New local anesthetics: Are they worth the cost?
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Bupivacaine, a long-acting local anesthetic agent, provides excellent epidural analgesia for labor and delivery and has remained a popular choice for regional and obstetric anesthesia over many years. Bupivacaine shows good separation between its motor and sensory effects without requiring epinephrine to prolong its effect [1] and is not subject to tachyphylaxis, as seen with lidocaine [2]. Some of the problems with bupivacaine include its potential for cardiac and central nervous system (CNS) toxicity. Numerous studies of bupivacaine toxicity have revealed the importance of chirality or stereochemistry as a vital component. This discovery has led to the development and use of newer agents, such as ropivacaine and levobupivacaine. Many animal and human studies that compared bupivacaine to these alternative local anesthetic agents have found more CNS and cardiac toxicity and more motor blockade with bupivacaine. These new local anesthetic agents are also significantly more expensive than bupivacaine. The purpose of this article is to assess not only the relative merits of these newer local anesthetic agents for obstetric anesthesia but also whether they are worth the increased cost.

Chemistry

Bupivacaine and ropivacaine are similar in chemical structure, whereby a four-carbon side-chain of bupivacaine is replaced with a three-carbon side-chain in ropivacaine (Fig. 1). Both molecules contain a chiral carbon in the heterocyclic ring that attaches to the amide linkage that is characteristic of all aminoamide local anesthetic agents. Bupivacaine is prepared as a racemic mixture, whereas levobupivacaine and ropivacaine are prepared in the almost pure -isomer form. Although the mechanism remains unknown, the -isomer of racemic bupivacaine has been shown to bind to cardiac sodium channels more intensely than the -isomers of levobupivacaine or ropivacaine [3]. As a result, levobupivacaine and ropivacaine are reportedly less cardiotoxic than bupivacaine.

Fig. 1. Chemical structures of ropivacaine and the two isomers of bupivacaine.

Toxicity

Levobupivacaine and ropivacaine recently were introduced as potential replacements for bupivacaine. In part, their development was a response to the reports of cardiac arrest associated with the inadvertent administration of large intravenous doses of bupivacaine [4]. In vitro and in vivo animal studies attest to the lower cardiotoxicity of levobupivacaine and ropivacaine (Table 1), as do some clinical studies.

Table 1. Some animal studies comparing the selective toxic effects of racemic bupivacaine, dextrobupivacaine, levobupivacaine, ropivacaine, and lidocaine

Author (Ref)	Model	Drugs	Dose	Design	Results
Arlock [6]	Guinea pig isolated cardiac muscle	RB,L,R	10 É M	Volatage clamp maximum upstroke of action potential (Vmax)	RB has most prominent cardiac sodium channel block; L the least
					RB and R interact with inactivated state; L interacts with both states
Avery et al [8]	Open-chested mechanically ventilated dogs	L, RB	2.7 and 5.4 mM K+		Seizure and cardiotoxic doses of intravenously administered L and RB in normokalemic and hyperkalemic dogs
					Hyperkalemia enhances the cardiotoxic effects of L and RB; more pronounced with RB
Clarkson and Hondeghen [5]	Guinea pig isolated cardiac muscle	RB, L	B = 0.2 É g/mL	Vmax	RB is fast-in-slow-out;
			L = 5–10 É g/mL		L is fast in fast out
Denson et al [14]	Adult Sprague-Dawley rats	RB	20 É M	Cells of the nucleus tractus solitarius were located and cell firing rate was continuously recorded	Conscious animals respond similarly to animals anesthetized with respect to the medullary effect of local anesthesia
Denson et al [15]	Adult Sprague-Dawley rats	RB, LB, DB	20 É M	Cells of the nucleus tractus solitarius were located and cell firing rate was continuously recorded	Severe bradycardia was accompanied by progressive hypotension in all animals receiving DB and becoming apneic and dying
					All animals receiving LB continued to breathe, and all but two survived

Dony et al [23] Male Wistar rats RB, R RB = 3 mg/kg/min Electrocardiogram, electroencephalogram, and invasive arterial blood pressure were continuously recorded Except for the first QRS modification, all the other toxic manifestations occurred at significantly larger doses in the two R groups in comparison to the RB group

R = 3 mg/kg/min Timing of the occurrence of local anesthetic-induced toxic events (first QRS modification, dysrhythmia, seizures, moderate and severe bradycardia, and hypotension, final systole) was recorded In awake rats, all the animals intoxicated by R easily recovered; in the RB group, two animals required cardiopulmonary resuscitation before any seizure activity could be detected, and only three rats survived

R = 4.5 mg/kg/min

Feldman et al[21] Beagle dogs RB, R CD of RB (4.3 mg/kg) and R (4.9 mg/kg) Rapid intravenous injections of R or B; initially, a dose sufficient to cause convulsions was given followed by twice the dose 48 hours later Two dogs in the RB group developed hypotension, respiratory arrest, ventricular tachycardia, and ventricular fibrillation, which were resistant to resuscitation

All of the animals in the R treated group survived the administration of the 2-CD dose

Graf et al [13] Guinea pig isolated heart DB, LB, RB 10 É m Atrial and ventricular bipolar electrodes measure heart rate and atrioventricular conduction time RB has an enatiomer-specific effect to delay atrioventricular conduction and to produce second-degree atrioventricular dissociation

Left ventricular pressure, coronary flow, and inflow and outflow oxygen tensions also were measured

Groban et al [22] Open-chested dogs RB, LB, R, L, The unbound plasma concentrations at collapse R = 19.8 É g/mL, RB = 5.7 É g/mL, and L = 9.4 É g/mL Incremental escalating infusions of RB, LB, R, L to the point of cardiovascular collapse Mortality from RB, LB, R, and L was 50%, 30%, 10%, and 0%, respectively

Huang et al [16] Conscious sheep LB, RB Doses were chosen to avoid convulsions (smaller dose 6.25–37.5 mg/min) or to be potentially toxic (larger dose 75–200 mg/3 min) Ventricular systolic contractility

Subconvulsive doses of both drugs produced similar time- and dose-dependent depression of left ventricular systolic contractility

dP/dt(max) depression Convulsions occurred consistently with > OR = 75 mg of RB and > OR = 100 mg of LB, producing an abrupt reversal of dP/dT (max) depression

Doses >75 mg of bupivacaine or >100 mg of levobupivacaine induced QRS widening and ventricular arrhythmias but significantly fewer and less deleterious arrhythmias than LB

Three animals died after 150, 150, and 200 mg of RB from the sudden onset of ventricular fibrillation; these doses of LB produced nonfatal arrhythmias that automatically returned to sinus rhythm

Lefrant et al [24] Ventilated piglets RB, R RB = 4 mg/kg Mean aortic pressure left ventricular pressure electrocardiographic parameters (eg, QT interval) 6 mg/kg R induced similar hemodynamic alterations as 4 mg/kg of RB; however, RB altered the variables of ventricular conduction (QRS and His ventricle) to a greater extent

R = 6 mg/kg

Mather et al [17] Ewes RB, LB RB (12.5–200 mg) Blood drug concentration-time data Higher mean total body clearance of DB than of LB

LB (6.25–200 mg) Regional myocardial and brain drug mass balance data No differences in the systemic pharmacokinetics of LB cf RB

No evidence of dose-dependent pharmacokinetics with either enantiomer

Myocardial tissue conc for both is 1%–4% at 3–5 min

Mazoit et al [12] Isolated rabbit heart model with constant coronary inflow DB, LB, RB 20 É M Myocardial uptake kinetics QRS duration QRS widening and the occurrence of severe arrhythmias was much less pronounced in LB than RB or DB

Morrison et al [19]Anesthetized swine RB,LB, R 0.375, 0.75, 1.5, 3, and 4 mg, with further doses increasing in 1-mg increments until death occurred QRS interval of the precordial electrocardiogram after intracoronary injection The lethal dose did not differ between DB and LB

Cardiotoxicity potency ratios for the three anesthetics based on lethal dose were: 2.1:1.2:1 (LB>R>RB)

Santos and DeArmas [20] Chronically prepared nonpregnant and pregnant sheep RB,LB R 0.52% LB, 0.52% RB, or 0.50% R, at a constant rate of 0.1 mL/kg/min until circulatory collapse Total and free

serum drug concentrations Pregnancy increases the risk of convulsions but not of more advanced manifestations of local anesthetic toxicity

Arterial blood pH and gas tensions The risk of toxicity is greatest with RB and least with R

Valenzuela et al [10] Cloned human cardiac potassium channel LB, DB 20 É M Whole-cell configuration of the patch-clamp technique DB and LB show similar binding characteristics; both bupivacaine

Valenzuela et al [3] Guinea pig ventricular myocytes RB, LB, DB 10 É M Whole-cell voltage clamp DB interacts faster and more potently and LB; both bind with high affinity to the activated similarly

Vanhoutte et al [11] Guinea pig isolated papillary muscle LB, DB 10 É M Transmembrane action potentials with the standard microelectrode technique (Vmax) LB affects Vmax and action potential duration less than the DB at different rates of stimulation and resting membrane potentials

Wheeler et al [9] Isolated, perfused canine hearts L,RB L up to 50 É g/mL Action potentials recording RB achieved twitch depression at a potency ratio of 8 cf L

RB up to 5 É g/mL Right atrial twitch amplitude Most prominent arrhythmia found was sinoatrial block, caused by both drugs

Abbreviations: CD, dose sufficient to cause convulsions; DB, dextrobupivacaine; L, lidocaine; LB, levobupivacaine; R, ropivacaine; RB, racemic bupivacaine.

In vitro studies

Bupivacaine inhibits voltage-gated sodium channels in peripheral nerves in a time- and voltage-dependent manner [5]. Interaction with other ion channels in excitable tissues, such as CNS and myocardial tissue, is similar to other local anesthetics. The dissociation time constant for bupivacaine from sodium channels is approximately 2 seconds. This, for comparison, is at least tenfold longer than that of lidocaine. The pharmacodynamics of lidocaine at the sodium receptor are commonly referred to as being "fast-in-fast-out," in contrast with bupivacaine being "fast-in-slow-out" [6]. This timing results in greater cardiac depression by bupivacaine, which is out of proportion to its potency at sodium channels [7].

Using whole cell voltage clamp techniques in isolated ventricular myocytes, it was shown that sodium channels show a marked stereoselectivity for the bupivacaine isomers, with a lower inactivated state block by dextrobupivacaine compared to levobupivacaine [3]. The arrhythmogenic potential of prolonging the QTc interval is a factor in the cardiotoxicity of bupivacaine, which suggests a blockade of potassium channels [8,9]. Dextrobupivacaine is sevenfold more potent in blocking potassium channels than levobupivacaine [10], a possible contributory factor in the selective cardiotoxicity of these agents. Electrophysiologic studies indicate a more profound blockade of sodium channels, along with a greater slowing of cardiac conduction, with dextrobupivacaine than with levobupivacaine [11]. Recovery from block is also slower with dextrobupivacaine compared to levobupivacaine, which suggests that any toxicity induced by levobupivacaine may be easier to overcome. Although studies to induce experimental arrhythmias show similar degrees of induced atrioventricular block [12], there is an increased likelihood of ventricular tachycardia, ventricular fibrillation, or asystole with dextrobupivacaine, when compared to levobupivacaine, accompanied by a longer atrioventricular conduction time [13].

The findings of a reduced block and faster dissociation from sodium channels by levobupivacaine, and most likely ropivacaine, and the decreased incidence of potassium block provide a rationale for their lower cardiotoxicity compared to dextrobupivacaine and racemic bupivacaine.

In vivo studies

In vivo work confirms the greater cardiovascular and CNS toxicity of racemic or dextrobupivacaine than that of levobupivacaine or ropivacaine. Intravenous administration of an arrhythmogenic dose of bupivacaine to a rat model reduced neuronal cell firing [14]. In a similar model, dextrobupivacaine led to substantial hypotension, bradycardia, apnea, and even death, whereas levobupivacaine produced only a mild effect in fewer animals [15].

Direct instillation of a local anesthetic into coronary arteries helps to distinguish the cardiovascular from the CNS effects. In studies performed in conscious adult ewes at doses less than those that induce seizures,

bupivacaine and levobupivacaine were seen to produce equivalent left ventricular depression and an increased frequency of arrhythmias with bupivacaine, compared to levobupivacaine [16,17]. Chang et al [18] injected levobupivacaine, ropivacaine, and bupivacaine into the left main coronary arteries of conscious ewes to determine their direct cardiovascular toxicity. All three drugs produced tachycardia, decreased myocardial contractility, and stroke volume and widening of electrocardiographic QRS complexes, with no significant differences in survival or fatal doses among these drugs. This result suggests that ropivacaine, levobupivacaine, and bupivacaine are similar in their intrinsic ability to cause direct fatal cardiac toxicity at equimolar concentrations. A study in pigs examined the direct administration of levobupivacaine, ropivacaine, and bupivacaine into coronary vessels [19]. Twenty-five percent more levobupivacaine than bupivacaine had to be administered to achieve a set level of QRS prolongation, with minimal differences seen between levobupivacaine and ropivacaine. These studies, combined together, suggest that the direct cardiac effect of the newer local anesthetic agents is similar even if somewhat reduced from that of bupivacaine.

In pregnancy, animal models have confirmed the reduced systemic toxicity of the newer anesthetic agents. Santos and DeArmas [20] compared levobupivacaine, ropivacaine, and bupivacaine in pregnant ewes and found that aside from the fact that pregnancy increased the risk of convulsions with all agents, the risk of systemic toxicity was greatest with bupivacaine and least with ropivacaine. The investigators tested all drugs at equal concentrations. Animal studies also demonstrated that resuscitation after development of toxicity is easier after lidocaine, levobupivacaine, or ropivacaine than it is after bupivacaine [21,22].

Recent work that compared the toxicity of ropivacaine to bupivacaine found that even after accounting for the possible differences in analgesic potency, ropivacaine is less toxic than bupivacaine (see later discussion of potency). Dony et al [23] showed that even at equipotent doses, ropivacaine was less toxic, as reflected in the dose required to induce arrhythmias and the need for cardiopulmonary resuscitation. Another study, performed in piglets, found that an equipotent dose of ropivacaine induced similar hemodynamic alterations to bupivacaine. Bupivacaine, however, did alter variables of ventricular conduction to a greater extent than ropivacaine [24].

Human studies

Three clinical pharmacologic studies have looked into the CNS and cardiovascular actions of levobupivacaine after intravenous dosing. In the first study, after familiarizing subjects to the symptoms of lidocaine toxicity, an intravenous infusion of levobupivacaine and bupivacaine was administered 7 days later. Thoracic bioimpedance was used as a measure of myocardial contractility. Despite the mean plasma concentrations of levobupivacaine being higher than those of racemic bupivacaine, levobupivacaine had less effect on acceleration index, mean stroke volume index, or ejection fraction [25].

Two other human studies have been performed by the manufacturer of levobupivacaine, although they are not yet published. The first study noted the effect of intravenous levobupivacaine and bupivacaine on QTc dispersion, which is a marker of a tendency to develop ventricular fibrillation. After exposure to a lidocaine pretest, volunteers were randomly allocated to receive either levobupivacaine or bupivacaine. There was no difference seen in either the mean dose or maximum plasma concentrations of these drugs, but in individuals who received more than 75 mg of drug, there was significantly less QTc dispersion with levobupivacaine [26]. The other volunteer study examined the electroencephalographic effects with the same intravenous dose of levobupivacaine, bupivacaine, or placebo over 35 minutes of drug administration. Both drugs caused slowing of the electroencephalograph consistent with CNS depression, but levobupivacaine had less of an effect in terms of magnitude and extent of brain involved. The volunteers, who received levobupivacaine, seemed to have fewer adverse effects, such as tinnitus and dizziness [27].

Human volunteer studies also confirm the reduced systemic toxicity of ropivacaine. Volunteers familiar with the CNS toxic symptoms of lidocaine experienced similar symptoms at lower arterial concentrations of bupivacaine than with ropivacaine. Mild cardiovascular depression also occurred at bupivacaine concentrations 25% to 50% lower than ropivacaine [28,29].

Recent case reports described the clinical manifestations of ropivacaine toxicity. Ala-Kokko et al reported two episodes of CNS toxicity during brachial plexus block with ropivacaine (in the same patient) that involved large doses (4.5 and 6 mg/kg-1). In neither episode did any cardiovascular toxicity occur [30]. Similarly, Muller et al reported that when 1.1 mg/kg-1 ropivacaine was inadvertently injected intravenously during a

brachial plexus block, grand mal seizures occurred but there was no cardiotoxicity [31]. Other researchers have reported modest CNS toxicity after unintentional intravenous injection or significant intravenous absorption of ropivacaine, but cardiovascular toxicity has been mild [32–35]. Conversely, Ruetsch et al [36] reported a case in which 30 mL of 0.75% ropivacaine (225 mg) was injected during a sciatic nerve block after twitch monitor localization of the nerve and negative aspiration test. The patient, a 74-year-old, 90-kg man who was premedicated with 7.5 mg of oral midazolam, became unresponsive and developed severe bradycardia and QRS widening. Plasma levels of ropivacaine were in the range reported to cause cardiac toxicity in human volunteers and experimental animals. The patient was resuscitated successfully [36].

In summary, the evidence from in vitro, large animal, and human volunteer studies demonstrated that ropivacaine and levobupivacaine are consistently less toxic than bupivacaine. There is a higher convulsive threshold in animal models and fewer CNS symptoms and fewer excitatory changes in the electroencephalograph in human volunteers after intravenous administration of levobupivacaine or ropivacaine. Levobupivacaine and ropivacaine have less arrhythmogenic potential than bupivacaine. Because of this, resuscitation seems to be more effective in animals. Both of these agents require higher lethal doses in animal models and in humans and disturb mechanical cardiac function less. Reported clinical data confirm the reduced, but not lack of, toxicity of these agents.

Clinical impact of bupivacaine toxicity in obstetric anesthesia

The appreciation of the cardiotoxicity of bupivacaine in the late 1970s was the impetus for the development of newer local anesthetics with less intrinsic toxicity. This heightened awareness also led to the widespread adoption of safer anesthetic practices, however, including careful test dosing, fractionation of epidural injections, reduced popularity of 0.75% bupivacaine (including withdrawal of its indication in obstetric anesthesia in 1984), and use of dilute solutions by continuous infusion or patient-controlled epidural analgesia (PCEA) rather than by intermittent bolus administration. In the most recent analysis of anesthetic-related maternal mortality, Hawkins et al [37] reported no bupivacaine-induced cardiac toxicity that resulted in maternal death during the period 1979 to 1990. By one estimate this time period represents more than 20 million administrations of epidural anesthesia [38]. The growing popularity of more dilute solutions of bupivacaine in labor makes it unlikely that bupivacaine cardiotoxicity will ever be a significant enough clinical issue by itself to justify the use of ropivacaine or levobupivacaine. When larger or more concentrated solutions are used, especially when fractionation over many minutes is impractical, such as in peripheral nerve blocks, then the new agents' reduced toxicity may be clinically important. For cesarean section anesthesia, large doses are used, but anesthesiologists are aware of the need to fractionate the dose and carefully and repeatedly test for intravascular injection. In the authors' opinion, in most cases lidocaine and 2-chloroprocaine are more appropriate choices for epidural anesthesia for cesarean section.

Motor block

An important purported advantage of ropivacaine is reduced motor block for a given degree of sensory block, when compared to bupivacaine. In an early preclinical study, Bader et al [39] demonstrated 16% less blockade of motor fibers with ropivacaine versus an equal concentration of bupivacaine in the isolated rabbit vagus nerve. In intact animal models, Feldman and Covino [40] found reduced motor block when ropivacaine was used for sciatic nerve block or epidural analgesia (but also it was less potent for epidural blockade). Clinical experience with ropivacaine seems to confirm this motor-sparing property, but the results have not been consistent. In a “prospective metaanalysis” of six manufacturer-sponsored studies of epidural ropivacaine compared to epidural bupivacaine, given as either intermittent boluses or as a continuous infusion in obstetric patients, Writer et al [41] concluded that not only was there less motor block but also there was a higher incidence of spontaneous vaginal delivery. The studies were not uniform in their design, and the results were not homogenous. It is difficult to draw any firm conclusions from this metaanalysis. Dresner et al [42] compared epidural 0.2% ropivacaine to 0.1% bupivacaine with fentanyl, 2 É g/mL. The investigators found equivalent motor block but fewer top-up doses in the ropivacaine group. Although the concentration of ropivacaine was double that of bupivacaine, both drugs caused equivalent motor block, which indirectly supports less motor block with the newer agent. Similarly, Fernandez-Guisasola et al [43] demonstrated equivalence in sensory and motor block between bupivacaine 0.0625% and ropivacaine 0.1%, both with fentanyl, 2 É g/mL

When dilute solutions are used, there seems to be some motor sparing with ropivacaine. Fischer et al [44] found less motor block with ropivacaine 0.1% with fentanyl than with bupivacaine 0.1%, also with fentanyl. Meister et al [45] compared 0.125% solutions of ropivacaine and bupivacaine, both with fentanyl, 2 É g/mL, by PCEA for labor analgesia and found less motor block with ropivacaine. Interestingly, the same group

failed to find any difference when the same concentration of local anesthetic was used alone, which they attributed to a greater total drug used when fentanyl was omitted [46]. Extension of their studies to examine 0.075% bupivacaine or ropivacaine with 2 É g/mL fentanyl found no difference in sensory or motor block [47]. In another study of similar design, Campbell et al [48] administered 0.08% local anesthetic with fentanyl, 2 É g/mL, by PCEA and found that a greater proportion of women in the ropivacaine group were able to perform a deep knee bend (Bromage SCALE = 0), ambulate without assistance, and micturate spontaneously.

When more concentrated solutions of bupivacaine and ropivacaine are used, no difference in sensory or motor block has been observed consistently. Plain 0.25% solutions of the two local anesthetic agents for labor analgesia are indistinguishable [49–52]. Similarly, more concentrated solutions, including 0.5% when used for cesarean section, produce equivalent sensory and motor block, although a somewhat faster recovery of motor function has been observed with ropivacaine [53–55].

There are limited data on the intrathecal use of ropivacaine, but it seems to offer little motor-sparing effect. Levin et al [56] combined 10 É g sufentanil with either bupivacaine, 2.5 mg, ropivacaine, 2.5 mg, or ropivacaine, 4 mg, for intrathecal labor analgesia as part of a combined spinal-epidural technique. They found a nearly identical duration of analgesia and indistinguishable sensory or motor effects. Chung et al [57] compared intrathecal hyperbaric ropivacaine (18 mg) and bupivacaine (15 mg) for cesarean section and found not only a faster resolution of motor block in the ropivacaine group but also a faster offset of sensory block. Hughes et al [58] compared 2.5 mg bupivacaine or ropivacaine each with 25 É g fentanyl for intrathecal labor analgesia and found a reduction in “detectable motor block” from 40% with bupivacaine to 5% with ropivacaine.

Relative potency

The foregoing discussion of the relative toxicity and motor-sparing effects of the newer local anesthetic agents presumes that the drugs are equipotent for sensory analgesia. That is, a finding of reduced cardiotoxicity of ropivacaine compared to an equal amount of bupivacaine is only relevant if the drugs are equally potent as anesthetic agents. Otherwise, the comparison would be biased by the fact that the less potent drug had been administered in effectively a lower dose. There is little controversy regarding levobupivacaine, which is virtually identical to racemic bupivacaine in anesthetic potency in vitro and in vivo [59,60]. There is considerable disagreement as to the relative potencies of bupivacaine and ropivacaine, however. This is particularly relevant to the discussion of obstetric use of ropivacaine, because the purported reduction in motor block could be merely an artifact from the use of effectively less local anesthetic.

One school of thought, championed by Polley et al, holds that ropivacaine is approximately 40% less potent than bupivacaine. This finding is based on determination of the minimum local anesthetic concentration (MLAC), a measure analogous to minimum alveolar concentration (MAC) for inhalation anesthetic, which is essentially the EC50, a concentration that produces analgesia in 50% of individuals. The MLAC is conveniently determined by the up-down sequential allocation technique of Dixon and Massey [61]. The first subject in a study is given an arbitrary concentration of local anesthetic and the analgesic response is determined. The method requires a “yes or no” binary response, and in most cases the requirement for defining an effective concentration has been a visual analogue pain score (VAPS) of 10 mm or less within 30 minutes of the epidural administration of 20 mL of the local anesthetic. The next subject then receives a concentration based on the response of the previous subject. An effective dose results in a small decrement, and an ineffective dose results in a small increment, in concentration for the succeeding subject. A series of study subjects eventually produces an oscillating pattern of effective and ineffective doses, which mathematically can be shown to estimate the EC50. The method is efficient in estimating this point but cannot give reliable information about other points on the dose-response curve.

Using this method, Polley et al [62] found the MLAC of bupivacaine to be 0.067% weight/volume (95% confidence interval [CI], 0.052–0.082), the MLAC of ropivacaine to be 0.111% weight/volume (95% CI, 0.100–0.122), and the potency ratio between the two to be 0.6 (95% CI, 0.49–0.74). Similarly, Capogna et al [63] found the MLAC of ropivacaine to be 0.156% (95% CI, 0.136–0.176) and that of bupivacaine to be 0.093% (95% CI, 0.076–0.110). Although the absolute values of the MLAC differed in this study from those of Polley et al, the analgesic potency of ropivacaine was an identical 0.6 (95% CI, 0.47–0.75), relative to bupivacaine. The MLAC of the combination of fentanyl and bupivacaine also has been determined by Polley et al [64]. The MLAC of bupivacaine + 60 É g epidural fentanyl was found to be 0.034% (0.017 CI, 0.050),

whereas the MLAC of bupivacaine + 60 É g intravenous fentanyl was essentially the same as previously determined for bupivacaine alone, 0.064% (0.049 CI, 0.080).

Another opinion, championed by D'Angelo et al, holds that clinically useful concentrations of ropivacaine and bupivacaine are equipotent [38,65]. These authors have argued that the EC50 measurement provided by the up-down study design only provides information about a single point on the dose-response curve for epidural ropivacaine or bupivacaine. Clinicians usually select a higher concentration to make 95% to 100% of patients comfortable rather than 50% as determined by the MLAC. In support of this position, numerous studies have found equivalent analgesia at concentrations of 0.25% [49–52] or 0.125% [46,66]. Addition of fentanyl [45] or sufentanil [67] to 0.125% bupivacaine or ropivacaine also produces similar analgesic efficacy. There is analgesic equivalence between 0.075% ropivacaine and bupivacaine when both drugs were combined with fentanyl 2 É g/mL [47]. The techniques used to measure efficacy in these studies were somewhat less precise than in the MLAC studies. In most studies, visual analogue pain scores, total local anesthetic consumption, and PCEA demands were compared.

Which view most accurately describes the relative potencies of ropivacaine and bupivacaine? In traditional pharmacologic studies, a full dose-response curve would be constructed and the question would be moot. It is unlikely, however, that investigators will undertake such a study of epidural ropivacaine and bupivacaine in labor because it is time consuming. The studies also would require the deliberate administration of subtherapeutic and excessive local anesthetic concentrations to a large number of parturients to gauge the fraction responding to a given concentration with effective analgesia. EC50 is a useful surrogate and is used widely to compare potencies of drugs. For example, the values of MAC for inhalation anesthetic were determined precisely this way and not, for example, by measuring total anesthetic consumed during an operation (analogous to PCEA consumption during labor) or by a formal dose-response curve determination. The EC50 is valuable because it falls on the steepest portion of the sigmoid-shaped dose-response curve (Fig. 2) and, as such, is known with the greatest certainty (smallest standard deviation). D'Angelo and James have argued correctly that such a comparison is only valid if the dose-response curves are parallel [65](Fig. 2A), which is likely in the case of ropivacaine and bupivacaine. The drugs have nearly identical chemical structure, similar physicochemical properties, and precisely the same molecular target and produce the clinical result (analgesia) via precisely the same mechanism (blockade of voltage-gated sodium channels). In animal models, peripheral nerve block with bupivacaine, levobupivacaine, or ropivacaine demonstrated parallel dose-effect curves for sensory block [68].

Fig. 2. Hypothetical concentration-response curves for bupivacaine and ropivacaine. (A) Parallel concentration-response curves. The difference in MLAC (EC50) is reflected throughout the concentration range, and ropivacaine is less potent. Administration of concentrations significantly higher than the MLAC, however, will produce indistinguishable results because both drugs will be being administered near the top of their respective concentration-response curves. (B) Concentration-response curves with different slopes. The difference in MLAC would not necessarily reflect a true difference in potency between the drugs.

If ropivacaine is less potent than bupivacaine, then the modest motor-sparing property noted in some studies must be reevaluated. Use of more dilute bupivacaine (ie, an equianalgesic concentration, not an equal concentration) might have produced a similar degree of motor block. This also may be the case for claims of less cardiotoxicity, although some studies have found this difference in cardiotoxicity even for equianalgesic concentrations of ropivacaine and bupivacaine [23].

How can one reconcile the finding of lower potency with functional equivalence when given by PCEA or continuous epidural infusion? The authors believe that the studies that support equal analgesic efficacy of the two anesthetic agents have been performed with concentrations that produce analgesia in nearly 100% of patients (ie, at the top of the dose-response curves for both drugs). As seen in Fig. 2A, the drugs are indistinguishable with regard to their analgesic efficacy. Because the dose-effect curves for motor block lie further to the right (motor block occurs at higher concentrations), however, a difference in motor block may be observed, but solely on the basis of anesthetic potency and not necessarily because of intrinsically less propensity to produce motor block. This is true even of the newest study that examined 0.075% concentrations [47], because the addition of fentanyl approximately halves the MLAC [64] and 0.075% is more than twice the EC50.

Cost

Ropivacaine and levobupivacaine are considerably more expensive than racemic bupivacaine. At Brigham and Women's Hospital in Boston, 30 mL of 0.5% bupivacaine costs $1.26, 30 mL of 0.5% ropivacaine costs $10.05, and 30 mL of 0.5% levobupivacaine costs $6.55. Levobupivacaine is more than 5 times—and ropivacaine more than 8 times—the cost of racemic bupivacaine. Using similar cost ratios found at multiple centers around the United States, D'Angelo calculated the approximate incremental cost of substituting ropivacaine for bupivacaine for labor analgesia to be $12 per patient [38]. Levobupivacaine would produce cost increases of a similar magnitude based on current pricing. Based on 1992 estimates of the use of epidural analgesia (42%) [69], this translated into $15 million per year if ropivacaine replaced bupivacaine nationwide for labor analgesia [37]. Accounting for the growth in popularity of epidural analgesia for labor over the last decade would only increase these estimates. Because most obstetric service is currently reimbursed on a fixed (global fee) basis, much of this incremental cost would be borne by hospitals and practitioners.

Summary

Epidural analgesia that uses dilute concentrations of bupivacaine with fentanyl or sufentanil provides excellent analgesia, good sensory-motor discrimination, and minimal toxicity and is inexpensive. The new local anesthetic agents, ropivacaine and levobupivacaine, offer potential improvements in the risk of toxicity when administered in large doses but probably no important clinical difference when used in dilute concentrations for labor analgesia. After accounting for the potency difference, ropivacaine offers little or no motor-sparing advantage over bupivacaine. Currently, epidural anesthesia with concentrated bupivacaine is rarely used for cesarean section, so there is little indication for the newer anesthetic agents in this setting either. The authors believe that large difference in cost cannot be justified on the basis of currently available data.