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REVIEW ARTICLE

Clinical Pharmacokinetics and Pharmacodynamics of Levobupivacaine

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Abstract
Levobupivacaine is a long-acting amide local anaesthetic used in analgesia and anaesthesia. Like other local anaesthetic drugs, levobupivacaine exhibits effects on motor and sensory nerves by inhibiting the opening of voltage-gated sodium channels, and hence propagation of neuronal action potentials. Levobupivacaine is the S(−) stereoisomer of dextrobupivacaine, although both are used commercially in the racemic form bupivacaine. A favourable safety and drug effect profile for levobupivacaine has led to widespread use. Levobupivacaine is generally well tolerated but dose adjustment is important in populations such as paediatrics and the elderly. The pharmacokinetic properties of levobupivacaine are similar to that of bupivacaine; both extensively metabolised in the liver, and excreted in the urine and faeces. In vitro, animal model and human studies confirm a lower risk of cardiac and central nervous system toxicity with levobupivacaine compared with bupivacaine. Clinical trials of relative potency are impaired by the variability in chosen endpoints for sensory and motor function blockade, but clinically significant differences in potency are minor, with most clinical trials showing similar duration and quality of anaesthesia between levo- and racemic bupivacaine. In practice, levobupivacaine is most commonly used in regional anaesthesia, neuraxial anaesthesia and local infiltration analgesia. This review includes an appraisal of evidence from clinical trials of the pharmacokinetic and pharmacodynamic properties of levobupivacaine.

1 Introduction

Local anaesthetic (LA) drugs block electrical signal conductivity along nerves by interfering with electrically charged solute flux across the cellular membrane. When LAs are applied to peripheral nerves and sympathetic nerves transmitting nociceptive or motor control signals, the result is provision of an analgesia and motor blockade. These properties are valuable for making surgery tolerable and comfortable for patients. They can also be used to provide pain control during labour, during the postoperative period or as relief therapies for patients with chronic pain syndromes.

Bupivacaine is a well-established LA drug, being included in the World Health Organization's list of essential medicines for healthcare systems; it is safe, effective, inexpensive (being first discovered in 1957 and now available in a generic form) and widely available. The long-acting amino-amide LA agent displays stereoisomerism because of the presence of a chiral centre attached to groups in different spatial orientations. This pair of stereoisomers are optically active and are differentiated by their effect on rotation of polarised light into either clockwise rotation (R+) or anticlockwise rotation (S−). Bupivacaine is commercially available in its racemic form comprising these two enantiomers in a 50:50 ratio, levobupivacaine, (the S− isomer) and dextrobupivacaine (the R + isomer).

Levobupivacaine is used widely in regional anaesthesia, and is marketed as being associated with fewer adverse outcomes and lower toxicity than racemic bupivacaine. The pharmacological profile of levobupivacaine has led to its use in spinal anaesthesia, epidural anaesthesia and analgesia, peripheral nerve blocks, ocular blocks, topic administration and local infiltration [1]. Despite being a widely used drug, several trials investigating the clinical pharmacological profile of levobupivacaine have been published in recent years. The aim of this narrative review is to provide a contemporaneous update on the efficacy, pharmacodynamics and pharmacokinetics of levobupivacaine, alongside

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Key Points

Levobupivacaine is a long-acting amide local anaesthetic, which exerts clinical effects by causing a reversible blockade of open neuronal sodium channels, in a time-dependent and voltage-gated manner. Thus, levobupivacaine produces analgesia and anaesthesia by inhibiting propagation of sensory and nociceptive nerve afferents to the central nervous system. These effects also result in the inhibition of efferent motor nerves.

Bupivacaine is clinically used in two preparations: a racemic form comprising two enantiomers in a 50:50 ratio and levobupivacaine, which is the S(−) isomer.

Levobupivacaine has advantages over racemic and dextrobupivacaine, exhibiting a favourable safety profile, which includes a reduced risk of central nervous system and cardiac toxicity effects. In contrast, evidence for clinical potency indicates the duration and quality of sensory nerve blockade with levobupivacaine is equivalent to bupivacaine, making levobupivacaine advantageous in clinical usage.

an appraisal of evidence for the reputed favourable safety profile of the drug.

2 Methods

A MEDLINE database search was performed using PubMed. The following "levobupivacaine" Medical Subject Heading terms were used: "administration and dosage" OR "pharmacokinetics" OR "Pharmacology" OR "toxicity" OR "adverse effects" OR "analysis". All articles published after 1 January, 1980, in English, with full text available and relating to human subjects were evaluated for relevancy. A full-text copy was obtained for all relevant publications. A further search of the bibliographies of all relevant articles was performed to identify any relevant publications missed during the initial search. Finally, a web search using the "Google Scholar" engine was used, with comparable search terms, to complete the literature search.

3 Pharmacodynamics

3.1 Mechanism of Action

Levobupivacaine attributes its action to the reversible blockade of open neuronal sodium channels, in a time-dependent and voltage-gated manner. Specifically, the drug binds to the intracellular part of the sodium channel and thus interferes with its opening and prevents the sodium influx required for depolarisation. An action potential is therefore interrupted in both motor and sensory nerves. Myelinated nerves are blocked at gaps in the myelin sheath (Nodes of Ranvier), and this occurs more readily than in unmyelinated nerves. Small nerves (such as those transmitting nociceptive signals) in particular are blocked more rapidly than larger motor nerves [2]. At low concentrations, bupivacaine provides a greater level of sensory block than a motor block, which is advantageous in labour and in the post-operative period where paralysis is unwanted [3]. In the presence of levobupivacaine, the threshold for excitation of an action potential is increased, the conduction rate is decreased and the rate of rise and amplitude of an action potential is decreased, resulting in a reduction of the maximum voltage of the action potential. These changes occur in a dose-dependent manner.

Levobupivacaine has a molecular weight of 288.4 g/mol and is a lipid-soluble highly potent LA with a pKa of 8.1, which is similar to that of the racemic bupivacaine. As a weak base, it is largely ionised at physiological pH 7.4, accounting for its slow speed of onset to effective actional potential blockade (usually < 15 min when applied in proximity to a nerve) compared with other LAs such as lidocaine (p*K*a 7.7). Commercial preparations of levobupivacaine present the drug as a hydrochloride salt. All references to doses within this review are for hydrochloride salts, unless otherwise stated. Protein binding is higher (97%) for levobupivacaine than the racemic bupivacaine (95%) and less than 3% circulates free in plasma. Therefore, these are both long-acting LAs with durations that are dose dependent. Levobupivacaine primarily binds to α_1-acid glycoprotein and in conditions where protein levels are low, e.g. nephrotic syndrome, malnutrition and in neonates, the proportion of free unbound drug component is increased. Higher proportions of unbound drug result in a greater risk of side effects and toxicity at lower drug concentrations [4, 5]. Further details regarding toxic mechanisms of levobupivacaine and implications for clinical practice are summarised below and in Sect. 5.

In vitro studies have demonstrated levobupivacaine and bupivacaine to have similar motor and sensory nerve blocking potency [6]. Clinical comparison studies of levobupivacaine nerve blocks have suggested a mixed picture of potency with respect to bupivacaine. Relative potency is difficult to interpret in clinical efficacy studies because doses of LA are generally at the top of the dose–response curve. Instead, most studies compare the minimum local analgesic concentration (MLAC) or median effective dose (ED_{50}), which represent the minimum concentration/dose that provides anaesthetic response in 50% of patients. Such study methodology involves sequentially increasing or decreasing drug dosing in response to effective or ineffective results in the preceding patient. As a consequence, drug doses oscillate

between minimum and maximum values, allowing comparison and extrapolation to a 95% proportion of the sample in whom a desired clinical effect can be expected. However, because the definition and testing modality for adequate sensory blockade varies between trials, direct comparison can be difficult to quantify. Overall, a small number of clinical studies found that levobupivacaine had higher MLAC and ED_{50} values compared with bupivacaine, indicating lower potency, but most indicated equianalgesic effects [7–10].

In human studies, there is a trend towards a longer duration of sensory pain block with levobupivacaine owing to its greater effects of local vasoconstriction compared to dextrobupivacaine [11]. These effects are seen in both peripheral nerve blocks and in epidural administration. With epidural administration, levobupivacaine produced a longer sensory block than a motor block, although these differential results were not observed in peripheral nerve blocks [6].

Like many LA drugs, levobupivacaine exerts a vasoactive effect on blood vessels, with implications for systemic absorption. Drugs that vasoconstrict have a potential clinical advantage by limiting systemic uptake and prolonging the duration of effect. Levobupivacaine has a biphasic action on the local dermal microcirculation around the injection site. Analgesic and anaesthetic doses of levobupivacaine cause rapid dose-dependent vasodilation effects and an increase in skin perfusion. However, this is followed by later minor vasoconstrictive effects, once local drug concentrations reaches subtherapeutic levels [12, 13].

3.2 Side Effects, Adverse Events and Non-neurological Effects

The most common side effects associated with levobupivacaine are hypotension, nausea, vomiting, headache, procedural pain and dizziness [1]. Local anaesthetic systemic toxicity (LAST) is a serious adverse reaction to LAs and occurs in 0.03% of peripheral nerve blocks [14]. During LAST, high doses of LA bind to voltage-gated sodium channels in the central nervous system (CNS) and heart—remote sites from their intended peripheral nerve targets. Individual effects of LAST on these organ systems are discussed below, with further review of risk factors for LAST under Sect. 5. As explained in further detail within this review, single thresholds for plasma concentration toxicity may not be applicable for all patient demographics or circumstances, although plasma concentration thresholds of approximately 2.6 μg/mL have been reputed to represent a common marker for toxicity effects.

Levobupivacaine also demonstrates local tissue toxicity [15]. Injection of LA into the epidural or subdural space can cause neurotoxicity where growth cones collapse and neurite degeneration and neuronal apoptosis can occur, although permanent neurological injury is very rare [16]. Skeletal muscle toxicity is another rare complication of LA, where effects are dose dependent and are likely to be mediated by increased Ca^{2+} levels directly causing myocyte injury. However levobupivacaine is thought to be less myotoxic than bupivacaine [15].

In keeping with growing evidence for other amide LA drugs, levobupivacaine has also been implicated in the rare complication of chondrolysis following an intra-articular injection during arthroscopic orthopaedic surgery [17]. Two in vitro studies have specifically demonstrated a dose-dependent reduction in human chondrocyte cell viability by light spectroscopy following exposure to clinically used concentrations of levobupivacaine [18, 19]. There is currently very limited evidence that single-dose exposure of articular cartilage to levobupivacaine confers a meaningful increase in the risk of chondrolysis, and the effect of repeated injections has yet to be investigated, but prolonged infusions may be associated with tissue toxicity.

In addition to its neuronal effects, limited in in vitro data suggest that levobupivacaine may also exhibit antibacterial properties [20–22]. In keeping with in vitro cultivation findings for several other LA drugs, antibacterial activity of levobupivacaine has been shown on major pathogens involved in infectious complications related to regional analgesia [23, 24]. However, the relevance of this antibacterial effect in vivo is unclear [25] and in vitro effects are less potent for levobupivacaine than racemic bupivacaine [26].

3.2.1 Neurological Signs and Symptoms of Toxicity

The neurological signs and symptoms of LAST typically manifest initially with perioral numbness, metallic taste sensation, tinnitus, agitation, dysarthria and confusion and are followed by more severe CNS effects with increasing toxicity such as reduced consciousness, muscular spasm, tremor, seizure activity, coma and respiratory arrest. These more severe symptoms can also occur in the absence of minor symptoms if injected intravenously or in more highly vascular areas. Neurological signs and symptoms of LAST typically manifest at much lower plasma concentrations than for cardiovascular signs [27] and are therefore the most common presenting feature of toxicity; with seizure activity being reported as the first sign in over half of reports [28]. Case reports of seizures have been described following the administration of levobupivacaine for epidural anaesthesia [27], brachial plexus blocks [29, 30], transversus abdominis plane (TAP) blocks [31] and lumbar plexus blocks [32, 33]. In all these cases, the patients recovered fully with appropriate treatment.

3.2.2 Cardiovascular Signs and Symptoms of Toxicity

Cardiovascular signs of LAST typically follow a biphasic pattern with early excitation phenomena characterised by

tachycardia, hypertension and ventricular arrhythmias followed by myocardial depression with bradycardia, hypotension, conduction block and ultimately asystolic cardiac arrest [34]. Cardiotoxic effects occur most commonly when plasma concentrations increase rapidly or become excessively high, and may also present without CNS signs [35]. Bupivacaine binds cardiac sodium channels in a "fast in/slow-out" fashion, meaning it rapidly binds a large proportion of sodium channels during the cardiac action potential, but releases from the channels quite slowly during diastole, resulting in drug accumulation [36]. This is in contrast to lidocaine, which quickly releases from sodium channels during diastole, and is therefore less likely to cause cardiac toxicity [36].

There are case reports of profound hypotension occurring following the administration of levobupivacaine for epidural anaesthesia [33], caudal anaesthesia [37] and with accidental intravenous (IV) administration [38]. The patients in these cases all responded to treatment with vasoactive drugs and in the first two cases with the administration of intra-lipid. Lipid emulsion is the first-line therapy in LAST, but recent analysis demonstrates that although there is a positive effect on survival in animal models, there is only evidence for a positive pharmacokinetic effect for IV lipid emulsion in humans [39]. There are increasing questions surrounding the clinical efficacy of this treatment and further human data are required to refine the current clinical recommendations [39].

3.2.3 Comparison of Levobupivacaine and Bupivacaine Toxicity Profile

In general, the risk of LAST occurring is greater for longer acting LAs, such as levobupivacaine, than for short acting LAs, such as lidocaine [40]. Numerous non-human studies in regional anaesthesia have shown that levobupivacaine has a decreased risk of CNS toxicity and adverse cardiovascular effects, compared with bupivacaine [4, 40–42]. For example, a study in sheep found that bupivacaine produced convulsions at lower doses than levobupivacaine, and was more likely to cause QRS widening and arrhythmias [40]. In addition, the median lethal dose (LD_{50}) of levobupivacaine has been found to be approximately 50% higher than that of bupivacaine [43, 44].

Levobupivacaine has also been compared to bupivacaine in trials of human volunteers. In a crossover study, levobupivacaine was associated with a smaller decrease in stroke index, acceleration index and ejection fraction compared with bupivacaine [45]. In other studies, levobupivacaine produced less of a negative inotropic effect and less elongation of the PR and QTc interval than bupivacaine [45–47]. A case report of an accidental IV injection of a large dose of levobupivacaine (142.5 mg) during an attempted epidural anaesthetic reported that no arrhythmias or other severe cardiovascular effects were observed [27]. The differences observed between these LAs have been attributed to levobupivacaine having a lower affinity for cardiac sodium channels than the racemic or dextrobupivacaine. However, studies that have compared effects of bupivacaine and levobupivacaine have administered doses at high enough concentrations to elicit CNS symptoms, whereas other studies that have shown no difference in cardiotoxicity were given at non-toxic doses [48, 49].

Cardiac toxicity for bupivacaine enantiomers does not correlate entirely with potency of inhibition of cardiac sodium channels, suggesting an alternate mechanism may also be involved. High bupivacaine concentrations cause abnormal mitochondrial autophagy with inhibition of ATP synthase and negative effects on oxidative phosphorylation and intracellular chemical energy exchange [50]. Levobupivacaine blocks the enzyme carnitine acylcarnitine transferase, which is used for transporting acylcarnitines across the mitochondrial membrane in fatty acids during aerobic metabolism [51]. Longer term exposure to bupivacaine has been shown to induce myopathies in rat and human cell studies, demonstrating structural alterations in muscle, the sarcomere and calcium homeostasis. Hence, cardiotoxic pathophysiology of levobupivacaine is more extensive than a simple extension of the direct intended effects on voltage-gated sodium channel use and treatment of these complications may require consideration of wider pharmacological targets.

Levobupivacaine and bupivacaine can block firing in the nucleus tractus solitarus, resulting in hypotension, bradycardia and arrhythmias. A study in rats showed that the time to maximum decrease in the cell firing rate was significantly longer with levobupivacaine, compared with dextrobupivacaine, suggesting that CNS uptake is slower for levobupivacaine than for dextrobupivacaine [52]. Those rats injected with dextrobupivacaine became apnoeic, whereas those given levobupivacaine continued to breathe, suggesting that there is also enantiomer selectivity in respiratory neurones. Another study in sheep demonstrated that the risk of CNS toxicity was also less in those given levobupivacaine compared with those administered bupivacaine [40]. Lower doses of bupivacaine were able to produce convulsions and CNS excitatory signs were quicker and lasted longer.

In human studies, the risk of CNS toxicity is also lower with levobupivacaine compared with bupivacaine. Both central and peripheral nervous system symptoms were experienced by a greater proportion of volunteers given bupivacaine compared with those administered with levobupivacaine [46]. In another study, a greater dose of levobupivacaine than bupivacaine was required to elicit clinically significant CNS symptoms [45]. In a randomised crossover study of 12 participants, levobupivacaine produced fewer signs of CNS depression on electroencephalography compared with bupivacaine [6]. Given the equivalent

potency and advantageous cardiovascular and CNS toxicity profile of levobupivacaine, there is reason for its preferential clinical use.

4 Pharmacokinetics

4.1 Absorption and Distribution

The absorption of levobupivacaine depends on the dose, route of administration and vascularity of the tissue. These variables influence the maximum plasma concentration reached (C_{max}), the time to maximum concentration (T_{max}) and area under the plasma concentration–time curve (AUC) [46]. The concentration of bupivacaine present in the aqueous portion of plasma is directly related to the myocardial tissue absorption, and hence cardiotoxicity. Maximum plasma concentration is therefore related to the apparent toxicity of levobupivacaine, with highly aerobic tissues, such as the myocardium, CNS and lung, being most vulnerable to toxic effects.

Levobupivacaine pharmacokinetic data are shown in Table 1. Levobupivacaine is not suitable for IV administration in clinical applications (such as may be used to provide anaesthesia to temporarily vascularly isolated limbs, with a Bier's block technique), and is clinically used only via peripheral peri-neural injection, spinal epidural administration or local infiltration. Evidence for absorption and distribution of the drug is derived predominantly from studies analysing systemic absorption from varying injectate sites, with very limited pharmacokinetic compartmental modelling data available. There is growing evidence of patient factors, particularly age and physiological status, as important variables in predicting levobupivacaine pharmacokinetics.

Plasma studies were conducted in young healthy human volunteers, with 40 mg of levobupivacaine being injected intravenously over 4 min. These showed C_{max} reached 1.4 µg/mL with T_{max} at 10.2 min and an AUC of 1.15 mg/L·h [46, 53]. A crossover study of 14 young male volunteers receiving 5 mg/mL of levobupivacaine at an infusion rate of 10 mg/min demonstrated a maximum tolerable plasma concentration of 2.6 µg/mL, at which point evidence of CNS toxicity became apparent; the comparable plasma concentration for racemic bupivacaine was only 2.25 µg/mL [45]. In a surreptitious investigation of accidental IV injection of 142 mg of levobupivacaine 7.5 mg/mL, the serum concentration at 14 min was recorded as 2.7 µg/mL [27]. Following a scalp block for craniotomy, levobupivacaine concentrations rose rapidly, which is consistent with effective vascular supply improving speed of absorption. After a dose of ≤ 40 mL of 5 mg/mL, the C_{max} was 1.58 µg/mL and T_{max} was 12 min [54].

A study further investigated the pharmacokinetic modelling of levobupivacaine using IV and epidural administration. Eight volunteers received 23 mg of both levobupivacaine (2.48 mg/mL) and deuterium-labelled levobupivacaine (2.41 mg/mL) by IV infusion over 15 min. Using venous samples, C_{max} was 574 ng/mL and 557 ng/mL, and using compartmental analysis AUC was 54.7 µg/mL·min and 53.5 µg/mL·min for levobupivacaine and radiolabelled levobupivacaine, respectively [55]. In the same study, 15 surgical patients received epidural administration of 95 mg of levobupivacaine (19 mL at 5 mg/mL) and 25 min later they received IV administration of 25 mg radiolabelled levobupivacaine 0.48 mg/mL at a rate of 5 mL/min. Using arterial samples, C_{max} of levobupivacaine was 1.086 mg/mL and T_{max} was 10.4 min. This study demonstrated that absorption was biphasic, with a small amount of the drug being rapidly absorbed, followed by a slower absorption of the remainder [55].

After a brachial plexus nerve block of 1 and 2 mg/kg, the maximum plasma concentrations were 0.47 and 0.96 µg/mL and the AUC was 3 and 5.31 mg/L·h [53]. The time to C_{max} was 20–40 min after an epidural or brachial plexus block [53, 56]. In patients receiving unusually high dosing of 250 mg of levobupivacaine 5 mg/mL in a posterior lumbar plexus block combined with a sciatic nerve block, the median plasma C_{max} was 2.2 µg/mL and the concentration rose rapidly after the injection [57]. The near toxic C_{max} in this study is likely to be a result of high dosing, with the specific block not particularly associated with rapid vascular absorption of a LA, provided that an intravascular injection is avoided. In patients receiving either a superficial or combined deep and superficial cervical plexus block of levobupivacaine 5 mg/mL at 0.35 mg/kg, C_{max} was 0.58 and 0.52 µg/mL, T_{max} was 30 and 20 min, and AUCs were similar in superficial or combined blocks, respectively [58]. Following a thoracic paravertebral block of 47.5 mg of levobupivacaine 2.5 mg/mL, C_{max} was 0.51 µg/mL and T_{max} was 15 min [4, 59]. In patients receiving a femoral and sciatic nerve block with levobupivacaine 3.75 mg/mL (2.5 mg/kg), the C_{max} was 1.145 µg/mL and T_{max} was 30 min [60].

A TAP block is increasingly being used following abdominal surgery as an alternative to neuraxial LA analgesia, in which the risk of spinal nerve injury is relatively higher (although still, in absolute terms, low at approximately 1:10,000). A randomised control study of patients undergoing gynaecological surgery were given 50 mg of levobupivacaine 2.5 mg/mL bilaterally in a TAP block and C_{max} was 0.99 µg/mL with a T_{max} of 10 min [61]. A study investigating the pharmacokinetics of levobupivacaine in TAP block administration found that after bilateral injection of 50 mg of levobupivacaine 2.5 mg/mL with epinephrine 5 µg/mL, C_{max} was 0.53 µg/mL and T_{max} was 30 min [62]. In another study to compare the effect of epinephrine,

Table 1 Summary of pharmacokinetic characteristics of levobupivacaine in clinical trials

Study (year)	Route of administration	Cohort	Concentration; volume; dose	C_{max} (μg·mL^{-1})	T_{max} (min)	AUC (μg·h·mL^{-1})	*Vd* (L)	$T_{1/2}$ (h)	CL (L/h)	Blood sampling
Corvetto et al. (2012)	US-guided TAP block (unilateral)	11 adults (male) Two-period, two-intervention crossover study	2.5 mg/mL; 20 mL (± 5 μg/mL epinephrine); 50 mg	Venous 0.49 Arterial 0.63	Venous 32 Arterial 21.5	–	–	–	–	Venous and arterial
Ishida et al. (2015)	US-guided TAP block (bilateral)	40 adults (female) Open gynaecological surgery	2.5 mg/mL; 20 mL per side (50 mg per side, 100 mg total)	0.99	10	–	–	–	–	Arterial
Lacassie et al. (2018)	US-guided TAP block (bilateral)	12 adults (female) Elective caesarean section	2.5 mg/mL; 20 mL per side + epinephrine 5 μg/mL (50 mg per side, 100 mg total)	0.53	30	–	–	–	–	Venous
Odor et al. (2019)	US-guided fascia iliaca block	12 adults aged ≥ 80 years Hip fracture	2.5 mg/mL; 30 mL; 75 mg	0.82	45	153.28	–	–	–	Venous
Crews et al. (2002)	Brachial plexus block	19 adults 11 with normal renal function 8 ESRD	5 mg/mL; 50–60 mL; 250–300 mg	1.2 (1.6 ESRD)	55 (48 ESRD)	11	–	–	–	Not stated
Simon et al. (2004)	Intravenous	8 volunteers	23 mg; 2.41 mg/mL; unlabelled 23 mg; 2.48 mg/mL labelled	0.574 0.557		0.9 0.89	62 64	–	27.9 28.5	Venous
	Epidural and intravenous	15 patients	5 mg/mL; 19 ml; 95 mg 0.48 mg/mL; 5 mL/min; 25 mg	1.1	10		56		20.9	Arterial
Costello et al. (2005)	Scalp	10 adults Elective neurosurgery	5 mg/mL; ≤ 40 mL; (± 5 μg/mL epinephrine); ≤200 mg	1.58	12	–	–	–	–	Arterial

Table 1 (continued)

Study (year)	Route of administration	Cohort	Concentration; volume; dose	C_{max} (μg·mL^{-1})	T_{max} (min)	AUC (μg·h·mL^{-1})	*Vd* (L)	$T_{1/2}$ (h)	CL (L/h)	Blood sampling
Chalkiadis et al. (2004)	Caudal	49 children (aged < 2 years) Elective subumbilical surgery (circumcision, inguinal hernia repair, orchidopexy)	2.5 mg/mL; 2 mg/kg	0.91	30	–	–	–	–	Venous
Chalkiadis et al. (2005)	Caudal	22 infants (< 3 months old) Elective subumbilical surgery	2.5 mg/mL; 2 mg/kg	0.69 (0.09 unbound)	49	–	202 L per 70 kg (1700 unbound)	–	12.8 L/h per 70 kg (104 unbound)	Venous
Ala-Kokko et al. (2005)	Ilioinguinal-iliohypogastric nerve block	20 children	2.5 mg/mL; mg/kg	1.85	28	2.4	–	–	–	Venous
Ala-Kokko et al. (2002)	Ilioinguinal-iliohypogastric nerve block	20 children	5 mg/mL; mg/kg	2.2	24	–	–	3.6	–	Venous
Gristwood et al. (1999)	Intravenous	11 volunteers	40 mg over 8 min	1.4	10	1.15	67	1.3	39	Not stated
Faccenda et al. (2003)	Epidural	9 patients	5 mg/mL; 15 mL; 75 mg	0.58	22.2	3.56	–	–	–	Not stated
		9 patients	7.5 mg/mL; 15 mL; 12.5 mg	0.81	17.4	4.93				
Bader et al. (1999)	Epidural	10 patients	5 mg/mL; 30 mL; 50 mg	1.02		4.08	–	–	–	Venous
Kopacz et al. (2000)	Epidural	10 patients	7.5 mg/mL; 20 mL; 150 mg	0.84	24	5.32	–	–	–	Venous
Purdue (1999)	Brachial plexus block	10 patients	2.5 mg/mL; 1 mg/kg	0.47	30	3	–	–	–	Not stated
		10 patients	5 mg/mL; 2 mg/kg	0.96	42.6	5.31				
Pintaric et al. (2008)	Cervical plexus block	Superficial: 7 patients Deep and superficial: 5 patients	5 mg/mL; 0.35 mg/kg 5 mg/mL; 0.35 mg/kg	0.58 0.52	30 20	21.0 21.1	–	–	–	Venous
Burlacu et al. (2007)	Thoracic paravertebral block	13 patients	2.5 mg/mL; 19 mL; 7.5 mg	0.51	15	–	–	–	–	Venous

Table 1 (continued)

Study (year)	Route of administration	Cohort	Concentration; volume; dose	C_{max} (μg·mL^{-1})	T_{max} (min)	AUC (μg·h·mL^{-1})	*Vd* (L)	$T_{1/2}$ (h)	CL (L/h)	Blood sampling
Altermatt et al. (2006)	Posterior lumbar plexus and sciatic nerve block	5 patients	5 mg/mL; 30 + 20 mL; 50 mg	2.2	–	–	–	–	–	Arterial
Sola et al. (2019)	TAP block	65 children	4 mg/mL; 0.4 mg/kg	0.389	25	$AUC_{0–75}$ 918	–	–	–	Venous
			2 mg/mL; 0.4 mg/kg	0.370	20	1008				
Chen et al. (2018)	Femoral and sciatic nerve block	6 patients	3.75 mg/mL; 2 mg/kg	1.145	30	$AUC_{0–infinity}$ 30	170		25.8	Venous
El-Shaarawy et al. (2018)	Epidural	51 patients	0.625 mg/mL; 15 mL	0.09	–	0.49	–	–	–	Venous
			1.25 mg/mL; 15 mL							
			2.5 mg/mL; 15 mL	0.19		1.2				
			Then 10-mL/h infusion	0.28		1.1				
Frawley et al. (2016)	Spinal	25 children (36–52 weeks post-menstrual age)	5 mg/mL; 1 mg/kg	0.34	30	–	–	–	–	Venous

AUC area under the plasma concentration–time curve, *CL* clearance, C_{max} maximum plasma concentration, *ESRD* end-stage renal disease, *TAP* transversus abdominis plane, T_{max} time to maximum plasma concentration, $T_{1/2}$ elimination half-life, *US* ultrasound, *VD* volume of distribution

50 mg of levobupivacaine 2.5 mg/mL was injected with or without epinephrine 5 µg/mL. The arterial C_{max} was 0.36 and 0.63 µg/mL, the venous C_{max} was 0.32 and 0.49 µg/mL, and the mean duration of the block was 10.2 and 10.3 h with and without epinephrine, respectively [63]. The arterial T_{max} was 21.5 min and venous T_{max} was 32 min [63]. Studies have since shown that epinephrine prolongs the absorption half-life and reduces its bioavailability and therefore has been recommended to be given with levobupivacaine TAP blocks to reduce toxicity and allow for higher doses to be injected [64]. Vasoconstrictor adjuncts are frequently used in clinical situations to reduce systemic absorption during regional anaesthesia with many LA drugs, with considerable evidence demonstrating similar specific effects for levobupivacaine combined with epinephrine [13, 62].

To delay the absorption of LAs, there have been studies investigating the use of encapsulating LAs within carrier molecules such as multivesicular liposomes. This preparation increases the duration of the drug and delays the peak plasma concentration. This method has been useful in the management of post-operative pain via local infiltration, but thus far is only available for bupivacaine, not levobupivacaine [65].

Although levobupivacaine is highly bound to plasma proteins, the drug is highly lipid soluble, resulting in widespread redistribution of the drug in the steady state. In one study, the volume of distribution of levobupivacaine was estimated to be 66.9 ± 18.2 L (following the IV administration of 40 mg in healthy participants) [46, 53]. In another study involving the IV administration of 25 mg of radiolabelled levobupivacaine at 0.48 mg/mL, the steady-state volume of distribution was 56 L [55]. This same study administered 23 mg of both levobupivacaine (2.48 mg/mL) and deuterium-labelled levobupivacaine (2.41 mg/mL) by IV infusion over 15 min and found the volume of distribution at steady state to be 62 L and 64 L for levobupivacaine and radiolabelled levobupivacaine, respectively [55]. In patients receiving a femoral and sciatic nerve block with levobupivacaine 3.75 mg/mL (2.5 mg/kg), the volume of distribution was 170 L [60].

The pharmacokinetic properties of levobupivacaine are similar to that of bupivacaine. Several studies comparing plasma concentrations following administration have found similar concentrations for both drugs [45, 46, 49] but others have found slightly higher concentrations of levobupivacaine compared with bupivacaine [56, 66]. Following administration of bupivacaine, total plasma concentrations of levobupivacaine were higher than dextrobupivacaine [41, 66, 67]. However, levobupivacaine has a higher unbound clearance rate, shorter elimination half-life, smaller volume of distribution, and decreased affinity to brain and myocardial tissues than dextrobupivacaine and these differences may explain their different toxicity profiles [68]. In contrast, systemic absorption does not appear to differ between enantiomers [67].

Finally, distribution of levobupivacaine may also be influenced by pre-treatment with IV lipid emulsion, which is more conventionally used as an emergency rescue therapy for LAST. Intravenous lipid emulsion is commercially available as Intralipid 20%, which consists of 20% purified soybean oil, 1.2% purified egg phospholipids and 2.2% anhydrous glycerol. A small, single-blind human volunteer study demonstrated C_{max} levobupivacaine concentrations were lower in an Intralipid group, who received a pre-loading dose of 1.5 mL/kg of Intralipid, than in control subjects (0.87 ± 98 vs 1.15 ± 177 µg/mL).

Although poorly defined by in vitro studies, the current hypothesis for lipid emulsion therapy efficacy in reducing systemic distribution and availability of levobupivacaine is the formation of a "lipid sink", which consists of an intravascular expanded lipid phase to absorb circulating lipophilic toxins. This theory states that highly lipid-soluble drugs, including levobupivacaine, are absorbed into the added lipid emulsion within plasma and therefore removed from tissues affected by toxicity. Animal models have shown increased washout of bupivacaine from myocardial tissues in the presence of lipid emulsion therapy [69], with lipid emulsion producing a concentration-dependent reduction in bupivacaine concentrations and a better early response than late response during recovery. In addition, it is postulated that an additional metabolic protective effect may also be a reason for preservation of cardiac activity. The fatty acid substrate of lipid emulsion therapy may act as a direct energy substrate for mitochondrial ATP production in myocardial cells, countering the deleterious effect of LAs on oxidative phosphorylation.

4.2 Metabolism and Excretion

Levobupivacaine is extensively metabolised into inactive metabolites by N-dealkylation and glucuronide conjugation in cytochrome P450 (CYP), primarily by CYP1A2 and CYP3A and then excreted in the urine and faeces [46]. Therefore, hepatic dysfunction or reduction in hepatic blood flow by disease or hypotension can lead to poor elimination of this drug. For example, a lower clearance following an intercostal neural blockade with both enantiomers was observed in liver transplant patients [70]. In addition, the metabolism of levobupivacaine can be increased or reduced by CYP inducers or inhibitors, respectively. Following the administration of 200 mg of oral itraconazole, a CYP3A4 inhibitor, the clearance of levobupivacaine after administration of IV bupivacaine was reduced by 25% [71].

The major metabolite of levobupivacaine is 3-hydroxy-levobupivacaine (the minor being desbutyl-levobupivacaine) and this is converted into glucuronic acid and sulphate ester

conjugates that are excreted in the urine [6]. Levobupivacaine does not undergo racemization in vivo [42]. Hepatic metabolism is extensive and no unchanged levobupivacaine is found in the urine. Resultantly, in renal dysfunction, levobupivacaine does not accumulate but the inactive metabolites do. Following IV administration of a single radiolabelled dose of levobupivacaine, 71% was found to be excreted in urine, and 24% in faeces [6]. There are few data surrounding the use of levobupivacaine in patients with hepatic impairment. However, a study compared patients undergoing major liver resection with those undergoing rectal resection (controls), and showed that following intraoperative epidural anaesthesia with levobupivacaine and postoperative epidural analgesia with levobupivacaine, those that had undergone liver resection revealed significantly higher levobupivacaine concentrations. This implies a risk of levobupivacaine accumulation in patients with poor hepatic function [72]. Exact specifications for levobupivacaine dose adjustment in liver impairment remain unclearly defined by current research.

Several studies have formally assessed the clearance of levobupivacaine in vivo. Following the intravenous administration of 40 mg of levobupivacaine in healthy participants, the half-life was around 80 min and the rate of clearance was 651 ± 221.5 mL/min [46, 53]. In volunteers receiving 23 mg of both levobupivacaine (2.48 mg/mL) and deuterium-labelled levobupivacaine (2.41 mg/mL) by IV infusion over 15 min, using compartmental analysis, clearance was 465 and 475 mL/min for levobupivacaine and radiolabelled levobupivacaine, respectively [55]. In the same study, patients received IV administration of 25 mg of radiolabelled levobupivacaine 0.48 mg/mL at a rate of 5 mL/min and clearance was 349 mL/min and the elimination half-life was 196 min [55]. In patients receiving a femoral and sciatic nerve block with levobupivacaine 3.75 mg/mL (2.5 mg/kg), the clearance was 430 mL/min [60].

4.3 Renal Impairment

There are limited data describing the pharmacokinetics of levobupivacaine in renal failure. A study comparing administration of 250–300 mg of levobupivacaine in an axillary brachial plexus block in patients with unimpaired renal function ($n = 20$) to those with end-stage renal disease ($n = 8$) found that there was no difference in onset, duration and quality of the block or pharmacokinetic properties [73]. The median time to sensory block was 12.5 and 12.9 min and the mean duration of the block was 19 h and 22 h in patients with unimpaired renal function patients and patients with end-stage renal disease, respectively. The AUC was 11 and 13 µg/mL·h, C_{max} was 1.2 and 1.6 µg/mL, and T_{max} was 55 and 48 min in patients with unimpaired renal function and those with end-stage renal disease, respectively [73]. Given the small size of this study, it is difficult to extrapolate this for the management of all patients with renal disease.

4.4 Paediatric Patients

Safe dose adjustment is required in paediatric patients given that their metabolic processes can be relatively immature. It is therefore important to separately investigate the pharmacokinetic profile of levobupivacaine in children. Whilst it is true that peak plasma concentrations of LA drugs are inversely related to patient weight and body mass index, the strength of association is far greater for children than adults. Although levobupivacaine is not commonly used in the context of paediatric dentistry, this generalised relationship has particular relevance in the infiltration of other local anaesthesia for dentistry, during which the dose-to-weight ratio can be more difficult to calculate for patients and thus potential excessive dosing and LAST is more likely. Likewise, early signs of systemic toxicity, including paraesthesia and mental state changes can be more challenging to detect in young children.

A study investigating ilioinguinal-iliohypogastric nerve blocks in children aged between 2 and 16 years undergoing elective inguinal surgery, randomised assigned patients to receive either 5 mg/mL of bupivacaine or 7.5 mg/mL of ropivacaine [74]. The C_{max} was significantly higher in the bupivacaine group than the ropivacaine group, 2.2 vs 1.2 µg/mL, the T_{max} was significantly shorter, 24 vs 35 min, and the initial distribution half-life of bupivacaine was significantly shorter (3.6 vs 6.5 min) [74]. In children aged between 2 and 10 years, receiving an ilioinguinal-iliohypogastric nerve block of levobupivacaine 5 mg/mL (2 mg/kg), the mean C_{max} was 1.85 µg/mL, the AUC was 2.4 µg/mL·h and T_{max} was 28 min [75]. Other blocks have also been investigated. In children receiving a TAP block of 0.4 mg/kg of levobupivacaine either as 0.2 mL/kg, 2 mg/mL or 0.1 mL/kg 4 mg/mL, the pharmacokinetic profile was comparable. The C_{max} was 379 ng/mL and T_{max} was 22.5 min [76].

Children undergoing spinal anaesthesia may develop the same adverse effects as adults, such as post-dural puncture headache and transient focal neurological deficits. However, cardiovascular compromise, with hypotension and bradycardia, is more uncommon as a result of differences in autonomic response to sympathetic blockade [77]. Caudal administration in paediatric patients has been investigated in several studies. In children under 2 years of age, caudal epidural administration of 2.5 mg/mL of levobupivacaine at 2 mg/kg revealed a mean C_{max} of 0.91 µg/mL and a median

T_{max} of 30 min, which was longer in infants aged less than 3 months [78]. This disparity was further investigated in infants less than 3 months old, where caudal epidural administration of levobupivacaine 2.5 mg/mL, at 2 mg/kg, resulted in C_{max} of 0.69 and 0.09 μg/mL for total and unbound levobupivacaine, respectively, and T_{max} of 0.82 h [79]. Clearance was 213.3 mL/min/70 kg and 1733 mL/min/70 kg (standardized to a 70-kg adult using allometric non-linear size models) and volume of distribution was 202 L/70 kg and 1700 L/70 kg for total and unbound levobupivacaine, respectively [79]. Volume of distribution was larger than in adults but the clearance in infants was approximately half that of adults, suggesting the immaturity of liver enzymes CYP3A4 and CYP1A2 that metabolise levobupivacaine. These data also suggested that the reduced clearance contributes to a delayed T_{max} [79].

To study the pharmacokinetic modelling of levobupivacaine in infants, a caudal-epidural loading dose and infusion was given to infants between 3 and 6 months of age, and total serum levobupivacaine concentration was measured at various times. After a 2-mg/kg loading dose, the serum concentration was 0.3 mg/L 1 h later and was 1.21 mg/L 47 h later following an infusion at 0.2 mg/kg/h. This study also found that unbound levobupivacaine quickly reached its steady-state concentration of 0.03 mg/L once the infusion was started [80]. In another study of caudal epidural administration in children < 18 years of age, 2.5 mg/mL of levobupivacaine was administered with epinephrine 5 μg/mL or clonidine 2 μg/mL or a combination, though the total volume of solution (and therefore total dose of LA and adjuvant) given was at the discretion of the anaesthetist. Absorption was faster when mixed with clonidine and slower when mixed with epinephrine, reducing the peak concentration by a half. Epinephrine gave a bifid absorption profile and the addition of clonidine had a minimal effect on this pattern. Neither epinephrine nor clonidine had any effect on clearance and the volume of distribution was estimated at 157 L/70 kg. Clearance was 6.5 L/h/70 kg at 1-month post-natal age and reached 18.5 L/h/70 kg by 5 months post-natal age, which is 90% of the mature value [81]. In a study of infants aged 36–52 weeks post-menstrual age receiving spinal anaesthesia with 1 mg/kg of levobupivacaine, the total plasma concentration was 330 ng/mL, the T_{max} was 30 min and the unbound concentration was 19.5 ng/mL [82].

Spinal anaesthesia has also been investigated in older children and adolescents. One group found that aspiration of 1–3 mL of cerebrospinal fluid prior to injection of levobupivacaine did not affect the spread or duration of the sensory block or side effects following spinal anaesthesia in children aged around 7.5 years [83]. Another study showed that levobupivacaine 5 mg/mL at a dose of 0.3 mg/kg has equivalent clinical efficacy to that of racemic bupivacaine when used in spinal anaesthesia [84].

4.5 Elderly Patients

Pharmacokinetics of levobupivacaine is affected by age, but has been investigated by only a few studies thus far. Age and comorbidities are particularly relevant when considering vulnerability to LAST. Cardiac pathology is of greater prevalence in the elderly, with ischaemic heart disease, conduction blocks and cardiac failure giving patients less myocardial reserve when impaired by systemic LA adverse actions. Likewise, the presence of renal and hepatic disease is also more common in the elderly. Homeostatic disturbance to physiological parameters, such as acid-base status, hypoxia and hypercarbia, can potentiate toxic effects on bupivacaine; all of which are more common in the elderly or unwell patient [85].

Following epidural administration of levobupivacaine observed in patients aged > 70 years, there was a lower fraction absorbed, a shorter initial absorption phase and a higher spread of analgesia compared with those aged 18–44 years [86]. In elderly patients receiving a fascia iliaca compartment block with 75 mg of levobupivacaine (30 mL 2.5 mg/mL), the C_{max} was 0.82 μg/mL, the T_{max} was 45 min and the AUC was 153.3 μg/mL·h [34]. No toxicity was observed, perhaps partly owing to slow absorption, and plasma concentrations were below the toxicity threshold associated with younger patients [34].

4.6 Obstetric Patients

Pregnancy is accompanied by physiological changes that result in the modification of pharmacokinetic properties of drugs. Bupivacaine and levobupivacaine are commonly used in labour and during a caesarean section and their interaction with organs and systems and their placental passage is important to evaluate before use. A study compared the effect of bupivacaine use in spinal anaesthesia on QTc interval in term and post-term pregnant women undergoing an elective caesarean section. They found that post-operative QTc was increased in patients with a gestational age of ≥ 42 weeks, making them more susceptible to arrhythmias. Prolonged careful cardiovascular monitoring is therefore required following induction of spinal anaesthesia particularly in this patient group [87]. Another study compared spinal anaesthesia with bupivacaine and levobupivacaine in patients scheduled for an elective caesarean section and found that the mean minimum and maximum QTc interval was higher in those receiving levobupivacaine. However, in the bupivacaine group, the maximum QTc was longer than levobupivacaine [88].

With respect to its pharmacokinetics, following epidural administration of 75–150 mg of levobupivacaine, the C_{max} were 0.58–1.02 μg/mL and AUC was 3.56–5.32 mg/L·h [49, 56, 66]. In another study, 15 mL of levobupivacaine,

combined with 2 µg/mL of fentanyl, was administered via the epidural route to pregnant women in three different concentrations followed by an infusion of this mixture at 10 mL/h. The mean C_{max} levels were 0.09, 0.19 and 0.28 µg/mL and AUC was 0.49, 1.2 and 1.1 µg/mL·h for 0.625 mg/mL, 1.25 mg/mL and 2.5 mg/mL of levobupivacaine, respectively [89]. This study determined terminal half-lives were 249, 299 and 270 min with clearances of 725, 668 and 813 mL/min for 0.625 mg/mL, 1.25 mg/mL and 2.5 mg/mL of levobupivacaine, respectively [89].

Given its high lipid solubility, levobupivacaine easily crosses the placenta [90]. Following the administration of 150 mg of levobupivacaine 5 mg/mL via the epidural route to women undergoing elective caesarean section, the umbilical vein/maternal vein drug concentration ratio was 0.3 and 0.25 for bupivacaine at the same dose [49]. However, placental transfer has not been associated with significant adverse effects in the foetus.

Another study evaluating placental transfer of levobupivacaine and bupivacaine in healthy pregnant women receiving epidural anaesthesia for an elective caesarean section found that the concentration of levobupivacaine in the maternal plasma were higher than the dextrobupivacaine concentrations but that there was no difference in concentrations in umbilical foetal vessels. The placental transfer was calculated to be 31% for levobupivacaine and 33% for dextrobupivacaine. The concentrations of levobupivacaine were 3.5 and 3.8 times higher in the placental intervillous space than in the umbilical vein and artery, respectively. In comparison, the concentrations of dextrobupivacaine were 2.9 and 3.16 times higher in the placental intervillous space than the foetal umbilical vein and artery, respectively [91].

5 Tolerability and Safety

Racemic bupivacaine has been used in clinical practice for over half a century and, as a result, has a comprehensive record for safety-related incidents [44]. As previously described, levobupivacaine has a marginally lower efficacy to racemic bupivacaine but with evidence of reduced cardiotoxicity and neurotoxicity [44].

5.1 Tolerability

Early phase II/III clinical trials demonstrated the safety of levobupivacaine in clinical use [53]. These trials, with a total of 1141 patients, demonstrated its use in epidurals for labour and post-operative analgesia, obstetric and non-obstetric surgery, peripheral nerve blockade and local infiltration.

Common adverse events, occurring with a frequency > 5% with levobupivacaine are reported by the manufacturer to be: hypotension (31%), nausea (21%), post-operative pain (18%), fever (17%), vomiting (14%), anaemia (12%), pruritus (9%), pain (8%), headache (7%), constipation (7%), dizziness (6%) and foetal distress (5%) [53]. The incidence of these events are characteristic of other amide-type LAs and are directly comparable to racemic bupivacaine [53] and ropivacaine [92]. It is important to note that the association of adverse events following use of levobupivacaine does not imply causality and many of the reactions cited are likely related to the underlying patient condition and other anaesthetic or surgical factors.

5.2 Risk Factors for Local Anaesthetic Toxicity

In summary, the risk of developing LAST is dependent on a number of factors relating to both the delivery of LA to myocardial or cerebral tissue and the predisposition of these tissues to the deleterious effects of the LA in question. There is a dose–response relationship between the plasma concentration of a LA and its systemic toxicity, though this relationship is neither simple nor monotonic and depends on a number of factors including the rate of change of plasma concentration [93] and the toxic potential of the LA in question. The primary determinants of the rate of plasma uptake are the dose of LA [94] and the site and speed of injection, with intravascular administration producing the fastest change in plasma concentration followed by administration to vascular-rich tissue beds [14].

It is the non-protein bound fraction of LA that is active and factors that influence the degree of protein binding will alter its toxicity [93]. The protein binding of LAs is concentration dependent, with higher concentrations being associated with a higher unbound fraction [93]. Other important factors influencing protein binding include the concentration of carrier proteins for LAs, primarily α_1-acid glycoprotein, and the acid-base balance [93]. Changes in protein binding in pregnancy, extremes of age, acute illness and other pathological conditions will therefore influence the likelihood of toxicity [14].

There are a number of pathological and physiological patient conditions that predispose to the toxic systemic effects of LAs. Elderly patients and those with underlying cardiac conduction abnormalities or severe heart failure, for example, will be more prone to toxicity [94, 95]. Hypoxia, hypercarbia and acidaemia also predispose cells to the toxic effects of local anaesthesia and has been demonstrated in animal studies [85]. Reduced metabolism of LAs, as a result of physiological or pathological changes, such as hepatic or renal failure, or concurrent drug use may also increase toxicity by reducing their clearance from at-risk tissues [94, 95].

5.3 Clinical Practice: Using Local Anaesthetics Safely

A number of steps can be taken in clinical practice to reduce the risk of the development of systemic toxicity, of which an inadvertent IV injection is a major cause. These are well summarised in the 2017 American Society of Regional Anaesthesia practice advisory [96]. These guidelines suggest the use of the lowest effective dose of LA with administration in discrete aliquots over a period of time, the aspiration of the needle or catheter before each injection, the inclusion of an appropriate dose of intravascular marker (such as epinephrine or fentanyl) that may provide earlier evidence of intravascular injection and the use of ultrasound guided infiltration where practicable [96].

There are well-established guidelines for the management of LAST that are provided by both the Anaesthetic Association of Great Britain and Ireland and American Society of Regional Anaesthesia [96, 97]. These guidelines detail the recognition of toxicity, supportive management, seizure control with benzodiazepines and administration of IV lipid emulsion.

6 Levobupivacaine in Current Anaesthetic Practice for Surgery

Local anaesthetics are used during the perioperative period to block nerve transmission at three principal sites: neuraxial blockade via spinal or epidural anaesthesia (termed "central" blockade), injection around a plexus, group or single peripheral nerve ("regional"), or "locally" via intra-articular, surgical site or dental infiltration.

6.1 Neuraxial Anaesthesia in Non-obstetric Surgery

Trial data exist for levobupivacaine use in spinal anaesthesia and both thoracolumbar and caudal epidural anaesthesia. The choice of neuraxial anaesthetic technique depends on a number of factors, including patient and surgical characteristics, the required density and extent of nerve blockade, and considerations regarding the speed of onset and duration of nerve blockade [98].

6.1.1 Spinal Anaesthesia

A number of randomised control trials have compared different regimes of levobupivacaine with both racemic bupivacaine and ropivacaine (summarised in Table 2). These studies compare the onset and offset of sensory and motor blocks, as well as providing a measure of the adequacy of anaesthesia and have been conducted in orthopaedic [99–102], urology [103–107] and general surgical [108] patients. Although these comparative studies have been conducted in adult populations, there is evidence that spinal anaesthesia in paediatric populations is both safe and effective [84, 109].

Spinal levobupivacaine is equally as efficacious as bupivacaine and ropivacaine with no significant difference in the quality of surgical block or post-operative analgesia [99–101, 103]. Data from trials suggest that the speed of the onset and offset of a spinal blockade correlates with the dose of LA used, though some studies found that the duration of sensory block is prolonged with levobupivacaine as compared with bupivacaine [105, 108] and ropivacaine [102, 104, 108]. A further study suggests that levobupivacaine has a faster block onset and offset when administered as a hyperbaric solution [106].

One study has described the dose response of spinal levobupivacaine, finding that the minimum LA dose (MLAD) of levobupivacaine was 11.7 mg, compared with that of 12.8 mg for ropivacaine [110]. In infants, another trial found the ED_{50} doses for bupivacaine, levobupivacaine and ropivacaine were 0.30 mg/kg, 0.55 mg/kg and 0.50 mg/kg respectively, with ED_{95} doses of 0.96 mg/kg, 1.18 mg/kg and 0.99 mg/kg, respectively [111].

A number of studies demonstrate that the addition of an opioid significantly reduces the required dose of intrathecal levobupivacaine [105, 112, 113] and a meta-analysis by Popping et al. concluded that the extent of this reduction in dose is about 40% [114]. A trial by Karsli et al. found that the ED_{50} and ED_{95} of levobupivacaine co-administered with 25 µg of fentanyl were 7.32 mg and 10.88 mg, respectively [113]. Other studies describe dose reductions with the addition of intrathecal clonidine [115] and enhancement and prolongation of a block with intrathecal dexamethasone [116], both of which appear to be safe in clinical practice [117, 118].

A number of randomised controlled trials found a shorter duration of motor block with spinal levobupivacaine compared with bupivacaine [102, 108], though ropivacaine seems superior in this regard [100, 102, 104]. Other common side effects reported in trials include hypotension, bradycardia, shivering, nausea and vomiting, though there seems to be no difference in incidence between levobupivacaine, bupivacaine and ropivacaine [102, 103, 106].

6.1.2 Thoracolumbar Epidural Anaesthesia and Post-operative Analgesia

Local anaesthetics can be administered via the thoracolumbar epidural route to provide both anaesthesia for surgery and post-operative analgesia. A number of randomised controlled trials compare the use of levobupivacaine with racemic bupivacaine and ropivacaine [66, 119–123], comparing

Table 2 Randomised controlled trials for spinal anaesthesia with levobupivacaine (LEV)

Study (year)	Surgical population	Drug (volume)	*N*	Mean time (min) ± SD, unless otherwise stated				Comments
				Sensory block onset[a]	Sensory block duration[b]	Motor block onset[c]	Motor block duration[d]	
Glaser et al. (2002)	Elective hip replacement	LEV 5 mg/mL (3.5 mL)	39	11 ± 6	228 ± 77	10 ± 7	280 ± 84	No significant differences
		BUP 5 mg/mL (3.5 mL)	40	13 ± 8 [maximum]	237 ± 88 [by 2 levels]	9 ± 7 [Bromage ≥ 1]	284 ± 80 [Bromage 0]	No significant differences in post-operative pain
Cappelleri et al. (2005)	Elective knee arthroscopy	LEV 5 mg/mL (1.0 mL)	30	10	–	–	150	No significant differences in post-operative pain
		LEV 5 mg/mL (1.5 mL)	30	11	–	–	162	
		ROP 5 mg/mL (1.5 mL)	31	10 [to T12]	–	–	135* [Bromage 0]	
Fattorini et al. (2006)	Elective knee replacement	LEV 5 mg/mL (3.0 mL)	29	12 ± 6	230 ± 78	11 ± 6	256 ± 86	No significant difference
		BUP 5 mg/mL (3.0 mL)	30	9 ± 5 [maximum]	222 ± 69 [to L2]	8 ± 4 [maximum]	245 ± 86 [to mobility]	No significant differences in post-operative pain
Bhatt et al. (2018)	Elective lower limb orthopaedic surgery	LEV 5 mg/mL (3.0 mL)	30	3.2 ± 1.5	60** ± 7	3.6 ± 1.8	170** ± 16	No significant difference in side effects
		ROP 5 mg/mL (3.0 mL)	30	3.0 ± 1.2 [to L1]	47 ± 4 [by 2 levels]	3.3 ± 1.2 [Bromage ≥ 1]	140 ± 10	
Vanna et al. (2006)	Transurethral resection of prostate	LEV 5 mg/mL (2.5 mL)	35	10	140	8	192	No significant difference
		hBUP 5 mg/mL (2.5 mL)	35	7 [to T10]	133 [by 2 levels]	5	154 [Bromage < 3]	No significant difference in pain scores or side effects
Mantouvalou et al. (2008)	Varicocoele surgery	LEV 5 mg/mL (3.0 mL)	39	11	230	11	273	More hypotension in bupivacaine group
		BUP 5 mg/mL (3.0 mL)	39	13	237	8*	278	
		ROP 7.5 mg/mL (3.0 mL)	39	12 [to T8]	220* [to recovery]	12	269*	
Erbay et al. (2010)	Transurethral resection of prostate	hLEV 5 mg/mL (1.5 mL) + fentanyl 25 μg	30	5 ± 2	157** ± 34	12** ± 5	105* ± 19	Post-operative analgesia requested at 389 and 305 min*
		hBUP 5 mg/mL (1.5 mL) + fentanyl 25 μg	30	6 ± 1 [to T10]	127 ± 14 [to recovery]	7 ± 3	113 ± 7	2-segment regression not significant
Sen et al. (2010)	Transurethral resection of prostate	hLEV 4.5 mg/mL (3.0 mL)	25	5**	65*	3*	60*	No significant difference in 2-segment regression
		LEV 4.5 mg/mL (3.0 mL)	24	7 [to T10]	100 [to L1]	6 [Bromage ≥ 1]	90	No significant difference in side effects

Table 2 (continued)

Study (year)	Surgical population	Drug (volume)	*N*	Mean time (min) ± SD, unless otherwise stated				Comments
				Sensory block onset[a]	Sensory block duration[b]	Motor block onset[c]	Motor block duration[d]	
Akan et al. (2013)	Transurethral resection of prostate	LEV 5 mg/mL (2.0 mL)	19	10.2* ± 2.0	64 ± 13	–	153* ± 38	Post-operative analgesia requested at 217, 310, and 332 min*
		LEV 5 mg/mL (1.5 mL) + fentanyl 25 µg	19	6.9 ± 1.7	62 ± 14	–	100 ± 22	
		LEV 5 mg/mL (1.5 mL) + sufentanil 2.5 µg	20	7.0 ± 1.4 [to T10]	64 ± 11 [by 2 levels]	–	103 ± 24	
Casati et al. (2004)	Inguinal hernia repair	hLEV 5 mg/mL (1.6 mL)	20	10 ± 5	210 ± 63	–	84%	All sensory blocks 100% effective
		hBUP 5 mg/mL (1.6 mL)	20	10 ± 4	190 ± 51	–	55%*	
		ROP 5 mg/mL (2.4 mL)	20	10 ± 6 [to T10]	166* ± 42 [to recovery]	–	95% [Bromage 0 at 180 min]	

BUP bupivacaine, *hBUP* hyperbaric bupivacaine, *hLEV* hyperbaric levobupivacaine, *ROP* ropivacaine, *SD* standard deviation

*Reaches statistical significance at $p < 0.05$

**Reaches statistical significance at $p < 0.001$

[a]Sensory block onset is defined as the time of loss of pinprick sensation at [the specified level]

[b]Sensory block duration is defined as the time for regression of block to [the specified level] or by two dermatomal levels

[c]Motor block onset, where assessed, is defined as the time for motor weakness to reach the specified [modified Bromage scale]

[d]Motor block duration is defined as the time for resolution of motor block to the [the specified level], unless stated

the onset and offset of sensory block, duration of motor block and efficacy of post-operative analgesia (see Table 3).

Epidural levobupivacaine provides equally effective intra-operative anaesthesia and post-operative analgesia [66, 119, 121–123], compared to racemic bupivacaine and ropivacaine. Most trials demonstrate no significant differences between the onset or duration of the sensory block or duration of the motor block between levobupivacaine, bupivacaine and ropivacaine, though Kopacz et al. found a slightly prolonged sensory block with levobupivacaine over bupivacaine [66].

Increasing the concentration of a particular volume of epidural levobupivacaine prolongs sensory block duration [119] and delays the time needed until rescue analgesia [120], though at the expense of increased motor block [119, 120]. There is a paucity of data with regard to non-obstetric use of epidural levobupivacaine and no published studies have looked to establish either an effective dose or MLAC in a different surgical population.

For post-operative analgesia, a LA can be delivered as a continuous epidural infusion, running at a fixed rate, or as a patient-controlled epidural infusion (PCEA), where the patient is able to control the delivery of a set volume of epidural mixture limited by a pre-programmed pump lock-out time. A trial by Ball et al. found that use of a continuous epidural infusion of levobupivacaine provided better post-operative analgesia than local wound infiltration and systemic opioids following aortic aneurysm repair [124]. Two studies by Sitsen et al. found that when used for analgesia post-abdominal hysterectomy or post-total knee replacement, there was no difference in the potency of levobupivacaine and ropivacaine when used in a PCEA combined with sufentanil [125, 126]. Similarly, another study by Senard et al. found no difference in analgesic efficacy between levobupivacaine and ropivacaine when used in a PCEA combined with morphine following major abdominal surgery [127].

A number of trials have examined the use of adjuvants to epidural levobupivacaine. The addition of fentanyl to epidural levobupivacaine was found to reduce basal and dynamic pain levels in patients undergoing total knee replacement the day after surgery [128] and in patients using PCEA after total joint arthroplasty [129], whereas epidural morphine provided a significant improvement in post-operative analgesia in patients following major abdominal surgery [130]. The addition of intrathecal dexmedetomidine prolongs the duration of anaesthesia and postoperative analgesia in patients undergoing lower limb vascular surgery [131] and the addition of intrathecal clonidine provides

Table 3 Randomised controlled trials for epidural anaesthesia with levobupivacaine (LEV)

Study (year)	Surgical population	Drug (volume)	*N*	Mean time (min) ± SD (or range)			Post-operative analgesia	Comments
				Sensory block onset[a]	Sensory block duration[b]	Motor block duration[c]		
Cox et al. (1998)	Elective lower limb surgery	LEV 5 mg/mL (15 mL)	29	8 ± 5	377 ± 128	185 ± 122	–	No statistically significant differences in rate of intra-operative block success
		LEV 7.5 mg/mL (15 mL)	30	6 ± 4	460* ± 111	256* ± 99	–	
		BUP 5 mg/mL (15 mL)	29	7 ± 4 [readiness]	345 ± 107 [to resolution]	192 ± 74 [to resolution]	–	
Kopacz et al. (2000)	Elective lower abdominal surgery	LEV 7.5 mg/mL (20 mL)	28	13.6 ± 5.6	551* ± 88	355 ± 83	–	Slower onset of motor block found with levobupivacaine ($p < 0.001$)
		BUP 7.5 mg/mL (20 mL)	28	14.0 ± 9.9 [to T10]	506 ± 71 [to resolution]	376 ± 99 [to resolution]	–	82% incidence of hypotension with LEV 7.5 mg/mL (20 mL)
Murdoch et al. (2002)	Elective lower limb arthroplasty	LEV 7.5 mg/mL (10–15 mL) + LEV 0.625 mg/mL(6 mL/h)	32	No statistically significant difference between groups	–	180	8.1 ± 5.0	–
		LEV 7.5 mg/mL (10–15 mL) + LEV 1.25 mg/mL (6 mL/h)	32		–	240	9.5 ± 7.0	
		LEV 7.5 mg/mL (10–15 mL) + LEV 2.5 mg/mL (6 mL/h)	32		–	420* [to resolution]	16.7** ± 8.3 [hours to rescue opioid]	
Casati et al. (2003)	Elective hip replacement	LEV 5 mg/mL (10–18 mL) + PCEA LEV 1.25 mg/mL[d]	15	31 ± 16	214 ± 61	No statistically significant difference between groups	No statistically significant difference between groups	No statistically significant differences in rate of intra-operative rescue analgesia
		BUP 5 mg/mL (10–18 mL) + PCEA BUP 1.25 mg/mL[d]	15	25 ± 19	213 ± 53			
		ROP 5 mg/mL (10–18 mL) + PCEA ROP 2.5 mg/mL†	15	30 ± 24 [to T10]	233 ± 34 [to T12]			
Peduto et al. (2003)	Elective lower limb surgery	LEV 5 mg/mL (15 mL)	30	29 ± 24	185 ± 77	105 ± 63	–	No statistically significant differences in rate of intra-operative rescue analgesia
		ROP 7.5 mg/mL (15 mL)	35	25 ± 22 [to T10]	201 ± 75 [to T12]	95 ± 48 [to resolution]	–	

Table 3 (continued)

Study (year)	Surgical population	Drug (volume)	*N*	Mean time (min) ± SD (or range)			Post-operative analgesia	Comments
				Sensory block onset[a]	Sensory block duration[b]	Motor block duration[c]		
Casimiro et al. (2008)	Elective lower limb surgery	LEV 5 mg/mL (1.2 mL/level) + fentanyl 100 µg	49	–	170 (140–185)	105 (90–150)	–	Statistically higher proportion of patients did not develop motor block in the levobupivacaine group (39% vs 13%); $p = 0.017$
		BUP 5 mg/mL (1.2 mL/level) + fentanyl 100 µg	46	–	195 (165–205) [to resolution]	120 (105–150) [to resolution]	–	

BUP bupivacaine, *PCEA* patient-controlled epidural anaesthesia, *ROP* ropivacaine, *SD* standard deviation

*Reaches statistical significance at $p < 0.05$

**Reaches statistical significance at $p < 0.001$

[a]Sensory block onset is defined as the time of loss of pinprick sensation at [the specified level] or to surgical readiness

[b]Sensory block duration is defined as the time for regression of block to [the specified level] or until complete resolution

[c]Motor block duration is defined as the time for resolution of motor block to the [the specified level], unless stated

[d]In this case with an infusion of 5 mL/h with patient-controlled boluses of 2 mL with a 20-min lock-out

superior analgesia for patients undergoing elective hip replacement compared with levobupivacaine alone [132] and many studies demonstrate their safe use in clinical practice [117]. Common adverse effects of epidural levobupivacaine reported included hypotension, bradycardia, urinary retention, and nausea and vomiting [120].

6.1.3 Caudal Epidural Anaesthesia

A caudal epidural block is a common regional technique in children [133], and a number of studies confirm that it is an effective and safe technique. American Society of Regional Anaesthesia guidelines recommend the use of levobupivacaine 2.5 mg/mL, bupivacaine 2.5 mg/mL or ropivacaine 2 mg/mL for caudal blocks in children [109]. The maximum recommended dose of levobupivacaine for paediatric caudal anaesthesia is 2.5 mg/kg [109]. The volume of injectate can be adjusted, as described by Armitage, using 0.5 mL/kg, 1.0 mL/kg or 1.25 mL/kg to block the sacral, lumbar or lower thoracic dermatomes, respectively [134]. It is noted that a volume of 1.25 mL/kg exceeds the maximum recommended dose when using levobupivacaine 2.5 mg/mL and clinicians may choose to reduce the LA concentration to keep the dose at this volume within safe limits.

Randomised controlled trials (see Table 4) demonstrate that caudal levobupivacaine, racemic bupivacaine and ropivacaine are equally effective for postoperative analgesia after subumbilical surgeries in paediatric patients [135–138]. The ED_{50} and ED_{95} for caudal levobupivacaine have been found to be 0.68 mg/mL and 2.0 mg/mL respectively, compared with 0.66 mg/mL and 2.25 mg/mL for ropivacaine, indicating a similar potency [139].

There are a number of trials that examine the use of adjuncts to levobupivacaine in caudal injections, reporting analgesic benefit with the addition of opioids [140, 141], α_2-receptor agonists such as clonidine or dexmedetomidine [142, 143] and ketamine [144]. High-quality evidence is available for the addition of α_2-receptor agonists and it has been demonstrated that caudal dexmedetomidine 1 µg/kg reduces the required dose of levobupivacaine and improves postoperative analgesia in children, with a reduction in MLAC from 1.03 mg/mL to 0.68 mg/mL [143].

A systematic review of trials found few adverse events associated with caudal levobupivacaine administration, though a degree of motor block is common. Compared to levobupivacaine, the risk of motor block appears to be greater with racemic bupivacaine and less with ropivacaine [145].

6.2 Regional Anaesthesia and Local Infiltration

Regional anaesthesia is performed by targeting the injection of LA around either a single peripheral nerve or a plexus or

Table 4 Randomised controlled trials for caudal anaesthesia with levobupivacaine (LEV)

Study (year)	Surgical population	Drug (volume)	*N*	Adequacy of intra-operative analgesia (%)	Mean time ± SD		Requiring post-operative analgesia (%)	Post-operative motor block[b] (%)
					Sensory block onset[a] (min)	Time to first analgesia (h)		
Ivani et al. (2002)	Subumbilical surgery	LEV 2.5 mg/mL (1 mL/kg)	20	100	8.8 ± 3.1	No significant differences between groups	25	50
		BUP 2.5 mg/mL (1 mL/kg)	20	100	8.8 ± 2.3		25	60**
		ROP 2 mg/mL (1 mL/kg)	20	100	8.4 ± 2.0		25	30 [motor block > 0]
Locatelli et al. (2005)	Subumbilical surgery	LEV 2.5 mg/mL (1 mL/kg)[c]	33	91	8 ± 3	1.7 ± 0.4	15	18
		BUP 2.5 mg/mL (1 mL/kg)[c]	33	94	8 ± 4	2.45 ± 0.6*	21	52*
		ROP 2.5 mg/mL (1 mL/kg)[c]	33	91	7 ± 3	1.6 ± 0.6	15	18 [motor block > 0]
Frawley et al. (2006)	Subumbilical surgery	LEV 2.5 mg/mL (1 mL/kg)	155	94	–	–	13	85
		BUP 2.5 mg/mL (1 mL/kg)	152	91	–	–	12	86 [motor block > 1]
Ingelmo et al. (2006)	Elective inguinal hernia repair or orchidopexy	LEV 2 mg/mL (1 mL/kg)	28	93	9 ± 4	2.0 ± 0.4	25	43
		BUP 2 mg/mL (1 mL/kg)	29	93	7 ± 4	2.0 ± 0.7	38	45
		ROP 2 mg/mL (1 mL/kg)	29	72*	9 ± 4	2.0 ± 0.8	21	59 [motor block > 0]

BUP bupivacaine, *ROP* ropivacaine, *SD* standard deviation

*Reaches statistical significance at $p < 0.05$

**Motor block: ROP < BUP*

[a]Sensory block onset is defined as the time at which there was no haemodynamic response to surgical stimuli

[b]Percentage of patients with motor block present within half an hour after surgery. Motor block 0: no block, motor block > 1: no leg movement

[c]Only 0.5 mL/kg used if dermatomal level of surgery was below L3

collection of nerves, thereby providing anaesthesia to the tissues from which they receive somatosensory information. Local anaesthetics can also be infiltrated at the surgical site, either directly or via an intra-articular or wound catheter.

6.2.1 Regional Anaesthesia

A regional anaesthetic block can be used as the sole technique providing intra-operative anaesthesia or as an adjunct providing post-operative analgesia. Table 5 summarises randomised control trials comparing the efficacy of levobupivacaine with other LAs when used for regional anaesthesia [146–155]. These demonstrate that levobupivacaine provides effective anaesthesia for surgery that is as efficacious as bupivacaine with no significant difference in the quality of surgical block or post-operative analgesia [146–148, 150]. A meta-analysis by Li et al. found that compared to ropivacaine, levobupivacaine provides a significantly longer duration of anaesthesia and a significantly lower incidence of postoperative rescue analgesia [156]. There were no statistically significant differences observed between bupivacaine and ropivacaine with respect to onset time of surgical anaesthesia, onset time of sensory block, onset time of motor block, duration of motor block and overall patient satisfaction.

Levobupivacaine used in a regional anaesthetic block provides excellent post-operative analgesia. Bartolek et al. demonstrated that compared with opioid analgesia, femoral nerve block with levobupivacaine provided superior analgesia and faster rehabilitation following anterior cruciate

ligament reconstructive surgery [157]. Another study by Mostafa et al. demonstrated that a fascia iliaca block with levobupivacaine significantly reduced pain scores and opioid consumption following elective hip replacement compared with fentanyl patient-controlled analgesia [158]. Watson et al. studied the use of 30 mL of levobupivacaine for femoral nerve blocks in patients with a fractured hip and found the EC_{50} and EC_{95} to be 0.26 mg/mL and 0.36 mg/mL, respectively [159].

Adjuvants have been used to improved post-operative analgesia when used with regional levobupivacaine. Burlacu et al. found that the addition of either fentanyl or clonidine in a paravertebral block significantly reduced post-operative opioid requirements following breast surgery [160], though at the expense of an increased rate of hypotension, nausea and vomiting. A meta-analysis of perineural dexamethasone use when used as an adjuvant to LA in peripheral nerve blockade found a statistically significant prolongation of analgesia with a good safety profile [161].

6.2.2 Wound and Intra-articular Infiltration

Levobupivacaine can be used for surgical wound infiltration to provide effect post-operative analgesia, as shown by studies comparing its use with a sham treatment (saline) [162, 163]. A further study by Bay-Nielsen et al. demonstrates analgesic equivalence with racemic bupivacaine on patients undergoing elective inguinal hernia repair [164]. A number of studies found that the use of intra-articular levobupivacaine, with or without adjuvants, provides good post-operative analgesia and reduces opioid requirements [165, 166] and is comparable to bupivacaine in terms of efficacy [167, 168].

6.3 Use of Levobupivacaine in Obstetric Anaesthesia

Levobupivacaine is used by obstetric anaesthetists to provide both analgesia for labour and anaesthesia for surgical intervention. This is achieved by neuraxial anaesthetic techniques, which include spinal anaesthesia, epidural anaesthesia and combined spinal epidural (CSE).

6.3.1 Caesarean Delivery

Caesarean delivery is a common surgical intervention, with 79,655 elective and 98,557 emergency procedures taking place in the UK in 2016–17 [169]. Both general and regional anaesthesia are options for caesarean delivery, though regional anaesthesia is recommended as it is safer and results in less maternal and neonatal morbidity than general anaesthesia [170]. The UK national statistics show that less than 3.9% of elective and 8.8% of emergency caesareans take place under general anaesthesia [169].

The choice of anaesthetic technique depends, amongst other variables, on patient and surgical factors, the urgency of delivery and the availability of a well-functioning epidural catheter, which may be in situ for the purpose of labour analgesia [171]. A recent retrospective study demonstrated that establishment of adequate anaesthesia is on average quickest by general anaesthesia followed by spinal anaesthesia, and then epidural top-up [172].

6.3.2 Spinal Anaesthesia

A number of randomised controlled trials compared different regimes of levobupivacaine with both ropivacaine and racemic bupivacaine (see Table 2), comparing the onset and offset of sensory and motor block, as well as providing a measure of the adequacy of anaesthesia [173–176]. These trials indicate that an appropriate volume of intrathecal levobupivacaine 5 mg/mL provides effective spinal anaesthesia that is comparable to bupivacaine 5 mg/mL and ropivacaine 7.5 mg/mL.

In one study, the MLAD of spinal isobaric levobupivacaine was found to be 10.58 mg and ropivacaine 14.22 mg, suggesting a potency ratio of 1.34. This gave ED_{95} values of 12.96 mg and 15.97 mg for levobupivacaine and ropivacaine, respectively [177]. In another study, the MLAD of levobupivacaine was found to be 10.65 mg and ropivacaine 14.12 mg. The addition of 3.3 µg of sufentanil significantly reduced the MLAD of both LAs to 4.73 mg and 6.44 mg, respectively, leaving their potency ratio relatively unaffected at 1.36 [178].

Other trials also demonstrate the potentiation of the effect of levobupivacaine with opioids, with one such trial demonstrating that the addition of fentanyl or sufentanil allowed for more rapid onset of sensory and motor block levels, superior block duration and better patient and surgical satisfaction [175]. Another study showed that when combined with intrathecal sufentanil 2.5 µg and intrathecal morphine 100 µg, the ED_{50} and ED_{95} of levobupivacaine were 6.2 mg and 12.9 mg, respectively, for caesarean delivery [179]. For comparison, in another trial, the ED_{50} and ED_{95} values for intrathecal isobaric bupivacaine, mixed with fentanyl 10 µg and morphine 200 µg, were 7.25 and 13.0 mg, respectively [180]. This similarity in relative potency is in contrast with the findings of other studies [173, 174] that indicate that bupivacaine is likely more potent.

An up-down sequential allocation study looking at the relative potencies of LAs to produce motor block in women undergoing elective caesarean delivery found ratios of 0.59 for ropivacaine/bupivacaine, 0.71 levobupivacaine/bupivacaine and 0.83 for ropivacaine/levobupivacaine, indicating

Table 5 Randomised controlled trials for regional anaesthesia with levobupivacaine (LEV)

Study (year)	Block/surgery	Drug (volume)	*N*	Mean time ± SD (or minimum–maximum), unless otherwise stated				Comments
				Sensory block onset[a] (min)	Sensory block duration[b] (h)	Intra-operative success (%)	Time to analgesia request (h)	
Cox et al. (1998)	Supraclavicular block/hand surgery	LEV 2.5 mg/mL (0.4 mL/kg)	25	7 ± 6	14.9 ± 4.2	68	–	Motor block figures available
		LEV 5 mg/mL (0.4 mL/kg)	26	6 ± 5	14.9 ± 4.7	80	–	No significant differences found
		BUP 5 mg/mL (0.4 mL/kg)	23	8 ± 8	17.3 ± 5.3	74	–	
Urbanek et al. (2003)	3-in-1 block	LEV 2.5 mg/mL (20 mL)	20	30 (23–36)	11.8* (9.2–14.4)	–	–	Block performed prior to spinal anaesthesia
		LEV 5 mg/mL (20 mL)	20	24 (18–30)	16.7 (14.1–19.3)	–	–	
		BUP 5 mg/mL (20 mL)	20	27 (20–33)	17.6 (13.4–21.7)	–	–	
Liisanantti et al. (2004)	Axillary block/forearm surgery	LEV 5 mg/mL (45 mL)	30	No differences	19.5 ± 8.0	80	17.1 ± 6.5	
		BUP 5 mg/mL (45 mL)	30		19.3 ± 7.7	90	17.8 ± 7.2	
		ROP 5 mg/mL (45 mL)	30		17.3 ± 6.6	87	15.0 ± 5.4	
Duma et al. (2005)	Axillary block/forearm surgery	LEV 4.8 mg/mL (41 mL) + clonidine 150 μg	20	5 (5–60)	22.8 (12–41)	–	–	Motor onset available
		LEV 4.8 mg/mL (41 mL)	20	10 (5–60)	18.1 (13–28)	–	–	Wide variation in response to clonidine
		BUP 4.8 mg/mL (41 mL) + clonidine 150 μg	20	10 (5–60)	17.3 (9–40)	–	–	
		BUP 4.8 mg/mL (41 mL)	20	10 (5–60)	17.7 (10–22)	–	–	
Casati et al. (2005)	Sciatic nerve block/foot surgery	LEV 5 mg/mL (20 mL)	15	30 (5–60)	Duration significantly longer in LEV 75–mg/mL group	73	16 (13–20)*	
		LEV 7.5 mg/mL (20 mL)	15	5 (5–40)*		100	18 (15–19)*	
		ROP 7.5 mg/mL (20 mL)	15	20 (5–50) [median times]		87	13 (11–14)*	
Piangatteli et al. (2006)	Infraclavicular block/hand surgery	LEV 5 mg/mL (30 mL)	15	13.5* ± 1.1	11.4* ± 2.2	100	–	
		ROP 7.5 mg/mL (30 mL)	15	14.2 ± 1.2	10.3 ± 1.4	100	–	

Table 5 (continued)

Study (year)	Block/surgery	Drug (volume)	*N*	Mean time ± SD (or minimum–maximum), unless otherwise stated				Comments
				Sensory block onset[a] (min)	Sensory block duration[b] (h)	Intra-operative success (%)	Time to analgesia request (h)	
Gonzalez-Suarez et al. (2009)	Axillary block/upper limb surgery	LEV 3.3 mg/mL (30 mL)	43	25.3 ± 6.4	11.3* ± 4.1	90.6	14.2 ± 3.8	Motor block onset faster with ROP ($p = 0.02$)
		ROP 5 mg/mL (30 mL)	43	25.2 ± 5.1	9.2 ± 3.1	79.1 [complete anaesthesia]	13.1 ± 5.0	Motor block offset comparable
Noulas et al. (2011)	Digital blocks/hand surgery	LEV 5 mg/mL (2.0 mL)	60	9.5 (7–15)	10.8* (7–15)	–	–	No statistically significant differences in pain scores
		ROP 5 mg/mL (2.0 mL)	60	11.3 (6–15)	6.7 (4–8)	–	–	
Aksu et al. (2009)	Peribulbar block/vitreoretinal surgery	LEV 5 mg/mL (5.0 mL)	45	2.2	251	–	–	Statistically significant reduction in motor block time with LID
		BUP 5 mg/mL (5.0 mL)	45	2.3	253	–	–	
		LID 2% (5.0 mL)	45	2.0	136*	–	–	
Di Donati et al. (2006)	Retrobulbar block/vitreoretinal surgery	LEV 5 mg/mL (4.0 mL) + HYA 50 U/mL	100	4** (2–6)	9.0**	–	–	Statistically significant reduction in motor block time with ROP
		ROP 7.5 mg/mL (4.0 mL) + HYA 50 U/mL	96	6 (4–8)	6.3	–	–	
						–	–	

BUP bupivacaine, *HYA* hyaluronidase, *LID* lidocaine, *ROP* ropivacaine, *SD* standard deviation

*Reaches statistical significance at $p < 0.05$

**Reaches statistical significance at $p < 0.001$

[a]Sensory block onset is defined as the time of loss of pinprick sensation

[b]Sensory block duration is defined as the time for resolution of block

[c]Number of patients not requiring intra-operative supplementation or general anaesthesia

the levobupivacaine causes less motor block than bupivacaine but more than ropivacaine [49].

Hypotension and nausea are very common side effects of spinal anaesthesia for caesarean delivery [181]. Hypotension is particularly common, found to occur in around 80% of cases in one randomised trial [182], and international consensus guidelines therefore recommend prophylactic use of vasopressors (phenylephrine has the most supporting evidence) with IV fluid co-loading [183]. The frequency of side effects appear to be similar with bupivacaine and ropivacaine [173].

6.3.3 Epidural Top-Up

A 2015 national survey of UK lead obstetric anaesthetists found that levobupivacaine 5 mg/mL was the preferred LA for extension of epidural analgesia for a caesarean section (preferred by 36.1%), followed by lidocaine 20 mg/mL with epinephrine (18.5%) and lidocaine 20 mg/mL with epinephrine and bicarbonate (17.6%) [184].

When used for epidural top-up for a caesarean delivery, a number of randomised control trials (see Table 6) found that there was no significant difference between levobupivacaine or bupivacaine, in terms of speed of onset or quality of sensory block [49, 56, 185]. However, a number of trials [186–188] and a subsequent meta-analysis found that lidocaine with epinephrine resulted in a significantly faster onset of sensory block compared with levobupivacaine or bupivacaine, which were in turn superior to ropivacaine [189]. The same meta-analysis demonstrated that levobupivacaine and bupivacaine were associated with a significantly increased risk of intra-operative supplementation compared with other epidural-top up mixtures (relative risk 2.03), especially compared with ropivacaine (relative risk 3.24) [189].

6.3.4 Labour Analgesia

Neuraxial blockade for labour analgesia is generally initiated using an epidural or combined spinal epidural technique, in which a dose of LA (with or without an opioid) is given intrathecally prior to establishment of an epidural blockade.

6.3.5 Epidural Technique

There are many studies investigating the effects of different LAs at different concentrations for labour epidurals. Low-concentration LAs can be defined as those with concentrations of ≤ 1 mg/mL of levobupivacaine (or equivalent potency for other LAs) [190]. One meta-analysis found that compared to higher concentrations of LAs, low-concentration LAs lead to lower rates of assisted vaginal delivery, urinary retention and motor block [191]. Compared with non-epidural analgesia, low-concentration LA use in labour epidurals is not associated with prolongation of the second stage of labour or an increase in instrumental delivery [7].

Used for labour analgesia, one randomised controlled trial found that the MLAC of 20 mL of levobupivacaine was 0.83 mg/mL and of 20 mL bupivacaine was 0.81 mg/mL [7]. In another trial, the MLAC of 20 mL levobupivacaine and ropivacaine was found to be 0.87 mg/mL and 0.89 mg/mL, respectively [192]. Another study demonstrated that 20 mL of epidural levobupivacaine has a lower EC80 than that of ropivacaine, with a value of 1.4 mg/mL compared with 2.4 mg/mL [193].

The addition of an opioid to an epidural solution significantly reduces the dose of LA required for labour analgesia, with one study demonstrating a reduction in MLAC of 20 mL of levobupivacaine from 0.91 mg/mL to 0.47 mg/mL with the addition of 2 µg/mL of fentanyl [194]. In another study, with the addition of sufentanil 0.5 µg/mL added to either 20 mL of ropivacaine or levobupivacaine, there was no significant difference in analgesic potency observed, with MLACs of 0.23 mg/mL and 0.20 mg/mL, respectively [195].

A small number of randomised controlled trials compared the efficacy of labour analgesia with epidural levobupivacaine. One trial found that analgesia was more efficacious with levobupivacaine 1.136 mg/mL than with levobupivacaine 0.568 mg/mL [48]. This was confirmed by another trial that found improved analgesic efficacy with an increase in concentration from 0.625 to 1.25 mg/mL, though without any increase in patient satisfaction [196]. Further studies found no difference in analgesic efficacy between levobupivacaine, bupivacaine and ropivacaine [48, 197–199].

A study examining motor MLACs with labour epidurals confirmed increasing motor-blocking potencies from ropivacaine to levobupivacaine to bupivacaine, with values of 3.4 mg/mL, 3.0 mg/mL and 2.6 mg/mL respectively, with 20 mL of LA use [200]. Increasing concentrations of LA are associated with increasing motor block, without necessarily improving patient satisfaction [196].

6.3.6 Combined Spinal Epidural Technique

As for epidural use, there appears to be no different in analgesic efficacy between levobupivacaine, bupivacaine and ropivacaine when used intrathecally for labour analgesia [201–203]. In one study, Camorcia et al. found that the MLAD of spinal levobupivacaine in labouring women was 2.94 mg, compared with 2.37 mg and 3.64 mg for racemic bupivacaine and ropivacaine, respectively. This provided relative analgesic potency ratios of 0.80 for ropivacaine:levobupivacaine and 0.81 for levobupivacaine:bupivacaine [8]. The addition of an opioid improves analgesic efficacy and reduces the required dose of LA [204]. Van de Velde et al. found that combined with sufentanil 1.5 µg, the ED_{50} of levobupivacaine, bupivacaine

Table 6 Randomised controlled trials for anaesthesia for caesarean delivery

Study (year)	Anaesthetic method	Drug concentration /(volume)	*N*	Mean time ± SD, unless otherwise stated				Adequacy of surgical block[e]
				Sensory block onset[a] (min) [sensory modality]	Sensory block duration[b] (h) [block regression]	Motor block onset[c] (min) [for Bromage score]	Motor block duration[d] (h)	
Bader et al. (1999)	Epidural top-up	LEV 5 mg/mL (30 mL)	60	8.2 ± 4.7	5.5 ± 1.3	17.2 ± 12.2	4.0 ± 1.5	No statistically significant difference between groups
		BUP 5 mg/mL (30 mL)		6.4 ± 4.0 [pinprick]	5.3 ± 1.3 [to T10]	12.5 ± 8.3 [Bromage > 1]	4.4 ± 1.4	
Faccenda et al. (2003)	Epidural top-up	LEV 5 mg/mL (25 mL)	31	10.0 ± 7.2	8.1 ± 2.4	–	4.0* ± 2.2	94%
		BUP 5 mg/mL (25 mL)	31	8.4 ± 6.7 [pinprick]	7.7 ± 2.3 [to recovery]	–	2.9 ± 1.2	94%
Ngampraser-twong et al. (2005)	Epidural top-up	LEV 5 mg/mL (25 mL)	31	16.7	4.1	12.3	2.1	–
		BUP 5 mg/mL (25 mL)	30	15.0 [pinprick]	4.7 [to T10]	12.0 [Bromage > 0]	2.2 [Bromage < 3]	–
Allam et al. (2008)	Epidural top-up	LID Fast mix (20 mL)[f]	20	7**/7**	–	Pre–existing motor block in both groups	–	81%
		LEV 5 mg/mL (20 mL)	20	11/14 [cold/touch]	–		–	68%
Sng et al. (2008)	Epidural top-up	LID + Ep/Fent Mix (15 mL)[f]	30	9.5	2.0*	–	–	93%
		ROP 7.5 mg/mL (15 mL)	30	10.0	2.4*	–	–	93%
		LEV 5 mg/mL (15 mL)	30	10.0 [cold]	2.6* [by 2 levels]	–	–	90%
Bajali et al. (2009)	Epidural top-up	LID Fast mix (20 mL)[g]	50	10	–	–	–	94%
		LEV 5 mg/mL (20 mL)	50	15 [touch to T7]	–	–	–	94%
Gautier et al. (2003)	CSE	BUP 5 mg/mL (1.6 mL) + sufentanil 2.5 µg	30	14 ± 9	2.2 ± 0.4	9 ± 6	2.4 ± 0.5	97%
		LEV 5 mg/mL (1.6 mL) + sufentanil 2.5 µg	30	17 ± 9	2.1 ± 0.4	13 ± 6	2.0* ± 0.4	80% (*vs BUP)
		ROP 5 mg/mL (1.6 mL) + sufentanil 2.5 µg	30	15 ± 9 [pinprick]	2.0 ± 0.5 [to T10]	14 ± 6 [to maximum]	1.9* ± 0.3	87%
Bremerich et al. (2007)	Spinal	hLEV 5 mg/mL (2.0 mL) + fentanyl 10 µg	10	8 ± 5	2.0* ± 0.4	1.7 ± 1.3 1.3 ± 0.5	1.7* ± 0.7	100%
		hLEV 5 mg/mL (2.0 mL) + fentanyl 20 µg	10	4 ± 4	2.2* ± 0.6	2.2* ± 0.6	1.4* ± 0.4	100%
		hLEV 5 mg/mL (2.0 mL) + sufentanil 5 µg	10	8 ± 5	2.2* ± 0.6	1.2 ± 0.4	1.4* ± 0.5	100%
		hBUP 5 mg/mL (2.0 mL) + fentanyl 10 µg	10	5 ± 4	2.6 ± 0.5	1.3 ± 0.7	2.4 ± 0.8	100%
		hBUP 5 mg/mL (2.0 mL) + fentanyl 20 µg	10	7 ± 5	2.8 ± 0.5	1.2 ± 0.4	2.5 ± 0.6	100%

Table 6 (continued)

Study (year)	Anaesthetic method	Drug concentration /(volume)	*N*	Mean time ± SD, unless otherwise stated				Adequacy of surgical block[e]
				Sensory block onset[a] (min) [sensory modality]	Sensory block duration[b] (h) [block regression]	Motor block onset[c] (min) [for Bromage score]	Motor block duration[d] (h)	
		hBUP 5 mg/mL (2.0 mL) + sufentanil 5 µg	10	7 ± 5 [cold]	2.7 ± 0.5 [to T10]	1.7 ± 1.1 [Bromage > 0]	2.1 ± 0.6	100%
Bozdogan et al. (2013)	Spinal	LEV 5 mg/mL (2.0–2.2 mL) + sufentanil 2.5 µg	31	8.5 ± 3.5	2.5 ± 0.7	3.8	2.4 ± 0.4	81%
		LEV 5 mg/mL (2.0–2.2 mL) + fentanyl 10 µg	31	7.5 ± 2.2	1.9 ± 0.4	3.0	2.5 ± 0.6	100%
		LEV 5 mg/mL (2.0–2.2 mL)	31	12.7** ± 3.7 [pinprick]	1.7* ± 0.3 [to T10]	10.0**	2.2 ± 0.6	78%
Debbarma et al. (2017)	Spinal	hBUP 5 mg/mL (1.5 mL) [L2/3]	25	5.4 ± 2.1	1.6 ± 0.2	3.1 ± 1.0	1.5 ± 0.5	96%
		hLEV 5 mg/mL (1.5 mL) [L2/3]	25	5.1 ± 1.2	1.6 ± 0.2	3.0 ± 0.7	1.4 ± 0.5	80%
		hBUP 5 mg/mL (2.0 mL) [L3/4]	25	4.9 ± 1.5	1.6 ± 0.2	3.1 ± 0.7	1.4 ± 0.2	96%
		hLEV 5 mg/mL (2.0 mL) [L3/4]	25	5.0 ± 1.2 [pinprick]	1.5 ± 0.2 [by 2 levels]	3.3 ± 0.7 [Bromage > 2]	1.3 ± 0.2	96%

BUP bupivacaine, *CSE* combined spinal epidural, *hBUP* hyperbaric bupivacaine, *hLEV* hyperbaric levobupivacaine, *LEV* levobupivacaine, *ROP* ropivacaine, *SD* standard deviation, *VAS* Visual Analog Scale of pain (out of 100)

*Reaches statistical significance at $p < 0.05$

**Reaches statistical significance at $p < 0.001$

[a]Sensory block onset defined as T4–T7 or maximum height achieved or surgical readiness

[b]Defined as regression of block to [specified level]

[c]Motor block onset defined as time to reach [specified motor block]. Bromage score = 0: no block, 1: unable to flex hip, 2: unable to flex knee, 3: unable to flex ankle

[d]Defined as return to full motor function or [specified level]

[e]Percentage of patients not requiring intra-operative supplementation

[f]LID Fast-mix = lidocaine 18 mg/mL + epinephrine 5 µg/mL + sodium bicarbonate 7.6 mg/mL

[g]LID + Ep/Fent Mix = lidocaine 19 mg/mL + epinephrine 4.74 µg/mL + fentanyl 2.37 µg/mL

and ropivacaine were 2.3 mg, 1.7 mg and 2.2 mg, respectively, with ED_{95} values of 5.0 mg, 3.3 mg and 4.8 mg [205].

Adverse effects reported with the use of intrathecal levobupivacaine for labour analgesia include foetal bradycardia, hypotension, pruritus, shivering, motor block, impaired perineal squeezing, nausea and vomiting [201–203, 205]. Levobupivacaine demonstrates less motor block [8, 201] and impairment of perianal squeezing [8] compared with bupivacaine, though there appears to be no other significant differences in adverse events between levobupivacaine, racemic bupivacaine and ropivacaine.

7 Conclusions

Levobupivacaine is a long-acting amide LA that displays good efficacy when administered by topical application, local infiltration, via the epidural or spinal route, and also by peripheral nerve and intra-articular blocks. This review has described that its clinical effects are largely similar to that of its racemic counterpart. However, levobupivacaine displays a more favourable toxicity effect profile compared with the racemic mixture, particularly with regard to cardiological and neurological adverse effects. This, in addition to the drug being well tolerated, makes levobupivacaine a preferential choice over bupivacaine for providing effective analgesia and anaesthesia to perioperative patients.

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Compliance with Ethical Standards

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