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Review Article

ROPIVACAINE –A NOVEL AND PROMISING LOCAL ANAESTHETIC DRUG

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ABSTRACT

Local anaesthetics are drugs that produce reversible conduction blockade of impulses along central and peripheral nerve pathways after regional anaesthesia with progressive increases in concentrations of local anaesthetics, the transmission of autonomic, somatic sensory and somatic motor impulses is interrupted, producing autonomic nervous system blockade, sensory anaesthesia and skeletal muscle paralysis in the area innervated by the affected nerve. Removal of the local anaesthetic is followed by spontaneous and complete return of nerve conduction with no evidence of structural damage to nerve fibres as a result of the drug's effects. Ropivacaine is the newer local anaesthetic.

Key Words: Ropivacaine, Local anaesthetic agents, regional anaesthesia

INTRODUCTION

The local anaesthetic molecules all have three characteristic portions (a) benzene ring-aromatic head (b)an intermediate chain (c) an amino group. The benzene ring is very soluble in lipids. The intermediate portion, a bridge between the other two, can have one of the two types of chemical structures either an ester or amide. Therefore, chemically, there are two large groups of local anaesthetics, depending on the intermediate portion of the molecule: Ester type and Amide type local anaesthetics. Procaine is the prototype of the first group and lignocaine is the prototype of the second one. The first group more commonly causes allergic reactions and has a short duration of action as they are rapidly metabolized by cholinesterase. In contrast, the second group i.e. amides rarely cause allergic reactions but are more likely to cause toxic reactions if the dose is exceeded. Depending upon 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. Ropivacaine is a newer local anaesthetic belonging to amide group.

HISTORICAL BACKGROUND

Ropivacaine is a pipecoloxylidide. Bupivacaine is other member of this group. The pipecoloxylidide local anaesthetics (bupivacaine and ropivacaine) are chiral drugs because their molecules possess an asymmetric carbon atom. As such, these drugs may have a left (S) or right (R) handed configuration. Bupivacaine is available for clinical use as racemic mixture (50:50 mixture) of the enantiomers. The enantiomers of a chiral drug may vary in their pharmacokinetics, pharmacodynamics and toxicity[1]. In contrast to bupivacaine, ropivacaine has been developed as a pure S enantiomer. When these drugs were first developed, bupivacaine was chosen to be marketed as a long acting local anaesthetic, its advanatages compared to lignocaine being long duration of action and differential sensory-motor block. Little further work was carried out on the other drugs in the group. However a number of deaths from cardiac arrest were reported in association with regional anaesthesia using bupivacaine[2] . All appeared to be caused by intravenous injection of these long acting local anaesthetics. This provided the impetus to develop a safer drug. It was possible that a less fat soluble drug than bupivacaine would be less cardiotoxic.

It was noted in 1977 that the propyl derivative of the pipecoloxylidides was less toxic than the butyl derivative (bupivacaine). Further work revealed that the nerve blocking properties of the R and S enantiomers were similar but that the S enantiomers was less cardiotoxic[3] . Thus the S enantiomer of the propyl derivative (ropivacaine) was chosen for further development.

ROPIVACAINE

It is a new aminoamide long acting local anaesthetic. It is the monohydrate of the hydrochloride salt of 1- propyl- 2', 6' – pipecoloxydide and is prepared as the pure S enantiomer. It is one of a group of local anaesthetic drugs, the pipecoloxydides[4]. The solution for injection is sterile, isotonic and isobaric aqueous solution. It is free from preservatives. Each ampule is intended for single use only.

STRUCTURE

It is having a propyl group on the piperidine nitrogen atom of the molecule in contrast to bupivacaine which contains butyl group[5].

MECHANISM OF ACTION

It is a Na+ channel blocker. The Na+ channel has an activation gate (A) near its extracellular mouth and an inactivation gate (I) at the intracellular mouth. Na+ channel exist in activated open, inactivated closed and rested closed states during various phases of the action potential. The local anesthetic (LA) receptor is located within the channel in its intracellular half. The LA transverses the membrane in its lipophilic form (B), reionises in the axoplasm and approaches the LA receptor through the intracellular mouth of the channel. It is the cationic form (BH+) of the local anaesthetic which primarily binds to the receptor. The receptor has higher affinity or is more accessible to LA in the activated state compared to resting state. Binding of LA to its receptor stabilises the channel in the inactive state and thus reduces the probability of channel opening. Sodium channels in the inactivated closed state are not permeable to sodium and thus conduction of nerve impulses in the form of propagated action potentials cannot occur[6].

PHARMACOLOGY

It is local anaesthetic with both anaesthetic and analgestic effect. At high doses it produces surgical anaesthesia and at lower doses it produces analgesia (sensory block) with limited and non-progressive motor block. The onset and duration of the local anaesthetic effect depends on the doses and site of administration.

SENSORY BLOCK

Equal volumes and concentrations of ropivacaine and bupivacaine provide similar onset, quality and duration of sensory block when used for infiltration anaesthesia, peripheral nerve, blachial plexus or extradural block[5].

MOTOR BLOCK

Ropivacaine has a differential blocking effect on nerve fibres and at the lowest concentration used, there is good differentiation between sensory and motor block. Small unmyelinated C fibres and small myelinated A fibres (Aδ) are responsible for pain transmission whereas large A fibres (Aβ) transmit motor impulses. Most local anaesthetic drugs block C fibres at approximately the same rate. The rate of A fibre block depends on the physiochemical properties of the individual drugs, high pKa and low lipid solubility favouring block of C fibres before A[7]. The pKa of bupivacaine and ropivacaine

are identical but ropivacaine is less fat soluble (Table 1), predicting that ropivacaine will block A fibres more slowly than bupivacaine. Motor block is slower in onset, less in intensity and shorter in duration with ropivacaine as compared to bupivacaine[8].

Table 1:

	Ropivacaine	Bupivacaine
PKa	8.1	8.1
Lipid solubility partition coefficient	2.9	10
Mean uptake ratio	1.8	3.3

PHARMACOKINETICS

The plasma concentration of ropivacaine depends upon the dose, the route of administration and the vascularity of the site of injection. Ropivacaine follows linear pharmacokinetics and the Cmax (maximum concentration) is proportional to the dose. The pharmacokinetics of ropivacaine and bupivacaine after intravenous (I.V.) and extradural administration have been determined in the dog and rhesus monkey [9]. The pharmacokinetic characteristics of ropivacaine after I.V. infusion have been determined in human volunteers. Clearance (0.82 ± 0.16 L min^{-1}) was found to be higher than the previously determined value for bupivacaine (0.58 L min^{-1}). Plasma binding of ropivacaine averaged $94 \pm 1\%$ (slightly lower than bupivacaine) and volume of distribution at steady state based on blood drug concentration was 59 ± 7 litre (of bupivacaine 73 litre). The terminal elimination half-life was 111 ± 62 min which is less than that determined previously for bupivacaine[10]. The higher clearance of ropivacaine compared with bupivacaine may offer an advantage in terms of systemic toxicity. The pharmacokinetic profiles of ropivacaine and bupivacaine in humans after extradural administration are similar to those determined in animal studies.

METABOLISM

It is extensively metabolized in the liver mainly by aromatic hydroxylation. 86% of the dose is excreted in the urine after I.V. administration of which only about 1% is unchanged drug. The major metabolite is 3-hydroxy-ropivacaine which possesses a local anaesthetic effect of much lower potency and shorter duration than the parent compound.

CONTRAINDICATIONS

1. Hypersensitivity to ropivacaine or to any other local anaesthetic of the amide type.

2. General contraindications related to epidural anaesthsia.

3. It is not recommended for emergency situations where a fast onset of surgical anaesthsia is necessary.

4. Intravenous regional anaesthesia.

INCOMPATIBILITIES

Preceiptation may occur in alkaline solutions because ropivacaine has poor solubility at pH more than 6. Addition of alikaline solutions may cause precipitation at higher pH.

TOXICITY

Central nervous system toxicity is directly related to local anaesthetic potency and the convulsant doses of ropivacaine and bupivacaine are similar. Cardiovascular toxicity, especially the arrhythmias, however is a particular problem with bupivacaine and the R enantiomer is more cardiotoxic than S enantiomer[11]. Cardiovascular toxicity is preceded by signs of central nervous system (CNS) toxicity. The first symptom of CNS toxicity are usually light headedness, circumoral paresthesia, numbness of the tongue, tinnitus and visual disturbances. Muscular twitching or tremors precede the onset of generalised convulsions. Unconsciousness and grandmal convelsions may follow. In severe cases apnea may occur. Acidosis, hyperkalemia, hypocalcemia and hypoxia increase and extend the toxic effects of local anaesthetics. Recovery is due to redistribution of the local anaesthetic agent from the central nervous system and subsequent metabolism and excretion. Recovery may be rapid unless large amounts of agent have been injected.

Local anaesthetics exert their direct toxic effects on the heart by blocking sodium influx through sodium channels. This causes depression of the maximal rate of increase (V_{max}), of the cardiac action potential and results in delayed conduction, seen on the ECG as prolongation of the PR interval and QRS complex. Re-entrant phenomenon and ventricular arryhythmias may occur. Ropivacaine depresses V_{max} less than bupivacaine and recovery is quicker after ropivacaine[12]. Ropivacaine causes less prolongation of the QRS complex and at supraconvulsant doses is less arrhythmogenic. Also it has less effect on cardiac conductivity and contractility than bupivacaine. After intravenous infusion, the clearance of ropivacaine is more rapid than previously determined for bupivacaine[13]

If signs of acute systemic toxicity appear, injection of local anaesthetic should be stopped immediately and symptoms must be promptly and appropriately treated. In case of cardiac arrest. a successful outcome may require prolonged resuscitative efforts.

CLINICAL INDICATIONS

The lower cardiotoxic potential, more rapid clearance and reduced motor block seen with ropivacaine compared to bupivacaine would seem to be advantageous, particularly when relatively large cumulative doses are required, for instance in obstetric anaesthesia/analgesia and for postoperative extradural infusions.

OBSTETRIC ANAESTHESIA AND ANALGESIA

Studies comparing ropivacaine with bupivacaine used as both top up and continuous infusion for extradural analgesia in labour have been published, [14, 15]. Both drugs provided effective pain relief.

POST OPERATIVE EXTRADURAL INFUSION

A dose finding study has confirmed that ropivacaine extradural infusion reduces morphine consumption from a PCA pump and reduces visual analogue pain scores[16]. Overall analgesia and degree of motor block were acceptable and the optimum concentration of ropivacaine at 10 ml/hour was 0.2%.

CONCLUSIONS

Ropivacaine is an effective long-acting local anaesthetic and is a pure enantiomer. It is less cardiotoxic and causes less motor block than bupivacaine. The motor block produced by ropivacaine is slower in onset, less intense and shorter in duration than after an equivalent dose of bupivacaine. It is the first local anaesthetic drug to have been evaluated definitively, at an early stage in its development as an analgesic for continuous extradural infusion.

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