

The place of ropivacaine in anesthesia

R. STIENSTRA

Summary : Ropivacaine has two advantages over bupivacaine. It provides more differential block when given epidurally, allowing for a better separation between sensory and motor block. This feature can be used to its advantage in obstetrics and in postoperative epidural pain relief.

Ropivacaine has a lower systemic toxicity than both racemic and levobupivacaine. Especially its better cardiotoxic profile has been well documented and is an important advantage when using techniques with a potential for high plasma concentrations.

Ropivacaine is less potent than bupivacaine and has a shorter duration of action. The magnitude of this potency difference however is not clearly quantified and differs with varying techniques. In some studies, the potency difference amounts up to 50% whereas in other studies the difference is negligible.

The lower systemic toxicity of ropivacaine compared to bupivacaine is not offset by a lower potency, as ropivacaine in a 50% higher dose is still less cardiotoxic.

INTRODUCTION

Ropivacaine is structurally closely related to bupivacaine, the difference being a propyl group instead of a butyl group linked to the piperidine ring. Contrary to racemic bupivacaine, ropivacaine is supplied as the pure S-enantiomer.

Compared to racemic bupivacaine, ropivacaine has more differential blockade and a lower systemic toxicity. Controversy exists regarding the potency of ropivacaine : in some areas it is clearly less potent, whereas in other areas this is less obvious.

In in-vitro (1, 2), clinical epidural (3-6) and volunteer studies (7, 8), the greater separation between sensory and motor blockade has been amply demonstrated.

The lower central nervous system toxicity compared to racemic bupivacaine is illustrated by the observation that in all animal species studied, a higher dose of ropivacaine is necessary to provoke convulsions (9-13). Ropivacaine has a lower cardiotoxicity than racemic bupivacaine in in-vitro as well as in animal studies (14-16) and in human volunteers, it is better tolerated than bupivacaine

(17, 18). The toxicity will be discussed later in more detail, together with the potency issue.

Based on its profile, ropivacaine may be preferable to bupivacaine. The greater sensory-motor separation is advantageous in situations where motor block is undesirable, such as in epidural labor and postoperative analgesia. The lower systemic toxicity is beneficial in situations with a potential for high plasma concentrations of local anesthetic, such as peripheral nerve block or epidural anesthesia.

ROPIVACAINE IN LABOR

A number of studies compared ropivacaine and racemic bupivacaine for epidural analgesia during labour and delivery (19-17). All these studies reported similar analgesia for both drugs.

In a meta-analysis comprising approximately 400 parturients designed to compare ropivacaine and racemic bupivacaine for labour analgesia with respect to mode of delivery and neonatal outcome, it was shown that the use of ropivacaine was associated with significantly less motor block, more spontaneous vaginal deliveries and less instrumental deliveries (28). This meta-analysis (29) has been criticized for the relatively high doses used. However, CAMPBELL *et al.* (29) studied ropivacaine and bupivacaine 0.08% with fentanyl 2 µg/ml in a PCEA setting. They found that pain relief was adequate and similar in both groups, and the amount of local anesthetic used per hour was also similar. The incidence of forceps delivery was significantly higher in the parturients receiving bupivacaine/fentanyl compared to ropivacaine/fentanyl (35% versus 10%).

Low-dose ropivacaine with fentanyl (30) or sufentanil (31) has been found to be equally effective in providing labour analgesia as racemic bupivacaine with fentanyl or sufentanil.

R. STIENSTRA, M.D., Ph.D., Dept. of Anesthesiology, Leiden University Medical Center, Leiden, The Netherlands.

These studies indicate that ropivacaine is well suited for epidural pain relief during labor and delivery.

ROPIVACAINE FOR POSTOPERATIVE EPIDURAL ANALGESIA

Epidural infusion of local anesthetics is one of the most effective ways of postoperative pain relief. Apart from providing adequate pain relief, epidural local anesthetics may promote reconvalescence by blunting autonomic and somatic reflexes to pain.

The greater sensory-motor separation of ropivacaine is a distinct potential advantage in this area. The use of bupivacaine for postoperative analgesia is often associated with partial and sometimes complete motor block of the lower limbs and an alternative drug with similar analgesic potency but with less motor block would be an improvement.

In recent years there is an increased awareness of the danger of low molecular weight heparin (given to almost all postoperative patients) in combination with central neuraxis blockade in terms of the risk of developing a "silent" epidural haematoma. The first symptom of an epidural haematoma is often the appearance of complete motor block of the lower limbs ; thus, the absence of motor block when using postoperative epidural pain relief is crucial in providing the clinician with a monitoring tool. Last but not least, patient comfort is greatly enhanced by the absence of motor block.

The efficacy of ropivacaine for postoperative epidural pain relief has been determined in a number of studies. Several dose-finding studies comparing different doses & volumes of ropivacaine versus placebo found that ropivacaine 0.2% in a volume of 6-14 mL/h provided the best balance between pain relief and side effects, i.c. motor block (32-35).

However, not everybody agrees. In one study investigating the efficacy of ropivacaine 0.2% for postoperative pain relief after lower abdominal surgery, it was concluded that ropivacaine had little effect on pain relief while in higher doses it may be associated with motor block (36).

In recent years, epidural pain relief has gradually shifted towards a multimodal approach, where opioids are added to allow for a reduction in the dose of local anesthetic and in line with this development, ropivacaine has been studied in combination with both fentanyl and sufentanil.

In a study designed to find the optimal fentanyl dose in combination with ropivacaine 0.2%, SCOTT *et al.* (37) found that 4 µg/mL fentanyl and

an hourly rate of 14 mL/h provided the best pain relief. The combination of ropivacaine 0.1% and sufentanil 1 µg/mL at a rate of 5-9 mL/h has been shown to result in a sixfold decrease in intravenous opioid requirements after total hip replacement (38). Finally, BRODNER *et al.* (39) found that sufentanil 0.75 µg/mL added to ropivacaine 0.2% provided the best combination in terms of effective postoperative analgesia and minimal side effects.

LIU and coworkers (40) studied three solutions of ropivacaine with fentanyl in a patient-controlled epidural analgesia setting. Patients received ropivacaine 0.2% + fentanyl 4 µg/mL, or ropivacaine 0.1% + fentanyl 2 µg/mL, or ropivacaine 0.05% + fentanyl 1 µg/mL. Background infusions and bolus doses were chosen in such a manner that ropivacaine and fentanyl doses were equivalent. They found that all three solutions provided comparable analgesia ; despite the fact that ropivacaine/fentanyl consumption was highest in the group receiving 0.1% ropivacaine + fentanyl 2 µg/mL, motor block was significantly more common and more intense in the group receiving 0.2% ropivacaine + fentanyl 4 µg/mL. These findings suggest that concentration rather than dose is the major determinant of motor blockade.

The studies presented sofar investigated the efficacy of ropivacaine, either alone or in combination with an opioid, in providing postoperative epidural pain relief ; however, ropivacaine was either compared to itself in various concentrations, or to placebo. Obviously the important question is how ropivacaine performs compared to bupivacaine.

Ropivacaine and bupivacaine 0.2% without opioids for postoperative epidural pain relief have been compared in three double-blind studies. MULDOON *et al.* (41) found that ropivacaine was associated with significantly less motor block in patients undergoing knee arthroplasty ; although VAS-scores were slightly higher in the ropivacaine group, the authors concluded that this latter difference was small and clinically debatable, the important finding being the difference in motor block. Similar findings were reported by BERTINI and coworkers, who found that ropivacaine and bupivacaine provided equally satisfactory analgesia after total hip replacement, but bupivacaine was associated with much more intense motor block (42). On the other hand, in women receiving epidural pain relief with either ropivacaine or bupivacaine after open hysterectomy, JORGENSEN *et al.* found no differences between the two drugs with respect to pain relief or motor block (43).

Similarly, a number of studies have compared the efficacy in providing postoperative pain relief of ropivacaine and bupivacaine in combination with fentanyl or sufentanil. In a study using continuous epidural infusion in combination with PCEA (patient-controlled epidural analgesia) boluses, BRODNER and colleagues (44) compared 1 µg/mL sufentanil in combination with either ropivacaine 0.2% or bupivacaine 0.175%. Patients underwent major abdominal surgery and the epidural catheters were placed at the lower thoracic levels (T8-T11). There were no differences in the quality of pain relief and in Bromage scores, but in patients receiving ropivacaine mobilization was restored earlier. The total volume of local anesthetic used in each group was approximately similar, indicating a 10-15% difference in drug consumption.

In a similar study comparing 2 µg/mL fentanyl in combination with either ropivacaine 0.2% or bupivacaine 0.125%, BERTI *et al.* (45) found no differences in terms of pain relief and motor block, but patients in the bupivacaine group requested more supplemental analgesia and had a higher volume of infused analgesic solution, indicating that the 40% gap in concentration was too large. HUBLER *et al.* (46) studied the efficacy of postoperative thoracic epidural pain relief in patients undergoing major urological surgery. They compared five groups, receiving either bupivacaine 0.25% alone or in combination with sufentanil 0.5 µg/mL, ropivacaine 0.2% alone or in combination with sufentanil 0.5 µg/mL, or sufentanil 0.5 µg/mL alone. They concluded that the combination of ropivacaine with sufentanil was preferable in terms of adequate pain relief and low incidence of motor block.

HODGSON and LIU (47) studied the efficacy of postoperative epidural pain relief with ropivacaine or bupivacaine in equal concentrations of either 0.05% or 0.1% in combination with 4 µg/mL fentanyl in patients who underwent abdominal surgery. They found no differences and concluded that bupivacaine and ropivacaine in the concentrations used appeared clinically equipotent.

Finally, POUZERATTE and colleague (48) compared ropivacaine 0.2% alone, ropivacaine 0.125% plus sufentanil 0.5 µg/mL and bupivacaine 0.125% with sufentanil 0.5 µg/mL for postoperative thoracic epidural pain relief after abdominal surgery. They concluded that the combination of bupivacaine and sufentanil was the most effective and did not result in a higher incidence of motor block.

Postoperative epidural pain relief is usually restricted to three days, but this may have pharma-

cokinetic consequences in terms of accumulation. However, during a 72 h infusion it was shown that total plasma concentrations of ropivacaine increase steadily, but unbound (free) concentrations stabilize (49); this is caused by an increase in the degree of protein binding, secondary to an increase in the plasma concentration of α_1 -acid glycoprotein over time. These observations were confirmed in a study where ropivacaine was infused for a period of 72-120 h (50).

In our hospital, postoperative epidural analgesia is provided with a mixture of ropivacaine 0.2% and sufentanil 1 µg/mL in a PCEA setting (background infusion 4-6 mL/h, bolus 2 mL, lock-out 20 min). With this mixture, adequate analgesia without significant motor block is achieved in the vast majority of patients provided the epidural catheter is sited properly.

ROPIVACAINE IN SURGERY

In epidural anesthesia for surgery, similar doses of ropivacaine and bupivacaine generally yield similar sensory blockade while motor blockade is less intense and of shorter duration (3-6). In two of these studies, the duration of sensory blockade with ropivacaine was significantly shorter (3, 4).

The two drugs have been compared for brachial plexus anesthesia (51-55). In equal doses, the two drugs provided similar and virtually indistinguishable anesthesia, but in one study, the duration of motor block at the wrist and hand when using ropivacaine was significantly shorter (54).

A comparison of bupivacaine and ropivacaine 0.5% for combined lumbar plexus and sciatic nerve block showed that both drugs were equally efficacious, but sensory block with bupivacaine lasted significantly longer (56).

POTENCY & TOXICITY

Potency

Originally ropivacaine was believed to be equipotent to bupivacaine with respect to sensory blocking capacity and less potent regarding motor blocking characteristics. This assumption was based on one in-vitro study, in which it was demonstrated that in equal doses the depressant effect of bupivacaine on A-fibers was 16% greater than that of ropivacaine, but only 3% greater on C-fibers (2).

Later, this sensory equipotency has been questioned and the issue of potency has become the subject of intense debate.

Initial studies comparing ropivacaine and racemic bupivacaine for epidural anesthesia in concentrations of 0.5% and 0.75% found sensory block characteristics to be similar (3-6), although duration of sensory blockade was significantly shorter in some studies (3, 4) and showed a trend toward shorter duration in other studies. In brachial plexus anesthesia, ropivacaine and racemic bupivacaine have been found to be equally efficacious (51-55).

Two studies comparing equal volumes of ropivacaine 0.2% and racemic bupivacaine 0.25% for caudal epidural analgesia in children found both drugs to be equally effective and duration of ropivacaine analgesia slightly longer, indicating that ropivacaine would be slightly more potent than bupivacaine (57, 58).

On the other hand, a study comparing ropivacaine and racemic bupivacaine for spinal anaesthesia, found ropivacaine to be 50% less potent (59), and this finding has been confirmed in a volunteer study (60).

Two studies aimed at determining the ED₅₀ of epidural ropivacaine and racemic bupivacaine in parturients by an up-down sequential allocation method found ropivacaine to be 40% less potent (61, 12).

Overlooking the present literature, a confusing picture regarding the potency of ropivacaine thus arises: it seems that ropivacaine is more potent than racemic bupivacaine when used for caudal epidural analgesia in children, but 50% less potent when used for spinal anesthesia!

Obviously, something is wrong with this picture. A confounding factor is that sensory equipotency in clinical terms is a qualitative, and not a quantitative endpoint: surgical anesthesia is adequate or inadequate. Assuming a potency difference between ropivacaine and bupivacaine, there is a fair chance that the dose-response curves will overlap especially at the high end, and together with the absence of a precise quantitative measuring tool, this will obscure differences in potency. A potency difference will be more visible in the lower dose-range, as demonstrated by the ED-50 studies in laboring women. However, although the ED₅₀ studies claiming a 40% potency difference are elegant in design, they have a strong limitation in that they only permit conclusions about one point of the dose-response curve and it is questionable whether or not an existing difference at the ED₅₀-level may be extrapolated to other parts of the dose-response

curve. In sharp disagreement with the conclusions of the two ED₅₀-studies mentioned above is that none of the other labor studies comparing racemic bupivacaine and ropivacaine have substantiated a 40% potency difference.

By contrast, these studies, that were aiming for adequate pain relief in all parturients and therefore compared the two drugs at the higher end of the dose-response curve, mostly came up with the same conclusion: Equal doses yield similar analgesia and the amount of drug used per unit of time is similar. Reconciling these clinical findings with a potency difference of 40% is clearly impossible. Moreover, from a clinical point of view the ED₅₀ is irrelevant, as providing adequate pain relief in only 50% of the patients is not an acceptable goal. Therefore, the clinical relevance of a potency difference that is only obvious at the ED-50 level is questionable. At least in obstetrics the question of a difference in potency is irrelevant, the clinical picture being that ropivacaine provides similar pain relief but less motor block compared to bupivacaine and is associated with less instrumental deliveries (28, 29)

Another confounding factor in assessing differences in potency arises when the clinical endpoint used for assessment is susceptible for bias, for example pain scores. Patients often become very appreciative of the extra medical attention associated with participation in a trial, and may become "eager to please" the investigator.

A third confounding factor is that ropivacaine has a shorter duration of action than bupivacaine. Generally speaking, there is an inverse relation between tachyphylaxis and duration of action, and this may obscure the picture when the drugs are administered over a longer time period, such as in postoperative epidural analgesia. Looking at the studies that compared both drugs in this field, it seems obvious that bupivacaine is more potent than ropivacaine. This difference with obstetrics is most likely explained on the basis of tachyphylaxis, as duration in obstetric analgesia seldom exceeds 10 h, whereas epidural analgesia in the postoperative period is often continued for several days.

The experience in our hospital supports the notion of a potency difference becoming more obvious over time. We have used a mixture of ropivacaine 0.1% + sufentanil 0.5 µg/mL for both postoperative and labor epidural pain relief for several years. Whereas this mixture provides excellent analgesia in more than 95% of laboring women without additional interventions and is consequently still in use today, it was not equally successful in

providing adequate postoperative analgesia and based on an evaluation showing that interventions were necessary in approximately 50% of the postoperative patients we have increased the concentrations of ropivacaine and sufentanil in our postoperative mixture to respectively 0.2% and 1 µg/mL (vide supra).

Toxicity

Ropivacaine is less toxic than bupivacaine. However, if ropivacaine is also less potent, the question is if the reduction in toxicity is significant, i.e., is ropivacaine still less toxic even when used in higher doses? Moreover, recently levobupivacaine has become available. Like ropivacaine, levobupivacaine also has a better toxicity profile but unlike ropivacaine, levobupivacaine seems to be equipotent to racemic bupivacaine. As a consequence, the important issue here is: How does the reduction in cardiotoxicity of levobupivacaine relative to racemic bupivacaine compare to the reduction in cardiotoxicity of ropivacaine relative to racemic bupivacaine, taking potency into account?

Cardiotoxicity of local anesthetics has several components. The blocking of sodium channels may interfere with cardiac impulse conduction and thus affect cardiac rhythm. In a study comparing the direct cardiotoxicity of the isomers of bupivacaine and ropivacaine, it was shown that in equal doses, both isomers of bupivacaine prolong AV conduction time significantly more than the ropivacaine isomers (63). In a study comparing the effects of ropivacaine, levobupivacaine and racemic bupivacaine on QRS-prolongation after intracoronary injection in anesthetised swine, it was found that ropivacaine induced the least degree of QRS and Q-T interval widening, but there was no difference in the lethal dose between levobupivacaine and ropivacaine (64). In the isolated rabbit heart it has been shown that racemic bupivacaine, levobupivacaine and ropivacaine induce an increase in QRS duration in the ratio of 1:0.4:0.3 (65). In a study in anesthetized dogs it was demonstrated that the cumulative dose necessary to cause cardiovascular collapse was significantly larger for ropivacaine compared to both levobupivacaine and racemic bupivacaine (66); plasma concentrations post-resuscitation were higher for ropivacaine than for both levobupivacaine and racemic bupivacaine, indicating a greater safety margin for ropivacaine; resuscitation was unsuccessful in 10% of the ropivacaine animals as opposed to 30% and 50% of the

dogs receiving levobupivacaine or racemic bupivacaine respectively.

In a comparative study in pregnant and non-pregnant ewes, the risk of systemic toxicity was greatest for racemic bupivacaine, intermediate for levobupivacaine and least with ropivacaine. A study comparing the systemic toxicity in rats demonstrated that the cardiac toxicity of levobupivacaine was intermediate between that of racemic bupivacaine and ropivacaine, and resuscitation in ropivacaine-induced asystole required a smaller amount of epinephrine as compared to both levobupivacaine and racemic bupivacaine (68).

As stated above, if ropivacaine and bupivacaine are not equipotent, then the difference in potency has to be brought into the equation when comparing systemic toxicity. Although the relationship between potency and systemic toxicity is not linear, differences in systemic toxicity found at equivalent doses may disappear at equipotent doses. Assuming a 50% difference in potency, DONY and colleagues (69) compared different doses of ropivacaine and racemic bupivacaine in Wistar rats and found that even at a 50% larger dose, ropivacaine still showed a wider therapeutic index. Similar results were obtained in a study where ropivacaine in a 50% larger dose affected ventricular conduction less than bupivacaine; this is an important observation because apart from haemodynamic depression, cardiac death as a result of systemic local anesthetic toxicity is thought to occur by the slowing of ventricular conduction which in turn facilitates reentrant ventricular arrhythmias & fibrillation (71).

Cardiotoxicity of local anesthetics is also attributed to their ability to interfere with mitochondrial respiration. In a study comparing the effects of ropivacaine and (racemic) bupivacaine on mitochondrial energy metabolism in rat heart isolated mitochondria, it was shown that ropivacaine depresses mitochondrial ATP-synthesis less than racemic bupivacaine (16). The same observation has been confirmed in a study comparing inhibition of ATP-synthesis in rat liver mitochondria (72). The observed difference between ropivacaine and racemic bupivacaine in inhibiting ATP-synthesis has been attributed to their difference in lipid solubility.

Since the lipid solubility of levobupivacaine is similar to racemic bupivacaine, the interference of levobupivacaine with mitochondrial respiration will be similar to that of racemic bupivacaine, an expectation that has recently been confirmed (73).

The fact that ropivacaine interferes with mitochondrial respiration to a lesser extent than both

racemic and levobupivacaine suggests that recovery from cardiac ropivacaine intoxication will be easier, and this has been observed in two studies (66, 68).

Reference List

- Rosenberg P. H., Heinonen E., *Differential sensitivity of A and C nerve fibres to long-acting amide local anaesthetics*, BR. J. ANAESTH., **55** (2), 163-167, 1983.
- Bader A. M., Datta S., Flanagan H., Covino B. G., *Comparison of bupivacaine- and ropivacaine- induced conduction in blockade in the isolated rabbit vagus nerve*, ANESTH. ANALG., **68** (6), 724-727, 1989.
- Kerckamp H. E. M., Gielen M. J. M., Edström H., *Comparison of 0.75% ropivacaine with epinephrine and 0.75% bupivacaine with epinephrine in lumbar epidural anesthesia*, REG. ANESTH., **15**, 204-207, 1990.
- Brown D. L., Carpenter R. L., Thompson G. E., *Comparison of 0.5% ropivacaine and 0.5% bupivacaine for epidural anesthesia in patients undergoing lower-extremity surgery*, ANESTHESIOLOGY, **72**, 633-636, 1990.
- Brockway M. S., Bannister J., McClure J. H., McKeown D., Wildsmith J. A. W., *Comparison of extradural ropivacaine and bupivacaine*, BRITISH JOURNAL OF ANAESTHESIA, **66**, 31-37, 1991.
- Morrison L. M. M., Emanuelsson B.-M., McClure J. H., Pollok A. J., McKeown D. W., Brockway M. S., Jozwiak R., Wildsmith J. A. W., *Efficacy and kinetics of extradural ropivacaine : Comparison with bupivacaine*, BRITISH JOURNAL OF ANAESTHESIA, **72**, 164-169, 1994.
- Zaric D., Nydahl P. A., Adel S. O., Enbom H., Magnusson M., Philipson L., Axelsson K., *The effect of continuous epidural infusion of ropivacaine (0.1%, 0.2% and 0.3%) on nerve conduction velocity and postural control in volunteers*, ACTA ANAESTHESIOL. SCAND., **40**, 342-349, 1996.
- Zaric D., Nydahl P. A., Philipson L., Samuelsson L., Heierson A., Axelsson K., *The effect of continuous lumbar epidural infusion of ropivacaine (0.1%, 0.2%, and 0.3%) and 0.25% bupivacaine on sensory and motor block in volunteers, a double-blind study*, REG. ANESTH., **21**, 14-25, 1996.
- Morishima H. O., Pedersen H., Finster M., Hiraoka H., Tsuji A., Feldman H. S., Arthur G. R., Covino B. G., *Bupivacaine toxicity in pregnant and nonpregnant ewes*, ANESTHESIOLOGY, **63**, 134-139, 1985.
- Nancarrow C., Rutton A. J., Runciman W. B., Mather L. E., Carapetis R. J., McLean C. F., Hipkins S. F., *Myocardial and cerebral drug concentrations and the mechanisms of death after fatal intravenous doses of lidocaine, bupivacaine and ropivacaine in the sheep*, ANESTH. ANALG., **69**, 276-283, 1989.
- Feldman H. S., Arthur G. R., Covino B. G., *Comparative systemic toxicity of convulsant and supraconvulsant doses of intravenous ropivacaine, bupivacaine and lidocaine in the conscious dog*, ANESTH. ANALG., **69**, 794-801, 1989.
- Santos A. C., Arthur G. R., Pederson H., Morishima H. O., Finster M., Covino B. G., *Systemic toxicity of ropivacaine during ovine pregnancy*, ANESTHESIOLOGY, **75**, 137-141, 1991.
- Santos A. C., Arthur G. R., Wlody D., De Armas P., Morishima H. O., Finster M., *Comparative systemic toxicity of ropivacaine and bupivacaine in pregnant and non-pregnant ewes*, ANESTHESIOLOGY, **82**, 734-740, 1995.
- Reiz S., Häggmark S., Johansson G., Nath S., *Cardiotoxicity of ropivacaine – a new amide local anaesthetic agent*, ACTA ANAESTHESIOL. SCAND., **33**, 93-98, 1989.
- Pitkänen M., Feldman H. S., Arthur G. R., Covino B. G., *Chronotropic and inotropic effects of ropivacaine, bupivacaine and lidocaine in the spontaneously beating and electrically paced isolated, perfused rabbit heart*, REG. ANESTH., **17**, 183-192, 1992.
- Sztark F., Malgat M., Dabadie P., Mazat J. P., *Comparison of the effects of bupivacaine and ropivacaine on heart cell mitochondrial bioenergetics*, ANESTHESIOLOGY, **88**, 1340-1349, 1998.
- Scott D. B., Lee A., Fagan D., Bowler G. M. R., Bloomfield P., Lundh R., *Acute toxicity of ropivacaine compared with that of bupivacaine*, ANESTH. ANALG., **69**, 563-569, 1989.
- Knudsen K., Beckman-Suurkula M., Blomberg S., Sjövall J., Edvardsson N., *Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers*, BRITISH JOURNAL OF ANAESTHESIA, **78**, 507-514, 1997.
- Stienstra R., Jonker T. A., Bourdrez P., Kuijpers J. C., Van Kleef J. W., Lundberg U., *Ropivacaine 0.25% versus bupivacaine 0.25% for continuous epidural analgesia in labor; A double-blind comparison*, ANESTH. ANALG., **80**, 285-289, 1995.
- Eddleston J. M., Holland J. J., Griffin R. P., Corbet A., Horsman E. L., Reynolds F., *A double-blind comparison of 0.25% ropivacaine and 0.25% bupivacaine for extradural analgesia in labour*, BRITISH JOURNAL OF ANAESTHESIA, **76**, 66-71, 1996.
- Muir H., Writer D., Douglas J., Weeks S., Gambling D., MacArthur A., *Double-blind comparison of epidural ropivacaine 0.25% and bupivacaine 0.25%, for the relief of childbirth pain*, CAN. J. ANAESTH., **44**, 599-604, 1997.
- Gaiser R. R., Venkateswaren P., Cheek T. G., Persiley E., Buxbaum J., Hedge J., Joyce T. H., Gutsche B. B., *Comparison of 0.25% ropivacaine and bupivacaine for epidural analgesia for labor and vaginal delivery*, J. CLIN. ANAESTH., **9**, 564-568, 1997.
- Gatt S., Crook S., Lockley S., Anderson A., Armstrong P., Alley L., *A double-blind, randomized parallel investigation into the neurobehavioural status and outcome of infants born to mothers receiving epidural ropivacaine 0.25% and bupivacaine 0.25% for analgesia in labour*, ANAESTH. INTENSIVE CARE, **24**, 108-109, 1996.
- McCrae A. F., Jozwiak H., McClure J. H., *Comparison of ropivacaine and bupivacaine in extradural analgesia for the relief of pain in labour*, BR. J. ANAESTH., **74**, 261-265, 1995.
- McCrae A. F., Westerling P., McClure J. H., *Pharmacokinetic and clinical study of ropivacaine and bupivacaine in women receiving extradural analgesia in labour*, BR. J. ANAESTH., **79**, 558-562, 1997.
- Benhamou D., Hamza J., Eledjam J. J., Dailland P., Palot M., Seebacher J., Milon D., Heeroma K., *Continuous extradural infusion of ropivacaine 2 mg/ml for pain relief during labour*, BR. J. ANAESTH., **78**, 748-750, 1997.
- Owen M. D., D'Angelo R., Gerancher J. C., Thompson J. M., Foss M. L., Babb J. D., Eisenach J. C., *0.125% ropivacaine is similar to 0.125% bupivacaine for labor analgesia using patient-controlled epidural infusion*, ANESTH. ANALG., **86**, 527-531, 1998.
- Writer D., Stienstra R., Eddleston J. M., Gatt S. P., Griffin R., Gutsche B. B., Joyce T. H., Hedlund C. C., Heeroma K., Selander D., *Neonatal outcome and mode of delivery after epidural analgesia for labour with ropivacaine and bupivacaine, a prospective meta-analysis*, BR. J. ANAESTH., **81**, 713-717, 1998.
- Campbell D. C., Zwack R. M., Crone L.-A.L., Yip R. W., *Ambulatory labor epidural analgesia : bupivacaine versus ropivacaine*, ANESTH. ANALG., **90**, 1384-1389, 2000.

30. SCRUTTON M. J., SRIKANTHARAJAH I., WILLIAMS H., PORTER J., O'SULLIVAN G., *0.125% ropivacaine is similar to 0.125% bupivacaine for labor analgesia using patient-controlled epidural infusion*, ANESTHESIOLOGY, **90** (Suppl.), A34, 1999. Ref Type, Abstract.
31. Gautier P., De Kock M., Van Steenberge A., Miclot D., Fanard L., Hody J. L., *A double-blind comparison of 0.125% ropivacaine with sufentanil and 0.125% bupivacaine with sufentanil for epidural labor analgesia*, ANESTHESIOLOGY, **90**, 772-778, 1999.
32. Scott D. A., Chamley D. M., Mooney P. H., Deam R. K., Mark A. H., Hagglof B., *Epidural ropivacaine infusion for postoperative analgesia after major lower abdominal surgery: a dose finding study*, ANESTH. ANALG., **81**, 982-986, 1995.
33. Badner N. H., Reid D., Sullivan P., Ganapathy S., Crosby E. T., McKenna J., Lui A., *Continuous epidural infusion of ropivacaine for the prevention of postoperative pain after major orthopaedic surgery: a dose finding study*, CAN. J. ANAESTH., **43**, 17-22, 1996.
34. Schug S. A., Scott D. A., Payne J., Mooney P. H., Hagglof B., *Postoperative analgesia by continuous extradural infusion of ropivacaine after upper abdominal surgery*, BR. J. ANAESTH., **76** (4), 487-491, 1996.
35. Turner G., Blake D., Buckland M., Chamley D., Dawson P., Goodchild C., Mezzatesta J., Scott D., Sultana A., Walker S., Hendrata M., Mooney P., Armstrong M., *Continuous extradural infusion of ropivacaine for prevention of postoperative pain after major orthopaedic surgery*, BR. J. ANAESTH., **76** (5), 606-610, 1996.
36. Etches R. C., Writer W. D., Ansley D., Nydahl P. A., Ong B. Y., Lui A., Badner N., Kawolski S., Muir H., Shukla R., Beattie W. S., *Continuous epidural ropivacaine 0.2% for analgesia after lower abdominal surgery*, ANESTH. ANALG., **84** (4), 784-790, 1997.
37. Scott D. A., Blake D., Buckland M., Etches R., Halliwell R., Marsland C., Merridew G., Murphy D., Paech M., Schug S. A., Turner G., Walker S., Huizar K., Gustafsson U., *A comparison of epidural ropivacaine infusion alone and in combination with 1, 2, and 4 g/mL fentanyl for seventy-two hours of postoperative analgesia after major abdominal surgery*, ANESTH. ANALG., **88**, 857-864, 1999.
38. Kampe S., Weigand C., Kaufmann J., Klimek M., Konig D. P., Lynch J., *Postoperative analgesia with no motor block by continuous epidural infusion of ropivacaine 0.1% and sufentanil after total hip replacement*, ANESTH. ANALG., **89** (2), 395-398, 1999.
39. Brodner G., Mertes N., Van Aken H., Mollhoff T., Zahl M., Wirtz S., Marcus M. A., Buerkle H., *What concentration of sufentanil should be combined with ropivacaine 0.2% wt/vol for postoperative patient-controlled epidural analgesia?*, ANESTH. ANALG., **90** (3), 649-657, 2000.
40. Liu S. S., Moore J. M., Luo A. M., Trautman W. J., Carpenter R. L., *Comparison of three solutions of ropivacaine/fentanyl for postoperative patient-controlled epidural analgesia*, ANESTHESIOLOGY, **90**, 727-733, 1999.
41. Muldoon T., Milligan K., Quinn P., Connolly D. C., Nilsson K., *Comparison between extradural infusion of ropivacaine or bupivacaine for the prevention of postoperative pain after total knee arthroplasty*, BR. J. ANAESTH., **80** (5), 680-681, 1998.
42. Bertini L., Mancini S., Di Benedetto P., Ciaschi A., Martini O., Nava S., Tagariello V., *Postoperative analgesia by combined continuous infusion and patient-controlled epidural analgesia (PCEA) following hip replacement, ropivacaine versus bupivacaine*, ACTA ANAESTHESIOL. SCAND., **45** (6), 782-785, 2001.
43. Jorgensen H., Fomsgaard J. S., Dirks J., Wetterslev J., Dahl J. B., *Effect of continuous epidural 0.2% ropivacaine vs 0.2% bupivacaine on postoperative pain, motor block and gastrointestinal function after abdominal hysterectomy [see comments]*, BR. J. ANAESTH., **84** (2), 144-150, 2000.
44. Brodner G., Mertes N., Van Aken H., Pogatzki E., Buerkle H., Marcus M. A., Mollhoff T., *Epidural analgesia with local anesthetics after abdominal surgery, earlier motor recovery with 0.2% ropivacaine than 0.175% bupivacaine*, ANESTH. ANALG., **88** (1), 128-133, 1999.
45. Berti M., Fanelli G., Casati A., Albertin A., Palmisano S., Deni F., Perotti V., Torri G., *Patient supplemented epidural analgesia after major abdominal surgery with bupivacaine/fentanyl or ropivacaine/fentanyl*, CAN. J. ANAESTH., **47** (1), 27-32, 2000.
46. Hubler M., Litz R. J., Sengebusch K. H., Kreinecker I., Frank M. D., Hakenberg O. W., Albrecht D. M., *A comparison of five solutions of local anaesthetics and/or sufentanil for continuous, postoperative epidural analgesia after major urological surgery*, EUR. J. ANAESTHESIOL., **18** (7), 450-457, 2001.
47. Hodgson P. S., Liu S. S., *A comparison of ropivacaine with fentanyl to bupivacaine with fentanyl for postoperative patient-controlled epidural analgesia*, ANESTH. ANALG., **92** (4), 1024-1028, 2001.
48. Pouzeratte Y., Delay J. M., Brunat G., Boccaro G., Vergne C., Jaber S., Fabre J. M., Colson P., Mann C., *Patient-controlled epidural analgesia after abdominal surgery, ropivacaine versus bupivacaine*, ANESTH. ANALG., **93** (6), 1587-92, table, 2001.
49. Burm A. G., Stienstra R., Brouwer R. P., Emanuelsson B. M., Van Kleef J. W., *Epidural infusion of ropivacaine for postoperative analgesia after major orthopedic surgery, pharmacokinetic evaluation*, ANESTHESIOLOGY, **93** (2), 395-403, 2000.
50. Wiedemann D., Muhlneckel B., Staroske E., Neumann W., Rose W., *Ropivacaine plasma concentrations during 120-hour epidural infusion*, BR. J. ANAESTH., **85** (6), 830-835, 2000.
51. Hickey R., Rowley C. L., Candido K. D., Hoffman J., Ramamurthy S., Winnie A. P., *A comparative study of 0.25% ropivacaine and 0.25% bupivacaine for brachial plexus block*, ANESTH. ANALG., **75**, 602-606, 1992.
52. Hickey R., Hoffman J., Ramamurthy S., *A comparison of ropivacaine 0.5% and bupivacaine 0.5% for brachial plexus block*, ANESTHESIOLOGY, **74**, 639-642, 1991.
53. Vainionpää V. A., Haavisto E. T., Huha T. M., Korpi K. J., Nuutinen L. S., Hollmén A. I., Jozwiak H. M., Magnusson A. A., *A clinical and pharmacokinetic comparison of ropivacaine and bupivacaine in axillary plexus block*, ANESTH. ANALG., **81**, 534-538, 1995.
54. McGlade D. P., Kalpokas M. V., Mooney P. H., Chamley D., Mark A. H., Torda T. A., *A comparison of 0.5% ropivacaine and 0.5% bupivacaine for axillary brachial plexus anaesthesia*, ANAESTH. INTENSIVE CARE, **26**, 515-520, 1998.
55. Klein S. M., Greengrass R. A., Steele S. M., D'Ercole F. J., Speer K. P., Gleason D. H., DeLong E. R., Warner D. S., *A comparison of 0.5% bupivacaine, 0.5% ropivacaine, and 0.75% ropivacaine for interscalene brachial plexus block*, ANESTH. ANALG., **87**, 1316-1319, 1998.
56. Greengrass R. A., Klein S. M., D'Ercole F. J., Gleason D. H., Shimer C. L., Steele S. M., *Lumbar plexus and sciatic nerve block for knee arthroplasty, comparison of ropivacaine and bupivacaine*, CAN. J. ANAESTH., **45**, 1094-1096, 1998.
57. Ivani G., Lampugnani E., Torre M., Calevo-Maria G., DeNegri P., Borometi F., Messeri A., Calamandrei M., Lonnqvist P. A., Morton N. S., *Comparison of ropivacaine with bupivacaine for paediatric caudal block*, BRITISH JOURNAL OF ANAESTHESIA, **81**, 247-248, 1998.

58. Ivani G., Lampugnani E., De Negri P., Lonnqvist P. A., Broadman L., *Ropivacaine vs bupivacaine in major surgery in infants*, CAN. J. ANAESTH., **46** (5 Pt 1), 467-469, 1999.
59. Gautier P. E., De Kock M., Van Steenberge A., Poth N., Lahaye-Goffart B., Fanard L., Hody J. L., *Intrathecal ropivacaine for ambulatory surgery*, ANESTHESIOLOGY, **91** (5), 1239-1245, 1999.
60. McDonald S. B., Liu S. S., Kopacz D. J., Stephenson C. A., *Hyperbaric spinal ropivacaine, a comparison to bupivacaine in volunteers*, ANESTHESIOLOGY, **90** (4), 971-977, 1999.
61. Capogna G., Celleno D., Fusco P., Lyons G., Columb M., *Relative potencies of bupivacaine and ropivacaine for analgesia in labour*, BR. J. ANAESTH., **82**, 371-373, 1999.
62. Polley L. S., Columb M. O., Naughton N. N., Wagner D. S., Van de Ven C. J. M., *Relative analgesic potencies of ropivacaine and bupivacaine for epidural analgesia in labor*, ANESTHESIOLOGY, **90**, 944-950, 1999.
63. Graf B. M., Abraham I., Eberbach N., Kunst G., Stowe D. F., Martin E., *Differences in cardiotoxicity of bupivacaine and ropivacaine are the result of physicochemical and stereoselective properties*, ANESTHESIOLOGY, **96** (6), 1427-1434, 2002.
64. Morrison S. G., Dominguez J. J., Frascarolo P., Reiz S., *A comparison of the electrocardiographic cardiotoxic effects of racemic bupivacaine, levobupivacaine, and ropivacaine in anesthetized swine*, ANESTH. ANALG., **90** (6), 1308-1314, 2000.
65. Mazoit J. X., Decaux A., Bouaziz H., Edouard A., *Comparative ventricular electrophysiologic effect of racemic bupivacaine, levobupivacaine, and ropivacaine on the isolated rabbit heart*, ANESTHESIOLOGY, **93** (3), 784-792, 2000.
66. Groban L., Deal D. D., Vernon J. C., James R. L., Butterworth J., *Cardiac resuscitation after incremental overdose with lidocaine, bupivacaine, levobupivacaine, and ropivacaine in anesthetized dogs*, ANESTH. ANALG., **92** (1), 37-43, 2001.
67. Santos A. C., DeArmas P. I., *Systemic Toxicity of Levobupivacaine, Bupivacaine, and Ropivacaine during Continuous Intravenous Infusion to Nonpregnant and Pregnant Ewes*, ANESTHESIOLOGY, **95** (5), 1256-1264, 2001.
68. Ohmura S., Kawada M., Ohta T., Yamamoto K., Kobayashi T., *Systemic Toxicity and Resuscitation in Bupivacaine-, Levobupivacaine-, or Ropivacaine-In fused Rats*, ANESTH. ANALG., **93** (3), 743-748, 2001.
69. Dony P., Dewinde V., Vanderick B., Cuignet O., Gautier P., Legrand E., Lavand'homme P., De Kock M., *The comparative toxicity of ropivacaine and bupivacaine at equipotent doses in rats [In Process Citation]*, ANESTH. ANALG., **91** (6), 1489-1492, 2000.
70. Lefrant J. Y., de La Coussaye J. E., Ripart J., Muller L., Lalourcey L., Peray P. A., Mazoit X., Sassine A., Eledjam J. J., *The comparative electrophysiologic and hemodynamic effects of a large dose of ropivacaine and bupivacaine in anesthetized and ventilated piglets*, ANESTH. ANALG., **93** (6), 1598-1605, 2001.
71. de La Coussaye J. E., Brugada J., Allessie M. A., *Electrophysiologic and arrhythmogenic effects of bupivacaine. A study with high-resolution ventricular epicardial mapping in rabbit hearts*, ANESTHESIOLOGY, **77** (1), 132-141, 1992.
72. Scutari G., Marian M., Bindoli A., Rigobello M. P., Deoni D., Vincenti E., Bragadin M., *Mitochondrial effects of 1-ropivacaine, a new local anesthetic*, BIOCHEM. PHARMACOL., **56**, 1633-1637, 1998.
73. Sztark F., Nouette-Gaulain K., Malgat M., Dabadie P., Mazat J. P., *Absence of stereospecific effects of bupivacaine isomers on heart mitochondrial bioenergetics*, ANESTHESIOLOGY, **93** (2), 456-462, 2000.