British Journal of Anaesthesia 1998; **80**: 594–598

Comparison of S(–)-bupivacaine with racemic (RS)-bupivacaine in supraclavicular brachial plexus block†

C. R. COX, M. R. CHECKETTS, N. MACKENZIE, N. B. SCOTT AND J. BANNISTER

Summary

Bupivacaine is used widely as a local anaesthetic but has potential for severe cardiovascular and central nervous system (CNS) toxicity. It has an asymmetric carbon atom giving it a chiral centre, and the commercial preparation is a racemic mixture of its two enantiomers: dextro or R(+)-bupivacaine and levo or S(−)-bupivacaine. Preclinical studies have demonstrated reduced cardiotoxicity and CNS toxicity for S(−)-bupivacaine. In this study we have compared the clinical efficacy of S(−)-bupivacaine with racemic RS-bupivacaine for supraclavicular brachial plexus block in 75 patients undergoing elective hand surgery. Patients received 0.4 ml kg^{-1} of either 0.25% or 0.5% S(−)-bupivacaine or 0.5% RS-bupivacaine in a randomized, double-blind study. Clinical assessments of sensory and motor block were performed at regular intervals. There were no significant differences in onset time, dermatomal spread or duration of both sensory and motor block between the three groups (the power of the study was 81% to detect a 4-h difference in duration). Duration of sensory block was prolonged with wide inter-patient variation: 892 (SD 250) min, 1039 (317) min and 896 (284) min for 0.25% S(−)-bupivacaine, 0.5% S(−)-bupivacaine and 0.5% RS-bupivacaine, respectively. There were no differences in the overall success rate of the technique. We conclude that S(−)-bupivacaine was suitable for local anaesthetic use in brachial plexus block anaesthesia. (*Br. J. Anaesth*. 1998; **80**: 594–598)

Keywords: anaesthetic techniques, regional, brachial plexus; anaesthetics local, bupivacaine; anaesthetics local, stereoiomers

Bupivacaine is a long-acting local anaesthetic used widely in modern anaesthetic practice. It is well recognized that inadvertent i.v. administration or administration of toxic doses by another route can result in severe central nervous system (CNS) toxicity and cardiovascular collapse, with potentially fatal arrhythmias. Albright's editorial in 1979 discussed six cases in which bupivacaine was implicated in sudden cardiovascular collapse (and subsequent death in one obstetric patient) after clinical doses of bupivacaine.[1] More recent cases include an overdose of bupivacaine resulting in convulsions and ventricular tachycardia,[2] and continuous caudal infusions in children causing convulsions and arrhythmias.[3] Bupivacaine is contraindicated in i.v. regional anaesthesia (Bier's block).[4] These cases and many unpublished anecdotal instances of bupivacaine toxicity result in the continuing search for new and safer agents for clinical use.

Bupivacaine is a chiral compound.[5] It contains an asymmetric carbon atom giving it a chiral centre, about which the molecule can rotate forming different enantiomers. Bupivacaine exists as two enantiomers: levo or S(−)-bupivacaine and dextro or R(+)-bupivacaine, and is commercially available as a racemic (RS) mixture of both enantiomers. The enantiomers have identical physical and chemical properties but increasing evidence suggests enantiomer selectivity in both pharmacodynamics and pharmacokinetics.

S(−)-bupivacaine has been shown to have less inherent toxicity than R(+)-bupivacaine. Preclinical data from small mammals demonstrated higher LD_{50} values (1.2–3.3 times) and convulsion thresholds (1.7 times) compared with R(+)-bupivacaine.[6] Cardiotoxicity (widened QRS and arrhythmias, including AV blockade, ventricular tachycardia and ventricular fibrillation) has been shown to be 3–4 times more likely after R(+)-bupivacaine than S(−)-bupivacaine in isolated rabbit hearts.[7] In a study in 12 rats given R(+)-bupivacaine 2 mg kg^{-1}, all animals became apnoeic, bradycardic, hypotensive and died, whereas all 12 rats treated with S(−)-bupivacaine continued to breathe and only four developed mild bradycardia.[8] Studies in sheep have shown a reduced incidence, severity and duration of arrhythmias after S(−)-bupivacaine compared with RS-bupivacaine.[9] The convulsion threshold for S(−)-bupivacaine was 1.25–1.5 times higher than that for RS-bupivacaine.[10] Human volunteer investigations have also demonstrated differences in cardiotoxicity,[11] with 40–60% less reduction in myocardial contractility, as measured by acceleration index, stroke index and ejection

C. R. COX,* FRCA, N. MACKENZIE, FRCA, J. BANNISTER, FRCA, Department of Anaesthesia, Ninewells Hospital and Medical School, Dundee DD1 9SY. M. R. CHECKETTS‡, FRCA, N. B. SCOTT, FRCA, Department of Anaesthesia, HCI International Medical Centre, Beardmore Street, Clydebank G81 4HX. Accepted for publication: December 21, 1997.

*Present address for correspondence: Department of Anaesthesia, Royal Infirmary of Edinburgh, 1 Lauriston Place, Edinburgh EH3 9YW.

‡Present address: University Department of Anaesthesia, Ninewells Hospital and Medical School, Dundee DD1 9SY.

†Presented in part at the XV Annual European Society of Regional Anaesthesia Congress, Nice, France, September 18—21, 1996.

Table 1 Patient characteristics (mean (SD or range))

	0.25% S(–)-bupivacaine	0.5% S(–)-bupivacaine	0.5% RS-bupivacaine
n	25	26	23
Age (yr)	53 (19–84)	56 (25–75)	55 (26–81)
Sex (M/F)	15/10	19/7	14/9
Weight (kg)	72 (12)	72 (15)	68 (14)
Height (cm)	171 (12)	171 (11)	167 (9)

fraction, after infusion of S(−)-bupivacaine compared with RS-bupivacaine.

Therefore, it appears that S(−)-bupivacaine has a significantly reduced potential for cardiovascular and CNS toxicity compared with RS-bupivacaine. In this randomized, double-blind study, we have compared the clinical efficacy of S(−)-bupivacaine with RS-bupivacaine in patients undergoing hand surgery under brachial plexus block.

Patients and methods

After obtaining approval from the local Medical Research Ethics Committee and written informed consent, we studied 76 patients undergoing elective hand surgery (mainly for Dupuytren's contracture or joint replacement) recruited from two centres. Patients were more than 18 yr of age and ASA I–III. Exclusion criteria included women who were pregnant, lactating or of childbearing potential and not using adequate contraceptive methods. Patients with severe renal, hepatic, respiratory or cardiac disease, drug or alcohol abuse or with neurological, psychiatric or neuromuscular disorders were also excluded.

On recruitment to the study, a blood screen for haematology measurements, urea and electrolyte concentrations, liver function tests, routine dipstick urinalysis and a 12-lead ECG were performed. Patients were allocated randomly, in a double-blind manner, to one of three groups: 0.25% or 0.5% S(−)-bupivacaine or 0.5% RS-bupivacaine (Marcaine, Astra).

Approximately 1 h before anaesthesia, patients were premedicated with temazepam 10–20 mg. On arrival in the anaesthetic room, i.v. access was established and standard monitoring commenced. An additional 16-gauge i.v. cannula was inserted into the contralateral antecubital fossa in 31 patients to allow multiple blood samples to be obtained for pharmacokinetic studies (data not yet available).

A single, experienced anaesthetist in each of the two centres performed the supraclavicular brachial plexus blocks. A 22-gauge insulated, short-bevelled needle was used with a nerve stimulator and the current reduced until appropriate twitching of the hand was achieved at 0.4 mA. After a negative aspiration test, 0.4 ml kg^{-1} of the study drug was injected over 1 min, with repeat aspirations every 5 ml. Assessments of the resulting block and haemodynamic variables were recorded as described below. After 30 min, if the block was considered to be adequate, surgery commenced. The patient was sedated, if requested, using infusion of propofol. If the block was considered to be inadequate for surgery, the patient was given a general anaesthetic using infusion of propofol with bolus doses of fentanyl 50 μg, as required.

Assessments were carried out at 2, 5, 10, 15, 20, 25 and 30 min, every 30 min until 5 h and hourly thereafter until the block had completely worn off, with time 0 min being the time of completion of the injection. Sensory block was measured as loss of pinprick sensation using the blunt end of a 27-gauge dental needle. Dermatomes C5 to T1 were assessed. Onset time was the time to first loss of pinprick sensation in any dermatome. Duration of sensory block was the time from onset to complete recovery of sensation. Motor block was recorded using a three-point scale (0 = no paralysis, 1 = difficulty in raising the shoulder and weakness of the hand, 2 = inability to move upper limb). Onset time was the time to first loss of motor power. Duration of motor block was the time from onset to complete recovery of motor power. Heart rate and arterial pressure were also recorded at these times. An overall assessment of the quality of the block was made on a three-point scale: 0 = complete failure; 1 = unsatisfactory block (inadequate analgesia, inadequate relaxation or patient requires a general anaesthetic because of agitation or restlessness) and 2 = satisfactory block. For statistical analysis, complete failure and unsatisfactory block were considered together as failures and compared with the successes (satisfactory block).

Postoperative analgesia comprised co-proxamol, two tablets 6-hourly, or morphine 10 mg i.m., 4-hourly, as required. Prochlorperazine 12.5 mg i.m. was given if required for nausea or vomiting.

At 24 h after surgery, a repeat blood screen for haematology measurements, urea and electrolyte concentrations, liver function tests, urinalysis and a 12-lead ECG were obtained. A follow-up telephone call was made to the patients 3–7 days after discharge to enquire about adverse events.

The results were analysed using the statistical package SAS (v6.07). The power of the study was calculated using an estimate of between-subject variability from a previous study (i.e. an SD associated with duration of sensory block of 5 h[12]). For a difference between groups in duration of sensory block of 4 h, the power of the study was 81%. Analysis of variance and the Student's *t* test were used to compare

Table 2 Sensory and motor block (mean (SD) on median (range))

	0.25% S(–)-bupivacaine	0.5% S(–)-bupivacaine	0.5% RS-bupivacaine
Sensory block			
n	25	24	22
Onset (min)	7 (6)	6 (5)	8 (8)
Duration (min)	892 (250)	1039 (317)	896 (284)
Motor block			
n	25	24	21
Onset (min)	9 (17)	5 (5)	6 (6)
Duration (min)	847 (276)	1050 (325)	933 (205)
Max. grade	2 (1–2)	2 (0–2)	2 (0–2)

Table 3 Sensory block at different dermatomes (median (range))

	0.25% S(–)-bupivacaine	0.5% S(–)-bupivacaine	0.5% RS-bupivacaine
T1			
n	19	21	17
Onset (min)	20 (2–240)	15 (2–150)	15 (2–720)
Duration (min)	658 (225–1115)	860 (5–1918)	825 (60–1185)
C8			
n	19	23	20
Onset (min)	15 (2–240)	10 (2–180)	13 (2–120)
Duration (min)	658 (60–1125)	895 (95–1498)	775 (170–1335)
C7			
n	23	21	20
Onset (min)	15 (2–120)	5 (2–60)	15 (2–120)
Duration (min)	635 (130–1180)	895 (160–1370)	773 (150–1120)
C6			
n	24	24	20
Onset (min)	10 (2–150)	15 (2–150)	13 (2–210)
Duration (min)	717 (235–1370)	803 (165–1258)	799 (60–1318)
C5			
n	23	23	20
Onset (min)	20 (2–150)	15 (2–150)	18 (2–240)
Duration (min)	720 (285–1420)	875 (270–1915)	810 (50–1258)

Table 4 Overall success of block (number of patients (%)). Groups 0 and 1 were considered together as treatment failures and group 2 as treatment success. No significant differences between groups

	0.25% S(–)-bupivacaine	0.5% S(–)-bupivacaine	0.5% RS-bupivacaine
Satisfactory block (2)	17 (68%)	21 (80%)	17 (74%)
Unsatisfactory block (1)	8 (32%)	3 (12%)	4 (17%)
Complete failure (0)	0	2 (8%)	2 (9%)

the groups after the Shapiro–Wilk test confirmed parametric data. The Kruskal–Wallis non-parametric analysis of variance and Z test were used for the remaining analyses. To compensate for multiple comparisons, a sequentially rejective Bonferroni–Holm method was used. Logistic regression was used to analyse the quality of block. All tests used a significance level of 5%.

Results

We studied 76 patients, of whom two were withdrawn. One patient was withdrawn before administration of the study drug because of pleuritic chest pain occurring while attempting to localize the brachial plexus. No subsequent pneumothorax or other sequelae were found. The other patient had what appeared to be i.v. injection of local anaesthetic (0.5% RS-bupivacaine) despite negative aspiration tests. After administration of approximately two-thirds of the injection, the patient lost consciousness and developed generalized twitching consistent with CNS toxicity. This was associated with sinus tachycardia and hypertension, but not hypoxia. The patient received 100% oxygen by face mask and propofol 40 mg. The episode resolved after 2–3 min with no sequelae. The characteristics of the remaining 74 patients are given in table 1. There were no differences between groups.

There were no significant differences between groups in onset time or duration of sensory block (tables 2, 3). There was a tendency for 0.5% S(−)-bupivacaine to have a longer duration of block. Spread of sensory block was similar in each group with the higher dermatomes being blocked more reliably.

Nearly all patients (except one) who achieved sensory block achieved motor block (table 2). Grade 2 (complete paralysis) was the most common grade reached. There were no significant differences between groups in onset time, maximum grade or duration of motor block. As with sensory block there was a tendency for 0.5% S(−)-bupivacaine to have a longer duration.

Four patients were assessed as complete failures (two each in the 0.5% S(−)-bupivacaine and 0.5% RS-bupivacaine groups) (table 4). These were caused by complete failure of the technique or inadequate block for surgery. General anaesthesia was required in these cases. Another 10 patients required general anaesthesia (eight in the 0.25% S(−)-bupivacaine group and two in the 0.5% RS-bupivacaine group). These were for patients with unsatisfactory blocks, as described above. There were no significant differences between groups.

There were no significant differences between groups in heart rate or arterial pressure for the first 30 min after drug administration. There were small reductions in heart rate and arterial pressure during this period (ns) but these were not clinically significant.

There were no clinically significant ECG changes in the perioperative period. Analysis of screening and postoperative ECG showed no evidence of dose-related trends or changes. There was no evidence of drug or dose-related changes in haematological, biochemical or urinalysis variables. One patient (0.5% S(−)-bupivacaine) complained of paraesthesia in the postoperative period. This was related to the surgical procedure. One patient had a major adverse event (this woman received what was suspected to be i.v. injection of 0.5% RS-bupivacaine, as described above). There were no other adverse events.

Discussion

We have demonstrated that S(−)-bupivacaine was suitable for brachial plexus block anaesthesia. There

were no significant differences in sensory or motor block between the three groups. We were unable to demonstrate a dose–response effect with the two concentrations of S(−)-bupivacaine, although there was a tendency for 0.25% S(−)-bupivacaine to have a slower onset, shorter duration of action and lower overall success rate than 0.5% S(−)-bupivacaine or RS-bupivacaine. The power of the study was low, with an 81% chance of detecting a 4-h difference in duration and only a 56% chance of detecting a 3-h difference. There was wide patient variation in these blocks.[12] The SD of the duration of sensory block was more than 4 h. However, the long duration of sensory block illustrates the benefit of bupivacaine and its enantiomers in providing prolonged postoperative analgesia. The study showed that the higher dermatomes were blocked more consistently than the lower ones, as expected with the supraclavicular approach. The overall success rate for the anaesthetic technique was 68–80%. Supplementary nerve blocks, which may have increased this rate, were not possible as pharmacokinetic studies were also being performed.

There was one serious adverse event during the study. This patient received what was presumed to be i.v. injection of RS-bupivacaine (despite regular negative aspiration tests) and developed CNS and related cardiovascular (tachycardia and hypertension) side effects. Fortunately, these resolved rapidly and resulted in no subsequent morbidity. This case, however, illustrates the risks associated with administration of large doses of bupivacaine, even in experienced hands, and emphasizes the need for safer agents.

The major impetus behind the search for new and safer local anaesthetics is the known cardiovascular and CNS toxicity of existing drugs. The mechanism for the cardiotoxicity of bupivacaine is complex. There is evidence of direct and indirect depression of cardiac conduction and contractility. Bupivacaine produces local anaesthesia by block of sodium channels and this action is probably the main mechanism responsible for its cardiotoxicity. Blocking of the sodium channel in the isolated guinea pig heart by bupivacaine resulted in a reduction in the maximum rate of depolarization ($v$max) and a shortening of the duration of the action potential (AP).[13] Slowing the conduction of the AP resulted in increased PR intervals and QRS durations and encouraged re-entrant arrhythmias (ventricular ectopics, tachycardia and fibrillation). Studies suggest that compared with S(−)-bupivacaine, R(+)-bupivacaine has 2.4 times higher affinity for the cardiac sodium channel and dissociates from it twice as slowly.[14] This results in a longer dwell time at the sodium channel making it potentially more arrhythmogenic. This study also showed that $v$max and AP duration are decreased more, and recovered more slowly with R(+)-bupivacaine compared with S(−)-bupivacaine. R(+)-bupivacaine had a higher potency (1.6 times) in blocking inactivated cardiac sodium channels, as shown in isolated animal heart studies.[15] Cardiac potassium channels have also been implicated in the cardiotoxicity of bupivacaine: R(+)-bupivacaine has been shown to be seven times more potent at blocking human cardiac potassium channels than S(−)-bupivacaine.[16] There is evidence that the CNS plays a role in the cardiotoxicity produced by bupivacaine. This indirect cardiotoxicity is also enantiomer selective with R(+)-bupivacaine having a greater depressant effect on the cell firing rate of the nucleus tractus solitarius and therefore the cardiovascular and respiratory centres of the brain.[8] Therefore, R(+)-bupivacaine appears to be the main culprit in the toxicity produced by RS-bupivacaine by its effect on the CNS and cardiac sodium and potassium channels.

This reduced toxicity does not appear to be at the expense of nerve blocking activity. In small mammals, the *in vitro* and *in vivo* efficacy of S(−)-bupivacaine and R(+)-bupivacaine was similar, although the duration of anaesthesia after subcutaneous infiltration was longer for S(−)-bupivacaine.[6] Apps and Reynolds' volunteer study of intradermal infiltration demonstrated that S(−)-bupivacaine, unlike R(+)-bupivacaine, had some vasoconstrictor activity.[17] This may explain the longer duration of action found in these studies. This contrasts with a recent study investigating the effects of S(−)-bupivacaine and (RS)-bupivacaine on human umbilical veins in which vascular activities were found to be similar.[18] Our study did not demonstrate any significant differences in duration of sensory or motor block between S(−)-bupivacaine and RS-bupivacaine. Further work investigating this feature of S(−)-bupivacaine is required.

Bupivacaine is used widely because of its long duration of action, differential block and, in obstetric use, lack of adverse neonatal neurobehavioural effects. The chiral nature of bupivacaine has been known for many years but it is only recently that the S(−)-enantiomer has been developed for clinical use. We have demonstrated that S(−)-bupivacaine was suitable for use in brachial plexus block anaesthesia. This, together with the reduced toxic potential compared with (RS)-bupivacaine, suggests that S(−)-bupivacaine may increase the margin of safety for regional anaesthesia.

Acknowledgements

C. R. C. was in receipt of a research fellowship from Chiroscience Ltd. S(−)-bupivacaine was supplied by Chiroscience Ltd, Cambridge, UK.

References

1. Albright GA. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. *Anesthesiology* 1979; **51**: 285–287.
2. Davis NL, de Jong RH. Successful resuscitation following massive bupivacaine overdose. *Anesthesia and Analgesia* 1982; **61**: 62–64.
3. McCloskey JJ, Haun SE, Deshpande JK. Bupivacaine toxicity secondary to continuous caudal epidural infusion in children. *Anesthesia and Analgesia* 1992; **75**: 287–290.
4. Rosenberg PH, Kalso EA, Tuominen MK, Linden HB. Acute bupivacaine toxicity as a result of venous leakage under the tourniquet cuff during a Bier block. *Anesthesiology* 1983; **58**: 95–98.
5. Calvey TN, Williams NE. Isomerism and anaesthetic drugs. In: Calvey TN, Williams NE, eds. *Principles and Practice of Pharmacology for Anaesthetists*, 3rd Edn. Oxford: Blackwell Science, 1997; 108–145.
6. Åberg G. Toxicological and local anaesthetic effects of optically active isomers of two local anaesthetic compounds. *Acta Pharmacologica et Toxicologica* 1972; **31**: 273–286.

7. Mazoit JX, Boico O, Samii K. Myocardial uptake of bupivacaine: Pharmacokinetics and pharmacodynamics of bupivacaine enantiomers in the isolated perfused rabbit heart. *Anesthesia and Analgesia* 1993; **77**: 477–482.
8. Denson DD, Behbehani MM, Gregg RV. Enantiomer-specific effects of an intravenously administered arrhythmogenic dose of bupivacaine on neurons of the nucleus tractus solitarius and the cardiovascular system in the anesthetised rat. *Regional Anesthesia* 1992; **17**: 311–316.
9. Pryor M, Huang YF, Mather L. Comparison of the cardiac effects of S- and RS-bupivacaine in awake sheep. 11th World Congress abstract book. *Anesthesiology* 1996; **333**: D457.
10. Mather LE, Huang YF, Veering BT, Pryor M. Comparative toxicity of bupivacaine and S(−)-bupivacaine in sheep—clinical implications. 11th World Congress abstract book. *Anesthesiology* 1996; **137**: F135.
11. Gristwood R, Bardsley H, Baker H, Dickens J. Reduced cardiotoxicity of S(−)-bupivacaine compared with racemic bupivacaine (marcaine): new clinical evidence. *Expert Opinion in Investigational Drugs* 1994 **3**: 1209–1212.
12. Hickey R, Hoffman J, Ramamurthy S. A comparison of ropivacaine 0.5% and bupivacaine 0.5% for brachial plexus block. *Anesthesiology* 1991; **74**: 639–642.
13. Clarkson CW, Hondeghem LM. Mechanism for bupivacaine depression of cardiac conduction: fast block of sodium channels during the action potential with slow recovery from the block during diastole. *Anesthesiology* 1985; **62**: 396–405.
14. Vanhoutte F, Vereecke J, Verbeke N, Carmeliet E. Stereoselective effects of the enantiomers of bupivacaine on the electrophysiological properties of the guinea-pig papillary muscle. *British Journal of Pharmacology* 1991; **103**: 1275–1281.
15. Valenzuela C, Snyders DJ, Bennett PB, Tamargo J, Hondeghem LM. Stereoselective block of cardiac sodium channels by bupivacaine in guinea pig ventricular myocytes. *Circulation* 1995; **92**: 3014–3024.
16. Valenzuela C, Delpon E, Tamkun MM, Tamargo J, Snyders DJ. Stereoselective block of a human cardiac potassium channel (Kvl.5) by bupivacaine enantiomers. *Biophysical Journal* 1995; **69**: 418–427.
17. Aps C, Reynolds F. An intradermal study of the local anaesthetic and vascular effects of the isomers of bupivacaine. *British Journal of Clinical Pharmacology* 1978; **6**: 63–68.
18. Fernandes L, Simonetti MPB. Vascular effects of S(−)-bupivacaine, RS bupivacaine and ropivacaine on isolated strips of human umbilical vein: preliminary results. *Regional Anesthesia* 1997; **22** (2 Suppl.): 65.