Developments in local anaesthetic drugs

J. B. Whiteside* and J. A. W. Wildsmith

University Department of Anaesthesia, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK

*Corresponding author

Br J Anaesth 2001; 87: 27–35

Keywords: anaesthetics, local

Most of the recent developments in local anaesthetics have been a direct consequence of the recognition, 20 yr ago, of the acute, life-threatening cardiotoxicity of bupivacaine. All local anaesthetics produce a dose dependent delay in the transmission of impulses through the cardiac conduction system by their action on the cardiac sodium and potassium channels. However, overt cardiotoxicity usually only becomes apparent as the last feature of a reasonably predictable sequence of changes. One of the specific features of bupivacaine is that clinical evidence of accumulation of the drug in plasma may be diminished until a fairly late stage because of its high affinity for plasma protein binding sites. The ‘free’ concentration of drug in plasma remains low until all the protein binding sites are fully occupied after which it increases rapidly, and toxicity can occur without patients exhibiting signs of CNS toxicity before cardiovascular collapse. In addition to, and probably more important than, this pharmacokinetic component to its toxicity, bupivacaine has been shown to have selective cardiac effects related to the slow rate at which it dissociates from the sodium channel. An important aspect of this toxicity is that it involves a significant degree of stereo-specificity, with the ‘S’ isomer showing significantly less cardio-depressant effect than the ‘R’.

These findings generated two parallel areas of research, one clinical and the other laboratory; the outcome of both has affected clinical practice. The clinical programme was aimed at avoidance of the rapid accidental intravascular injection of a large dose of bupivacaine, the common factor in all serious reactions. Much study of ‘test’ doses has shown that no such test is completely reliable at identifying accidental intravascular placement. Thus, it is still essential that the main dose of local anaesthetic is injected incrementally (4–5 ml at a time) with sufficient pause between each bolus to allow identification of any systemic consequences. The laboratory research programme was aimed at identifying a local anaesthetic with a similar clinical profile, but with less cardiotoxicity than bupivacaine. Given that a more cautious approach to clinical use seems to have prevented any further deaths, it may be argued that the expense of a new agent is unnecessary. However, it is an agent with a relatively low therapeutic index, and as little as 50 mg has caused primary ventricular fibrillation on accidental i.v. administration in a susceptible patient. Less risk of toxicity may be justification alone for new drugs when very large doses are required as in brachial plexus block. However, perhaps a new drug should offer additional advantages when used in other ways if the expense is to be justified.

The search for alternatives to bupivacaine has concentrated on amide-linked agents, which in current practice have largely superseded the ester type drugs. Investigation of the possible aetiological mechanisms of local anaesthetic induced cardiotoxicity, along with advances in stereoselective synthesis, have demonstrated the potential clinical advantages of agents comprised of a single enantiomer. Of the commonly used, older amide drugs, only lidocaine is not ‘chiral’; for example, it exists as a single structural entity at molecular level. Prilocaine, mepivacaine, and bupivacaine all have an ‘asymmetric’ carbon atom which means that traditional manufacturing methods result in the production of equal amounts of ‘S’ and ‘R’ isomers, something which is reflected in the clinically available preparations. Ropivacaine and levobupivacaine are two relatively new amide local anaesthetic agents that have been produced in order to address the issue of bupivacaine cardiotoxicity. Each is produced as a pure ‘S’ isomer. Levobupivacaine is the ‘S’ isomer of bupivacaine. Ropivacaine is the propyl analogue of, bupivacaine having a butyl group in the same position.

Current developments are not exclusively restricted to variations on the traditional amide drug theme as a response to rare toxic reactions. Other work is looking to identify
agents that interrupt nerve transmission in a more specific way with the aim of maximizing analgesia and minimizing other manifestations of nerve block. Much of this research is concentrating on the modulation of synaptic transmission at spinal cord level and is beyond the scope of this review. However, manipulation of the effects of the physicochemical properties of local anaesthetic drugs can influence the degree of differential nerve block,103 and the lower lipid solubility of ropivacaine results in less motor block than bupivacaine. Studies of an agent with very significantly lower lipid solubility than these (butyl amino-benzoate68 91 92) may yet provide the practising anaesthetist with this review will concentrate on drugs. Problems with the incorporation of standard drugs into liposomes,16 38 53 71 but this review will concentrate on drugs. Problems with the liposome method have been reported.29

The clinical use of the new drugs mentioned above will be the prime focus of this review, but the obvious importance of chirality to the pharmacology of ropivacaine and levobupivacaine means that some explanation is appropriate. Butyl amino-benzoate represents an extreme example of the differential nerve blocking effect of local anaesthetics, as well as an indication of how slow release preparations may be used to prolong their action. Finally, there will be some consideration of articaine. This is not a new drug and, unlike the others mentioned above, it has a relatively short duration, but there has been some renewed interest in it. This interest may be increased by the recent withdrawal of a large number of prilocaine preparations because articaine has similar properties.17

Chirality and local anaesthetics

Chirality is a word derived from the Greek chiro meaning ‘handed’. Chemically, a chiral compound is one that contains at least one tetraco-ordinate carbon (or sulphur) atom to which four different atoms or chemical groups are attached. If a molecule contains one such ‘asymmetric’ carbon atom, two distinct spatial arrangements are possible, each a mirror image of the other. These ‘stereo-isomers’ are molecules with identical atomic composition and chemical properties, but the different spatial arrangement of their atoms means that they do not match when superimposed one upon the other. A pair of such stereo-isomers are called enantiomers, and each rotates plane-polarized light in equal magnitude, but in opposite directions. When a compound contains equimolar amounts of the two enantiomers it is referred to as a ‘racemate’ or ‘racemic’ mixture. Enantiomers have identical physico-chemical properties, so they will have the same pKa and lipid solubility figures.95 However, they differ, both qualitatively and quantitatively, in regard to pharmacokinetic and pharmacodynamic properties, because of stereoselective interactions (i.e., those as a result of differences in three-dimensional structure) at molecular sites of drug action.

Each stereo-isomer of any pair may be described in a number of ways, but the current standard is the ‘Sequence Rule Notation’.25 This is based on attaching an order of priority to substituent groups (or atoms) attached to the central chiral atom, having identified the ‘smallest’ of the four first. The molecule is ‘positioned’ with this smallest group directed away from the ‘viewer’ and note taken of the sizes of the other three. If the sequence from smallest to largest is ‘clockwise’, it is defined as a ‘R’ isomer from the Latin rectus (right), whereas if the sequence is ‘anticlockwise’ the isomer is defined as ‘S’ from the Latin sinister (left). These are known as absolute descriptors and may be most simply illustrated by reference to the isomers of lactic acid (Fig. 1).

However, the best-known method of referring to the chirality of a molecule relates to the effect it has on the rotation of plane polarized light, either clockwise (+) or anticlockwise (−)—the relative descriptors. Unfortunately, there is no consistency between the absolute and relative descriptors. Within an homologous series of compounds the S/R notation may change as the length of a particular side chain increases so the full description of a chiral compound may be given by a combination of both descriptors (e.g. S(−) bupivacaine).

Differences in both the pharmacokinetic and pharmacodynamic properties of the different isomers of various local anaesthetic drugs have been recognized for many years. Prilocaine was probably the first agent to be studied extensively,2 but the costs of production were then prohibitive for clinical availability and the differences between the isomers were of relatively little clinical impact. The local anaesthetic and toxic effects of the enantiomers of bupivacaine were first described in 1972 by Aberg and colleagues,1 who showed that the S(−) enantiomer is less toxic than the R(+) form. Subsequent studies confirmed the lower neurotoxicity and cardiotoxicity of the S(−) enantiomer in animal models.60 72 99 Human studies have also
shown that larger doses of S(-) bupivacaine than racemic bupivacaine are required before the onset of neurological symptoms.12

Ropivacaine is the ‘S’ isomer of the propyl analogue of mepivacaine and bupivacaine. The parent compound of ropivacaine was, like the other two, first synthesized in the 1950s,4 but they were selected for further development as short and long-acting agents, respectively. It was only when concerns about the cardiotoxicity of bupivacaine became apparent that ropivacaine was evaluated fully. The S(-) enantiomer was selected initially because it has a longer duration of action than the R(+),3 but later animal studies showed that ropivacaine dissociates from sodium channels more rapidly, produces less accumulation of sodium channel block and is less cardiotoxic than racemic bupivacaine.7 78 85 Infusion studies in human volunteers have confirmed that larger doses are required to produce early features of neurotoxicity and cardiotoxicity than racemic bupivacaine.65 88 The commercial preparation has an enantiomeric purity of 99.5%.44

**Table 1** Physico-chemical properties and plasma protein binding characteristics of local anaesthetic agents.95 104 PKa = dissociation constant

<table>
<thead>
<tr>
<th>Drug</th>
<th>PKa</th>
<th>Partition coefficient</th>
<th>Percentage protein bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine</td>
<td>7.8</td>
<td>43</td>
<td>64</td>
</tr>
<tr>
<td>Prilocaine</td>
<td>7.8</td>
<td>25</td>
<td>55</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>7.8</td>
<td>21</td>
<td>77</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>8.2</td>
<td>346</td>
<td>95.5</td>
</tr>
<tr>
<td>Levobupivacaine</td>
<td>8.2</td>
<td>346</td>
<td>93.4</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>8.2</td>
<td>115</td>
<td>94</td>
</tr>
</tbody>
</table>

Thus, ropivacaine has other potential advantages besides that of reduced cardiotoxicity.

Further evaluation in both animal and volunteer human studies confirmed that ropivacaine is an effective local anaesthetic and showed that, unlike bupivacaine, it has a slight vasoconstrictor effect at lower concentrations.28 36 66 Epinephrine was found to have little effect on the local action or the resultant systemic concentrations of ropivacaine in human studies.28 56 81

**Clinical efficacy**

Ropivacaine has been compared with bupivacaine in many clinical trials involving most forms of regional anaesthesia. Most studies have shown that the onset, potency and duration are very similar to those of bupivacaine. However, some studies, particularly those utilizing the concept of Minimum Local Analgesic Concentration (MLAC) in epidural analgesia, have questioned whether the difference in cardiotoxicity seen between the two agents is in fact a result of an absolute difference in potency.27 84 The suggestion is that the therapeutic ratio of the two may be the same. Such concerns must be viewed against the important basic principle that the local, and subsequent systemic, dynamics of a particular local anaesthetic will depend on the site of injection.8 Thus, each clinical application must be considered in turn.

**Wound infiltration**

Ropivacaine has been used successfully for post-operative analgesia in patients undergoing inguinal herniorrhaphy and open cholecystectomy.61 Equal doses (100 mg) of ropivacaine and bupivacaine have been shown to provide similar analgesia after inguinal hernia surgery.41 The intrinsic vasoconstrictive properties of ropivacaine may help explain the findings of one study which demonstrated cutaneous anaesthesia two to three times longer than that produced by bupivacaine.28 Some authors have questioned the safety of this because of the possibility of inducing microcirculatory insufficiency or compromising end-arterial blood supply.64 There has been one report of local ischaemia after the use of 0.75% ropivacaine for penile block, but no long-term sequelae were observed.21 Therefore, ropivacaine may be unsuitable for infiltration in tissues without collateral blood supply.

**Major nerve block**

A large number of studies on the use of ropivacaine for brachial plexus anaesthesia, utilizing a variety of techniques, have been published.43 57 The majority of studies suggest that the clinical outcome is similar to that of equivalent doses of bupivacaine,58 59 96 with the 0.25% concentration of both drugs being associated with an unacceptable incidence of inadequate block of either sensory or motor nerves. Some, more recent studies have shown a significantly faster onset in both upper and lower limb blocks with ropivacaine than with an equal dose of...
bupivacaine.\textsuperscript{15,43} Bertini and colleagues also demonstrated a better quality of block with ropivacaine as indicated by intra-operative opioid requirements and patient satisfaction scores.\textsuperscript{15}

Although there is some variation between the reports in the literature, an overview suggests that there may be no more than slight differences in onset, but no difference between ropivacaine and bupivacaine in completeness or duration of block. Both drugs produce effective long-acting local anaesthesia.

**Spinal anaesthesia**

Ropivacaine has been used relatively infrequently for spinal anaesthesia. Its very early evaluation included two studies of the intrathecal injection of glucose-free solutions performed primarily for safety reasons to confirm that accidental intrathecal injection during epidural block would be without adverse sequelae.\textsuperscript{98,100} Sensory block of variable extent and intermediate duration was produced. Currently, ropivacaine is not licensed for intrathecal use, but two more recent, clinical studies have compared ropivacaine unfavourably with bupivacaine.\textsuperscript{51,77}

Gautier and colleagues\textsuperscript{51} used glucose-free preparations, but in larger volumes of less concentrated solutions than are normally used in clinical practice. The onset and extent of sensory block were similar, but both the duration of that sensory block and the degree of motor block produced were less with ropivacaine. These findings, particularly the shorter duration of action, led the authors to claim that ropivacaine is less potent than bupivacaine and that it offers no significant advantage. However, it is noteworthy that the patients who received ropivacaine passed urine and mobilized more rapidly than those who received bupivacaine.

McDonald and colleagues\textsuperscript{77} compared hyperbaric preparations of the two drugs in volunteers not undergoing surgery. The concentrations of their solutions were also less than are normally used clinically, as were the total doses injected. The two drugs produced sensory blocks of similar onset and extent, but there was less motor block, which regressed faster, with ropivacaine. Again, on the basis of the shorter duration of action and despite equivalence in the onset and extent of sensory block, the conclusion was that ropivacaine is less potent than bupivacaine. This study also noted a higher incidence of backache after ropivacaine and concluded that the incidence of side effects was higher, even though the difference was not statistically significant.

However, more recent work has shown that glucose containing solutions of ropivacaine in concentrations and doses more appropriate to spinal anaesthesia produce a clinical block profile that is very appropriate to much of the surgery for which this application of regional anaesthesia is currently used.\textsuperscript{102} No direct comparison of ropivacaine and bupivacaine in formulations more suited to clinical use is yet available, but ropivacaine does seem worthy of more definitive study for spinal anaesthesia. There is also some need for questioning the interpretation of a difference in duration as an indicator of a difference in potency.\textsuperscript{105}

**Epidural anaesthesia and analgesia**

The historical background, the potential for less cardio-toxicity, and the early evidence suggesting that the motor block produced by ropivacaine is less intense and of shorter duration than with bupivacaine, have all led to extensive evaluation of its role in epidural block.\textsuperscript{18–19,47,63,107–108} These are ideal qualities for an agent for epidural use, where accidental i.v. injection of large doses of local anaesthetic is a potential hazard and where preservation of lower limb motor function is often desirable.

Early, ‘open’ studies of ropivacaine showed that it could be used to provide long-acting, good quality anaesthesia for surgery when administered by the lumbar route.\textsuperscript{31,101} The lower lipid solubility of ropivacaine, and the in vitro and in vivo demonstration of slightly lower potency than bupivacaine,\textsuperscript{46,86} led some investigators to compare ropivacaine with somewhat lower concentrations of bupivacaine.\textsuperscript{62,107–108} They demonstrated similar onset and extent of both motor and sensory block, and similar duration of motor block, but slightly longer duration of analgesia with the more concentrated solutions of ropivacaine. However, when direct comparison of equal concentrations have been made, in both the obstetric and non-obstetric population, no significant differences in onset, speed or duration of sensory block were found, but the motor block was less intense and of shorter duration.\textsuperscript{18,54,79}

This work was for ‘anaesthetic’ use in a wide range of clinical settings, but most of the studies of ropivacaine as an ‘analgesic’ have been performed in the obstetric population. Maternal safety, good patient mobility during labour and minimal need for obstetric intervention are key outcomes in this field of practice and the lower cardiotoxic potential and the greater degree of sensory and motor block separation have led some to suggest that ropivacaine offers significant advantages over bupivacaine.\textsuperscript{74}

Many studies have compared the two during labour, all of them demonstrating similar degrees of pain relief with equal doses of the agents.\textsuperscript{14,40,50,75–76,82} A meta-analysis of such studies showed that ropivacaine was associated with significantly more spontaneous vaginal deliveries, fewer instrumental deliveries and better neonatal outcome scores than bupivacaine.\textsuperscript{105} Both agents have also been shown to be equally effective when combined in low doses with opioids.\textsuperscript{26,52,89}

However, more recent studies have questioned the relative potencies of ropivacaine and bupivacaine.\textsuperscript{27,84} Using an ‘up–down’ sequential allocation method to compare the minimum local analgesic concentration (MLAC) of these agents it has been suggested that ropivacaine may be 40% less potent than bupivacaine. This method, first described by Columb and Lyons in 1995,\textsuperscript{30} aims to determine the ‘ED$_{50}$’, or more correctly the
effective concentration of each agent for 50% of patients, using a fixed volume of local anaesthetic. The results have been used to support an argument that any advantages that ropivacaine may have over bupivacaine in terms of reduced motor block and risk of cardiotoxicity must be balanced against the apparent reduction in potency. The implication is that more drug will be required and any potential advantage lost.

Against this conclusion, a number of authorities have questioned the basic validity of the MLAC method for determining local anaesthetic potency. First, the clinical relevance of the figure obtained has been questioned, because only 50% of patients studied receive obtain pain relief. Second, while the results are expressed as a concentration, it is inherent in the method that the dose of drug injected changes as well as the concentration. Third, analyses based on the results of the MLAC method make assumptions about the shape of the remainder of the ‘dose’ response curve even though only one point on it has been obtained. Without formal studies to define the dose response curves for both ropivacaine and bupivacaine it is impossible to speculate on the shape of the curves based on a single data point. Thus, the findings of the two MLAC studies comparing ropivacaine and bupivacaine must be questioned because they contradict directly the results of other clinical analyses based on the results of the MLAC method make assumptions about the shape of the remainder of the ‘dose’ response curve even though only one point on it has been obtained. Without formal studies to define the dose response curves for both ropivacaine and bupivacaine it is impossible to speculate on the shape of the curves based on a single data point. Thus, the findings of the two MLAC studies comparing ropivacaine and bupivacaine must be questioned because they contradict directly the results of other clinical studies in which pain relief has been provided for all the patients. These, as has already been noted, have shown equal degrees of pain relief with equal concentrations of the two agents, but with significant other advantages for ropivacaine.

### Levobupivacaine

At the time that ropivacaine was being developed, it was not fully appreciated that the cardiotoxicity of bupivacaine exhibits a significant degree of enantioselectivity. However, once this was recognized, the S(–) enantiomer (levobupivacaine) was developed as an alternative long-acting local anaesthetic. Human volunteer studies have demonstrated that S(–) bupivacaine is better tolerated than racemic bupivacaine, although it produces a greater prolongation of the QRS complex than ropivacaine in conscious rats. The pharmacology of levobupivacaine has been reviewed extensively elsewhere.

Levobupivacaine has only been introduced into clinical practice recently and, as a consequence, experience of its use is more limited than with ropivacaine. One important point that must be noted by clinicians using the commercial preparation is that there has been a change in the regulations governing the way in which drug salts are presented and labelled in Europe. As a new drug, levobupivacaine comes under the aegis of Directive 91/507 of the European Union Part 2, section A. Clause 3.3 of this directive states that formulations of a drug which exists as a hydrate or salt (both apply to most local anaesthetics) must be expressed in terms of the milligram concentration of the active moiety. Thus, a solution of levobupivacaine 0.5% contains 5 mg ml⁻¹ of the base drug. However, both ropivacaine and racemic bupivacaine predate this directive so 0.5% solutions of these drugs contain 5 mg ml⁻¹ of the hydrochloride salt. Thus, an ampoule of levobupivacaine contains 11% more molecules of local anaesthetic than an ampoule of racemic bupivacaine of the same concentration.

### Clinical efficacy

As with ropivacaine, most of the studies of levobupivacaine have used racemic bupivacaine as the comparator agent. Given that isomers have identical physico-chemical properties, it would be expected that the clinical performances of the two would be identical. As is the case with ropivacaine, the S(–) isomer of bupivacaine produces more vasoconstriction than the R(+) isomer. In theory, this might be detrimental in some vascular beds (e.g. by decreasing uterine blood flow), but no adverse effects on uterine blood flow were seen in animal models after the administration of levobupivacaine.

### Wound infiltration

Two studies have demonstrated similar effects on pain relief, supplementary analgesic requirements and patient satisfaction when 0.25% levobupivacaine and 0.25% bupivacaine were used for analgesia after inguinal hernia repair.

### Major nerve block

A double-blind comparison of equal doses of levobupivacaine and bupivacaine for supraclavicular brachial plexus block found almost no difference in clinical block profile. There was a slightly longer duration of sensory block with levobupivacaine, but the difference was not statistical significant.

### Spinal anaesthesia

One open, non-comparative study of the clinical effects of a plain solution of levobupivacaine in spinal anaesthesia for lower limb surgery has been published. Variable spread of block, which was occasionally unsatisfactory for surgery, was found. As with bupivacaine, this can be attributed largely to the hypobaric nature of the solution at 37°C.

### Epidural block

In the non-obstetric population, two studies have compared levobupivacaine with bupivacaine in epidural block. Comparable degrees of sensory and motor block were produced with 15 ml of 0.5% solution of either drug in patients undergoing lower limb surgery. There were no differences in the quality of surgical anaesthesia and similar findings were reported when the two drugs were compared for lower abdominal surgery.

In the obstetric population, the two drugs have been compared in 0.5% solutions during epidural anaesthesia for Caesarian section. There were no differences in block characteristics, quality of anaesthesia or neonatal outcome.
In addition, there have been two comparisons of their use for epidural analgesia during labour. The analgesia produced by the drugs was broadly similar, but significantly more patients in the levobupivacaine group required a second injection to achieve pain relief in one of the studies. However, this appears to have been related to the inclusion in that group of patients with a greater degree of cervical dilation and a higher proportion of those in whom labour had been induced in the levobupivacaine group.

Ropivacaine and levobupivacaine
An overview of the relatively small amount of published information on the clinical use of levobupivacaine seems to be that its clinical effects are, as might be expected, identical to those of bupivacaine. Thus, its only potential advantage is a potential safety one when large doses are required. There are, as yet, no definitive published comparisons with ropivacaine, and certainly no clinical ones, although it seems reasonable to conclude that ropivacaine differs from levobupivacaine in the same ways as bupivacaine. Some basic science work suggests that the risk of clinical toxicity is less with ropivacaine, but the key to safe practice must remain the avoidance of accidental intravascular injection. Time will tell whether either drug will displace bupivacaine as the standard long-acting local anaesthetic.

Other developments
Butyl amino-benzoate
Butyl amino-benzoate (BAB) is an amino ester first discovered in 1923. Initially, it was thought unsuitable for anaesthetic use because of its extremely low pKa, low water solubility, poor dural permeability, and rapid hydrolysis. However, over 60 yr after it was first discovered, suspension preparations in polyethylene glycol and polysorbate-80 (Butamben) were manufactured which produced long-lasting analgesia when given epidurally to cancer patients as an alternative to alcohol or phenol neurolysis. More recently, BAB has also been used successfully in the treatment of both cancer and non-cancer pain.

One attribute claimed for this preparation is an apparent selectivity of effect on A6- and C-fibres, so that it produces minimal motor block with sparing of bladder and bowel function. Attempts to formulate other agents, such as lidocaine, in a similar suspension preparation were associated with more neuropaethological changes and a much shorter duration of action. It seems likely that the low lipid solubility of BAB means that it is unable to diffuse through the myelin sheaths of other types of nerve fibre, with the long duration of effect being to the ‘slow release’ properties of the suspension. Further study of a drug with a very interesting clinical profile is warranted.

Articaine
Although not as old as BAB, this is also not a new agent. It has been used widely in dental practice in Canada and parts of Europe for many years, but is not being introduced into other countries. It is an anilide local anaesthetic agent, differing from the standard amide agents such as lidocaine by having a thiophene instead of a benzene ring within its structure. Initially, dental practitioners felt that it had a faster onset and wider spread than other agents, and this prompted further evaluation. However, double-blind comparisons with prilocaine and lidocaine in infiltration, IVRA and epidural blocks failed to demonstrate any significant differences. It is, therefore, unlikely that a place will be found for this agent within current anaesthetic practice although the recent reduction in availability of prilocaine might change this because it has similarly low potential for systemic toxicity.

Declaration of interest
Both authors have received financial support for research projects from AstraZeneca.

References
5. Albright GA. Cardiac arrest following regional anaesthesia with etidocaine or bupivacaine. Anesthesiology 1979; 51: 285–7
7. Arlock P. Actions of three local anaesthetics: lidocaine, bupivacaine and ropivacaine on guinea pig papillary muscle sodium channels (V_{ma}.). Pharmacol Toxicol 1988; 63: 96–104
11. Bader AM, Tsen LC, Camaan WR, Nephew E, Datta S. Clinical effects and maternal and fetal plasma concentrations of 0.5% epidural levobupivacaine versus bupivacaine for caesarean delivery. Anesthesiology 1999; 90: 1596–601
15 Bertini L, Tagariello V, Mancini S, Ciaschi A, Posteroaro CM, Di Benedetto P, Martini O. 0.75% and 0.5% ropivacaine for axillary brachial plexus block: A clinical comparison with 0.5% bupivacaine. Reg Anesth Pain Med 1999; 24: 514–8
19 Brown DL, Carpenter RL, Thomson GE. Comparison of 0.5% ropivacaine and 0.5% bupivacaine for epidural anesthesia in patients undergoing lower-extremity surgery. Anesthesiology 1990; 72: 633–6
24 Burke D, Henderson DJ, Simpson AM, Facenda KA, Morrison LMM, McGrady EM, McLeod GA, Bannister J. Comparison of 0.25% S(−)-bupivacaine with 0.25% RS-bupivacaine for epidural analgesia in labour. Br J Anaesth 1999; 83: 750–5
29 Clarkson CW, Hondegheim LM. Mechanism for bupivacaine depression of cardiovascular conduction: fast block of sodium channels during the action potential with slow recovery from block during diastole. Anesthesiology 1985; 62: 396–405
32 Convery PN, Milligan KR, Veir P. Comparison of 0.125% levobupivacaine and 0.125% bupivacaine epidural infusions for labour analgesia (abstract). Br J Anaesth 1999; 82(suppl 1): 163
37 D’Angelo R, James RL. Is ropivacaine less potent than bupivacaine? Anesthesiology 2000; 92: 283–4
40 Eddleston JM, Holland JJ, Griffin RP, Corbett A, Horsman EL, Reynolds F. A double-blind comparison of 0.25% ropivacaine and 0.25% bupivacaine for extradural analgesia in labour. Br J Anaesth 1996; 76: 66–71
42 Ericsson AC, Avensson M. Effects of ropivacaine, bupivacaine and S(−) bupivacaine on the ECG after rapid IV injections to conscious rats. Int Monitor Reg Anaesth 1996; 6: 51
48 Foster RH, Markham A. Levobupivacaine: a review of its pharmacology and use as a local anaesthetic. Drugs 2000; 59: 551–79
54 Griffin RP, Reynolds F. Extradural anaesthesia for caesarean section: a double-blind comparison of 0.5% ropivacaine and 0.5% bupivacaine. Br J Anaesth 1995; 74: 512–6
58 Hickey R, Hoffman J, Ramamurthy S. A comparison of ropivacaine 0.5% and bupivacaine 0.5% for brachial plexus block. Anesthesiology 1991; 74: 639–642
62 Katz JA, Knarr D, Bridenbaugh PO. A double-blind comparison of 0.5% bupivacaine and 0.75% ropivacaine administered epidurally in humans. Reg Anesth Pain Med 1990; 15: 250–2
63 Kerkkamp HEM, Gielen MJM, Edstrom HH. Comparison of 0.75% ropivacaine with epinephrine and 0.75% bupivacaine with epinephrine in lumbar epidural anaesthesia. Reg Anesth Pain Med 1990; 15: 204–7
64 Kingsnorth A, Bennet D, Cummings C. A randomised, double blind study to compare the efficacy of 0.25% levobupivacaine with 0.25% bupivacaine (racemic) infiltration anaesthesia in elective inguinal hernia repair. Reg Anesth Pain Med 1998; 23(suppl.): 106
69 Luduena FP, Bogado EF, Tullar BF. Optical isomers of mepivacaine and bupivacaine. Arch Int Pharmacodyn 1972; 200: 359–69
74 McClure JH. The obstetric challenge. Am J Anaesthesiol 1997; 24 (5; Suppl): 18–21
77 McDonald SB, Liu SS, Kopacz DJ, Stephenson CA. Hyperbaric spinal ropivacaine: A comparison to bupivacaine in volunteers. Anesthesiology 1999; 90: 971–77
78 Moller R, Covino BG. Cardiac electrophysiologic properties of bupivacaine and lidocaine compared with those of ropivacaine, a new amide local anesthetic. Anesthesiology 1990; 72: 322–9
80 Mulroy MF, Burgess FW, Emanuelsson BM. Ropivacaine 0.25% and 0.5%, but not 0.125% provide effective wound infiltration analgesia after outpatient hernia repair, but sustained plasma drug levels. Reg Anesth 1999; 23: 136–41
82 Owen MD, D’Angelo R, Gerancher JC, Thompson JM, Foss ML, Babb JD, Eisenach JC. 0.125% ropivacaine is similar to 0.125% bupivacaine for labor analgesia using patient-controlled epidural infusion. Anesth Analg 1998; 86: 527–31
84 Polley LS, Columb MO, Naughton NN, Wagner DS, Cosmas JM. Relative analgesic potencies of ropivacaine and bupivacaine for epidural analgesia in labour. Anesthesiology 1999; 90: 944–50
87 Santos AC, Karpel B, Noble G. The placental transfer and fetal effects of levobupivacaine, racemic bupivacaine and ropivacaine. Anesthesiology 1999; 90: 1698–703
89 Scrutton MJ, Srikantnarajah L, Williams H, Porter J, O’Sullivan G. Comparison of ropivacaine with bupivacaine for epidural analgesia in labour. Anesthesiology 1994; 80 (suppl.): A34
98 van Kleef JW, Veering BT, Burm AGL. Spinal anaesthesia with ropivacaine: a double-blind study on the efficacy and safety of 0.5% and 0.75% solutions in patients undergoing minor lower limb surgery. Anesth Analg 1994; 78: 1125–30
102 Whiteside JB, Burke D, Wildsmith JAW. Spinal anaesthesia with ropivacaine 5 mg ml⁻¹ in glucose 10 mg ml⁻¹ or 50 mg ml⁻¹. Br J Anaesth 2001; 86: 241–4
105 Wildsmith JAW. Relative potencies of ropivacaine and bupivacaine. Anesthesiology 2000; 92: 283
108 Wood MB, Rubin AP. A comparison of epidural 1% ropivacaine and 0.75% bupivacaine for lower abdominal gynaecological surgery. Anesth Analg 1993; 76: 1274–8
111 Zaric D, Axelsson K, Nydahl PA, Philipsson L, Larsson P, Jansson JR. Sensory and motor blockade during epidural analgesia with 1.0%, 0.75% and 0.5% ropivacaine – a double-blind study. Anesth Analg 1991; 72: 509–15
112 Zaric, D, Axelsson K, Nydahl PA, Philipsson L, Samuelsson L. Sensory and motor blockade during continuous epidural infusion of ropivacaine 0.1%, 0.2% and 0.3% in volunteers – a double-blind study. Reg Anesth Pain Med 1994; 19(Suppl 2S): 60