Update on the clinical utility and practical use of ropivacaine in Chinese patients

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Abstract: We reviewed the Chinese and English literature for efficacy and tolerability data as well as pharmacological properties of ropivacaine in Chinese patients. Ropivacaine is a long-acting amide local anesthetic agent that elicits nerve block via reversible inhibition of sodium ion influx in nerve fibers. The available evidence in the literature on anesthesia practice indicates that ropivacaine produces equally surgical sensory block and postoperative and obstetrics analgesia with good maternal and fetal outcome to those of bupivacaine or levobupivacaine. It appears to be associated with comparable onset, quality, and duration of sensory block, but with a lower incidence or grade of motor block, compared to bupivacaine. The satisfaction of both patients and surgeons is high when ropivacaine is used. Thus, ropivacaine appears to be an important option for regional anesthesia and for the management of postoperative and labor pain, with its enhanced sensorimotor differentiation blockage at lower concentrations and enhanced safety at higher concentrations.

Keywords: local anesthetics, anesthesia, analgesia, pharmacology, efficacy, side effect

Introduction
Ropivacaine is the pure S(−)-enantiomer of propivacaine, synthesized in 1957 and then released into clinical practice in 1996 in the US and subsequently introduced into the People's Republic of China in 1999. This new molecule was developed for the purpose of achieving a lower risk of cardiovascular toxicity and improving the relative sensory and motor block profiles compared to previous local anesthetics.1 Ropivacaine has been reported to have been safely used in peripheral nerve blockade via different routes.1 Since Wong et al reported the efficacy and safety of ropivacaine in Chinese patients undergoing caesarean section in 2003, use of ropivacaine for spinal anesthesia in obstetric and non-obstetric patients has been increasing nationwide.2 According to the China Hospital Pharmaceutical Audit, ropivacaine, among several available long-acting agents (bupivacaine and levobupivacaine), is the most commonly prescribed local anesthetic for regional anesthesia and pain management in the People's Republic of China.3 This review focuses on the efficacy and tolerability of ropivacaine when used in regional anesthesia and pain management and provides an overview of its pharmacological properties in Chinese patients.

Pharmacodynamic properties
Like other local anesthetics, ropivacaine causes reversible inhibition of sodium ion influx in nerve fibers, thus preventing depolarization of cell membrane and subsequently impairing impulse propagation.4,5 This action is potentiated by dose-dependent
inhibition of potassium channels. Ropivacaine is less lipophilic than bupivacaine and is less likely to penetrate large myelinated motor fibers. Therefore, it is more selective for pain transmitting nerves than motor function fibers.

Clinical studies in various patient populations suggest that ropivacaine is less potent than bupivacaine and levobupivacaine. These studies evaluated the minimum local analgesia concentration (MLAC) or the median effective dose (ED50) of ropivacaine and the comparator agents and found that MLAC and ED50 values were higher for ropivacaine than bupivacaine or even levobupivacaine. An obstetric study comparing the MLAC of ropivacaine with levobupivacaine in women in labor showed that the MLAC for ropivacaine (0.092%, 95% confidence interval [CI]: 0.082%–0.102%) was higher than levobupivacaine (0.077%, 95% CI: 0.058%–0.096%), indicating that levobupivacaine may be 19% more potent than ropivacaine. A recent study that was designed to evaluate the analgesic potency ratios for intrathecal ropivacaine, levobupivacaine, and bupivacaine found that the intrathecal minimum local analgesia dose was 3.64 (95% CI: 3.33–3.96) mg for ropivacaine, 2.94 (95% CI: 2.73–3.16) mg for levobupivacaine, and 2.37 (95% CI: 2.17–2.58) mg for bupivacaine, which suggested a potency hierarchy of spinal bupivacaine > levobupivacaine > ropivacaine. Other clinical trials enrolling Chinese patients also demonstrated the lower potency of ropivacaine. One study investigating the ED50 of intrathecal ropivacaine, levobupivacaine, and bupivacaine for lower limb surgery in Chinese patients found that the ED50 were 8.41 (95% CI: 7.15–9.67) mg for ropivacaine, 5.68 (95% CI: 4.92–6.44 mg) for levobupivacaine, and 5.5 (95% CI: 4.90–6.10) mg for bupivacaine. The relative anesthetic potency ratios are 0.97 (95% CI: 0.81–1.17) for levobupivacaine/bupivacaine, 0.65 (95% CI: 0.54–0.80) for ropivacaine/bupivacaine, and 0.68 (95% CI: 0.55–0.84) for ropivacaine/levobupivacaine. Although ropivacaine has lower potency than bupivacaine or levobupivacaine at lower doses (MLAC or ED50), it has similar efficacy to these two agents at clinically relevant doses and concentrations in surgical anesthesia.

### Pharmacokinetic properties

The route of administration of ropivacaine as well as tissue vascularity at the site of administration determines the absorption. After epidural administration of ropivacaine 1.5 mg/kg, the mean plasma maximum concentration (C max) was 1.31 µg/mL, and the mean time to C max was 11.8 minutes. Using 0.1%–0.5% solutions of ropivacaine, the ED50 to initiate epidural analgesia in early labor was 18.4 (95% CI: 13.4–25.4) mg. Several studies were designed to evaluate the pharmacokinetics of ropivacaine in Chinese patients, and the plasma ropivacaine absorption data in Chinese patients are summarized in Table 1. Amide local anesthetics always display a biphasic absorption pattern, with rapid absorption of a small quantity of drug by highly perfused tissues/organs, followed by a slower absorption of the remainder of the drug into less perfused tissues/organs. The early absorption speed of ropivacaine can be affected by ropivacaine-induced vasoconstriction. However, a study examining the effects of various ropivacaine concentrations (0.25%, 0.5%, and 0.75%) on pharmacokinetic profiles following transversus abdominal plane did not find any difference among the concentrations. The mean half-time of the rapid absorption is approximately 14 minutes, while the mean absorption half-time of the slower phase is approximately 4.2 hours. Epidural ropivacaine pharmacokinetics were found to be affected by age, as the fraction absorbed was decreased and the elimination half-time was longer in older compared with younger patients. Based on these

### Table 1 Summary of absorption pharmacokinetics of ropivacaine in Chinese patients

<table>
<thead>
<tr>
<th>Route of administration (number of patients)</th>
<th>Concentration of ropivacaine used</th>
<th>Total doses of ropivacaine</th>
<th>C max, arterial (µg/mL)</th>
<th>C max, venous (µg/mL)</th>
<th>t max, arterial (min)</th>
<th>t max, venous (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult studies</td>
<td></td>
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<tr>
<td>Lee et al [14]</td>
<td>Epidural block (24)</td>
<td>NA</td>
<td>1.5 mg/kg</td>
<td>1.31 (0.39)</td>
<td>8.8 (5.3–14.6)</td>
<td>11.8 (6.6–21.1)</td>
</tr>
<tr>
<td>Karmakar et al [14]</td>
<td>Thoracic paravertebral block (20)</td>
<td>10 mg/mL</td>
<td>2 mg/kg</td>
<td>2.47 (0.5)</td>
<td>NA</td>
<td>7.5 (2.5–25)</td>
</tr>
<tr>
<td>Chen et al [17]</td>
<td>Intra-articular administration (18)</td>
<td>7.5 mg/mL</td>
<td>150 mg</td>
<td>0.91 (0.4)</td>
<td>NA</td>
<td>55.8 (33.6)</td>
</tr>
<tr>
<td>Child study</td>
<td>Caudal block (20)</td>
<td>2 mg/mL</td>
<td>2 mg/kg</td>
<td>0.67 (0.16)</td>
<td>NA</td>
<td>61.9 (20.6)</td>
</tr>
</tbody>
</table>

**Note:** Values are mean (SD), or mean (95% confidence interval) if SD could not be found in the paper.

**Abbreviations:** C max, maximum concentration; NA, related data not available; SD, standard deviation; t max, time to C max.
clinical findings, it is recommended that elderly patients receive reduced doses of ropivacaine, according to their physical status.

Alpha-1-acid glycoprotein (AAG) is the main binding site for ropivacaine, binds basic drugs in a low-capacity, high-affinity fashion. The unbound drug concentration is considered to be related to systemic toxicity. Plasma levels of AAG are increased by trauma, surgery, and other pathophysiological states, which in turn can alter total and unbound plasma concentration of ropivacaine. Ropivacaine is predominantly eliminated by extensive metabolism in liver, which depends on hepatic blood flow as well as the degree of protein binding. Two cytochrome P450 (CYP) isoenzymes, CYP1A2 and CYP3A4, are responsible for the formation of 3′-hydroxy-ropivacaine and 2′,6′-pipecoloxylidide, respectively, with typical hepatic extraction ratios between 0.3 and 0.7. After administration of a single intravenous dose of radiolabeled ropivacaine, 86% of the dose was excreted in the urine after 96 hours, mainly as 3′-hydroxy-ropivacaine (37% of the dose), with only 1% of the dose being excreted unchanged. Most of the radioactivity (about 68%) was excreted within 12 hours.

**Therapeutic efficacy**

Ropivacaine has increasingly been used in clinical anesthesia practice and pain management over the last few years in the People’s Republic of China. Numerous clinical trials have evaluated the efficacy of ropivacaine by comparing primarily with bupivacaine or levobupivacaine, and the efficacy in providing a profound sensory block suitable for surgical anesthesia and postoperative and labor analgesia when administered by various routes has been established.

**Epidural administration**

Epidural ropivacaine provided effective anesthesia for Chinese patients undergoing elective cesarean section, abdominal surgery, breast cancer surgery, and hip or lower limb surgery, as well as effective analgesia following different surgeries. Ropivacaine 0.5% or 0.75% epidurally has been demonstrated to provide a clinically similar onset of sensory and motor block to that of bupivacaine 0.5%,. When 0.5% ropivacaine was administered, the median duration of analgesia for surgery (spinal nerves T6–S3) was 1.7–4.2 hours, whereas the median duration of complete motor block was 0.9 hours. Compared with 0.5% bupivacaine, 0.75% ropivacaine resulted in greater decrease of maternal heart rate; however, it did not influence neonatal well-being, which was evaluated by Apgar scores 1, 5, and 10 minutes after delivery and by umbilical arterial blood-gas analysis. Patients showed slightly higher satisfaction with ropivacaine anesthesia compared with bupivacaine anesthesia (93% versus 87%), although there was no significant difference. By conducting a meta-analysis, Hillyard et al found that, for emergency cesarean section anesthesia, neither epidural ropivacaine nor bupivacaine is the first choice. If the speed of onset is important, a lidocaine and epinephrine solution appears optimal; if the quality of anesthesia is paramount, 0.75% ropivacaine is suggested.

Pouzeratte et al reported that patient-controlled epidural analgesia with 0.125% bupivacaine was more effective than a mixture of 0.125% ropivacaine and 0.5 µg/mL sufentanil in patients after abdominal surgery, and that 0.2% ropivacaine alone was less effective than the mixture. However, a recent study showed that patient-controlled epidural infusion of 0.2% ropivacaine, 0.125% bupivacaine, or 0.125% levobupivacaine produced similar pain relief and postoperative sensorimotor differentiation in patients undergoing lower limb surgery.

**Intrathecal administration**

Bupivacaine was formerly considered as the first choice for spinal anesthesia in most hospital in the People’s Republic of China. Since very small doses of local anesthetic are required in spinal anesthesia, the risk for bupivacaine-related systemic toxicity has not been an issue. Nevertheless, ropivacaine has been administered intrathecally for regional anesthesia for obstetric patients and non-obstetric patients in recent years. The efficacy of intrathecal ropivacaine for regional anesthesia is mainly concluded from studies of Chinese patients undergoing cesarean section, urological surgery, or orthopedics surgery. Doses of ropivacaine used for spinal anesthesia have ranged from 8 to 22.5 mg, and it has been suggested that ropivacaine is less potent than bupivacaine. A comparative study enrolling parturients undergoing elective cesarean showed that intrathecal ED50 for motor block was 5.79 (95% CI: 4.62–6.96) mg for ropivacaine, 4.83 (95% CI: 4.35–5.32) mg for levobupivacaine, and 3.44 (95% CI: 2.55–4.34) mg for bupivacaine. However, McNamee et al reported that 17.5 mg plain ropivacaine 0.5% provided similarly effective spinal anesthesia as 17.5 mg plain bupivacaine 0.5% for total hip arthroplasty. Ropivacaine is associated with a more rapid postoperative recovery of sensory and motor function. Whiteside et al found the same results by comparing 15 mg hyperbaric ropivacaine 0.5% with 15 mg hyperbaric bupivacaine...
0.5%. When compared with 7.5 mg of 0.5% hyperbaric levobupivacaine for outpatient knee arthroscopy, 7.5 mg of 0.5% ropivacaine was also associated with shorter block time and faster home discharge.

A dose-finding study conducted with Chinese patients found that anesthesia was successful in 70% of patients undergoing cesarean section with spinal ropivacaine 20 mg. The ED50 was 16.7 (95% CI: 14.1–18.8) mg and the ED95 (“an effective dose [success] was defined as a dose that provided adequate sensory dermatomal anesthesia to pin prick to T7 or higher and required no epidural top-up for surgery to be completed”) was 26.8 (95% CI: 23.6–34.1) mg. Hyperbaric ropivacaine is associated with higher cephalic spread (median [range] maximum block height to pinprick, T1 [T4–C2] versus T3 [T11–C3]) and faster onset to T4 dermatome (mean [standard deviation, SD] of 7.7 [4.9] versus 16.4 [14.1] minutes) when compared with plain ropivacaine.

Peripheral nerve and ocular block
Ropivacaine is the most frequently used anesthetic for peripheral nerve block in the People’s Republic of China. However, clinical trials comparing ropivacaine with bupivacaine or levobupivacaine in different peripheral nerve blocks are limited in the People’s Republic of China. In other countries, there are some randomized, double-blind, single-center and multicenter trials comparing ropivacaine with bupivacaine or levobupivacaine in axillary brachial plexus, interscalene brachial plexus, gluteal nerve block, and popliteal sciatic nerve, and anterior tibial/peritoneal nerve blocks for upper and lower limb surgery. Ropivacaine was also compared with levobupivacaine, lidocaine, and a mixture of bupivacaine and lidocaine in bulbar nerve block for eye surgery. A prospective double-blind study compared 0.5% ropivacaine and 0.5% levobupivacaine with 1:200,000 epinephrine for axillary brachial plexus block, and found that the duration of sensory analgesia was significantly longer with levobupivacaine than with ropivacaine, but return of motor activity was faster with ropivacaine. However, another prospective randomized double-blind study showed that 0.5% ropivacaine was associated with longer mean onset time (SD) for sensory block (13.5 [2.9] versus 11.1 [2.6]) and motor block (19.0 [2.7] versus 17.1 [2.6]) compared to 0.5% levobupivacaine for infraclavicular brachial plexus block, but there was no significant difference in terms of effectiveness of analgesia 6 hours postoperatively.

When using continuous peripheral infusion of low concentration of ropivacaine for postoperative analgesia, ropivacaine showed a similar quality of pain relief as provided by bupivacaine or levobupivacaine. However, patients receiving ropivacaine consumed more local anesthetic than patients receiving levobupivacaine. Ropivacaine 0.3% is associated with a significant reduction of morphine consumption and better sleep quality for the first operative night compared with ropivacaine 0.2% for continuous interscalene analgesia.

Local infiltration and intra-articular administration
Local anesthetics have become increasingly popular for management of postoperative pain for their good analgesic effects and simple, safe, and inexpensive properties. The efficacy of local infiltration with ropivacaine for postoperative analgesia was investigated in a large number of trials in Chinese patients undergoing laparoscopic cholecystectomy, open hepatic surgery, gynecological hysteroscopy, and laparoscopy. Pre- or postoperative wound infiltration with ropivacaine was associated with short-term, dose-dependent relief of postoperative pain in patients. The analgesia effect provided by ropivacaine was similar to that achieved with bupivacaine in patients undergoing inguinal hernia repair, while it was much better than that achieved with levobupivacaine in patients undergoing minor breast surgery. Most of the studies about intra-articular administration of ropivacaine involved patients undergoing knee surgery. In a randomized, double-blind study, intra-articular 30 mL ropivacaine 0.75% provided better postoperative analgesia than bupivacaine and placebo. The visual analogue scale scores at rest and during mobilization were lower in patients who received ropivacaine.

Management of labor pain
Lumbar epidural ropivacaine for pain relief during active labor is as established practice in Chinese patients. Across the epidural ropivacaine trials, there were no significant differences between ropivacaine and bupivacaine according to analgesia or motor block, although ropivacaine may be 25% less potent than bupivacaine in achieving analgesia in 50% of women. The volume and concentration were not significant factors influencing the efficacy of a single 30 mg bolus of epidural ropivacaine for labor analgesia. In a large, randomized, double-blind trial, epidural infusion of 0.25% ropivacaine was associated with shorter duration of the first stage of labor compared with 0.25% bupivacaine; however, there was no difference in any other obstetric or neonatal outcome. A recent study supported the conclusion that a bolus of 15 mL of 0.0625% ropivacaine, bupivacaine, or levobupivacaine...
with fentanyl 2 µg/mL epidurally in nulliparous women
confers adequate analgesia, with no significant influence
on mode of delivery, duration of labor, or neonatal out-
come.28 The addition of fentanyl to epidural ropivacaine
was shown to significantly prolong the analgesia duration
and increase patient satisfaction.80

Dosage and administration
In the People’s Republic of China, ropivacaine is available in
0.2%, 0.5%, 0.75%, and 1% solutions in 10 mL ampoules. It
is indicated for surgical anesthesia (epidural adminis-
tration, intrathecal administration, peripheral nerve block, or
cutaneous infiltration); for postoperative pain relief (epidural
administration, peripheral nerve block, or wound instillation);
and for labor analgesia (epidural administration). In children,
it is indicated for epidural administration and peripheral nerve
block for postoperative or acute pain management.

Toxicity and tolerability
Unlike other drugs, local anesthetics are administered in
close proximity to their intended site of action. The systemic
absorption occurs generally slowly, thus extremely rare sys-
temic toxic reactions can occur. However, local anesthetics
have the potential to induce central nervous system (CNS)
and cardiovascular toxicity at high plasma concentration.7 As
a pure left-isomer, ropivacaine has been shown to have less
toxic effects on the CNS and the cardiovascular system.58

As data on toxicity of ropivacaine in humans are lim-
ited, many data are derived from in vitro studies or animal
studies. One in vitro study suggested that half-maximal
neurotoxic concentration of ropivacaine is lower than that
of bupivacaine.81 Intrathecally administered ropivacaine was
also demonstrated in animal studies to be less neurotoxic
than bupivacaine.58,82,83 Ropivacaine decreases the maximum
rate of depolarization and prolongs QRS in isolated heart
study.44 A classic study conducted with volunteers found
that the threshold for CNS toxicity was apparent at a mean
free plasma concentration of approximately 0.6 mg/L for
ropivacaine and 0.3 mg/L for bupivacaine.85 Another study
demonstrated that the majority of cardiovascular and CNS
symptoms occurred at plasma concentration of 1–2 µg/
mL in healthy volunteers.86 Compared to bupivacaine, the
cardiac toxicity, neurological injury after peripheral nerve
block, and unwanted CNS effects may be less common for
ropivacaine.12

Two comprehensive reviews have summarized ropivacaine-
associated side effects.12,87 Ropivacaine produces similar
side effects to those caused by bupivacaine and other local
anesthetics for nerve block.12 The most common adverse
event reported in adult patients following regional or local
anesthesia using ropivacaine is hypotension (30.1%–52.3%),
followed by nausea (11.3%–40.4%), fever (1.1%–20.7%),
and vomiting (5.5%–20%).83 Epidural administration of
ropivacaine for surgery generally produces dose-dependent
adverse events similar to those observed with equal doses
of bupivacaine. A randomized, open-label study found that
doses of 0.75% plain ropivacaine at both 26.25 mg and 33.75
mg have the same efficacy and safety in Chinese patients
undergoing spinal anesthesia.89 The adverse effects during
surgery were shivering (15%), nausea (5%), vomiting (5%),
hypotension (5%), inadequate analgesia (5%), and bradycar-
dia (5%) when 0.75% ropivacaine 26.25 mg was administered
intrathecally.89 The incidence of epidural ropivacaine-induced
cardiovascular symptoms may be age-related: elderly patients
were found to have a higher incidence of bradycardia and
hypotension.90 However, the risk of systemic toxicity is
independent of age.21

The quality of recovery after surgery is becoming a clinical
issue of increasing significance, which is reflected in a change
in focus from hospital-based to patient-based outcomes. A lot
of clinical trials demonstrated that ropivacaine provided
similar patient satisfaction compared to bupivacaine78,91,92
or levobupivacaine,57,93,94 regardless of the route of admin-
istration, although these trials were not primarily designed
to investigate patient satisfaction. However, when compared
to lidocaine, ropivacaine provided significantly higher rates
of maternal satisfaction (84.3% versus 45.1%),95 Patients’
overall satisfaction was 77% and 79% when ropivacaine
was used for anesthesia or analgesia, respectively, with
mean satisfaction scores of 9.6 out of 10 after 24 hours.59
A study conducted to investigate the postoperative quality
of recovery in patients over the age of 65 years demonstrated
that peripheral nerve block with ropivacaine was associated
with better recovery in physiological, emotive (depression
and anxiety), nociceptive (pain and nausea), and modified
cognitive recovery than general anesthesia.96

Conclusion
Ropivacaine is a well-tolerated local anesthetic that is effec-
tive when administered as a peripheral nerve or ocular block,
epidural or spinal block, or by topical application or local
infiltration. In comparative trials, its clinical efficacy is not
generally significantly different from that of bupivacaine
or levobupivacaine, although it may have lower potency at
lower doses. Ropivacaine has provided effective anesthesia
for surgery and effective analgesia for postoperative and
labor pain, and appears to be associated with less motor
block, reduced CNS and cardiovascular toxicity, and higher
satisfaction compared with bupivacaine. Ropivacaine is of
particular importance in clinical use as regional anesthesia
and the management of postoperative and obstetric pain.

Disclosure
The authors report no conflicts of interest in this work.

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