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Levobupivacaine

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Contents

Abstract

▲ Levobupivacaine is an enantiomer of the long-acting local anaesthetic bupivacaine, which, although currently the most widely used agent in surgery and obstetrics, is associated with potentially fatal cardiotoxicity.

▲ Levobupivacaine 75 to 122mg was less arrhythmogenic than the same dose range of bupivacaine in healthy volunteers. Its effects on the corrected QT interval were significantly weaker than those of bupivacaine, and it tended to have a weaker effect on QRS duration.

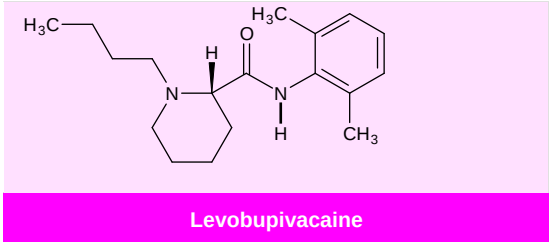
▲ The CNS depressant effect of intravenous levobupivacaine 40mg was less than that of bupivacaine 40mg in healthy volunteers, both in terms of the magnitude of the effect and the regions of the cortex affected.

▲ Clinical studies have demonstrated that epidural levobupivacaine produces a sensory and motor block clinically similar to that of bupivacaine in patients requiring anaesthesia during surgery. However, the duration of sensory block was significantly longer with levobupivacaine 0.75% than with levobupivacaine 0.5% or bupivacaine 0.5% or 0.75% in one study.

▲ Levobupivacaine 0.25% was as effective as bupivacaine 0.25% in women requiring epidural anaesthesia during labour with respect to time to onset of pain relief, overall quality of analgesia, extent of sensory blockade and number of patients reporting motor block.

▲ Levobupivacaine is as well tolerated as bupivacaine. In a clinical study involving 88 patients who received either drug, intraoperative hypotension was the most commonly reported adverse event with levobupivacaine and no serious arrhythmias occurred.

Features and properties of levobupivacaine	
Indications	
Major and minor nerve block during surgery; postoperative pain management; obstetrics	
Mechanism of action	
Local anaesthetic	Motor and sensory blockade
Dosage and administration	
Usual dosage in clinical trials	10-30ml of a 0.25%, 0.5% or 0.75% solution
Route of administration	Epidural, spinal, nerve block or local infiltration
Pharmacokinetic profile of levobupivacaine (dose)	
Peak plasma concentration	0.582 mg/L (15ml of 0.5% solution via epidural injection)
Time to peak plasma concentration	0.37h (15ml of 0.5% solution via epidural injection)
Area under the plasma concentration-time curve	3.561 mg/L • h (15ml of 0.5% solution via epidural injection)
Volume of distribution	66.91L (40mg intravenous injection)
Mean residence time	1.423h (40mg intravenous injection)
Plasma clearance	39.06 L/h (40mg intravenous injection)
Protein binding	>97%
Elimination half-life	2.06h (40mg intravenous injection)
Excretion	≈70% urine
Adverse events	
Most frequent	Intraoperative hypotension



Levobupivacaine

Racemic bupivacaine is a local anaesthetic with advantages over other agents such as lidocaine (lignocaine) in that it has a sustained duration of action and a beneficial ratio of sensory to motor blockade. Although currently the most widely used agent in surgery and obstetrics, its use has sometimes resulted in fatal cardiotoxicity, generally after accidental intravascular injection or sudden cuff deflation.[1]

The drug has a chiral centre and therefore exists as a 50 : 50 mixture of 2 enantiomers, levobupivacaine and dextrobupivacaine.[1] The preclinical profile of levobupivacaine suggested that it may be less cardiotoxic than bupivacaine (section 1); therefore, its anaesthetic efficacy has been investigated.

1. Pharmacodynamic Profile

Cardiotoxic Potential

- Levobupivacaine had less affinity for myocardial sodium channels than dextrobupivacaine in isolated guinea-pig ventricular myocytes[2] and affected the maximal rate of depolarisation (V_{max}) and the action potential duration less than dextrobupivacaine in guinea-pig papillary muscle.[3] In normal Tyrode's solution containing 5.4 mmol/L potassium ions and at a stimulation frequency of 1Hz, V_{max} in guinea-pig papillary muscle was reduced to 76.7% of control in the presence of levobupivacaine 10 μmol/L compared with 59.9% of control in the presence of dextrobupivacaine 10 μmol/L ($p < 0.001$) [fig. 1].[3] In addition, dissociation from sodium channels was faster with levobupivacaine than with dextrobupivacaine.[3]

- Recovery of contraction amplitude and V_{max} in isolated guinea-pig papillary muscle was faster after washout of levobupivacaine than after washout of bupivacaine.[4]

- Levobupivacaine was 3 to 4 times less toxic than equivalent concentrations of bupivacaine in isolated perfused rabbit hearts. QRS widening, as well as the occurrence of severe arrhythmias, was less marked in hearts perfused with levobupivacaine than in those perfused with the same concentration of dextrobupivacaine or bupivacaine. The maximum increase in QRS duration was 59 msec for levobupivacaine, 236 msec for dextrobupivacaine and 194 msec for bupivacaine. Ventricular fibrillation occurred in 0, 83 and 67% of hearts receiving each drug, respectively.[5]

- After injection into the nucleus tract solitarius in rats, the time taken to produce the maximum reduction in the cell firing rate was longer for levobupivacaine than for dextrobupivacaine (68 *vs* 34 sec; $p < 0.05$). Whereas all 12 animals died after

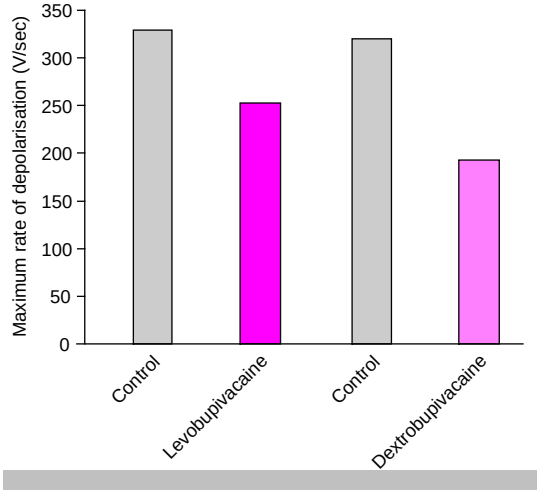


Fig. 1. *In vitro* myocardial effects of levobupivacaine 10 μmol/L and dextrobupivacaine 10 μmol/L. The direct myocardial effects of levo- and dextrobupivacaine were assessed after 15 minutes' superfusion of isolated guinea-pig papillary muscle using a standard microelectrode technique and were compared with those of a control solution. The preparation was stimulated at 1Hz and perfused with normal Tyrode's solution containing 5.4 mmol/L external potassium ions.[3]

dextrobupivacaine injection, 10 of 12 survived levobupivacaine injection ($p < 0.001$).[6]

- Both bupivacaine and levobupivacaine had a negative chronotropic effect in spontaneously beating right atrium from male Wistar rats, but atrial arrest developed at concentrations of bupivacaine lower than those of levobupivacaine (0.03 to 0.1 mmol/L *vs* 0.1 to 0.3 mmol/L).[7] In electrically paced left atrium from the same animals, levobupivacaine 0.03 to 0.1 mmol/L and bupivacaine 0.01 to 0.1 mmol/L induced a 100% decrease in contractile force.[7]

- Levobupivacaine was not fatal when infused in doses up to 200mg in sheep, whereas 3 of 7 animals died of ventricular fibrillation after 150, 150 and 200mg doses of bupivacaine. Levobupivacaine-induced ventricular arrhythmias spontaneously returned to sinus rhythm.[8]

- Levobupivacaine had less effect on myocardial contractility and stroke index than bupivacaine in 12 healthy volunteers who received an intravenous infusion of each drug in a double-blind, crossover manner. The drugs were given at a rate of 10 mg/min until a maximum of 150mg had been administered or CNS effects developed. Levobupivacaine (mean total dose 54.0mg) and bupivacaine (45.6mg) reduced the myocardial contractility index by 4.5 and 13%, respectively, ($p < 0.02$) and the stroke index by 6 and 20% ($p < 0.01$).[1]

- Single dose intravenous levobupivacaine 75 to 122mg had a significantly weaker effect on the corrected QT interval (QT_c; a primary indicator for arrhythmogenic potential) than the same dose of bupivacaine in 22 healthy volunteers. The mean maximum increase from baseline with each drug was 0.0030 and 0.0238 sec, respectively, ($p = 0.022$).[9] In addition, the mean maximum increase in QRS duration from baseline tended to be smaller with levobupivacaine (0.0025 *vs* 0.0213 sec; $p = 0.097$).[9]

CNS Effects

- Levobupivacaine had less CNS toxicity than bupivacaine in conscious sheep. The mean intravenous dose infused to the onset of convulsions in these animals was 103mg with levobupivacaine and 85mg with bupivacaine.[8] In addition, excitatory signs (generalised excitement followed by nystagmus, hypertonia and clonic-tonic convulsions) began at significantly lower doses of bupivacaine than levobupivacaine, and lasted longer with the former.

- The CNS depressant effect of intravenous levobupivacaine 40mg was less than that of the same dose of bupivacaine in a double-blind crossover study involving 12 healthy volunteers. Both agents significantly reduced high alpha power at all electrode positions, but the magnitude of the effect of levobupivacaine was less than that of bupivacaine. In addition, levobupivacaine did not cause the increase in theta power in the parietal, temporal and central regions seen after bupivacaine.[10] Therefore, although both agents had similar qualitative effects on the electroencephalogram, the threshold for the effects was higher for levobupivacaine.[9]

- In 11 volunteers who experienced CNS symptoms such as tinnitus, dry mouth and numbness of the tongue or lips with bupivacaine, an equivalent intravenous dose of levobupivacaine was associated with fewer central or peripheral nervous system disorders. 36% of levobupivacaine recipients reported no CNS events at all.[9]

Uterine Effects

- Uterine blood flow and intra-amniotic pressure were not significantly affected by levobupivacaine, bupivacaine or ropivacaine when each drug was administered as a 2-step intravenous infusion (0.07 mg/kg/min for 15 minutes then 0.035 mg/kg/min for 45 minutes) in 30 near-term pregnant ewes (10 per group).[11] This rate of infusion was chosen to achieve serum drug concentrations similar to those expected during epidural anaesthesia for caesarean section. Fetal serum concentrations of levobupivacaine were lower than those of ropivacaine and bupivacaine (0.20, 0.51 and 0.61 μg/ml, respectively) but the differences were not statistically significant (fig. 2).[12]

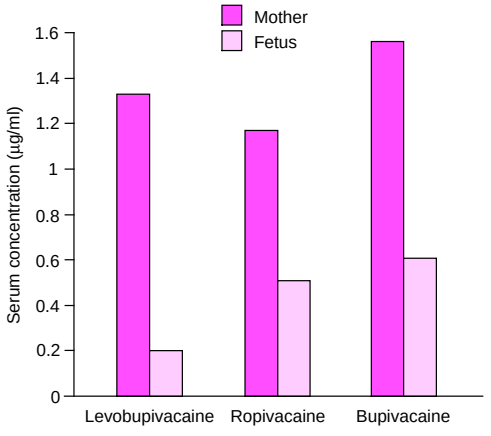


Fig. 2. Maternal and fetal serum concentrations of levobupivacaine, ropivacaine or bupivacaine. 30 near-term pregnant ewes (10 per group) received a 2-step intravenous infusion (0.07 mg/kg/min for 15 minutes then 0.035 mg/kg/min for 45 minutes) of 1 of the drugs; serum drug concentrations were assessed at the end of the infusion.[12]

- The vascular effects of levobupivacaine 0.0003 to 3 mmol/L were similar to those of equivalent concentrations of bupivacaine in potassium chloride-contracted human umbilical veins. Both agents caused concentration-dependent relaxation of all vein preparations. In contrast, ropivacaine had a biphasic effect, causing contraction at lower concentrations (0.0001 to 0.03 mmol/L) and relaxation at higher concentrations (0.1 to 3 mmol/L).[13]

Local Anaesthetic Activity in Volunteers

- The local anaesthetic effect of levobupivacaine 0.125 to 0.5% did not differ significantly from that of bupivacaine 0.25% in a double-blind study involving 20 healthy male volunteers who received a 5ml injection in the ulnar nerve. Both agents blocked nerve function, with evidence of a dose-response relationship for levobupivacaine (fig. 3). The mean durations of blockade of sensory pain, sensory touch and motor function did not differ significantly between groups.[14] With both drugs, the duration of sensory pain blockade was longer than that of motor blockade.[14]

2. Pharmacokinetic Profile

- After a 15ml epidural injection of levobupivacaine 0.5% or 0.75% in 18 patients, peak plasma concentrations (0.582 and 0.811 mg/L) were reached in 0.37 and 0.29 hours, respectively.[15] The area under the plasma concentration-time curve (AUC) was 3.561 and 4.930 mg/L · h for each dose, respectively.[15]
- Levobupivacaine was highly protein bound (>97%) in human plasma (data on file[16]).
- After an 8-minute intravenous infusion of levobupivacaine 40mg in 12 volunteers, the volume of distribution of the drug was 66.91L, the mean residence time was 1.423 hours and the total plasma clearance was 39.06 L/h (data on file[17]).
- After a 15-minute intravenous infusion of [^{14}C]-levobupivacaine 40mg in 12 volunteers, the terminal elimination half-life of the drug was 2.06 hours when determined by liquid chromatography mass spectroscopy (data on file[18]).
- Levobupivacaine undergoes NADPH-dependent metabolism in the liver prior to excretion (data on file[19]). No parent compound was detected in urine

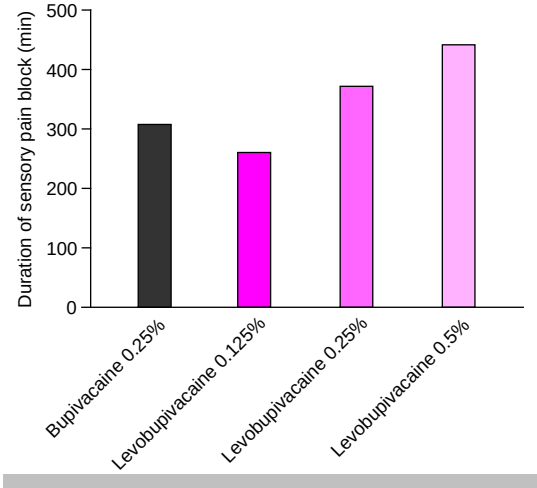


Fig. 3. Duration of sensory pain block achieved after local infiltration of the ulnar nerve with bupivacaine or levobupivacaine. Male volunteers received a 5ml injection of bupivacaine 0.25% (n = 17) or levobupivacaine 0.125% (n = 6), 0.25% (n = 5) or 0.5% (n = 6).[14]

or faeces after an intravenous dose of radiolabelled levobupivacaine 40mg in 12 volunteers (data on file[18]).

• Levobupivacaine metabolites are primarily excreted in the urine (≈70%); most (≈95%) of an administered dose is recovered within 48 hours (data on file[20]).

• The elimination of levobupivacaine (after bupivacaine injection) was prolonged in liver transplant recipients requiring postoperative analgesia.[21]

3. Therapeutic Trials

Major and Minor Nerve Block During Surgery

• Evidence suggests that levobupivacaine produces a sensory and motor block clinically indistinguishable from that of racemic bupivacaine. There was no significant difference in onset time (fig. 4) and maximum spread of sensory block or onset time and intensity of motor block between patients undergoing elective lower limb surgery under lumbar epidural anaesthesia who received 15ml of bupivacaine 0.5% (n = 29), levobupivacaine 0.5% (n = 29) or levobupivacaine 0.75% (n = 30) in a randomised, double-blind study.[22] Maximum cephalad spread occurred after 25 minutes in all 3 groups and the segmental spread of sensory block did not differ between treatments. The duration of sensory block was significantly longer in the levobupivacaine 0.75% group (mean 460 minutes) than in the levobupivacaine 0.5% group (377 minutes) and the bupivacaine 0.5% group (345 minutes) [$p < 0.05$].

• In a randomised, double-blind study in 74 patients scheduled for elective hand surgery after supraclavicular brachial plexus blockade, there were no significant differences between groups treated with 0.4 ml/kg of levobupivacaine 0.25%, levobupivacaine 0.5% or bupivacaine 0.5% with respect to duration and onset of sensory and motor blockade.[23] Complete block was achieved in a higher percentage of patients who received levobupivacaine 0.5% (81%) than in those who received levobupivacaine 0.25% (68%) or bupivacaine 0.5% (74%), but these differences were not statistically significant (fig. 5).[23]

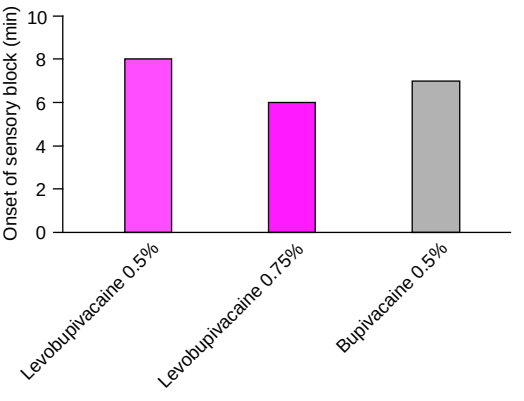


Fig. 4. Onset of sensory block achieved with levobupivacaine and bupivacaine. Time to loss of sensation in patients undergoing elective lower limb surgery under lumbar epidural anaesthesia who received 15ml of levobupivacaine 0.5% (n = 29), levobupivacaine 0.75% (n = 30) or bupivacaine 0.5% (n = 29) in a randomised, double-blind study.[22]

• Epidural administration of 20ml levobupivacaine 0.75% produced a similar onset of sensory blockade (mean 14 minutes) and a similar onset and duration of motor blockade to that produced by 20ml bupivacaine 0.75% in 56 patients undergoing major lower abdominal surgery in a randomised, double-blind study.[24] However, the total duration of sensory blockade was significantly longer with levobupivacaine (551 *vs* 505 minutes; $p = 0.02$).[24] The adequacy of abdominal muscle relaxation [measured using the abdominis muscle (RAM) test] was rated as 'good' or 'excellent' in 91% of the overall patient population.

• In a noncomparative study involving 90 patients scheduled for primary hip arthroplasty, 15ml of levobupivacaine 0.75% (administered epidurally in 3 equal doses at 5-minute intervals) achieved adequate sensory blockade within 5 minutes of completion of the infusion in all patients.[25] 84 patients (93%) had a bilateral sensory block to at least T10 immediately after the third injection.

• The efficacy of levobupivacaine 0.75% was similar to that of bupivacaine 0.75% in 50 elderly

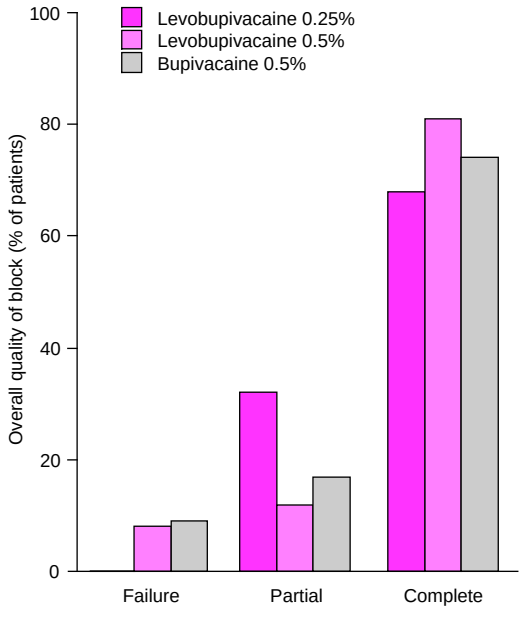


Fig. 5. Overall quality of sensory and motor block in patients receiving supraclavicular brachial plexus blockade for elective hand surgery. Patients were randomised to receive 0.4 ml/kg of levobupivacaine 0.25% (n = 25), levobupivacaine 0.5% (n = 26) or bupivacaine 0.5% (n = 23).[23]

patients requiring peribulbar anaesthesia during ophthalmic surgery. No statistically significant differences were observed in anaesthetic requirements, time to onset of block or quality of block.[26]

• The findings of a study involving 69 patients suggest that levobupivacaine has an efficacy similar to that of bupivacaine when used for infiltration anaesthesia in elective inguinal hernia repair.[27] However, levobupivacaine recipients had a slightly higher requirement for postoperative analgesia (equivalent to ≈300mg ibuprofen per 24 hours; p = 0.041).

Obstetrics

• Levobupivacaine 0.25% was as effective as bupivacaine 0.25% in 137 women requiring epidural anaesthesia during labour.[28] In this multicentre, randomised, double-blind study, the median time to onset of pain relief after a 10ml injection was 12 minutes for each drug, and after a 10ml 'top-up' injection was 7 minutes for levobupivacaine and 6 minutes for bupivacaine. The median duration of pain relief after the first injection did not differ significantly between groups (49 and 51 minutes, respectively), although a greater number of levobupivacaine recipients did not achieve sufficient pain relief (20 *vs* 10; p = 0.039). However, this may have been related to a higher number of inductions in the levobupivacaine group (17 *vs* 11). Overall, the treatment groups did not differ with respect to overall quality of analgesia, extent of sensory blockade or number of patients reporting motor block.[28]

• Levobupivacaine and bupivacaine demonstrated similar potencies in a randomised, double-blind study involving 60 women who required epidural anaesthesia during labour.[29] The minimum local anaesthetic concentrations (MLAC) calculated for each drug were 0.083% and 0.081%, respectively.

Postoperative Pain Management

• In a study involving 64 patients, the combination of levobupivacaine 0.25% and morphine 0.005% (administered as a 4ml epidural bolus followed by an additional 2 ml/h upon request) demonstrated greater postoperative analgesic efficacy after major abdominal surgery than either agent alone.[30] Fewer patients randomised to combination therapy requested analgesic supplements or ketorolac rescue compared with those randomised to monotherapy (p < 0.05). In addition, the time taken to request additional analgesia was significantly longer with combination therapy.[30]

• Epidural levobupivacaine 0.125% in combination with fentanyl 0.004% was more effective than either agent alone when used postoperatively in patients who had undergone lower extremity orthopaedic surgery.[31] The time to first supplemental analgesic request was significantly longer with combination therapy than with levobupivacaine or fentanyl monotherapy (10.1 *vs* 7.0 or 6.1h, respectively; p < 0.05 for both).

• After total hip replacement surgery, levobupivacaine 0.125% and clonidine 0.008% (administered by epidural infusion at a rate of 6 ml/h) provided more effective postoperative pain management than either agent alone, both in terms of supplemental morphine requirements and the time to the first request for supplemental analgesia.[31]

• Levobupivacaine (0.25 ml/kg per side operated) effectively produced ilioinguinal/iliohypogastric nerve block in children when administered after surgical hernia repair. Of 35 children aged 6 months to 12 years who were randomised in a double-blind manner to receive levobupivacaine or placebo, those who received active treatment had a longer interval to rescue analgesia (44 *vs* 31 min; p = 0.015), fewer rescue analgesic doses (0.7 *vs* 1.4; p = 0.058) and lower pain scores at 15, 20, 30 and 60 min compared with those randomised to placebo.[32]

4. Tolerability

• Levobupivacaine was as well tolerated as bupivacaine in 88 patients who received a 15ml epidural injection of levobupivacaine 0.5%, levobupivacaine 0.75% or racemic bupivacaine 0.5%.[22] Hypotension, which was reported during surgery in a total of 18 patients, was the most commonly reported adverse event. Overall, the effects on cardiovascular variables (heart rate and blood pressure) did not differ significantly between groups. No serious arrhythmias occurred; minor ECG abnormalities were reported in 3 of 59 levobupivacaine recipients and 2 of 29 bupivacaine recipients.

5. Levobupivacaine: Current Status

Levobupivacaine is a local anaesthetic which is undergoing late phase clinical trials. The drug has demonstrated anaesthetic efficacy similar to that of racemic bupivacaine, but has shown a reduced potential for CNS toxicity and cardiotoxicity in laboratory experiments and in healthy volunteers.

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