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Review

Pharmacology, toxicology, and clinical use of new long acting local anesthetics, ropivacaine and levobupivacaine

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Abstract. Levobupivacaine and ropivacaine, two new long-acting local anesthetics, have been developed as an alternative to bupivacaine, after the evidence of its severe toxicity. Both of these agents are pure left-isomers and, due to their three-dimensional structure, seem to have less toxic effects on the central nervous system and on the cardiovascular system. Many clinical studies have investigated their toxicology and clinical profiles: theoretically and experimentally, some differences have been observed , but the effects of these properties on clinical practice have not been shown. By examining randomised, controlled trials that have compared these three local agents, this review supports the evidence that both levobupivacaine and ropivacaine have a clinical profile similar to that of racemic bupivacaine, and that the minimal differences reported between the three anesthetics are mainly related to the slightly different anesthetic potency, with racemic bupivacaine > levobupivacaine > ropivacaine. However, the reduced toxic potential of the two pure left-isomers suggests their use in the clinical situations in which the risk of systemic toxicity related to either overdosing or unintended intravascular injection is high, such as during epidural or peripheral nerve blocks. (www.actabiomedica.it)

Key words: Pharmacology, local anesthetic: bupivacaine, ropivacaine, levobupivacaine, regional anesthesia techniques

Introduction

Levobupivacaine and ropivacaine are two relatively new long-acting local anesthetics introduced into the market in the last few years, that have been developed after reports of simultaneous seizure and cardiac arrest with prolonged resuscitation after accidental intravascular injection of bupivacaine (1).

Due to their three- dimensional structure, local anesthetics molecules can also have a stereospecificity, with two enantiomer molecules that may exist in two different spatial configurations, like left- and right-handed gloves. The molecules of local anaesthetics possess an asymmetric carbon atom which is bound to four different substitutes. The structures of these compounds are defined as chiral. Enantiomers are optically active, and can be differentiated by their effects on the rotation of the plan of a polarized light into dextrorotatory [clockwise rotation (R+)] or levorotatory [counterclockwise rotation (S-)] stereoisomers. A solution of bupivacaine contains equal amounts of the two enantiomerics and is called racemic solution, while technological advancements allowed the production of solutions containing only one enantiomer of a chiral molecule, which is optically pure. The physicochemical properties of the two enantiomeric molecules are exactly the same, but the two enantiomers can have substantially different behaviors in their affinity for either the site of action or the sites involved in the generation of side effects.

R- and S- enantiomers of local anesthetics have been demonstrated to have a different affinity for the different ion channels of sodium, potassium, and calcium (2), and this results in a significant reduction of

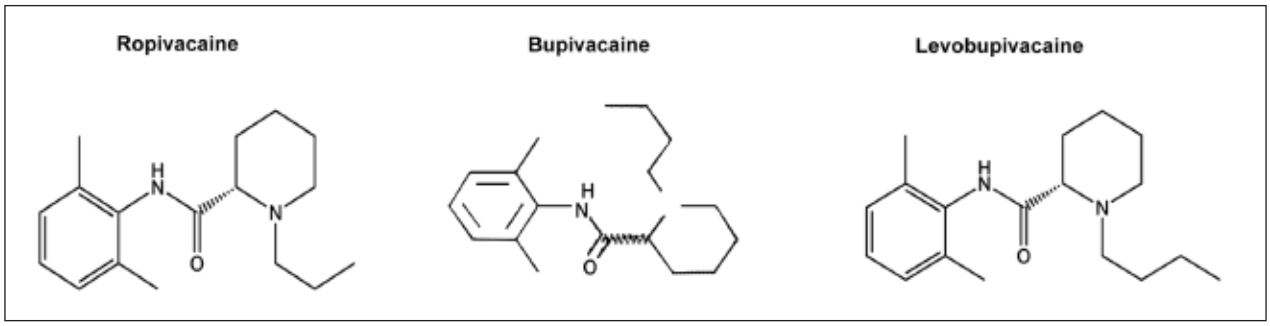

Figure 1. Structure of the three local anaesthetics

central nervous system and cardiac toxicity of the S-enantiomer as compared with the R-enantiomer (3). Ropivacaine and levobupivacaine are available as optically pure solutions.

The aim of this review is to provide the reader with an overview of the clinical pharmacology and toxicology of these two agents and their clinical application in different fields of anesthesia.

Pharmacology and toxicology

Bupivacaine is an amino-amide local anesthetic which belongs to the family of the n-alkylsubstituted pipecoloxylidide, which were first synthesized by Ekenstam in 1957 (4). Its molecular structure is highly lipid-soluble, and contains a chiral center on the piperidine ring, resulting in two optically active stereoisomers. Ropivacaine also belongs to the same pipecoloxylidide group (Fig. 1), but whereas ropivacaine has a propyl group, bupivacaine has a butyl group on the amine portion of pipecoloxylidide. The pKa of the three agents are similar, as well as their protein binding, while ropivacaine is much less lipophilic than the two other molecules because of the substitution of the pipecoloxylidine with a 3-carbon side-chain instead of a 4-carbon side-chain (Tab. 1).

Central Nervous System Toxicity

Systemic toxicicty of local anesthetics may occur as a consequence of unwanted intravascular or intrathecal injection, or after the administration of an excessive dose of these drugs. Systemic toxicity of local anesthetic drugs primarily involves the central nervous system (CNS) and then the cardiovascular system. Usually, the CNS is more susceptible to the actions of local anesthetics than the cardiovascular

Table 1. Physico-chemical and pharmacokinetic properties of the three considered long-acting local anaesthetics

	Bupivacaine	Ropivacaine	Levobupivacaine
Molecular Weight[a]	288	274	288
Pka[a]	8.1	8.1	8.1
Liposolubility[a]	30	2.8	30
Partition coefficient[b] (octanol/buffer)	346,0	115,0	346,0
Protein Binding[a]	95%	94%	95%
Vd_{ss} (L)[c]	73	59	54
T $^1/_2$ (min)[c]	210	111	157
Clearance[c] (l min^{-1})	0.58	0.72	0.32

[a] From Fanelli G, Casati A, Chelly Jacques E, Bertini L. Blocchi Periferici Continui. *Mosby Italia*, 2001; pag. 31
[b] From Strichartz GR, Sanchez V, Arthur GR. Fundamental properties of local anesthetics. II. Measured octanol: buffer partition coefficients and pKa values of clinically used drugs. *Anesth Analg* 1990; 71: 158.
[c] From Adams AP, Grounds RM, Cashman Jeremy N. Recent Advances and Intensive Care, Inc NetLibrary, 2002.

system; thus signs of CNS intoxication are usually evident before the appearance of cardiovascular toxicity.

Initial signs of CNS toxicity are usually excitatory and include shivering, muscle twitching, and tremors, which are produced by a preferential block of inhibitory central pathways. With the increase of the local anesthetic plasma concentrations, the excitatory pathway of CNS toxicity is blocked and signs of CNS excitation are followed by a generalized CNS depression with hypoventilation and respiratory arrest, and, finally, generalized convulsions. The convulsive threshold dose is one of the objective measures of CNS toxicity.

For ethical reasons, human subjects can only be given mildly toxic doses when local anesthetics are deliberately administered intravenously for research, until initial subjective signs of CNS toxicity are shown (5-10). Further information on more serious toxicity should therefore be derived from laboratory animal "models." On the other hand, it must be also considered that specie to specie variability, and differences between human and animal models can affect the strength of external validity (11). Table 2 shows the convulsive local anesthetic doses of bupivacaine, levobupivacaine and ropivacaine in different animal models: bupivacaine has a 1.5- to 2.5-fold lower convulsive threshold when compared to the two S-isomers (12).

A recent study has confirmed a better neurotoxic profile of levobupivacaine when compared to racemic bupivacaine, and this is indicative of a safer profile of levobupivacaine in clinical practice (12). The authors compared the neurotoxicity of racemic bupivacaine and levobupivacaine in a mouse model of NMDA-induced seizures and in a vitro model of excitotoxic cell death. At high doses (36 mg/kg) both bupivacaine and levobupivacaine reduced the latency to NMDA-induced seizures and increased seizure severity. However, levobupivacaine-treated animals underwent less severe seizures when compared with bupivacaine-treated animals. At doses of 5 mg/kg, levobupivacaine increased the latency of partial seizures and prevented the occurrence of generalized seizures, whereas bupivacaine decreased the latency of partial seizures and did not influence the development of generalized seizures (12). Convulsant doses of levobupivacaine and ropivacaine are similar in the anaesthetized ventilated rat, but they are slightly higher with ropivacaine than levobupivacaine in sheep that are awake (11).

The absolute doses of local anesthetic inducing toxic effects is affected by several factors, including the way and rate of administration, the rapidity with which a certain plasma level is achieved, and whether the animal is under the influence of anesthesia. This often makes it difficult to compare and extrapolate the results of animal studies to human patients.

Few clinical studies have evaluated the dose of local anesthetics tolerated by human volunteers before the occurrence of initial signs of CNS toxicity (dizziness, ear disorder and deafness, tinnitus, speech disorders, circumoral paresthesia, and taste perversion). Stewart et al (10) compared the CNS and cardiovascular effects of levobupivacaine and ropivacaine given intravenously to healthy male volunteers in a double-

Table 2. Convulsive doses of racemic bupivacaine, levobupivacaine, and ropivacaine in various animal species and dosing regimens (modified by Groban [11])

Animal model	Route of administration	Dosing of Bupivacaine	Dosing of Levobupivacaine	Dosing of Ropivacaine
Rat	Intravenous infusion	2.8 mg/kg		4.5 mg/kg
Dog	Intravenous infusion	9.3 mg/kg	12.8 mg/kg	13.2 mg/kg
Sheep	Intravenous infusion (plasma concentration)	0.014 mmol/kg 2.49 μg/ml	0.018 mmol/kg 5.59 μg/ml	0.21 mmol/kg 4.7 μg/ml
Sheep	Intravenous bolus (plasma concentration) (total dose)	1.6 mg/kg 10 μg/ml (69 mg)		3.5 mg/kg 17 μg/ml (155 mg)
Sheep	Intravenous bolus	69-85 mg	103-127 mg	

blind, cross-over study, and reported that the two left isomers produced similar CNS effects when intravenously infused at equal concentrations, milligram doses, and infusion rates; without differences in terms of time of onset of CNS symptoms and in terms of mean total volume of drug administered at the onset of the first CNS symptom.

Similar volunteer studies compared CNS toxicity of ropivacaine and levobupivacaine, and showed that both left isomers are less neurotoxic than racemic bupivacaine, with doses of levobupivacaine and ropivacaine inducing initial signs of CNS toxicity 10–25% larger than those of bupivacaine (9, 13, 14). Levobupivacaine has also been demonstrated to have less depressant effects on the electroencephalogram than racemic bupivacaine (15).

Based on animal and volunteer studies, it can be concluded that both levobupivacaine and ropivacaine seem to be less neurotoxic than bupivacaine. They have a higher convulsive threshold in different animal models, fewer CNS symptoms after intravenous administration in human volunteers, and fewer excitatory changes in the EEG than bupivacaine.

Cardiovascular Toxicity

The first signs of cardiac toxicity are related to the CNS excitatory phase with the activation of the sympathetic nervous system, which can mask direct myocardial depression. However, with increasing plasma concentrations of the local anesthetic this stage is followed by arrhythmias and profound cardiac depression, resulting in cardiovascular collapse (15).

All three long-acting local anesthetics show a dose-dependent prolongation of cardiac conduction, with an increase in the PR interval and QRS duration on the electrocardiogram. These effects are explained by the persisting block of sodium channels into diastole, predisposing to re-entrant arrhythmias (15). Since the dissociation caused by bupivacaine is nearly 10 times longer than that of lidocaine, bupivacaine-induced block can accumulate, resulting in a more marked cardiac depression (16, 17). Local anesthetics also affect the conductivity of potassium channels, increasing the QTc interval and enhancing the block of the inactivated state of the sodium channel (18). The levorotatory isomer of bupivacaine is seven-fold less potent in blocking the potassium channel than the dextrorotatory one (19). Moreover, the potency and affinity of the R(+) enantiomer for the potassium channel mostly depends on the length of the alkyl substitute at position 1, being more marked for the butylic than propylic and methylic chains (20, 21). Local anesthetics block adenosine triphosphate-sensitive potassium (KATP) channels, with an approximately eight-fold higher potency than vascular KATP channels, and bupivacaine is more potent than both levobupivacaine and ropivacaine in blocking cardiac KATP channels (22).

Despite the electrophysiological evidence of stereoselective binding to sodium and potassium channels, Groban et al. (23) reported that the plasma concentrations resulting in a 35% reduction in dP/dt-max and ejection fraction were 4.0 and 3.0 mg/ml for ropivacaine, 2.4 and 1.3 mg/ml for levobupivacaine, and 2.3 and 2.1 mg/ml for racemic bupivacaine. Similar results have been reported in awake sheep (24) and isolated heart preparations (25), and might be related to the lack of enantiomer-selective inhibition of calcium channels (26) or to the different effects of the three long-acting anesthetics on mitochontrial energy metabolism (27, 28).

The inhibition of cardiac contractility is also proportional to the lipid solubility and nerve-blocking potency of the local anesthetics, suggesting a rank order (from lowest to highest) of the cardiotoxic potency of the three local anesthetics with ropivacaine <S() bupivacaine <racemic bupivacaine <R(+) bupivacaine (29).

Royse et al (30) used pressure volume loops to separate myocardial and vascular effects infusing the drugs at a ratio of 0.125: 0.2 for levobupivacaine and bupivacaine/ropivacaine to simulate clinical use. They found that bupivacaine and levobupivacaine reduced ejection fraction (EF) and cardiac index, but not ropivacaine. A recent study investigated the influence of ropivacaine on cardiac contractility confirming the low cardiotoxic potency of this drug (31).

Groban et al (32) also evaluated cardiac resuscitation after incremental overdose with lidocaine, bupivacaine, levobupivacaine and ropivacaine in anaes-

thetized dogs, reporting significant differences in the inability to resuscitate the intoxicated dogs between racemic bupivacaine- and levobupivacaine-treated animals (50 and 30%, respectively) and ropivacaine- and lidocaine-treated ones (10 and 0%, respectively). On the contrary, no differences in the numbers of successfully resuscitated animals were reported between ropivacaine, levobupivacaine and bupivacaine in rats (92, 92 and 83%, respectively), even though the cumulative dose producing cardiac arrest was greater for ropivacaine (108 ± 27 mg/kg) than for levobupivacaine (57 ± 8 mg/kg) and racemic bupivacaine (39 ± 9 mg/kg) (33). However, significantly less adrenaline (epinephrine) was required to treat ropivacaine-induced cardiac arrest than for levobupivacaine- or bupivacaine-treated rats (33).

When the cardiovascular effects of levobupivacaine and ropivacaine are compared after intravascular injection in healthy volunteers, no differences in mean percentage changes from baseline to the end of infusion were reported for stroke index, cardiac index, acceleration index, or for PR interval, QRS duration, QT interval and heart rate (10). Depression of conduction and contractility appeared at lower doses and plasma concentration with bupivacaine than ropivacaine (9,13) or levobupivacaine (14).

Relative Potency

Local anaesthetics bind directly to the intracellular voltage-dependent sodium channels. They block primarily open and inactive sodium channels, at specific sites within channel. Lipid solubility appears to the primary determinant of intrinsic anesthetic potency. Chemical compounds which are highly lipophilic tend to penetrate the nerve membrane more easily, so that less molecules are required for conduction blockade resulting in enhanced potency. For this reason, a strict correlation between the lipid solubility of the local anesthetic and its potency and toxicity exists. Brau et al (34) reported that levobupivacaine or racemic bupivacaine were nearly 50% more potent than ropivacaine in inhibiting tetrodoxin-resistant sodium channels; whereas Kanai et al (35) compared the anesthetic effects of S(-)bupivacaine, R(+)bupivacaine and ropivacaine on action potential amplitude and maximal rate of rise of action potential in crayfish giant axon, and reported that S(-) bupivacaine has a more potent phasic blocking effect than ropivacaine. Sinnott et al (36) compared three concentrations of either ropivacaine or levobupivacaine (0.0625, 0.125 and 0.25%) for sciatic nerve block in the rat, and demonstrated that the duration of block induced by 0.25% levobupivacaine was nearly 30% longer than that of ropivacaine.

The evaluation of relative potencies of local anesthetics by determining the whole dose–response curve is not feasible in humans. Alley et al (37) evaluated three intrathecal doses of levobupivacaine and bupivacaine (4, 6 and 8 mg) in healthy volunteers and found no differences in clinical profile of sensory and motor blocks and recovery from spinal anesthesia. The same group also compared the same doses of ropivacaine and bupivacaine in a similar study on volunteers (38) and reported that ropivacaine is half as potent as bupivacaine.

The relative potency of these three long-acting local anesthetics has been also evaluated in patients by determining the minimum local anesthetic concentration (MLAC) producing adequate pain control in 50% of patients receiving an epidural block for labor pain with an up-and-down sequential allocation technique; clinical findings confirmed results of animal studies, showing no differences in the MLAC of levobupivacaine (0.083%) and bupivacaine (0.081%) (39), and nearly 50% higher MLAC values for ropivacaine (40, 41). Sia et al (42) reported a minimum effective dose of intrathecal levobupivacaine of 1.07 mg (95% CI, 0.88-1.25) as compared with 1.40 mg (95% CI, 1.20-1.61) for ropivacaine. Accordingly, levobupivacaine was 1.31 times more potent than ropivacaine (95% CI: 1.04-2.01), but this ratio reduced when the comparison was based on molar potency.

More recently, Camorcia et al (43) reported that the ED50 for motor block after spinal injection was 4.8 mg (95% CI, 4.49-5,28) with levobupivacaine and 5.9 mg (95% CI, 4.82-6.71) with ropivacaine, with a 0.85 potency ratio between the two drugs (95% CI, 0.69-0.99).

However, contrasting results have been reported in other clinical settings. Casati et al (44) evaluated

the minimum volume of local anesthetic required to produce an effective block of the femoral nerve in 50% of patients within 20 min after the injection, similar to that required when using 0.5% bupivacaine.

Clinical applications

Epidural Anesthesia/Analgesia

Despite the potency ratio issue discussed above, there is a large number of clinical studies showing that, when used at clinically relevant concentrations (0.5-0.75%), epidural ropivacaine produces an epidural blockade, which is substantially similar to that produced by equivalent concentrations and doses of racemic bupivacaine (45-50).

When evaluating the use of levobupivacaine for epidural anesthesia for both lower limb and abdominal surgery, the first studies reported in the literature showed that clinical profile of the 0.5% levobupivacaine and the 0.75% ropivacaine are similar to that produced by the same concentrations of racemic bupivacaine (50-52). When injecting up to 25 ml of either levobupivacaine or racemic bupivacaine at 0.5% concentration for elective caesarean section, Faccenda et al (53) reported that levobupivacaine provided a less motor block than bupivacaine.

Based on the potency ratio between levobupivacaine and ropivacaine reported in MLAC studies during epidural labor analgesia, Peduto et al (54) reported that epidural injection of 15 ml of either 0.5% levobupivacaine or 0.75% ropivacaine produced similar epidural blockade in patients undergoing lower limb surgery; moreover Casati et al (55) in a similar setting reported that patients receiving 0.5% ropivacaine had more frequently an inadequate motor blockade during surgery than those receiving the same concentration of either levobupivacaine or racemic bupivacaine. In the same study, the authors also evaluated the quality of postoperative analgesia provided with a patient-controlled epidural infusion of 0.125% bupivacaine, 0.125% levobupivacaine or 0.2% ropivacaine, and showed similar pain relief and postoperative sensory/motor differentiation (Tab. 3). On the contrary, Bertini et al (56) reported that epidural infusion of 0.2% ropivacaine after hip replacement provided similar pain relief but less motor blockade and higher patient satisfaction than the same concentration of bupivacaine (Tab. 4).

Pouzeratte et al (57) reported that thoracic epidural analgesia with 0.125% bupivacaine was more effective than 0.125% ropivacaine when used in combination with 0.5 μg/ml sufentanil; while 0.2% ropivacaine alone was less effective than the mixture of 0.125% ropivacaine and sufentanil. However, contrasting results have been reported by other studies, showing similar clinical profile of epidural analgesia produced with ropivacaine and bupivacaine (58-60).

A similar dose-dependent effect was also reported with levobupivacaine for lumbar epidural analgesia after orthopedic surgery (61). On the other hand, if the total hourly dose is kept constant, using large-concentration/small-volume (3 ml/h of 0.5% levobupiva-

Table 3. Epidural anaesthesia: onset times and duration of the three considered long-acting local anaesthetics

Reference	Dose/Concentration	n° pts	Type of surgery	Onset time (min)	Duration of the block (min)	Percentage of motor block
Anaesthesia						
[52]	20 ml levobupivacaine 0.75%	28	Abdominal	13.6 ± 5.6	550 ± 87	
	20 ml bupivacaine 0.75%	28		14.0 ± 9.9	505 ± 71	
[54]	15 ml ropivacaine 0.75%	30	Lower limb	25 ± 22	201 ± 48	
	15 ml levobupivacaine 0.5%	35		29 ± 24	185 ± 77	
[55]	15 ml bupivacaine 0.5%	15	Hip surgery	25 ± 19	213 ± 53	100%
	15 ml ropivacaine 0.5%	15		30 ± 24	233 ± 34	60%[a]
	15 ml levobupivacaine 0.5%	15		31 ± 16	214 ± 61	80%

[a] $P < 0.05$ versus bupivacaine and levobupivacaine

Table 4. Epidural analgesia: percentage of motor block and consumption of the three considered long-acting local anaesthetics

Reference	Dose/Concentration		Type of surgery	Percentage of motor block	Consumption of L.A.
Analgesia					
[56]	6 ml/h ropivacaine 0.2% + PCEA[c]	25	Hip surgery	0%	175 ± 12 ml
	6 ml/h bupivacaine 0.2% + PCEA[c]	26		27%[a]	178 ± 12 ml
[66]	0.1% ropi. + 0.1 mg/h morphine	25	Abdominal	6 / 25	347 ± 199 mg
	0.1% bupi. + 0.1 mg/h morphine	25		13 / 25[b]	344 ± 178 mg

[a] P < 0.05 versus ropivacaine;
[b] P < 0.05 versus ropivacaine;
[c] PCEA: Patient Controlled Epidural Analgesia

caine) resulted in similarly effective analgesia with less motor blockade and hemodynamic side effects than using a small-concentration/ large-volume regimen (10 ml/h of 0.15% levobupivacaine) (62-64).

Launo et al (65) compared 0.125% levobupivacaine and 0.2% ropivacaine in combination with fentanyl 2 μg/ml for thoracic epidural analgesia after aortic surgery, and reported no differences in quality of analgesia and degree of motor block. Senard et al (66) compared the efficacy, dose requirements, side effects and motor block with epidural infusion of 0.1% levobupivacaine or 0.1% ropivacaine with added 0.1 mg/h morphine after major abdominal surgery, and showed no differences in quality of pain relief and hourly consumption of the local anesthetic mixture between the two groups (Tab. 4); however recovery of unassisted ambulation was quicker with ropivacaine than levobupivacaine (76% of patients able to ambulate on the second postoperative day with ropivacaine versus 48% with levobupivacaine; P <0.05).

When considering the effects of adding additives like epinephrine, clonidine and opioids for epidural anesthesia and analgesia, no advantages were reported with the addition of epinephrine at 2.5 or 5 μg/ml concentrations (67); while the addition of opioids improved the quality of pain relief without affecting the degree of motor blockade (68-70). On the other hand, clonidine improves postoperative analgesia with a dose dependent effect on motor blockade (71), (Tab. 3).

Spinal anesthesia

Racemic bupivacaine has been considered as the elective long-acting local anesthetic in most of the regional anesthesia procedures, especially for spinal anesthesia. Moreover, spinal anesthesia requires very small doses of local anesthetic, making the risk for bupivacaine-related systemic toxicity not an issue. Nonetheless, several studies have been published in the last years on intrathecal use of the two new long acting anesthetics.

The two dose-finding volunteer studies discussed above (37, 38) are particularly interesting because they clearly pointed out that whereas levobupivacaine and racemic bupivacaine have a similar clinical profile and potency ratio, intrathecal ropivacaine was half as potent as bupivacaine.

McNamee et al (72) reported that intrathecal administration of 17.5 mg plain ropivacaine 0.5% or plain bupivacaine 0.5% resulted in a similarly effective spinal anesthesia for total hip arthroplasty (Tab. 5).

Gautier et al (73) compared 8, 10, 12 and 14 mg ropivacaine with 8 mg bupivacaine for ambulatory surgery, and concluded that, not only ropivacaine 10 mg induced a shorter-lasting block than bupivacaine 8 mg, but was also associated with a poorer quality of intraoperative anesthesia. Whiteside et al (74) compared 15 mg of either 0.5% ropivacaine or 0.5% bupivacaine in 8% glucose and reported that ropivacaine provided reliable spinal anesthesia of shorter duration and with less hypotension than bupivacaine. A more recent study compared the effects of intrathecal ropivacaine with bupivacaine in a 2:1 dose ratio for outpatient arthroscopic knee surgery, and that ropivacaine 15 mg produced a higher level of sensory block with faster onset and offset times than 7.5 mg bupivacaine (75). Similar findings have also been reported when comparing ropivacaine and bupivacaine, alone or in addi-

Table 5. Spinal anaesthesia characteristics with the three long-acting agents

Reference	Dose/Concentration	n° pts.	Type of surgery	Onset time (min)	Max. sensory level	Duration of the block	complete motor block	Time to walk/void
[72]	17.5 mg plain ropivacaine 0.5%	32	Hip surgery	2 (2-5)		3.0 (1.5.4.6) hours	100%	
	3.5 ml plain bupivacaine 0.5%	34		2 (2-9)		3.5 (2.7-5.2) hours	100%	
[73]								Time to walk
	8 mg bupivacaine 0.5%	30	Outpatient	14 ± 6	T8	181 ± 4.4 min	73%	192 ± 48 min
	8 mg ropivacaine 0.5%	30	knee	15 ± 6	T9	130 ± 27 min	26%[a]	107 ± 25 min
	10 mg ropivacaine 0.5%	30	arthroscopy	18 ± 5	T8	152 ± 44 min	77%	135 ± 31 min
	12 mg ropivacaine 0.5%	30		18 ± 6	T8	176 ± 42 min	96%[a]	162 ± 37 min
[77]								
	20 mg ropivac. + 0.1 mg morphine	30	Cesarean	12 ± 5	T4	211 ± 48 min	100%	
	15 mg bupivac.+ 0.1 mg morphine	30	section	8 ± 2	T4	254 ± 76 min	100%	
[78]								Time to void
	60 mg lidocaine	20	Outpatient	6 ± 4		145 ± 30 min[c]	96%[b]	245 ± 65 min
	15 mg ropivacaine	20	knee	7 ± 4		167 ± 49 min	100%	285 ± 65 min
	10 mg levobupivacaine	20	arthroscopy	8 ± 6		173 ± 47 min[c]	89%[b]	284 ± 57 min
[79]								Time to void
	7.5 mg hyperbaric ropivac. 0.5%	31	Outpatient	10 (9-13)	T8	135 (126-154) min[d]	94%	*189 (126-154) min*
	7.5 mg hyperb levobupiv. 0.5%	30	knee	10 (9-12)	T7	162 (148-201) min	93%	*238 (221-276) min*
	5 mg hyperbaric levobupiv. 0.5%	30	arthroscopy	10 (9-13)	T10	150 (136-185) min[d]	83%	*190 (181-247) min*
[80]	3.5 ml plain levobupiv. 0.5%	40	Hip surgery	11 ± 6	T8	237 ± 88 min	100%	
	3.5 ml plain ropivacaine 0.5%	40		13 ± 8	T8	284 ± 80 min	100%	
[83]								Time to void
	8 mg hyperbaric bupiv. 0.5%	20	Inguinal	10 ± 4	T6	190 ± 51 min[e]	100%	298 ± 68 min
	8 mg hyperbaric levobupiv. 0.5%	20	hernia	10 ± 5	T8	210 ± 63 min	100%	255 ± 58 min
	12 mg hyperbaric ropivac. 0.5%	20	repair	10 ± 6	T5	166 ± 42 min[e)]	100%	302 ± 48 min

[a] P < 0.05 versus bupivacaine; [b] P < 0.05 versus ropivacaine; [c] P < 0.05 versus lidocaine; [d] P< 0.05 versus 7.5 mg levobupivacaine;
[e] P < 0.05% versus ropivacaine

tion to small doses of morphine, in women undergoing elective caesarean section (76, 77). Breebaart et al (78) compared 10 mg levobupivacaine and 15 mg ropivacaine for outpatient knee arthroscopy, and reported L2 regression of sensory block after 173 and 167 minutes, with home discharge after 311 and 305 minutes, respectively. Cappelleri et al (79) compared unilateral spinal block produced with 7.5 mg of hyperbaric ropivacaine 0.5% or either 7.5 mg or 5 mg of hyperbaric levobupivacaine, showing that 7.5 mg of 0.5% hyperbaric ropivacaine and 5 mg of 0.5% hyperbaric levobupivacaine provided adequate spinal block for outpatient knee arthroscopy, with a faster home discharge as compared with 7.5 mg of 0.5% hyperbaric levobupivacaine.

On the other hand, levobupivacaine and racemic bupivacaine show an undistinguishable clinical profile of spinal block (80-83).

Peripheral nerve blocks

Animal studies on conduction block produced by bupivacaine, levobupivacaine and ropivacaine on isolated nerves showed that the onset and duration of nerve block induced by equimolar doses of these three agents were similar (84).

In agreement with these findings several studies comparing ropivacaine with other local anesthetics for different peripheral nerve blocks showed that nerve blocks produced by ropivacaine have a clinical profile

similar to that obtained with racemic bupivacaine and levobupivacaine, when used at similar concentrations and doses; on the contrary increasing the concentration and dose of ropivacaine at 0.75%-1% concentration shortened the onset time and prolonged the duration of ropivacaine's nerve block as compared to the other two agents (85-92).

Cline et al (93) compared 0.5% levobupivacaine and 0.5% ropivacaine in combination with 1:200,000 epinephrine for axillary brachial plexus block, and found that sensory analgesia was significantly longer with levobupivacaine than with ropivacaine, but ropivacaine patients showed a faster recovery of motor function, while Piangatelli et al (94) showed a faster onset of infraclavicular brachial plexus block with 0.5% levobupivacaine than with 0.5% ropivacaine.

Several different studies compared the use of levobupivacaine for sciatic nerve block for foot surgery with bupivacaine, ropivacaine, and levobupivacaine at concentrations ranging between 0.5% and 0.75% (95-97) showing a substantially similar clinical profile at 0.5% concentrations; while the use of 0.75% levobupivacaine provided a shorter onset time and longer duration of postoperative analgesia than the same volume of 0.75% ropivacaine, also reducing total consumption of rescue tramadol during the first 24 hours after surgery (97).

In agreement with these findings Piangatelli et al (98) compared the clinical profile of psoas compartment and sciatic nerve blocks performed with either 0.5% levobupivacaine or 0.75% ropivacaine in patients undergoing lower extremity surgery, and found that levobupivacaine showed a faster onset time with a larger differentiation between the duration of sensory and motor blocks than ropivacaine, resulting in less rescue analgesia request postoperatively.

When considering continuous perineural infusion of low concentrations of local anesthetics for postoperative analgesia, 0.2% ropivacaine was similarly effective in terms of pain relief and anesthetic consumption as an equipotent concentration of racemic bupivacaine (0.15% concentration), but allowed a better sensory motor differentiation (99). On the other hand, Casati et al (100) compared 0.125% levobupivacaine and 0.2% ropivacaine for continuous interscalene analgesia after major shoulder surgery and showed no differences in the quality of postoperative analgesia and recovery of motor function, but levubupivacaine patients consumed less local anesthetic during the first 24 hours than patients receiving ropivacaine. Borghi et al (101) compared pain relief and postoperative motor function of 0.25% levobupivacaine with either an equivalent (0.25%) or equipotent (0.4%) concentration of ropivacaine in a similar clinical setting, and reported similar quality of pain relief, recovery of motor function, and number of patient-controlled boluses with 0.25% levobupivacaine and 0.4% ropivacaine, while patients receiving 0.25% ropivacaine significantly needed more boluses and rescue analgesia to achieve the same quality of postoperative analgesia.

Casati et al (102) also compared the efficacy of continuous popliteal sciatic nerve block produced with 0.2% ropivacaine with either an equivalent (0.2%) or equipotent (0.125%) concentration of levobupivacaine in patients receiving hallux valgus repair, and reported no differences in degree of pain both at rest and during motion, but patients receiving 0.2% levobupivacaine less frequently showed a complete recovery of foot motor function as compared with patients receiving both 0.2% ropivacaine and 0.125% levobupivacaine, suggesting that the 0.125% concentration of levobupivacaine can be considered a good compromise between adequate pain relief and no motor block, providing a sensory/motor differentiation similar to that provided by 0.2% ropivacaine (Tab. 6).

Conclusions

When new molecules are introduced into the market, it is not always simple to understand whether their potential advantages are really relevant to the daily practitioner and worthy of the increased costs of the newest agents compared to the previous ones. Ropivacaine and levobupivacaine have been developed to offer a safer alternative to bupivacaine, having the desirable blocking properties of racemic bupivacaine with a greater margin of safety due to their reduced toxic potential.

The extensive clinical use of these two local anesthetics has confirmed that both of them provide a

Table 6. Peripheral nerve block characteristics with the three long-acting agents

Reference	Dose/Concentration	n° pts.	Type of block	Onset time (min)	Success rate	Duration of the block	Postoperative analgesia
[85]	30 ml ropivacaine 0.75%	49	Supraclavi-	Not	35/49	11.3-14.3 h	
	30 ml bupivacaine 0.5%	49	cular	significant	30/49	10.3-17.1 h	
[86]	30 ml ropivac.0.75%	15	Sciatic/	14 ± 17	100%	670 ± 220 min	
	30 ml bupivacaine 0.5%	15	femoral	37 ± 27[a]	100%	880 ± 312 min	
[87]	30 ml ropivacaine 0.5%	30		16 ± 4[b]	100%	654 ± 224 min	
	30 ml ropivac. 0.75%	30		14 ± 3[b]	100%	666 ± 174 min	
	30 ml bupivacaine 0.5%	30		22 ± 8	100%	666 ± 210 min	
[88]	20 ml ropivacaine 0.5%	15	Interscalene	22 ± 8		11.0 ± 5 h	
	20 ml bupivacaine 0.5%	15		28 ± 15		10.9 ± 4 h	
[89]	0.4 ml/kg levobup. 0.5%	25	Supraclavi-	7 ± 6	100%	892 ± 250 h	
	0.4 ml/kg levobup. 0.25%	26	cular	6 ± 5	92%	1039 ± 317 h	
	0.4 ml/kg bupivac. 0.5%	23		8 ± 8	91%	896 ± 284 h	
[92]	45 ml bupivacaine 0.5%	30	Axillary		77%[a]	17.8 ± 7.0 h	
	45 ml levobupivac. 0.5%	30		Not	57% [a)]	17.1 ± 6.5 h	
	45 ml ropivacaine 0.5%	30		Significant	83%	15.3 ± 5.0 h	
[100]	30 ml levobupivac. 0.5%	25	Continuous	20 (15-45)	92%	similar recovery	Levobupivacaine 0.125% (147 ml/24 h)
	30 ml ropivacaine 0.5%	25	interscalene	20 (10-40)	96%	of motor function	Ropivacaine 0.2% (162 ml/24h)[c]
[102]	30 ml ropivacaine 0.2%	20	Continuos	28 ± 15			Ropivacaine 0.2% at 48 h: 150 (144-164) ml
	30 ml levobupiv. 0.2%	20	sciatic	34 ± 17			Levobupiv. 0.2% at 48 h: 154 (144-176) ml[d)]
	30 ml levobupiv. 0.125%	20		32 ± 15			Levobupiv. 0.125% at 48 h: 151 (144-216) ml[d)]

[a] P < 0.05 versus ropivacaine; [b] P < 0.05 versus bupivacaine; [c] P < 0.05 versus levobupivacaine; [d] P < 0.05 versus ropivacaine

long-lasting block, with a clinical profile of nerve block very similar to that provided by racemic bupivacaine. However, the reduced toxic potential of both levobupivacaine and ropivacaine is strongly supported by animal and volunteer studies, resulting not only in higher plasma concentrations and doses before signs of systemic toxicity occur, but also in no cardiovascular toxicity or only minimal signs of cardiac effects after CNS toxicity occurs. Moreover a higher success rate of cardiopulmonary resuscitation after cardiac collapse is induced in animals as compared with racemic bupivacaine.

As compared with racemic bupivacaine, ropivacaine also showed the clinically relevant advantage of a stronger differentiation between sensory and motor blocks, which is particularly useful when early mobilization is important to accelerate postoperative recovery. Ropivacaine is 40-50% less potent than bupivacaine and levobupivacaine because of its lower lipid solubility; however, a reduced potency does not imply that this agent is less effective than the other two, and using an equipotency ratio of 1.5 : 1 between ropivacaine and the two other drugs results in a substantially similar clinical profile with a good preservation of motor function.

In conclusion, the reduced toxic potential of both levobupivacaine and ropivacaine should be carefully considered when choosing the local anesthetic for regional anesthesia techniques requiring large volumes and infusion rates, such as for epidural anesthesia/analgesia, peripheral nerve blocks, and local infiltration.

References

1. Albright GA. Cardiac arrest following regional anesthesia with etidocaine and bupivacaine. *Anesthesiology* 1979; 51: 285-7.
2. Buyse I, Stockman W, Columb M, Vandermeersch E, Van de Velde M. Effect of sufentanil on minimum local analgesic concentrations of epidural bupivacaine, ropivacaine and levobupivacaine in nullipara in early labour. *International Journal of Obstetric Anesthesia* 2007; 16: 22-8.

3. Aberg G. Toxicological and local anesthetic effects of optically active isomers of two local anesthetic compounds. *Acta Pharmacol Toxicol Scand* 1972; 31: 273-86.
4. Ekenstam BAF, Egner B & Petterson GN. N-alkyl pyrrolidine and N-alkyl piperidine carboxylic acid amines. *Acta Chem Scand* 1957; 11: 1183-90.
5. Mather LE, Copeland SE, Ladd LA. Acute Toxicity of Local Anaesthetics: Underlying Pharmacokinetic and Pharmacodynamic Concepts. *Reg Anesth Pain Med* 2005; 30: 553-66.
6. Mather LE, Long GJ, Thomas J. The intravenous toxicity and clearance of bupivacaine in man. *Clin Pharmacol Ther* 1971; 12: 935-43.
7. Mather LE, Tucker GT, Murfy TM, Stanton Hicks MD, Bonica JJ. Cardiovascular and subjective central nervous system effects of long-acting local anaesthetics in man. *Anaesth Intensive Care* 1979; 7: 215-21.
8. Scott DB, Lee A, Fagan D, Bowler GM, Bloomfield P, Lundh R. Acute toxicity of ropivacaine compared with that of bupivacaine. *Anaesth Analg* 1989; 69: 563-9.
9. Knudsen K, Suurkula MB, Blomberg S, Sjovall J, Edvardsson N. Central nervous and cardiovascular effects of i.v. infusion of ropivacaine, bupivacaine and placebo in volunteers. *Br J Anaesth* 1997; 78: 507-14.
10. Stewart J, Kellett N, Castro D. The central nervous system and cardiovascular effects of levobupivacaine and ropivacaine in healthy volunteers. *Anesth Analg* 2003; 97: 412-6.
11. Groban L. Central nervous system and cardiac effects from long-acting amide local anesthetic toxicity in the intact animal model. *Reg Anesth Pain Med* 2003; 28: 3-11.
12. Marganella C, Bruno V, Matrisciano F, Reale C, Nicoletti F, Melchiorri D. Comparative effects of levobupivacaine and racemic bupivacaine on excitotoxic neuronal death in culture and N-methyl-D-aspartate-induced seizures in mice. *Eur J Pharmacol* 2005; 518: 111-5.
13. Scott DB, Lee A, Fagan D, Bowler GM, Bloomfield P, Lundh R. Acute toxicity of ropivacaine compared with that of bupivacaine. *Anesth Analg* 1989; 69: 563-9.
14. Bardsley H, Gristwood R, Baker H, Watson N, Nimmo W. *A* comparison of the cardiovascular effects of levobupivacaine and rac-bupivacaine following intravenous administration to healthy volunteers. *Br J Clin Pharmacol* 1998; 46: 245-9.
15. Gristwood RW. Cardiac and CNS toxicity of levobupivacaine: strengths of evidence for advantage over bupivacaine. *Drug Saf* 2002; 25: 153-63.
16. Clarkson CW, Hondeghem LM. Mechanism for bupivacaine depression of cardiac conduction: fast block of sodium channels during the action potential with slow recovery from block during diastole. *Anesthesiology* 1985; 62: 396-405.
17. Arlock P. Actions of three local anesthetics: lidocaine, bupivacaine and ropivacaine on guinea pig papillary muscle sodium channels (Vmax). *Pharmacol Toxicol* 1988; 63: 96-104.
18. Avery P, Redon D, Schaenzer G, Rusy B. The influence of serum potassium on cerebral and cardiac toxicity of bupivacaine and lidocaine. *Anesthesiology* 1984; 61: 134-8.
19. Valenzuela C, Delpon E, Tamkun MM, Tamargo J, Snyders DJ. Stereoselective block of a human cardiac potassium channel (Kv1.5) by bupivacaine enantiomers. *Biophys J* 1995; 69: 418-27.
20. Longobardo M, Delpon E, Caballero R, Tamargo J, Valenzuela C. Structural determinants of potency and stereoselective block of hKv1.5 channels induced by local anesthetics. *Mol Pharmacol* 1998; 54: 162-9.
21. Gonzalez T, Arias C, Caballero R, Moreno I, Delpon E, Tamargo J, et al. Effects of levobupivacaine, ropivacaine and bupivacaine on HERG channels: stereoselective bupivacaine block. *Br J Pharmacol* 2002; 137: 1269-79.
22. Kawano T, Oshita S, Takahashi A, Tsutsumi Y, Tomiyaama Y, Kithata H, et al. Molecular mechanisms of the inhibitory effects of bupivacaine, levobupivacaine, and ropivacaine on sarcolemmal adenosine triphosphate-sensitive potassium channels in the cardiovascular system. *Anesthesiology* 2004; 101: 390-8.
23. Groban L, Deal DD, Vernon JC, James RL, Butterworth J. Does local anesthetic stereoselectivity or structure predict myocardial depression in anesthetized canines? *Reg Anesth Pain Med* 2002; 27: 460-8.
24. Chang DH, Ladd LA, Copeland LA, et al. Direct cardiac effects of intracoronary bupivacaine, levobupivacaine, and ropivacaine in sheep. *Br J Pharmacol* 2001; 132: 649-58.
25. Pitkanen M, Feldman HS, Arthur GR & Covino BG. Chronotropic and inotropipc effects of ropivacaine, bupivacaine, and lidocaine in the spontaneously beating and electrically paced isolated, perfused, rabbit heart. *Reg Anesth Pain Med* 1992; 17: 182-92.
26. Zapata-Sudo G, Trachez MM, Sudo RT, Nelson TE. Is comparative cardiotoxicity of S(−) and R(+) bupivacaine related to enantiomer-selective inhibition of L-type Ca2C channels? *Anesth Analg* 2001; 92: 496-501.
27. Sztark F, Malgat M, Dabadie P, Mazat JP. Comparison of the effects of bupivacaine and ropivacaine on heart cell mitochontrial bioenergetics. *Anesthesiology* 1998; 88: 1340-9.
28. Sztark F, Nouette-Gaulain K, Malgat M, Dabadie P, Mazat JP. Absence of sterospecific effects of bupivacaine isomers on heart mitochontrial bioenergetics. *Anesthesiology* 2000; 93: 456-62.
29. Heavner JE. Cardiac toxicity of local anesthetics in the intact isolated heart model: a review. *Reg Anesth Pain Med* 2002; 27: 545-5.
30. Royse Colin F, Royse Alistair G. The Miocardial and Vascular Effects of Bupivacaine, Levobupivacaine, and Ropivacaine Using Pressure Volume Loops. *Anesth. Analg* 2005; 101: 679-87.
31. Tsibiribi P, Bui-Xuan C, Bui-Xuan B, Tabib A, Descotes J, Chevalier P. The effects of ropivacaine at clinically relevant doses on myocardial ischemia in pigs. *J Anesth* 2006; 20: 341-3.
32. Groban L, Deal DD, Vernon JC, Jaqmes RL, Butterworth J. Cardiac resuscitation after incremental overdosage with lidocaine, bupivacaine, levobupivacaine, and ropivacaine in anesthetized dogs. *Anesth Analg* 2001; 92: 37-43.

33. Ohmura S, Kawada M, Ohta T, Yamamoto K, KobayashiT. Systemic toxicity and resuscitation in bupivacaine-, levobupivacaine-, or ropivacaine-infused rats. *Anesth Analg* 2001; 93: 743-8.
34. Brau ME, Branitzki P, Olschewski A, Vogel W, Helpelmann G. Block of neuronal tetrodoxin-resistant Na+ channels by stereoisomers of piperidine local anesthetics. *Anesth Analg* 2000; 91: 1499-505.
35. Kanai Y, Katsuki H & Takasaki M. Comparison of the anesthetic potency and intracellular concentrations of S(–) and R(+) bupivacaine and ropivacaine in crayfish giant axon in vitro. *Anesth Analg* 2000; 90: 415-20.
36. Sinnott CJ, Stricharts GR. Levobupivacaine versus ropivacaine for sciatic nerve block in the rat. *Reg Anesth Pain Med* 2003; 28: 294-303.
37. Alley EA, Kopacz DJ, McDonald SB, Liu SS. Hyperbaric spinal levobupivacaine: a comparison to racemic bupivacaine in volunteers. *Anesth Analg* 2002; 94: 188-93.
38. McDonald SB, Liu SS, Kopacz DJ, Stephenson CA. Hyperbaric spinal ropivacaine: a comparison to bupivacaine in volunteers. *Anesthesiology* 1999; 90: 971-7.
39. Lyons G, Columb M, Wilson RC, Johnson RV. Epidural pain relief in labour: potencies of levobupivacaine and racemic bupivacaine. *Br J Anaesth* 1998; 81: 899-901.
40. Polley LS, Columb MO, Naughton NN, Wagner DS, van de Ven CJ. Relative analgesic potencies of ropivacaine and bupivacaine for epidural analgesia in labor. *Anesthesiology* 1999; 90: 944-50.
41. Capogna G, Celleno D, Fusco P, Lyons G, Columb M. Relative potencies of bupivacaine and ropivacaine for analgesia in labour. *Br J Anaesth* 1999; 82: 371-3.
42. Sia AT, Goy RW, Lim Y, Ocampo CE. A comparison of median effective doses of intrathecal levobupivacaine and ropivacaine for labor analgesia. *Anesthesiology,* 2005; 102: 651-6.
43. Camorcia M, Capogna G, Lyons G, Columb M. Epidural test dose with levobupivacaine and ropivacaine: determination of ED_{50} motor block after spinal administration. *Br J Anaesth* 2004; 92: 850-3.
44. Casati A, Fanelli G, Magistris L, Beccarla P, Berti M, Torri G. Minimum local anesthetic volume blocking the femoral nerve in 50% of cases. A double-blinded comparison between 0.5% ropivacaine and 0.5% bupivacaine. *Anesth Analg* 2001; 92: 205-8.
45. Katz JA, Knarr D, Bridenbaugh PO. A double-blind comparison of 0.5% bupivacaine and 0.75% ropivacaine administered epidurally in humans. *Reg Anesth* 1990; 15: 250-2.
46. Kerkkamp HE, Gielen MJ, Edstrom HH. Comparison of 0.75% ropivacaine with epinephrine and 0.75% bupivacaine with epinephrine in lumbar epidural anesthesia. *Reg Anesth* 1990; 15: 204-7.
47. Wolff AP, Hasselstrom L, Kerkkamp HE & Gielen MJ. Extradural ropivacaine and bupivacaine in hip surgery. *Br J Anaesth* 1995; 74: 458-60.
48. McGlade DP, Kalpokas MV, Mooney PH, Buckland MR, Vallipuram SR, Hendrata MV, et al. Comparison of 0.5% ropivacaine and 0.5% bupivacaine in lumbar epidural anaesthesia for lower limb orthopaedic surgery. *Anaesth Intensive Care* 1997; 25: 262-6.
49. Crosby E, Sandler A, Finucane B, Writer D, Reid D, Mc Kenna J, et al. Comparison of epidural anaesthesia with ropivacaine 0.5% and bupivacaine 0.5% for caesarean section. *Can J Anaesth* 1998; 45: 1066-71.
50. Kampe S, Tausch B, Paul M, Kasper SM, Bauer K, Diefenbach C, et al. Epidural block with ropivacaine and bupivacaine for elective cesarean section: maternal cardiovascular parameters, comfort and neonatal well-being. *Curr Med Res Opin* 2004; 20: 7-12.
51. Cox CR, Faccenda KA, Gilhooly C, Bannister J, Scott NB, Morrison LM. Extradural S(–)bupivacaine: comparison with racemic RS-bupivacaine. *Br J Anaesth* 1998; 80: 289-93.
52. Kopacz DJ, Allen HW, Thompson GE. A comparison of epidural levobupivacaine 0.75% with racemic bupivacaine for lower abdominal surgery. *Anesth Analg* 2000; 90: 642-8.
53. Faccenda KA, Simpson AM, Henderson DJ, Smith D, McGrady EM, Morrison LM. A comparison of levobupivacaine 0.5% and racemic bupivacaine for extradural anesthesia for cesarean section. *Reg Anesth Pain Med* 2003; 28: 394-400.
54. Peduto VA, Baroncini S, Montanini S, Proietti R, Rosignoli L, Tufano R, et al. A prospective, randomized, double-blind comparison of epidural levobupivacaine 0.5% with epidural ropivacaine 0.75% for lower limb procedures. *Eur J Anaesthesiol* 2003; 20: 979-83.
55. Casati A, Santorsola R, Aldegheri G, Ravasi F, Fanelli G, Berti M, et al. Intraoperative epidural anesthesia and postoperative analgesia with levobupivacaine for major orthopedic surgery: a double-blind, randomised comparison of racemic bupivacaine and ropivacaine. *J Clin Anesth* 2003; 15: 126-31.
56. Bertini L, Mancini S, Di Benedetto P, Ciaschi A, Martini O, Nava S, et al. Postoperative analgesia by combined continuous infusion and patient-controlled epidural analgesia following hip replacement: ropivacaine versus bupivacaine. *Acta Anaesthesiol Scand* 2001; 45: 782-5.
57. Pouzeratte Y, Delay JM, Brunat G, Boccara G, Vergne C, Jaber S, et al. Patient-controlled epidural analgesia after abdominal surgery: ropivacaine versus bupivacaine. *Anesth Analg* 2001; 93: 1587-92.
58. Senard M, Joris JL, Ledoux D, Toussaint PJ, Lahaye-Goffart B, Lamy ML. A comparison of 0.1% and 0.2% ropivacaine and bupivacaine combined with morphine for postoperative patient-controlled epidural analgesia after major abdominal surgery. *Anesth Analg* 2002; 95: 444-9.
59. Macias A, Monedero P, Adame M, Torre W, Fidalgo I, Hidalgo F. A randomised, double-blinded comparison of thoracic epidural ropivacaine, ropivacane/fentanyl, or bupivacaine/fentanyl for post-thoracotomy analgesia. *Anesth Analg* 2002; 95: 1344-50.
60. Berti M, Fanelli G, Casati A, Albertin A, Palmisano S, Deni F, et al. Patient supplemented epidural analgesia after major abdominal surgery with bupivacaine/fentanyl or ropivacaine/fentanyl. *Can J Anaesth* 2000; 47: 27-32.

61. Murdoch JA, Dickson UK, Wilson PA, Berman JS, Gad-Elrab RR, Scott NB. The efficacy and safety of three concentrations of levobupivacaine administered as a continuous epidural infusion in patients undergoing orthopedic surgery. *Anesth Analg* 2002; 94: 438-44.
62. Dernedde M, Stadler M, Bardiau F & Boogaerts J. Comparison of different concentrations of levobupivacaine for post-operative epidural analgesia. *Acta Anaesthesiol Scand* 2003; 47: 884-90.
63. Dernedde M, Stadler M, Bardiau F & Boogaerts JG. Continuous epidural infusion of large concentration/small volume versus small concentration/large volume of levobupivacaine for postoperative analgesia. *Anesth Analg* 2003; 96: 796-801.
64. Zasa M, Baciarello M, Leone S, Mazzani R, Danelli G, Casati A, et al. A comparison of 0.125% and 0.75% Levobupivacaine for Postoperative Lumbar Epidural Analgesia. *Anesthesiology* 2006; 105.
65. Launo C, Gastaldo P, Piccardo F, Palermo S, Demartini A, Grattarola C. Perioperative thoracic epidural analgesia in aortic surgery: role of levobupivacaine. *Minerva Anestesiol* 2003; 69: 751-60.
66. Senard M, Kaba A, Jacquemin MJ, Maquoi LM, Geortay MP, Honore PD, et al. Epidural levobupivacaine 0.1% or ropivacaine 0.1% combined with morphine provides comparable analgesia after abdominal s*urgery. Anesth Analg* 2004; 98: 389-94.
67. Kopacz DJ, Helman JD, Nussbaum CE, Hsiang JN, Nora PC, Allen HW. A comparison of epidural levobupivacaine 0.5% with or without epinephrine for lumbar spine surgery. *Anesth Analg* 2001; 93: 755-60.
68. Kopacz DJ, Sharrock NE, Allen HW. A comparison of levobupivacaine 0.125%, fentanyl 4 mg/mL, or their combination for patient-controlled epidural analgesia after major orthopedic surgery. *Anesth Analg* 1999; 89: 1497-503.
69. Berti M, Casati A, Fanelli G, Albertin A, Palmisano S, Danelli G, et al. 0.2% ropivacaine with or without fentanyl for patient-controlled epidural analgesia after major abdominal surgery: a double-blind study. *J Clin Anesth* 2000; 12: 292-7.
70. De Cosmo G, Mascia A, Clemente A, Congedo E, Aceto P. Use of levobupivacaine for the treatment of postoperative pain after thoracotomies. *Minerva Anestesiol*. 2005; 71: 347-51.
71. Milligan KR, Convery PN, Weir P, Quinn P, Connolly D. The efficacy and safety of epidural infusions of levobupivacaine with and without clonidine for postoperative pain relief in patients undergoing total hip replacement. *Anesth Analg* 2000; 91: 393-7.
72. McNamee DA, McClelland AM, Scott S, Milligan KR, Westman L, Gustafsson U. Spinal anaesthesia: comparison of plain ropivacaine 5 mg ml-1 with bupivacaine 5 mg ml-1 for major orthopedic surgery. *Br J Anaesth* 2002; 89: 702-6.
73. Gautier P, de Kock M, Van Steenberge A, Poth N, Lahaye-Goffart B, Fanart L, et al. Intrathecal ropivacaine for ambulatory surgery. A comparison between intrathecal bupivacaine and intrathecal ropivacaine for knee arthroscopy. *Anesthesiology* 1999; 91: 1239-45.
74. Whiteside JB, Burke, Wildsmith JA. Comparison of ropivacaine 0.5% (in glucose 5%) with bupivacaine 0.5% (in glucose 8%) for spinal anaesthesia for elective surgery. *Br J Anaesth* 2003; 90: 304-8.
75. Boztug N, Bigat Z, Karsli B, Saykal N, Ertok E. Comparison of ropivacaine and bupivacaine for intrathecal anesthesia during outpatient arthroscopic surgery. *J Clin Anesth* 2006; 18: 521-5.
76. Ogun CO, Kirgiz EN, Duman A, Okesli S, Akyurek C. Comparison of intrathecal isobaric bupivacaine-morphine and ropivacaine-morphine for cesarean delivery. *Br J Anaesth* 2003; 90: 659-64.
77. Danelli G, Fanelli G, Berti M, Cornini A, Lacava L, Nuzzi M, et al. Spinal ropivacaine or bupivacaine for cesarean delivery: a prospective, randomized, double-blind comparison. *Reg Anesth Pain Med* 2004; 29: 221-6.
78. Breebaart MB, Vercauteren MP, Hoffmann VL & Adriaensen HA. Urinary bladder scanning after day-case arthroscopy under spinal anaesthesia: comparison between lidocaine, ropivacaine, and levobupivacaine. *Br J Anaesth* 2003; 90: 309-13.
79. Cappelleri G, Aldegheri G, Danelli G, Marchetti C, Nuzzi M, Iannandrea G, et al. Spinal anestesia with Hyperbaric levobupivacaine and ropivacaine for outpatient knee arthroscopy: a prospective, randomized. Double-blind study. *Anesth Analg. 2*005; 101: 77-82.
80. Glaser C, Marhofer P, Zimpfer G, Heinz MT, Sitzwohl C, Kapral S, et al. Levobupivacaine versus racemic bupivacaine for spinal anesthesia. *Anesth Analg* 2002; 94: 194-8.
81. Fattorini F, Ricci Z, Rocco A, Romano R, Pascarella MA, Pinto G. Levobupivacaine versus racemic bupivacaine for spinal anaesthesia in orthopedic major surgery. *Minerva Anestesiol* 2006; 72: 637-46.
82. Gautier P, de Kock M, Huberty L, Demir T, Izydorczic M, Vanderick B. Comparison of the effects of intrathecal ropivacaine, levobupivacaine, and bupivacaine for Caesarean section. *Br J Anaesth* 2003; 91: 684-9.
83. Casati A, Moizo E, Marchetti C, Vinciguerra F. A prospective, randomized, double-blind comparison of unilateral spinal anesthesia with hyperbaric bupivacaine, ropivacaine, or levobupivacaine for inguinal herniorraphy. *Anesth Analg* 2004; 99: 1387-92.
84. Dyhre H, Lang M, Wallin R, Renck H. The duration of action of bupivacaine, levobupivacaine, ropivacaine in peripheral nerve block in the rat. *Acta Anaesthesiol Scand* 1997; 41: 1346-352.
8. Vaghadia H, Chan V, Ganapathy S, Lui A, McKenna J, Zimmer K. A multicentre trial of ropivacaine 7.5 mg/ml(K1) vs bupivacaine 5 mg/ml(K1) for supra clavicular brachial plexus anesthesia. *Can J Anaesth* 1999; 46: 946-51.
86. Fanelli G, Casati A, Beccaria P, Aldegheri G, Berti M, Tarantino F, et al. A double-blind comparison of ropivacaine, bupivacaine and mepivacaine during sciatic and femoral nerve blockade. *Anesth Analg* 1998; 87: 597-600.
87. Bertini L, Tagariello V, Mancini S, Ciaschi A, Posteraro

CM, Di Benedetto P, et al. 0.75% and 0.5% ropivacaine for axillary brachial plexus block: a clinical comparison with 0.5% bupivacaine. *Reg Anesth Pain Med* 1999; 24: 514-8.
88. Casati A, Fanelli G, Cappelleri G, Beccarla P, Magistris L, Borghi B, et al. A clinical comparison of ropivacaine 0.75%, ropivacaine 1% or bupivacaine 0.5% for interscalene brachial plexus anaesthesia. *Eur J Anaesth* 1999; 16: 784-9.
89. Casati A, Fanelli G, Albertin A, Deni F, Anelati D, Antonino FA, et al. Interscalene brachial plexus anesthesia with either 0.5% ropivacaine or 0.5% bupivacaine. *Minerva Anestesiol* 2000; 66: 39-44.
90. Cox CR, Checketts MR, MacKenzie N, Scott NB, Bannister J. Comparison of S(−)bupivacaine with racemic (RS)-bupivacaine in supraclavicular brachial plexus block. *Br J Anaesth* 1998; 80: 594-8.
91. Crews JC, Weller RS, Moss J, James RL. Levobupivacaine for axillary brachial plexus block: a pharmacokinetic and clinical comparison in patients with normal renal function or renal disease. *Anesth Analg* 2002; 95: 219-23.
92. Liisanantti O, Luukkonen J, Rosenberg PH. High-dose bupivacaine, levobupivacaine and ropivacaine in axillary brachial plexus block. *Acta Anaesthesiol Scand* 2004; 48: 601-6.
93. Cline E, Franz D, Polley RD, Maye J, Burkard J, Pellegrini J. Analgesia and effectiveness of levobupivacaine compared with ropivacaine in patients undergoing an axillary brachial plexus block. *AANA J* 2004; 72: 339-45.
94. Piangatelli C, De Angelis C, Pecora L, Recanatini F, Cerchiara P, Testasecca D. Levobupivacaine and ropivacaine in the infraclavicular brachial plexus block. *Minerva Anestesiol* 2006; 72: 217-21.
95. Casati A, Chelly JE, Cerchierini E, Santorsola R, Nobili F, Grispigni C, et al. Clinical properties of levobupivacaine or racemic bupivacaine for sciatic nerve block. *J Clin Anesth* 2002; 14: 111-4.
96. Casati A, Borghi B, Fanelli G, Cerchierini E, Santorsola R, Sassoli V, et al. A double-blind, randomized comparison of either 0.5% levobupivacaine or 0.5% ropivacaine for sciatic nerve block. *Anesth Analg* 2002; 94: 987-90.
97. Casati A, Vinciguerra F, Santorsola R, Aldegheri G, Putzu M, Fanelli G. Sciatic nerve block with 0.5% levobupivacaine, 0.75% levobupivacaine or 0.75% ropivacaine: a double- blind, randomised comparison. *Eur J Anaesthesiol* 2005; 22: 452-6.
98. Piangatelli C, De Angelis C, Pecora L, Recanatini F, Testasecca D. Levobupivacaine versus ropivacaine in psoas compartment and sciatic nerve block in orthopedic surgery of the lower extremity. *Minerva Anestesiol* 2004; 70: 801-7.
99. Borgeat A, Kalberer F, Jacob H, Ruetsch YA, Gerber C. Patient-controlled interscalene analgesia with ropivacaine 0.2% versus bupivacaine 0.15% after major open shoulder surgery: the effects on hand and motor function. *Anesth Analg* 2001; 92: 218-23.
100. Casati A, Borghi B, Fanelli G, Montone N, Rotini R, Fraschini G, et al. Interscalene brachial plexus anestesia and analgesia for open shoulder surgery: a randomized, double-blinded comparison between levobupivacaine and ropivacaine. *Anesth Analg* 2003; 96: 253-9.
101. Borghi B, Facchini F, Agnoletti V, Adduci A, Lambertini A, Marini E, et al. Pain relief and motor function during continuous interscalene analgesia after open shoulder surgery: a prospective, randomised, double-blind comparison between levobupivacaine 0.25%, and ropivacaine 0.25% or 0.4%. *Eur J Anaesthesiol*. 2006: in press.
102. Casati A, Vinciguerra F, Cappelleri G, Aldegheri G, Grispigni C, Putzu M, et al. Levobupivacaine 0.2% or 0.125% for continuous sciatic nerve block: a prospective, randomized, double-blind comparison with 0.2% ropivacaine. *Anesth Analg* 2004; 99: 919-23.

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