

## **Ropivacaine A Review of Its Use In Regional Anaesthesia, Choric Pain Management And In Patients With Cardiac Diseases In Non Cardiac Surgeries**

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**Abstract:** Ropivacaine is a long acting amide local anesthetic agent, it is the pure S(-)- enantiomer of propivacaine, and is a long acting amide local anaesthetic agent, eliciting nerve block via reversible inhibition of sodium on influx in nerve fibres. Ropivacaine is less lipophilic than bupivacaine and is less likely to penetrate large myelinated motor fibres, resulting in a relatively reduced motor blockade. The reduced lipophilicity is also associated with decreased potential for central nervous system toxicity and cardiotoxicity.

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### **I. Introduction**

The important property of a long acting local anesthetic is to reversibly inhibit the nerve impulses, thus causing a prolonged sensory or motor blockade appropriate for anaesthesia in different types of surgeries<sup>(1)</sup>.

Bupivacaine is associated with cardiotoxicity when used in high concentration or when accidentally administered intravascularly. Ropivacaine is a long-acting regional anaesthetic that is structurally related to bupivacaine. It is a racemate, developed for the purpose of reducing potential toxicity and improving relative sensory and motor block profiles<sup>(1)</sup>.

#### **Structure And Stereospecificity**

Enantiomers exist in two different configurations and are present in equal amounts in a racemic solution. They are optically active and can be differentiated by their effects on the rotation of a polarized light into dextrorotatory or levorotatory stereoisomers. The physicochemical properties of the two enantiomers can have substantially different behaviours 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 anaesthetics have been demonstrated to have different affinity for different ion channels of sodium, potassium, and calcium; this results in a significant reduction in central nervous system and cardiac toxicity of the S(-) enantiomers as compared with the R(-) enantiomer.<sup>(2)</sup> The technological development has made it possible to develop Ropivacaine as an optically pure S(-) enantiomer from the parent chiral molecule propivacaine. It belongs to the group of local anaesthetics, the piperidylidides and has a propyl group on the piperidine nitrogen atom compared to bupivacaine, which has a butyl group.

#### **Mechanism of Action**

Ropivacaine causes reversible inhibition of sodium ion influx, and thereby blocks impulse conduction in nerve fibres.<sup>(1)</sup> This action is potentiated by dose-dependent inhibition of potassium channels.<sup>(4)</sup> The pKa of ropivacaine is approximately 8.2 with lower lipid solubility than bupivacaine. Ropivacaine is less lipophilic than bupivacaine and is less likely to penetrate large myelinated motor fibres; therefore it has selective action on the pain-transmitting A $\delta$  and C nerves rather than A $\beta$  fibres, which are involved in motor function. The order of blockade affecting the nerve fibres is: autonomic, sensory, and motor; and the effects disappear in the reverse order. Clinically the order of loss of sensations is: pain, temperature, touch, proprioception, and skeletal muscle tone. Repeated activation by a train of depolarizing pulses increases the inhibitory effects of ropivacaine and produces a hyperpolarizing shift.

### **II. Pharmacodynamics**

#### **Central Nervous System And Cardiovascular Side Effects**

Ropivacaine is less lipophilic than bupivacaine and that, together with its stereoselective properties,<sup>5</sup> contributes to ropivacaine having a significantly higher threshold for cardiotoxicity and CNS toxicity than bupivacaine in animals<sup>5,6</sup>. And healthy volunteers,<sup>7</sup> Ropivacaine acts by blocking the generation and conduction of nerve impulses, presumably by increasing the threshold for electrical

excitation in the nerves. It reduces the speed of nerve impulse - conduction, and reduces the rate of rise of the action potential.

The lower lipophilicity of ropivacaine versus bupivacaine correlate with the lesser cardiodepressant effects of both ropivacaine isomers than of the bupivacaine isomers in animal studies.<sup>{5}</sup> The CNS effects occurred earlier than cardiotoxic symptoms during an intravenous infusion of local anaesthetic (10mg/min of ropivacaine or bupivacaine) in human volunteers and the infusion was stopped at this point. Significant changes in cardiac function involving the contractility, conduction time and QRS width occurred and the increase in a QRS width was found to be significantly smaller with ropivacaine than with bupivacaine,<sup>{8,9}</sup>

### **Other Effects**

Ropivacaine inhibits platelet aggregation in plasma at concentration of 3.75 and 1.88mg/ml which correspond to those that occur in the epidural space during infusion<sup>{10}</sup> Ropivacaine has antibacterial activity in vitro, inhibiting the growth of staphylococcus aureus<sup>{11,12}</sup> Escherichia coli,<sup>{11}</sup> and Pseudomonas aeruginosa.<sup>{12}</sup>

### **Pharmacokinetics**

#### **Absorption and distribution:**

The absorption of ropivacaine depends on the total dose and route of administration and also haemodynamic and circulatory condition of patient and vasculature of site of administration.

When ropivacaine is administered intravenously in subjects, its pharmacokinetics were linear and dose proportional up to 80mg<sup>{13}</sup>. The absorption of ropivacaine from epidural space is complete and biphasic. The mean absorption of ropivacaine from epidural space is complete and biphasic. The mean half life of the initial phase is approximately 14 minutes, followed by a slower phase with a mean absorption of approximately 4.2 hours. Ropivacaine is extensively (94%) bound to plasma proteins, mainly alpha-1-acid glycoprotein; and the systemic toxicity is related to the unbound drug concentration. After intravascular administration, the volume of distribution of ropivacaine at steady state was 41L. The total plasma concentration increase during continuous epidural infusion of ropivacaine is caused by an increase in the degree of protein binding and decrease in clearance of ropivacaine.<sup>{14}</sup>

Ropivacaine rapidly crosses the placenta during epidural administration for caesarean section, however the total plasma concentration was lower in the foetal circulation than maternal circulation, reflecting the binding of drug to alpha-1-glycoprotein, which is more concentrated in maternal than foetal plasma.

### **TOLERABILITY**

Ropivacaine is generally well tolerated regardless of route of administration. Reactions to ropivacaine are characteristic of those associated with other amide-type local anaesthetic. Common adverse effects that may occur were hypotension, nausea, vomiting bradycardia and headache. Epidural administration of ropivacaine for surgery produced – dependant adverse effects less as compared to those observed with equal doses of bupivacaine. Ropivacaine is generally well tolerated in the fetus or neonate following maternal epidural administration. The incidence of cardiovascular and central nervous system toxicity as a result of inadvertent intravascular injection of ropivacaine appears to be low.

The tolerability of ropivacaine is generally good as compared to levobupivacaine or bupivacaine. The most frequently occurring adverse effects were nausea and vomiting. The incidence of ropivacaine-induced cardiovascular symptoms may be age related;<sup>{18}</sup> patients aged more than 60 yrs who received epidural ropivacaine 1% had a significantly higher incidence of bradycardia.

Ropivacaine was generally well tolerated in paediatric patients regardless of route of administration. Ropivacaine was generally well tolerated in foetus or neonate following use of regional anaesthesia in women undergoing caesarean section or during labour.<sup>{13}</sup>

The most common foetal or neonatal adverse events with ropivacaine were fetal bradycardia, neonatal jaundice, and nonspecific neonatal complications. According to a meta-analysis of six double blind trials, ropivacaine did not influence the neonatal neurological and adaptive capacity (NAC) Score at a hours after delivery and at 24hrs after delivery, total NAC scores were significantly higher in neonates whose mothers had received ropivacaine rather than bupivacaine<sup>{20}</sup>

### **Cardiotoxicity and CNS toxicity in comparison to bupivacaine.**

The incidence of cardiotoxicity and central nervous system toxicity as a result of inadvertent intravascular injection of ropivacaine appears to be low<sup>{21}</sup>, The convulsive local anaesthetic doses of bupivacaine and ropivacaine were studied in different animal models; bupivacaine has a 1.5 to 2.5 –fold lower convulsive threshold when compared to ropivacaine. on the basis of animal and volunteer

studies . it can be concluded that ropivacaine seems to be less neurotoxic and cardiotoxic than bupivacaine.

#### Drug interactions;

Ropivacaine should be used carefully in patients receiving other local anaesthetics or agents structurally related to amide type of local anaesthetics as toxic effects of these drugs are additive .

Cytochrome P4501A2metabolises ropivacaine to 3- hydroxyl ropivacaine to 3-hydroxy ropivacaine, the major metabolite, Thus, strong inhibitors of cytochrome P4501A2, such as fluvoxamine, given concomitantly during administration of ropivacaine, can interact with ropivacaine and thus lead to increased ropivacaine plasma levels. Caution should be excercised when co-administering CYP1A2 inhibitors. Possible interactions with drugs known to be metabolized by CYP1A2 via competitive inhibition such as theophylline and imipramine may occur.

The administration of adrenaline with ropivacaine may improve analgesia by reducing vascular uptake of the local anaesthetic and by a direct agonist effect on spinal alpha2 receptors .The addition of adrenaline 5microgram /ml to epidural ropivacaine (initial dose 30mgm followed by an infusion of 10 mgm/hr) resulted in reduced mean plasma ropivacaine concentrations (0.31 vs 0.17 mg/l ;p,0.05)after.

Drogs like fluvoxamine, ciprofloxacin and erythromycin that inhibit CYP1A2 reduce the plasma clearance of ropiacaine significantly. Drugs such as Ketoconazole reduced the in vivo clearance of ropivacaine by 15%; however, this effect was not clinically significant. The CYP3A4 inhibitors clarithromycin and itraconazole had no significant effect on the pharmacokinetics of ropivacaine. Rifampicin an inducer of CYP3A4 increased the plasma clearance of ropivacaine by 93% in healthy volunteers (p<0.001)

#### Therapeutic Efficacy and clinical applications

Numerous clinical trials have evaluated the efficacy of ropivacaine for surgical anesthesia and postoperative and labour pain ,and for postoperative pain .

#### Surgical anaesthesia

Clinical trials indicate that ropivacaine is an effective regional anaesthetic when administered via several routes.

#### Epidural administration

Epidural ropivacaine, administered primarily in the lumber region, has an effect of anaesthetic for number of surgical procedures. A majority of studies on epidural ropivacaine are in caesarean section and although the drug has been investigated as an anaesthetic agent for other abdominal or gynecological procedures, orthopedics and vascular surgery the major use of epidural ropivacaine in the latter procedures is for postoperative pain relief.

In patients undergoing lumbar epidural anaesthesia for lower limb surgery , ropivacaine provided a similar anaesthetic profile (with regard to onset of analgesia or anaesthesia and onset of motor block) to those of bupivacaine <sup>{25}</sup> .

Clinical trials of epidural anaesthesia for elective caesarean section indicate that ropivacaine (.75%,.5%) provides a clinically similar onset of sensory and motor block to that of bupivacaine.5%. <sup>{23}</sup>

#### Dosage recommendations for ropivacaine in adults and children

Indication in adults	concentration (%)	volume	Dose
<b>In adults</b>			
Surgical anesthesia			
Lumber epidural (caesarean section)	.75	15-20 ml	113-150u
Lumber epidural (other surgery)	.75	15-25ml	113-188mg
Intrathecal administration	0.5	3-4 ml	15-20mg
Peripheral nerve block	.75	10-40ml	75-300mg
Field block	0.75	1-30ml	7.5-225mg
<b>In children</b>			
Caudal epidural block	0.2	1ml/kg	2 kg
Peripheral nerve block	0.5	0.6 ml/kg	3mg/kg

## **INTRATHECAL ADMINISTRATION**

Single doses of 2-4 ml of 0.5%-2% solutions of ropivacaine have been shown to be less potent than bupivacaine when administered intrathecally and is generally administered at a higher dose than bupivacaine. Hyperbaric solutions of ropivacaine have been compared to isobaric solution of the drug for various procedures and generally resulted in a faster onset and recovery from blocks. The hyperbaric solution provide predictable block but spread and duration may vary. The co-administration of opiates reduces the total dose of local anaesthetic required for anesthesia and prolongs the duration of complete and effective analgesia without prolonging the motor block<sup>[25]</sup>. It is suggested that on a milligram for milligram basis, the potency of ropivacaine relative to bupivacaine is two-third with regards to sensory block and half with regard to sensory block and half with regard to motor block<sup>[26]</sup>.

## **Peripheral nerve blocks**

Peripheral nerve block is employed for anesthesia for orthopedics surgery, and the onset and spread of local anesthetic is influenced by the site of injection<sup>[18]</sup>. The long-acting sensory and motor block provided by ropivacaine is .5% or .75% for axillary, interscaene and subclavian perivascular brachial plexus block for hand or arm surgery compared with bupivacaine .5%. In lower limb surgeries where sciatic or combined femoral and sciatic block was given for knee, ankle, or foot procedures, ropivacaine .75% 25ml had faster onset of sensory and motor block than 25ml bupivacaine .5%. The ropivacaine had a significantly shorter duration of sensory block, the duration of motor block remained similar with both agents<sup>[28]</sup>.

## **Management of postoperative pain**

Lower doses of local anaesthetics are generally required for postoperative pain relief than for anaesthesia.

Ropivacaine is administered epidurally (via lumbar or thoracic route) for postoperative pain following abdominal (upper or lower), gynaecological, orthopaedic and other surgeries.

Following abdominal surgery- The efficacy of epidural ropivacaine has been compared with intravenous morphine, epidural bupivacaine, and ropivacaine in combination with fentanyl.

Ropivacaine with or without morphine, was more effective at relieving postoperative pain than intravenous morphine alone<sup>[28]</sup>.

Following orthopaedic surgery – Patients who had undergone hip arthroplasty had significantly more effective pain relief with epidural ropivacaine than with intravenous morphine and supplementary analgesia was administered to numerically more patients in the morphine group than in ropivacaine group<sup>[20]</sup>.

In a study comparing ropivacaine with bupivacaine in patients who had undergone hip arthroplasty<sup>[21]</sup>.

The significantly lower incidence of motor block in ropivacaine recipients was accompanied by similarly effective pain relief among treatment groups and greater patient satisfaction<sup>[21,22]</sup>.

Patients who received combined femoral and sciatic nerve block<sup>[23]</sup> with ropivacaine to facilitate foot/ankle<sup>[23]</sup> surgery had similar or better postoperative pain relief and a longer duration of analgesia than recipients of mepivacaine.

Epidurally administered ropivacaine is effective in providing relief from labour pain. It is recommended to administer 10-20 ml bolus of ropivacaine 0.2% with intermittent 20-30mg top up injections or a continuous epidural infusion of ropivacaine 0.2% (6-10ml/hr) for labour analgesia. The analgesic efficacy of ropivacaine bupivacaine related toxicity. The clinical safety profile of ropivacaine is more favorable, the myotoxicity associated with levobupivacaine is also less with ropivacaine it is nearly identical to bupivacaine in onset, quality and duration of sensory block, but it produces less motor block and has a better safety profile<sup>[28]</sup>.

Is similar to bupivacaine. The addition of narcotics like fentanyl 2mcg/ml to ropivacaine 0.1% solution administered at 10ml/hr significantly reduces local anaesthetic concentration, as the quality of analgesia is similar to ropivacaine 0.2% - only solution or ropivacaine 0.2% plus fentanyl 2 mcg /ml infused at a slower rate of 8ml/hr<sup>[42]</sup>.

## **Role of ropivacaine in chronic pain management**

Ropivacaine .2% has analgesic effect in chronic backache. In migraine trigger point inactivation can be an effective palliative measure in the prophylactic management of severe refractory migraine<sup>[25]</sup>.

## Safety of Ropivacaine

Ropivacaine and levobupivacaine were developed after evidence of bupivacaine related severe toxicity. Ropivacaine causes fewer cardiotoxic effects, as lipophilicity is known major determinant in local anaesthetic toxicity, the clinical safety profile of ropivacaine is favorable. Ropivacaine has greatest margin of safety of all local anaesthetics at present.<sup>{17}</sup>.

## III. Conclusion

Ropivacaine is a long acting amide local anaesthetic, equally effective for infiltration, epidural and peripheral nerve block for surgery, labour, and post-operative analgesia. It provides more differential block when given epidurally, allowing for a better separation between sensory and motor block. Better cardiotoxic profile of ropivacaine is a great advantage.<sup>{18}</sup>. Ropivacaine can avoid complications in cardiac patients.

## References;

- [1]. Hansen TG. Ropivacaine: A pharmacological review. *Expert Rev Neurother* 2004 ;781-91.
- [2]. Kindler CH, Paul M, Zou H, Liu C, Winegar BD, Gray AT, et al. Amide local anesthetics potently inhibit the human tandem pore domain background K<sup>+</sup> channel TASK -2 (KCNK5). *J Pharmacol EXP Ther* 2003;306:84-92.
- [3]. Graf BM, Abraham I, Eberbach N, Kunust G, Stowe DF, Martin E. Differences in cardiotoxicity of bupivacaine and ropivacaine are the result of physicochemical and stereoselective properties. *Anaesthesiology* 2002 ;96:1427-34.
- [4]. Graf BM. The cardiotoxicity of local anaesthetics: The place of ropivacaine. *Curr Top Med Chem* 2001;1:207-14.
- [5]. Cederholm I, Evers H, Lofstrom JB. Skin blood flow after intradermal injection of ropivacaine in various concentrations with and without epinephrine evaluated by laser Doppler flowmetry. *Reg Anesth* 1992 ;17:322-8.
- [6]. Porter J, Crowe B, Cahill M, Shorten G. The effects of ropivacaine hydrochloride on platelet function: An assessment using the platelet function analyser (PFA-100). *Anaesthesia* 2001;56:15-8.
- [7]. Batai I, Kerenyi, Falvi J, Szabo G. Bacterial growth in ropivacaine hydrochloride. *Anaesth Analg* 2002;94:729-31.
- [8]. Kampe S, Potter C, Buzello S, Wenchel HM, Paul M, Kiencke P, et al. Ropivacaine 0.1% with sufentanil 1microg/mL inhibits in vitro growth of *Pseudomonas aeruginosa* and does not promote multiplication of *staphylococcus aureus*. *Anesth Analg* 2003;97:409-11.
- [9]. Simpson D, Curran MP, Oldfield V, Keating GM, Ropivacaine :A review Of its use in regional anaesthesia and acute pain management *Drugs* 2005 ;65:2675-717.
- [10]. Burm AG, Stienstra R, Brouwer RP, Emanuelsson BM, van Kleef JW. Epidural infusion of ropivacaine for postoperative analgesia after major orthopedic surgery: evaluation. *Anesthesiology* 2000;93:395-403.
- [11]. Simon MJ, Veering BT, Stienstra R, Van Kleef JW, Burm AG. The effects of age on neural blockade and hemodynamic changes after epidural anesthesia with ropivacaine. *Anesth Analg* 2002;94:1325-30.
- [12]. Writer WD, Stienstra R, Eddleston JM, Gatt SP, Griffin R, Gutsche BB, et al. Neonatal outcomes and mode of delivery after epidural analgesia with ropivacaine and bupivacaine :A prospective meta-analysis. *Br J Anaesth* 1998;81:713-7.
- [13]. Selander D, Sjavoll J, Waldenlind L. Accidental iv injections of ropivacaine: Clinical experience of six cases [abstract]. *Reg Anaesth* 1997;22:70.
- [14]. Crosby E, Sandler A, Finucaine B, Writer D, Reid D, McKenna J, et al. Comparison of epidural anaesthesia with ropivacaine 0.5% and bupivacaine 0.5% for caesarian section. *Can J Anaesth* 1998;45:1066-71.
- [15]. McGlade DP, Kalpokas MV, Mooney PH, Bukland MR, Vallipuram SK, Hendra 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.
- [16]. Chung CJ, Yun SH, Hwang GB, Park JS, Chin YJ. Intrathecal fentanyl added to hyperbaric ropivacaine for cesarean delivery. *Reg Anesth Pain Med* 2002;27:600-3.
- [17]. Kallio H, Snall EV, Kero MP, Rosenberg PH. A comparison of intrathecal plain solutions containing ropivacaine 20 or 15mg versus bupivacaine 10mg. *Anesth Analg* 2004;99:713-7.
- [18]. Hofmann-Kiefer K, Herbrich C, Seebauer A, Schwender D, Peter K. Ropivacaine 7.5mg/ml versus bupivacaine 5mg/ml for interscalene brachial plexus block :A comparative study. *Anaesth Intensive Care* 2002;30:331-7.
- [19]. Jayr C, Beaussier M, Gustafsson U, Letournier Y, Nathan N, Plaud B, et al. Continuous epidural infusion of ropivacaine for postoperative analgesia after major abdominal surgery ;Comparative study with iv PCA morphine. *Br J Anaesth* 1998;1:887-92.
- [20]. Wulf H, Biscoping J, Beland B, Bachmann-Mennenga B, Mostch J, Ropivacaine epidural anaesthesia and analgesia versus general anaesthesia and intravenous patient-controlled analgesia with morphine in the perioperative management of hip replacement. Ropivacaine Hip Replacement Multicenter Study Group. *Anesth Analg* 1999;89:111-6.
- [21]. 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 (PCEA) following hip replacement :Ropivacaine versus bupivacaine. *Acta Anaesthesiol Scand* 2001;45:782-5.
- [22]. Lorenzini C, Moreira LB, Ferreira MB, Efficacy of ropivacaine compared with ropivacaine plus sufentanyl for postoperative analgesia after major knee surgery. *Anaesthesia* 2002;57:424-8.
- [23]. 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.
- [24]. Atienzar MC, Palanca JM, Borrás R, Esteve I, Fernandez M, Miranda A. Ropivacaine 0.1% with fentanyl 2 microg mL(-1) by epidural infusion for labour analgesia. *Eur J Anaesthesiol* 2004;21:770-5.
- [25]. Garcia-Leiva JM, Hidalgo J, Rico-Villademoros F, Moreno V, Calandre EP. Effectiveness of ropivacaine trigger points inactivation in the prophylactic management of patients with severe migraine. *Pain Med* 2007;8:65-70.
- [26]. Zinka W, Graf BM. The toxicity of local anesthetics: the place of ropivacaine and levobupivacaine. *Curr Opin Anaesthesiol Scand*. 2003Mar;47(3):355-60.
- [27]. Stienstra R. The place of ropivacaine in anesthesia. *Acta Anaesthesiol Belg*. 2003;54(2):141-8.
- [28]. Owen MD, Dean L S, Ropivacaine. *Expert Opin Pharmacother*. 2000Jan ;1(2):325-36.