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Original Research Paper

Anesthesiology

Levobupivacaine: pharmacological 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 is the S (−)-enantiomer of bupivacaine, has strongly emerged as a safer alternative for regional anesthesia than its racemic sibling, bupivacaine. Most adverse effects are related to faulty administration technique (resulting in systemic exposure) or pharmacological effects of anesthesia; however, allergic reactions can also occur rarely. The present review aims to discuss the pharmacological profile of levobupivacaine.

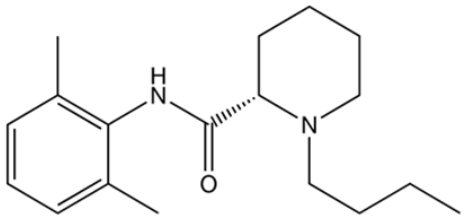
KEYWORDS : Levobupivacaine, adverse effects, pharmacological action.

Levobupivacaine

Levobupivacaine is an amino-amide local anesthetic drug belonging to the family of n-alkyl substitute pipecoloxylidide. The levorotatory isomer i.e. levobupivacaine isproved to be having a safer pharmacological profile[1-3]with less cardiac and neurotoxic adverse effects.[4,5]

Chemical formula

$C_{18}H_{28}N_2O$



IUPAC Name

2– piperidine carboxamide 1–Butyl–N–(2,6–dimethyl phenyl)–hydrochloride monohydrate

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.[6] 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.[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.

Absorption

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.

Distribution

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).[8] 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.

Metabolism and excretion

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. 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. Systemic effects of Levobupivacaine: It is relatively free of side effects if administered in an appropriate dosage. It is less cardiotoxic than bupivacaine and this is made worse by hypoxia, hypercapnia and by pregnancy.

1. Central nervous system

CNS is more susceptible to levobupivacaine. The initial symptoms involve feeling of light headedness and dizziness followed by visual and auditory disturbances. Disorientation and occasional feeling of drowsiness may occur. Objective signs are usually excitatory in nature which includes shivering, muscular twitching and tremors; initially involving muscles of the face (perioral numbness) and part of extremities. At still higher doses cardiovascular or respiratory arrest may occur. Acidosis increases the risk of CNS toxicity from, since an elevation of $PaCO_2$ enhances cerebral blood flow, so that more anaesthetic is delivered rapidly to the brain.

2. Cardiovascular system

It depresses rapid phases of depolarization (Vmax) in

purkinje fibres and ventricular musculature to a greater extent than lignocaine. It also decreases the rate of recovery from a dependent block than that of lignocaine. This leads to incomplete restoration of Vmax between action potential at high rates, in contrast to complete recovery by lignocaine.

3. Respiratory system

Respiratory depression may be caused if excessive plasma level is reached which in turn results in depression of medullary respiratory center. Respiratory depression may also be caused by paralysis of respiratory muscles as may occur in high spinal or total spinal anaesthesia.

4. Autonomic nervous system

Myelinated preganglionic beta fibres have a faster conduction time and are more sensitive to the action of local anaesthetic including levobupivacaine. Involvement of preganglionic sympathetic fibres is the cause of widespread vasodilation and consequent hypotension that occurs in epidural and paravertebral block. When used for conduction blockade all local anaesthetic particularly levobupivacaine produces higher incidence of sensory blockade than motor fibres. Dosage: Maximal dose is 2mg/kg body weight (25-30 ml 0.5% solution). Levobupivacaine is available in following concentration: 0.25% and 0.5% 0.25% and 0.5% in isotonic solution 0.125% - 0.75% used for nerve block and epidural anaesthesia or analgesia. 0.5% or 0.75% plus 80% of dextrose to make solution hyperbaric for SAB.

Adverse effects

Levobupivacaine produces the same adverse effects as seen with racemic bupivacaine and other local anesthetics. The most common adverse drug reactions reported are: hypotension (31%), nausea (21%), vomiting (14%), headache (9%), procedural pain (8%), 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. Accidental intrathecal injection during epidural blockade can produce high spinal anesthesia with severe hypotension and loss of consciousness.

CONCLUSION

Levobupivacaine is a long-acting local anesthetic with a clinical profile similar to that of bupivacaine.

REFERENCES

1. af Ekenstam B, Egnér B, Pettersson G. Local Anesthetics I. N-Alkyl Pyrrolidine and N-Alkyl Piperidine Carboxylic Acid Amides. Acta Chem Scand. 1957;11:1183–90.
2. McLeod GA, Burke D. Levobupivacaine. Anaesthesia. 2001;56:331–41.
3. Casati A, Baciarello M. Enantiomeric Local Anesthetics: Can Ropivacaine and Levobupivacaine Improve Our Practice? Curr Drug ther. 2006;1:85–9.
4. Huang YF, Pryor ME, Mather LE, Veering BT. Cardiovascular and central nervous system effects of intravenous levobupivacaine and bupivacaine in sheep. Anesth Analg. 1998;86:797–804.
5. Morrison SG, Dominguez JJ, Frascarolo P, Reiz S. A comparison of the electrocardiographic cardiotoxic effects of racemic bupivacaine, levobupivacaine, and ropivacaine in anesthetized swine. Anesth Analg. 2000;90:1308–14.
6. Leone S, Di Cianni S, Casati A, Fanelli G. Pharmacology, toxicology, and clinical use of new long acting local anesthetics, ropivacaine and levobupivacaine. Acta Biomed. 2008;79:92–105.
7. Burlacu CL, Buggy DJ. Update on local anesthetics: focus on levobupivacaine. Ther Clin Risk Manag. 2008;4:381–92.
8. Bajwa SJS, Kaur J. Clinical profile of levobupivacaine in regional anesthesia: A systematic review. J Anaesthesiol Clin Pharmacol. 2013;29:530–9.