Update on local anesthetics: focus on levobupivacaine

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Abstract: In recent years levobupivacaine, the pure S (–)-enantiomer of bupivacaine, emerged as a safer alternative for regional anesthesia than its racemic parent. It demonstrated less affinity and strength of depressant effects onto myocardial and central nervous vital centers in pharmacodynamic studies, and a superior pharmacokinetic profile. Clinically, levobupivacaine is well tolerated in a variety of regional anesthesia techniques both after bolus administration and continuous postoperative infusion. Reports of toxicity with levobupivacaine are scarce and occasional toxic symptoms are usually reversible with minimal treatment with no fatal outcome. Yet, levobupivacaine has not entirely replaced bupivacaine in clinical practice. In anesthesia and analgesia practice, levobupivacaine and bupivacaine produce comparable surgical sensory block with similar adverse side effects, and equal labor pain control with comparable maternal and fetal outcome. The equipotency of the two drugs has been recently questioned, prompting clinicians to increase the dose of levobupivacaine in an attempt to ensure adequate anesthesia and analgesia and offsetting, therefore, the advantages of less motor block with levobupivacaine. In this review we aim to discuss the pharmacological essentials of the safer profile of levobupivacaine, and analyze the evidence regarding the current clinical indications.

Keywords: regional anesthesia, levobupivacaine, pharmacodynamics, pharmacokinetics, therapeutic use

Reports of fatalities through cardiovascular toxic effects after regional anesthesia with bupivacaine in the late 1970s (Albright 1979) triggered pharmacological research that emphasized the selective behavior of the two enantiomers of racemic bupivacaine, ie, levo- or S (–)-bupivacaine and dextro- or R (+)-bupivacaine, once in contact with biological receptors in the body. Levo-enatiomer appeared to have a safer pharmacological profile than its dextro-partner. Efforts were intensified to synthesize a pure S (–)-bupivacaine enantiomer, and Chirocaine® (levobupivacaine) Injection (Darwin Discovery Ltd., distributed by Purdue Pharma LP, Connecticut, US) was approved by the United States Food and Drug Administration in 1999. Ropivacaine (Naropin® (ropivacaine HCL) injection, Astra Zeneca Int., distributed by Abraxis BioScience, California, US), another pure S (–)-enantiomer, became also available as an alternative to the racemic mixture for regional anesthesia. This review discusses the pharmacological rationale behind the safer profile of levobupivacaine, and its up-to-date use in anesthesia. The descriptors bupivacaine, levobupivacaine and dextrobupivacaine are used for the racemic mixture and its selective enatiomers, respectively.

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Pharmacodynamic foundation of the lesser cardiovascular and central nervous toxicity of levobupivacaine

In common to all local anesthetics levobupivacaine reversibly blocks the transmission of action potential in sensory, motor and sympathetic nervous fibers by inhibiting the passage

of sodium through voltage-sensitive ion channels in the neuronal membrane. Whereas the inhibitory action is intended to be localized at the site of administration, excessive doses or accidental intravascular injection may lead to activity at the level of other ion channels in excitable tissues followed by unwanted central nervous and cardiovascular adverse effects. The current pharmacodynamic evidence from animal and human studies suggests that levobupivacaine has a potentially greater margin of safety than the racemic bupivacaine.

Cardiovascular toxicity

Levobupivacaine demonstrated less affinity and strength of inhibitory effect onto the inactivated state of cardiac sodium channels than the racemic parent or dextrobupivacaine in in vitro animal tissue experimental studies (Vanhouette et al 1991; Valenzuela et al 1995a). It also showed less depressant effect on the atrioventricular conduction (Graf et al 1997) and QRS complex duration (Mazoit et al 2000), and provoked less impairment of the contractile function of the isolated animal heart (Simonetti and Fernandes 1997). Levobupivacaine was also less potent in blocking cloned human heart sodium and potassium channels (Valenzuela et al 1995b; Nau et al 2000).

Similarly, in vivo animal studies showed that the cardiotoxic dose of intravenous bupivacaine and its pure S (−)-enantiomers followed the order ropivacaine >levobupivacaine >bupivacaine (Huang et al 1998; Ohmura et al 2001). The estimated mean (standard deviation) fatal dose through severe arrhythmias after intravenous administration of levobupivacaine in sheep is 277 (51) mg, which is significantly larger than the fatal dose of bupivacaine of 156 (31) mg (Chang et al 2000). In regards to the reversibility of cardio-toxic effects, evidence is less clear. It was shown in anaesthetized open chest dogs receiving a continuous infusion of local anesthetic until cardiovascular collapse that animals receiving bupivacaine were more likely to have a fatal outcome than animals receiving levobupivacaine and ropivacaine but the differences were not significant (Groban et al 2001). In another study, there was no difference in the number of successfully resuscitated anaesthetized rats after the administration of bupivacaine, levobupivacaine or ropivacaine (Ohmura et al 2001). However, less epinephrine was required for the successful resuscitation of rats receiving ropivacaine than those receiving levobupivacaine or bupivacaine.

Central nervous toxicity

The uptake of bupivacaine by the central nervous cells is also enantio-selective. For example, experiments in anesthetized rats receiving arrhythmogenic intravenous doses of levobupivacaine or dextrobupivacaine showed a less rapid blockage of the cell firing in the nucleus tractus solitarius after levobupivacaine than after dextrobupivacaine (Denson et al 1992). All animals receiving dextrobupivacaine developed apnea and died whereas those receiving levobupivacaine continued to breathe and all but two survived.

The mean (standard deviation) convulsive dose after intravenous levobupivacaine in conscious sheep is 103 (18) mg, significantly higher than the convulsive dose of bupivacaine of only 85 (11) mg (Huang et al 1998). The convulsive dose of ropivacaine is 155 mg (Nancarrow et al 1989). The susceptibility for seizure activity after intoxication with levobupivacaine and ropivacaine is 1.5–2.5 times less than that after racemic bupivacaine (Groban 2003).

In human volunteers studies, the mean dose of intravenous levobupivacaine and bupivacaine associated with central nervous system symptoms was similar, ie, 56–68 mg and 48–65 mg, respectively (Bardsley et al 1998; Nimmo 1998). At this similar dose, levobupivacaine showed significantly less myocardial contractility and atrio-ventricular conduction depressant effect than bupivacaine.

Pharmacokinetic foundation of the lesser cardiovascular and central nervous toxicity of levobupivacaine

In human volunteers studies, the volume of distribution and overall clearance of levobupivacaine was significantly lower than that of dextrobupivacaine (Burm et al 1994). Nevertheless, the pharmacokinetics of the unbound fraction of levobupivacaine accounts for its less toxicity. The unbound fraction of levobupivacaine was significantly lower than that of unbound dextrobupivacaine because of its increased protein-binding affinity. Together with a higher clearance of the unbound levobupivacaine, this explains the shorter elimination half-life of levobupivacaine while the volume of distribution of both unbound drug was similar (Burm et al 1994). An increase in postoperative levels of alpha-1-glycoprotein (Dauphin et al 1997) that binds large amounts of levobupivacaine, may further explain the lack of toxicity even when large volumes of racemic bupivacaine were administered in clinical studies (Berrisford et al 1993; Blake et al 1994; Mather et al 1995). No clinical signs of cardio-vascular toxicity were demonstrated despite consistent significantly

higher total plasma concentrations of levobupivacaine vs dextrobupivacaine.

Various factors such as site of administration, duration of continuous infusion and/or addition of agents with vasomotor effect may influence the degree of systemic uptake of levobupivacaine. For example, the administration of levobupivacaine in paravertebral anesthesia and analgesia was characterized by rapid absorption after bolus injection and progressive accumulation after continuous infusion with maximum plasma concentrations at 24 hours (Burlacu et al 2007). A similar rapid absorption from the paravertebral space was reported in other studies (Berrisfort et al 1993; Perttunen et al 1995), fortunately without clinical signs of toxicity. The addition of epinephrine decreased peak plasma levels of levobupivacaine after epidural analgesia (Kopacz et al 2001). In research carried out by our own group, the addition of clonidine to low concentration levobupivacaine (0.05%) was followed by a more erratic pattern of systemic absorption of levobupivacaine from the paravertebral space, which, although did not reach toxic levels, may raise concerns of increased potential for toxicity due to the combined vasodilator effects of the two drugs (Burlacu et al 2007).

Clinical toxicity and tolerability

Regardless of the type of regional blockade with levobupivacaine, 78% of patients may experience at least one adverse effect such as hypotension (20%), nausea (12%), postoperative pain (18%), fever (17%), vomiting (14%), anemia (12%), pruritus (9%), back pain (8%), headache (7%), constipation (7%), dizziness (6%) and fetal distress (5%) (Purdue Pharma L.P.1999). The incidence of adverse events with levobupivacaine was similar to that after bupivacaine in comparative trials.

The early clinical presentation of toxicity after levobupivacaine appears to consist of central nervous symptoms (disorientation, drowsiness, slurred speech), which may culminate with tonic-clonic seizures in some cases (Kopacz and Allen 1999a; Pirotta and Spriqqe 2002; Khan and Atanassoff 2003; Crews and Rothman 2003; Breslin et al 2003). These excitatory symptoms are generally self-limiting, or respond easily to anticonvulsant treatment. In anaesthetized patients, however, sudden cardiovascular collapse may emerge which appears to be relatively easily treated with moderate doses of sympathomimetics (Salomaki et al 2005).

Levobupivacaine in current regional anesthesia practice for surgery

Spinal anesthesia

Because of the small doses of local anesthetic used for subarachnoid administration, systemic toxicity is not a problem. Not surprisingly therefore, bupivacaine remains the most widely and cost-efficient long acting local anesthetic used in spinal anesthesia. A surgical sensory and motor block of similar characteristics and recovery over equal dose ranges of levobupivacaine and bupivacaine was demonstrated in healthy volunteers (Alley et al 2002) and confirmed in surgical patients (Glaser et al 2002; Lee et al 2003; Casati et al 2004a; Fattorini et al 2006) (Table 1). The regression of motor block was significantly more rapid after levobupivacaine and ropivacaine than bupivacaine in a study by Casati and colleagues, which may be advantageous for early ambulation after day-case surgery (Casati et al 2004a).

Traditionally, the dose of levobupivacaine used for spinal anesthesia is 15 mg. This dose provides an adequate sensory and motor block for most surgical procedures lasting approximate 6.5 hours (Burke et al 1999a). An up-and-down sequential design study recommends a minimum effective local anesthetic dose (MLAD) of levobupivacaine 11.7 mg (Sell et al 2005). Smaller doses (ie, 5–10 mg) have been used in ambulatory surgery, and allow a more rapid recovery and subsequent discharge home (Breebaart et al 2003, Capelleri et al 2005). The addition of fentanyl 15 μg demonstrate a sparing effect on the requirement of levobupivacaine while maintaining excellent clinical efficacy with less hemodynamic variation (Lee et al 2005) (Table 1).

Epidural anesthesia and analgesia

Table 2 presents a summary of studies regarding the use of levobupivacaine in epidural anesthesia and analgesia for surgery. The onset of sensory block (8–30 min), maximum upper spread (T7-T8 after L2-L3 or L3-L4 lumbar injection) and duration (4–6 hours) are similar after equal doses of levobupivacaine and bupivacaine (15 mL 0.5%) (Cox et al 1998a; Casati et al 2003a). The onset of motor block is slower with levobupivacaine (Kopacz et al 2000), and its quality follows the rank of order bupivacaine >levobupivacaine >ropivacaine (Cox et al 1998a; Kopacz et al 2000; Casati et al 2003a; Peduto et al 2003). The duration of motor block, however, appears to be similar (Cox et al 1998a; Kopacz et al 2000; Peduto et al 2003). Increasing the concentration of levobupivacaine (ie, 15 mL 0.75% vs 0.5%) prolongs the duration of sensory and motor block without increasing the incidence of adverse side effects (Cox et al 1998a). However increasing both volume and concentration to 20 mL levobupivacaine 0.75% is associated with a high incidence of hypotension (82%) and delayed block regression (Kopacz et al 2000).

Table 1 Summary of patient studies that used levobupivacaine in spinal anesthesia

Reference	Dose/concentration	No. of patients	Type of surgery	Onset time of sensory block, mean (SD) or median (range), min	Maximum (range) sensory dermatome level	Duration of sensory block mean (SD) or median (range), min	Complete sensory block (% patients)	Onset time of motor block mean (SD) or median (range), min	Duration of motor block mean (SD) or median (range), min	Complete motor block (% patients)	Outcome (time to void), min
Burke et al 1999a	3 mL levobupivacaine 0.5%	20	Varicose veins surgery	2 (2–10)	T8 (T4–L3)	388 (295–478)	90%	5 (2–10)	266 (170–415)	95%	
Glaser et al 2002	3.5 mL levobupivacaine 0.5%	39	Hip surgery	11 (6)	T8	228 (77)	100%	10 (7)	280 (84)	100%	
	3.5 mL bupivacaine 0.5%	40		13 (8)	T8	237 (88)	100%	9 (7)	284 (80)	100%	
Lee et al 2003	2.6 mL levobupivacine 0.5%	24	Urological surgery	10 (6)	T7 (T3–T10)					37%	
	2.6 mL bupivacaine 0.5%	26		8 (4)	T8 (T3–T10)					49%	
Breebaart et al 2003	10 mg levobupivacaine	20	Ambulatory knee arthroscopy	8 (6)	T10 (C8–L1)	173 (47)	97%		137 (40)	74%	284 (57)
	15 mg ropivacaine	20		7 (4)	T11 (T3–L2)	167 (49)	97%		142 (44)	85%	285 (65)
	60 mg lidocaine	20		6 (4)	T10 (T3–L2)	145 (30)[a]	94%		127 (29) Regression at 180 min	85%	245 (65)[a]
Casati et al 2004a	8 mg hyperbaric levobupivacaine 0.5%	20	Inguinal hernia repair	10 (5)	T8 (T12–L5)	210 (63)	100%		84%	100%	255 (58)
	8 mg hyperbaric bupivacaine 0.5%	20		10 (4)	T6 (T12–L5)	190 (51)	100%		55%[c]	100%	298 (68)
	12 mg ropivacaine 0.5%	20		10 (6)	T5 (T10–L2)	166 (42)[b]	100%		95%	100%	302 (48)
Cappelleri et al 2005	7.5 mg hyperbaric levobupivacaine 0.5%	30	Ambulatory knee arthroscopy	11 (10–16)	T8 (T7–9)	162 (148–201)	100%				238 (221–276)
	5 mg hyperbaric levobupivacaine 0.5%	30		10 (9–12)	T10 (T7–10)	150 (136–185)	97%				190 (181–247)[e]
	7.5 mg hyperbaric ropivacaine 0.5%	31		10 (9–13)	T9 (T8-L1)	135 (126–154)[d]	97%				189 (126–154)[e]
Lee et al 2005	2.6 mL levobupivacaine 0.5%	25	Urological surgery	8 (4.5)	T6 (T3–T10)					96%	
	2.3 mL levobupivacaine 0.5% + 15 μg fentanyl	25		7.4 (2.8)	T7 (T4–T10)					84%	
Fattorini et al 2006	3 mL levobupivacaine 0.5%	29	Hip or knee replacement surgery	12 (6)	T8 (4–12)	391 (96)	69%	11 (6)	256 (86)	86%	
	3 mL bupivacaine 0.5%	30		9 (5)	T8 (4–12)	381 (105)	82%	8 (4)	245 (86)	100%	

[a]$p < 0.05$ lidocaine vs levobupivacaine and ropivacaine; [b]$p < 0.05$ ropivacaine vs levobupivacaine and bupivacaine; [c]$p < 0.05$ bupivacaine vs levobupivacaine and ropivacaine; [d]$p < 0.05$ ropivacaine vs levobupivacaine 7.5 mg; [e]$p < 0.05$ ropivacaine and levobupivacaine 5 mg vs levobupivacaine 7.5 mg.

A better way to control the quality and duration of epidural block with levobupivacaine without excessive motor block and hemodynamic consequences is via continuous epidural infusion. It was shown that a continuous epidural infusion is associated with excellent postoperative analgesia and similar recovery of sensory and motor function after equipotent doses of levobupivacaine, bupivacaine and ropivacaine (Casati et al 2003a). The spread, quality and haemodynamic effects are also similar after equal doses of levobupivacaine and ropivacaine, self-administered via postoperative patient-controlled epidural analgesia, but ropivacaine-receiving patients appear to ambulate earlier (Senard et al 2004).

The effective dose of epidural levobupivacaine for continuous postoperative analgesia approaches 15 mg/hour (Murdoch et al 2002). The concentration of levobupivacaine solution determines the quality of analgesia, ie, 0.25% 6 mL/hour providing better analgesia than same volume more diluted solutions (0.125% and 0.0625%), although some prolongation of the motor blockade may be expected with more concentrated solutions (Murdoch et al 2002). Dernedde and colleagues encourage the use of large concentration-small volume epidural infusion (ie, 3 mL/h levobupivacaine 0.5% or 2 mL/hour levobupivacaine 0.75%) which provide similar quality of analgesia as the small concentration-large volume infusion (10 mL/hour levobupivacaine 0.15%) but with less motor block and significantly increased hemodynamic stability (Dernedde et al 2003a,b, 2006). In regards to the mode of delivery, patient-controlled epidural top-ups offer the advantage of equal quality analgesia with that after continuous infusion, but with less consumption of local anesthetic and better motor function (Dernedde et al 2005, 2006). Furthermore, the self-administration of levobupivacaine 15 mg either as low concentration large volume (1.5 mg/mL, bolus 3.3 mL, lockout 20 min) or high concentration small volume (5 mg/mL, 1 mL bolus, lockout 20 min) provides an equal quality of analgesia with no difference in the incidence of side effects (Dernedde et al 2005).

The addition of adjunctive agents (epinephrine, opioids or clonidine) to levobupivacaine in epidural anesthesia and analgesia may increase the duration and quality of analgesia, and further decrease the risk of toxicity. Epinephrine does not significantly influence the onset, spread and duration of sensory and motor epidural block, or the systemic absorption of levobupivacaine (Kopacz et al 2001). The addition of opioids (fentanyl, morphine) to levobupivacaine improves analgesia compared to levobupivacaine- or opioid-only infusions (Kopacz et al 1999b; Crews et al 1999). It also decreases the risk of local anesthetic toxicity by allowing the use of a small dose levobupivacaine (5–10 mg/hour) and a decline in self-administered analgesia requirements (Kopacz et al 1999b; Crews et al 1999). For example, with combined morphine background infusion (0.1 mg/hour), the effective analgesic dose of levobupivacaine ranges from 8 to 9 mg/hour during the first 24 hours and 7 mg/hour thereafter (Senard et al 2004). Similar improved analgesia and local anesthetic sparing-effect is noticed when clonidine (8 μg/mL) is added to small volume dilute levobupivacaine epidural infusions (0.125% 6 mL/hour) (Milligan et al 2000). The motor block tends to be denser with clonidine and some degree of arterial hypotension is expected, rarely of clinical importance (Milligan et al 2000).

Peripheral nerve blocks

Table 3 summarizes published studies comparing the characteristics of peripheral nerve blocks with levobupivacaine, bupivacaine and ropivacaine. A sensory and motor block of similar onset (6–10 min) and duration (14–16 hours) followed the administration of an equal dose of levobupivacaine 0.5% or bupivacaine 0.5% in brachial plexus nerve blocks (Cox et al 1998b; Liisanantti et al 2004; Duma et al 2005). As expected for larger diameter nerves, the onset time of sciatic nerve block is delayed to approximate 25–30 min, but the average duration remains 14–16 hours (Casati et al 2002a; Urbanek et al 2003). The quality of sensory and motor block appears to be similar in most studies after equal doses of levobupivacaine and bupivacaine (Cox et al 1998b, Casati et al 2002a,b, 2003b, 2005; Urbanek et al 2003). Ropivacaine 0.5% gives a less profound motor block than levobupivacaine and bupivacaine (Casati 2003b; Liisanantti et al 2004). Higher concentrations of levobupivacaine, ie, 0.5%–0.75% speed up the onset, and increase the duration and quality of peripheral nerves blockade (Cox et al 1998b; Urbanek et al 2003; Casati et al 2005). Similar to epidural analgesia, continuing the administration of levobupivacaine via a peripheral nerve block continuous catheter is associated with excellent postoperative analgesia as demonstrated by a significant decline in the postoperative systemic opioids requirements (Kean et al 2006).

Adding adjunctive analgesics such as epinephrine, clonidine or opioids to local anesthetic are also used to increase the quality of analgesia and improve safety by decreasing the requirements of levobupivacaine. The long duration of sensory and motor peripheral blockade after levobupivacaine of approximate 14–16 hours diminish the clinical importance of adding epinephrine to levobupivacaine. However, epinephrine may help decrease the potential for systemic toxicity in

Table 2 Summary of research investigating the quality of surgical epidural block after levobupivacaine

Reference	Dose/concentration and technique	No. of patients	Type of surgery	Onset time to surgical block, mean (SD) or median (range), min	Maximum sensory dermatome level	Duration of sensory block; mean (SD) or median (range), min or h	Onset time of motor block; mean (SD) or median (range), min	Duration of motor block; mean (SD or range), min or h	Completeness of motor block (% patients)	Adverse events(arterial hypotension)
Cox et al 1998a	15 mL levobupivacaine 0.5%	29	Lower limb	8 (5)	T8 (T2–12)	377 (128)	25 (23)	185 (122)	62%	Hypotension in 18 patients evenly distributed
	15 mL levobupivacaine 0.75%	30		6 (4)	T8 (C6–T11)T7	460 (111)[a]	27 (30)	256 (99)		
	15 mL bupivacaine 0.5%	29		7 (4)	(C6–L2)	345 (107)	17 (7)	192 (74)		
Casati et al 2003a	15 (10–18) levobupivacaine 0.5% + CEI levobupivacaine 0.125% 5 mL/h		Hip replacement							
	+ PCEA 2 mL bolus, lockout 20 min	15		31 (16)	T7 (T10–T4)	214 (61)			80	
	14 (10–18) mL bupivacaine 0.5% + CEI bupivacaine 0.125% 5 mL/h + PCEA 2 mL bolus, lockout 20 min	15		25 (19)	T6 (T10–T4)	213 (53)			100	
	15 (10–18) mL ropivacaine 0.5% + CEI ropivacaine 0.2% 5 mL/h + PCEA 2 mL bolus, lockout 20 min	15		30 (24)	T6 (T10–T4)	233 (34)			60[b]	
Kopacz et al 2000	20 mL levobupivacaine 0.75%	28	Lower abdominal	13 (10–18)	T5–T6	550.6 (87.6)[c]	Delayed by levobupivacaine	355.4 (83.4)	28%	82%
	20 mL bupivacaine 0.75%	28		13 (7–21)	T5–T6	505.9 (71)		375.7 (99.2)	25%	61%
Peduto et al 2003	15 mL levobupivacaine 0.5%	35	Lower limb	29 (24)		185 (77)		105 (63)	33%	3%
	15 mL ropivacaine 0.75%	30		25 (22)		201 (75)		95 (48)	11%	12%
Murdoch et al 2002	10–15 mL levobupivacaine 0.75%+ CEI levobupivacaine 0.0625% 6 mL/h	32	Hip or knee replacement			8.1 (5.0)		3[e]	8%[e]	
	10–15 mL levobupivacaine 0.75% + CEI levobupivacaine 0.125% 6 mL/h	32				9.5 (7.0)		4	25%	
	10–15 mL levobupivacaine 0.75% + CEI levobupivacaine 0.25% 6 mL/h	32				16.7 (8.3)[d]		7	22%	
Senard et al 2004	PCEA 0.1% levobupivacaine + CEI 0.1 mg/h morphine	25	Major abdominal surgery		T4–T5			4		20%
	PCEA 0.1% ropivacaine + CEI 0.1 mg/h morphine	25			T4–T5			4		20%

[a]$p < 0.05$ levobupivacaine 0.75% vs levobupivacaine 0.5% and bupivacaine 0.5%; [b]$p < 0.05$ ropivacaine vs levobupivacaine and bupivacaine; [c]$p = 0.01$ levobupivacaine vs bupivacaine; [d]$p < 0.001$ CEI levobupivacaine 0.25% vs levobupivacaine 0.125% and levobupivacaine 0.0625%; [e]$p < 0.002$ CEI levobupivacaine 0.0625% vs levobupivacaine 0.25%.

Abbreviations: CEI, continuous epidural infusion; PCEA, patient controlled epidural analgesia.

Table 3 Summary of published research using levobupivacaine in single-shot or continuous infusion in peripheral nerve blocks

Reference	Dose/concentration	No. of patients	Type of peripheral nerve block	Onset sensory block; mean (SD) or median (range), min	Success rate%	Duration of sensory block; mean (SD) or median (range), min or h	Onset motor block; mean (SD) or median (range), min	Duration of motor block; mean (SD) or median (range), min or h	Satisfactory motor block %	24 h local anesthetic consumption in continuous infusion; median (range), mL	Postoperative rescue analgesia consumption/24 h; % or n patients
Cox et al 1998b	0.4 mL/kg levobupivacaine 0.25%	25	Brachial plexus (supraclavicular)	7 (6)	100%	892 (250)	9 (17)	847 (246)	68%		
	0.4 mL/kg levobupivacaine 0.5%	26		6 (5)	92%	1039 (317)	5 (5)	1050 (325)	80%		
	0.4 mL/kg bupivacaine 0.5%	23		8 (8)	91%	896 (284)	6 (6)	933 (205)	74%		
Casati et al 2003b	30 mL levobupivacaine 0.5% + PCA levobupivacaine 0.125% 6 mL/h; 2 mL bolus; lockout 15 min	25	Brachial plexus (interscalene)	20 (15–45)	92%			24 h complete regression >90%	80% at 4 h[a]	147 (144–196)	47%
	30 mL ropivacaine 0.5% + PCA ropivacaine 0.2% 6 mL/h; 2 mL bolus; lockout 15 min	25		20 (10-40)	96%			>90%	60% at 4 h	162 (144–248)[b]	55%
Liisanantti et al 2004	45 mL levobupivacaine 0.5%	30	Brachial plexus (axillary)		57%	17.1 (6.5)			30%		21
	45 mL bupivacaine 0.5%	30			77%[c]	17.8 (7.2)			47%		22
	45 mL ropivacaine 0.5%	30			83%[c]	15.0 (5.4)			67%[d]		26
Duma et al 2005	40 mL levobupivacaine 0.5%	20	Brachial plexus (axillary)	10 (5–60)		1083 (785–1680)	10 (5–120)				
	40 mL levobupivacaine 0.5% + clonidine 150 μg	20		5 (5–60)		1365 (705–2465)	10 (5–180)				
	40 mL bupivacaine 0.5%	28		10 (5–60)		1063 (600–1310)	10 (5–60)				
	40 mL bupivacaine 0.5% + clonidine 150 μg	20		10 (5–60)		1040 (520–2380)	30 (5–60)				
Piangatteli et al 2006	30 mL levobupivacaine 0.5%	15	Brachial plexus (infraclavicular)	13.46 (1.06)		11.40 (2.2) h[e]	19.33(2.58)	.42 (0.8) h[e]			
	30 mL ropivacaine 0.75%	15		14.20 (1.17)		10.26 (1.38) h	20.20 (2.39)[f]	8.33 (1.48) h			
Casati et al 2002b	20 mL levobupivacaine 0.5%	25	Sciatic nerve	30 (5–60)	92%	16 (8–24)		13 (4–22)			12%
	20 mL ropivacaine 0.5%	25		15 (5–60)	96%	16 (8–24)		12 (6–20)			16%
Casati et al 2004b	30 mL levobupivacaine 0.5% + levobupivacaine 0.2% 6 mL/h	20	Continous sciatic nerve (popliteal)	34 (17)				24 h complete regression 35%		150(144–200)	5.5%
	30 mL levobupivacaine 0.5% + levobupivacaine 0.125% 6 mL/h	20		32 (15)				95%[g]		148(144–164)	11%
	30 mL ropivacaine 0.5% + ropivacaine 0.2% 6 mL/h	20		28 (15)				85%[g]		148(144–228)	27%
Piangatteli et al 2004	30 mL levobupivacaine 0.5%	40	Lumbar + sciatic (30/10 mL)	10.63 (1.39)		15.52 (2.78)		12.17 (1.69)			
	30 mL ropivacaine 0.75%	40	Lumbar + sciatic (30/10 mL)	17.15 (2.87)[h]		14.80 (1.91)		12.30 (1.60)			

(*Continued*)

Table 3 (*Continued*)

Reference	Dose/concentration	No. of patients	Type of peripheral nerve block	Onset sensory block; mean (SD) or median (range), min	Success rate%	Duration of sensory block; mean (SD) or median (range), min or h	Onset motor block; mean (SD) or median (range), min	Duration of motor block; mean (SD) or median (range), min or h	Satisfactory motor block %	24 h local anesthetic consumption in continuous infusion; (median (range), mL	Postoperative rescue analgesia consumption/24 h; % or n patients
Casati et al 2002a	20 mL levobupivacaine 0.5%	15	Sciatic nerve	32 (5)	94%	814 (96)		716 (80)			
	20 mL bupivacaine 0.5%	15		35 (5)	94%	790 (110)		761 (112)			
Casati et al 2005	20 mL levobupivacaine 0.5%	15	Sciatic nerve	30 (5–60)[i]	75%	16 (13–20)[j]					8[k]
	20 mL levobupivacaine 0.75%	15		5 (5–40)	100%	18 (15–19)[j]					3
	20 mL ropivacaine 0.75%	15		20 (5–50)	87%	13 (11–14)					9[k]
Urbanek et al 2003	20 mL levobupivacaine 0.5%	20	3-in-1 block	24 (18–30)	80%[l]	1001 (844–1158)[m]					
	20 mL levobupivacaine 0.25%	20		30 (23–36)	45%	707 (551–863)					
	20 mL bupivacaine 0.5%	20		27 (20–33)	80%[l]	1053 (802–1304)[m]					

[a]$p = 0.003$ levobupivacaine vs ropivacaine; [b]$p = 0.02$ ropivacaine vs levobupivacaine; [c]$p < 0.01$ ropivacaine and bupivacaine vs levobupivacaine; [d]$p < 0.01$ ropivacaine vs levobupivacaine and bupivacaine; [e]$p < 0.05$ levobupivacaine vs ropivacaine; [f]$p < 0.05$ ropivacaine vs levobupivacaine; [g]$p = 0.0005$ ropivacaine 0.2% and levobupivacaine 0.125% vs levobupivacaine 0.2%; [h]$p < 0.05$ ropivacaine vs levobupivacaine; [i]$p = 0.02$ levobupivacaine 0.5% vs levobupivacaine 0.75%; [j]$p = 0.002$ levobupivacaine 0.5% and levobupivacaine 0.75% vs ropivacaine 0.75%; [k]$p = 0.05$ levobupivacaine 0.5% and ropivacaine 0.75% vs levobupivacaine 0.5% and bupivacaine 0.5% vs levobupivacaine 0.25%; [m]$p = 0.01$ levobupivacaine 0.5% and bupivacaine 0.5% vs levobupivacaine 0.25%.

case of overdose by decreasing systemic absorption through vasoconstriction or by signaling the accidental intravascular injection. The addition of clonidine to levobupivacaine in axillary plexus or psoas compartment was not followed by any significant effect on block's characteristics and postoperative analgesic requirements (Duma et al 2005; Mannion et al 2005). In contrast, our group found a significant decrease in postoperative systemic morphine use when clonidine was added to levobupivacaine in continuous paravertebral nerve block (Burlacu et al 2006). Similarly, we found that the addition of fentanyl to levobupivacaine is also followed by excellent analgesia as demonstrated by a significant decrease in rescue morphine analgesia. Furthermore, we demonstrated that clonidine and fentanyl had a strong local anesthetic sparing effect, as the concentration of levobupivacaine (0.05%) used for continuous infusion was the lowest ever used in paravertebral block (Burlacu et al 2006).

Levobupivacaine in obstetric anesthesia and analgesia

Spinal anesthesia for caesarean section

The concept of pharmacological equipotency of levobupivacaine and bupivacaine was challenged in several dose-finding studies in obstetric patients receiving spinal anesthesia for caesarean section. For example, Khaw and colleagues found that levobupivacaine is 38% less potent than bupivacaine, with an ED50 and ED95 values of 9.3 and 13.6 mg vs 6.8 and 9.8 mg, respectively (Khaw et al 2004). Parpaglioni and colleagues estimated a similar ED95 levobupivacaine of 12.56 mg, whereas the ED95 ropivacaine was 15.97 mg (Parpaglioni et al 2006). The above potency hierarchy ie, bupivacaine >levobupivacaine > ropivacaine was confirmed in clinical studies in caesarean section patients (Gautier et al 2003; Buyse et al 2007). Based on these studies and our own experience, we recommend that levobupivacaine 12.5–13.5 mg should be used for successful spinal anesthesia for caesarean section. A test dose of 10 mg levobupivacaine is sufficient to confirm at 5 min the accidental intrathecal placement of an epidural-intended catheter (Camorcia et al 2004).

Analgesia for labor

Minimum effective local anesthetic concentration (MLAC) studies using a combined spinal-epidural analgesia technique (CSE) for labor also confirm the potency arrangement bupivacaine >levobupivacaine >ropivacaiane for spinal sensory block (Camorcia et al 2005). However, the above hierarchy is not so clear in regards to epidural only analgesia

Table 4 Summary of clinical studies of epidural (with its versions ie single bolus, continuous infusion or patient-controlled epidural analgesia) and combined spinal-epidural analgesia in labour.

Reference	Dose/concentration	No. Subjects	Anesthetic technique	Onset time of sensory block, mean (SD) or median (range), min	Maximum sensory dermatome level	Duration of sensory block mean (SD) or median (range), min	Successful sensory block (% patients)	Modified Bromage > 0 (% patients)	Maternal arterial hypotension (% patients)
Burke et al 1999b	10 mL levobupivacaine 0.25%	68	10 mL epidural bolus +	12 (5–39)	T8	49 (3–129)	85%	16%	11%
	10 mL bupivacaine 0.25%	69	10 mL top-ups	12 (2–50)	T9	51 (7–157)	91%	17%	7%
Convery et al 1999	10 mL levobupivacaine 0.25%	38	10 mL epidural bolus +		Similar		43.3%	Less motor block with levobupivacaine	
	10 mL bupivacaine 0.25%	42	CEI 0.125% 12 mL/h + 10 mL 0.25% top-ups				43.7%		
Supandji et al 2004	10 mL levobupivacaine 0.2%	20	10 mL epidural bolus		T8 (6–10)	90.50 (31.72)	100%	20%	0
	10 mL ropivacaine 0.2%	20			T8 (6–10)	103.30 (37.52)	100%	30%	0
Purdie and McGrady 2004	15 mL levobupivacaine 0.1% with fentanyl 2 μg/mL	28	15 mL epidural bolus; PCEA 5 mL; lockout 5 min	38 (19–51)	T6 (3–11)	34 (25–50)		32%	32%
	15 mL ropivacaine 0.1% with fentanyl 2 μg/mL	26		30 (15–45)	T8 (4–11)	35 (20–37)		30%	50%
Lim et al 2004a	2.5 mg levobupivacaine	20	CSE	5	T4 (1–9)	51.5 (3.4)	100%	0%	5%
	2.5 mg bupivacaine	20		5	T3 (1–8)	76.3 (5.9)[a]	100%	25%[a]	5%
	2.5 mg ropivacaine	20		5	T4 (1–9)	52.6 (4.0)	100%	10%	0%
Lim et al 2004b	2.5 mg levobupivacaine	20	CSE; CEI levobupivacaine 0.125% with fentanyl 2 μg/mL		T4 (1–9)	361 (66)	43.8%	15%	0%
	2.5 mg levobupivacaine + 25 μg fentanyl	20			T3 (1–8)	530 (65)[b]	87.5%[b]	25%	15%
Chang and Chiu 2004	2.5 mg levobupivacaine + fentanyl 25 μg	20	CSE	15	T4 (2–10)	101.4 (26.64)	95%	75%[c]	10%
	1.25 mg levobupivacaine + fentanyl 12.5 μg	20		15	T4 (3–10)	90.6 (28.03)	100%	25%	5%
Soetens et al 2006	Levobupivacaine 0.125% + sufentanyl 2.5 μg/mL + 1:800000 epinephrine	34	CEI 10 mL/h + 10 mL mixture top-up				88% [d]	50%	6%
	Levobupivacaine 0.125% + sufentanyl 2.5 μg/mL	33					66%	27%	9%

[a]$p < 0.05$ bupivacaine vs levobupivacaine and ropivacaine; [b]$p < 0.05$ levobupivacaine and fentanyl vs levobupivacaine only; [c]$p < 0.01$ levobupivacaine 2.5 mg with fentanyl 25 μg vs half dose of each; [d]$p < 0.05$ epinephrine group vs the other group.

Abbreviations: CEI, continuous epidural infusion; CSE, combined spinal-epidural; PCEA, patient-controlled epidural analgesia.

for labor. Up-and-down sequential allocation studies in patients receiving epidural analgesia for labor pain show that levobupivacaine and bupivacaine on one side (Lyons et al 1998), and levobupivacaine and ropivacaine on the other side (Polley et al 2003; Benhamou et al 2003) are equipotent. One would reasonably assume that the three local anesthetics are equipotent. Intriguingly however, in other similar design studies (Polley et al 1999; Capogna et al 1999), ropivacaine was found to be 40% to 50% less potent than bupivacaine. The minimum effective local anesthetic concentration of levobupivacaine for motor block (MMLAC) is significantly greater than that of bupivacaine indicating that levobupivacaine is less potent at motor block than bupivacaine when administered in epidural analgesia for labor (Lacassie and Columb 2003).

The relative potency of the three most commonly used drugs in obstetric anesthesia remains to be further elucidated, but the current evidence from MLAC and MMLAC studies suggest a potency hierarchy of bupivacaine >levobupivacaine >ropivacaine. However, the epidural and spinal MLAC or MMLAC studies estimate the concentration at which only 50% of laboring patients will have adequate pain control with minimal motor block. In clinical practice, anesthetists are inclined to administer larger doses of local anesthetic to ensure adequate pain relief in the majority of patients. Because of the variety of doses and adjunctive analgesics combinations used in clinical studies (Table 4), the rank of order established by the MLAC studies is not always easy to corroborate (Burke et al 1999b; Convery et al 1999; Purdie and McGrady 2004; Lim et al 2004a; Suspandji et al 2004).

Table 4 also shows the results of several studies using levobupivacaine combined with opioids with or without epinephrine in epidural or CSE analgesia in labor. In particular, the addition of fentanyl to levobupivacaine prolongs the duration and increases the success rate of the sensory block after intrathecal administration in a CSE analgesia technique (Lim et al 2004b). A local anesthetic sparing effect of fentanyl is also demonstrated as intrathecal levobupivacaine 1.25 mg with fentanyl 12.5 μg was followed by effective analgesia with less motor block compared with a double dose of each drug (Chang and Chiu 2004). The addition of epinephrine to a mixture of levobupivacaine and opioid increased the success rate of sensory block but appeared to also increase the frequency of motor blockade (Soetens et al 2006).

In our experience, using an epidural bolus of 10 mL levobupivacaine 0.2%–0.25% followed by epidural infusions or top-ups of low concentrations levobupivacaine (ie, 0.1%–0.125%) combined with opioids based on institutionally designed protocols, provides the same good quality labor analgesia as bupivacaine, but possibly with less motor block. A combined spinal-epidural technique with intrathecal levobupivacaine 1.2–2.5 mg combined with small dose opioid (eg, fentanyl 12.5–25 μg) provides excellent prolonged sensory block with minimum motor blockade.

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