# Pediatric Pharmacological Considerations

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Derek Dillane

## Contents



D. Dillane, MB BCh BAO, MMedSci, FCARCSI
Department of Anesthesiology and Pain Medicine,
University of Alberta, 2-150 Clinical Sciences Building,
Edmonton, AB, Canada
e-mail: dillane@ualberta.ca



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## 7.1 Introduction

The first amino-amide local anesthetic was developed by Swedish chemists Löfgren and Lundquist in 1943, and this xylidine derivative, which they called lidocaine, was first marketed in 1948 [1]. Lidocaine has been in clinical use for almost 60 years, is the most widely used local anesthetic worldwide, and remains one of the safest and most efficacious local anesthetic agents ever manufactured. One of its main drawbacks, however, is a short duration of action. The longer acting amino-amide, bupivacaine, was synthesized by Bo af Ekenstam in 1957 and introduced into clinical practice 10 years later [2]. It would take a further 10 years of clinical use before serious cardiac toxicity was reported, and this important safety issue led to the continuing search for a long-acting and safe agent. In the 1980s, the development of new, long-acting amides took advantage of the fact that most of these molecules have a chiral center. These three-dimensional stereoisomers have an identical chemical composition but differ in spatial orientation [3]. This led to the development of the single stereoisomers levobupivacaine and ropivacaine, first approved for clinical use in 1996.

## 7.2 Structure and Physiochemical Properties

All local anesthetics are weak bases. They have a molecular weight ranging from 220 to 288 Da [4]. Their formula consists of a lipophilic aromatic ring connected to a hydrophilic residue by a hydrocarbon chain. They are clinically classified as amino-esters or amino-amides depending on the link between the lipophilic ring and the hydrophilic tertiary amine (Fig. 7.1). Amino-ester local anesthetics are hydrolyzed in the plasma by cholinesterases, whereas the amides are metabolized in the liver by the cytochrome P450 enzyme system. The amino-amide group is most commonly used for pediatric regional anesthesia and, as such, will be the focus of this chapter.

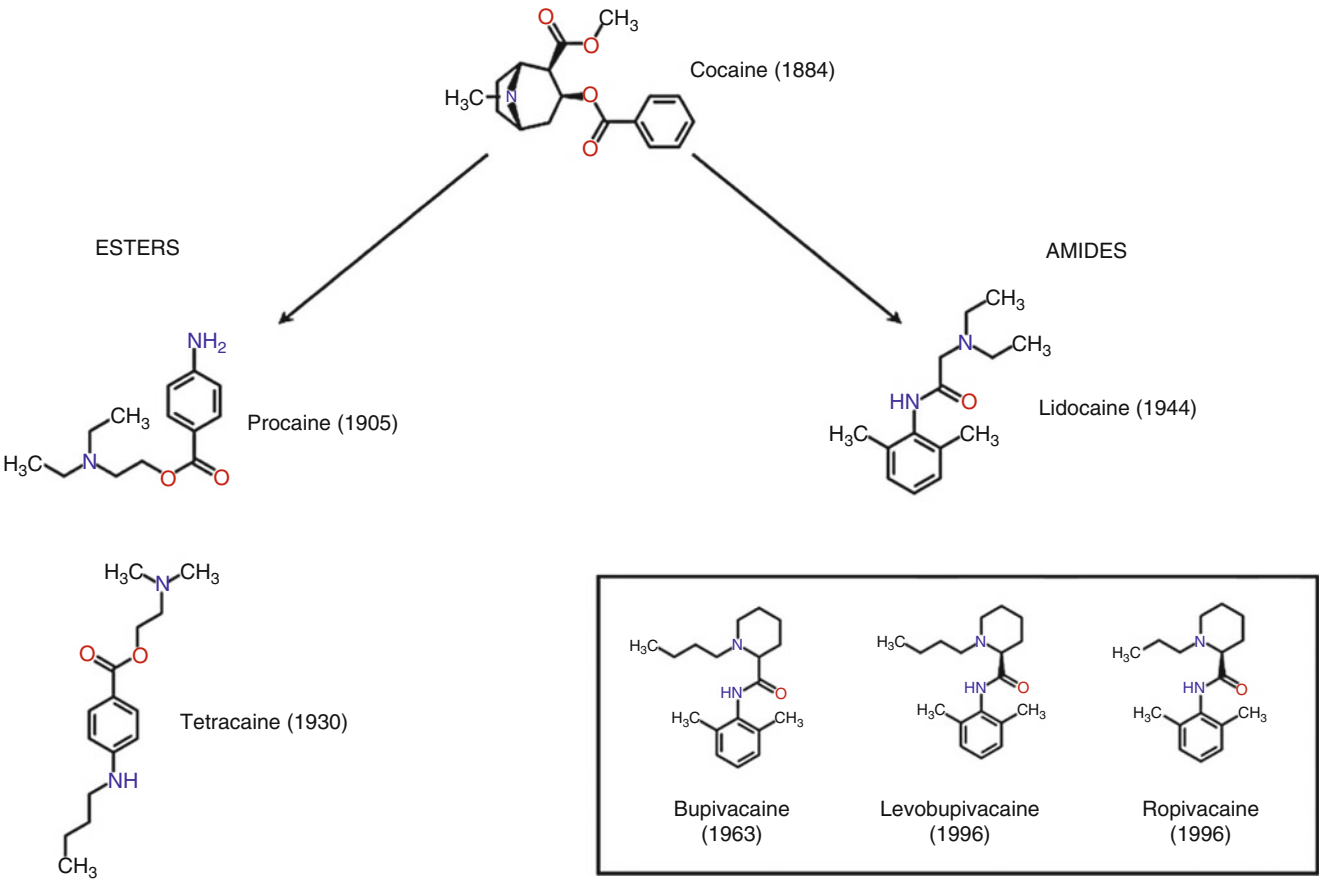


**Fig. 7.1** Derivation of ester- and amide-class local anesthetics from cocaine. Shown are chemical structures and years in which each drug was first used

### 7.2.1 Onset of Action, Potency, and Duration

Being weak bases, local anesthetics exist in solution as both ionized (water soluble) and non-ionized (lipid soluble) molecules. Local anesthetics traverse phospholipid membranes in their non-ionized form. The degree of drug ionization is determined by the dissociation constant (pKa) and the pH of the surrounding fluid. The pKa of a molecule represents the pH at which 50 % of the molecules exist in a lipid-soluble form and 50 % in a water-soluble form. Local anesthetic molecules with a pKa that approaches physiologic pH have a higher concentration of the non-ionized lipid-soluble form. As the pKa of a drug increases, a greater proportion exists in the ionized hydrophilic form at physiological pH. Commonly used local anesthetics have a pKa between 7.8 (lidocaine) and 8.1 (ropivacaine and bupivacaine) (Table 7.1). Drugs with a lower pKa (e.g., lidocaine) exist to a greater degree in a non-ionized form and diffuse more easily across cell membranes. This explains why lidocaine has a faster *onset of action* than ropivacaine or bupivacaine. Moderately lipophilic drugs are most effective clinically due to the drug having to cross several membranes to reach its target site. At physiological pH, a significant fraction of the drug is in a non-ionized form and readily crosses the membrane to the cytosolic side of the nerve cell. Excessively lipophilic drugs remain in the first membrane encountered [6]. For the drug to effectively block the sodium channel, it must become re-ionized on the cytosolic side of the membrane.

*Potency* is directly related to lipid solubility which is expressed as lipid/water partition coefficient. Drugs with low lipid solubility need higher concentrations to produce a block of similar intensity to that produced by local anesthetics with higher lipid solubility (e.g., 2 % lidocaine (partition coefficient 43) vs. 0.5 % bupivacaine (partition coefficient 346)). *Duration of action* is largely determined by the degree of plasma protein binding.

**Table 7.1** Comparative physicochemical properties of local anesthetics

| Agent | Potency | pKa | Molecular weight (Da) | Toxic plasma concentration (μg/mL) | % protein binding |
|---|---|---|---|---|---|
| Lidocaine | 1 | 7.8 | 234 | >5 | 70 |
| Prilocaine | 1 | 7.8 | 220 | >5 | 55 |
| Mepivacaine | 1 | 7.6 | 246 | >5 | 77 |
| Bupivacaine | 4 | 8.1 | 288 | >3 | 95 |
| Levobupivacaine | 4 | 8.1 | 288 | | >97 |
| Ropivacaine | 4 | 8.1 | 274 | >4 | 94 |

| Agent | % ionized at pH 7.4 | Partition coefficient with h-octanol/buffer | Volume of distribution (L) | Clearance (L/min) |
|---|---|---|---|---|
| Lidocaine | 25 | 43 | 91 | 0.95 |
| Prilocaine | 24 | 25 | 191 | |
| Mepivacaine | 39 | 21 | 84 | 9.78 |
| Bupivacaine | 17 | 346 | 73 | 0.47 |
| Levobupivacaine | 17 | 346 | 55 | |
| Ropivacaine | 17 | 115 | 59 | 0.44 |

### 7.2.2 Sodium Channel

Voltage-dependent $Na^+$ channels in nerves contribute to the control of membrane excitability and are responsible for action potential generation. When the cell membrane is depolarized by a few millivolts, sodium channels activate and inactivate within milliseconds (Fig. 7.2). Influx of sodium ions through the channel depolarizes the membrane further and initiates the action potential. Local anesthetics prevent neural excitation and subsequent propagation of action potential by inhibiting passage of $Na^+$ ions through these channels. The drug may access the $Na^+$ channel through the hydrophilic inner pore or traverse the hydrophobic cell membrane when the channel is closed [7]. The local anesthetic must be re-ionized to prevent passage of $Na^+$ ions. An equilibrium exists between the ionized and unionized forms in the $Na^+$ channel.

The voltage-gated sodium channel is a large, multimeric complex comprised of an α subunit and one or more smaller β subunits. The α subunit contains all the features necessary for a functional ion channel including voltage sensor, activation/inactivation gates, and ion pore. The β subunits play a role in membrane localization of the channel as well as modulation of channel gating [8]. $Na^+$ channels exist in a closed, open, and inactivated state [7]. Local anesthetics bind more tightly to the $Na^+$ channel during the open and inactivated state than the closed state. In effect, this means that they show high affinity for their site of action during high-frequency action potentials, such as those that occur during sensory transmission or motor activity [9]. This is a phenomenon known as frequency-dependent or use-dependent blockade.

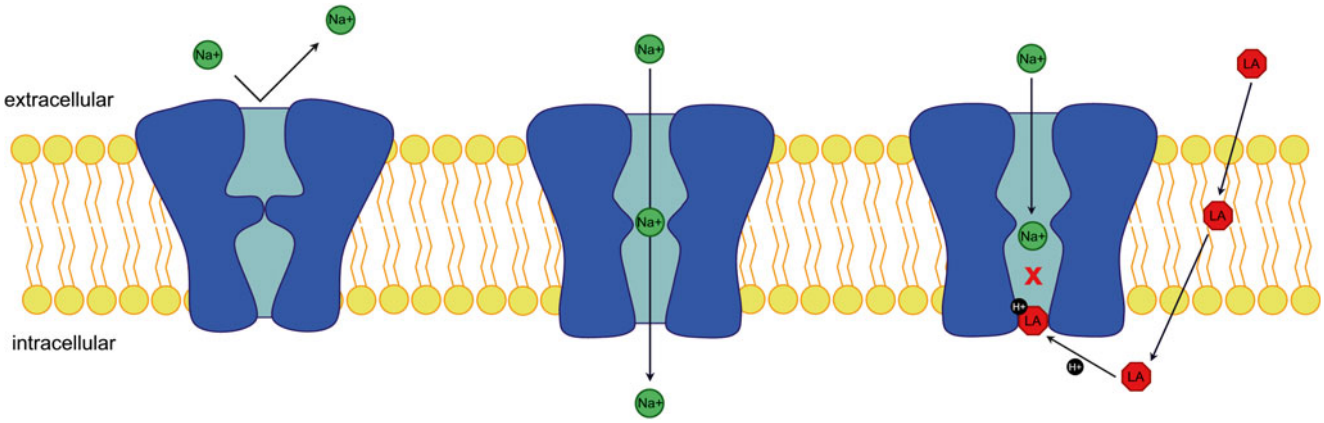


**Fig. 7.2** Schematic diagram of a sodium channel in a neuron cell membrane. *Left*, the deactivated form is impermeable to sodium ions; *middle*, the activated form allows sodium ions to flow into the cell; *right*, the channel is blocked by local anesthetic. Local anesthetics traverse the phospholipid membrane in their non-ionized form. Drugs with a low pKa (e.g., lidocaine) exist to a greater degree in a non-ionized form and more readily cross the cell membrane. The drug must become re-ionized in the intracellular environment to effectively block the sodium channel

### 7.2.3 Physiological Considerations

The diameter and degree of myelination of a nerve fiber determines the nature of impulse conduction and the effectiveness of local anesthetic drugs. There are three major anatomical categories: myelinated somatic nerves (A fibers), myelinated preganglionic autonomic nerves (B fibers), and unmyelinated axons (C fibers). The A fibers are subdivided into four groups according to decreasing speed of impulse conduction and diameter (Table 7.2). The thinnest A fibers, the Aδ group, are responsible for pain and cold temperature transmission. Aγ fibers are responsible for muscle tone. C fibers are thinner than myelinated axons, have a much lower conduction velocity, and are also responsible for the transmission of pain signals. Aδ fibers are responsible for fast pain transmission, whereas C fibers are responsible for second or slow pain transmission [6]. Differential nerve blockade has been demonstrated in animal studies after administration of local anesthetic (i.e., fibers of smaller diameter are blocked before those of larger size with recovery from blockade occurring in the reverse order) [10]. Clinically, it is more likely that the action of local anesthetic on nerve fibers is multifactorial (e.g., peripheral versus core nerve fiber, state of activation of the nerve, length of nerve exposed to local anesthetic, and degree of myelination in addition to nerve diameter).

Myelination is not complete before the age of 12 years. The relative absence of a myelin sheath coupled with the smaller nerve fiber diameter may explain why infants and children are subject to prolonged motor blocks with local anesthetic solutions of lower concentration [4]. In addition, the endoneurium of developing nerves is loose and easily penetrated by local anesthetic molecules in both directions. This may account for both the shorter onset and shorter duration of effect of local anesthetic action in younger age groups. Beyond infancy, the endoneurium contains more connective tissue, making it more difficult for the local anesthetic to traverse [9].

**Table 7.2** Classification and properties of peripheral nerve fibers

| Nerve class | Aα | Aβ | Aγ | Aδ | B | C |
|---|---|---|---|---|---|---|
| Function | Motor | Pressure/touch | Proprioception/motor tone | Pain/temperature | Preganglionic autonomic | Pain/temperature |
| Diameter (μm) | 12–20 | 5–12 | 1–4 | 1–4 | 1–3 | 0.5–1 |
| Conduction speed (m/s) | 70–120 | 30–70 | 10–30 | 12–30 | 10–15 | 0.5–1.2 |
| Local anesthetic sensitivity (+++ most susceptible) | ++ | ++ | +++ | +++ | +++ | + |

## 7.3 Pharmacokinetics

Pharmacologists and anesthesiologists share a common interest in pharmacokinetics, but rather than being concerned with volumes of distribution and total body clearance, the pediatric anesthesiologist wants to know how much local anesthetic can be safely administered to produce an effective nerve block in a timely fashion. However, these empirical and abstract concepts are not mutually exclusive.

Unlike other therapeutic agents administered to infants and children, local anesthetics can be delivered directly to their site of action. Traditionally, a large volume and high concentration of local anesthetic has been injected to ensure adequate anesthesia and analgesia. This was, in part, due to the relatively small number of local anesthetic molecules thought to reach the target nerves. The nerve sheath or perineurium is a very effective diffusion barrier. A large fraction of the delivered agent is absorbed by the surrounding tissue or is removed by the systemic circulation. Direct measurement in an animal model demonstrates that <2–3 % of an injected dose enters the target nerve. In addition, more than 90 % of an injected dose is taken up by the systemic circulation within 30 min of injection [11]. Ultrasound guidance may allow for more accurate deposition, necessitating a smaller volume and dose of local anesthetic.

Neonates and infants present significant pharmacokinetic peculiarities possibly leading to an increased risk of toxicity. Immature hepatic metabolism and marked differences in serum protein binding serve to increase serum concentrations of unbound amide local anesthetic.

### 7.3.1 Absorption

Regional anesthesia in the pediatric population involves the injection of a relatively large volume of a concentrated local anesthetic solution into a compact anatomical space. The rate of absorption into the bloodstream is a major determinant of systemic toxicity. This has been studied predominantly for epidural/caudal anesthesia. Explicit detail on the kinetics of other routes of administration is lacking for this population. What is evident, though, for both central and peripheral blocks, is the more rapid rate of absorption from the cephalic parts of the body [4]; for example, a cervical epidural leads to higher plasma levels of local anesthetic than a caudal epidural. Similarly, absorption decreases from head to foot for peripheral conduction and infiltration blocks due to the relative difference in vascularity between these areas.

### 7.3.2 Absorption from Epidural Space

The main component of the epidural space is fat, which is an important determinant of local anesthetic systemic uptake. More lipophilic local anesthetic molecules will be retained to a greater degree by epidural fat leading to subsequent delayed absorption. It has been demonstrated in adults that after a single-shot epidural injection, 30 % of a dose of lidocaine and 50 % of a dose of bupivacaine remained in the epidural space for 3 h after injection [12]. The time to maximum peak plasma concentration ($T_{max}$) in infants for lidocaine and bupivacaine is 30 min after caudal or lumbar epidural injection [13]. Ropivacaine $T_{max}$ is longer in infants than in children and longer in children compared to adults. In children aged 1–2 years, ropivacaine $T_{max}$ is 115 min, whereas in children aged 5–8 years, ropivacaine $T_{max}$ is closer to the adult value of 30 [14]. The vasoconstrictive properties of ropivacaine may contribute to its prolonged absorption from the epidural space. After $T_{max}$ has been achieved, the rate of absorption slows down significantly so that it becomes longer than that of elimination, leading to a flip-flop effect in plasma drug concentration [4]. This continuous, protracted systemic absorption during the elimination phase, in combination with the buffering effect of plasma protein binding, limits the plasma concentration of unbound drug and is protective against toxicity.

### 7.3.3 Absorption from Other Routes of Administration

Absorption rates at different block sites are directly related to local blood flow and inversely related to local tissue binding [15]. As a consequence, plasma uptake is faster from the more vascular intercostal space or the axilla than from the caudal space. Vascular uptake of local anesthetic after intercostal nerve block occurs more rapidly than with any other regional technique [16]. Despite recently published epidemiologic data indicating up to a fivefold increase in the utilization of peripheral nerve blockade in the pediatric population, specific pharmacokinetic data are lacking [17]. Ilioinguinal-iliohypogastric nerve blockade is the only peripheral block whose kinetics have been reported with any degree of regularity. Significantly higher plasma concentrations of both bupivacaine and ropivacaine have been reported in one study following ilioinguinal-iliohypogastric nerve block as compared to caudal blockade [18]. Times to peak plasma concentration were much faster for both drugs following ilioinguinal-iliohypogastric nerve block. The narrow inter-fascial space at this block location may facilitate absorption. This, coupled with greater uptake of local anesthetic into epidural fat, may account for the lower plasma levels seen after caudal injection.

### 7.3.4 Distribution

Local anesthetics are distributed to the tissues and body fluid compartments after systemic absorption to the plasma. Volume of distribution (Vd) is a mathematical expression which depicts the distribution characteristics of a drug in the body. It is a measure of the degree to which a drug is delivered by the plasma to the organs and tissues of the body. Drugs with a small calculated Vd have a high concentration of drug in the plasma, have a concomitant low tissue concentration, and are more likely to accumulate to toxic levels. Drugs with a larger Vd are subject to slower elimination. Vd is influenced by degree of ionization/lipophilicity, plasma protein binding, and molecular size [19]. Since local anesthetics are weak bases that have dissociation constants (pKa values) above physiological pH, more than 75 % of the commonly used amide local anesthetic drugs exist in a hydrophilic ionized form at physiological pH (Table 7.1). Hence, they are highly water-soluble molecules but are less likely to cross lipid cell membranes. As a result of the delayed systemic absorption of local anesthetic drugs, it is impossible to calculate a volume of distribution with any accuracy. One study found bupivacaine to have a higher Vd in neonates and infants [20], which may be related to the higher fraction of unbound drug to plasma protein (see next section). Following adult epidural anesthesia, ropivacaine appears to have a smaller Vd than bupivacaine [21, 22], and indirect evidence points to a similarly reduced Vd in infants. Following single-shot caudal anesthesia, peak concentration of ropivacaine is higher than bupivacaine [23]. Two further studies have demonstrated that Vd of ropivacaine appears slightly smaller before the age of four [14, 24].

Local anesthetic is distributed to organs according to their vascular density. The local anesthetic is taken up within each organ according to the tissue-plasma partition coefficient (Table 7.3). The lungs play an important buffering role by taking the full impact of drug-laden venous blood. A variety of investigational techniques, including autoradiography, scintillation counts, and tissue assays, confirm the lung's ability to quickly extract local anesthetic [25], although this buffering action of the lung is saturable.

**Table 7.3** Tissue-blood partition coefficients (lidocaine)

| Organ | Tissue-plasma λ | Tissue-blood λ |
|---|---|---|
| Spleen | 3.5 | – |
| Lung | 3.1 | 5.4 |
| Kidney | 2.8 | – |
| Stomach | 2.4 | – |
| Fat | 2.0 | 2.9 |
| Brain | 1.2 | 1.7 |
| Heart | 1.0 | – |
| Muscle | 0.7 | 0.9 |
| Liver | 0.6 | 2.9 |
| Skin | 0.6 | – |
| Bone | 0.4–0.9 | – |

Based on data from de Jong [59]

### 7.3.5 Plasma Protein Binding

Local anesthetics bind tightly to serum proteins, greatly limiting the free fraction of available drug. This is clinically relevant as it is only the free or unbound fraction that is bioactive (i.e., readily available to cross cell membranes to become active at the sodium channel). Volume of distribution (see above) is inversely related to protein binding. Drugs which are highly protein-bound have limited passage into tissues resulting in a high drug plasma concentration and a low Vd. In adults, lidocaine is up to 70 % protein bound while bupivacaine, levobupivacaine, and ropivacaine are over 90 % protein bound [19].

Three principal blood components are involved in local anesthetic binding: the plasma proteins alpha-1-acid glycoprotein (AAG), human serum albumin (HSA), and erythrocytes. Like most weak bases, local anesthetics bind mainly to AAG. AAG has a greater affinity for binding local anesthetic by an order of magnitude of 5,000–10,000 compared to albumin [26]. Capacity for binding is relatively low, however, and saturation occurs at clinically relevant concentrations. Even though albumin is the most abundant plasma protein (50–80 times more abundant than AAG), it has a low affinity for amide local anesthetic drugs [4]. By virtue of its enormous binding capacity (it is almost unsaturable), together with its abundance, the role of HSA becomes significant when AAG is saturated.

AAG concentration is very low at birth (less than 30 % of the adult concentration) and progressively increases to adult levels during the first year of life [5]. The unbound fraction of local anesthetic is higher during infancy which increases susceptibility to toxicity. Conversely, a consequence of this high free drug concentration is a greater hepatic clearance than would be expected with immature hepatic microsomal metabolism.

AAG is a major acute-phase protein, and its concentration rapidly increases in the first 24–48 h after surgery. The resulting AAG level *in infants* remains lower than that which is present in children and adults, but the subsequent decrease in free drug concentration may provide some protection against toxicity in the early postoperative period. This elevation in AAG levels may diminish on the third postoperative day, leading to a sudden rise in the unbound fraction, which can precipitate toxicity. A total cessation or reduction in the infusion dose of local anesthetic has been recommended in the neonatal age group beyond 48 h [9].

Affinity for red blood cells is low and not saturable. This may be considered as a buffer system when toxic concentrations occur. It is especially relevant in infants with a low AAG concentration. It is important to remember that infants have a physiologic anemia which reduces storage capacity and favors increased fraction of unbound drug [26].

### 7.3.6 Hepatic Metabolism

Local anesthetics undergo extensive hepatic biotransformation prior to renal excretion. Clearance is low at birth and does not reach adult levels until 6–9 months [27, 28]. The terminal half-life of amide local anesthetics is three to eight times longer in neonates when compared to adults [4]. Amide local anesthetics are metabolized in the liver by oxidative pathways involving the cytochrome P450 enzyme superfamily (Fig. 7.3). Lidocaine and bupivacaine are metabolized mainly by CYP3A4, an enzyme system which is not fully mature at birth. However, most biotransformation activities are achieved by CYP3A7, an enzyme which is present only in the fetus and during the first months of life [29].

Ropivacaine is metabolized by CYP1A2, which is not fully functional before the age of 3 years. Consequently, it is reasonable to assume that bupivacaine clearance should be at or near normal adult levels from birth and that ropivacaine clearance should be markedly deficient; however, this is not the case. Clearance of bupivacaine is markedly deficient at birth and increases slightly in the first year of life. Conversely, ropivacaine clearance is not very low at birth; however, it does not fully reach adult values before the age of 5 years [14]. This enzymatic immaturity is clinically relevant to a limited extent but does not preclude the use of local anesthetics in neonates and infants.

Only a small fraction of unmetabolized amide local anesthetic is excreted in the urine. Thus, renal dysfunction affects local anesthetic clearance less than hepatic failure, notwithstanding the accumulation of potentially harmful metabolites [25]. The clearance of one of the main metabolites of ropivacaine, 2,6-pipecoloxylidide (PPX), is decreased in uremic patients. Its cardiotoxicity in rat studies is reported as half that of bupivacaine.

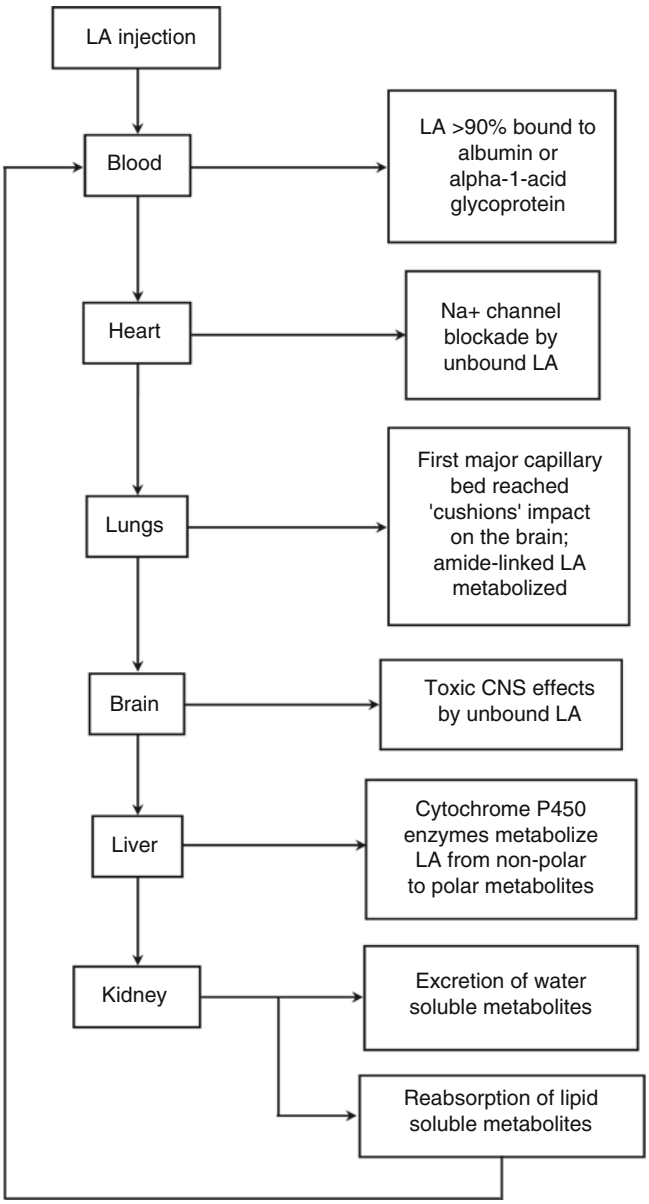


**Fig. 7.3** Sites of local anesthetic action and metabolism following plasma absorption. Local anesthetic molecules are bound to plasma proteins, and this limits the free fraction of available drug. The unbound fraction is metabolized in the liver by the cytochrome p450 enzyme superfamily

## 7.4 Toxicity

Local anesthetics have the same toxic effects in infants and children as those seen in adults. The major toxic effects are on the cardiovascular and central nervous systems. In the adult patient, neurologic toxicity occurs at lower concentrations followed by cardiac toxicity at higher concentrations. This is not always true for bupivacaine, an assumption which may be broadened to include the entire spectrum of local anesthetic toxicity in the pediatric population. Early signs of cerebral toxicity are subjective (dizziness, drowsiness, tinnitus). These will not be related by the young or anesthetized child (and most pediatric blocks are performed under anesthesia or heavy sedation). Moreover, general anesthesia itself raises the cerebral toxicity threshold, and neuromuscular blockade will preclude the onset of generalized tonic-clonic seizures. Consequently, the first manifestation of an accidental intravascular injection or rapid absorption may be cardiovascular collapse (Table 7.4) [9].

**Table 7.4** Dosage recommendations for regional blocks in pediatric patients

| Route of administration | Recommended agent | Maximum dose single shot | Maximum dose reinjection | Maximum dose continuous |
|---|---|---|---|---|
| Caudal epidural | Bupivacaine[a]<br>Bupivacaine with epinephrine | 2 mg/kg<br>2.5 mg/kg | Not recommended | |
| Lumbar epidural | Bupivacaine with epinephrine<br>Bupivacaine | 1.25–1.75 mg/kg | 0.75–1 mg/kg | Infants 1 month–1 year:<br>0.2–0.25 mg/kg/h<br>1–4 years old:<br>0.25–0.35 mg/kg/h<br>4 years:<br>0.25–0.4 mg/kg/h |
| Peripheral blocks | Lidocaine<br>Lidocaine with epinephrine | 6 mg/kg<br>7 mg/kg | | As for lumbar epidural |

[a]Use bupivacaine-equivalent doses (i.e., 1:1) for ropivacaine and levobupivacaine

### 7.4.1 Central Nervous System Toxicity

Local anesthetics readily cross the blood-brain barrier to disrupt cerebral function. The central toxic response is specifically related to plasma levels of local anesthetic in the central nervous system (CNS) and their effect on the complex interplay between excitatory and inhibitory pathways that facilitate neurotransmission. Initially, there is a generalized excitatory phase, as manifested by seizure activity. This initial phase appears to be the result of blocking inhibitory pathways in the amygdala which allow excitatory neurons to function unopposed. When levels of local anesthetic in the CNS increase further, both inhibitory and excitatory pathways (being more resistant to the effects of local anesthetic toxicity) are inhibited, leading to CNS depression, a reduced level of consciousness, and eventually coma.

The reported incidence of cerebral toxicity is low. Two large surveys (each greater than 20,000 regional anesthesia procedures in the pediatric population) indicate that the incidence of seizures is <0.01–0.05 % [30, 31]. There have been several case reports of children experiencing seizures after a regional anesthesia procedure, most of which involved continuous lumbar or caudal epidural anesthesia with bupivacaine [32–35]. Bupivacaine is associated with seizures at blood levels as low as 4.5–5.5 μg/mL. Rather alarmingly on occasion, these toxic blood levels were reached even after adhering to the recommended therapeutic range [32, 34]. Cerebral toxicity is associated with lidocaine, prilocaine, and mepivacaine at blood levels of 5–10 μg/mL.

### 7.4.2 Cardiac Toxicity

The potentially devastating sequelae of cardiovascular toxicity may be the first manifestation of local anesthetic toxicity in infants and children, although the overall incidence in this population is remarkably low. Several large series of regional anesthesia procedures in infants and children report no cases of cardiovascular toxicity [32, 35–37]. A prospective study of more than 24,000 regional anesthesia procedures reported four patients who developed a cardiac arrhythmia, and none of these progressed to cardiac arrest or collapse [31].

For obvious ethical reasons, most available information on this subject comes from animal studies and case reports. The principal mechanism relates to the blockade of myocardial voltage-dependent sodium channels leading to an increase in the PR interval and QRS duration, provoking a dose-dependent prolongation of conduction time and eventual depression of spontaneous pacemaker activity. Persistent sodium channel blockade predisposes to reentrant arrhythmias. Subtle T-wave changes on the electrocardiogram may progress to ventricular arrhythmias, the most malignant being torsades de pointes. These arrhythmias may subsequently be followed by ventricular fibrillation. Alternatively, profound bradycardia may ensue, followed by asystole [4]. Because of their higher heart rate, neonates and infants may be more susceptible to the use-dependent blockade of sodium channels produced by bupivacaine. These electrophysiological effects are compounded by a direct negative inotropic effect of local anesthetic drugs. A number of the reported fatalities due to cardiovascular toxicity resulting from the use of bupivacaine in caudal anesthesia were associated with doses in excess of the recommended therapeutic range [38, 39]. Nevertheless, there have been reports of cardiovascular collapse requiring resuscitation in infants who received caudally administered bupivacaine within the recommended dose range [40, 41].

The levorotatory isomer (S-) of bupivacaine has less potential for cardiac toxicity than the dextrorotatory one (R+) or racemic mixture of both [25]. This led to the development of the single stereoisomers levobupivacaine and ropivacaine. It has been purported that lidocaine blocks sodium channels in a "fast-in/fast-out" fashion, whereas bupivacaine blocks these channels in either a "slow-in/slow-out" manner in low concentrations or a "fast-in/slow-out" manner at higher concentrations [42]. Ropivacaine, on the other hand, has been shown to block sodium channels in a "fast-in/medium-out" fashion [43]. The dissociation constant (between ligand and receptor) for bupivacaine is almost ten times longer than that of lidocaine, resulting in a prolonged and near irreversible cardiac depressant effect [42]. There is a positive correlation between local anesthetic lipid solubility and inhibition of cardiac contractility – further evidence for the clinically relevant finding that ropivacaine is less toxic than racemic bupivacaine [44]. In vitro studies appear to concur with animal studies which have demonstrated that bupivacaine has the most potent myocardial depressant effect, followed by ropivacaine and lidocaine [45].

The true equipotency ratio between the enantiomeric agents has been the subject of much conjecture. Results from a number of animal and clinical studies would suggest a rank order of potency of ropivacaine < levobupivacaine < bupivacaine [3]. This suggests that any theoretical cardioprotective benefit derived from ropivacaine would be negated by the clinical need for higher doses due to its lower potency. The difference in potency does not appear to be clinically relevant for surgical blocks (both peripheral and epidural) when the newer agents are used at concentrations of 0.5–0.75 %, with the clinical profile of the nerve block being similar to that obtained with racemic bupivacaine. However, the lower potency of ropivacaine becomes relevant when used for postoperative analgesia with both epidural and continuous peripheral nerve blockade. For this application, 0.2 % ropivacaine appears to be as effective as 0.125–0.15 % levobupivacaine, which in turn is identical to racemic bupivacaine [3].

### 7.4.3 Treatment of Toxicity

Immediate intervention at the earliest sign of toxicity is of prime importance and improves the chances of successful treatment. General supportive measures are warranted, including Advanced Life Support Guidelines (ACLS) and more specific measures directed at local anesthetic toxicity. All patients subject to a regional anesthesia procedure must have electrocardiography, pulse oximetry, and blood pressure monitoring. Acute morbidity from seizure activity is due in large part to airway complications. Hypoxia, hypercarbia, and acidosis all worsen prognosis. Consequently, airway control must be achieved prior to management of seizure activity. Seizure control can be achieved with midazolam (0.05–0.2 mg/kg) or small doses of propofol if there are no signs of cardiovascular instability. The approach to cardiovascular collapse must be similarly methodical and must prioritize oxygenation and ventilation. Increasing the heart rate may be imperative in infants especially in the presence of profound intraventricular block. Though contentious as to its effect on long-term survival, epinephrine has been recommended for the treatment of cardiac toxicity [4, 46]; however, careful titration is required with individual boluses of less than 1 μg/kg in order to avoid ventricular fibrillation or tachycardia. Vasopressin is contraindicated for the treatment of local anesthetic-induced cardiovascular collapse.

Experimental animal studies and clinical case reports suggest that lipid emulsion is effective in the reversal of local anesthetic toxicity [47–49]. Intralipid® 20 % is a Food and Drug Administration-approved hyperalimentation source comprised of soybean oil, glycerol, and egg phospholipids. The mechanism of action of lipid emulsion in the reversal of local anesthetic toxicity has not been fully elucidated but may act as a circulating lipid sink extracting lipophilic local anesthetic from plasma or tissues [50]. Alternatively, it may facilitate the reversal of local anesthetic inhibition of myocardial fatty acid oxidation, thereby restoring the myocardial adenosine triphosphate (ATP) supply [51]. Lipid emulsion may act as a direct inotrope by increasing intracellular myocardial calcium [52]. Weinberg et al. conducted the original research involving the successful resuscitation of rats in whom cardiovascular collapse was induced with intravenous bupivacaine [47], and these findings were successfully repeated in a canine model of bupivacaine toxicity [50]. It would take a further 8 years after publication of the original animal studies before the appearance of the first clinical case report of the successful use of lipid emulsion in the treatment of bupivacaine-induced cardiac toxicity [48]. Its successful use has subsequently been reported for the treatment of toxicity induced by ropivacaine [53], levobupivacaine [54], and mepivacaine [55, 56]. It has had a favorable outcome in the treatment of a 13-year-old child when administered for ropivacaine- and lidocaine-induced ventricular arrhythmia following posterior lumbar plexus blockade [57].

Intralipid 20 % should be administered as a bolus of 1.5 mL/kg over 1 min followed immediately by an infusion at a rate of 0.25 mL/kg/min. It is important that chest compressions continue to allow the lipid to circulate. Two further boluses of 1.5 mL/kg with 5 min between boluses may be considered if the initial response is inadequate. The infusion may be continued until hemodynamic stability is restored. The rate may be increased to 0.5 mL/kg if blood pressure remains low (Fig. 7.4).

In light of the current evidence, it would appear prudent to ensure immediate availability of Intralipid 20 % in areas where regional anesthesia is performed. For patients in cardiac arrest due to local anesthetic toxicity and who are being resuscitated following current ACLS guidelines, it is appropriate to administer lipid emulsion. It is equally justifiable to administer lipid emulsion to patients displaying overt neurologic toxicity in an attempt to preempt cardiac toxicity.

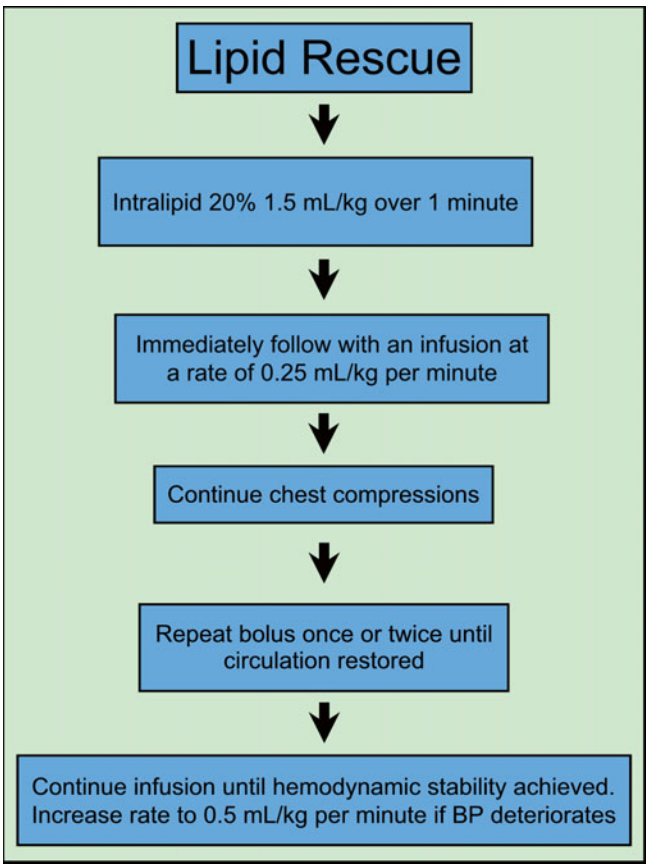


**Fig. 7.4** Pathway for use of Intralipid® in treating local anesthetic toxicity

### 7.4.4 Prevention of Toxicity

Unintentionally high blood levels of local anesthetic lead to a spectrum of neurological and cardiac complications with potentially devastating effect. This usually results from unintentional intravascular injection and may be prevented by careful observation of a number of safety steps. Slow, incremental injection of an appropriate dose of a safe agent should be standard practice. The dose should be determined according to age and lean body mass and modified according to physical status. Higher plasma concentrations may occur after injection into a vascular area. There are no corresponding pediatric data, but in adults, the highest plasma levels are achieved after intercostal nerve blocks, followed by caudal, epidural, brachial plexus, femoral, and sciatic blockade. The use of a vasoconstrictor will serve to reduce the rate of uptake in addition to prolonging the block. An epinephrine concentration of 1:200,000 or less is appropriate. The authors prefer to add epinephrine (1:200,000) to a dextrose solution, the primary purpose of which is ultrasonographic observation of the spread of injectate. This is used in 0.5–1 mL increments as a test dose prior to injection of local anesthetic. A rise in heart rate of ten beats per minute or more is indicative of intravascular injection.

The use of ultrasound-guided regional anesthesia may be as important for local anesthetic systemic toxicity as the pharmacological advances of previous decades. For the first time in the century-old practice of regional anesthesia, it is now possible to visualize the target neural structure, potential vascular hazards, and the spread of local anesthetic solution. This allows for more accurate deposition of smaller volumes of local anesthetic. The largest registry in the ultrasound era (over 25,000 peripheral nerve blocks) reports a reduction in local anesthetic systemic toxicity of 65 % when ultrasound guidance is used [58]. The use of ultrasound does not negate the need for the more conventional safety mechanisms but when used in combination with them makes for an entirely more scientific proposition.

## 7.5 Dosing

- Clearance is reduced in infants less than 6 months of age, and dosing must be modified accordingly.
- Infants less than 6 months have a larger Vd. Despite this, care is needed with reinjection and infusion. When the compartments are saturated, the reduced drug clearance in this age group can rapidly lead to toxic drug levels.
- After 1–2 years of age, the higher ratio of liver volume to total body volume leads to a higher clearance ratio. It is safe to administer higher doses than in adults.
- In children over 30 kg, regardless of age, dose should be reduced to adult dose.
- Local anesthetic doses need to be modified in the presence of pathology which affects drug clearance (e.g., liver or cardiac disease).

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