Drugs and Clinical Pharmacology of Central Blocks in Infants and Children

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12.1 Drugs and Clinical Pharmacology of Central Blocks in Infants and Children

Even though more than 100 years have passed since the first description of the use of central blocks in children (Bier, 1899, Tyrell-Gray, 1909), there are still new and important things to learn within this particular field of anesthesia. Therefore, to perform safe and effective regional anesthesia in infants and children, a solid knowledge of the age-related pharmacology of both local anesthetics and their adjuncts is an absolute prerequisite. Although not as extensive as in adults, the published literature within the field of clinical pharmacology of local anesthetics and their adjuncts in infants and children is quite substantial at this point in time.

To avoid redundant publications and the repetition of already published material within this field, I have refrained from producing yet another text on this topic. Instead, the current chapter provides a synopsis of the current knowledge and incorporates the reproduction of a review article by Professor Jean-Xavier Mazoit, titled *Local Anesthetics and their Adjuncts*, which was recently published in *Pediatric Anesthesia* (http://onlinelibrary.wiley.com/doi/10.1111/j.1460-9592.2011.03692.x/pdf). This has been made possible by the kind permission of Professor Mazoit, the editor-in-chief Neil Morton, and by Wiley-Blackwell Publishing Ltd. For information on the toxicity aspects, the reader is referred to another review from the same themed issue of *Pediatric Anesthesia* [1] (works cited in paragraph 12.1 have been kept separately in the first group of references listed at the end of the chapter).

Following the publication of the review article reproduced herein, further information and discussion has been published with regard to the use of ketamine as an adjunct in newborns and infants. Thus, in rodent experiments, Walker and colleagues have been able to show that the application of clinically relevant doses of

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intrathecal ketamine in young rodents does result in apoptosis of spinal neurons as previously shown for cortical neurons [2]. This is in sharp contrast to findings from similar studies for morphine and clonidine, both appearing to be associated with a comfortable margin of safety with regard to programmed spinal cord cell death [3,4]. Based on these findings, a recent editorial in the *British Journal of Anaesthesia* questioned the use of ketamine as an adjunct to caudal and epidural blocks in newborns and infants and instead recommended the use of clonidine in a situation when an adjunct drug is deemed necessary in this age group [5].

Therefore, the key points are:

1. Due to the reduced toxicity risk compared to racemic bupivacaine, the regular use of ropivacaine or levobupivacaine is advocated in infants and children (with the exception of intrathecal blockade).
2. There is little evidence for the efficacy of the use of opioids as adjuncts to central blocks in children (with the exception of preservative-free morphine). Within this context, it should also be remembered that opioids, apart from being associated with a risk of respiratory depression, are also associated with a number of less serious but still very distressing side effects (e.g., postoperative nausea and vomiting, pruritus, urinary retention, and interference with gastrointestinal motility) [6].
3. For a single-injection caudal block in children above 1 year of age, the use of ketamine appears the most effective adjunct in prolonging the duration of the block.
4. Clonidine is associated with a good safety profile and can be used as an adjunct drug in all age groups. It can also be used as an adjunct for both central and peripheral nerve blocks [7].
5. The use of adjuncts other than preservative-free solutions of clonidine, ketamine, and morphine must still be seen as experimental and should not be used routinely [8].

When reading the review by Professor Mazoit which follows, the reader should be mindful of a typographical error. With regard to the dosing of the lipid rescue, mL (milliliters) rather than mg (milligrams), should have been used throughout. The initial dose of Intralipid is 2–5 mL/kg^{-1} and can be repeated up to a total of 10 mL/kg^{-1}, rather than 10 mg/kg^{-1}.

12.2 Local Anesthetics and Their Adjuncts: A Review Article by Jean-Xavier Mazoit

Local anesthetics (LA) block propagation of impulses along nerve fibers by inactivation of voltage-gated sodium channels, which initiate action potentials [1]. They act on the cytosolic side of phospholipid membranes. Two main chemical compounds are used, amino esters and amino amides. Amino esters are degraded by pseudocholinesterases in plasma. Aminoamides are metabolized exclusively by the liver. Only amide LAs will be considered in this article.

12.2.1 Pharmacokinetics

Local anesthetics (LAs) are small molecules with molecular weights ranging from 220 to 288 [2]. They contain an aromatic ring, an intermediate chain (amide group), and a hydrophilic residue with a tertiary amine. They are weak bases with pKas between 7.6 (mepivacaine) and 8.1 (bupivacaine and ropivacaine). At a pH of 7.40, 60–85% of the molecules are ionized and diffuse in hydric compartments. LAs are also soluble in lipids and then easily cross cell membranes. Bupivacaine is ten times more liposoluble than lidocaine; ropivacaine is four times as soluble as lidocaine (partition coefficient from XlogP) (Table 12.1). With the exception of lidocaine, all amide LAs possess an asymmetric carbon. Although the physiochemical properties (pKa, distribution coefficient) of the isomers are identical, the enantiomers have different affinities for the biological effectors (channels, receptors, proteins) [3]. Ropivacaine and levobupivacaine are pure S-(–) enantiomers. LAs are marketed as hydrochloride salts in water at pH of 4–5 to prevent them from precipitation [4]. Plain solutions of amide LAs are preservative-free; only epinephrine-containing solutions include metabisulfite.

Table 12.1 Physicochemical properties of local anesthetics

Drug	Molecular weight[a] (Da)	pKa[b]	Partition[c] coefficient	Protein binding (%)	Onset of action	Duration of action	Potency[d]
Amides							
Lidocaine	234	7.8	234	65	Short	1 h 30 min–2 h	1
Prilocaine	220	8.0	126	55	Short	1 h 30 min–2 h	1
Mepivacaine	246	7.7	79	75	Short	1 h 30 min–2 h	1
Bupivacaine[e]	288	8.1	2512	95	Intermediate	3 h–3 h 30 min	4
Ropivacaine	274	8.1	794	96	Intermediate	2 h 30 min–3 h	3.3

[a]Free base.
[b]pKa at 37°C.
[c]Octanol/buffer partition calculated from XlogP.
[d]Potency is relative to lidocaine.
[e]Levobupivacaine has similar physicochemical properties with a slightly lower potency.

12.2.1.1 Binding to Blood Components

Amide LAs distribute in red cells (20–30% depending on the hematocrit) and bind to serum proteins [2,5]. Like most weak bases, amide LAs bind to both a1-acid glycoprotein (AGP) and to human serum albumin (HSA). The stereospecificity of this binding is insignificant, at least on a clinical point of view [6]. Despite its low concentration in serum (< 1 g/L^{-1} in adults), AGP is the major protein that binds LAs. AGP concentration is very low at birth and progressively increases during the first year of life [5,7]. It is why neonates and young infants have a much higher free fraction of LAs than adults. AGP is an acute phase protein, and its concentration increases rapidly in inflammatory states like in the postoperative period [7]. LAs also bind to HSA, but with a very low affinity. It is only because HSA is the most abundant protein in serum that its binding capacity is significant.

12.2.1.2 Absorption

After applying topical anesthesia to the upper airway, LAs are rapidly absorbed. This may induce toxicity, particularly in young children. This is why it is important to use nozzles that deliver no more than 10 mg with each squeeze [8]. The EMLA (Eutectic Mixture of Local Anesthetics) cream is absorbed in significant amounts in premature babies and neonates [9]. The cream contains prilocaine, which produces methemoglobinemia in neonates and infants, especially if they are also treated with trimethoprim-sulfamethoxazole [10]. The efficacy of the cream has been questioned in premature babies because of a high skin blood flow [9].

After injection, amide LAs have a bioavailability of one (metabolism is exclusively hepatic) [11]. They bind to tissues, which delays their absorption. This delay varies depending on the site of injection. In adults, 3 h after an epidural injection, only 70% of a dose of lidocaine and 50% of a dose of bupivacaine or of ropivacaine are absorbed, which are safety factors [11]. From adult studies, it is clear that the speed of drug absorption decreases from head to foot and from the thoracic to the caudal portion of the epidural space. Lidocaine and bupivacaine concentrations peak about 30 min after caudal or lumbar injection in infants and adults [5,12–17]. The Tmax for ropivacaine is much longer in infants than in children [18,19] and possibly in children than in adults [18–26]. CYP1A2, which metabolizes lidocaine and ropivacaine, is immature before 4–7 years of age [27].

Levobupivacaine is principally metabolized by the CYP3A4/7, which has full enzymatic capacity by the age of 1 year [28].

12.2.1.3 Distribution

The volume of distribution of LAs at steady state (V_{ss}) is slightly < 1 L/kg^{-1} (Table 12.2) [5,11–26]. Because of delayed drug absorption leading to the 'flip-flop' effect,[1] terminal half-lives and volumes calculated after non-intravenous (i.v.) routes of administration are markedly overestimated [11,20,29–31]. Only total body clearance of the drug is measured accurately following extravascular administration (but sampling must take place over a prolonged period of time). It is highly probable that LAs distribute in a larger volume in neonates and in infants than in adults, thus preventing high serum drug concentrations from occurring after a single injection, but not following several injections. The volume of distribution of ropivacaine is smaller than that of bupivacaine in adults and probably in pediatric patients [2].

12.2.1.4 Elimination

All amide LAs are metabolized by the liver cytochrome P450 enzymes. Bupivacaine is predominantly metabolized into pipecoloxylidide (PPX) by CYP3A4/7 [28]. Ropivacaine is predominantly metabolized to 3'- and 4'-OH-ropivacaine by CYP1A2

[1] Because compartmental pharmacokinetics are based on the assumption of linearity, concentration is described by a sum of exponentials with the assumption that absorption is faster than distribution and distribution is faster than elimination. If absorption is longer than elimination, it is not possible to distinguish between the phases. In other words, if absorption continues during elimination, the terminal phase appears falsely prolonged.

Table 12.2 Bupivacaine, levobupivacaine, and ropivacaine pharmacokinetics after different routes in infants and children compared with adults

	Free fraction	V_{ss}[a] (L/kg^{-1})	CLT/f ($mL/min^{-1}/kg^{-1}$)	CLU/f ($mL/min^{1}/kg^{-1}$)	T1/2[a] (h)
Bupivacaine					
i.v. adults	0.05	0.85–1.3	4.5–8.1	100	1.8
Epidural adults			4–5.6		5.1–10.6
Infants caudal single shot children	0.16 (0.05–0.35)	3.9	7.1		
(5–10 years)		2.7	10		
Infants epidural	(0.06–0.24)[b]		5.5–7.5[b]	36–73	
prolonged	(0.03–0.18)[c]		3.5–4[c]	36–73	
Levobupivacaine					
i.v. adults	0.045	0.72	4.2	116	2.6
Caudal, infants 0.6–2.9 months	0.13	2.87	6.28	51.7	
Ropivacaine					
i.v. adults	0.05	0.5–0.6	4.2–5.3	100	1.7
Epidural adults			4.0–5.7	70	2.9–5.4
Caudal single shot					
Neonates	0.07			50–58	
Infants	0.05–0.10	2.1	5.2		
Children	5.2 (1.3–7.3)	2.4	7.4	151	
Epidural prolonged					
Neonates		2.4	4.26		
Infants		2.4	6.15		
Children	0.04		8.5	220	

Vss, volume of distribution at steady state, *CLU/f*, total body clearance over bioavailability (*T*, total fraction; *U*, unbound fraction), *T1/2*, terminal half-life.

For adults, a mean body weight (BW) of 75 kg has been assumed. Injections are overestimated because of a flip-flop effect (i.e., because absorption last longer than elimination).

[a]Apparent value, T1/2 and volumes measured after non-i.v.

[b]After 3-h infusion.

[c]After 48-h infusion, CLT decreases with time because protein binding increases.

and to a minor extent to PPX by CYP3A4 [27]. These enzymes are not fully mature at birth and have important differences in their developmental expression. Contrary to lidocaine, bupivacaine and ropivacaine have a relatively low hepatic extraction ratio (0.30–0.35) and are considered rate limited for their elimination. Thus, the intrinsic hepatic clearance and the free fraction are the major determinants of total clearance. After surgery, serum AGP concentrations increase, which increases protein binding. A parallel decrease in total clearance is observed [7]. However, this only leads to a resetting in total serum concentration, and the unbound concentration remains constant. Bupivacaine clearance is low at birth and increases slightly during the first 6–9 months of life (Fig. 12.1). Ropivacaine clearance, which

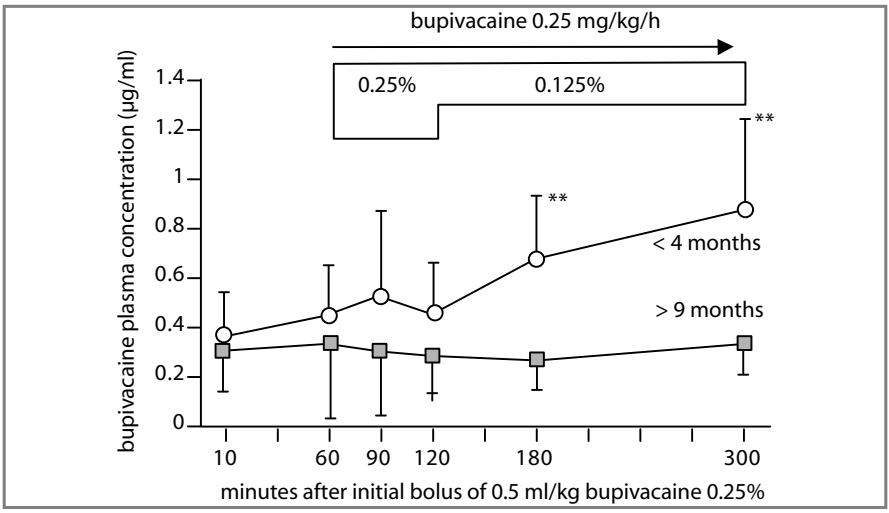

Fig. 12.1 Bupivacaine plasma concentrations measured in two groups of infants receiving continuous bupivacaine infusion by the caudal route for postoperative analgesia. Dosing was calculated to maintain steady concentrations in the older patients (> 9 months old). The bupivacaine concentrations increased with infusion time in the younger infants (< 4 months old), thus demonstrating that clear¬ance was markedly lower in the younger patients. Reproduced from Luz G, Innerhofer I, Bachmann B et al. Bupivacaine plasma concentrations during continuous epidural anesthesia in infants and children. Anesth Analg 1996; 82: 231–234. February 1, Lippincott Williams & Wilkins [78]

is also low in neonates and infants, increases during the first 2–6 years of life [19]. This is likely the cause of the delayed ropivacaine Cmax observed in the younger patients after caudal injection.

Concentrations leading to toxicity are largely unknown. In adult volunteers, the threshold of toxicity is about 0.2–0.3 mg/L^{-1} of unbound bupivacaine and 0.4–0.6 mg/L^{-1} of unbound ropivacaine or levobupivacaine [32–35]. Neonates and infants seem to be more prone to develop toxicity [36,37] because of a higher serum free fraction, a lower clearance, and an increased susceptibility to cardiac toxicity. During prolonged administration of LAs for postoperative pain relief, it is assumed that the intrinsic unbound clearance is unaffected during the whole period of administration and the unbound concentration reaches a steady level 12–18 h after the initiation of infusion. Because of the inflammatory process leading to increased serum binding capacity, the plasma concentrations of total (levo) bupivacaine and ropivacaine tend to increase postoperatively during more than 2–4 days.

12.2.2 Pharmacodynamics

Local anesthetics block the propagation of impulses along nerve fibers because of the inactivation of voltage-gated sodium channels. LAs cross membranes as

free bases (unionized). Inside the cells, they become ionized and bind to specific amino acids within the channel pore, thus mechanically blocking the pore [1]. LAs also block potassium and calcium channels at slightly higher drug concentrations than those needed to block sodium channels [38,39]. Voltage-gated potassium channels initiate repolarization in the nerve. In the myocardium, some of these channels [including the human ether-à-go-go related gene (hERG) channel] are responsible for genetically induced arrhythmias, such as the long-QT, short-QT, or Brugada syndromes. These channels are blocked by LA concentrations just slightly higher than those needed to block sodium channels [38,39]. Unlike the central nervous system (CNS) and heart, peripheral nerves only express a small number of potassium channels. Both sodium and potassium channel blockades are stereospecific [38–40]. The S enantiomers induce less block than R enantiomers. LAs bind to the myocardial ryanodine receptor and L-type calcium channels [41,42], but it is unclear if blockade of these channels affect the cardiotoxicity of long-lasting LAs.

Nerve fibers are either myelinated or unmyelinated. After initial depolarization, the sodium channels become unreceptive to stimulation (refractory period), which prevents backward propagation of impulses. The action potential of unmyelinated fibers propagates continuously.

Myelin insulates myelinated fibers, and this layer is interrupted regularly by the nodes of Ranvier. The sudden depolarization of the node induces an electrical field, which extends to 2–3 nodes. Action potentials "jump" rapidly from one node to the next. Because the distance between nodes is greater in heavily myelinated fibers (there are 3–4 nodes per cm in Aa fibers and 20–30 nodes per cm in Ad fibers), the conduction velocity is faster in motor than in small sensory fibers and faster in small sensory fibers than in high threshold fibers that conduct pain signals [43]. Small unmyelinated or lightly myelinated fibers–the fibers that conduct pain signals–are blocked by lower concentrations of drug and during a longer period of time than heavily myelinated fibers. Myelinization begins during the third trimester of pregnancy and is incomplete at birth. After birth, myelinization increases rapidly and is almost complete by 3–4 years of age [44,45]. In rats, the nodes of Ranvier are fully mature at 2–3 weeks of age. Interestingly, the internode distance is similar between 2-week-old and adult rats. This may explain why infants and young children need larger volumes per kg of LAs than older children or adults (Fig. 12.2) [46].

Fortunately, the concentration of LA needed to cause the block is lower. Surprisingly, infants require larger doses of LAs for spinal anesthesia, and the duration of the spinal block is shorter. Some authors have attributed this difference to larger volumes and a more rapid turnover of cerebrospinal fluid (CSF) in neonates and infants than in older children and adults. However, MRI studies have shown that the CSF volume and CSF turnover are lower in neonates and infants than in children and adults [47,48]. The major factor responsible for this short effect seems to depend on the number of nodes of Ranvier blocked because the distance between nodes is fixed soon after birth [44,45].

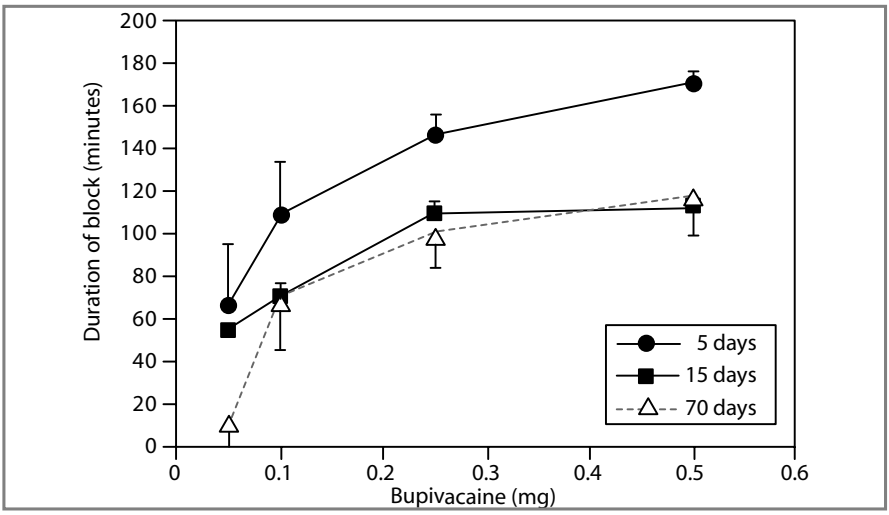

Fig. 12.2 Duration of sciatic nerve motor block in infant rats according to the dose of bupivacaine used. Rats aged 5 days had a prolonged block as compared to the other two groups. Two-week¬-old rats had a similar duration of block as compared to 10-week-old rats despite an 8–10 times difference in body weight: The same dose gave the same duration of block likely because the internode distance is fixed after the age of 1–2 weeks [drawn from the data of Kohane DS, Sankar WN, Shubina M et al. Sciatic nerve blockade in infant, adolescent, and adult rats: a comparison of ropivacaine with bupivacaine. Anesthesiology 1998; 89: 1199–1208. November, Lippincott Williams & Wilkins [46]

12.2.2.1 Effects on the Central Nervous System and Cardiovascular System

Like all inhibitors of sodium channels, LAs possess anticonvulsive effects at low dosage, which is why lidocaine is still used to treat intractable epilepsy in neonates and infants [49]. At higher doses, LAs induce convulsions and coma. However, the therapeutic ratio is low. In similar concentrations to those that cause convulsions, long-lasting LAs can induce cardiac arrhythmias. With the exception of nodal conduction, which depends on calcium channels, conduction in the heart depends on sodium channels. LAs prolong the refractory period, but the balance between the increase in effective refractory period and the decrease in the ventricular conduction velocity does not favor LAs. Long-lasting LAs, like bupivacaine, profoundly decrease ventricular conduction velocity [50–52]. This phenomenon is markedly amplified by tachycardia–it is the phasic block. Because neonates and infants have higher heart rates than adults, they are likely more sensitive to LA-induced blocks than adults. LAs also impair myocardial contractility but without any stereospecificity [52]. The S enantiomers (ropivacaine and levobupivacaine) have mild vasoconstrictive properties.

12.2.2.2 Stereospecificity

Mepivacaine, prilocaine, bupivacaine, and ropivacaine have an asymmetric carbon. Protein binding, pharmacokinetics, and nerve blocks have little stereoselectivity,

which is why levobupivacaine has almost the same blocking properties as its racemic counterpart. In the heart, the effect on cardiac conduction is stereospecific (ropivacaine and levobupivacaine induce much less block than their corresponding R (+) enantiomer or the racemic mixture), whereas contractility is unaffected by stereoselectivity [51,52].

LAs have anti-inflammatory properties and inhibit platelet aggregation [53], decrease leukocyte priming and the production of free radicals [54–56]. Systemically administered lidocaine has antinociceptive effects, particularly on neuropathic pain [57]. Consequently, LAs are now used preoperatively to prevent postoperative hyperalgesia in adults [58]. Interestingly, LAs can prevent and even treat complex regional pain syndrome in adults and children by limiting the neuropathic inflammatory processes [59,60].

12.2.2.3 Toxicity of Local Anesthetics

At the site of injection, the minimum concentration required to produce a nerve blockade is 300–1500 μM for lidocaine and 100–500 μM for bupivacaine [61]. These concentrations (in the millimolar range) impair mitochondrial function and may be responsible for the observed nerve and muscle toxicity. Care should be taken when regional anesthesia is provided for eye surgery in adults, for children with myopathies (bupivacaine is an *in vitro* model of Duchene's myopathy), and perhaps for children with mitochondrial cytopathy [62,63]. With that respect, the site of injection for central blocks is far from any muscle.

After both local and regional anesthesia, neurological or cardiac toxicity related to excessive blood concentration may occur [64,65]. Because of their low protein binding and intrinsic clearance, infants are more prone to LA toxicity than adults. General anesthesia may conceal the early signs of LA toxicity in children. In addition to pharmacokinetic factors, the rapid heart rate of children may increase the risk of cardiac toxicity induced by LA toxicity. Ropivacaine and levobupivacaine [S-())-enantiomers] are less toxic than racemic bupivacaine [32–35]. Even if toxic events occur with ropivacaine, small doses of epinephrine should produce rapid recovery. Impaired ventricular conduction is the primary manifestation of LA toxicity. QRS widening, bradycardia, and torsades de pointe are followed by either ventricular fibrillation and/or asystole [65]. The slight decrease in myocardial contractility caused by LAs is usually not a major problem. Treatment includes oxygenation, cardiac massage, and epinephrine, which is given in small incremental boluses beginning with 1–2 $\mu g/kg^{-1}$ [66]. If ventricular fibrillation persists, defibrillation (2–4 J/kg^{-1}) is performed. Although resuscitation measures must be initiated immediately, the specific treatment of LA toxicity is rapid administration of Intralipid (Kabivitrum Inc., Stockholm, Sweden). Numerous case reports have shown that rapid bolus injections of a lipid emulsion reverse the toxic effects of LAs [66–69]. Because 1 mole of Intralipid (Kabivitrum Inc.) binds > 3000 times more molecules of bupivacaine than a mole of buffer, the volume of distribution suddenly increases [70]. The recommended dose of 20% Intralipid (Kabivitrum Inc.) for pediatric patients is 2–5 mL/kg^{-1} by i.v. bolus. If cardiac function does not return, this dose (up to 10 mg/kg^{-1}) is

repeated. The lipid emulsion decreases LA elimination; thus, the cardiac effects may recur later.

12.2.2.4 Adjuvants

Adjuvants are often used to prolong the duration of analgesia.

Adrenaline (5 μg/mL^{-1} = 1/200,000) decreases bupivacaine Cmax, without affecting the time to peak concentration. In < 6-month-old infants, 2.5 μg/mL^{-1} 1/400,000 epinephrine has been recommended [71]. However, the drug is less efficacious with long-acting S-())- enantiomers and has limited use with these solutions. Plain solutions of LAs must be used for penile, interdigital, and eye blocks. Adrenaline also slightly increases the duration of postoperative analgesia after caudal anesthesia. Clonidine 1–2 μg/kg^{-1}, either i.v. or in the epidural space, prolongs the duration of caudal blocks [72]. Clonidine also enhances the efficacy of dilute long-acting agents (e.g., 0.1% ropivacaine). More than 2 g/kg^{-1} may lead to hypotension.

Clonidine is not recommended for infants < 3 months of age because it can cause apnea in this age group. It has been shown that clonidine injected i.v. has a similar effect than when epidurally injected [73].

Ketamine is also used as an adjuvant for epidural block [74]. The pure preservative-free S(+) ketamine is preferable because it is less toxic for the nervous structures than the racemic mixture. However, some authors recommend avoiding the use of ketamine because of its potential toxicity [75,76]. The usual dose injected caudally is 1 and 0.5 mg/kg^{-1} for the S(+) and racemic ketamine, respectively.

Opioids are often used as adjuvants for epidural block. After 6–9 months of age, adding opioids to LAs prolongs epidural analgesia for up to 24 h. Hydrophobic agents (fentanyl, sufentanil) must be placed at the metameric level where the pain will occur [77]. Preservative-free morphine easily spreads rostrally and can be placed at a lower metameric level. The bolus dose of morphine is 25–30 μg/kg^{-1} in the epidural space, which is followed by a continuous infusion of 1 μg/kg^{-1}/h^{-1}. When continuous epidural administration of fentanyl or sufentanil is combined with LAs, the doses are 0.2 and 0.1 μg/kg^{-1}/h^{-1}, respectively. Morphine 5–10 μg/kg^{-1} can be used as the sole agent for spinal analgesia during general anesthesia. In case of urinary retention, naloxone 1 μg/kg^{-1} or nalbuphine 0.1 mg/kg^{-1} can be injected as an i.v bolus. An i.v. bolus of naloxone 1–2 μg/kg^{-1} followed by a continuous infusion of 1–2 μg/kg^{-1}/h^{-1} is usually efficacious in case of pruritus.

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