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Benefit-Risk Assessment of Ropivacaine in the Management of Postoperative Pain

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Contents

Abstract

Ropivacaine is a long-acting amide-type local anaesthetic, released for clinical use in 1996. In comparison with bupivacaine, ropivacaine is equally effective for subcutaneous infiltration, epidural and peripheral nerve block for surgery, obstetric procedures and postoperative analgesia. Nevertheless, ropivacaine differs from bupivacaine in several aspects: firstly, it is marketed as a pure S(−)-enantiomer and not as a racemate, and secondly, its lipid solubility is markedly lower. These features have been suggested to significantly improve the safety profile of ropivacaine, and indeed, numerous studies have shown that ropivacaine has less cardiovascular and CNS toxicity than racemic bupivacaine in healthy volunteers.

Extensive clinical data have demonstrated that epidural 0.2% ropivacaine is nearly identical to 0.2% bupivacaine with regard to onset, quality and duration of sensory blockade for initiation and maintenance of labour analgesia. Ropivacaine also provides effective pain relief after abdominal or orthopaedic surgery, especially when given in conjunction with opioids or other adjuvants. Nevertheless, epidurally administered ropivacaine causes significantly less motor blockade at low concentrations. Whether the greater degree of blockade of nerve fibres involved in pain transmission (Aδ− and C-fibres) than of those controlling motor function (Aα− and Aβ-fibres) is due to a lower relative potency compared with

bupivacaine or whether other physicochemical properties or stereoselectivity are involved, is still a matter of intense debate.

Recommended epidural doses for postoperative or labour pain are 20–40mg as bolus with 20–30mg as top-up dose, with an interval of ≥30 minutes. Alternatively, 0.2% ropivacaine can be given as continuous epidural infusion at a rate of 6–14 mL/h (lumbar route) or 4–10 mL/h (thoracic route).

Preoperative or postoperative subcutaneous wound infiltration, during cholecystectomy or inguinal hernia repair, with ropivacaine 100–175mg has been shown to be more effective than placebo and as effective as bupivacaine in reducing wound pain, whereby the vasoconstrictive potency of ropivacaine may be involved. Similar results were found in peripheral blockades on upper and lower limbs. Ropivacaine shows an identical efficacy and potency to that of bupivacaine, with similar analgesic duration over hours using single shot or continuous catheter techniques.

In summary, ropivacaine, a newer long-acting local anaesthetic, has an efficacy generally similar to that of the same dose of bupivacaine with regard to postoperative pain relief, but causes less motor blockade and stronger vasoconstriction at low concentrations. Despite a significantly better safety profile of the pure S(−)-isomer of ropivacaine, the increased cost of ropivacaine may presently limit its clinical utility in postoperative pain therapy.

Regional anaesthesia, for central neural blockade as well as blockade of the peripheral nerves and plexus, has become a vital part of the present clinical practice of anaesthetists.[1] However, toxicity issues have tarnished the history of regional anaesthesia and, although great improvements have been made, they continue to be an important consideration.[2] Nevertheless, the benefits of local and regional anaesthesia are increasingly appreciated and the use of continuous catheter techniques for central and peripheral neuronal blockades has been established as a standard procedure in the postoperative period.[1]

Bupivacaine, a highly lipophilic long-acting local anaesthetic, has been the most commonly used anaesthetic agent in its class to date. The molecular structure of this drug is characterised by an 'asymmetric' carbon atom, indicating the existence of two stereo-isomers (enantiomers): the S(−)-enantiomer and the R(+)-enantiomer. Commercially available bupivacaine, however, is a racemate, an equimolar mixture of both enantiomers.

Intriguingly, racemic bupivacaine is characterised by a remarkably high rate of cardiac and local toxicity.[3,4] An important aspect of this toxicity is that it involves stereo-specificity, with the S(−)-enantiomer showing significantly less cardiodepressant effects than the R(+)-enantiomer.[5,6]

Based on investigations of the aetiological mechanisms of local anaesthetic-induced cardiotoxicity, the search for less toxic alternatives to bupivacaine has concentrated on amide-linked agents comprised of a single enantiomer.[7] As result of these efforts, the long-acting local anaesthetics ropivacaine, and in some countries levobupivacaine, have recently been introduced.

In this review, the effects of ropivacaine are mainly compared with those of bupivacaine, as the current 'gold standard' long-acting local anaesthetic. To our knowledge only a few definitive clinical comparisons of the efficacy of ropivacaine and levobupivacaine have been published.[8,9] Therefore, the potential benefits and risks of this agent in comparison with ropivacaine will not be discussed in detail, despite the fact that it is supposed to be a less toxic and an equally potent alternative to racemic bupivacaine.[10]

1. Physicochemical Characterisation and Pharmacokinetics of Ropivacaine

Bupivacaine, ropivacaine and mepivacaine are very similar in their chemical structure as deriva-

tives of pipecoloxylidide, which was first synthesised in 1957. In the ropivacaine molecule, the four-carbon side-chain of bupivacaine or the one-carbon chain of mepivacaine, is replaced by a three-carbon chain on the piperidine nitrogen atom. Thus, ropivacaine represents the monohydrate of the hydrochloride salt of 1-propyl-2´,6´-pipecoloxylidide.

As would be anticipated, levobupivacaine and bupivacaine have identical physicochemical properties, whereas ropivacaine shows different characteristics. Molecular weight and lipophilicity are the main physicochemical differences between these methyl-, propyl- and butyl-analogues. Bupivacaine, the heaviest molecule in this group, is also the most lipophilic agent, which is important regarding onset, duration of action and toxicity of the three substances.

The proton binding affinity (pK_a) values are also of special importance, because they determine the penetration time of the drug at the binding site. Specific pK_a values are 7.6 for mepivacaine and 8.1 for both ropivacaine and bupivacaine. Therefore, at a given pH value, equal amounts of protonised and deprotonised ropivacaine molecules are present. As protein fixation also depends on pK_a value and lipophilicity, the rate of protein binding is similar for ropivacaine and bupivacaine (95% and 94%, respectively).

In addition, the pipecoloxylidide derivatives are chiral drugs, because their molecules possess an 'asymmetric' carbon atom, meaning that they may have a left and a right handed configuration. While bupivacaine and mepivacaine are used as racemic mixtures of the left- and the right-handed isomer in clinical practice, ropivacaine, in contrast, is marketed as a pure single S(−)-isomer with a purity of 99.5%.

In addition to lower lipid solubility, this pure propyl-derivative is characterised by a significantly lower systemic toxicity compared with bupivacaine and levobupivacaine.[11-13] The maximal dose of bupivacaine is 150mg, whereas the maximal dose of ropivacaine is strongly supposed to be significantly higher, although this figure has not yet been confirmed in humans. With regard to animal studies, the maximal dose for the propyl-derivative ropivacaine would be nearly twice the dose described for bupivacaine.[11-13]

Ropivacaine is characterised by a smaller volume of distribution (59L vs 73L for ropivacaine and bupivacaine, respectively), a greater plasma clearance (0.73 L/min vs 0.58 L/min) and a significantly shorter elimination half-time (111 minutes vs 162 minutes) than bupivacaine.[14]

In healthy male volunteers, the pharmacokinetics, biotransformation and urinary excretion of ^{14}C-marked ropivacaine 152 μmol (50mg) have been studied after intravenous (IV) infusion.[15] The maximum plasma concentration of ropivacaine was 5.9 ± 2.6 μmol/L (1.6 ± 0.7 mg/L), with an elimination half-life of 2.0 ± 0.3 hours and a total plasma clearance of 397 ± 127 mL/min. The maximum plasma concentration value for the total radioactivity was 5.5 ± 2.4 μmol/L (1.5 ± 0.7 mg/L) and the elimination half-life was 5.4 + 2.9 hours.^{14}C-Ropivacaine and its metabolites were mainly excreted in the urine and only 9 ± 1% in the faeces after 96 hours. Only 1 ± 0.6% of the ropivacaine dose was found to be excreted unchanged in urine.

McCann and coworkers revealed that the pharmacokinetic variables of lumbar epidural bolus ropivacaine in paediatric patients aged 3–48 months were similar to those of adults. However, it was noted that drug clearance was less in infants compared with older children.[16,17] In addition, 0.2% ropivacaine compared with 0.2% bupivacaine, administered by 2 mg/kg epidural injection, has been shown to undergo slower systemic absorption from the caudal epidural space in children aged 1–7 years.[18-20]

According to their physicochemical similarities, speed of onset, duration of neuronal blockade, potency and sensory-motor differentiation should not be substantially different between ropivacaine and bupivacaine. In early laboratory studies, latency of blockade onset was reported to be comparable between ropivacaine and bupivacaine with a tendency towards a more rapid onset with ropivacaine.[21] Reasons include the lower lipophilicity of ropivacaine and its lower binding affinity to extra-neuronal fat and tissues, resulting in a faster transfer of this drug to the site of action in the nerve, as shown in multiple human studies.[22-28] In several studies ropivacaine had a longer duration of sensory block-

ade relative to motor blockade compared with bupivacaine and levobupivacaine.[28-34] However, some studies showed a slower onset and shorter duration of ropivacaine compared with bupivacaine.[35]

Meanwhile, it seems relatively well established that ropivacaine is less potent than bupivacaine, especially when used in epidural and spinal anaesthesia.[36-38] In contrast, other studies, including minimal local anaesthetic concentration (MLAC) studies, suggest that both drugs are similar in potency, not only for peripheral nerve blockade, but also for epidural blockade[37,39] (for details see section 2.1).

Furthermore, the markedly lower lipid solubility of ropivacaine suggests that it produces a significantly greater differential blockade of sensory and motor function than bupivacaine, as can be seen in several experimental studies.[40-43] Therefore, the higher degree of differential blockade with ropivacaine at low concentrations and the ability of ropivacaine to produce frequency-dependent blockade has been supposed to offer considerable clinical advantages. Whether the lower solubility of ropivacaine in the myelin of motorneurons is solely responsible for its higher differential blockade or whether use of the pure optical S-isomer of the propyl-derivative is of major importance remains unanswered.

2. Ropivacaine in the Management of Postoperative Pain

2.1 Clinical Efficacy of Ropivacaine

A large number of open-label and double-blind studies have been carried out on human volunteers and patients in order to determine the clinical efficacy of ropivacaine in comparison with bupivacaine. It is a well known phenomenon that there may be substantial differences between laboratory predictions and the specific effects of an agent in the clinical setting. Thus, it is not surprising that the results of these trials have been non-uniform and even contradictory.[44]

On one hand, multiple studies have shown that the onset, duration of action and potency of ropivacaine are very similar to those of bupivacaine.[7,8,39,45,46] On the other hand, two studies have concluded that ropivacaine is significantly less potent than bupivacaine in equivalent concentrations, particularly those studies using the concept MLAC in epidural anaesthesia. These authors concluded that the differences observed in the rate of toxicity are the result of an absolute difference in potency, and furthermore, that the therapeutic ratio of ropivacaine and bupivacaine may be comparable.[37,47]

In order to resolve the obvious contradiction, Whiteside and Wildsmith considered each clinical application on an individual basis to clearly assess and compare the efficacy of bupivacaine and ropivacaine, as the local and systemic dynamics of these agents are known to closely depend on the site of injection.[7,48] Consequently, focussing on the potential benefits and risks of ropivacaine in the management of postoperative pain, it is necessary to evaluate each clinical application separately.

2.1.1 Infiltration Anaesthesia

Intraoperative wound infiltration is increasingly used in adults, children and infants to provide significant pain relief in the early postoperative period.[49-52] Among other mechanisms, the local action of a specific agent at the site of injection and the resultant systemic concentration are closely dependent on the rate of regional blood flow. In consequence, small doses of vasoconstrictors are occasionally injected as adjuvants in order to prolong the duration of anaesthetic effects and to avoid toxic plasma levels.

Experimental studies have shown that subcutaneous injections of ropivacaine at low concentrations markedly reduced cutaneous blood flow in pigs.[53] Analogously, ropivacaine has vasoconstrictive effects on the ring segments of canine femoral vessels *in vitro*.[54] Bupivacaine in contrast, the agent of reference in these experiments, produced vasodilation at all tested concentrations. Intradermally injected ropivacaine has also been shown to be two to three times longer acting than equal doses of bupivacaine in guinea-pigs, probably due to its intrinsic vasoconstrictor effects.[21]

Numerous studies in human volunteers comparing the effects of ropivacaine and bupivacaine on cutaneous blood flow have confirmed these results: bupivacaine causes vasodilation, whereas small doses of ropivacaine decreases blood flow at the site of injection.[55] Intriguingly, ropivacaine is believed

to have a biphasic vascular effect, as highly concentrated solutions (1%) are known to have no vasoconstrictive properties in humans.[56] Nevertheless, the vasoconstriction at low concentrations is likely to contribute to ropivacaine's long duration of action. In one study, ropivacaine produced a markedly longer lasting anaesthetic effect than bupivacaine.[56] The addition of adrenaline (epinephrine) significantly increased the duration of action of both drugs, but interestingly, ropivacaine diminished the vasoconstrictive effects of adrenaline.[56,57]

The clinical impact of these findings is still controversial, as cutaneous vasoconstriction was assessed after strict intradermal injection of very small amounts of ropivacaine in an experimental set-up.[43] Thus, many authors suggest that vasoconstrictive effects may not be relevant with the doses used in clinical practice, as no difference was found in surgical bleeding after subcutaneous injection of these agents prior to skin incision.[7,43,58] In contrast, others are concerned about infiltrating ropivacaine into areas with end-arterial blood supply.[59] One case report has been published describing a period of temporary ischaemia of the glans penis 40 minutes after dorsal penile block with 0.75% ropivacaine. The authors concluded that theoretical concerns regarding the vasoconstrictive properties of this agent may be sufficient to avoid its use when the potential for ischaemia to end organs is present.[60]

To assess the effects of ropivacaine after wound infiltration for postoperative pain relief in a clinical set-up, several well conducted studies have been performed in patients undergoing open cholecystectomy and inguinal herniorrhaphy. Preoperatively infiltrated 0.25% ropivacaine 70mL significantly decreased postoperative pain in comparison with equal volumes of 0.125% ropivacaine and saline, after open cholecystectomy. Additionally, the time to first request for supplementary analgesics significantly increased with 0.25% ropivacaine.[61]

Analogously, the postoperative local infiltration of 0.5% and 0.25% ropivacaine 40mL caused a significant and dose-related pain relief after inguinal hernia repair when compared with saline, with markedly longer lasting effects experienced with 0.5% ropivacaine.[62]

In a similar study, these results have been confirmed in outpatients undergoing hernia repair. Interestingly, the authors did not find any significant difference between the local application of 30mL of 0.125% ropivacaine and an equal volume of saline with regard to postoperative pain relief.[63]

In a further clinical trial, wound infiltration with ropivacaine compared with bupivacaine (40mL of 0.25% solutions), found both agents to be equally effective in the management of postoperative pain after herniotomy. There were no clinically relevant differences between both local anaesthetics in terms of intensity of pain relief or duration of analgesia.[46]

However, comparing the effects of 40mL of 0.75% ropivacaine with those of 0.25% bupivacaine in a randomised double-blind study, no significant differences in pain at rest, on mobilisation or during coughing could be assessed within the first 24 hours postoperatively.[64,65]

Summary

In summary, these studies show that ropivacaine is effective in providing sufficient pain relief, at least in the immediate postoperative period, when injected into wound margins. In comparison with bupivacaine in equivalent doses, there appears to be no clinically significant difference in terms of intensity of pain relief, but several data point to a markedly longer duration of pain relief after ropivacaine infiltration. Reviewing all present data, the addition of adrenaline to ropivacaine solution in order to prolong the duration of effect does not seem to be markedly effective and thus may not be necessary in infiltration anaesthesia.[56]

Ropivacaine solutions of 0.2–0.5% are recommended for infiltration techniques because lower concentrations (0.125%) are not thought to be effective for these purposes. With regard to its slight vasoconstrictive effects, most probably occurring at low and sub-clinical concentrations, ropivacaine should not be injected into tissues with end arterial blood supply, as a precaution, to avoid the occurrence of microcirculatory insufficiency.[7]

2.1.2 Peripheral Neural Blockade and Plexus Anaesthesia

Lower Limb

A considerable amount of the recent literature about ropivacaine focuses on peripheral neural blockades of the lower limb (i.e. sciatic and femoral nerve blocks).

The efficacy of ropivacaine in peripheral nerve blocks of the lower extremity was tested in a prospective, randomised, double-blind study,[66] in which ropivacaine, bupivacaine and mepivacaine were compared during combined sciatic-femoral nerve blockade. While increasing the concentrations of ropivacaine from 0.5–1.0% had no effect on the success rate, it shortened the latency to onset of blockade and resulted in a prolongation of postoperative analgesia, whereby 2% mepivacaine was found to be equal to 1% ropivacaine regarding onset time.[66]

Casati et al.[39] conducted a prospective, randomised, double-blind study to directly compare the effects of the ropivacaine/bupivacaine potency ratio on MLAC required to produce effective blockade of the femoral nerve in 50% of patients, according to Dixon's 'up-and-down' method.[67] The MLAC providing successful nerve block in 50% of cases was 14 ± 2mL in the ropivacaine group and 15 ± 2mL in the bupivacaine group (p = 0.155). In contrast to epidural MLAC studies, the volume of 0.5% ropivacaine required to produce effective blockade of the femoral nerve in 50% of patients was similar or even less than that required when using 0.5% bupivacaine.[39]

Similar results were found in a clinical study[68] using a lumbar plexus and sciatic nerve block in patients undergoing total knee arthroplasty. Patients were assigned (n = 20 per group) to receive lumbar plexus block using 30mL and a sciatic nerve block using 15mL, of either 0.5% bupivacaine or 0.5% ropivacaine. Each solution contained adrenaline at a concentration of 1 **:** 400 000. The mean onset time of motor and sensory blockade was 14–18 minutes in both groups and the duration of sensory blockade was longer in the bupivacaine group (17 ± 3 hours) than in the ropivacaine group (13 ± 2 hours). Thus, the authors concluded that 0.5% bupivacaine and 0.5% ropivacaine show similar potency when used for lumbar plexus and sciatic nerve block using a single shot drug application. Analgesic duration from 0.5% bupivacaine was prolonged by 4 hours compared with an equal volume of 0.5% ropivacaine, in the presence of adrenaline.

Upper Limb

Similar effects were also seen when comparing ropivacaine and bupivacaine in upper limb blockades. For axillary plexus block, Raeder and coworkers[69] compared the efficacy and safety of ropivacaine 7.5 mg/mL (300mg) and bupivacaine 5 mg/mL (200mg) in 104 adult patients in a prospective, double-blind study. No differences in the time to onset and duration of the blockade were seen, but 40mL of ropivacaine 7.5 mg/mL produced axillary plexus block of a better quality than 40mL of bupivacaine 5.0 mg/mL.

In a dose-finding study, Bertini et al.[70] investigated the clinical features of axillary brachial plexus anaesthesia with two different concentrations (0.5% and 0.75%) of ropivacaine and compared the results with those obtained with 0.5% bupivacaine. The quality of anaesthesia was higher with ropivacaine, as measured by the intraoperative need for opioids, and overall patient satisfaction. However, significant differences were found between the two ropivacaine concentrations. It can be concluded that 0.75% does not add benefit and therefore, 0.5% ropivacaine should be used to perform axillary brachial plexus blocks and for postoperative therapy.

In a study by McGlade et al.,[23] it was found that 40mL of 0.5% ropivacaine induced anaesthesia at a frequency of 70–90% compared with 81–87% in the 0.5% bupivacaine group, using axillary brachial plexus anaesthesia. The parameters investigated in this study were not statistically different, except for the duration of the partial motor block at the wrist and hand, which was significantly longer with bupivacaine.[23]

One study compared the efficacy of mepivacaine with ropivacaine for axillary blockade. Casati et al.[9] used 20mL of 0.75% ropivacaine or 2% mepivacaine in a prospective, randomised, double-blind study for axillary brachial plexus block in two groups of 15 patients. Time to onset of sensory block was similar in the two groups (ropivacaine 10 minutes, mepivacaine 8 minutes), while resolution of motor block in the operated hand, and the time to first requirement of a postoperative analgesic drug, occurred significantly later with ropivacaine (9 hours 50 minutes and 10 hours, respectively) than with mepivacaine (3 hours 50 minutes and 6 hours, respectively). As a result, significantly more pa-

tients in the mepivacaine-treated group than in the ropivacaine-treated group required further postoperative analgesia.[9]

Using the continuous catheter technique, Rawal and coworkers[71] investigated the analgesic efficacy of 0.125% bupivacaine and ropivacaine use in classical brachial plexus blocks after ambulatory hand surgery, in a randomised, double-blind study. Agents were administered by patient-controlled regional analgesia, and analgesic efficacy was evaluated by self assessment using the pain intensity by visual analogue and verbal scales. The results showed that ropivacaine and bupivacaine provided comparative analgesia when used for postoperative pain relief after hand surgery.

Ropivacaine was used in different studies not only for classical axillary blockade, but also for other upper limb blockades. Vaghadia et al.[72] compared the efficacy of 0.75% ropivacaine with 0.5% bupivacaine for subclavian perivascular brachial plexus block. The results obtained for the subclavian perivascular route were found to be similar to those for axillary blockades. Onset times and duration of sensory and motor blockades were comparable after injecting 30mL of either 0.75% ropivacaine or 0.5% bupivacaine. The median time to the first request for an analgesic drug postoperatively was also similar between both groups (11–12 hours). In addition, the presence of adrenaline did not alter the pharmacokinetic properties of ropivacaine when used for subclavian perivascular brachial plexus block. Therefore, the addition of a vasoconstrictor to ropivacaine is not thought to be necessary to prolong postoperative analgesia.[73]

Summary

In summary, ropivacaine is at least as efficient as bupivacaine in peripheral nerve blockade in terms of quality, postoperative duration of analgesia, anaesthesia and motor blockade. In terms of onset time of sensory and motor blockade, ropivacaine could even have some advantages over bupivacaine, showing a similar pharmacokinetic profile. Its minimal effective anaesthetic concentration is 0.5% and the benefit of increasing its concentration to 0.75% or 1% remains debatable.

2.1.3 Retrobulbar and Peribulbar Application

Special forms of peripheral nerve anaesthesia include retrobulbar and peribulbar blockades for ophthalmic surgery. For retrobulbar anaesthesia in cataract surgery 1% ropivacaine mixed with 2% lidocaine, and 0.5% bupivacaine mixed with 2% lidocaine were equally effective in producing ocular analgesia and akinesia. Thus, no change of drugs appears necessary for this procedure at present.[34]

However, particularly for retrobulbar injections of local anaesthetics, multiple case reports of myotoxicity have been described.[74] Therefore, the use of ropivacaine may be of advantage since both *in vitro* and *in vivo* studies have shown that propyl-derivatives affect muscular Ca^{2+}-homeostase significantly less than butyl-derivatives of pipecoloxylidide.[75,76] Thus, using ropivacaine instead of bupivacaine is believed to reduce myotoxic effects[4] (see section 2.2.3).

Peribulbar anaesthesia for eye surgery is an excellent alternative to the more traditional retrobulbar anaesthesia because it is technically easier to perform and causes fewer complications. In a comparative study,[77] peribulbar anaesthesia with 0.75% ropivacaine alone provided better ocular akinesia 8–10 minutes after block placement than a 1 : 1 mixture of 0.5% bupivacaine and 2% lidocaine. In addition, ropivacaine has a tendency towards a faster onset of peribulbar block, causes less pain during injection and provides a better quality of postoperative analgesia, which is especially important for ambulatory eye surgery.

Peribulbar anaesthesia with 1% ropivacaine and 0.75% bupivacaine, both with hyaluronidase, was assessed in a prospective, randomised, double-blind study of 100 patients undergoing cataract surgery.[78] Interestingly, lid akinesia was significantly more complete in the ropivacaine group, while there were no differences between the groups with regard to analgesia or duration of akinesia. Since no drug-related adverse effects were observed and no clinically significant differences found, both substances appeared to be equally potent when used for peribulbar anaesthesia.

Nociti et al.[79,80] compared the effects of ropivacaine and bupivacaine on intraocular pressure (IOP) during peribulbar blocks. The 1% ropivacaine combined with hyaluronidase was found to be better

than 0.75% bupivacaine for lowering IOP during peribulbar block in intraocular surgery. This effect is probably due to the relaxation of extraocular muscles after the block with both anaesthetics, and possibly to a smaller intraocular blood volume due to vasoconstriction by ropivacaine.

Summary

Ropivacaine and bupivacaine (with or without adjuvants or lidocaine) both seem to be suitable agents for local anaesthesia in ophthalmic surgery. Nevertheless, recent studies tend to favour ropivacaine in this field, because it is thought to provide better surgical conditions (lid akinesia, lower IOP, etc.) and to cause less damage in extraocular muscles.

2.1.4 Spinal Anaesthesia

Currently, ropivacaine is not licensed for use in spinal anaesthesia in all countries due to a lack of data from controlled clinical trials. So far, research efforts on this topic have mainly focussed on safety and dose-finding issues.

In general, spinal anaesthesia *per se* is not considered to be a suitable technique for long-acting postoperative pain management. Nevertheless, sensory recovery from a spinal blockade using long-acting local anaesthetics is known to be rather slow (approximately 3–4 hours) and thus may provide adequate postoperative pain relief, at least in the very first period after surgical procedures. For this reason, the clinical efficacy of ropivacaine in spinal anaesthesia will be briefly discussed.

Several animal studies in spinal anaesthesia in the guinea-pig, rat and dog have shown that ropivacaine and bupivacaine were equipotent with regard to the sensory blockade. Nevertheless, the duration of motor blockade was significantly shorter with ropivacaine.[21,81] Additionally, ropivacaine induced a dose-dependent spinal anaesthesia, and did not induce any neurotoxicological lesions in an experimental setting in rabbits.[82]

Safety studies in healthy human volunteers and patients have confirmed that intrathecal injections of plain ropivacaine solutions produce sensory blockade of dose-dependent extent and duration without having toxic effects on neural structures.[83,84] However, in a comparison of the intrathecal administration of ropivacaine and bupivacaine in outpatients undergoing knee surgery, both the duration of sensory blockade and the extent of motor blockade were found to be less with ropivacaine. Nevertheless, the patients receiving ropivacaine mobilised and passed urine more rapidly than those receiving bupivacaine.[85,86]

Following intrathecally injected doses of hyperbaric ropivacaine and bupivacaine (4mg, 8mg and 12mg), both agents provided prolongation of sensory and motor blockade, and time until achievement of specific discharge criteria, in a dose-dependent manner. Nevertheless, spinal anaesthesia with ropivacaine was significantly different from bupivacaine of equal dose, for all criteria examined (pinprick test, transcutaneous electrical stimulation, tolerance of high tourniquet, electromyography and isometric force dynamometry). Additionally, the incidence of back pain was significantly higher in the ropivacaine group. Therefore, these authors concluded that intrathecal ropivacaine is approximately half as potent as bupivacaine, with a higher rate of adverse effects and thus, does not offer any advantage.[36]

However, these results need to be carefully interpreted with regard to the relatively sub-clinical doses of ropivacaine administered in these studies.[44,87] More recent trials on obstetric and non-obstetric patients, in contrast, have shown that hyperbaric solutions of ropivacaine in appropriate concentrations and doses are able to produce excellent spinal blockade during relevant surgical procedures.[87-93]

Summary

The role of ropivacaine in spinal anaesthesia has not yet been fully evaluated and many experts conclude that there is still a need for more definitive clinical studies evaluating ropivacaine in spinal anaesthesia in terms of dose-finding and assessment of clinical efficacy in comparison with other long-acting agents.[7,44]

2.1.5 Epidural Anaesthesia

Epidural anaesthesia with long-acting local anaesthetics (especially the use of continuous catheter techniques) is considered to be a very effective and safe method for the management of postoperative pain. In this respect, the epidural application of ropivacaine for anaesthesia and analgesia has been

extensively studied and evaluated in numerous experimental and clinical studies.

Analgesia for Labour Pain

The efficacy of epidurally administered 0.2% ropivacaine as a monotherapy for labour pain has been assessed in many open-label, dose-finding and randomised double-blind studies in comparison with bupivacaine. In addition, numerous trials examined the efficacy of ropivacaine in combination with epidural opioids and clonidine.

Continuously administered 0.2% ropivacaine has been shown to provide excellent labour pain relief (initial boluses of 10–18ml, followed by maintenance rates of 4–10 mL/h),[94] with minimal motor blockade.[95,96] Furthermore, patient-controlled epidural analgesia (PCEA) with 0.2% ropivacaine was as effective as continuously administered 0.2% ropivacaine (8 mL/h) in terms of pain relief, but intriguingly, motor blockade was significantly less extensive in the PCEA group.[97,98]

The efficacy of ropivacaine and bupivacaine in equivalent concentrations, in the presence or absence of epidural opioids, were similar during labour; the onset of analgesia, quality of pain relief and the extent of motor blockade (mild in most patients) did not differ significantly in these studies.[31,45,99-108]

A meta-analysis comparing the effects of ropivacaine and bupivacaine during labour showed that the use or ropivacaine was associated with significantly more spontaneous vaginal deliveries, fewer instrumental deliveries and better neonatal outcome scores.[109]

The combination of epidural opioids (sufentanil and fentanyl) and ropivacaine has been shown to markedly reduce the concentrations of ropivacaine needed for sufficient pain relief.[31,99,103,107,110] Furthermore, fixed-dose combinations of opioids and ropivacaine resulted in significantly less motor blockade than the combination of opioids and bupivacaine in equivalent concentrations.[99,103] Nevertheless, recent studies resulted in similar incidences of motor blockade when comparing epidural bupivacaine and ropivacaine, combined with sufentanil (potency ratio 1 : 0.6), during labour.[111,112]

During the second stage of labour, however, there was a tendency towards lower maternal satisfaction in one study, pointing to a lower potency of ropivacaine in this period.[103]

Analogously, the effects of adding clonidine 60–75μg to 0.1–0.2% ropivacaine for epidural labour analgesia were recently studied. Clonidine increased analgesia duration and produced a dose-sparing effect when compared with ropivacaine alone.[113,114] Despite a tendency for hypotension in women receiving clonidine, there was no apparent effect on delivery mode or neonatal outcome.

In summary, 0.2% ropivacaine has been shown to provide sufficient pain relief with minimal motor blockade, at least in the first stage of labour. There seem to be no marked differences in terms of onset time and quality of pain relief compared with an equivalent concentration of bupivacaine. Additionally, the presence of adjuvant agents are suggested to be favourable in order to further decrease the concentration of ropivacaine and consequently, to minimise motor blockade.

Surgical Anaesthesia

Early open-label studies evaluating the effects of lumbar extradural application of ropivacaine boluses showed that concentrations of 0.5–1% provided long-acting surgical anaesthesia and good quality analgesia.[115-118] With increasing concentrations of ropivacaine, onset time of anaesthetic effects decreased, whereas duration and extent of sensory and motor blockade increased (generally measured using the pinprick test and a modified Bromage scale, respectively).

With regard to the physicochemical properties of ropivacaine and experimental results suggesting a slightly lower potency than bupivacaine,[81] clinical studies were carried out comparing ropivacaine with lower concentrated bupivacaine, at dose ratios of up to 1.5 : 1.[119-122] As a result, there were no significant differences in onset time and both sensory and motor blockade in the respective study groups, but higher concentrated ropivacaine tended to increase the duration of analgesia.

However, the comparison of ropivacaine and bupivacaine in equal concentrations (0.5%) in obstetric and non-obstetric patients also resulted in a similar onset time and duration of sensory blockade. Intriguingly, in most studies, motor blockade in patients treated with ropivacaine was of shorter du-

ration and markedly less intense.[22,35,123-126] In one study, however, sensory analgesia was considered satisfactory in only 76% of ropivacaine- and 62% of bupivacaine-treated patients, suggesting that lumbar epidural anaesthesia may be insufficient with plain 0.5% solutions of both agents.[22]

In summary, epidural ropivacaine in concentrations ≥0.5% provides effective surgical anaesthesia, with a tendency towards a lower intensity of motor blockade when compared with bupivacaine in equal concentrations.

Continuous Postoperative Analgesia

The efficacy of continuous epidural infusion with ropivacaine has been assessed in numerous studies in patients undergoing orthopaedic and abdominal surgery. In these randomised, double-blind studies, the extent of concomitant opioid use in the 21- to 72-hours following surgery that was required for adequate postoperative pain relief, was considered to be the primary indicator of analgesic efficacy. It was found that 10 mL/h of epidurally infused 0.1–0.3% ropivacaine decreased patient-controlled morphine doses in a dose-dependent way after abdominal and orthopaedic surgery. The extent of motor blockade also appeared to be dose-dependent, with a maximum observed in patients receiving 0.3% ropivacaine.[127-130]

Further studies examining different infusion rates of 0.2% ropivacaine resulted in a rate-dependent efficacy. In this respect, infusion rates of 10–14 mL/h have been shown to significantly reduce the need of morphine after orthopaedic and lower abdominal surgery.[131,132]

Clinical trials comparing the effects of plain epidural 0.2% ropivacaine and 0.2% bupivacaine suggested a slightly less analgesic potency of ropivacaine at a rate of 8 mL/h in orthopaedic patients. Interestingly, the incidence and extent of motor blockade was markedly lower in the ropivacaine group.[127]

However, after total hip replacement, epidural infusions of 0.2% ropivacaine combined with PCEA provided higher patient satisfaction than equal doses of bupivacaine, despite similar analgesic effects, due to a lack of motor blockade.[133]

The combination of ropivacaine and epidurally injected opioids like fentanyl, morphine and sufentanil is known to markedly improve the quality of postoperative pain relief. In this respect, the administration of 10 mL/h of 0.2% ropivacaine in combination with fentanyl 4 μg/mL provided significantly more effective dynamic analgesia than 0.2% ropivacaine with fentanyl 2 μg/mL and 1 μg/mL, or ropivacaine alone in a 72-hour period after major abdominal surgery.[134]

After total hip replacement, 0.1% ropivacaine with sufentanil 1 μg/mL was significantly more effective in providing pain relief than 0.1% ropivacaine alone at a rate of 5–9 mL/h, resulting in a 6-fold reduction of supplementary opioid doses.[135]

However, one study comparing the effects of 0.2% ropivacaine alone with those of 0.2% ropivacaine combined with sufentanil 1 μg/mL, using a patient-controlled analgesia technique, failed to demonstrate any clinical benefit from the opioid addition. There was an improvement in analgesic effects due to the combination of both agents, but there was also an increase in the number of patients who reported adverse effects, such as pruritus, nausea and vomiting.[136] Consequently, there is still a need to establish the optimal dose of sufentanil for combination with ropivacaine in epidural analgesia, and with regard to adverse effects, some authors question the value of adding opioids to epidural local anaesthetics.[137,138]

In a comparative study, 0.2% ropivacaine with fentanyl 2 μg/mL provided more effective pain relief than 0.125% bupivacaine with fentanyl 2 μg/mL at a basal rate of 4–6 mL/h and additional patient-controlled 1.5mL supplementary doses. The extent of postoperative analgesia did not differ in both groups, but patients of the bupivacaine/fentanyl group required significantly more incremental doses.[139]

Analogously, patient-controlled analgesia with 0.1/0.2% ropivacaine and 0.1/0.2% bupivacaine, both combined with epidural morphine 0.1 mg/h, resulted in comparable pain relief after major abdominal surgery.[140] In this trial, the use of 0.2% ropivacaine and morphine increased local anaesthetic consumption without improving analgesia compared with 0.1% ropivacaine and morphine. Thus, the authors concluded that small doses (0.1%) of ropivacaine and bupivacaine, in combination with epidural morphine, have a similar potency and result

in comparable postoperative analgesia. Both 0.2% ropivacaine and 0.175% bupivacaine, combined with sufentanil 1 μg/mL, provided a comparable extent of postoperative pain relief after major abdominal surgery. Despite the fact that the incidence of motor blockade did not differ significantly in both groups, patients receiving ropivacaine tended to mobilise faster.[141]

In the 72-hour period after major urological surgery, the combination of 0.2% ropivacaine with sufentanil 0.5 μg/mL was as effective as the combination of 0.25% bupivacaine with sufentanil 0.5 μg/mL in terms of postoperative pain relief. The combination of ropivacaine and sufentanil, however, appeared preferable in this study because of the markedly lower incidence of motor blockade.[142] Another comparative study showed that after major abdominal surgery thoracic epidural analgesia was more effective with 0.125% bupivacaine than with 0.125% ropivacaine when these two local anaesthetics were used in a mixture with sufentanil 0.5 μg/mL in PCEA. Additionally, plain 0.2% ropivacaine was less effective than 0.125% ropivacaine in combination with sufentanil.[143]

The efficacy of epidural ropivacaine has also been compared with patient-controlled analgesia by IV opioids. All of these studies concluded that epidural ropivacaine is significantly more effective than patient-controlled analgesia in the postoperative period. One clinical trial in 130 patients after major abdominal surgery showed that the group treated with 0.2% ropivacaine (initial 20mL bolus application, followed by 10 mL/h of continuous infusion) had significantly lower visual analogue scale scores at rest and on coughing, in the 24-hour period after surgery than the patient-controlled analgesia group.[144]

In another study, epidural ropivacaine for both surgical anaesthesia (1% ropivacaine 15–25mL) and postoperative analgesia (0.2% ropivacaine 4–6 mL/h over 24 hours; additional top-up doses of 6–10mL on demand for 48 hours) was compared with general anaesthesia and postoperative self-administered analgesia (morphine) in patients undergoing total hip replacement.[145] Again, patients in the ropivacaine group had significantly better pain relief in the first 24 hours postoperatively and could be discharged from the postoperative care unit sooner compared with the general anaesthesia/patient-controlled analgesia group.

Similar results have been achieved comparing continuous epidural 0.1% ropivacaine and sufentanil 1 μg/mL with postoperative patient-controlled analgesia using piritramide, in patients after total hip replacement.[146] The ropivacaine group had significantly lower visual analogue scale scores at rest and on movement than the patient-controlled analgesia group. Additionally, patients receiving piritramide experienced significantly more adverse events (hypotension, nausea, vomiting) than those receiving ropivacaine. Thus, the epidural infusion of ropivacaine and sufentanil was superior to patient-controlled analgesia, based on the extent of IV opioid use, in preventing postoperative pain after total hip replacement, with fewer adverse effects and greater patient satisfaction.

In summary, epidural ropivacaine 20–40mg as bolus with 20–30mg as top-up are recommended in order to provide effective postoperative pain control, with a lockout interval of ≥30 minutes. Alternatively, 0.2% ropivacaine can be given as continuous epidural infusion at a rate of 6–14 mL/h (lumbar route) or 4–10 mL/h (thoracic route). In this respect, the addition of epidural opioids seems to be reasonable in order to minimise the effective concentration of ropivacaine.

Again, numerous studies point to a lower incidence of motor blockade when using ropivacaine for postoperative pain management. Nevertheless, as studies comparing bupivacaine and ropivacaine during the postoperative period have not yet well been performed, further investigations are warranted and definite conclusions regarding the lower motor blockade can not be drawn at this time.

Paediatric Patients

In paediatric patients, ropivacaine may be administered as an epidural analgesic via the caudal or, less frequently, the lumbar[147] route.

Numerous randomised, double-blind studies on this topic have concluded that in children, 1 mL/kg caudal 0.2–0.25% ropivacaine provides similar or even better postoperative analgesia in comparison with caudal 0.25% bupivacaine 1 mL/kg.[27,30,148-153] These studies have shown that the onset time, duration of analgesic effects and need for additional pain

medication in order to provide reasonable analgesia were similar. Intriguingly, the incidence and duration of motor block tended to decrease significantly with the use of caudal ropivacaine in comparison with caudal bupivacaine. In one study, 0.5% ropivacaine 0.75 mL/kg was significantly more potent than both 0.25% ropivacaine 0.75 mL/kg and 0.25% bupivacaine 0.75 mL/kg, but was also associated with a markedly increased incidence and duration of motor block.[152]

A further study evaluated the efficacy of caudal 0.1–0.3% ropivacaine 1 mL/kg in children after inguinal surgery. These investigators concluded that 0.2% ropivacaine for caudal block provided satisfactory postoperative pain relief in paediatric patients after minor surgical procedures (herniorrhaphy etc.). Furthermore, 0.1% ropivacaine showed less efficacy, while the use of 0.3% ropivacaine was associated with a higher incidence of motor block with minimal improvement in postoperative pain relief.[154] Therefore, on the basis of all these studies, 0.2% ropivacaine seems to be a suitable, and perhaps the optimal, concentration for paediatric caudal block.[51]

In order to prolong postoperative analgesic effects and to decrease the required doses of ropivacaine, the co-administration of clonidine, ketamine and opioids, has recently been evaluated in children. The combination of caudal clonidine 2 μg/kg and 0.1% ropivacaine 1 mL/kg has been shown to be associated with an improved quality of postoperative analgesia compared with 0.2% ropivacaine 1 mL/kg alone, without causing any significant degree of postoperative sedation in children undergoing subumbilical surgery.[147] However, when using a continuous epidural infusion of ropivacaine and clonidine in children, a dosage range for clonidine of 0.08–0.12 μg/kg/h has been suggested to be the most effective.[155]

The caudal co-administration of S(−)-ketamine 0.25 mg/kg and 0.2% ropivacaine 1 mL/kg has been compared with 0.2% ropivacaine 1 mL/h alone in boys scheduled for circumcision under general anaesthesia.[156] The median duration of analgesia was significantly longer in the ketamine/ropivacaine group, with significantly fewer requests for postoperative analgesia than in the ropivacaine group. In addition, no differences between both study groups were seen in the incidence of postoperative nausea, sedation, emergence delirium and hallucinations.

The effects of caudal ropivacaine and clonidine or S(−)-ketamine, have also been compared directly. One trial in 63 children undergoing minor subumbilical surgery demonstrated that the addition of S-ketamine 0.5 mg/kg to caudal 0.2% ropivacaine 1 mL/kg provided better postoperative analgesia than clonidine 2 μg/kg, without causing clinically significant adverse effects.[157] In addition, preliminary evidence suggest that the epidural co-administration of opioids and adrenaline may provide better postoperative pain relief in children in comparison with plain solutions of ropivacaine.[158]

In summary, caudal 0.2% ropivacaine 0.75-1 mL/kg may provide excellent postoperative pain relief with a low rate of motor block in children. In terms of pain relief, the clinical efficacy of plain caudal ropivacaine does not differ significantly from equivalent bupivacaine in these patients.

Additionally, in paediatric caudal blocks, the co-injection of clonidine, ketamine and opioids, appears to be a promising method in order to prolong the analgesic effects of ropivacaine.

The Epidural 'Potency Problem': Minimum Local Analgesic Concentration Studies

Despite the results of studies indicating no significant differences in the clinical efficacy of ropivacaine and bupivacaine in epidural analgesia, some authors have questioned these relative potencies, using an up-down sequential allocation method to compare the MLAC of both agents.[67]

Polley and coworkers[37] compared the effects of 20mL of bupivacaine and ropivacaine, in the first stage of labour (25 women in each group; cervical dilation 3–7cm). They found that the MLAC for ropivacaine (0.111%) was significantly higher compared with bupivacaine (0.067%), without any differences in the motor blocking effects in both groups.

Using an identical study design, Capogna et al. examined 80 women with cervical dilation of 2–5cm. Again, the MLAC for ropivacaine (0.156%) was significantly higher than that for bupivacaine (0.093%) in the first stage of labour.[38,159] In consequence, these authors suggested that ropivacaine may be up to 40% less potent than bupivacaine, at

least in providing sufficient epidural pain relief in the first stage of labour.

However, comparing the relative analgesic potencies of levobupivacaine and ropivacaine in labour, both agents appeared to be of similar potency for epidural analgesia (0.087 vs 0.089), again with no significant differences in motor effects.[8] Intriguingly, comparing the potencies of levobupivacaine and racemic bupivacaine in labour, Lyons and coworkers showed similar MLAC values for levobupivacaine (0.083%) and racemic bupivacaine (0.081%),[160] which is contradictory to the recent result of Polley.[8]

The MLAC concept was also used to determine the 'motor block MLAC' for epidural ropivacaine and bupivacaine and their relative potency ratio during labour. The authors reported that the 'motor block MLAC' for ropivacaine was 0.326% and for bupivacaine 0.497%, with a resulting potency ratio of 0.66.[161] Thus, it was suggested that the motor block potency relation was similar to the sensory potency ratio for these two drugs which have been described in the above-mentioned MLAC studies.

The results of these MLAC studies are rather confusing and appear even contradictory to trials comparing higher concentrations of epidural ropivacaine and bupivacaine. The majority of MLAC studies resulted in the fact that ropivacaine is significantly less potent than bupivacaine, at least in labour analgesia. Consequently, the respective authors concluded that any advantages that ropivacaine may have over bupivacaine – reduced cardiotoxicity and motor blockade – have to be balanced against an apparent reduction in potency. In other words: more drug will be necessary and any potential advantage is likely to be lost.[7] This conclusion immediately provoked a lively discussion focussing on the basic validity of the MLAC concept for determining local anaesthetic potency.[7,44,162-164]

In conclusion, the clinical relevance of this concept remains to be determined. The results of MLAC studies directly contradict the results of numerous clinical studies in which all patients received sufficient pain relief. Using equal concentrations of ropivacaine and bupivacaine, these studies resulted in equal degrees of pain relief with marked advantages seen with ropivacaine.[7,163,165]

2.1.6 Other Applications (Intraperitoneal, Intra-articular Injection)

Pasqualucci et al.[166] described a significant dose-response relationship for the intraperitoneal application of local anaesthetics, suggesting that the absolute doses used may be of primary importance following laparoscopic surgery. Chundrigar et al.,[167] in a randomised, placebo-controlled study on 60 patients, confirmed that 0.25% bupivacaine reduced postoperative pain within the first 1–2 hours, but with similar analgesic consumption over the first 24 hours, proving the efficacy of intraperitoneal installation. Bisgaard et coworkers[168] investigated the intraperitoneal effects of installed ropivacaine on pain and nausea in patients undergoing elective laparoscopic cholecystectomy, whereby patients received a total of 286mg (66mL) ropivacaine or 66mL saline via periportal and intraperitoneal infiltration. Ropivacaine reduced nausea and overall pain within first 2 hours and incision pain within the first 3 postoperative hours, but had no apparent effects on intra-abdominal or shoulder pain.

Similar results were demonstrated in a study[169] after laparoscopic application of Filshie clips to relieve pain following this gynaecological procedure. Either ropivacaine (200mg) or normal saline were installed through the umbilical port following the clip application and postoperative pain score was measured using a visual analogue scale. Compared with nearly half of the patients in the control group, only 10% of the women in the ropivacaine group complained of postoperative nausea. In addition, 80% of the women in the ropivacaine group were satisfied with their pain relief compared with 56% in the control group.

Recently, Goldstein et al.[170] installed 20mL of 0.5% bupivacaine, 0.75% ropivacaine or saline for postoperative pain therapy at the end of laparoscopic gynaecological procedures. The authors could show that ropivacaine 150mg significantly reduced the need for morphine compared with bupivacaine 100mg. Thus, ropivacaine appeared to be the best choice for intraperitoneal injection because of its higher efficacy and wide safety margin. In a similar double-blind dose-response study,[171] 20mL of 0.9% saline solution (placebo), 0.25% ropivacaine or 0.75% ropivacaine were injected immediately after trochar placement and at the end of surgery.

Visceral pain at rest, during cough, and on movement, total consumption of morphine and score of characteristic of postoperative pain were significantly smaller after injection of 0.25% and 0.75% ropivacaine when compared with saline. Since 0.25% ropivacaine provided similar analgesia with significantly smaller non-toxic plasma concentrations, 0.25% ropivacaine up to 20mL seemed most appropriate for intraperitoneal installation.

Gupta et al.[172] used a catheter technique at the end of the surgery to inject 20mL of saline or 0.5% ropivacaine into the bed of the gall bladder. Postoperatively, intermittent injections (10mL) of the study solution were given when required for pain, whereby ketobemidone 1–2mg was given as IV rescue medication. In the early postoperative period, patients receiving ropivacaine had lower scores for deep pain and during coughing compared with control, while no differences were found in the postoperative consumption of ketobemidone and in the late postoperative phase after ambulatory laparoscopic cholecystectomy.

Intra-articular local anaesthetics and other drugs such as clonidine and opioids are often used for the management and prevention of pain, particularly after arthroscopic knee surgery. Surprisingly, Rautoma and coworkers[173] could not demonstrate an analgesic spare effect after intra-articular injection of 0.5% ropivacaine 20mL and saline 20mL. In contrast, pre-medication with oral diclofenac significantly reduced the visual analogue scale scores for 8 hours postoperatively. However, these results are in contradiction to a recent study[174] on postoperative pain relief after arthroscopy using intra-articular morphine or ropivacaine. Morphine 1mg or 5mg, ropivacaine 150mg or morphine 5mg and ropivacaine 75mg (compared with saline as control) were installed intra-articularly in a randomised order to evaluate their analgesic effect. In this study, intra-articular ropivacaine following elective knee-arthroscopy reduced postoperative analgesic consumption significantly and markedly improved patient comfort. After 48 hours no difference between the different groups could be confirmed.

As for intraperitoneal installation, intra-articular analgesia with a continuous infusion of local anaesthetics using a disposable infusion pump seems to have advantages. In a prospective double-blind study,[175] a single-dose interscalene block with 40mL of 0.5% ropivacaine was compared with a single-dose interscalene block with 40mL of 1.5% mepivacaine plus continuous intra-articular infusion of 0.5% ropivacaine 2 mL/h for 48 hours. Using the visual analogue scale it was shown that a brachial plexus block with 1.5% mepivacaine and a continuous intra-articular infusion of 0.5% ropivacaine at 2 mL/h improved analgesia at 24 and 48 hours compared with a single injection interscalene block with 0.5% ropivacaine.

Summary

In summary, local anaesthetics are also effective in reducing postoperative pain by installation into the abdominal cavity or intra-articularly. No significant potency differences were seen using identical concentrations of ropivacaine and bupivacaine. However, 0.25% ropivacaine produced an equal analgesic effect as higher concentrations of this agent, and is therefore believed to be the most suitable concentration for these techniques.

As the peritoneal surface is characterised by a high absorption feature, ropivacaine should be clinically preferred with regard to safety features.

2.2 Toxicity of Ropivacaine

Particularly in peripheral nerve blocks, the use of large doses of bupivacaine or ropivacaine is necessary. Thus, the toxic potential of these agents is of special interest in regional anaesthesia.

In a human study on volunteers receiving infusions of 10 mg/min of either ropivacaine or bupivacaine, there were significantly fewer CNS symptoms with ropivacaine and the mean dose of ropivacaine tolerated was 124mg, compared with 99mg bupivacaine.[176] In a similar volunteer study, the 95% CI for the difference in mean doses of ropivacaine and bupivacaine were 30mg and 7mg, respectively, whereby the maximal tolerated ropivacaine dose was also significantly higher.[177] In addition, it is important to realise that with doses producing CNS symptoms and cardiovascular adverse effects (depression of conduction and contractility etc.), symptoms are markedly less pronounced with ropivacaine than with bupivacaine, which is a very useful feature to indicate an intravascular injection in a clinical application.[177] In this respect, the

higher lipophilicity of bupivacaine appears beneficial since it may reduce the absorption rate at the site of action. However, most toxic reactions are not related to local absorption, but rather to an accidental intravascular injection.

2.2.1 CNS Toxicity

The CNS is one of the main targets for toxicity with local anaesthetics. The presumed aetiology of the CNS toxicity appears to be a two-stage process.[178] The affinity of most local anaesthetics for inhibitory neurons results in a depressive effect when first entering the limbic system, allowing excitatory neurons to act unopposed and creating an excitatory state, which culminates in generalised convulsions. At higher local anaesthetic levels, all neurons are affected, leading to global CNS depression and ultimately, a zero EEG, clinically seen as coma and cardiovascular collapse. During continuous or intermittent injection of local anaesthetics the toxic level of these drugs can be passed and signs of systemic poisoning may be seen. This toxic limit is different for each patient depending on age, type of disease and infusion speed. Although seizures and general convulsions are impressive clinical syndromes of local anaesthetic toxication, they can be handled safely without permanent damage for the patients.

2.2.2 Cardiovascular Toxicity

More complicated and with significantly higher risk for the patients are cardiac adverse effects due to long-acting local anaesthetics, since, next to the CNS, cardiac excitatory tissues are the preferred target sites for these drugs. From different studies[3,179,180] and case reports[3,181] it is generally accepted that death by local anaesthetic toxicity is mainly due to severe cardiac arrhythmia and, consequently, cardiodepression.

On a molecular basis, it is well known that the S(−)-isomers of both ropivacaine and bupivacaine are significantly less depressive than the R(+)-isomers and the racemic mixtures.[182] This was also found using an isolated heart model, which showed that the S(−)-isomers of ropivacaine had less cardiodepressant effect than racemic bupivacaine.[183] Most interestingly, these differences were also found using models of pigs and dogs. In these animal studies, the cardiac, as well as the cerebral, toxicity of bupivacaine was nearly twice as high as of ropivacaine.[11-13] In addition, resuscitation after cardiac arrest following ropivacaine toxicity was significantly more successful than after bupivacaine and levobupivacaine, which appears to prove – at least in animal studies – that ropivacaine is the safest long-acting local anaesthetic.

Although the majority of toxicology data have been generated in animal studies, clinical data in humans are markedly more important. Scott et al.[176] compared the acute central nervous and cardiovascular effects of ropivacaine and bupivacaine in 12 volunteers in a randomised, double-blind study, with IV infusions at a rate of 10 mg/min up to a maximal dose of 150mg. Cardiovascular signs of toxicity were monitored using an interpretative ECG and echocardiography to register changes in conductivity and myocardial contractility. Although ropivacaine caused fewer CNS symptoms and was at least 25% less toxic than bupivacaine in regard to the dose tolerated, no differences in cardiotoxicity could be found in this study. Knudsen and his coworkers[177] performed a similar cross-over study also in 12 volunteers to investigate the effect of IV injection of ropivacaine and bupivacaine. The infusion rate was 10 mg/min and infusions were terminated upon first signs of cerebral or cardiovascular toxicity. In all volunteers receiving an active drug, the infusion was stopped because of CNS symptoms before any arrhythmia or other cardiovascular changes in echocardiography or ECG occurred. However, when comparing cardiac function via ECG and transthoracic echocardiography during these non-cardiotoxic doses, the results showed statistically significant changes in contractility, cardiac conduction and QRS width, explained by an enlarged atrio-ventricular conduction time. This increase in QRS width, which has been correlated with cardiotoxicity of local anaesthetics and also of quinidine and tricyclic antidepressants, was significantly smaller after ropivacaine than after bupivacaine, which is similar to previous findings in animals[184] and humans.[176] When bupivacaine was administered, both systolic and diastolic left ventricular functions were significantly reduced in comparison with placebo. When using ropivacaine, only significant changes in systolic variables were noted, tending also to have a shorter restoration period. These

data were supported by preclinical studies showing that ropivacaine is less CNS- and cardio-toxic than bupivacaine. Also in humans, ropivacaine showed a higher tolerated dose and unbound plasma concentration based on the shift in dose-response and concentration-response curves for CNS symptoms. At doses producing CNS symptoms, cardiovascular changes were less pronounced with ropivacaine compared with bupivacaine.

In conclusion, cardiotoxicity is especially a problem after high doses and accidental intravascular injection. Thus, for postoperative pain therapy, toxicity appears to be of minor importance at first sight. But, even with non-cardiotoxic doses, cardiovascular effects were more pronounced after bupivacaine than after ropivacaine in the study of Knudsen et al.,[177] so that this difference in systemic toxicity between ropivacaine and bupivacaine is likely to be clinically important, even in postoperative pain therapy.

2.2.3 Myotoxicity

Intramuscular and perineural injections of local anaesthetics regularly result in myonecrosis of various extent and reversibility.[185,186] As the use of continuous catheter techniques for peripheral neural blockades has become more and more popular during recent years, case reports of clinically relevant skeletal muscle injury due to continuous application of local anaesthetic agents have been published with increasing frequency.[74,187-190] At present, all clinically used local anaesthetics are known to be myotoxic, and the extent of skeletal muscle damage is agent-specific and dose-dependent, worsening with serial or continuous administration.[191] In this respect, tetracaine and procaine have been identified to produce the least, and bupivacaine the most severe muscle injury.[186,187,191,192] The pathohistological patterns and the time course of skeletal muscle injury following local anaesthetic administration appear rather uniform: several minutes after injection, hypercontracted myofibrils become evident, followed by lytic degeneration of striated muscle sarcoplasmic reticulum (SR), and by myocyte oedema and necrosis over the next hours. Generally, satellite cells (myoblasts), basal laminae and vascular, neuronal and connective tissue elements remain intact, which often ensures tissue regeneration within 3-4 weeks.[186,192-197]

Although Benoit et al. suggested the presence of increased levels of intracellular calcium due to an alteration of Ca^{2+} homeostasis, to be the major pathomechanism, pathways of local anaesthetic myotoxicity have not been fully understood in detail.[198] In a recent study bupivacaine has been shown to induce Ca^{2+} release from the SR and to simultaneously inhibit Ca^{2+} reuptake into the SR, resulting in persistently elevated levels.[75] These effects are strongly supposed to significantly contribute to bupivacaine's myotoxicity, as in contrast, the less myotoxic tetracaine inhibits Ca^{2+} release without affecting Ca^{2+} reuptake.[186,187,192] Furthermore, bupivacaine in clinically relevant concentrations may induce apoptosis in adult skeletal muscle fibres *in vivo*, and it has been suggested that this pathway of programmed cell death may also play an important role with regard to its rate of myotoxicity.[4]

In contrast to bupivacaine, only a few experimental studies have been carried out in order to assess ropivacaine's rate of myotoxicity. As with bupivacaine, ropivacaine induces Ca^{2+} release from the SR and simultaneously inhibits Ca^{2+} reuptake into the SR. Nevertheless, ropivacaine's effects on intracellular Ca^{2+} homeostasis are significantly more moderate in comparison with bupivacaine, suggesting a minor rate of myotoxicity of ropivacaine.[76] This hypothesis has been confirmed in a histopathological study comparing the specific effects of ropivacaine and bupivacaine on skeletal muscle tissue following continuous femoral nerve blockades in pigs.[4]

In conclusion, present data suggest that ropivacaine in clinical concentrations induces less skeletal muscle damage in comparison with bupivacaine. As the clinical relevance of local anaesthetic myotoxicity is not entirely evaluated yet, further investigation on this topic are warranted in order to improve patients' safety during regional anaesthesia and analgesia.

3. Cost-Effectiveness of Ropivacaine

Multiple studies have demonstrated that acute pain management after major operations can influ-

ence the length of stay in the intensive care unit and improve patients' homeostasis and rehabilitation. Multiple approaches were used to reach improved outcome and to shorten intensive care unit stay, whereby PCEA, IV analgesia or peripheral neuronal blockade were used after surgery. In most studies, either low concentrated bupivacaine or ropivacaine, with or without opioids, were applied epidurally.

Brodner et al.[199] confirmed that the epidural approach for postoperative pain therapy was superior to IV patient-controlled analgesia, although initial costs were higher for epidurally-treated patients. The final cost analysis revealed a significant final saving of €91 620 for the year 1998, obviating the need for an intensive care unit stay totalling 433 days at a German university hospital. In this study, both long-acting anaesthetics ropivacaine and bupivacaine were used independently.

Similar results were found in a study using continuous perineural analgesia after orthopaedic surgery. Analgesic efficacy and adverse effects were monitored for 24 hours, whereby ambulant patients were not excluded. It could be shown that this continuous postoperative perineural analgesia – even at home – is safe, effective and less expensive, with high patient satisfaction after surgery.[200] By this procedure hospitalisation costs analysis showed a significant 27–46% decrease in surgery costs, although the more expensive ropivacaine was used for postoperative pain therapy.

Because of a lack of well conducted clinical studies on the cost-effectiveness of ropivacaine, it is not possible to draw any definitive conclusions on this topic at this time. It can be speculated that the higher costs of ropivacaine compared with bupivacaine may be compensated by the higher clinical safety profile and the better sensory-motor differentiation of this drug in lower concentrations, so that the use of ropivacaine may be characterised by an adequate cost-effectiveness. However, it must be stressed again that further investigations are warranted and appropriate studies on this topic are still to be carried out.

4. Conclusion

Epidural ropivacaine has frequently been supposed to be significantly less potent than bupivacaine, mainly in obstetric patients. Consequently, a possible lower potency of ropivacaine would be of great clinical importance, since claims for reduced toxicity and motor blockade have had to be re-evaluated with analgesic efficacy in mind. Nevertheless, in several MLAC studies both long-acting substances were estimated to be nearly equipotent when used in peripheral blockades. Analogously, further clinical studies could also show that both agents in equal concentrations (in milligrams) produced comparable sensory block in peripheral and central neuronal blockades.

In comparison with bupivacaine, ropivacaine causes significantly less motor block at equimolar concentrations. For postoperative pain, reduced motor blockade is a significant advantage and may result in early mobilisation, which can be an important co-factor for early recovery and hospital discharge, significantly reducing healthcare costs.

Multiple *in vivo* and *in vitro* studies have confirmed a markedly reduced systemic and local toxicity of ropivacaine compared with bupivacaine and also to the recently released levobupivacaine. While acute toxicity is mainly important for higher concentrations (e.g. for clinical anaesthesia), the toxicity of continuously infused ropivacaine and bupivacaine, respectively, is of special interest during the postoperative period. Nevertheless, no evaluated data are available yet focussing on the 'chronic' toxicity of these agents.

In conclusion, the lower incidence of motor blockade and the lower toxicity appear to warrant the clinical use of ropivacaine for postoperative pain therapy despite higher costs.

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