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Levobupivacaine

A Review of its Pharmacology and Use as a Local Anaesthetic

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Data Selection

Sources: Medical literature published in any language since 1983 on levobupivacaine, identified using AdisBase (a proprietary database of Adis International, Auckland, New Zealand), Medline and EMBASE. Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: AdisBase, Medline and EMBASE search term was 'levobupivacaine'. Searches were last updated 24 Feb 2000.

Selection: Studies in patients who received levobupivacaine. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Levobupivacaine, local anaesthesia, regional anaesthesia, pharmacodynamics, pharmacokinetics, therapeutic use.

Contents

Summary

Abstract

Based on findings that the cardiotoxicity infrequently observed with racemic bupivacaine shows enantioselectivity, i.e. it is more pronounced with the R(+)-enantiomer, the *S*(–)-enantiomer (levobupivacaine) has been developed for clinical use as a long acting local anaesthetic.

The majority of *in vitro*, *in vivo* and human pharmacodynamic studies of nerve block indicate that levobupivacaine has similar potency to bupivacaine. However, levobupivacaine had a lower risk of cardiovascular and CNS toxicity than bupivacaine in animal studies. In human volunteers, levobupivacaine had less of a negative inotropic effect and, at intravenous doses >75mg, produced less prolongation of the QT_c interval than bupivacaine. Fewer changes indicative of CNS depression on EEG were evident with levobupivacaine.

Levobupivacaine is long acting with a dose-dependent duration of anaesthesia. The onset of action is ≤15 minutes with various anaesthetic techniques. In studies of surgical anaesthesia in adults, levobupivacaine provided sensory block for up to 9 hours after epidural administration of ≤202.5mg, 6.5 hours after intrathecal 15mg, and 17 hours after brachial plexus block with 2 mg/kg. Randomised, double-blind clinical studies established that the anaesthetic and/or analgesic effects of levobupivacaine were largely similar to those of bupivacaine at the same dose. Sensory block tended to be longer with levobupivacaine than bupivacaine, amounting to a difference of 23 to 45 minutes with epidural administration and approximately 2 hours with peripheral nerve block. With epidural administration, levobupivacaine produced less prolonged motor block than sensory block. This differential was not seen with peripheral nerve block. Conditions satisfactory for surgery and good pain management were achieved by use of local infiltration or peribulbar administration of levobupivacaine. Levobupivacaine was generally as effective as bupivacaine for pain management during labour, and was effective for the management of postoperative pain, especially when combined with clonidine, morphine or fentanyl.

The tolerability profiles of levobupivacaine and bupivacaine were very similar in clinical trials. No clinically significant ECG abnormalities or serious CNS

events occurred with the doses used. The most common adverse event associated with levobupivacaine treatment was hypotension (31%).

Conclusions: Levobupivacaine is a long acting local anaesthetic with a clinical profile closely resembling that of bupivacaine. However, current preclinical safety and toxicity data show an advantage for levobupivacaine over bupivacaine. Clinical data comparing levobupivacaine with ropivacaine are needed before the role of the drug can be fully established. Excluding pharmacoeconomic considerations, levobupivacaine is an appropriate choice for use in place of bupivacaine.

Pharmacodynamics

Levobupivacaine is a long acting, amide-type local anaesthetic that is the *S*(–)-isomer of the racemate bupivacaine. In general, *in vitro*, *in vivo* and human volunteer studies of nerve block indicate that levobupivacaine is as potent as bupivacaine and produces similar sensory and motor block. A trend towards a longer sensory block with levobupivacaine was seen in some studies, and may be related to the greater vasoconstrictive activity of levobupivacaine than that of the *R*(+)-enantiomer (dexbupivacaine) at lower doses. The minimum local analgesic concentration was 0.083% for epidural levobupivacaine 20ml and 0.081% for bupivacaine 20ml in women in the first stage of labour.

Levobupivacaine has been consistently less toxic than bupivacaine in animal models. The lethal dose of levobupivacaine was 1.3- to 1.6-fold higher than that of bupivacaine in most animal studies, providing supportive evidence for a safety advantage over bupivacaine. *In vitro* findings indicating a lower risk of cardiotoxicity with levobupivacaine compared with dexbupivacaine and/or bupivacaine have included lesser effects or lower potency in: blocking cardiac sodium channels in the inactivated state; blocking cardiac potassium channels; reducing the maximal rate of depolarisation; prolonging atrioventricular conduction; and prolonging QRS interval duration. Differences between the agents with regards to effects on contractility seem to be less consistent, but levobupivacaine also appears to be less detrimental in this regard. In animal studies, levobupivacaine was associated with fewer and less severe cardiac disturbances, especially ventricular arrhythmias. In human volunteers, intravenous levobupivacaine (mean dose 56mg) produced less of a negative inotropic effect than bupivacaine (48mg). In another study of intravenous administration, the mean maximum increase in QT_c interval was significantly less with levobupivacaine than with bupivacaine (3 *vs* 24 msec) in volunteers receiving >75mg.

A lower risk of CNS toxicity with levobupivacaine compared with dexbupivacaine and/or bupivacaine has also been reported, including less propensity to cause apnoea and higher convulsive doses (levobupivacaine 103mg *vs* bupivacaine 85mg) in animal studies. In human volunteers, 64% of intravenous bupivacaine recipients (mean dose 65.5mg) compared with 36% of levobupivacaine (67.7mg) recipients experienced central or peripheral nervous system disorders. Intravenous levobupivacaine 40mg produced fewer changes indicative of CNS depression on EEG than bupivacaine 40mg in volunteers.

When compared with ropivacaine in animals, levobupivacaine had similar or more pronounced nerve blocking effects, depending on the concentration and model. Levobupivacaine and ropivacaine had generally similar cardiovascular effects in *in vitro* and animal studies, although some studies reported greater QRS interval prolongation and/or arrhythmogenic risk with levobupivacaine at some concentrations, but no difference in mortality rates. However, cardiotoxicity has not been compared at established equipotent anaesthetic doses.

Pharmacokinetics

Only limited pharmacokinetic data are available for levobupivacaine. The plasma concentrations of levobupivacaine are dependent on dose and route of administration. Maximum plasma concentrations were 0.58 to 1.02 mg/L after epidural administration of 75 to 150mg, and 0.47 and 0.96 mg/L after brachial plexus block with 1 and 2 mg/kg, respectively, in patients. The elimination half-life after intravenous administration of 40mg in volunteers was 1.3 hours and the volume of distribution was 67L. Levobupivacaine is highly protein bound (>97%). The drug is extensively metabolised by the cytochrome P450 (CYP) system, primarily CYP1A2 and CYP3A4 isoforms, and then excreted in the urine (71% within 48 hours) and faeces (24%).

Levobupivacaine crosses the placenta, with an umbilical vein/maternal vein drug concentration ratio of 0.3 after epidural levobupivacaine 0.5% (150mg) in women undergoing Caesarean section.

After administration of racemic bupivacaine, it appears that systemic disposition is enantioselective, particularly with regards to plasma protein binding, which is higher with levobupivacaine than dexbupivacaine. Levobupivacaine does not undergo racaemisation *in vivo*.

Therapeutic Use

Most trials of levobupivacaine have been randomised and double-blind and have involved 20 to 137 patients. All but 1 trial were in adults.

Surgical Anaesthesia: Levobupivacaine is long acting with an onset of action ≤15 minutes. The duration of action is dose-dependent and varies according to the anaesthetic technique. Adequate sensory and motor block for surgery was achieved in ≥90% of adult patients receiving adequate doses of levobupivacaine with satisfactory anaesthetic technique in most of the 10 available clinical trials. The anaesthetic and/or analgesic effects of levobupivacaine were largely similar to those with bupivacaine at the same dose in all comparative studies, including those of epidural, peripheral nerve block (supraclavicular or axillary brachial plexus nerve block), local infiltration and peribulbar administration. The duration of sensory block tended to be longer with levobupivacaine, although the difference was not statistically significant compared with bupivacaine in most cases. After epidural administration, the duration of sensory block with levobupivacaine was 8 to 9 hours with 0.75% (112.5 to 202.5mg), 7.5 hours with 0.5% (150mg) and 6 hours with 0.5% (75mg), and was 23 to 45 minutes longer than with bupivacaine at the same dose. The duration of sensory block after intrathecal levobupivacaine 15mg was 6.5 hours. With peripheral nerve block, the duration of sensory block was 17 hours with levobupivacaine 0.5% (2 mg/kg) versus 15 hours with bupivacaine 0.5% (2 mg/kg) or levobupivacaine 0.25% (1 mg/kg). With epidural administration, levobupivacaine produced less prolonged motor block than sensory block. This differential was not seen with peripheral nerve block.

Pain Management: Analgesia attained with epidural levobupivacaine was generally similar to that with bupivacaine in women in labour in the 2 available studies. The median time to onset of pain relief was 12 minutes and the duration of pain relief was approximately 50 minutes with levobupivacaine or bupivacaine 0.25% (25mg). With another regimen (mean dose of levobupivacaine 28 mg/h, bupivacaine 27 mg/h), 43% of the first stage of labour was pain free in both groups.

Effective postoperative pain relief was attained by combining epidural levobupivacaine 0.125% (7.5 mg/h) with clonidine, levobupivacaine 0.25% (10 mg/h)

with morphine or levobupivacaine 0.125% (5 mg/h) with fentanyl or using higher doses of levobupivacaine 0.25% (15 mg/h). The time to first request for rescue analgesia was 10 to 17 hours. The combined regimens were more effective than any of the comparator agents alone, and the higher dose was more effective than lower doses of levobupivacaine. Ilioinguinal/iliohypogastric nerve block with levobupivacaine 0.5% (1.25 mg/kg per operated side) at the conclusion of surgery provided better pain relief than placebo in children.

When used at the lower doses needed for pain management, most patients did not have significant motor block.

Tolerability

The tolerability profiles of levobupivacaine and bupivacaine were very similar in clinical trials. The most common adverse events associated with levobupivacaine anaesthesia in 1141 patients in phase II/III trails (regardless of causality to the drug; route not stated) were: hypotension (31%), nausea (21%), postoperative pain (18%), fever (17%), vomiting (14%), anaemia (12%), pruritus (9%), pain (8%), headache (7%), constipation (7%), dizziness (6%) and fetal distress (5%).

Levobupivacaine and bupivacaine generally exerted similar effects on blood pressure and heart rate. No clinically significant ECG abnormalities occurred in clinical trials. No serious adverse CNS events were caused by levobupivacaine at the doses used; a small number of patients reported transient hypoaesthesia or paraesthesia, but these effects may have been operation-related. When levobupivacaine was used in obstetric indications, fetal outcome was not significantly different with levobupivacaine and bupivacaine. No significant CNS toxicity or cardiotoxicity was seen in a patient who received prompt treatment following an unintentional intravascular injection of levobupivacaine 142.5mg.

Dosage and Administration

Indications and recommended dosages for levobupivacaine differ markedly between Europe and the US.

The indications for levobupivacaine in Europe include epidural, intrathecal, peripheral nerve block, peribulbar administration and local infiltration for surgical anaesthesia in adults. Levobupivacaine is also indicated for epidural use for the management of pain, including labour and postoperative pain in adults. In children, levobupivacaine is indicated for ilioinguinal/iliohypogastric nerve block. The recommended maximum single dose for surgical anaesthesia in adults (other than for intrathecal administration) is generally 150mg. Additional doses may be required for a prolonged procedure. The recommended maximum single dose for intrathecal administration is 15mg. The recommended maximum epidural dose for labour analgesia is a 0.125% infusion of 12.5 mg/h or epidural injections of 0.25% up to 25mg at ≥15-minute intervals. For postoperative pain management in adults, the dose should not exceed 18.75 mg/h. The maximum dose for children undergoing ilioinguinal/iliohypogastric block is 1.25 mg/kg/side.

In the US, levobupivacaine is indicated for epidural, peripheral nerve block, peribulbar administration and local infiltration for surgical anaesthesia in adults. Levobupivacaine is also indicated for epidural use for the management of pain, including labour and postoperative pain in adults. The drug is not currently indicated in the US for intrathecal administration or use in children. Surgical anaesthesia doses are similar to those in Europe, but doses of up to 50mg can be given for labour analgesia and up to 25 mg/h for postoperative pain management.

According to European prescribing information, the use of 0.75% (7.5 mg/ml) of levobupivacaine is contraindicated in obstetric patients; this is based on expe-

rience with bupivacaine and the 0.75% concentration of levobupivacaine has not been studied in obstetric patients. Concentrations up to 0.5% (150mg) can be used for Caesarean section. The drug is contraindicated for paracervical block in obstetrics and intravenous regional anaesthesia (Bier's block) as well as in patients with severe hypotension or known hypersensitivity to local anaesthetics of the amide type.

US product labelling carries warnings against the use of levobupivacaine in obstetric patients at the 0.75% concentration, obstetrical paracervical block, and intravenous regional anaesthesia. Use of levobupivacaine in patients with known hypersensitivity to amide-type local anaesthetics is contraindicated.

Levobupivacaine should be used with caution in patients with impaired cardiovascular function or liver disease or reduced liver blood flow.

As with all local anaesthetics, epidural levobupivacaine can cause hypotension, bradycardia and possibly cardiac arrest. Appropriate treatments, equipment and personnel should be readily available in the event that a serious adverse event occurs. The toxic effects of other local anaesthetics, antiarrhythmic agents with local anaesthetic activity or class III antiarrhythmic agents may be additive to those of levobupivacaine.

1. Introduction

Anaesthesia is defined as abolition of sensation thereby artificially inducing insensibility to pain.[1] Local anaesthetics produce a reversible regional inhibition of sensory nerve impulse conduction, preventing transmission of sensory information to the CNS without a loss of consciousness. Local anaesthetics may be used alone or in combination with general anaesthetics during surgery to prevent pain and to attenuate the stress response to surgery, and to provide postoperative pain relief.[2] Longer acting agents are also used for other forms of pain management, one of the most common uses being during labour.[1,2]

Levobupivacaine is the *S*(–)-enantiomer of the local anaesthetic bupivacaine. Racemic bupivacaine (herein called bupivacaine) has traditionally been the longest acting local anaesthetic commercially available and is widely used.[1-3] Its prolonged duration of action reduces the need for repeated administration or top-up doses. Furthermore, bupivacaine has a differential sensory to motor block (i.e. sensory block is more pronounced than motor block).[1,3] This is important for retaining sufficient motor activity so that women can actively participate in childbirth while still obtaining pain relief, for early discharge after day surgery, and for postoperative rehabilitation when local anaesthetic is used for postoperative pain relief. While bupivacaine is effective as an anaesthetic, safety concerns emerged when some deaths related to cardiovascular and/or CNS toxicity occurred, including some during obstetric use.[4,5] These events occurred primarily in the context of excessively high or rapidly escalating plasma concentrations caused by a failure in technique [e.g. unintentional intravascular injection or sudden cuff deflation during regional intravenous anaesthesia (Bier's block)] or inappropriately high or rapidly administered doses.

Bupivacaine has a chiral centre and thus exhibits stereoisomerism. It is available commercially as the racemic mix (approximately 50 : 50) of its 2 enantiomers. Preclinical studies established that both enantiomers have anaesthetic activity, but that toxicity is enantioselective to some degree, with levobupivacaine being associated with a lower risk of toxicity (section 2).[6,7] This review describes the pharmacology and therapeutic use of levobupivacaine. It expands on an earlier, more preliminary review published in *Drugs*.[8]

2. Pharmacodynamic Properties

Levobupivacaine is an amide-type local anaes-

thetic. As with all local anaesthetic agents, levobupivacaine acts via blockade of voltage-sensitive ion channels in neuronal membranes, preventing transmission of nerve impulses.[9] Localised and reversible anaesthesia is produced by interference with the opening of the sodium channel, which inhibits conduction of the action potential in nerves involved in sensory and motor activity and sympathetic activity.[1,9]

2.1 Anaesthetic Potency

The nerve blocking potency of levobupivacaine is similar to that of bupivacaine and the *R*(+)-enantiomer of bupivacaine (dexbupivacaine) *in vitro*.[6] *In vivo*, the comparative effects of levobupivacaine and dexbupivacaine or bupivacaine were affected by the route of administration and concentration.[9] In general, the onset and duration of sensory and motor block were similar for levobupivacaine, dexbupivacaine and bupivacaine and the agents were equipotent in animal models.[6,7,9-11] Some animal studies detected a longer duration of anaesthesia and/or greater potency with levobupivacaine than dexbupivacaine or bupivacaine.[6,7,9] It has been suggested that this is related to a greater vasoconstrictor action with levobupivacaine at lower doses (see section 2.2) and is in line with the trend towards a longer duration of sensory block observed with epidural levobupivacaine compared with bupivacaine in clinical studies (section 4.1.1). One study in rats reported a shorter duration of motor block with levobupivacaine 0.5% than with bupivacaine 0.5% (0.1ml epidural or 0.03ml intrathecal),[11] and another reported a more pronounced anaesthetic effect with bupivacaine 0.125% than levobupivacaine 0.125% (0.2ml infraorbital nerve block).[10] However, these differences tended not to be seen at higher concentrations (≤0.75%) and the findings are not consistently supported by clinical data (section 4). Depending on the concentration and animal model, levobupivacaine had either similar[10,11] or significantly more prolonged sensory and/or motor block than ropivacaine at the same dose.[11]

Studies in humans confirm that levobupivacaine has similar potency to bupivacaine. The first clinical evidence of the local anaesthetic activity of levobupivacaine was provided by a small randomised, double-blind study in volunteers who underwent bilateral ulnar nerve blockade.[12] Block of sensory pain and touch were assessed on the palmar aspect of the distal fifth finger using needle prick and cotton wool touch tests, respectively; sensory touch block was not normally assessed in other clinical studies (section 4). Motor function was assessed by the opposition force of the distal fifth finger to the thumb. Levobupivacaine 0.25% (12.5mg in 5ml) had a similar effect to that of bupivacaine 0.25% (12.5mg; fig. 1), although there was a slight trend towards a longer duration of sensory pain block with levobupivacaine. Motor block was shorter with levobupivacaine 0.25% than with bupivacaine 0.25%, but was longer with levobupivacaine 0.125% or 0.5%. The effect of levobupivacaine 0.125, 0.25 and 0.5% was dose-dependent for the duration of sensory pain block, but not the duration of sensory touch or motor block.

In another approach to comparing potencies, the minimum local analgesic concentrations (MLAC) of epidural levobupivacaine and bupivacaine 20ml were determined in a randomised double-blind trial in 60 women in the first stage of labour.[13] Women were treated sequentially with doses determined by the response of the previous woman in the treatment group. The MLAC for levobupivacaine was 0.083% and the MLAC for bupivacaine was 0.081%. A bigger difference was evident when considered on an equivalent molar basis (MLAC 2.87 *vs* 2.49 mmol/L). Nevertheless, the difference is unlikely to be clinically important, and levobupivacaine and bupivacaine at equal concentrations had largely similar efficacy in clinical studies in women in labour (see section 4.2.1). In a study with very similar methods in 90 women in labour,[14] the addition of fentanyl significantly reduced the MLAC of epidural levobupivacaine from 0.091% without fentanyl to approximately 0.05% with fentanyl 2 or 3 mg/L. Fentanyl has also

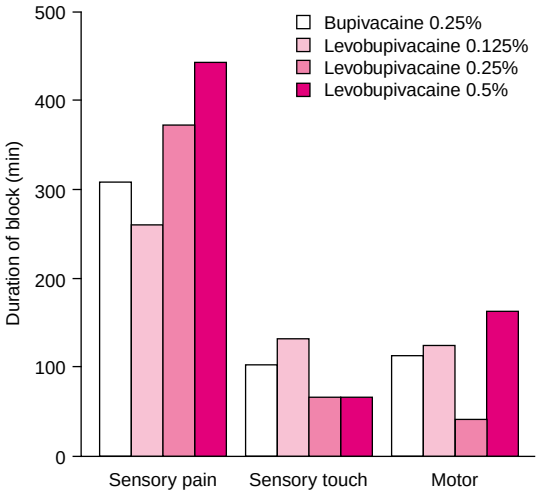

Fig. 1. Mean duration of sensory (pain and touch) and motor block with levobupivacaine compared with bupivacaine for ulnar nerve blockade in volunteers.[12] In a randomised, double-blind study, 20 volunteers were injected with 5ml of 0.25% (12.5mg) bupivacaine in 1 arm and placebo (data not reported), levobupivacaine 0.125% (6.25mg), 0.25% (12.5mg) or 0.5% (25mg) in the other arm.

been used successfully in combination with epidural levobupivacaine for postoperative pain (see section 4.2.2).

Levobupivacaine appeared to be more potent than dexbupivacaine in a double-blind crossover study of intradermal administration in 17 volunteers.[15] The duration of analgesia was significantly longer with levobupivacaine than dexbupivacaine in concentrations between 0.48 and 3.84 mmol/L (≈0.016 to 0.125% in 0.1ml), but not above or below these concentrations. This was considered to be related to differences in vasoactivity (see section 2.2).[15] However, other researchers have disputed the relationship between analgesic efficacy and vasoconstriction.[10]

Importantly, while levobupivacaine has similar potency to bupivacaine as an anaesthetic, it has been consistently less toxic than bupivacaine in animals. The lethal dose was higher with levobupivacaine than bupivacaine (in the range of 1.3- to 1.6-fold higher in most animal studies), providing supportive evidence for a safety advantage for levobupivacaine over bupivacaine.[6,7,9,16]

2.2 Vasoactivity

The vasoactivity of the levo and dextro enantiomers of bupivacaine differ,[15] and it has been suggested that the greater vasoconstrictor effects of levobupivacaine may explain its longer duration of sensory block (sections 2.1 and 4) and lower risk of CNS toxicity (section 2.4).[7] At concentrations between 0.24 and 3.84 mmol/L (≈0.008 to 0.125% in 0.1ml), levobupivacaine, but not dexbupivacaine, had vasoconstrictor effects in a double-blind crossover study of intradermal administration in volunteers.[15] At 7.69 mmol/L (0.25%), both levobupivacaine and dexbupivacaine acted as vasodilators. In another double-blind study, intradermal levobupivacaine or bupivacaine 0.125 to 0.75% in 0.1ml or saline placebo were administered to volunteers.[17] At concentrations ≤0.25%, levobupivacaine had vasoconstrictive activity that was greater than that of bupivacaine, and at higher concentrations levobupivacaine had vasodilator activity that was less than that of bupivacaine (overall $p = 0.019$).

Local anaesthetics that produce vasoconstriction in some vascular beds may also reduce uteroplacental blood flow, which could potentially adversely affect the fetus.[18] Administration of levobupivacaine to ewes near term of pregnancy did not adversely affect uterine blood flow or intra-amniotic pressure, and the effects with levobupivacaine were similar to those with bupivacaine and ropivacaine.[18] In an *in vitro* study using human umbilical cords contracted with potassium chloride, both levobupivacaine and bupivacaine 0.0003 to 0.3 mmol/L caused relaxation of the vein in a dose-dependent manner.[19] Ropivacaine had a biphasic effect, causing contraction at lower concentrations and relaxation at higher concentrations.[19]

2.3 Cardiovascular Effects

There is potential for cardiovascular toxicity with local anaesthetics because they block ion

channels not only in the nerve cell membranes but also in other excitable tissues such as the heart.[9,20] The risk of toxicity is greater for longer acting local anaesthetics.[21] With bupivacaine, cardiotoxicity generally manifests as cardiac arrhythmias (including ventricular fibrillation and tachycardia) and severe cardiac collapse that can be rapid, irreversible and fatal.[4,9] Studies have aimed to determine the risk of levobupivacaine precipitating similar cardiotoxic events. However, cardiotoxicity most commonly occurs when plasma concentrations are excessively high or increase too rapidly, and may occur without significant CNS warning signs.[4,5] It would not be ethical in humans to simulate the conditions leading to these events. On this basis, animal studies are the best approximation, and have been emphasised in this section.

Cardiotoxicity is probably the result of both direct and indirect cardiac effects; the indirect effects may involve blockade of sympathetic cardiac innervation or other CNS-mediated mechanisms (see section 2.4).[9,22] Blockade of myocardial sodium channels causes conduction delay and QRS interval prolongation, and blockade of potassium and calcium channels may also contribute to cardiotoxicity.[9]

2.3.1 In Vitro *and Animal Studies*

In vitro studies have indicated that levobupivacaine has the lesser cardiotoxic potential of the 2 enantiomers of bupivacaine. Levobupivacaine was less potent than dexbupivacaine in blocking cardiac sodium channels in the inactivated state in isolated guinea-pig ventricular myocytes[20] and in blocking cloned human cardiac potassium channels.[23] In line with this, levobupivacaine had less of a detrimental effect at the same concentration and/or was less potent in terms of reducing the maximal rate of depolarisation ($\dot{V}_{max}$),[22,24] prolonging atrioventricular conduction[25] and prolonging QRS interval duration[26,27] when compared with dexbupivacaine and/or bupivacaine in other animal or human tissue studies. Consequently, levobupivacaine was less likely than dexbupivacaine or bupivacaine to induce severe arrhythmia, especially ventricular fibrillation, in isolated hearts.[26] Differences between the agents with regards to effects on cardiac contractility appeared to be less consistent,[24,25] but higher concentrations of levobupivacaine than bupivacaine were reported to be required for a negative inotropic effect in myocytes[24] and for complete loss of contractile force and atrial arrest in isolated atria.[28] Recovery from drug-induced disturbances in cardiac electrophysiology and contractility was more rapid with levobupivacaine than bupivacaine.[24] In most studies that included ropivacaine, the *in vitro* cardiac effects of levobupivacaine were largely similar to those of ropivacaine,[24,27] although levobupivacaine ≤10 μmol/L had greater negative inotropic and chronotropic effects than the same concentration of ropivacaine in 1 study in isolated guinea-pig hearts.[29]

Studies in animals have further demonstrated that levobupivacaine has less potential for cardiotoxicity than dexbupivacaine or bupivacaine[16,21,30,31] (reviewed by Gristwood and Greaves[9]). In a representative study, 24 anaesthetised rats received rapid intravenous injection of levobupivacaine or dexbupivacaine at an arrhythmogenic dose (2 mg/kg).[30] This caused a significant decrease in the cell firing rate of the nucleus tractus solitarus (see section 2.4), which is involved in cardiovascular functions. Fewer animals treated with levobupivacaine than with dexbupivacaine experienced cardiotoxicity, including Wenckebach rhythm (second degree heart block; 2 *vs* 12 animals; $p < 0.001$), malignant ventricular arrhythmia (0 *vs* 4; $p < 0.05$) and death (2 *vs* 12; $p < 0.001$). Death was primarily caused by persistent profound hypotension and bradycardia. Severe bradycardia accompanied by hypotension occurred in 12 animals treated with dexbupivacaine, whereas bradycardia was mild and experienced by only 4 animals in the levobupivacaine group. In conscious sheep, levobupivacaine induced fewer and less severe ventricular arrhythmias than bupivacaine.[21] Three of 7 sheep died after receiving intravenous bupivacaine 150 or 200mg when they had earlier survived receiving the same dose of levobupivacaine. Levobupivacaine and bupivacaine produced

similar depression of left ventricular contractility, but this and other cardiovascular effects were reversed at doses that caused CNS excitation (see section 2.4). Pregnancy did not enhance the cardiotoxicity of levobupivacaine, bupivacaine or ropivacaine in another study in sheep.[32]

Levobupivacaine and ropivacaine had generally similar cardiovascular effects in animal studies, although greater QRS interval prolongation and/or arrhythmogenic risk was seen with levobupivacaine at some concentrations. However, it is important to note that these studies did not compare the cardiotoxicity of levobupivacaine and ropivacaine at established equipotent anaesthetic doses. Thus, clear conclusions cannot yet be drawn. In anaesthetised pigs, the lethal dose and the dose required to produce a 40msec prolongation of the QRS interval were similar with levobupivacaine and ropivacaine; however, unlike levobupivacaine, ropivacaine did not produce >60 msec QRS prolongation at the doses tested.[16] Both levobupivacaine and ropivacaine required significantly higher doses than that of bupivacaine to cause death and QRS interval prolongation. In conscious rats, levobupivacaine produced greater prolongation of the QRS interval than ropivacaine at the same dose.[33] At the highest dose (20 μmol/kg) ventricular tachycardia occurred in 7 of 8 levobupivacaine-treated animals compared with 1 of 8 ropivacaine recipients, but no such difference was seen at lower doses and the mortality rate was similar for both drugs.

2.3.2 Studies in Human Volunteers

The cardiovascular effects of levobupivacaine administered intravenously were less than those of bupivacaine in 2 randomised, double-blind studies in volunteers (n = 14[34] and 22[9,35]). In both studies, volunteers were familiarised with the typical CNS effects of local anaesthetics by administration of lidocaine (lignocaine). In a crossover study, levobupivacaine or bupivacaine 0.5% was infused at 10 mg/min until clinically significant CNS symptoms (e.g. lightheadedness, tinnitus, numbness) occurred or a maximum of 150mg was reached; the mean dose administered was 56mg for levobupivacaine and 48mg for bupivacaine (corresponding maximum plasma concentrations 2.62 and 2.25 mg/L).[34] Despite the slightly higher dose, levobupivacaine had less of a negative inotropic effect than bupivacaine; the mean percentage reduction from baseline for the stroke index was 9.7 *vs* 21.4% ($p = 0.001$), for acceleration index was 6.6 *vs* 14.6% ($p = 0.011$) and for ejection fraction was 3.9 *vs* 6.6% ($p = 0.024$). Both drugs slightly increased the PR and corrected QT (QT_c) intervals, but the change was statistically significant with bupivacaine only.

In the other study, volunteers were administered bupivacaine until CNS symptoms occurred (bupivacaine dose 34 to 122mg).[9,35] Subsequently, in a double-blind phase, levobupivacaine or bupivacaine was administered up to the same dose as in the earlier nonblind bupivacaine phase. The mean dose was 67.7mg for levobupivacaine and 65.5mg for bupivacaine. In patients receiving >75mg, the mean maximum increase in QT_c interval was 3 msec with levobupivacaine versus 24 msec with bupivacaine ($p = 0.022$). At lower doses, the difference between levobupivacaine and bupivacaine was not significant (11 *vs* 6 msec).

These studies were designed to detect a difference in cardiotoxicity risk between levobupivacaine and bupivacaine in a scenario in which plasma concentrations are high enough to produce perceptible CNS symptoms. In clinical trials in which obviously the aim was to treat the patients with effective but nontoxic levels of anaesthetic, there were no significant differences between the drugs in terms of cardiovascular parameters and only minor ECG abnormalities were reported (see section 5.2).[36-42] Furthermore, signal-averaged ECGs showed no significant differences in QT intervals between groups in 20 women who received epidural levobupivacaine or bupivacaine 0.5% (150mg in 30ml) for Caesarean section.[37]

2.4 CNS Toxicity

Application of local anaesthetic to the nucleus tractus solitarus causes hypotension, bradycardia and arrhythmias.[30] Although both levobupiva-

caine and dexbupivacaine totally or almost totally blocked cell firing in the nucleus tractus solitarus, the time to maximum decrease in cell firing rate was significantly longer after intravenous administration of levobupivacaine 2 mg/kg than after dexbupivacaine 2 mg/kg (68 *vs* 34 seconds; $p < 0.05$) in anaesthetised rats (see also section 2.3.1).[30] This suggests that uptake of bupivacaine by the CNS is enantiomer selective, and is slower for levobupivacaine than dexbupivacaine. All animals receiving dexbupivacaine became apnoeic, whereas those treated with levobupivacaine continued to breathe, suggesting that the enantiomers have differing effects on respiratory neurons. The direct effect of levobupivacaine on nerve structures after local epidural or intrathecal administration has not been studied.

The risk of CNS toxicity with intravenous levobupivacaine was less than that with bupivacaine at the same dose in a representative study in conscious sheep.[21] The mean convulsive dose of levobupivacaine was 103mg, compared with 85mg with bupivacaine ($p = 0.004$). CNS excitatory signs began sooner and lasted longer with bupivacaine. Similar findings were reported from other animal studies comparing levobupivacaine with dexbupivacaine.[6]

The risk of CNS toxicity was also less with levobupivacaine than bupivacaine in human volunteers. Central or peripheral nervous system disorders were experienced by 64% of bupivacaine recipients compared with 36% of levobupivacaine recipients in the study described in section 2.3.2 where volunteers received intravenous doses of levobupivacaine (mean 67.7mg) or bupivacaine (65.5mg) titrated according to previous experience of CNS symptoms with bupivacaine.[9,35] The incidence of tinnitus was significantly lower in the levobupivacaine group (9 *vs* 36%). In another study of intravenous administration, the mean dose to produce clinically significant CNS symptoms was slightly higher for levobupivacaine (56mg) than bupivacaine (48mg) [section 2.3.2].[34] Similarly, intravenous levobupivacaine 40mg produced fewer changes indicative of CNS depression on EEG than bupivacaine 40mg in a double-blind randomised crossover study in 12 volunteers.[43] The magnitude of the effect and the area affected was less with levobupivacaine. For instance, levobupivacaine was associated with a lesser decrease in high alpha power and did not cause the increase in theta power in the parietal, temporal and central regions that occurred with bupivacaine.

3. Pharmacokinetic Properties

Only a limited amount of information on the pharmacokinetics of levobupivacaine is available (table I). Much of the following data is from prescribing information,[44,46] or a review of the pharmacological properties of the drug that was based primarily on data from the manufacturer.[9] Some absorption data are available from subgroups of patients in clinical trials,[37,42,45] and supplementary information is provided by studies of the pharmacokinetics of the enantiomers after administration of racemic bupivacaine. Although the pharmacokinetics of levobupivacaine were investigated after intravenous administration to volunteers, the drug is never administered intravenously in the clinical situation (section 6). Where stated, sampling was venous. Cited values are means.

By definition, local anaesthetics act at the site of administration and thus uptake and distribution by systemic mechanisms are not factors in reaching the site of action. However, uptake into the general circulation is important in terminating anaesthetic action.[2] The maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) of levobupivacaine are dose proportional.[9,44,46] Absorption of levobupivacaine from the site of administration is determined by the vascularity of the tissue. Thus, plasma concentrations are also influenced by the route of administration.[9,44,46] C_{max} was 0.58 to 1.02 mg/L after epidural administration of 75 to 150mg,[37,42,45] and 0.47 and 0.96 mg/L after brachial plexus block with 1 and 2 mg/kg, respectively, in patients;[44] the corresponding AUC values were 3.56 to 5.32 mg/L · h with epidural administration and 3 and 5.31 mg/L · h after bra-

Table I. Overview of pharmacokinetic data for single dose levobupivacaine. Studies were conducted in surgical patients (pt) or healthy volunteers (vo). Values are means

Route	Pt/vo (no)	Conc	Total dose (mg)	C_{max} (mg/L)	t_{max} (h)	AUC (mg/L • h)	Vd (L)	$t_{½}$ (h)	CL (L/h)
Intravenous[9,44]	vo (11)		40	1.4	0.17	1.15	67	1.3	39
Epidural[45]	pt (9)	0.5%	75	0.58	0.37	3.56			
	pt (9)	0.75%	112.5	0.81	0.29	4.93			
Epidural[37]	pt (10)	0.5%	150	1.02		4.08			
Epidural[42]	pt (10)	0.75%	150	0.84	0.4	5.32			
Brachial plexus block[44]	pt (10)	0.25%	1 mg/kg	0.47	0.5	3			
	pt (10)	0.5%	2 mg/kg	0.96	0.71	5.31			

AUC = area under the plasma concentration-time curve; **CL** = total plasma clearance; **conc** = concentration; **C_{max}** = maximum plasma concentration; **$t_{½}$** = elimination half life; **t_{max}** = time to C_{max}; **Vd** = volume of distribution.

chial plexus block (table I). Time to C_{max} was approximately 20 to 40 minutes after epidural administration or brachial plexus block.[44,45]

The elimination half-life of levobupivacaine after intravenous administration of 40mg in volunteers was 1.3 hours and the volume of distribution was 67L.[9,44,46] Levobupivacaine was highly protein bound (>97%) in human plasma *in vitro* at concentrations of 0.1 to 1 mg/L.[44,46] It is believed that highly protein bound agents remain associated with proteins on the neuronal membrane for longer, prolonging the duration of action.[47]

Levobupivacaine crosses the placenta.[18] The umbilical vein/maternal vein drug concentration ratio at the time of delivery was 0.3 in women undergoing elective Caesarean section who received 30ml of levobupivacaine 0.5% (150mg) epidurally and 0.25 for women who received the same dose of bupivacaine;[37] however, if not at steady-state, measurement at a single time-point may not be reliable. Placental transfer of levobupivacaine has not been associated with significant adverse effects to the fetus (section 5.6). The excretion of levobupivacaine in breast milk has not been studied, but it is known that some local anaesthetic drugs are excreted in breast milk.[44]

Levobupivacaine is extensively metabolised by the cytochrome P450 (CYP) system, primarily CYP1A2 and CYP3A4 isoforms.[9,44,46] Thus, hepatic dysfunction is likely to have a significant effect on the elimination of the drug.[44] Supporting this, a lower than expected clearance rate was reported for both enantiomers after administration of bupivacaine for intercostal neural blockade in liver transplant recipients.[48] It is anticipated that the metabolism of levobupivacaine will be affected by concomitant administration of CYP3A4 and CYP1A2 inhibitors and inducers.[44] The clearance of levobupivacaine after administration of intravenous bupivacaine 0.3 mg/kg was reduced by 25% during concomitant administration of oral itracaonzole 200mg, which is a CYP3A4 inhibitor.[49]

The major metabolite of levobupivacaine (3-hydroxy-levobupivacaine) is converted to glucuronic acid and sulphate ester conjugates that are excreted in the urine. No unchanged levobupivacaine is excreted in the urine. Thus, whereas unchanged levobupivacaine will not accumulate in patients with renal failure, the metabolites that are excreted in the urine may accumulate.[44] In volunteers, recovery of radioactivity after intravenous administration of a single dose of radiolabelled drug showed 71% excretion in the urine and 24% in the faeces within 48 hours.[44,46]

The pharmacokinetic properties of levobupivacaine are largely similar to those of bupivacaine,[9,44,46] although some enantioselective features have been reported. Two studies reported higher plasma concentrations after administration of epidural levobupivacaine than bupivacaine at the same dose,[42,45] but others reported plasma concentrations to be similar for the 2 drugs.[9,34,37]

Total plasma concentrations of levobupivacaine are higher than those of dexbupivacaine after administration of bupivacaine.[42,44,50,51] It has been suggested that systemic disposition of bupivacaine is enantioselective, particularly with regards to plasma protein binding; unbound plasma drug concentrations are lower with levobupivacaine than dexbupivacaine after administration of bupivacaine.[50,51] Systemic absorption does not appear to be enantioselective.[50] It has been proposed that the pharmacokinetic differences between the enantiomers of bupivacaine may, in part, explain the differences in their toxicity profiles (section 2); levobupivacaine has a higher unbound clearance rate, shorter elimination half-life, smaller volume of distribution and decreased affinity to brain and myocardial tissues than dexbupivacaine.[47] Levobupivacaine does not undergo racaemisation *in vivo*.[9,44,46]

4. Anaesthetic and Analgesic Activity

Clinical trials of levobupivacaine for surgical anaesthesia (section 4.1) or pain management during labour (section 4.2.1) have largely compared the drug with bupivacaine. Trials of levobupivacaine as postoperative analgesia (section 4.2.2) have mostly investigated use of the drug alone or in combination with other analgesic options, including clonidine, morphine, and fentanyl. All but 4 trials[52-55] were randomised and double-blind. The studies were small-to-moderately sized, each involving 20 to 137 patients. A large range of age groups were studied, including 1 study in children[40] and 1 in the elderly.[41] Unless otherwise stated, studies were in adults. Those studies that specified patient age included patients of approximately 18 to 80 years of age for surgical anaesthesia, and 18 to 40 years of age for obstetric indications. Where stated, patients in the trials had American Society of Anesthesiologists (ASA) physical status I-II or I-III. Surgery (including Caesarean section) was often stated to be elective. Women participating in the obstetric studies had uncomplicated, full term singleton pregnancies.

A variety of anaesthetic techniques were used in clinical trials of levobupivacaine, including lumbar epidural or intrathecal anaesthesia (L2-L3 or L3-L4 interspace),[36-38,42,53,55-59] thoracic epidural anaesthesia (T8-T10 to T10-12 interspace),[60] peribulbar injection,[41] peripheral nerve block (i.e. injection in close proximity to the nerve)[39,40,52] and infiltration anaesthesia (e.g. intracutaneous, subcutaneous and subfascial injections within the area of the procedure).[61])

Additional local anaesthetic doses and/or general anaesthesia could be given if there was not adequate block with levobupivacaine or bupivacaine after ≥30 minutes or during surgery in some studies.[38,42,52,53,55,61] In most surgical studies, patients could receive some form of sedation, in addition to local anaesthetic, if desired.

The concentration of levobupivacaine used was 0.25 to 0.75% for non-obstetric surgical procedures, 0.5% for Caesarean section, 0.125 to 0.25% for women in labour and 0.0625 to 0.5% for postoperative pain management. The total dose (concentration times volume) used depended on the nature of the procedure and the anaesthetic technique. Doses tended to be lower for pain management (including labour analgesia) than for surgical anaesthesia. Other than the lower range doses in dose-finding studies, the doses of levobupivacaine used were generally in line with those recommended for bupivacaine.[2] Of note, the use of bupivacaine 0.75% is contraindicated for use in obstetric procedures.[2] Consequently, levobupivacaine has not been tested at this concentration in obstetric patients.

Efficacy assessments included the onset, duration and extent of sensory and motor block and intra- and postoperative pain. Where stated, sensory block was tested by pinprick test. Two studies of epidural administration specified block adequate for surgery as bilateral sensory block to T10,[42,53] whereas another specified block to T4 to T6.[37] Dermatomes C5 to T1 were assessed for sensory block in a study of supraclavicular brachial plexus block, and onset was block at any dermatome.[39] In a study of intrathecal administration,

onset of sensory block was defined as block at any dermatome.[36] The criteria used to assess whether block was adequate for surgery and/or quality of block were not clearly stated in other studies, and appeared to be largely determined by anaesthetist judgement. Motor block was normally assessed by the modified Bromage scale (0 = no paralysis, able to flex knee and ankle; 1 = unable to raise extended leg but able to flex knee and ankle; 2 = unable to flex knee but able to flex ankle; 3 = unable to move lower limb). Pain was primarily assessed by visual analogue scale (VAS) and/or global verbal rating and use of analgesics.

A number of the studies have not yet been published in full.[52-54,56,57,59,62] Relevant outcomes in the following sections are expressed as mean or median values.

4.1 Surgical Anaesthesia

The use of levobupivacaine for surgical anaesthesia has been investigated in 10 trials, 7 of which were randomised and double-blind and compared the drug with bupivacaine.[37-39,41,42,52,53,55,61,62] Like bupivacaine, levobupivacaine is a long acting local anaesthetic and the anaesthetic action is prolonged with higher doses. The onset of action depends on the route of administration, but was ≤15 minutes in all studies. In all studies, the anaesthetic and analgesic effects with levobupivacaine were largely similar to those with bupivacaine at the same dose. However, there was a trend towards a longer duration of sensory block with levobupivacaine than with bupivacaine. The results are described more fully in the following subsections.

Some studies allowed top-up doses to be given if the initial dose of local anaesthetic did not provide adequate block for the surgery to be conducted. The total dose required was similar with levobupivacaine and bupivacaine.[41,42,61] Most patients had adequate block with the initial dose, but 3.5 to 9% of levobupivacaine and 7 to 15% of bupivacaine recipients required additional doses.[42,61]

Adequate sensory and motor block for surgery was achieved in 90 to 100% of patients treated with the upper dose range of levobupivacaine in most studies.[37,41,42,52,53,55,61] In 2 studies,[38,39] success rates were slightly lower (77 and 80%), but the highest total dose of levobupivacaine in these trials was lower than in some other similar studies, and success rates may have been greater if top-up doses had been given. Also, these studies appeared to include technical failures that were excluded from analysis in other studies.

4.1.1. Epidural and Spinal Anaesthesia

Non-obstetric Surgery

When used as a lumbar epidural anaesthetic in non-obstetric surgery, levobupivacaine and bupivacaine 0.5 or 0.75% (75 to 202.5mg in 15 to 27ml) were given in 2 to 4 divided doses over a period of 5 to 10 minutes.[38,42,53] Because of differences in the way in which the doses were divided, up to 5 minutes difference between studies in onset of block can be anticipated. Nevertheless, the available studies suggest an initial onset time for sensory block of approximately 5 to 15 minutes from completion of injection for levobupivacaine,[38,42,53] and similar onset time for bupivacaine (table II).[38,42] Cephalad spread was maximal (median T8[38] or T5/T6[42] with levobupivacaine and T7[38] or T5/T6[42] with bupivacaine) after a median of 25 minutes with levobupivacaine and 20 or 25 minutes with bupivacaine.[38,42]

The duration of sensory block was approximately 8 or 9 hours with levobupivacaine 0.75% (112.5 to 202.5mg), and approximately 6 hours with levobupivacaine 0.5% (75mg) [table II].[38,42] At the same dose, sensory block was 32 or 45 minutes longer with levobupivacaine than bupivacaine (table II). The difference in sensory block duration was statistically significant with levobupivacaine 0.75% versus bupivacaine 0.75% (551 *vs* 506 minutes; $p = 0.02$)[42] and levobupivacaine 0.75% versus bupivacaine 0.5% (467 *vs* 341 minutes; $p < 0.05$) but not with levobupivacaine 0.5% versus bupivacaine 0.5% (373 *vs* 341 minutes).[38]

The effect of both levobupivacaine and bupivacaine on motor function was less than that on sensory function.[38,42] Accordingly, onset of motor block was slower (≤29 minutes) and duration shorter (≈3 to 6 hours) than for sensory block (table

Table II. Overview of clinical trials of epidural or intrathecal anaesthesia or peripheral nerve block with levobupivacaine (LEV). Studies were randomised, double-blind comparisons with bupivacaine (BUP) or noncomparative trials. Where a range of doses is given, all patients were given the lower dose and those patients who did not have adequate block received top-up doses to the upper dose range stated. Values are means or medians

Anaesthetic technique (study design)	Surgery type	Drug regimen; % conc (vol in ml)	Total dose (mg)	No. of pts	Sensory block (min)		Motor block (min)	
					onset	total duration	onset	total duration
Epidural								
Lumbar[38] (r,db)	Lower limb	LEV 0.5 (15)[a]	75	29	8[b]	373[b]	25.5[b]	195[b]
		LEV 0.75 (15)[a]	112.5	30	6.5[b]	467*[b]	29[b]	256[b]
		BUP 0.5 (15)[a]	75	29	6.5[b]	341[b]	17.5[b]	189[b]
Lumbar[42] (r,db)	Lower abdominal	LEV 0.75 (20-27)[c]	150-202.5	28	13.6	551**	NR	355
		BUP 0.75 (20-27)[c]	150-202.5	28	14	506	NR	376
Lumbar[53][d] (nc)	Hip arthroplasty	LEV 0.75 (15)[e]	112.5	90	≤5	NR	NR	NR
Lumbar[37] (r,db)	Cesarean section	LEV 0.5 (30)	150	30	8.2	451	17.2	241
		BUP 0.5 (30)	150	30	6.4	428	12.5	265
Intrathecal								
Intrathecal[55] (nc)	Lower limb	LEV 0.5 (3)[f]	15	20	2	388	5	266
Peripheral nerve block (NB)								
Supraclavicular brachial plexus NB[39] (r,db)	Hand	LEV 0.25 (0.4/kg)[a]	1 mg/kg	25	7	892	9	847
		LEV 0.5 (0.4/kg)[a]	2 mg/kg	26	6	1039	5	1050
		BUP 0.5 (0.4/kg)[a]	2 mg/kg	23	8	896	6	933
Axillary brachial plexus NB[52][d] (nc)	Upper extremity orthopaedic	LEV 0.5 (50-60)	250-300	20	NR	≈1200[g]	NR	≈1200[g]

a Pts were premedicated with oral temazepam 10-20mg. Pts could receive propofol for sedation if desired. Only those pts in whom block was inadequate for surgery received general anaesthesia with propofol and fentanyl. In the epidural study, the injection site was infiltrated with lidocaine (lignocaine) 1%.

b Values averaged for the right and left sides.

c Pts were premedicated with midazolam and received intraoperative midazolam, propofol and nitrous oxide for sedation/light general anaesthesia if desired.

d Abstract.

e Pts were sedated with propofol after adequate sensory and motor block for surgery was reached.

f Pts were sedated with propofol if desired.

g Duration of sensory/motor block in at least 2 nerve distributions.

conc = concentration; **db** = double-blind; **nc** = noncomparative; **NR** = not reported; **pts** = patients; **r** = randomised; **vol** = volume; * $p < 0.05$ *vs* BUP or LEV 0.5; ** $p = 0.02$ *vs* BUP.

II). In contrast to sensory block, there was no significant difference between levobupivacaine and bupivacaine in duration of motor block, although in 1 study the mean duration of motor block was 21 minutes shorter with levobupivacaine at the same dose (150 to 202.5mg).[42] Only 14% of levobupivacaine recipients, compared with 71% of bupivacaine recipients ($p < 0.001$), had detectable lower extremity motor block within 30 minutes, but ≥89% of patients in both groups eventually had some motor block.[42] In this study of abdominal surgery, abdominal muscle relaxation was adequate for surgery (rectus abdominis muscle score 3 to 5) in 93% of levobupivacaine recipients and 89% of bupivacaine recipients.[42] In another study, motor block was not seen in 48, 23 and 31% of patients who received levobupivacaine 0.5% and 0.75% and bupivacaine 0.5% (75, 112.5 and

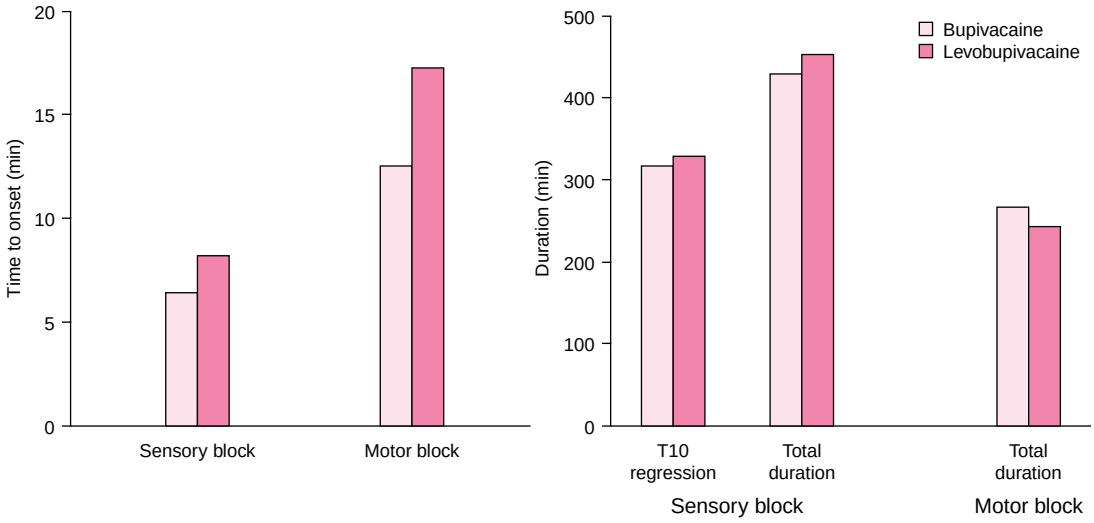

Fig. 2. Mean time to onset and duration of sensory and motor block with epidural levobupivacaine compared with epidural bupivacaine in obstetric patients.[37] 60 patients undergoing elective Caesarean section received lumbar epidural anaesthesia with 30ml of levobupivacaine 0.5% (150mg) or bupivacaine 0.5% (150mg) in a randomised double-blind study.

75mg), respectively.[38] The reported median maximum grade of motor block with levobupivacaine on the modified Bromage scale varied between studies as 1,[38] 2[42] or 3.[53]

In the study of abdominal surgery, the overall quality of sensory and motor block was considered by the investigator to be good or excellent in 96% of levobupivacaine and 82% of bupivacaine recipients.[42]

Caesarean Section

One randomised double-blind study has compared lumbar epidural levobupivacaine 0.5% with bupivacaine 0.5% [150mg in 30ml in divided doses over 10 minutes] in 60 patients undergoing elective Caesarean section (table II).[37] Onset and duration of sensory and motor block are shown in figure 2. Results were very similar to those with epidural levobupivacaine in non-obstetric surgery, although the differences between levobupivacaine and bupivacaine did not reach statistical significance. The total duration of sensory block was 23 minutes longer with levobupivacaine than bupivacaine, whereas motor block was 24 minutes shorter. All patients had modified Bromage motor block scores of 2 or 3. Pain scores were low and not significantly different between groups.

Intrathecal Use

In a noncomparative study of intrathecal use of plain levobupivacaine 0.5% (15mg in 3ml), the onset of block was very rapid and the duration of sensory and motor block was 6.5 and 4.4 hours, respectively (table II).[55] The extent of cephalad spread was highly variable between patients, with the maximum height ranging from L3 to T4; this was likely related to the physical properties of the plain (dextrose/glucose-free) solution of the drug that was used, which is slightly hypobaric and has a density of 1.0005 g/ml at 37°C. Maximum spread occurred after a median of 25 minutes. Complete motor block was seen in 95% of patients.

4.1.2 Peripheral Nerve Block Studies

The duration of block in a study of supraclavicular brachial plexus blockade was markedly longer than reported for epidural administration. A trend towards a longer duration of block with levobupivacaine than with bupivacaine and with higher

rather than with lower doses of levobupivacaine was evident (table II).[39] The duration of sensory block with levobupivacaine 0.5% (2 mg/ kg in 0.4 ml/kg) was 17 hours, compared with 15 hours with bupivacaine 0.5% (2 mg/kg) or levobupivacaine 0.25% (1 mg/kg); however, these differences did not reach statistical significance. The duration of motor block was very similar to that of sensory block (table II), in contrast to the situation with epidural administration. The onset of action was ≤9 minutes. The median maximum motor block was a modified Bromage score of 2.[39]

Similarly, the duration of sensory plus motor block in at least 2 nerve distributions was 20 hours with levobupivacaine 0.5% (250 to 300mg in 50 to 60ml) in a small noncomparative study of axillary brachial plexus neural blockade.[52] However, it should be noted that this study used a higher initial dose than is currently recommended (150mg; see section 6).

A further study that aimed to determine whether postoperative analgesia is best achieved by pre- or post-operative interscalene administration of levobupivacaine is discussed in section 4.2.2.[63]

4.1.3 Infiltration Anaesthesia

Intra- and/or postoperative pain relief with levobupivacaine 0.25% as infiltration anaesthesia was generally similar to that with bupivacaine 0.25% in patients undergoing inguinal hernia repair in 2 studies (table III).[61,62] Postoperative intake of ibuprofen was significantly greater with levobupivacaine than with bupivacaine in 1 study.[62] However, this is unlikely to be clinically significant because the difference equates to approximately one-half of a 600mg ibuprofen tablet per 24 hours. No difference in this parameter was seen in the other study.[61] Patient satisfaction with anaesthesia was high and not significantly different between the groups in the study that reported this parameter (table III).[61]

4.1.4 Use in Ophthalmic Surgery

Peribulbar anaesthesia with levobupivacaine 0.75% (37.5mg in 5ml plus top-up doses to a maximum of 112.5mg) provided good conditions for surgery and had similar effects as the same regimen of bupivacaine in a randomised, double-blind study in 50 elderly patients undergoing ophthalmic surgery.[41] Muscle block satisfactory for surgery was achieved within a mean of 12.5 minutes with levobupivacaine and 11 minutes with bupivacaine. Most patients were caused little pain by the peribulbar injection and no patients reported pain during the surgical procedure.

This study used a regimen including oxybuprocaine and lidocaine, as well as levobupivacaine or bupivacaine with hyaluronidase. This is in line with accepted regimens[64] and aims to provide rapid onset, intense motor block and sufficient anaesthetic duration for the surgery.[41] For the akinesia rating in the study, each muscle was scored from 0 (no block) to 4 (complete akinesia) [maximum possible score 24]. 18 was deemed adequate

Table III. Overview of clinical trials of infiltration anaesthesia with levobupivacaine (LEV) compared with bupivacaine (BUP) in patients undergoing inguinal hernia repair. Studies were randomised and double-blind

Reference	Drug regimen; % conc (vol in ml)	Total dose (mg)	No. of pts	Intraoperative pain[a]		Pt satisfaction[b]	Postoperative ibuprofen dose (mg/h; median)
				Nil/slight (% of pts)	Moderate/severe (% of pts)		
Bay-Nielsen et al.[61]	LEV 0.25 (50-60)[c]	125-150	33	64	36	77	52
	BUP 0.25 (50-60)[c]	125-150	33	79	21	80	51
Kingsnorth et al.[62][d]	LEV 0.25 (NR)	NR	69 (total)	NR	NR	NR	63*
	BUP 0.25 (NR)	NR		NR	NR	NR	43

a Based on pt global verbal ratings.

b Median score of pt satisfaction with anaesthesia measured on visual analogue scale (0-100mm).

c Pts received midazolam 2-5mg for intraoperative sedation.

d Abstract (sedative medications not stated).

conc = concentration; **NR** = not reported; **pt** = patient; **vol** = volume; * p = 0.041 *vs* BUP.

for surgery. It has been suggested that this criterion was too high, and that a score of 12 would have been acceptable and would have allowed lower doses of levobupivacaine to be used.[65]

4.2 Pain Management

4.2.1 Labour Analgesia

Analgesia attained with lumbar epidural levobupivacaine was generally similar to that with bupivacaine in women in labour in 2 randomised, double-blind studies (n = 137 and 80).[36,56]

After administration of 10ml of levobupivacaine or bupivacaine 0.25% (25mg) in 1 study, the median time to onset of complete pain relief was 12 minutes and the duration of pain relief was approximately 50 minutes for both drugs.[36] A significant difference between the drugs was observed in the number of patients requiring a second injection to achieve adequate pain relief (20 of 68 levobupivacaine *vs* 10 of 69 bupivacaine recipients; p = 0.04). However, this may have been related to the greater degree of cervical dilation and higher number of women in the levobupivacaine group in whom labour was induced (17 *vs* 11 in the bupivacaine group). In the other study, women received 10 to 15ml of levobupivacaine or bupivacaine 0.25% (25 to 37.5mg) to achieve sensory block and freedom from pain.[56] A continuous epidural infusion of 15 mg/h (12 ml/h of 0.125% solution) of the study drug was then initiated. Patients could receive up to 4 top-up doses of 10ml of 0.25% (25mg) of study drug as required for pain. With this regimen, 43% of the first stage of labour was pain free in both groups. The mean dose (levobupivacaine 28 mg/h, bupivacaine 27 mg/h) and the number of patients requiring top-up doses (87 *vs* 81%) was similar between the groups.

The extent of sensory blockade was similar with levobupivacaine and bupivacaine in both studies.[36,56] In one trial, the percentage of patients without significant motor block (modified Bromage score 0) after the initial dose was 84% in the levobupivacaine group and 83% in the bupivacaine group; respective percentages after the first top-up dose were 66 and 63%.[36] In the other study, there was a nonsignificant trend towards less motor block with levobupivacaine.[56] During labour, it is desirable to maintain motor function so that the woman can actively participate in the birthing process.

4.2.2 Postoperative Pain Management

Continuous epidural administration for 24 hours of levobupivacaine either in a low dose in combination with other agents or alone at a higher dose provides effective postoperative pain relief (table IV). In 3 randomised double-blind trials, levobupivacaine 0.125% (7.5 mg/h at 6 ml/h) plus clonidine,[57] levobupivacaine 0.25% (10 mg/h at 4 ml/h) plus morphine,[60] and levobupivacaine 0.125% (5 mg/h at 4 ml/h) plus fentanyl[58] were more effective than any of the agents alone. In another study, levobupivacaine 0.25% (15 mg/h at 6 ml/h) was more effective than lower doses of levobupivacaine.[59] With these regimens, the time to first request for rescue analgesia was 10 to 17 hours. These regimens were generally superior to any of the agents alone or a lower dose of levobupivacaine in terms of the time to rescue analgesia, the amount of rescue analgesia consumed and/or pain scores (table IV).

Ilioinguinal/iliohypogastric nerve block with levobupivacaine 0.5% (1.25 mg/kg in 0.25 ml/kg per operated side) at the conclusion of surgery was superior to placebo in 35 children (aged 6 months to 12 years) undergoing inguinal hernia repair under general anaesthetic (table IV).[40] The superiority of levobupivacaine was evident according to pain measures (mean time-weighted Children's Hospital of Eastern Ontario Pain Scale 6.4 *vs* 6.9 with placebo; p = 0.03) and a longer time to rescue analgesia (p = 0.04). Additionally, there was a trend towards greater block quality (median 2 *vs* 1 with placebo, where 0 = poor, 1 = fair, 2 = good, 3 = excellent; p = 0.083), fewer patients requiring rescue analgesics (45 *vs* 73%; p = 0.18) and lower mean number of rescue analgesia doses (p = 0.058) in the levobupivacaine compared with the placebo group.

In a nonblind study of interscalene block in association with intraoperative general anaesthesia,

Table IV. Overview of trials of levobupivacaine (LEV) as postoperative analgesia. All trials were randomised and double-blind, other than a study comparing pre- and postoperative interscalene LEV.[53] Continuous epidural infusions were given for 24 hours. Values are means or medians

Surgery type	Regimen	No. of pts	Rescue analgesia			Pain score[a]
			time to request (h)	type of analgesia	dose required	
Continuous lumbar[56-58] or thoracic[59] epidural						
Hip replacement[57]b,c	LEV 0.125% 7.5 mg/h + CLO 50 μg/h	90 (total)	13	MOR	14mg**	LEV + CLO < LEV or CLO
	LEV 0.125% 7.5 mg/h		5	MOR	35mg	
	CLO 50 μg/h		7.2	MOR	22mg	
Major abdominal[60]c	LEV 0.25% 10 mg/h + MOR 0.005% 0.2 mg/h	21	16††	LEV+MOR/KET	LEV+MOR ≡ LEV ≡ MOR[d]	LEV + MOR < LEV or MOR
	LEV 0.25% 10 mg/h	21	4.3	LEV/KET		
	MOR 0.005% 0.2 mg/h	22	10.9	MOR/KET		
Hip or knee replacement[58]c	LEV 0.125% 5 mg/h + FEN 16 μg/h	21	10***	PCEA LEV + FEN	5.7 ml/h†	LEV + FEN < LEV or FEN
	LEV 0.125% 5 mg/h	22	7	PCEA LEV	7.3 ml/h	
	FEN 16 μg/h	22	7	PCEA FEN	6.9 ml/h	
Hip or knee replacement[59]b,c	LEV 0.0625% 3.75 mg/h	32	8.1	MOR	1.5 mg/h	LEV 0.25 < LEV 0.125 or LEV 0.0625
	LEV 0.125% 7.5 mg/h	27	9.5	MOR	0.96 mg/h	
	LEV 0.25% 15 mg/h	32	16.7*	MOR	0.21 mg/h*	
Ilioinguinal/iliohypogastric nerve block						
Inguinal hernia repair in children[40]e	LEV 0.5% 1.25 mg/kg per operated side	20	LEV > PL[d]	MOR/KET[f]	0.7 doses	LEV < PL[g]
	PL	15		MOR/KET[f]	1.4 doses	
Interscalene block						
Shoulder surgery[54,63]b,h	Preoperative LEV 0.5% 150mg	35	11.5	NR	NR	LEV pre < LEV post
	Postoperative LEV 0.5% 150mg	39	10.9			

a Measured on visual analogue scale, unless otherwise stated.

b Abstract.

c Surgical anaesthesia was provided with epidural LEV 0.75% (45-150mg) with or without other sedative/anaesthetic agents.

d Numerical values not clearly stated.

e All pts received paracetamol (acetaminophen) 15 mg/kg before surgery; pts <1y of age received atropine 0.01 mg/kg. General anaesthesia was given (inhaled sevoflurane, halothane, nitrous oxide).

f Pts could receive up to 3 doses of MOR 0.05 mg/kg then 1 dose of KET 1 mg/kg.

g Measured on Children's Hospital of Eastern Ontario Pain Scale.

h Pts received intraoperative general anaesthesia.

CLO = clonidine; **FEN** = fentanyl; **KET** = ketorolac; **MOR** = morphine; **NR** = not reported; **PCEA** = patient-controlled epidural analgesia (supplemental doses); **PL** = placebo; **pts** = patients; < indicates significantly lower at some or all time points; > indicates significantly longer; ≡ indicates no significant difference; * $p < 0.01$ vs other groups; ** $p < 0.005$ vs LEV or CLO alone; *** $p < 0.01$ *vs* LEV or FEN alone; † $p < 0.05$, †† $p < 0.001$ *vs* LEV alone.

postoperative pain relief was better achieved with administration of levobupivacaine immediately before compared with immediately after surgery (table IV).[54,63] Patients receiving pre-emptive treatment had less pain in the day after surgery than those receiving postoperative treatment, but this difference was lost over the following days emphasising the need for follow-up postoperative analgesia.

It is not desirable to have a high degree of motor block postoperatively in most cases. The degree of motor block was acceptable in the 3 studies that reported this parameter.[58-60] In 1 study, significant motor block (modified Bromage score 3) occurred

in 6, 26 and 22% of patients receiving levobupivacaine 0.0625%, 0.125% and 0.25% (3.75, 7.5, 15 mg/h), respectively.[59] In the other studies, most patients had regained full movement of lower limbs within 12 hours postoperatively and the remaining few patients had only slight or moderate residual motor block.[58,60]

5. Tolerability

5.1 Overview

The primary aim in the development of levobupivacaine was to produce an agent with a lower risk of toxicity than, but equal efficacy to, bupivacaine. *In vivo*, the potential for toxicity with levobupivacaine is less than that with bupivacaine (section 2). In particular, advantages in terms of cardiotoxicity and CNS toxicity in animal and human volunteer studies have been demonstrated (sections 2.3 and 2.4). In the controlled conditions of clinical trials (described in section 4), few significant adverse events were reported for either levobupivacaine or bupivacaine.[36-41,55] The incidence of adverse events with levobupivacaine was similar to that with bupivacaine in comparative trials (fig. 3).[44] According to the manufacturer's database of 1141 patients treated with levobupivacaine in phase II/III clinical trials, 78% of patients experienced at least 1 adverse event.[44] The most common adverse events (regardless of causality to the drug; route not stated) were: hypotension (31%), nausea (21%), postoperative pain (18%), fever (17%), vomiting (14%), anaemia (12%), pruritus (9%), pain (8%), headache (7%), constipation (7%), dizziness (6%) and fetal distress (5%).[44] Adverse events are typical of those expected with amide-type local anaesthetics.[44]

Of note, no toxicity occurred in a study of brachial plexus block with levobupivacaine 0.5% (initial dose 250mg)[52] that exceeded the maximum recommended single dose of levobupivacaine (150mg; section 6).

5.2 Cardiovascular Effects

Levobupivacaine and bupivacaine exerted similar effects on blood pressure and heart rate in most clinical trials.[36-40] In a study of epidural levobupivacaine and bupivacaine 0.5% (150mg) in women undergoing Caesarean section, the incidence of hypotension (defined as a decrease of >30% from baseline in systolic arterial pressure) tended to be lower in levobupivacaine than bupivacaine recipients (84.4% *vs* 100%; p = 0.053).[37] However, the decreases in mean systolic blood pressure were relatively small (fig. 4). Furthermore, the incidence of hypotension after epidural administration is affected by factors such as the degree of spread of segmental sympathetic blockade, bodyweight, intravascular volume status, as well as the type of anaesthetic.[3,66] The incidence of hypotension reported in other studies was lower; 12% to 32% with levobupivacaine and 7 to 32% with bupivacaine.[36,38,42]

Bradycardia (heart rate <30 beats/min) was experienced by 1 patient in each group in a study comparing levobupivacaine and bupivacaine 0.25% (125 to 150mg) as infiltration anaesthesia in 66 patients undergoing inguinal hernia repair.[61] Although other studies also reported a slight transient decrease in heart rate,[38,39] in some studies small increases in heart rate were evident at some time points.[36,37]

No clinically significant ECG abnormalities occurred in clinical trials.[37-39,41,42] Minor ECG abnormalities that arose after treatment with epidural levobupivacaine 0.5% (75mg) or 0.75% (112.5mg) in 1 study (n = 59) were sinus tachycardia, sinus bradycardia with atrial ectopic and sinus tachycardia with minor T-wave inversion in 1 patient each.[38]

Although no serious cardiovascular events were reported in clinical trials of levobupivacaine, theoretically the myocardial depression that has been seen with other amide-type local anaesthetics could occur with levobupivacaine. The manufacturer of levobupivacaine describes possible cardiotoxicity as including a decrease in cardiac output, hypotension and ECG changes indicative of

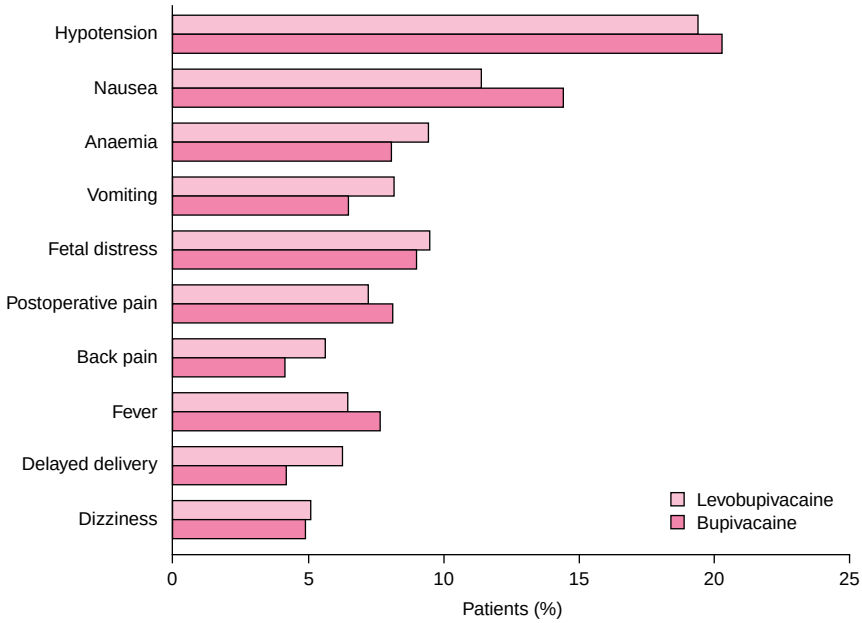

Fig. 3. Incidence of adverse events in phase II/III comparative trials of levobupivacaine (n = 509) and bupivacaine (n = 453).[44]Adverse events that occurred with an incidence ≥5% are shown.

heart block, bradycardia or ventricular tachyarrhythmias that can cause cardiac arrest.[46]

5.3 Neurological Events

Minor neurological abnormalities in the form of transient hypoaesthesia or paraesthesia were reported in a small number of patients who received levobupivacaine or bupivacaine while undergoing lower limb or hand surgery,[38,39] but these effects may have been related to the operation.

No serious adverse CNS events were caused by levobupivacaine in any of the studies. Nevertheless, the manufacturer of levobupivacaine warns that CNS toxicity can occur with amide-type local anaesthetics, manifesting as tongue numbness, light headedness, dizziness, blurred vision and muscle twitching that can progress to drowsiness, convulsions, loss of consciousness and respiratory arrest.[46]

5.4 Ocular Events

Persistent diplopia the day following surgery was reported by 40% of patients receiving levobupivacaine 0.75% and 52% of patients receiving bupivacaine 0.75% (37.5mg plus top-up doses to a maximum of 112.5mg) after peribulbar anaesthesia in elderly patients undergoing ophthalmic surgery.[41] Diplopia lasted up to 46 hours. This study has been criticised for administering too high a dose of anaesthetic, leading to the high incidence of diplopia.[65]

5.5 Unintentional Intravascular Administration

One of the limiting factors in the use of bupivacaine is that fatal cardiovascular and/or CNS toxicity has been occasionally reported after unintentional intravascular administration.[4,5] A single case report is available on the favourable outcome of a patient undergoing epidural anaes-

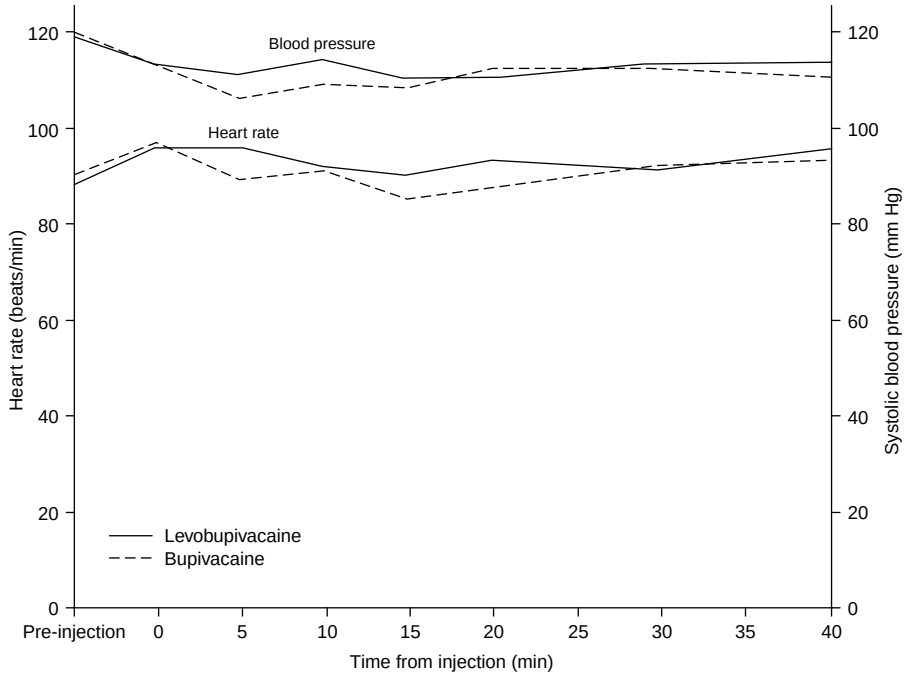

Fig. 4. Mean systolic blood pressure and heart rate after administration of levobupivacaine or bupivacaine.[37] 60 women undergoing elective Caesarean section received 30ml of epidural levobupivacaine 0.5% (150mg) or bupivacaine 0.5% (150mg) in a randomised double-blind study.

thesia who received rapid intervention after detection of unintentional intravascular administration of levobupivacaine 0.75% (total dose administered 142.5mg).[67] In the last 5ml of the injection, the patient became disoriented and drowsy and her speech became slurred. She then became agitated. The levobupivacaine injection was stopped, and the patient was given prophylactic thiopental and supplemental oxygen; she had received midazolam preoperatively. The patient did not exhibit significant CNS or cardiotoxicity. She recovered within 10 minutes and without sequelae. Of note, intravascular administration occurred despite adherence with the administration procedures outlined in section 6 (i.e. aspiration, use of a test dose with epinephrine (adrenaline), slow administration of fractionated doses).

Two patients received unintentional intravascular administration of bupivacaine during comparative trials with levobupivacaine.[37,39] One patient received an unstated amount of a 150mg dose of bupivacaine 0.5% while undergoing epidural anaesthesia and did not experience significant adverse consequences.[37] The other patient received approximately two-thirds of a 2 mg/kg dose of bupivacaine 0.5% while undergoing supraclavicular brachial plexus block. The patient lost consciousness and developed generalised twitching, sinus tachycardia and hypertension. The patient received oxygen and propofol, and had been premedicated with temazepam. The episode resolved after a few minutes and with no sequelae.[39]

5.6 Fetal Outcome

When levobupivacaine was used in obstetric indications, fetal outcome was not significantly different from that after bupivacaine.[36,37,56] For instance, Apgar scores were <7 at 1 minute in 6 of 68

neonates of levobupivacaine recipients and 9 of 69 neonates of bupivacaine recipients in a study in women in labour who received epidural levobupivacaine or bupivacaine 0.25% (maximum 2 mg/kg per 4 hours).[36] Similarly, Neurological and Adaptive Capacity (NAC) score was <35 at 2 hours in 5 of 22 neonates of women treated with levobupivacaine versus 5 of 19 neonates of women treated with bupivacaine. Apgar scores were >7 at 5 minutes and NAC scores were >35 at 24 hours in all but 1 or 2 babies in each group. In women undergoing Caesarean section, it was noted that no neonatal adverse events were related to the study drugs (levobupivacaine or bupivacaine).[37]

6. Dosage and Administration

Levobupivacaine is indicated for various types of surgical anaesthesia and pain management. Indications and recommended dosages for levobupivacaine differ markedly between Europe[46] and the US,[44] and consequently are presented separately in the following subsections.

Although dosage guidelines are provided, factors such as the patient's weight and physical status should be considered for all cases (e.g. reduce doses in low bodyweight, debilitated, frail, elderly or acutely ill patients).[44,46] Individual variation in the onset and duration of block can occur. When levobupivacaine is used for postoperative pain relief, the local anaesthetic dose used during surgery should be taken into account.

6.1 Indications and Dosages in Europe

The indications for levobupivacaine in Europe include epidural, intrathecal, peripheral nerve block, peribulbar administration and local infiltration for surgical anaesthesia in adults (table V). Levobupivacaine is also indicated for epidural use for the management of pain, including labour and postoperative pain in adults. In children, levobupivacaine is indicated for ilioinguinal/iliohypogastric nerve block.[46]

Lower doses are normally required for analgesia, whereas higher doses are needed for more profound and prolonged anaesthesia with dense motor block. In adults, the recommended maximum single dose for surgical anaesthesia (other than for intrathecal administration) is generally 150mg (table V). Additional doses may be required for a prolonged procedure. The recommended maximum single dose for intrathecal administration is 15mg.[46]

The concentration used for Caesarean section must not exceed 0.5% (150mg). The recommended maximum epidural dose for labour analgesia is a 0.125% infusion of 12.5 mg/h or epidural injections of 0.25% up to 25mg at ≥15-minute intervals.[46]

For postoperative pain management in adults, the dose should not exceed 18.75 mg/h. Levobupivacaine can be administered in combination with other analgesic agents, including opioids, for postoperative pain management.[46]

The maximum dose for children undergoing ilioinguinal/iliohypogastric block is 1.25 mg/kg/side.

6.2 Indications and Dosages in the US

In the US, levobupivacaine is indicated for epidural peripheral nerve block, peribulbar administration and local infiltration for surgical anaesthesia in adults (table V). Levobupivacaine is also indicated for epidural use for the management of pain, including labour and postoperative pain in adults. However, the drug is not currently indicated in the US for intrathecal administration or use in children.[44]

As in Europe, the recommended maximum single dose for most surgical anaesthesia is 150mg (table V), with additional doses for prolonged procedures if necessary. Epidural doses of 0.5% up to 150mg are appropriate for Caesarean section, and for labour analgesia 0.25% up to 50mg per dose can be given.[44] For postoperative pain management, the maximum recommended epidural dose is 25 mg/h. Levobupivacaine can be administered in combination with epidural fentanyl or clonidine for postoperative pain; no specific recommendation regarding the use of levobupivacaine in com-

Table V. Dosage guidelines for levobupivacaine.[44,46] The lowest possible dose and concentration to achieve the desired effect should be used, but the maximum dose stated should not be exceeded. Levobupivacaine is available in 2.5 (0.25%), 5 (0.5%) and 7.5 mg/ml (0.75%) solutions

Anaesthetic technique	Indication	Concentration	Volume (dose)		Motor block	Comment
			European recommendations	US recommendations		
Surgical anaesthesia in adults						
Epidural slow injection	Surgery	0.5-0.75%	10-20ml (50-150mg)	10-20ml (50-150mg)	Mod/max	Give over ≥5 mins
Epidural slow injection	Caesarean section	0.5%	15-30ml (75-150mg)	20-30ml (100-150mg)	Mod/max	Give over 15-20 mins
Intrathecal	Surgery	0.5%	3ml (15mg)	Not indicated	Mod/max	
Peripheral nerve block	Surgery	0.25-0.5%	1-40ml (max 150mg)	30ml or 0.4 ml/kg (75-150mg or 1-2 mg/kg)	Mod/max	
Peribulbar	Ophthalmic	0.75%	5-15ml (37.5-112.5mg)	5-15ml (37.5-112.5mg)	Mod/max	
Local infiltration	Surgery	0.25%	1-60ml (max 150mg)	≤60ml (max 150mg)	NA	
Surgical anaesthesia in children						
Ilioinguinal/ iliohypogastric nerve block	Surgery in children <12y	0.25-0.5%	0.25-0.5 ml/kg (1.25 mg/kg per side)	Not indicated	NA	
Pain management in adults						
Epidural injection	Labour	0.25%	6-10ml (15-25mg)	10-20ml (25-50mg)	Min/mod	Wait ≥15 mins between doses
Epidural infusion	Labour	0.125%	4-10 ml/h (5-12.5 mg/h)	No recommendation	Min/mod	Dilute to 0.125% with saline 0.9%
Epidural infusion	Postoperative pain	0.125[a]-0.25%	5-15 ml/h (12.5-18.75 mg/h)	4-10 ml/h (5-25 mg/h)	Min/mod	Dilute to 0.125% with saline 0.9%

a The 0.125% concentration is preferable for combined use with other analgesic agents.

max = maximal; **min** = minimal; **mins** = minutes; **mod** = moderate; **NA** = not applicable.

bination with morphine is made in US product labelling.[44]

6.3 Cautions and Contraindications

In Europe, specified contraindications for levobupivacaine are the following:[46]

- use of 0.75% (7.5 mg/ml) of levobupivacaine in obstetric patients; levobupivacaine has not been studied at this concentration in obstetric patients, but bupivacaine has been associated with occasional cardiotoxicity in this scenario and is similarly contraindicated
- use in paracervical block in obstetrics
- use in intravenous regional anaesthesia (Bier's block); again this reflects occasional fatal experiences with bupivacaine in this indication
- known hypersensitivity to levobupivacaine or any local anaesthetic of the amide type
- use in patients with severe hypotension (e.g. cardiogenic or hypovolaemic shock).

US product labelling carries warnings against the use of levobupivacaine in obstetric patients at the 0.75% concentration, obstetrical paracervical block, and intravenous regional anaesthesia.[44] Use of levobupivacaine in patients with known hypersensitivity to amide-type local anaesthetics is contraindicated.

As with all long acting local anaesthetics, epidural levobupivacaine can cause hypotension, bradycardia and possibly cardiac arrest. Appropriate treatments, equipment and personnel should be readily available in the event that a serious adverse event occurs. Levobupivacaine should be used

with caution in patients with impaired cardiovascular function.[44,46]

To prevent intravascular injection, careful aspiration should be performed before and during injection. When a large dose is to be injected (e.g. epidural block), a 3 to 5ml test dose with a fast acting local anaesthetic (e.g. lidocaine) and, if appropriate, epinephrine is recommended; a temporary increase in heart rate indicates that the test dose has been administered intravascularly and signs of spinal block indicate that the test dose has been administered intrathecally.[44,46] Large doses should be injected slowly and incrementally (7.5 to 30 mg/min). Thus, the use of levobupivacaine may not be appropriate in emergency situations where a fast onset of surgical anaesthesia is required.[44]

Use in early pregnancy is recommended only if the benefits outweigh the risks. Caution is required in the use of levobupivacaine in breast-feeding mothers.[44,46]

Levobupivacaine should be used with caution in patients with liver disease or reduced liver blood flow, as the drug is metabolised in the liver. Metabolism of levobupivacaine may be affected by drugs that are CYP3A4 and CYP1A2 inhibitors or inducers; dosage adjustment may be warranted when levobupivacaine is concurrently administered with CYP3A4 and CYP1A2 inhibitors. The toxic effects of other local anaesthetic agents, antiarrhythmic agents with local anaesthetic activity or class III antiarrhythmic agents may be additive to those of levobupivacaine.[44,46]

7. Place of Levobupivacaine in Surgical Anaesthesia and Pain Management

Local anaesthetics are generally well tolerated. However, serious CNS or cardiovascular complications can occasionally arise, normally in the context of high or rapidly escalating plasma concentrations resulting from a problem in technique, drug accumulation or administration of inappropriately high or rapidly administered doses.[1,3] Local anaesthetic-related cardiotoxicity may be preceded by more minor CNS symptoms, providing a window of opportunity for effective intervention if the early warning signs are recognised. However, bupivacaine can cause sudden and potentially fatal ventricular arrhythmias and cardiac collapse in the absence of significant CNS warning signs.[1,4,5] Furthermore, cardiotoxicity associated with bupivacaine can be difficult to reverse. Bupivacaine is associated with greater cardiotoxicity than the shorter acting agents (e.g. lidocaine, prilocaine).[3,9,68] Nevertheless, bupivacaine has conventionally had an important role as the longest acting local anaesthetic and continues to be widely used.[2,3,68] Long acting agents are preferred for use in situations requiring prolonged anaesthesia, as this minimises the risk of cumulative systemic toxicity.[2] Furthermore, bupivacaine is particularly suitable for continuous epidural analgesia in labour or postoperatively because it produces more pronounced sensory than motor block.[2,3,68] An agent with a duration of action and efficacy similar to those of bupivacaine, but with a lower risk of toxicity, would be desirable.

Clinical studies have established that levobupivacaine has a clinical profile that is largely similar to that of bupivacaine at the same dose. Levobupivacaine is long acting with an onset of action ≤15 minutes with various anaesthetic techniques. Levobupivacaine provided sensory block for up to 9 hours after epidural administration of ≤202.5mg, 6.5 hours after intrathecal 15mg, and 17 hours after brachial plexus block with 2 mg/kg. The duration of effect was dose-dependent. Conditions satisfactory for surgery and good pain management were achieved by use of local infiltration or peribulbar administration of levobupivacaine. Levobupivacaine was generally as effective as bupivacaine for pain management during labour, and was effective for the management of postoperative pain, especially when combined with clonidine, morphine or fentanyl. A trend towards more prolonged sensory block with levobupivacaine than bupivacaine at the same dose was observed in surgical anaesthesia studies. This amounted to a difference of approximately 20 to 40 minutes with

epidural administration and 2 hours with peripheral nerve block. It has not been established whether clinical practice should be altered accordingly. Overall, current data show that levobupivacaine can be used in place of bupivacaine using similar doses for various types of surgical anaesthesia and pain management in adults. It would be useful to have further data on intrathecal use, which is an approved indication in Europe but not the US. The use of levobupivacaine has not yet been compared with that of bupivacaine in children, but further paediatric studies are ongoing. The contraindications for levobupivacaine are similar to those for bupivacaine, including use in Bier's block and use of the 0.75% concentration in obstetrics;[2,46] however, this reflects experience with bupivacaine rather than any events occurring with levobupivacaine.

Given that levobupivacaine and bupivacaine have similar anaesthetic potency, the pivotal issue is the comparative risk for toxicity. A potential safety and toxicity advantage for levobupivacaine has been shown *in vitro* and in animal studies. For instance, levobupivacaine was associated with a higher lethal dose and a higher convulsive dose and induced fewer and less severe arrhythmias than bupivacaine at the same dose in animals. In human volunteers, levobupivacaine had less of a negative inotropic effect and less arrhythmogenic potential (indicated by less prolongation of the QT_c interval at high doses), compared with bupivacaine. The incidence of central or peripheral nervous system disorders was lower and fewer changes indicative of CNS depression on EEG were evident with levobupivacaine. Caution is required though, because it is not yet known whether levobupivacaine is safer than bupivacaine in potentially dangerous clinical situations, such as when intravascular injection occurs. The one available case report of unintentional intravascular administration of levobupivacaine reported no significant toxicity when the situation was treated rapidly and appropriately.[67] Results so far are promising, but only extensive clinical experience will confirm the safety advantage of levobupivacaine. Furthermore, although toxicity with levobupivacaine may require higher doses to occur, the potential for serious toxicity remains, as is true for all local anaesthetics. Data comparing the difficulty of resuscitation after levobupivacaine-induced versus bupivacaine-induced arrhythmia are not yet available.

Like bupivacaine, levobupivacaine produces differential sensory and motor block when administered epidurally or intrathecally, i.e. sensory block has a more rapid onset and longer duration than motor block. The same trend was not detected with the doses used for peripheral nerve block.[39] The differential between sensory and motor block after epidural administration is an advantage for women in labour, so that they can actively participate in the birthing process, and for ease of rehabilitation when local anaesthetic is used postoperatively for pain relief. Only limited data are available, but most patients receiving levobupivacaine during labour or postoperatively did not have significant motor block. During surgery, motor block may be desirable. Although the motor block was moderate (i.e. modified Bromage score ≤ 2) in a number of patients undergoing surgical anaesthesia with levobupivacaine as an epidural or peripheral nerve block, in the vast majority of patients conditions were satisfactory for surgery to proceed.

An important issue that requires investigation is how levobupivacaine compares to ropivacaine. Ropivacaine is a long acting agent that is enantiomerically pure and was introduced in the early to mid 1990s. Levobupivacaine has been reported to have either similar or significantly more prolonged anaesthetic effects than ropivacaine in animal models. Although levobupivacaine and ropivacaine have not been compared clinically, some data suggest that ropivacaine is less potent than bupivacaine.[69-71] It has been reported that at the lower end of the dosage scale, ropivacaine produces greater differentiation between sensory and motor effects than bupivacaine, raising the possibility of an advantage for ropivacaine in terms of reduced motor impairment in women in labour and postoperative patients.[69] Ropivacaine has also

been reported to have a lower risk of CNS and cardiotoxicity than bupivacaine at the same dose. However, the clinical value of these reported differences depends on whether higher doses of ropivacaine are needed to produce the same effect. At the same dose, *in vitro* and *in vivo* cardiac effects of levobupivacaine have been reported to be largely similar to those of ropivacaine, although some studies reported greater QRS interval prolongation and/or arrhythmogenic risk with levobupivacaine at some doses. However, to adequately compare levobupivacaine and ropivacaine, it will be important to compare toxicity at equipotent anaesthetic doses.

Pharmacoeconomic evaluations of levobupivacaine would also be useful in establishing the ultimate place of the agent. The incidence of serious toxicity with bupivacaine is low, and has been reduced further by improvements in anaesthetic techniques, such as fractionating doses and use of epidural test doses.[68] If levobupivacaine is priced higher than bupivacaine, it would be of interest from an economic perspective to determine the cost-benefit ratio. From an ethical viewpoint, it can be argued that even 1 death avoided is worth the cost.

In conclusion, levobupivacaine is a long acting local anaesthetic with a clinical profile closely resembling that of bupivacaine. Clinical data comparing levobupivacaine with ropivacaine are needed before the drug's role can be fully established. The pharmacoeconomic value of levobupivacaine is also yet to be determined. Nevertheless, the anaesthetic and analgesic properties of levobupivacaine are clearly similar to those of bupivacaine. Importantly, preclinical studies indicate a potential safety and toxicity advantage for levobupivacaine. Excluding pharmacoeconomic considerations, levobupivacaine is an appropriate choice for use in place of bupivacaine.

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