0.25% and 0.50%

doses, respectively; this coefficient was less for IQB-9302, which was 52% and 16%, respectively, for the same doses. The differences of the coefficients of variation with data on bupivacaine reported in the literature may be attributable to the fact that some of these data were obtained from studies using different nerves (intercostal nerve block, sciatic, and femoral nerve block).

Two phase I clinical trials were made before the beginning of this study (3). The first one, which evaluated the tolerance and local anesthetic effects of increasing intradermal doses of IQB-9302, included 12 healthy male volunteers. Placebo and increasing concentrations of IQB-9302 (0.1%, 0.25%, 0.50%, 0.75%, and 1%) were injected in volumes of 0.2 mL subcutaneously. No local or systemic side effects were reported, and tolerance was excellent in all volunteers at tested doses. In the range 0.1% to 0.75%, IQB-9302 exhibited linear dose-response relationships in the duration of anesthesia, which was very prolonged. Most volunteers exhibited some pallor surrounding the injected area, suggesting a vasoconstrictor effect. The second one was a double-blinded comparison of increasing intradermal doses of IQB-9302 and bupivacaine in 12 healthy volunteers. The subjects received intradermal doses of 0.1 mL of IQB-9302, bupivacaine, or placebo at different concentrations (0.25%, 0.50%, and 0.75%). All concentrations of IQB-9302 induced a very long-lasting effect. Dose-related effects were more evident with IQB-9302, and local anesthesia ranged between 105 ± 16 minutes (0.25%) and 129 ± 15 minutes (0.75%). Dose-related effects were less evident for bupivacaine, and the duration of the local anesthetic effects ranged between 37 ± 7 minutes (0.25%) and 43 ± 8 minutes (0.75%). When 0.1 mL of IQB-9302 0.25% was compared with bupivacaine 0.75%, the anesthetic effects of IQB-9302 were also longer. In this study, capillary blood flow was measured in subjects treated with bupivacaine 0.75% and IQB-9302 0.25%, and a moderate increase of blood flow after bupivacaine and a moderate decrease after IQB-9302 was observed. Differences were statistically significant after 15 and 60 minutes, suggesting a vasoconstrictor effect of IQB-9302 (3).

Several factors must be considered in choosing a local anesthetic to provide effective anesthesia and analgesia: these include the expected duration of the surgical procedure and requirements for postoperative analgesia. Of primary concern, however, is patient safety. In this study, IQB-9302 at 0.25% showed acceptable activity, and we did not find any serious adverse effects. The incidence of paresthesias with IQB-9302 was 8.7% (2 of 23 blocks), similar to other

studies. In a previous study (15), neuropathy developed in 7 of 44 patients (16%) receiving bupivacaine 0.25% or 0.5% as a wrist and metacarpal block. The hypesthesias lasted from one week to four months.

Skin temperature decreased more with IQB-9302 administration than with bupivacaine just after drug administration. This decrease in the hand temperature may have been caused by a vasoconstrictor effect of IQB-9302, because the drug remains at the site of injection instead of being removed by the circulation as occurred with the remainder of the amide anesthetics that have an intrinsic vasodilator effect. Afterward, this effect was masked by the drug's autonomic blocking effect. Therefore, because IQB-9302 exhibited a vasoconstrictor effect could be an important advantage, because the drug could be administrated without a vasoconstrictor.

In conclusion, IQB-9302 is an effective new local anesthetic for blockade of ulnar nerve at the concentrations tested.

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