NEW DRUGS: ROPIVACAINE

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INTRODUCTION

Ropivacaine is a new aminoamide local anaesthetic drug which has recently been granted licenses for use in the USA, UK and Australasia. It is one of a group of local anaesthetics, the pipecoloxylidides, which were first synthesized in 1957. Bupivacaine and mepivacaine are members of this group and have been in clinical use for more than thirty years. Bupivacaine has a butyl group, mepivacaine a methyl group and ropivacaine a propyl group on the pipreridine nitrogen atom (Figure 1). Ropivacaine is unique amongst this group in that it is prepared for clinical use as the pure s enantiomer rather than a racemic mixture.

When these drugs were first developed bupivacaine was chosen to be marketed as a long acting local anaesthetic, its advantages 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, with time, a number of deaths from cardiac arrest were reported in association with regional anaesthesia using bupivacaine (and etidocaine) [1]. All appeared to be caused by accidental
intravenous injection of these long acting local anaesthetics, and the doses required to produce cardiotoxicity seemed to be close to the convulsant doses. These deaths, and subsequent recommendations of the United States Food and Drug Administration provided the impetus to develop a safer drug. It was possible that a less fat soluble drug than bupivacaine would be less cardiotoxic.

![Structures of mepivacaine, ropivacaine and bupivacaine.](image)

It was noted in 1977 that the propyl derivative of the pipecoloxylidides was less toxic than the butyl derivative (bupivacaine) [2]. Further work revealed that the nerve blocking properties of the r and s enantiomers were similar but that the s-enantiomer was less cardiotoxic [3]. Thus the s enantiomer of the propyl derivative (ropivacaine) was chosen for further development.
1. GENERAL OVERVIEW

Compared with bupivacaine, ropivacaine produces a similar pattern of sensory block, but less motor block when given by some routes. It also seems to be a less hazardous drug if overdose or accidental intravenous injection occur. My lecture will concentrate on motor block and cardiotoxicity and will include evidence from pre-clinical and clinical studies. Most comparisons will be made with reference to bupivacaine.

2. SENSORY BLOCK

In general, and in keeping with in vitro studies, equal volumes and concentrations of ropivacaine and bupivacaine provide similar onset, quality and duration of sensory block when used for infiltration anaesthesia, peripheral nerve, brachial plexus, or extradural block [4].

3. MOTOR BLOCK

Small unmyelinated C fibres and small myelinated A fibres are responsible for pain transmission whereas large A fibres transmit motor impulses. In vitro, most local anaesthetic drugs block C fibres at approximately the same rate. The rate of A fibre block depends on the physicochemical properties of the individual drugs, high pKa and low lipid solubility favouring block of C fibres before A [5]. The pKa of bupivacaine and ropivacaine are identical but ropivacaine is less fat soluble (Table), predicting that ropivacaine will block A fibres more slowly than bupivacaine - this has been confirmed in vitro [6]. From this it would be anticipated that ropivacaine would cause less motor block than bupivacaine.

Studies of lumbar extradural block in humans have confirmed that equal volumes and concentrations of ropivacaine and bupivacaine produce a similar pattern of sensory block but motor block is slower in onset, less in intensity and shorter in duration with ropivacaine [7].

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<tr>
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<th>Ropivacaine</th>
<th>Bupivacaine</th>
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<tbody>
<tr>
<td>pKa</td>
<td>8.1</td>
<td>8.1</td>
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<tr>
<td>Lipid solubility</td>
<td></td>
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</tr>
<tr>
<td>Partition coefficient*</td>
<td>2.9</td>
<td>10</td>
</tr>
<tr>
<td>(N heptane/buffer)</td>
<td></td>
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<tr>
<td>Mean uptake ratio*</td>
<td>1.8</td>
<td>3.3</td>
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<td>(Sciatic nerve)</td>
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*Lignocaine =1
In clinical studies motor block is commonly assessed using a modified Bromage scale [8] which is an easily applied qualitative measure of motor block in a number of muscle groups. A more precise and reproducible method is mechanical measurement of isometric muscle force (IMF) [9] which provides a quantitative measurement of intensity of motor block in single muscle groups and has been used in volunteer studies. Using IMF, motor block was compared in volunteers given 10 ml 0.1 %, 0.2 % or 0.3 % ropivacaine or 10 ml 0.25 % bupivacaine followed by an infusion of the same drug and concentration at 10 ml h⁻¹ for 21 h.

There was similar sensory spread with each solution but the bupivacaine group developed the most intense motor block. When the infusion was stopped regression of motor block after all three concentrations of ropivacaine was significantly faster than after 0.25 % bupivacaine [10].

Although not intended for use in spinal anaesthesia ropivacaine has been given by the subarachnoid route as part of overall safety analysis. Of note is that only 10 of 19 patients given 3 ml 0.5 % subarachnoid ropivacaine developed complete motor block, suggesting that this dose of ropivacaine would not be a reliable way of excluding accidental intrathecal catheter placement.

4. 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 development of arrhythmias, however is a particular problem with bupivacaine [1] and the r enantiomer is more cardiotoxic than the s-enantiomer [11]. Local anaesthetics exert their direct toxic effect on the heart by blocking sodium influx through sodium channels. This causes depression of the maximal rate of increase (Vmax), 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 phenomena and ventricular arrhythmias may occur.

Ropivacaine depresses Vmax less than bupivacaine and recovery is quicker after ropivacaine [12]. In animals ropivacaine causes less prolongation of the QRS complex and at supraconvulsant doses is less arrhythmogenic.

Convulsant and greater doses of local anaesthetics obviously cannot be given deliberately to humans but some data are available. In a comparative study in humans ropivacaine and bupivacaine were given by intravenous infusion until mild CNS symptoms occurred. Ropivacaine was tolerated to a greater dose than bupivacaine and at these doses ropivacaine had less effect than bupivacaine on cardiac conductivity and contractility [13]. After intravenous infusion the clearance of ropivacaine was more rapid than previously determined for bupivacaine [14].
5. 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 post operative extradural infusions.

5.1. OBSTETRIC ANAESTHESIA AND ANALGESIA.

Studies comparing ropivacaine with bupivacaine, used as both « top up » [15] and continuous infusion [16], for extradural analgesia in labour have been published. Both drugs provided effective pain relief. There were no statistically significant differences in motor block as assessed by the Bromage scale in either study. However, the majority of patients in each drug group developed only grade I block consistent with the segmental block required for analgesia in labour. There were no differences in mode of delivery or neonatal outcome. In Caesarean section 0.5 % ropivacaine and 0.5 % bupivacaine provided similar profiles of sensory block but duration of motor block was significantly shorter with ropivacaine [17]. Again, neonatal outcomes and umbilical cord blood gas tensions were similar.

5.2. POST OPERATIVE EXTRADURAL INFUSION

A dose finding study [18] has confirmed that ropivacaine extradural infusion reduces morphine consumption from a PCA pump, reduces visual analogue pain scores (during coughing) and produces a dose related increase in the degree of motor block. Overall, analgesia and degree of motor block were acceptable and the optimum concentration of ropivacaine at 10ml.h-1 was 0.2 %.

CONCLUSION

Ropivacaine has been given to more than 2500 patients in closely monitored clinical trials involving anaesthesia and analgesia for a wide variety of surgical subspecialties. It would appear to be a safe and effective long lasting local anaesthetic drug which is less cardiotoxic and causes less motor block than bupivacaine. Now that ropivacaine is available commercially further comparative studies will help establish the appropriate uses for this new local anaesthetic drug.
REFERENCES BIBLIOGRAPHIQUES

[1] Albright GA. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. Anesthesiology 1979;51:285-287
[10] Zaric D, Nydahl P, Philipson L, Samuelsson L, Heierson A, Axelsson K. The effect of continuous lumbar epidural infusion of ropivacaine (0.1%, 0.2%, and 0.3%) and 0.25% bupivacaine on sensory and motor blockade in volunteers: a double blind study. Reg Anesth 1996;21:14-20
[17] Griffin RP, Reynolds F. Extradural anaesthesia for Caesarean section: a double blind comparison 0.5% ropivacaine with 0.5% bupivacaine. Br J Anaesth 1995;74:512-516