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EDITORIAL

Pharmacokinetics and systemic toxicity of local anesthetics in children

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Introduction

With the development of ultrasound-guided regional anesthetic techniques, peripheral nerve block has become popular and is being performed safely in an increased number of children. From the point of neuronal toxicity and duration of action, long-acting local anesthetics such as bupivacaine, levobupivacaine and ropivacaine are more frequently used than lidocaine for both neuraxial and peripheral nerve block in children. As these anesthetics have higher toxic potency than lidocaine, extensive knowledge of their toxicity and pharmacokinetics in children would contribute to avoiding adverse effects and improving the quality of anesthesia practice.

Systemic toxicity

Local anesthetics exert central nervous system (CNS) and cardiac toxicity by increasing plasma concentrations, with protein unbound fraction playing an important role. Although large inter-individual differences exist in plasma concentrations for inducing systemic toxicity, studies with adult human volunteers revealed that the threshold for CNS toxicity is 2–3 μg/ml of total (protein bound and unbound) and 0.1–0.2 μg/ml of unbound bupivacaine, levobupivacaine and ropivacaine [1, 2]. Notably, the intra-arterial concentration of unbound bupivacaine for inducing CNS toxicity is approximately 50 % of unbound ropivacaine, both of which are three- and four-fold higher, respectively, than the intravenous concentration [1]. Cumulative case reports and animal experiments have also shown that the systemic toxicity of levobupivacaine and ropivacaine is less than bupivacaine [3, 4]. Infants are prone to develop CNS toxicity by bupivacaine at total and unbound concentrations lower than these values [5]. Although the threshold plasma concentration for cardiac toxicity is higher than for CNS, symptoms such as dysrhythmia and QRS widening due to decreased intraventricular conduction by long-acting local anesthetics may appear prior to any neurological manifestations in infants [6]. As neonates and infants have a higher heart rate than adults, the intensity of the block is also higher (use-dependent block) and they are more prone to the toxic effects of bupivacaine, levobupivacaine and ropivacaine than adults. Hypoxia, acidosis, hypothermia and electrolyte disorders increase cardiac toxicity [3].

Protein binding and disposition

Amide local anesthetics are predominantly bound to plasma alpha$_1$-acid glycoprotein (AAG), and to a minor extent to albumin. The plasma concentration of AAG at birth is approximately 20–50 % of that in adults. During the first 6–9 months of life, it progressively increases to reach adult levels by the end of the first year [7] (Fig. 1a). Although the levels of albumin in neonates are also lower than in adults, its affinity to local anesthetics is approximately 5,000–10,000 times lower than AAG, suggesting that albumin

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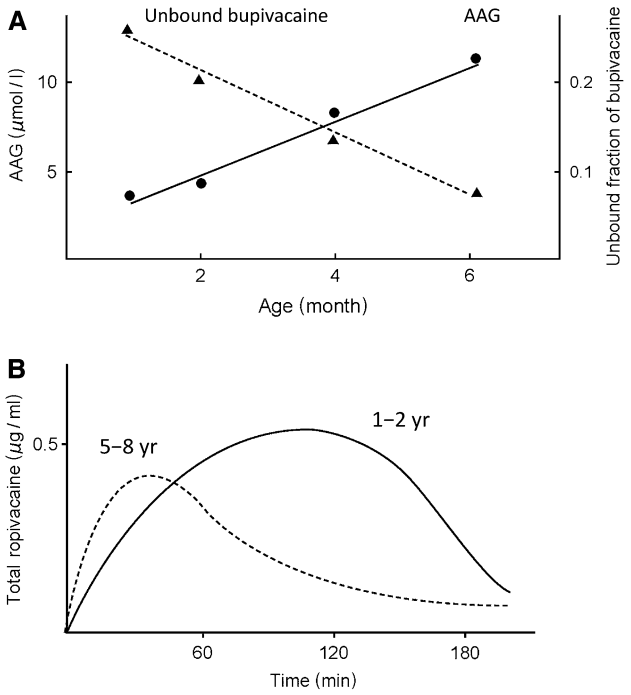

Fig. 1 **a** Plasma concentration of alpha$_1$-acid glycoprotein (AAG, *circle* and *solid line*) and unbound fraction of bupivacaine (*triangle* and *dashed line*) [7]. Plasma concentration of AAG progressively increases and the fraction of unbound bupivacaine gradually decreases during the first year of life. **b** Plasma concentration of total ropivacaine in children aged 1–2 years (*solid line*) and 5–8 years (*dashed line*) following caudal block with 2 mg/kg ropivacaine [18]. Time to maximum concentration is 115 and 30 min; maximum concentration of total ropivacaine is 0.52 and 0.42 μg/ml in children aged 1–2 and 5−8 years, respectively

plays a minor role in protein binding. Because of low AAG levels at birth, the concentration of unbound local anesthetics is higher than in adults and older children. The unbound fraction of lidocaine, bupivacaine and ropivacaine in neonates is approximately 60, 20 and 20 %, respectively [7, 8], and gradually decreases during the first year of life (Fig. 1a). The unbound fraction in children aged >1 year is similar to that in adults, approximately 35 % for lidocaine and 5 % for bupivacaine, levobupivacaine and ropivacaine.

Because AAG is a stress protein, its concentration increases after surgery, resulting in a rapid decrease in the unbound fraction. This is of importance for long-acting local anesthetics including bupivacaine, levobupivacaine and ropivacaine because only the unbound fraction undergoes metabolism and their hepatic extraction ratio (first-pass effect) is relatively low, suggesting that an increase in AAG concentration decreases the clearance of these anesthetics, resulting in an increase in plasma concentration over >24 h.

The total amount of local anesthetics administered for epidural or peripheral nerve block is considered to be absorbed into the systemic circulation [9]. Since they are all lipid-soluble and bind to the tissue into which they are injected, they undergo a delayed absorption process. Bupivacaine and ropivacaine are more strongly bound to the tissue at the injection site and more slowly absorbed into the blood vessels than lidocaine [10], suggesting that their blood concentration increases slowly and their peak plasma concentrations tend to be low. On this basis, repeated epidural administration of lidocaine would result in a rapid increase of plasma concentration, leading to systemic toxicity.

Metabolism and elimination

Bupivacaine is predominantly metabolized to an active metabolite, 2′,6′-pipecoloxylidide by cytochrome P450 (CYP) 3A4 [11]. Ropivacaine is mainly metabolized to hydroxy ropivacaine by CYP1A2 and to a minor extent to 2′,6′-pipecoloxylidide by CYP3A4 [12, 13]. Unlike lidocaine, the hepatic extraction ratio of bupivacaine, levobupivacaine and ropivacaine is relatively low (0.30–0.35) and their elimination is predominantly dependent on hepatic metabolic activity and protein-binding. The content of both CYP 1A2 and 3A4 is low in infants. Although CYP 3A7 is a major isozyme in the fetus that contributes to the biotransformation of bupivacaine, the clearance of both bupivacaine and ropivacaine is lower in younger children compared with elderly children and adults.

Pharmacokinetics of bupivacaine, levobupivacaine and ropivacaine after epidural administration

Caudal block with local anesthetics has been extensively used for laparoscopic minor procedures such as inguinal hernia repair. Kundu et al. [14] recently reported the effectiveness of caudal block using bupivacaine combined with morphine for analgesia after laparoscopic major abdominal surgery in children, suggesting that this technique could be more widely applied. However, avoiding accidental dural puncture and intrathecal injections by proper placement of the needle as well as knowledge of the anatomy of the sacral canal, is required to perform this technique safely [15]. An understanding of the pharmacokinetics of local anesthetics would also be helpful to prevent these adverse effects.

After an epidural injection, the time to peak concentration (t_{max}) of bupivacaine and levobupivacaine is similar among infants, children and adults, i.e., approximately 30 min after injection, although the clearance is lower in infants and young children than in adults. The plasma concentration of bupivacaine is higher in children aged

<4 months than older ones after an epidural bolus 0.5 ml/kg followed by continuous infusion at 0.25 ml/kg/h of 0.25 % bupivacaine, starting 60 min after the bolus, for 3 h and longer (0.67 ± 0.24 vs 0.27 ± 0.11 μg/ml at 3 h and 0.86 ± 0.36 vs 0.34 ± 0.12 μg/ml at 5 h) [16]. The pharmacokinetics of ropivacaine after an epidural injection (3 mg/kg) in children aged between 4 and 12 years is similar to adults, and the maximum concentration (C_{max}) of total ropivacaine is <2 μg/ml, with no adverse effects [17]. On the other hand, the t_{max} of ropivacaine is profoundly longer in younger children than in adults [18]. After an epidural injection of ropivacaine at 2 mg/kg, the t_{max} is 115 and 30 min in children aged 1–2 and 5–8 years, respectively (Fig. 1b) [18]; this would probably result from the vasoconstrictive effect of ropivacaine in the epidural space [19]. Despite this prolonged t_{max}, the C_{max} of ropivacaine in children aged 1–2 years tends to be higher than those aged 5–8 years (0.52 vs 0.42 μg/ml), resulting from low clearance during the first 1–3 years of life.

Pharmacokinetics after other routes of administration

The C_{max} after bilateral rectal sheath block with a total of 1.0 mg/kg 0.25 % bupivacaine is approximately 0.6 μg/ml and the t_{max} is 45 min in children aged between 2 and 16 years [20], similar to those reported in adults [21].

There have been few studies elucidating the pharmacokinetics of local anesthetics after intrathecal injections. Because of the decreased density of vascularities of the pia mater and the spinal cord, the rate of absorption of anesthetics from the subarachnoid space is much slower than after epidural administration [10]. Recently the safety and effectiveness of awake spinal anesthesia in neonates at risk of postoperative apnea has promoted the use of combined spinal and caudal epidural anesthesia for lower abdominal surgery. It should be noted that neonates are at an increased risk of systemic toxicity from long-acting local anesthetics.

According to studies describing the pharmacokinetics of bupivacaine and levobupivacaine in infants aged <55 weeks postconceptual age, the total and unbound concentration was 0.3–0.8 μg/ml and 20–70 ng/ml, respectively, and the t_{max} was 30 min, after an intrathecal injection of 0.2 ml/kg (1 mg/kg) of 0.5 % solution [22, 23]. These results suggest that the plasma concentrations of both bupivacaine and levobupivacaine after spinal anesthesia are below the toxic level. However, the total plasma concentration of bupivacaine exceeded 2.5 μg/ml with unbound fraction >0.25 μg/ml in neonates after a supplemental epidural dose of 1.25 mg/kg of 0.25 % bupivacaine following spinal anesthesia with 1 mg/kg of 0.5 % bupivacaine [24], suggesting the possibility of inducing systemic toxicity after spinal epidural anesthesia.

References

1. Knudsen K, Beckman Suurkula M, Blomberg S, Sjovall J, Edvardsson N. Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers. Br J Anaesth. 1997;78:507–14.
2. Bardsley H, Gristwood R, Baker H, Watson N, Nimmo W. A comparison of the cardiovascular effects of levobupivacaine and rac-bupivacaine following intravenous administration to healthy volunteers. Br J Clin Pharmacol. 1998;46:245–9.
3. Mazoit JX, Dalens BJ. Pharmacokinetics of local anaesthetics in infants and children. Clin Pharmacokinet. 2004;43:17–32.
4. Oda Y, Ikeda Y. Effect of lipid emulsion on the central nervous system and cardiac toxicity of bupivacaine and levobupivacaine in awake rats. J Anesth. 2013;27:500–4.
5. Luz G, Wieser C, Innerhofer P, Frischhut B, Ulmer H, Benzer A. Free and total bupivacaine plasma concentrations after continuous epidural anaesthesia in infants and children. Paediatr Anaesth. 1998;8:473–8.
6. Maxwell LG, Martin LD, Yaster M. Bupivacaine-induced cardiac toxicity in neonates: successful treatment with intravenous phenytoin. Anesthesiology. 1994;80:682–6.
7. Mazoit JX, Denson DD, Samii K. Pharmacokinetics of bupivacaine following caudal anesthesia in infants. Anesthesiology. 1988;68:387–91.
8. Hansen TG, Ilett KF, Reid C, Lim SI, Hackett LP, Bergesio R. Caudal ropivacaine in infants: population pharmacokinetics and plasma concentrations. Anesthesiology. 2001;94:579–84.
9. Burm AG, Vermeulen NP, van Kleef JW, de Boer AG, Spierdijk J, Breimer DD. Pharmacokinetics of lignocaine and bupivacaine in surgical patients following epidural administration. Simultaneous investigation of absorption and disposition kinetics using stable isotopes. Clin Pharmacokinet. 1987;13:191–203.
10. Burm AG. Clinical pharmacokinetics of epidural and spinal anaesthesia. Clin Pharmacokinet. 1989;16:283–311.
11. Gantenbein M, Attolini L, Bruguerolle B, Villard PH, Puyoou F, Durand A, Lacarelle B, Hardwigsen J, Le-Treut YP. Oxidative metabolism of bupivacaine into pipecolylxylidine in humans is mainly catalyzed by CYP3A. Drug Metab Dispos. 2000;28:383–5.
12. Arlander E, Ekstrom G, Alm C, Carrillo JA, Bielenstein M, Bottiger Y, Bertilsson L, Gustafsson LL. Metabolism of ropivacaine in humans is mediated by CYP1A2 and to a minor extent by CYP3A4: an interaction study with fluvoxamine and ketoconazole as in vivo inhibitors. Clin Pharmacol Ther. 1998;64:484–91.
13. Oda Y, Furuichi K, Tanaka K, Hiroi T, Imaoka S, Asada A, Fujimori M, Funae Y. Metabolism of a new local anesthetic, ropivacaine, by human hepatic cytochrome P450. Anesthesiology. 1995;82:214–20.
14. Kundu R, Baidya DK, Arora MK, Maitra S, Darlong V, Goswami D, Mohanaselvi S, Bajpai M. Caudal bupivacaine and morphine provides effective postoperative analgesia but does not prevent hemodynamic response to pneumoperitoneum for major laparoscopic surgeries in children. J Anesth. 2015;29:618–21.
15. Cicekcibasi AE, Borazan H, Arican S, Yilmaz MT, Sakarya ME. Where is the apex of the sacral hiatus for caudal epidural block in the pediatric population? A radio-anatomic study. J Anesth. 2014;28:569–75.
16. Luz G, Innerhofer P, Bachmann B, Frischhut B, Menardi G, Benzer A. Bupivacaine plasma concentrations during continuous epidural anesthesia in infants and children. Anesth Analg. 1996;82:231–4.

17. Bosenberg AT, Thomas J, Lopez T, Huledal G, Jeppsson L, Larsson LE. Plasma concentrations of ropivacaine following a single-shot caudal block of 1, 2 or 3 mg/kg in children. Acta Anaesthesiol Scand. 2001;45:1276–80.
18. Lonnqvist PA, Westrin P, Larsson BA, Olsson GL, Lybeck A, Huledal G, Bielenstein M. Ropivacaine pharmacokinetics after caudal block in 1–8 year old children. Br J Anaesth. 2000;85:506–11.
19. Dahl JB, Simonsen L, Mogensen T, Henriksen JH, Kehlet H. The effect of 0.5 % ropivacaine on epidural blood flow. Acta Anaesthesiol Scand. 1990;34:308–10.
20. Flack SH, Martin LD, Walker BJ, Bosenberg AT, Helmers LD, Goldin AB, Haberkern CM. Ultrasound-guided rectus sheath block or wound infiltration in children: a randomized blinded study of analgesia and bupivacaine absorption. Paediatr Anaesth. 2014;24:968–73.
21. Yasumura R, Kobayashi Y, Ochiai R. A comparison of plasma levobupivacaine concentrations following transversus abdominis plane block and rectus sheath block. Anaesthesia. 2016;71:544–9.
22. Beauvoir C, Rochette A, Desch G, D'Athis F. Spinal anaesthesia in newborns: total and free bupivacaine plasma concentration. Paediatr Anaesth. 1996;6:195–9.
23. Frawley G, Hallett B, Velkov T, Bjorksten A. Pharmacokinetics of levobupivacaine following infant spinal anesthesia. Paediatr Anaesth. 2016;26:575–81.
24. Frawley G, Ragg P, Hack H. Plasma concentrations of bupivacaine after combined spinal epidural anaesthesia in infants and neonates. Paediatr Anaesth. 2000;10:619–25.