Introduction
The property of isomerism occurs when two or more compounds have the same molecular composition, but a different structure which often results in different properties. There are two types of isomerism - structural and stereoisomerism.

Structural isomerism means that the compounds have the same molecular formula, but a different chemical structure. This may result in the compounds having similar actions like the anaesthetic volatile agents isoflurane and enfurane or different actions like promazine and promethazine.

Stereoisomerism describes those compounds which have the same molecular formula and chemical structure, but the atoms are orientated in a different direction. There are two isomers, each a mirror image of the other, called enantiomers. They are also called optical isomers because they rotate the plane of polarised light either to the right referred to as +, dextro, d or D isomer, or to the left referred to as -, laevo (levo), l or L isomer. More recently this classification has been replaced by the R-/S- notation, which describes the arrangement of the molecules around the chiral centre (R is for rectus the Latin for right, and S for sinister, left). The R enantiomer rotates light to the right and the S enantiomer to the left. As with other isomers, they can have different properties.

The molecule of bupivacaine, a long acting local anaesthetic, has an asymmetric carbon atom. For this reason, with this asymmetric carbon as a chiral centre, bupivacaine exhibits this phenomenon. In the commercial presentation of this local anaesthetic there is a 50:50 proportion: levobupivacaine, L (-) isomer, and dextrobupivacaine D (+) isomer. This preparation which contains both enantiomers is called a racemic mixture

The preparation of levobupivacaine contains only the levorotatory isomer present in the commercial preparations of bupivacaine.

Interest in levobupivacaine arose after several cases of severe cardiotoxicity (including death) were reported where it was shown that the D isomer of bupivacaine had a higher potential for toxicity. Consequently, it was thought that if it was possible to use only the levorotatory isomer, levobupivacaine, the risk for cardiac and neurotoxicity could be less than with the racemic bupivacaine but with similar clinical effects.

Chemistry
Here we will expose some general concepts about all local anaesthetics, with a special reference to levobupivacaine.

Local anaesthetic molecules all have three characteristic portions (figure 1):

- A benzene ring - aromatic head
- An intermediate chain
- An amino group

The benzene ring is very soluble in lipids.

The intermediate portion, a bridge between the other two, can have one of two types of chemical structures: Ester (COO-), or Amide (CONH-) (figure 2). Therefore, chemically, there are two large groups of local anaesthetics, depending on this intermediate portion of the molecule: Ester type and Amide type local anaesthetics. Procaine is the prototype of the first group (figure 3), and lignocaine is the prototype of the second one (figure 4). The first group more commonly cause allergic reactions and have a short length of action as they are rapidly metabolized by cholinesterase. In contrast the second group, amides, rarely case allergic reactions but are more likely to cause toxic reactions if the dose is exceeded. Levobupivacaine is an amide, which like the other amides, is a weak base.

Depending on the pH, the amino group can adopt the tertiary or the quaternary form. The drug is in dynamic balance between the tertiary form, a free base, and the quaternary form, which has a positive charge, making it very water-soluble.
Tertiary amine with the D isomer being more potent and faster than the L that blockade of the inactive sodium channels is stereoselective, electrophysiological studies have been made which demonstrate bupivacaine, but with similar clinical activity. Additionally, to conclude that levobupivacaine was less toxic than the racemic This work together with other similar studies, led the investigators and brain than the concentration of the levo isomer. was administered in toxic quantities, it was found that the animals of the dextro group developed apnoea, bradycardia, ventricular tachycardia and fibrillation than either the L isomer D isomer had a lower threshold for causing tachycardia and dysrhythmias, which include, AV block, QRS widening and tachycardia and fibrillation than either the L isomer or the racemic preparation. Differences were found between the two isomers. The concentration necessary to produce cardiac and neurotoxicity is higher for levobupivacaine than for racemic bupivacaine. The concentration necessary to produce cardiac and neurotoxicity is higher for levobupivacaine than for racemic bupivacaine. The duration of action is also similar to that of the racemic substance.

Pharmacokinetics

There are difficulties in carrying out pharmacokinetic studies with bupivacaine. Classic pharmacokinetic studies are usually performed using an intravenous application of the drug. These studies are more accurate because there are fewer possible causes of error, than when other access routes are used, such as intramuscular or subcutaneous infiltration. With both these routes of administration, the rate of absorption is an important but unknown factor affecting the rate of absorption between patients with different pathologies. In addition intravenous administration of bupivacaine or levobupivacaine, for pharmacokinetic studies has limitations, because of the risk of fatal toxicity. Additionally, in clinical practice this drug is not used intravenously.

Practical clinical studies have been carried out giving the drug for epidural and regional blocks. Placental transfer of levobupivacaine is similar to that of bupivacaine resulting in lower risk to the fetus. Like racemic bupivacaine, levobupivacaine is metabolised in the liver, primarily by the cytochrome P450, specially the CYP1A2 and CYP3A4 isosforms. Clearance is reduced when the hepatic function is damaged.

Pharmacodynamics

The mechanism of action of levobupivacaine is exactly the same as that of racemic bupivacaine and that of all the local anesthetic drugs in clinical use today. When the minimum local analgesic concentration (MLAC) close to the membranes of the axons is reached, the molecules block the sodium channels, in the resting position. In this way, the transmission of the nerve impulses stops. This action is produced with an onset very similar to that of racemic bupivacaine. The duration of action is also similar to that of the racemic substance.

Recent research work has been directed at the toxicity associated with the levo isomer, and how it compares with the racemic preparation. Differences were found between the two isomers. The concentration necessary to produce cardiac and neurotoxicity is higher for levobupivacaine than for racemic bupivacaine. The safety margin is estimated at 1.3 which means that toxic effects are not seen until the concentration rises by 30%

Toxicity

Volunteers have been given bupivacaine or levobupivacaine intravenously at a rate of 10mg/min, until the appearance of early symptoms of central nervous system toxicity. These appeared at a lower dose (Mean 47.1mg) with bupivacaine than with levobupivacaine (56.1mg). Similarly there was a greater reduction in the myocardial ejection fraction and systolic and acceleration index with racemic bupivacaine when compared to levobupivacaine. When 40mg of either levobupivacaine or
racemic bupivacaine were administered over a 10 min period, the EEG was significantly slower after racemic bupivacaine. Thus at similar doses, electrical activity is more affected by racemic bupivacaine.\(^2\)

Levobupivacaine appears to cause less myocardial depression than both bupivacaine and ropivacaine, despite being in higher concentrations.

**Clinical Applications**

Levobupivacaine has been introduced into clinical practice within the last few years. It has been used at all sites: epidural, subarachnoid, different levels of brachial plexus block - interscalene, supra and infraclavicular, intercostal and peripheral nerve blockade, peribulbar and retrobulbar blockade, local infiltration, obstetric analgesia, postoperative pain management, acute and chronic pain management. The doses used are very similar to those of bupivacaine. As a result of its lower cardiac and neurotoxicity compared to racemic bupivacaine, anaesthetists feel safer working with levobupivacaine, than with bupivacaine.

Nevertheless, we must always remember that it is still a potentially toxic local anaesthetic. The initial licensing authority recommended a maximum single dose of 2mg/kg, and 400mg (5.7mg/kg) in 24h. Since then, some studies have shown that higher doses are safe, but further work is required. Special caution is recommended for hypoproteinememic patients, including adults with nephrotic syndrome, severe hepatic disease and the newborn.

In Colombia, we have been using this new local anaesthetic for a year, with excellent results.\(^3\) We only have the 0.75% formulation and use almost the same dose as when using bupivacaine. We have had no reports of toxic reactions. During the Colombian Congress of Anesthesiology (2001), a paper was presented, comparing levo-bupivacaine with ropivacaine in epidural anaesthesia. The two drugs were comparable, with a very good quality of epidural anaesthesia. However there were three cases of bradycardia in the levobupivacaine group which were treated successfully with atropine. The duration of the motor blockade in the postoperative period was less than after racemic bupivacaine.

**Adverse Effects**

These are the same as caused by racemic bupivacaine and any other local anaesthetic. They include hypotension, bradycardia, nausea, vomiting, pruritus, headache, tinnitus, dizziness, constipation, vomiting and convulsions.

There have been reports of cases where the drug has been given in higher doses than that recommended, with no apparent toxicity. In one case, a single dose of levobupivacaine of 250mg for a brachial plexus block, far exceeding the maximum recommended dose (150mg), without toxicity symptoms, although further data will be needed before the safety of this level of dosage is confirmed.

There is a report where approximately 1.7mg/kg racemic bupivacaine was injected probably by an accidental intravenous injection during an attempted supraclavicular brachial plexus block. The patient lost consciousness, developed a tachycardia, hypertension and generalized twitching, was managed with oxygen and propofol, with a successful recovery after a few minutes with no sequelae.\(^4\) The authors stressed the risks associated with administration of high doses of bupivacaine, even in experienced hands and underline the need for possibly safer agents such as levobupivacaine.

**Conclusion**

Levobupivacaine is a relatively new long acting local anaesthetic, with a pharmacological activity very similar to that of racemic bupivacaine. The first studies in humans confirm the animal studies and the in vitro studies, which showed that this new molecule is less cardiotoxic and less neurotoxic than the racemic bupivacaine. Levobupivacaine can be used for all indications in which the anaesthetist needs a long acting local anaesthetic. The reduced toxicity of this new local anaesthetic is an advantage for the patient. The cost in Colombia is 40% higher, than racemic bupivacaine.

**References**


**Further reading**

McLeod GA, Burke D. Levobupivacaine. Anaesthesia 2001;56:331-341