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Enantiomeric Excess of Bupivacaine (S75:R25): Laboratory Study, Clinical Application and Toxicity

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Abstract

Local anesthetics are drugs that produce temporary and localized blockage of nerve conduction. Depending on the place of administration and the dose used, they can lead to interruption of sensitivity, autonomous innervation and motricity, and must associate properties that, in addition to efficacy, ensure safety.

Most pharmaceutical drugs are released in racemic form. The study of the chirality of substances is an important field in the pharmaceutical industry and agrochemicals. Several review articles on chirality have been published, but none of them address the presence of an enantiomeric excess. In Brazil, an enantiomeric excess local anesthetic containing 75% of the S-enantiomer and 25% of the R-enantiomer was investigated, and later approved for use in regional anesthesia.

In several articles published in Brazil with the enantiomeric mixture of bupivacaine (S75:R25) whether in epidural, brachial or lumbar plexus block, postoperative analgesia by bilateral pudendal nerve block, there is no report of toxicity with cardiac arrest.

Keywords: Bupivacaine• Levobupivacaine hydrochloride in 50% enantiomeric excess • Levobupivacaine • Laboratory studies • Clinical uses

Introduction

The study of the chirality of substances is an important field in the pharmaceuticals industry and agrochemicals. The vast majority of commercialized substances are presented as a racemic mixture, despite the significant pharmacological, pharmacodynamic and pharmacokinetic differences of the individual isomers. Although most substances are produced in racemates, one isomer may be more potent than the other. In 1992, R-bupivacaine was shown to be 3 times more potent than S-bupivacaine [1]. With prilocaine, the S(+) enantiomer is slowly hydrolysed, but the R(+) enantiomer is rapidly hydrolysed forming toluidine, which causes methemoglobinemia [2]. Mepivacaine is also clinically administered as a racemate where the S(-) enantiomer is the more active configuration [3]. The results obtained with the isomers of mepivacaine and bupivacaine strongly suggest that the long duration of anesthesia that the racemic forms production in man is mainly due to one of the optical isomers. Etidocaine is similar to lidocaine and is presented in the racemic mixture [4]. Several review articles on chirality address the separation of isomers from local anesthetics and never address the study of the presence of an enantiomeric excess [5-10].

Stereoisomerism

About 82% of the drugs used in medicine, they are chiral compounds and presented in the racemic form [11]. The therapeutically active isomer does not mean that the other is really inactive; it may contribute to side effects. The therapeutically inactive isomer in a racemate should be considered as an impurity in a proportion of 50% or more [12]. The stereoisomerism is emerging as an imperative for therapeutic rationalization. The approach of science with technology will reformulate concepts of local anesthetics, with regard to three-dimensional biochemistry. In 1979, an editorial views was denounced the toxicity bupivacaine and etidocaine [13]. Although the bupivacaine has been recognized as isomeric, there was no correlation between its peculiar cardiotoxicity and stereoisomeric nature of this local anesthetic. Ropivacaine is a new aminoamide prepared as the pure S-enantiomer, which were synthetized in 1957 [14]. In 1991, electrophysiological studies were carried out with bupivacaine separated into its enantiomers [15]. These authors demonstrated lower depressant activity with S(-) bupivacaine compared to R(+) bupivacaine on the maximum depolarization velocity in the guinea pig papillary muscle. This study succeeded to articles from two distinct groups, which observed less toxicity (30% to 40%) with levorotatory bupivacaine, when administered in the vein of animals, compared to dextrorotatory bupivacaine.

In this way, once recognized the stereoisomeric nature of bupivacaine and therefore the existence of two molecules twins in the commercial composition of this agent, research continued under this optics. Several groups started to study the effects of the two enantiomers in the nucleus of the solitary tract, in the appearance of dysrhythmias, alterations cardiovascular diseases and cardiodepressant effect in an isolated heart [16-18].

Levobupivacaine (The pure S(-) enantiomer of bupivacaine)

With the increasing cardiotoxicity of racemic bupivacaine, the study of the chirality of local anesthetics showed a more pronounced enantioselective with the R(+) enantiomer, the S(-) enantiomer was developed for clinical use as a long-acting local anesthetic. Levobupivacaine is the S(-) enantiomer was developed in 1999 as a long acting local anaesthetic with a potentially reduced toxicity compared with bupivacaine [19]. Levobupivacaine is no longer marketed in the USA.

Enantiomeric excess of bupivacaine

Previous preclinical studies and clinical article suggest that S(-) enantiomer (Levobupivacaine) is lower than that of either R(+) enantiomer or racemic (RS ±) bupivacaine. The specificity for sodium channels is more pronounced with the R(+) enantiomer than with the S(-) enantiomer. This facilitates the understanding of cardiotoxicity of racemic bupivacaine containing two enantiomers in the same equimolar ratio (50:50), the presence of the form R(+) accounts for the worsening of this cardiotoxicity [20]. With genuinely Brazilian technology, the dextroenantiomer R(+) was separated from the levoenantiomer S(-). The lowest potency was demonstrated cardiodepressant of levobupivacaine in relation to racemic bupivacaine in atrial pacemaker (chronotropism) and in the force of contraction of the left atrium electrically stimulated (inotropism) of rats, confirming the results in the literature [21].

In order to study the influence of the R-isomer of bupivacaine in the

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rat nerve *in vivo*, an investigation was carried out with two formulations: S-bupivacaine 90% plus R-bupivacaine 10% (S90:R10) and S-bupivacaine 75% plus R-bupivacaine 25% (S75:R25), both compared to the racemic mixture (S50:R50). The S75:R25 mixture needs a larger dose than racemic bupivacaine to sacrifice rats. The effects of bupivacaine isomers showed to be stereospecific. The results of this study demonstrated that the combination of isomers provides an important efficacy in the activity of the local anesthetic, in terms of onset and duration of neuronal blockade. Both parameters were improved by the contamination of 10% R-isomers in the formulation. This might interfere with the dwelling of this isomer in the nerve Na^+ channel [22]. On the other hand, the action on C and A delta fibres appeared to require a more intense contamination with the R-isomer once a greater analgesic activity was observed with S75:R25 formulation. The conclusion of this study shows that the presence of the R-isomer improves the quality of the blockade without the cardio toxic effects.

This new solution was patented by the National Institute of Industrial Property, the regulatory body of the Brazilian Government (INPI), and registered with ANVISA (National Agency of Sanitary Surveillance), and marketed under the name Novabupi, in its S75:R25 formulation, for use in regional anesthesia.

Literature Review

Laboratory studies

A study was carried out on the effects of racemic bupivacaine (S50:R50) and its isomers S(-) bupivacaine and R(+) bupivacaine on the Ca^{2+} handling by ventricular myocytes from wistar rats [23]. This study demonstrates that S(-) isomer, but not R(+) bupivacaine, significantly increases Ca^{2+} transients in ventricular myocytes. This could explain the decreased toxicity of S(-) bupivacaine to induce cardiac depression.

In order to prolong the duration of action and reduce the systemic toxicity of these drugs have been developed formulations containing local anesthetics added with cyclodextrins and cyclic oligosaccharides. Comparing racemic bupivacaine with the enantiomeric mixture (S75:R25) both complexed with cyclodextrin in spinal block anesthesia in rats, showed an increase in the aqueous solubility of both solutions [24]. *In vivo* tests with both solutions plus cyclodextrin reduced latency, without changing motor block duration, and prolonged analgesia duration when compared to free substances.

Levobupivacaine has fewer central nervous system side effects than those induced by racemic bupivacaine; however, the anesthetic effect is less intense. An experimental study was carried out to compare adverse effects of large volumes of bupivacaine (S50:R50), enantiomeric excess of bupivacaine (S75:R25) and levobupivacaine (pure S-enantiomer) when injected into the subarachnoid space of guinea pigs [25]. Large volumes of levobupivacaine caused little damage in the central nervous system when compared with bupivacaine racemic. Statistically significant changes were not observed between levobupivacaine and S75:R25 bupivacaine.

In order to find a safer drug than racemic bupivacaine, a study was carried out with digital infrared image analysis of the vasomotor effect of acute intoxication with bupivacaine racemic compared with that of enantiomeric excess of bupivacaine (S75:R25) *via* intraperitoneal in rats [26]. The results showed that the vasomotor effect of acute toxicity of enantiomeric excess of bupivacaine (S75:R25) was similar to the control group with saline, through macroscopic studies by infrared digital filming, and that there were vasomotor changes (vasoconstriction) with the racemic bupivacaine intoxication. The potency of S(-) bupivacaine to block the motor activity in the sciatic nerve was enhanced when 25% of the S(-) isomer was replaced by the antipode R(+) bupivacaine. This effect was not associated with increased toxicity [27].

Clinical Studies with Enantiomeric Excess of Bupivacaine

Spinal anesthesia

- **Enantiomeric excess of bupivacaine (S75:R25) 0.5% isobaric:** Commercially available bupivacaine is a racemic mixture of S(-) and R(+) enantiomers. A study was carried out comparing isomeric bupivacaine (S50:R50) with a mixture with enantiomeric excess of bupivacaine (S75:R25) at the same dose and concentration, for spinal anesthesia in lower limb orthopedic surgeries [28]. The enantiomeric mixture (S75:R25) at 0.5% isobaric, injected into the subarachnoid space, produces blockage sensory and motor similar to the same dose of bupivacaine 0.5% isobaric racemic for orthopedic surgery. Both the S75:R25 isobaric enantiomeric mixture as isobaric racemic bupivacaine (S75:R25) presented the same density and had the same behavior in the cephalic dispersion of analgesia up to 30 minutes, after injection in lateral decubitus [29].
- **Enantiomeric excess of bupivacaine (S75:R25) 0.4% hyperbaric:** Hyperbaric bupivacaine commercially used is presented as a racemic form. In Brazil, 50% enantiomeric excess bupivacaine (S75:R25) was released only in isobaric form. In order to assess the quality of analgesia, dispersion, regression of hyperbaric S75:R25 0.4% bupivacaine with 5% glucose, in different volumes was performed spinal anesthesia in infra-umbilical surgical procedures [30]. Patients were randomly divided into 4 groups of 10 patients: Group 1: received 2.5 mL of the solution (10 mg), Group 2: received 3 mL (12 mg), Group 3: received 4 mL (16 mg) and Group 4: received 5 mL (20 mg). Excessive 0.4% hyperbaric bupivacaine 50% enantiomeric (S75:R25) with 5% glucose provided quick start of installation, with level of sensitive block, block motor, and dose-dependent block duration. The incidence of bradycardia or hypotension was related with the increase in the dose.

In a recent study, the incidence of unilateral blockade was evaluated using different doses of excess levobupivacaine enantiomeric (S75:R25) at 0.4% hyperbaric with glucose 5%, injected in the lateral decubitus position, in patients undergoing orthopedic surgery in only one limb [31]. The onset of analgesia was rapid and comparable between groups. Sensory block was significantly higher in the operated than in nonoperated limb at all times of evaluation. Increasing the dose by 1 mL (2 mg) corresponded to an increase of two segments in the mode for the operated side. In the operated side, motor block (MB=3) of patients occurred in 31 (77.5%) with 4 mg, 38 (95%) with 6 mg, and 40 (100%) with 8 mg. There was a positive correlation between increased dose, blockade duration, and hypotension. All patients were satisfied with the technique used. The lowest dose (4 mg) provided the highest incidence of selectivity, both in analgesia and in motility.

Epidural anesthesia

The cardiotoxic effect of racemic bupivacaine (S50:R50) is still the major safety-related variable for regional blocks requiring higher concentrations and volumes. Recent animal studies suggested that the manipulation of racemic bupivacaine enantiomers could contribute for a better therapeutic efficacy by decreasing its potential toxicity. In a study aimed at evaluating the efficacy of 0.5% bupivacaine enantiomeric mixture (S75:R25) as compared to plain S(100%) bupivacaine in lumbar epidural anesthesia for varicose vein surgery [32]. Faster spread and lower analgesic effects of the isomeric mixture were statistically significant. Motor block was significantly deeper in the S75:R25 compared to the pure S(-) enantiomer of bupivacaine,

The enantiomeric mixture of bupivacaine (S75:R25) has been used for its anesthetic property with less toxicity than racemic bupivacaine. The anesthetic efficacy of the enantiomeric mixture was evaluated of bupivacaine (S75:R25) when administered epidurally compared to racemic bupivacaine (S50:R50) in surgical procedures vascular or orthopedic, in the lower limb [33]. Enantiomeric bupivacaine (S75:R25) resulted in longer analgesia and less intense motor block as compared to racemic bupivacaine.

Comparing the two solutions in epidural anesthesia for orthopedic surgeries of the lower limbs, it showed adequate motor blockade and sensitive in both groups, with few side effects, suggesting that solutions are safe in epidural anesthesia for surgery orthopedic [34].

Peripheral nerve block

A study was carried out to verify the degree of motor blockade and its onset time, comparing 0.5% enantiomeric excess bupivacaine (S75:R25), 0.5% racemic bupivacaine and 2% lidocaine programmed for cataract surgery under retro bulbar block, preceded by facial nerve block using the O'Brien technique [35]. There were no differences regarding the length of time until the beginning of the blockade and its degree between racemic bupivacaine and enantiomeric excess bupivacaine. Both bupivacaine and 50% enantiomeric excess bupivcaine (S75:R25) are good options to achieve paralysis of the eyelids and eyebrow with facial nerve block by the O'Brien technique.

Usually brachial plexus block may require high doses of local anesthetic. Thus, a comparative study was carried out on the safety and efficacy of enantiomeric excess bupivacaine (S75:R25) with vasoconstrictor compared to ropivacaine [36]. This study showed similar efficacy between bupivacaine S75:R25 for brachial plexus blockade and ropivacaine, with similar incidences of supraventricular arrhythmias.

Comparing racemic bupivacaine with the enantiomeric mixture (S75:R25) both at 0.5% for upper limb surgeries with brachial plexus block showed that there was adequate sensory and motor blocks in both groups, with few side effects, suggesting that the 0.5% enantiomeric mixture (S75:R25) of bupivacaine with epinephrine is safe and effective for brachial plexus block of upper orthopedic limb surgeries [37].

Hemorrhoidectomy may be performed under several anesthetic techniques and in outpatient regimen. Postoperative pain is severe and may delay discharge. Bilateral pudendal nerves block with 0.25% S75:R25 bupivacaine was performed with nerve stimulator in 35 patients submitted to hemorrhoidectomy under spinal anesthesia, being evaluated parameters were pain severity, duration of analgesia, demand analgesia and possible technique-related complications [38]. Bilateral pudendal nerve block provided excellent quality analgesia, with low need for opioids, without local or systemic complications and no urinary retention, and with perineal anesthesia stay for 21 hours.

In another study with 200 patients scheduled for hemorrhoidectomy were randomly divided into two groups: Control and pudendal [39]. With the aid of a neurostimulator and with levobupivacaine enantiomeric excess (S75:R25), with an average duration of 24 hours, residual analgesia for more than 24 hours in 41% of patients, providing considerable reduction of postoperative pain, decrease of analgesic doses, better quality at first defecation and high level of patient satisfaction.

Obstetric anesthesia and analgesia

- **Epidural anesthesia for cesarean delivery:** Epidural 0.5% racemic bupivacaine associated with opioids is a technique used in cesarean sections; however, its toxicity has been questioned. 50% Enantiomeric excess bupivacaine has lower cardio and neurotoxicity. The efficacy of epidural 0.5% racemic bupivacaine and 0.5% enantiomeric excess bupivacaine associated with sufentanil in parturients undergoing cesarean sections was evaluated [40]. Latency, maximal level of sensitive blockade, degree of motor blockade, and duration of analgesia were similar in both groups; the mean time for regression of the motor blockade was significantly smaller in enantiomeric excess bupivacaine, being an alternative alternative for this procedure, since it has faster regression of the motor blockade, which is desirable in obstetric patients

  A study was carried out evaluating the quality of anesthesia and maternal/fetal repercussions of 0.5% bupivacaine, enantiomeric 0.5% bupivacaine (S75:R25) and 0.75% ropivacaine, all associated to fentanyl, in epidural cesarean section anesthesia [41]. The results in 90 patients (with a group of 30 patients) will show that the enantiomeric mixture 0.5% bupivacaine (S75:R25) and 0.75% ropivacaine for epidural anesthesia have provided as good conditions as racemic 0.5% bupivacaine for the surgical act. Newborn repercussions have shown that all solutions are equally safe

- **Spinal anesthesia for labor analgesia:** Spinal anesthesia is used for relief of pain during labor and it is associated with low indices of complications. Studies with levorotatory enantiomers of local anesthetics demonstrate higher safety due to the lower cardiotoxicity. The objective of this study was to evaluate the latency and duration of analgesia and maternal and fetal repercussions with bupivacaine (S75:R25) and ropivacaine in spinal anesthesia for labor analgesia [42]. A statistically significant difference was observed between the two groups 30 minutes after the spinal anesthesia, and pain scores were higher in the ropivacaine group. When comparing two local anesthetics, bupivacaine (S75:R25) and ropivacaine, whose profile is associated with lower neuro and cardiotoxicity, we conclude that both drugs in low concentrations can be used for labour analgesia

- **Epidural anesthesia for labor analgesia:** Continuous epidural block is used for relief of labor pain and it is associated with a low incidence of complications. In order to compare analgesia and motor blockade of 0.125% bupivacaine (S50:R50) and 0.125% and 0.25% 50% enantiomeric excess bupivacaine (S75:R25) in continuous epidural block for labor analgesia, a study was carried out in 3 groups of 25 parturients [43]. The latency of analgesia, levels of sensorial blockade, volume of local anesthetic, duration of labor and analgesia, frequency of instrumental delivery, Apgar scores, or pH of umbilical cord blood showed no statistically significant differences. In conclusion, the motor blockade was less intense with bupivacaine (S75:R25) regardless the concentration, resulting in analgesia of better quality without interfering with the evolution of labor or the vitality of newborns

- **Combined spinal-epidural for labor analgesia:** Studying 40 parturients in labor, they were divided into two groups with continuous epidurals: Group 1, patients received 8 mL (20 mg) of 0.25% enantiomeric excess bupivacaine (S75:R25) with epinephrine, associated with 100 µg of fentanyl or in group II, received 8 mL (20 mg) of 0.25% racemic bupivacaine (S50:R50) with epinephrine, associated with 100 µg of fentanyl. Motor block, Romberg test, walking ability and spontaneous urination, duration of labor and period expulsive, maternal hemodynamic and respiratory changes in addition to the vitality of newborns [44]. There were no statistically significant differences between groups in all evaluated parameters. All parturients presented with muscle strength and ambulation ability. Both racemic and S75:R25 0.25% bupivacaine asssociated to fentanyl were effective for labor analgesia

Spinal pediatric anesthesia

Commercially available bupivacaine is a racemic mixture of S(-) and R(+) enantiomers. Although the S(-) bupivacaine enantiomer is less toxic than R(+) bupivacaine to cardiovascular and central nervous systems. Participated in this prospective study 40 patients aged 1 to 5 years submitted to spinal anesthesia with 0.5 mg/kg of a 0.5% isobaric mixture of 75% S(-) bupivacaine plus 25% R(+) bupivacaine, being were observed: Onset of analgesia, degree of motor block, duration of effects, cephalad spread of analgesia, cardiovascular changes, incidence of headache and transient neurological symptoms [45]. Isobaric 0.5% levobupivacaine (S75:R25) induces a safe spinal anesthesia in patients aged 1 to 5 years scheduled for outpatient procedures, with a high success rate, short-lasting motor block, relatively low incidence of side effects and at a lower cost, in outpatient procedures.

In another study with 307 pediatric patients under the age of 13 years of age, it showed that the use of excess enantiomeric (S75:R25) isobaric bupivacaine was in 73% of the children [46]. The onset of sensory block occurred at 2.36 min ± 0.95 min , with duration of surgery was 1.29 hour ± 0.83 hour and the duration of stay in the post anesthesia care unit was 39.72 min ± 26.84 min, and was 54% less than the cost of general anesthesia.

Ophtalmic surgery

Minimum anesthetic volume of local anesthetics corresponds to the effective volume for regional anesthesia in 50% of patients. This volume was calculated with 0.5% racemic bupivacaine, 0.5% levobupivacaine and

Table 1. Various types of surgery, S75:R25 solution, dose used and toxicity.

Ref	Technique	Surgery	Patients	Solution	Dose	Toxicity
1	Epidural	Surgical cure for varicose veins	15	0.50%	20 ml	No
2	Epidural	Surgical cure for varicose veins + Orthopedic	22	0.50%	16 ml-24 ml	No
3	Epidural	Orthopedic	18	0.50%	30 ml	No
4	Brachial Plexus	Orthopedic	22	0.50%	30 ml	No
5	Brachial Plexus	Orthopedic	20	0.50%	30 ml-40 ml	No
6	Pudendal Block	Hemorrhoid	35	0.25%	40 ml	No
7	Pudendal Block	Hemorrhoid	100	0.25%	40 ml	No
8	Epidural	Caesarean	24	0.50%	20 ml	No
9	Epidural	Labor	20	0.25%	8 ml	No
10	Epidural	Labor	23	0.25%	10 ml	No
11	Epidural	Labor	25	0.13%	10 ml	No
		Labor	25	0.25%	10 ml	No
12	Epidural	Labor	20	0.25%	8 ml	No
13	Lumbar Plexus	Orthopedic	105	0.25%	40 ml	No
	Total	-	454	-	-	-

0.5% enantiomeric S75:R25 bupivacaine [47]. Similar volumes of 0.5% racemic bupivacaine, 0.5% levobupivacaine and 0.5% enantiomeric S75:R25 bupivacaine are needed for extraconal retrobulbar anesthesia, ranging from 5.7 ml to 6.2 ml.

In order to compare the anesthetic efficacy of two bupivacaine solutions, a study was carried out in 22 volunteers randomly received in a crossover, double-blind two way inferior alveolar nerve block with 1.8 mL of racemic bupivacaine and one mixture of 75% levobupivacaine and 25% dextrobupivacaine (S75:R25), both 0.5% and with 1:200,000 epinephrine [48]. No differences were found between the solutions for onset and duration of pulpal anesthesia and duration of soft tissue anesthesia. Both solutions have similar anesthetic efficacy.

Geriatric analgesia

With the objective of implementing a project to ACEleration of Postoperative Total Recovery (ACERTO Project), 105 patients were studied who underwent different types of surgical correction on the femur, operated under spinal anesthesia and analgesia through lumbar plexus block with 40 mL of 0.25% enantiomeric excess bupivacaine (S75:R25), in elderly patients over 60 years [49]. Hospitalization ranged from 3 to 86 days, with fasting time from 9:15 to 19:30. Hypotension occurred in 5.7%. Feeding with maltodextrin in the Post Anesthetia Care Unit (PACU) ranged from 50 mins to 3:45 hours and the length of stay in PACU the ranged from 50 mins to 4 hours. The duration of analgesia with lumbar plexus block ranged from 14 to 33 hours, with a mean of 22:26 hours ± 3:99 hours. No patient needed a urinary catheter delay, nor was he referred to the ICU. All patients were able to be discharged from the hospital on the first postoperative day.

Toxicity

The use of levorotatory anesthetics both in animals and in humans proved to be less toxic than the racemic mixture and dextrogyros anesthetics for the cardiovascular and central nervous system. In rat sciatic nerve it showed that S75:R25 maintains the anesthetic property similar to racemic mixture (S50:R50). With the intravenous bolus injection of S75:R25 it proved to be less cardiotoxic than the racemic mixture, and this characteristic was attributed to the reduction of the R(+) isomer in this new mixture.

In several articles published in Brazil with the enantiomeric mixture of bupivacaine (S75:R25) whether in epidural, brachial or lumbar plexus block, postoperative analgesia by bilateral pudendal nerve block, there is no report of toxicity with cardiac arrest (Table 1).

Conclusion

Enantiomeric excess bupivacaine (S75:R25) is a local anesthetic derived from bupivacaine developed in Brazil during the last two decades of the 20th Century. Due to the concepts of optical isomery, it has a pharmacological profile that is unique and distinct from the racemic mixture (S50:R50), as well as from that of the pure enantiomers R(+) and S(-).

In vivo experiments with mouse sciatic nerve, the enantiomeric mixture in the S90:R10, S80:R20, and S75:R25 proportions produced greater nerve block than the pure S(-) enantiomer. In other studies with animals with the intravenous use of the enantiomeric mixture in different proportions, pure S(-) and R(+) enantiomers, and the racemic mixture, the racemic form was associated with cardiac collapse in the majority of cases. The R isomer shows stronger binding to sodium channels and slower dissociation than the S isomer, which is responsible for its lower cardiotoxicity.

Brazilian pharmaceutical industry introduced in the enantiomeric mixture of levobupivacaine (S75:R25) having been patented by the National Institute of Industrial Property (NIPI), the regulatory body of the Brazilian Government,

and registered with ANVISA (Agencia Nacional de Vigilancia Sanitaria) Or National Agency of Sanitary Surveillance.

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