Clinical profile of levobupivacaine in regional anesthesia: A systematic review

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Abstract

The quest for searching newer and safer anesthetic agents has always been one of the primary needs in anesthesiology practice. Levobupivacaine, the pure S (−)-enantiomer of bupivacaine, has strongly emerged as a safer alternative for regional anesthesia than its racemic sibling, bupivacaine. Levobupivacaine has been found to be equally efficacious as bupivacaine, but with a superior pharmacokinetic profile. Clinically, levobupivacaine has been observed to be well-tolerated in regional anesthesia techniques both after bolus administration and continuous post-operative infusion. The incidence of adverse drug reactions (ADRs) is rare when it is administered correctly. Most ADRs are related to faulty administration technique (resulting in systemic exposure) or pharmacological effects of anesthesia; however, allergic reactions can also occur rarely. The available literary evidence in anesthesia practice indicates that levobupivacaine and bupivacaine produce comparable surgical sensory block, similar adverse side effects and provision of similar labor analgesia with good comparable maternal and fetal outcome. The present review aims to discuss the pharmacokinetic and pharmacological essentials of the safer profile of levobupivacaine as well as to discuss the scope and indications of levobupivacaine based on current clinical evidence.

Key words: Adverse drug reactions, bupivacaine, levobupivacaine, local anesthetics, regional anesthesia

Introduction

The quest for searching newer and safer anesthetic agents has always been one of the primary needs in anesthesiology practice. Regional anesthesia techniques have seen numerous modifications over the last two decades with the advent of many new and safer local anesthetics. Bupivacaine, the widely used local anesthetic in regional anesthesia is available in a commercial preparation as a racemic mixture (50:50) of its two enantiomers, levobupivacaine, S (−) isomer and dextrobupivacaine, R (+) isomer. Severe central nervous system (CNS) and cardiovascular adverse reactions reported in the literature after inadvertent intravascular injection or intravenous regional anesthesia have been linked to the R (+) isomer of bupivacaine. The levorotatory isomers were shown to have a safer pharmacological profile[1,2] with less cardiac and neurotoxic adverse effects.[3,4] The decreased toxicity of levobupivacaine is attributed to its faster protein binding rate.[5] The pure S (−) enantiomers of bupivacaine, i.e., ropivacaine and levobupivacaine were thus introduced into the clinical anesthesia practice. Levobupivacaine has been recently introduced into Indian market and is being widely used in various health set-ups. Such an increased usage mandates documentation of evidence based literature with regards to risk and safety concerns as well as clinical issues related to levobupivacaine.

The current pharmacological review was drafted after searching various internet based databases carrying the detailed information related to levobupivacaine. The review is generated from the information available from full text articles downloaded from PubMed, Scopus, Science Direct, Medscape Anesthesiology, Embase and Google Scholar. Pharmacological information was also extracted from various book chapters of clinical pharmacology and anesthesiology.

Stereoisomerism

Bupivacaine exhibits the phenomenon of stereoisomerism because of the presence of an asymmetric carbon, which acts as a chiral center.

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Chemical Structure

Levobupivacaine ([2S]-1-butyl-N-[2, 6-dimethylphenyl] piperidine-2-carboxamide) is an amino-amide local anesthetic drug belonging to the family of n-alkyl substitute pipecoloxylidide. Its chemical formula is $C_{18}H_{28}N_2O$ [Figure 1].

Mechanism of Action

Levobupivacaine exerts its pharmacological action through reversible blockade of neuronal sodium channels. Myelinated nerves are blocked through exposure at the nodes of Ranvier more readily than unmyelinated nerves; and small nerves are blocked more easily than larger ones. In general, the progression of anesthesia is related to the diameter, myelination and conduction velocity of the affected nerve fibers. Specifically, the drug binds to the intracellular portion of sodium channels and blocks sodium influx into nerve cells, which prevents depolarization. It blocks nerve conduction in sensory and motor nerves mainly by interacting with voltage sensitive sodium channels on the cell membrane. It also interferes with impulse transmission and conduction in other tissues.[6,7]

Pharmacokinetics

The dose as well as the route of administration of levobupivacaine determines the plasma concentration following therapeutic administration as the absorption is dependent upon the vascularity of the tissue. After epidural administration of levobupivacaine, the absorption is biphasic, with rapid absorption of a small quantity of drug into the circulation and slower absorption of the remainder of the drug. It has been observed that peak levels of levobupivacaine in the blood reaches approximately 30 min after epidural administration and doses up to 150 mg had resulted in mean C_{max} levels up to 1.2 μg/mL. The epidural absorption gets affected by age as the fraction absorbed decreases and the fast absorption phase is shorter in older (aged > 70 years) compared with the younger (aged 18-44 years) patients. The older patients also have a higher spread of analgesia by ~ 3 dermatomes. Therefore, in the elderly patients a lower dose of levobupivacaine, according to their physical status is recommended. The volume of distribution is estimated at 66.91 ± 18.23 L (after intravenous administration of 40 mg in healthy volunteers). The pKa of levobupivacaine is 8.1, similar to the pKa of the racemic bupivacaine. The half-life is 3.3 h. The rate of clearance is 39.06 ± 13.29 L/h (after intravenous administration of 40 mg in healthy volunteers).[6,7]

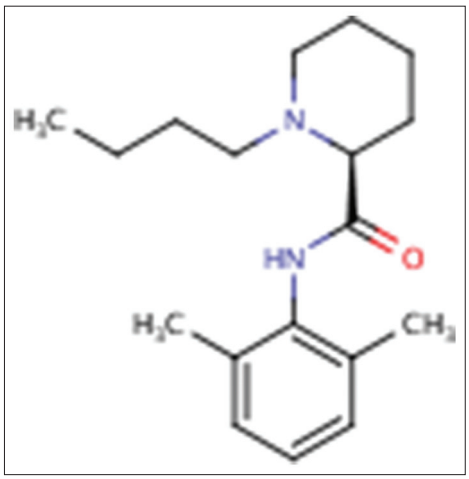

Figure 1: Chemical structure of levo-bupivacaine

Alpha1-glycoprotein is the main binding site for levobupivacaine. Protein binding of levobupivacaine is more (97%) than that of racemic bupivacaine (95%). Less than 3% of the drug circulates free in plasma. The free proportion of the drug can have an action on the other tissues, causing unwanted side-effects and toxic manifestations. In newborns and in protein-deficient states like under nutrition and nephrotic syndrome, lesser amount of protein is available for binding, causing higher levels of free drug, resulting in toxic effects at lower doses.[6,7]

Levobupivacaine is extensively metabolized with no unchanged levobupivacaine detected in urine or feces. *In vitro* studies using (14 C) levobupivacaine showed that cytochrome (CYP) CYP3A4 isoform and CYP1A2 isoform mediate the metabolism of levobupivacaine to inactive metabolites, desbutyl levobupivacaine and 3-hydroxy levobupivacaine, respectively. *In vivo*, the 3-hydroxy levobupivacaine appears to undergo further transformation to glucuronide and sulfate conjugates, which are excreted in urine. Metabolic inversion of levobupivacaine to R (+)-bupivacaine was not evident both *in vitro* and *in vivo*.[6,7]

Following intravenous administration, recovery of the radio-labeled dose of levobupivacaine was essentially quantitative with a mean total of about 95% being recovered in urine and feces in 48 h. Of this 95%, about 71% was in urine while 24% was in feces.

Clinical Utility

Levobupivacaine has increasingly been used in the clinical anesthesia practice since last few years because of its safer pharmacological profile. Literary evidence has established the safety of levobupivacaine over bupivacaine when used in regional anesthesia as the incidence of various adverse outcomes is higher with the latter as compared to levobupivacaine. The incidence of adverse cardiac and neurological events was significantly higher with bupivacaine as compared to levobupivacaine when used in regional anesthesia. Similarly,

the potential for CNS toxicity is lower with levobupivacaine as compared to bupivacaine.[3,5,7] The low cardiovascular and neurological toxicity of levobupivacaine has led to its application as a local anesthetic in a wide variety of specialist applications including sub-arachnoid block, epidural anesthesia and analgesia, brachial plexus blocks, peripheral nerve blocks, ocular blocks as well as local infiltration. It is also being used for intraoperative anesthesia, labor analgesia, post-operative pain as well as management of acute and chronic pain. The introduction of levobupivacaine into Indian market recently has spurred the interest among Anesthesiologists to possibly use it in various clinical situations requiring regional anesthesia.

Subarachnoid block

Levobupivacaine is an interesting alternative to bupivacaine for spinal anesthesia.[8] Levobupivacaine produces subarachnoid block with similar sensory and motor characteristics and recovery like bupivacaine.[9-14] The onset of sensory and motor block is hastened with the use of hyperbaric levobupivacaine as compared to isobaric levobupivacaine.[15] The regression of motor block occurs earlier with levobupivacaine and ropivacaine as compared with bupivacaine.[12] Intrathecal administration of 15 mg of levobupivacaine provides an adequate sensory and motor block lasting for approximately 6.5 h.[16] Smaller doses (i.e., 5-10 mg) are used in day-case surgeries. At low concentrations, levobupivacaine produces a differential neuraxial block with preservation of motor function,[17] which may be favorable for ambulatory surgery. Minimum effective local anesthetic dose of levobupivacaine as recommended by an up- and-down sequential design study is 11.7 mg.[18]

The literary evidence has established that addition of opioids provides a dose sparing effect of levobupivacaine, with improved quality of the block and less hemodynamic variations during peri-operative period[19-23] [Table 1].

Epidural anesthesia

Levobupivacaine has been successfully used in providing epidural anesthesia and analgesia for surgical procedures, which is clearly evident from the summary of various research works [Table 2]. Equal doses of levobupivacaine and bupivacaine (15 mL of 0.5%) provide similar onset of sensory block (8-30 min), maximum cephalic spread (T7-T8) and duration of analgesia (4-6 h).[24,25] Though, the onset of motor block is delayed with levobupivacaine[26] it is less dense as compared to bupivacaine but with a similar duration.[24-27] Higher concentration of levobupivacaine (i.e., 0.75% vs. 0.5%) provides a longer duration of sensory and motor block without any increase in the incidence of adverse side effects.[24] An increase in both volume and concentration of levobupivacaine is however associated with a higher incidence of hypotension (82%) and delayed block regression.[26] The incidence of hypotension is similar when either levobupivacaine or bupivacaine is used for epidural anesthesia for cesarean section.[28] Levobupivacaine and bupivacaine when used in thoracic epidural anesthesia provide comparable sensory block and intraoperative hemodynamics as well as similar duration of post-operative analgesia after thoracic surgery.[29]

Post-operative analgesia

Epidural analgesia

A continuous epidural infusion of low concentration of local anesthetics with or without adjuvants provides excellent post-operative analgesia. Equipotent doses of levobupivacaine, bupivacaine and ropivacaine provide comparable post-operative pain relief and recovery of sensory and motor function.[25] A continuous infusion of 15 mg/h of levobupivacaine provides effective pain relief in the post-operative period.[30] The quality of analgesia is also determined by the concentration of levobupivacaine, i.e., 0.25% solution provides better analgesia as compared to 0.125% or 0.0625% solutions.[30] Levobupivacaine, self-administered via post-operative patient-controlled epidural analgesia also provides good post-operative pain control, similar to ropivacaine, but ambulation occurs earlier in ropivacaine-receiving patients.[31]

The addition of adjunctive agents (epinephrine, opioids or clonidine) to levobupivacaine in epidural anesthesia and analgesia may provide a dose-sparing effect and increase the duration and quality of analgesia. Epinephrine does not influence the onset, spread and duration of sensory and motor epidural block or the systemic absorption of levobupivacaine.[32] The addition of opioids (fentanyl, morphine) improves the quality of analgesia and decrease the effective dose of levobupivacaine for post-operative analgesia or opioid-only infusions.[33,34] Clonidine added to levobupivacaine also enhances the quality of analgesia and provides a local anesthetic sparing effect. The motor block tends to be denser with clonidine and some degree of arterial hypotension occurs.[35]

Wound infiltration

Local anesthetic infiltration along the incision line is used frequently to provide post-operative analgesia. Post-incisional wound infiltration with 0.125% levobupivacaine provides more effective and longer duration of analgesia and early mobilization as compared to rectal paracetamol, in children after unilateral inguinal hernia surgery.[36] Wound infiltration with levobupivacaine with or without tramadol provide good post-operative analgesia following a cesarean section or lumbar disc surgery.[37,38]

A recent study conducted to evaluate the effects of local infiltration of levobupivacaine on post-operative wound healing

Table 1: Literary evidence with comparative evaluation of subarachnoid block administration of levobupivacaine

Author	Dose/concentration	Type surgery	Onset time of sensory block (min)	Maximum sensory dermatomal level	Duration of sensory block mean (SD) or median (range), min	Onset time of motor block mean (SD) or median (range), min	Duration of motor block mean (SD) or median (range), min	Incidence of hypotension (%)
Guler *et al.* 2012	2 ml levobupivacaine 0.5%+15 μg fentanyl 2 ml bupivacaine 0.5%+15 μg fentanyl	Caesarean section	4.6 (1.41) 4.46 (1.07)	T4 (2-4) T3 (2-4)		4.1 (0.88) 2.36 (0.61)	99 (9.13) 132.66 (7.15)	16.6 36.6
Sananslip *et al.* 2012	3 ml isobaric levobupivacaine 0.42% 3 ml hyperbaric levobupivacaine 0.42%	Gynecologic surgery	6.6 (4.7) 2.8 (1.1)	T8 (C8-L1) T4 (2-7)		6.9 (5.3) 2.9 (2.9)		70 60
Cuvas *et al.* 2010	2.5 ml levobupivacaine 0.5% 2.2 ml levobupivacaine 0.5%+15 μg fentanyl	Transuretheral endoscopic surgery	6.50 (2.62) 6.32 (3.50)	T9 (4-10) T6 (3-10)	377 (80) 337 (61)	4 (1.5) 3.6 (1.0)	291 (81) 214 (51)	15 15
Erbay *et al.* 2010	7.5 mg hyperbaric bupivacaine+25 μg fentanyl 7.5 mg hyperbaric levobupivacaine+25 μg fentanyl	Transuretheral endoscopic surgery	6 (1) 5 (2)		127 (14) 157 (34)		113 (7) 105 (19)	13.3 10.0
Santiago *et al.* 2009	10 mg lidocaine 2% +10 μg fentanyl 3 mg levobupivacaine 0.5% +10 μg fentanyl	Laparoscopic tubal ligation	8.1 (1) 7.7 (1)	T4 (4-6) T3 (2-4)	93 105			0 0
Mantouvalou *et al.* 2008	15 mg isobaric bupivacaine0.5% 15 mg isobaric ropivacaine 0.5% 15 mg isobaric levobupivacaine 0.5%	Lower abdominal surgery		T8 (L2-T4) T8 (4-12) T8 (L1-T4)	240 200 230	2 (1) 3 (1) 2 (1)	278 (70) 269 (20) 273 (80)	42.5 25 17.5
Vanna *et al.* 2006	2.5 ml isobaric levobupivacaine 0.5% 2.5 ml hyperbaric bupivacaine 0.5%	Transuretheral endoscopic surgery	10.0 (4.3) 7.3 (3.6)	T9 (4-10) T9 (6-10)	256.2 (48.0) 215.1 (50.8)	3.9 (1.7) 3.0 (1.3)	232.1 (51.8) 192.9 (50.9)	5.7 11.4

SD=Standard deviation

Table 2: A comparative evaluation of clinical profile of levobupivacaine in epidural block

Author	Dose/concentration	Type of surgery	Onset time of sensory block (min)	Maximum sensory dermatoma l level	Duration of sensory block mean or median (range), min or h	Onset time of motor block mean (SD) or median (range), min	Duration of motor block mean (SD) or median (range), min or h	Incidence of hypotension (%)
Cok *et al.* 2011	0.1 ml/kg 0.25% levobupivacaine+CEI 0.1 ml/kg/h	Thoracic surgery	4.8±4.1	T8 (T7-9)				0
	0.1 ml/kg 0.25% bupivacaine+CEI 0.1 ml/kg/h		4.8±3.1	T9 (T8-9)				0
Bergamaschi *et al.* 2005	100 mg levobupivacaine+10 μg sufentanil	Cesarean section		T6-12				66.7
	100 mg bupivacaine+10 μg sufentanil			T6-12				43.5
Peduto *et al.* 2003	15 ml levobupivacaine 0.5%	Lower limb	29 (24)		185 (77)		105 (63)	3
	15 ml ropivacaine 0.75%		25 (22)		201 (75)		95 (48)	12
Murdoch *et al.* 2002	10-15 ml levobupivacaine 0.75%+CEI	Hip or knee replacement		8.1 (5.0)			3	
	levobupivacaine 0.0625% 6 ml/h			9.5 (7.0)			4	
	10-15 ml levobupivacaine 0.75%+CEI levobupivacaine 0.125% 6 ml/h			16.7 (8.3)			7	
	10-15 ml levobupivacaine 0.75%+CEI levobupivacaine 0.25% 6 ml/h							
Kopacz *et al.* 2000	20 ml levobupivacaine 0.75%	Lower abdominal	13 (10-18)	T5-6	550.6 (87.6)		355.4 (83.4)	82
	20 ml bupivacaine 0.755		13 (7-21)	T5-6	505.9 (71)		375.7 (99.2)	61
Cox *et al.* 1998a	15 ml levobupivacaine 0.5%	Lower limb	8 (5)	T8 (T2-12)	377 (128)	25 (23)	185 (122)	
	15 ml levobupivacaine 0.75%		6 (4)	T8 (T6-11)	460 (111)	27 (30)	256 (99)	
	15 ml bupivacaine 0.5%		7 (4)	T6-L2	345 (107)	17 (7)	192 (74)	

CEI=Continuous epidural infusion, SD=Standard deviation

has reported that levobupivacaine has a positive effect on wound healing in the earlier period, but had negative effects thereafter. It decreased wound tension strength on 8th day, but increased it on the 21st day. It also increased the inflammatory response and collagen synthesis on both the 8th and 21st days.[39]

Peripheral Nerve Blocks

Different studies have compared levobupivacaine, ropivacaine and bupivacaine in brachial plexus block for upper limb surgery[40-42] [Table 3]. Levobupivacaine is a good substitute for bupivacaine. Compared to ropivacaine, levobupivacaine provides a significantly longer duration of analgesia.[43] The return of motor activity is earlier with ropivacaine.[44] The long duration of sensory block associated with good analgesia and less toxicity of levobupivacaine makes it a better choice for upper extremity blocks.[42] Levobupivacaine 0.5% provides a longer duration of sensory block after sciatic nerve block using the Labat approach than the same dose of ropivacaine in foot and ankle surgery.[45] The use of a single dose of 0.5% levobupivacaine to block the tibial and peroneal nerves for hallux valgus surgery using popliteal approach is preferable over 0.5% ropivacaine for good anesthesia and better control of post-operative pain.[46] Levobupivacaine 0.5% is as effective as bupivacaine 0.5% and is recommended for the 3-in-1 block.[47]

The quality and duration of peripheral nerve block is improved with the use of higher concentrations of levobupivacaine, (0.5-0.75%).[47,48] Levobupivacaine administered via a peripheral nerve block continuous catheter provides excellent post-operative analgesia and decreases the post-operative systemic opioids requirements.[49] The addition of adjuvants to the local anesthetics in peripheral nerve blocks such as epinephrine, clonidine or opioids improve the quality of analgesia and provide a dose-sparing effect, thereby decreasing the potential for systemic toxicity. Epinephrine does not add to the inherent long duration of sensory and motor block with levobupivacaine in peripheral nerve blocks but may help to decrease the potential for systemic toxicity. The addition of clonidine and fentanyl to levobupivacaine in paravertebral nerve block provide excellent analgesia and local anesthetic sparing effect and decrease post-operative systemic morphine requirement.[50] Similarly, the addition of tramadol to levobupivacaine in middle interscalene block significantly increases the duration of sensory block.[51]

Obstetric Anesthesia and Analgesia

Subarachnoid block for cesarean delivery

The time to onset of sensory and maximum motor block as well as the duration of analgesia is slightly longer with

Table 3: Peripheral nerve block with levobupivacaine-a comparison of block characteristics

Author	Dose/concentration	Type of peripheral nerve block	Onset of sensory block; mean (SD) or median (range), min	Onset of motor block; mean (SD) or median (range), min	Success rate %	Duration of sensory block; mean (SD) or median (range), min or h	Duration of motor block; mean (SD) or median (range), min or h
Alemanno *et al.* 2011	0.4 ml/kg of levobupivacaine+isotonic NaCl (0.03 ml/kg) and i.m. isotonic NaCl (0.03 ml/kg) 0.4 ml/kg of levobupivacaine+tramadol (1.5 mg/kg) and i.m. isotonic NaCl (0.03 ml/kg) 0.4 ml/kg of levobupivacaine+isotonic NaCl (0.03 ml/kg) and i.m. tramadol (1.5 mg/kg)	Middle interscalene block	20.9±5.5 20.2±7.4 22.2±7.5		95 95 97.5	7.6±2.9 h 14.5±4.0 h 10.1±5.3 h	
Fournier *et al.* 2010	20 ml 0.5% levobupivacaine 20 ml 0.5% ropivacaine	Sciatic nerve block	15 (5-40) 15 (5-60)	30 (5-60) 25 (5-40)	97.5 100	1275 (420-1720) 945 (490-1630)	
Piangatelli *et al.* 2006	30 ml levobupivacaine 0.5% 30 ml ropivacaine 0.75%	Brachial plexus (infraclavicular)	13.46 (1.06) 14.20 (1.17)	19.33 (2.58) 20.20 (2.39)		11.40 (2.2) h 10.26 (1.38) h	42 (0.8) h 8.33 (1.48) h
Duma *et al.* 2005	40 ml levobupivacaine 0.5% 40 ml levobupivacaine 0.5%+clonidine 150 μg 40 ml bupivacaine 0.5% 40 ml bupivacaine 0.5%+clonidine 150 μg	Brachial plexus (axillary)	10 (5-60) 5 (5-60) 10 (5-60) 10 (5-60)	10 (5-120) 10 (5-180) 10 (5-60) 30 (5-60)		1083 (785-1680) 1365 (705-2465) 1063 (600-1310) 1040 (520-2380)	
Liisanantti *et al.* 2004	45 ml levobupivacaine 0.5% 45 ml bupivacaine 0.5% 45 ml ropivacaine 0.5%	Brachial plexus (axillary)			57 77 83	17.1 (6.5) 17.8 (7.2) 15.0 (5.4)	

SD=Standard deviation

intrathecal levobupivacaine as compared to bupivacaine in cesarean section.[52] A potency hierarchy of intrathecal bupivacaine > levobupivacaine > ropivacaine in cesarean section patients has been confirmed in clinical studies[53,54] The accidental intrathecal placement of an epidural-intended catheter can be confirmed with a test dose of 10 mg levobupivacaine.[55]

Labor analgesia

Combined spinal-epidural labor analgesia

Combined spinal-epidural (CSE) technique is widely used in obstetric practice to provide optimal analgesia. It offers effective, rapid-onset analgesia with minimal risk of toxicity or impaired motor block. Minimum effective local anesthetic concentration studies using a CSE analgesia technique (CSE) for labor confirm the potency hierarchy of bupivacaine > levobupivacaine > ropivacaine for spinal sensory block. The intrathecal minimum local analgesic doses were 2.73-3.16 mg for levobupivacaine and 3.33-3.96 mg for ropivacaine.[56] 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.[57] The addition of fentanyl to intrathecal levobupivacaine provides a local anesthetic sparing effect with more effective analgesia and less motor block as compared with a double dose of each drug.[58] The addition of epinephrine to a mixture of levobupivacaine and opioid increase the success rate of sensory block, but also increases the frequency of motor blockade.[59]

Epidural labor analgesia

Both levobupivacaine and ropivacaine are being favored in labor analgesia because of less motor block and less toxicity as compared to bupivacaine. During the early labor, equipotent low concentrations of levobupivacaine, bupivacaine and ropivacaine, all with the addition of sufentanil 10 mcg, produce similar pain relief and motor block, but levobupivacaine and ropivacaine produce a longer lasting analgesia.[60] In patient-controlled epidural analgesia, concentrations of >0.1% levobupivacaine, bupivacaine and ropivacaine with sufentanil produce similar analgesia and motor block and safety for labor analgesia. The analgesic efficacy mainly depends on the concentration rather than the type of anesthetics and at least 0.1% is needed for satisfactory analgesia.[61] Levobupivacaine, ropivacaine and bupivacaine all confer adequate and safe labor analgesia, with no significant influence on the mode of delivery, duration of labor, or neonatal outcome.[62]

Ophthalmic Surgery

The low cardiovascular and neurological toxicity of levobupivacaine has led to its application as a preferred local anesthetic in various ocular blocks including peribulbar block for cataract surgery and retro bulbar block for vitreo-retinal surgery.

At equipotent doses and concentrations, 0.75% levobupivacaine provides more effective peribulbar anesthesia and more effective post-operative analgesia for vitreo-retinal surgery compared with 0.75% ropivacaine.[63] Topical anesthesia with levobupivacaine 0.75% has been found to be more effective than lidocaine 2% in preventing pain and improving patient and surgeon comfort during cataract surgery, with similar toxicity.[64] Levobupivacaine (0.5%) has better anesthetic properties with respect to 0.75% ropivacaine and is well-suited for peribulbar block in cataract surgery.[65]

Pediatric Anesthesia

Levobupivacaine is also increasingly being used in pediatric anesthesia for subarachnoid block, caudal block, epidural anesthesia and as a continuous epidural infusion for post-operative analgesia.

Subarachnoid block

The dose of levobupivacaine for spinal anesthesia in neonates is slightly higher than for bupivacaine or ropivacaine. Appropriate doses for infant spinal anesthesia are 1 mg/kg of isobaric 0.5% bupivacaine and ropivacaine and 1.2 mg/kg of isobaric 0.5% levobupivacaine.[66]

Caudal block

The recommended dose of levobupivacaine for effective caudal anesthesia has been reported to be 2.5 mg/kg. It appears to be of equivalent potency to racemic bupivacaine in children requiring lower abdominal surgery.[67] Post-operative epidural infusions of 0.125% levobupivacaine or ropivacaine in children produce significantly less motor blockade with equally good analgesia as compared to a similar infusion of bupivacaine.[68]

Geriatric Anesthesia

Elderly patients coming up for various surgeries including transurethral resection of the prostate or bladder tumour, orthopaedic trauma or joint replacement, cataract surgery, usually have some coexisting cardiac or pulmonary disease.[69] Owing to its safer pharmacological profile, levobupivacaine is considered to be a better local anesthetic than bupivacaine when used for subarachnoid block in the geriatric population having co-morbid systemic diseases and undergoing prostatic resections. The addition of fentanyl can further reduce the side-effects by decreasing the effective dose of levobupivacaine for adequate analgesia.[21]

Adverse effects

Levobupivacaine produces the same adverse effects as seen with racemic bupivacaine and other local anesthetics. The most common adverse drug reaction reported is hypotension (31%) followed by nausea (21%), vomiting (14%), headache (9%), procedural pain (8%) and dizziness (6%). The cardiac toxicity, neurological injury after peripheral nerve block and unwanted CNS effects, may be lower than bupivacaine. Allergic type reactions are rare and range in severity from urticaria to anaphylactoid-like reaction. During the administration of epidural anesthesia, it is recommended that a test dose is administered initially and the effects monitored before the full dose is given. A test dose of a short-acting amide anesthetic, such as three milliliters (3 mL) of lignocaine, is recommended to detect unintentional intrathecal administration. Accidental intrathecal injection during epidural blockade can produce high spinal anesthesia with severe hypotension and loss of consciousness.

Safety issues in case of inadvertent intravenous administration

Levobupivacaine has a safety margin of 1.3, which means toxic effects are not seen until the concentration rises by 30%. The concentration necessary to produce cardiac and neurotoxicity is higher for levobupivacaine than for racemic bupivacaine. There are three case reports of successful resuscitation after inadvertent intravenous injection. The presentations were severe hypotension and bradycardia after a drug error; loss of consciousness, convulsions, hypotension and changes in QRS pattern of ECG after presumed intravenous injection during lumbar plexus block and loss of consciousness and convulsions after (a) spinal (b) sciatic nerve and (c) continuous lumbar plexus blocks. In all cases, resuscitation was successful with supportive measures, with or without pressor drugs and intravenous lipid emulsion.[6,7] Recently studies have been carried out comparing the beneficial effects of vasopressor drugs and lipid therapy in local anesthetic systemic toxicity (LAST). Epinephrine should be used in small doses (10-100 μg) in adults. The use of vasopressin is not recommended. Lipid emulsion therapy should be considered at the first signs of LAST, after airway management.[70] Successful resuscitation has been reported with intralipid emulsions in a peri-arrest condition following use of levobupivacaine in lumbar plexus block.[71]

Conclusion

Levobupivacaine is a long-acting local anesthetic with a clinical profile similar to that of bupivacaine. In an individual patient, the clinical anesthetic effect from the drug is indistinguishable from that of bupivacaine. The better safety profile of levobupivacaine confers an advantage over its racemic parent, bupivacaine.

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