17 Local Anesthetics

Eva Rioja Garcia
School of Veterinary Science, University of Liverpool, Leahurst Campus, UK

Chapter contents

Introduction

Local anesthetics reversibly block the generation and propagation of electrical impulses in nerves, thereby causing sensory and motor blockade. Their use dates from the late 1880s when cocaine was first used for ophthalmologic procedures by Carl Köller and Sigmund Freud. However, cocaine was found to be highly toxic and addictive. Since then, new agents with better pharmacologic profiles and less potential for systemic toxicity have been developed. Today, local anesthetics are widely used for local and regional anesthetic techniques. These techniques cause desensitization of a localized area of the body, which allows surgical procedures to be performed in the conscious animal. Alternatively, these techniques may be performed in the anesthetized animal where they decrease the need for general anesthetics and promote greater cardiorespiratory stability. Sustained analgesia when a long-acting local anesthetic is used is also beneficial in the recovery period. Additionally, the local anesthetic lidocaine may also be administered systemically for a variety of indications including management of ventricular arrhythmias, augmentation of intestinal motility, reduction in general anesthetic requirements, and analgesia.

Pharmacology

Molecular mechanism of action

Local anesthetics are considered primarily ion channel blockers, acting mainly on voltage-gated Na^+ channels. However, they also block voltage-dependent K^+ and Ca^{2+} channels, though with lower affinity [1–5]. Some studies also suggest that local anesthetics act on intracellular sites involved in the signal transduction of G-protein coupled receptors [6]. This range of molecular targets may explain some of the adverse and toxic effects that this group of drugs produces on various organ systems.

The most important mechanism of action leading to local anesthesia involves the blockade of inward Na^+ currents through voltage-gated Na^+ channels, thereby impeding membrane depolarization and nerve excitation and conduction [7]. The Na^+ channel is a multimolecular complex with a large α-subunit composed of almost 2000 amino acids that traverses the cell membrane several times. This subunit forms the channel's pore and gating apparatus [7]. Some smaller auxiliary β-subunits influence the activation-inactivation states of the channel [8]. The α-subunit consists of four domains (DI to DIV), each containing six helical segments (S1 to S6). The binding site for local anesthetic, antiarrhythmic and anticonvulsant drugs is located on the DIV S6 segment of the α-subunit [8]. It appears that this binding site is localized within the pore of the Na^+ channel and therefore is only accessible from the intracellular side [9].

The channel is a gated conduit for Na^+ ions and exists in three different gating states: resting (closed), open, and inactivated (Fig. 17.1), depending on the membrane potential and time. At resting membrane potential, the channel is predominantly in its resting state. During depolarization, the channel opens to allow passage of Na^+ ions and, after a few milliseconds, it spontaneously closes into an inactivated state to allow repolarization of the membrane. After repolarization the channel reverts to a resting state [8,10].

There is evidence that local anesthetics may interact with the lipid membrane, altering its fluidity, causing membrane expansion, and thus reducing Na^+ conductance [11]; however, this does not

Veterinary Anesthesia and Analgesia: The Fifth Edition of Lumb and Jones.
Edited by Kurt A. Grimm, Leigh A. Lamont, William J. Tranquilli, Stephen A. Greene and Sheilah A. Robertson.

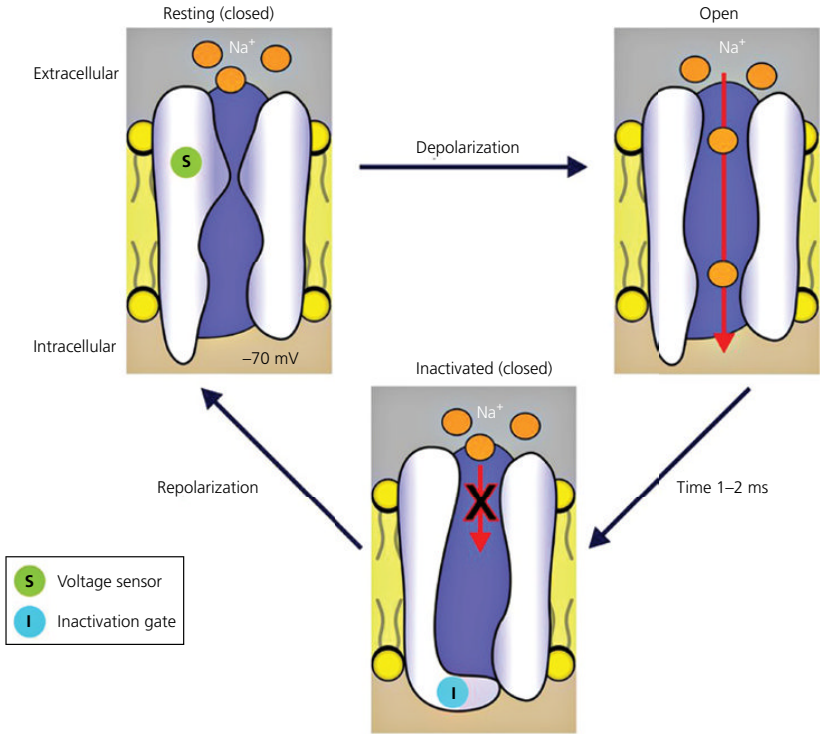

Figure 17.1 The Na^+ channel has two gates: an activation ('voltage sensor') and an inactivation gate. At resting membrane potential the channel exists in its resting (closed) state. Depolarization of the membrane is 'sensed' by the voltage sensor and the channel opens, allowing Na^+ ions to flow intracellularly. Within 1-2 ms the inactivation gate closes automatically (inactivated channel), allowing repolarization to occur. Repolarization leads to conformation changes with closure of the activation gate and opening of the inactivation gate within 2-5 ms (=refractory period). After repolarization, the channel is in a resting state again.

completely explain the mechanism of action of modern clinically used local anesthetics.

The 'modulated-receptor hypothesis' proposes that local anesthetics have high binding affinity for the Na^+ channel in its open and inactivated states, but low affinity for the resting state [7,12]. Lipid-soluble drug forms are thought to enter and leave the receptor via a hydrophobic region of the membrane, while charged less lipid-soluble forms pass via a hydrophilic region (the inner channel pore) [12]. The hydrophilic pathway is open only when the gates of the channel are open, which causes cumulative binding of local anesthetics to the Na^+ channel when the channels are active. The 'guarded-receptor hypothesis' proposes that the receptor for local anesthetics is located inside the channel and that the drug binds to this receptor with constant affinity [13]. Access to the receptor is regulated by the channel gates and therefore the channel needs to be open for the receptor to be accessible to the local anesthetic. Increasing the frequency of stimulation increases the number of Na^+ channels in the open and inactive states, which increases the binding of local anesthetics.

Both hypotheses explain the property of tertiary amine local anesthetics whereby the depth of the block increases with repetitive membrane depolarization, which has been termed 'use-dependent block' or 'phasic block' [14,15]. On the other hand, blockade obtained on unstimulated nerves is constant, which is termed 'tonic block' [14,15].

Mechanism of blockade of neural tissue

Local anesthetics show a differential pattern of sensory and motor blockade that can be observed clinically when applied to peripheral nerves and the central neuraxis [16,17]. Vasodilation occurs first, followed by loss of sensation of temperature, sharp pain, light touch, and finally loss of motor activity (Table 17.1) [18]. This property is called 'differential block' and was first described by Gasser and Erlanger in 1929 when they observed that, within myelinated A fibers, cocaine reduced compound action potentials from slower and smaller fibers more rapidly than from faster and larger fibers [19]. However, this differential block *in vivo* cannot be simply explained by the size of the fiber, but rather is influenced by numerous factors including type of fiber (size and myelination), frequency of stimulation, length of nerve exposed to the local anesthetic, and choice and concentration of local anesthetic drug.

Initially it was hypothesized that the differential block produced by local anesthetics when applied to peripheral nerves was due to a greater susceptibility of small, unmyelinated C fibers compared to larger, myelinated A fibers. However, *in vitro* [20] and *in vivo* studies [14,21] have shown that A fiber susceptibility to phasic and tonic block is actually greater than that of C fibers, with the order of blockade from fastest to slowest being $A\gamma > A\delta = A\alpha > A\beta > C$. This would suggest that motor and proprioceptive deficits should occur prior to loss of nociception, but this is opposite to what is clinically observed.

Anatomic features such as myelination may also account for some differences in susceptibility, since myelin can effectively pool anesthetic molecules close to the axon membrane [22]. Experimental studies have found that unmyelinated fibers are less sensitive to lidocaine than myelinated fibers [23]. This is contrary to clinical observations of differential block which is manifested by the loss of small fiber-mediated sensation (e.g., temperature) two or more dermatomes beyond the sensory limit for large fiber-mediated sensations.

Table 17.1 Classification of nerve fibers and order of blockade.

Classification	Diameter (μM)	Myelin	Conduction (m/s)	Location	Function	Order of blockade
A-α	15–20	+++	30–120	Afferent/efferent for muscles and joints	Motor and proprioception	5
A-β	5–15	++	30–70	Efferent to muscle Afferent sensory nerve	Motor function and sensory (touch and pressure)	4
A-γ	3–6	++	15–35	Efferent to muscle spindle	Muscle tone	3
A-δ	2–5	+	5–25	Afferent sensory nerve	Pain (fast), touch, temperature	2
B	1–3	+	3–15	Preganglionic sympathetic	Autonomic function	1
C	0.4–1.5	–	0.7–1.3	Postganglionic sympathetic	Autonomic function, pain (slow), temperature	2

Adapted from references 15 and 36.

Exposure length of the nerve to the local anesthetic may in part explain differential block *in vivo*, as smaller fibers need a shorter length exposed than larger fibers for block to occur [24]. This has been called the 'critical length' to completely block conduction, which in myelinated fibers corresponds to three or more nodes of Ranvier [25]. Therefore, larger fibers with greater internodal distances are less susceptible to local anesthetic blockade.

Another important mechanism of local anesthetic blockade is the phenomenon of decremental conduction, which describes the diminished ability of successive nodes of Ranvier to propagate the impulse in the presence of a local anesthetic [26]. This principle explains why the propagation of an impulse can be stopped even if none of the nodes has been rendered completely inexcitable [25], as occurs for example with low concentrations of local anesthetics. Concentrations of local anesthetic that block 74–84% of the sodium conductance at successive nodes cause a progressive decrease in amplitude of the impulse, until it eventually decays below the threshold [25]. Higher concentrations that block greater than 84% of the sodium conductance at three consecutive nodes will prevent impulse propagation completely [25]. This explains why blocks of greater extent and duration result from injection of small-volume/high-concentration solutions versus large-volume/low-concentration solutions, despite the same total drug dose [27].

Some authors suggest that a large portion of the sensory information transmitted by peripheral nerves is carried via coding of electrical signals in after-potentials and after-oscillations [28]. Subblocking concentrations of local anesthetics can suppress these intrinsic oscillatory after-effects of impulse discharge without significantly affecting action potential conduction [29]. Thus, another possible mechanism of blockade of nerve function, especially at low concentrations of local anesthetics, is by disruption of coding of electrical information [15].

When local anesthetics are administered in the central neuraxis (epidurally or intrathecally) or systemically, they may possess other mechanisms of analgesic action at the level of the spinal cord in addition to the previously discussed ones. Local anesthetics inhibit other ion channels such as K^+ or Ca^{2+} channels at the level of the dorsal horn of the spinal cord. This may affect central neuroprocessing of sensory information, thereby contributing to their antinociceptive effects [30–32]. In addition to ion channels, nociceptive transmission is mediated by several neurotransmitters in the dorsal horn, such as the tachykinins (e.g., substance P). Local anesthetics have been shown to inhibit substance P binding and evoked increases in intracellular Ca^{2+} [33]. Additionally, local anesthetics also inhibit glutamatergic transmission in spinal dorsal horn neurons, reducing *N*-methyl-D-aspartate (NMDA)- and neurokinin-mediated postsynaptic depolarizations [34,35].

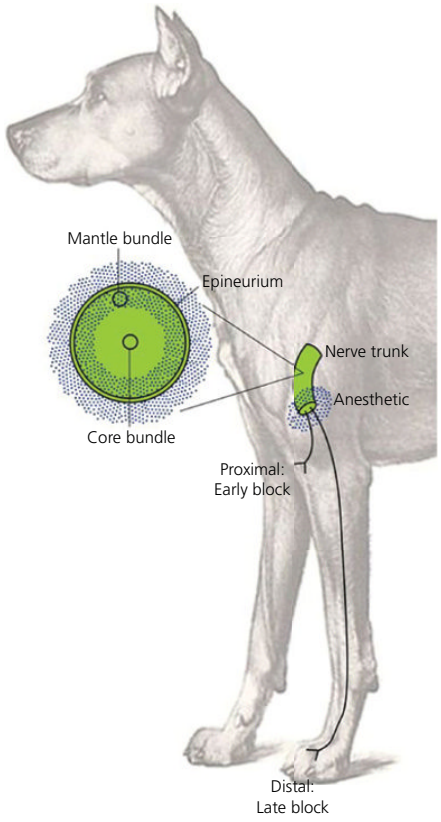

Figure 17.2 Nerve fibers in the mantle or peripheral bundles innervate primarily motor fibers of the proximal limb, whereas nerve fibers in the core or center bundles mainly innervate the sensory fibers of the distal foot. Therefore, the concentration gradient that develops during initial diffusion of local anesthetic into the nerve trunk causes onset of anesthesia to proceed from proximal to distal. Recovery from anesthesia also proceeds from proximal to distal because of absorption of local anesthetic into the circulation surrounding the nerve trunk. Source: Adapted from [36].

When nerve trunks or large nerves are targeted (e.g., brachial plexus), the somatosensory arrangement of the nerve fibers also affects the progression of the block (Fig. 17.2) [36].

Chemical structure

Clinically useful local anesthetic drugs are composed of a lipophilic, benzene ring with different substitutions (aromatic ring) and a hydrophilic amine group (tertiary or quaternary amine), which are linked through an intermediate chain, either an ester or an amide. Depending on the type of link, local anesthetics are classified as amino-esters, hydrolyzed by plasma cholinesterases, or amino-amides, metabolized by the liver.

Physicochemical properties

The physicochemical properties influencing local anesthetic activity include molecular weight, pKa, lipid solubility, and degree of protein binding (Table 17.2) [37,38].

The molecular weight of clinically used local anesthetics is very similar, ranging between 220 and 288 Da. The diffusion coefficient is thus not significantly affected and molecular weight seems not to be an important factor determining differences in activity of local anesthetics [37]. However, changes in molecular weight due to alkyl substitutions may influence other properties such as lipid solubility and pKa.

All clinically useful local anesthetics are weak bases, and as such they exist in equilibrium between the neutral, non-ionized, lipid-soluble form (B) and the ionized (charged), water-soluble form (BH^+). They are formulated as acidic solutions of hydrochloride salts (pH 4–7), which are more highly ionized and thus water soluble.

The receptor for local anesthetics appears to be located within the pore of the Na^+ channel close to the cytoplasm [9] and only the ionized, charged form of the local anesthetic can interact with this receptor [39]. However, the main access of local anesthetics to the cell is by penetration of the lipophilic neutral form through the lipid membrane (Fig. 17.3).

Table 17.2 Physicochemical properties and relative potencies of clinically used local anesthetics.

Local anesthetic	pKa[a]	% Ionized (at pH 7.4)	Lipid solubility[b]	% Protein binding	Relative anesthetic potency[c]	Relative potency for CNS toxicity[d]	CV:CNS ratio[e]
Ester linked							
Low potency, short duration							
Procaine	8.89	97	100	6	1	0.3	3.7
Chloroprocaine	9.06	95	810	7	1	0.3	3.7
High potency, long duration							
Tetracaine	8.38	93	5822	94	8	2	ND
Amide linked							
Intermediate potency and duration							
Lidocaine	7.77	76	366	64	2	1	7.1
Mepivacaine	7.72	61	130	77	2	1.4	7.1
Prilocaine	8.02	76	129	55	2	1.2	3.1
Intermediate potency, long duration							
Ropivacaine	8.16	83	775	94	6	2.9	2
High potency, long duration							
Bupivacaine	8.1	83	3420	95	8	4	2
Levobupivacaine	8.1	83	3420	>97	8	2.9	2
Etidocaine	7.87	66	7317	94	6	2	4.4

[a] Measured with spectrophotometric method at 36°C, except prilocaine and ropivacaine measured at 25°C.
[b] Partition coefficients expressed as relative concentrations (mol/L) in octanol and buffer at 36°C, except prilocaine and ropivacaine measured at 25°C.
[c] Potency relative to procaine.
[d] Potency relative to lidocaine.
[e] Cardiovascular to central nervous system toxicity ratio. CV denotes the disappearance of pulse and CNS denotes the onset of seizures.
Data obtained from references 36, 38, and 40. ND = no data.

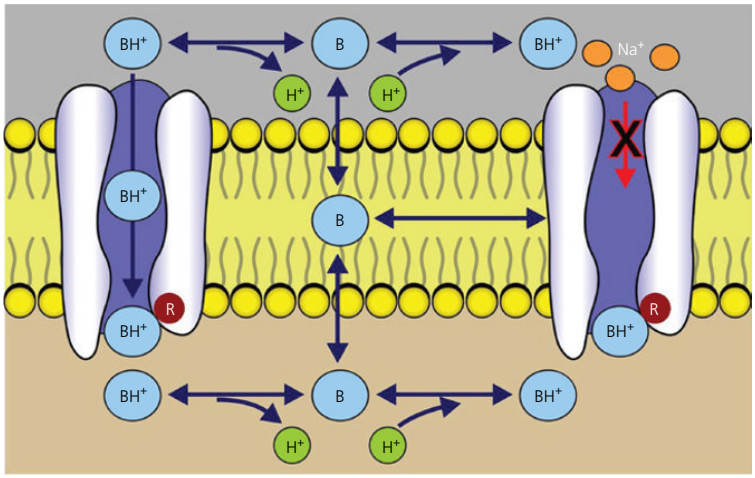

Figure 17.3 The cell membrane lipid bilayer with the Na^+ channel. Local anesthetics exist as a neutral base (B) and an ionized form (BH^+) in equilibrium. The neutral form is lipid soluble and easily crosses the cell membrane. The ionized form is more water soluble and can cross through the open channel. The neutral form can cause membrane expansion and closure of the Na^+ channel. The ionized form interacts with its receptor on the intracellular side of the Na^+ channel.

The pKa of a drug is the pH at which the two forms exist in equal amounts and is alkaline (pH >7.4) for all clinically used local anesthetics.

$$pKa = pH - \log([B]/[BH^+])$$

The higher the pKa, the greater the degree of ionization or proportion of local anesthetic in the ionized, charged hydrophilic form at physiologic pH (7.4), and the slower the onset of action. On the other hand, a local anesthetic with a low pKa will have a greater proportion of the non-ionized lipid-soluble form at physiologic pH and a more rapid onset of action.

Lipid solubility is the main determinant of intrinsic local anesthetic potency and it will determine the clinically relevant concentrations needed to produce effective conduction blockade [40–42]. Increasing lipid solubility facilitates the penetration through lipid membranes, potentially hastening onset of action; however, highly lipid-soluble agents will also become sequestered within the myelin and other lipid compartments. Thus, the net effect of increasing lipid solubility is delayed onset of action of local anesthetics [43]. On the other hand, sequestration of local anesthetic in myelin and other lipid compartments creates a depot for slow release of the drug, increasing the duration of the effect [43].

The degree of protein binding also influences activity of local anesthetics, as only the unbound, free fraction is pharmacologically active. Higher protein binding is associated with increased duration of action. This cannot be explained by slower dissociation kinetics from the Na^+ channel, as this dissociation occurs within seconds regardless of the degree of protein binding [44]. Increased duration of action of highly protein-bound local anesthetics is probably associated with other membrane or extracellular proteins [45].

Most clinically available local anesthetics are racemic mixtures of the *R*- and *S*-enantiomers in a 50:50 mixture. The exceptions are lidocaine, procaine, and tetracaine, which are achiral, and levobupivacaine and ropivacaine, which are the pure *S*-enantiomers or levoisomers [37,46]. Although both enantiomers have the same physicochemical properties, they have different affinities for the ion channels of Na^+, K^+ and Ca^{2+}, with the *R*-enantiomer having greater *in vitro* potency and thus greater therapeutic efficacy but also greater potential for systemic toxicity [47,48]. There is less potential for nervous and cardiac toxicity with the *S*-enantiomer compared with the *R*-enantiomer or the racemic mixture [49].

Studies *in vitro* have characterized the relative potencies of local anesthetic agents, which depend on their physicochemical properties (i.e., lipid solubility) but also the individual nerve fibers and frequency of stimulation [50]. However, *in vivo* potencies do not necessarily correlate with *in vitro* studies [51], because of the complex interaction of factors including site of administration, dose and volume of local anesthetics, and other environmental factors.

Local anesthetics with an amide group, high pKa, and lower lipid solubility show greater differential blockade, with more potent blockade of C fibers than of fast-conducting A fibers [43,52]. This is believed to be due to the slower diffusion across permeability barriers present in A fibers. The relative order of differential rate of blockade is chloroprocaine > ropivacaine > bupivacaine, levobupivacaine > lidocaine, mepivacaine > etidocaine [53,54]. This is especially true at low concentrations and the differential rate of blockade tends to disappear as local anesthetic concentrations increase.

Clinical pharmacology

Pharmacokinetics

Absorption

Disposition of local anesthetics within the body after local administration is governed by several competing factors including bulk flow, diffusion and binding to neural and non-neural structures, and vascular uptake (Fig. 17.4). The rate and extent of systemic absorption of the local anesthetic are important as toxic plasma concentrations may be achieved. Therefore, local anesthetics with lower systemic absorption will have a greater margin of safety. Systemic absorption depends on several factors including the site of

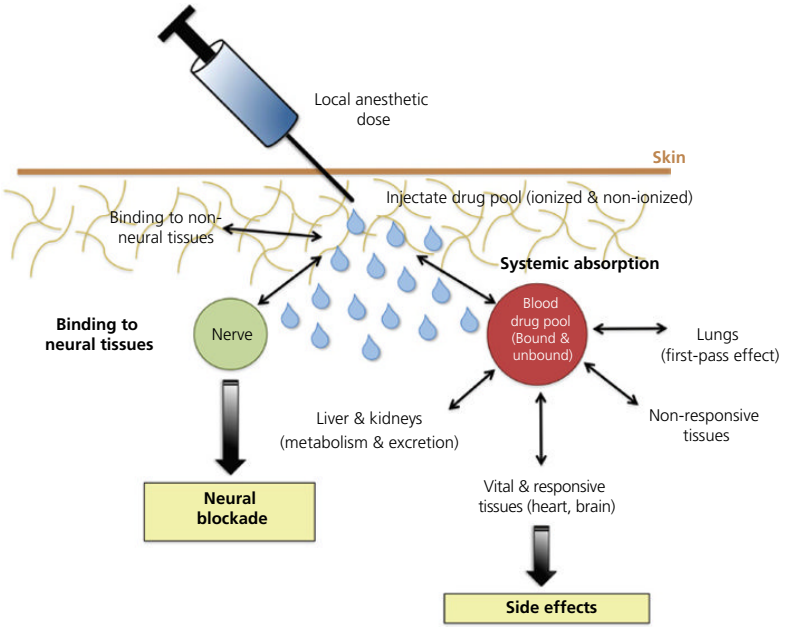

Figure 17.4 Disposition of local anesthetics within the body following peripheral administration.

injection (i.e., vascularity), the intrinsic lipid solubility and vasoactivity of the agent, the dose administered, the presence of additives such as vasoconstrictors, other formulation factors that modify local drug residence and release, the influence of the nerve block in the region (i.e., vasodilation), and the (patho)physiologic state of the patient [37].

In general, areas with greater vascularity will have a more extensive and rapid systemic absorption than areas with more fat, regardless of the agent used [15]. Areas with greater vascularity will have a greater peak plasma concentration (C_{max}) and a shorter time to peak plasma concentration (T_{max}). In an experimental study in pigs, lidocaine rate of absorption following subcutaneous administration was highest in the pectoral region, followed by the face and neck, with the slowest being the abdomen [55]. With regard to specific blocks, the degree of systemic absorption is as follows, in decreasing order: intercostal > epidural > brachial plexus > sciatic/femoral [56]. Following administration of lidocaine via inverted L nerve block in cows, the serum C_{max} was 572 ng/mL which occurred at T_{max} 0.52 h, while lidocaine via a caudal epidural block was undetectable in serum [57]. Systemic absorption of local anesthetic drugs is much lower after spinal (intrathecal) than after epidural administration [58,59]. Normally, the greatest risk of systemic toxicity coincides with T_{max} in arterial blood, which will vary from 5 to 45 min after injection, depending on the site of the block, speed of injection, and drug injected [37]. However, T_{max} is independent of the dose injected [60]. Faster speed of injection is associated with greater C_{max}, and therefore with increased risk of systemic toxicity [61].

Physicochemical properties of local anesthetics will also influence systemic absorption. In general, drugs with greater lipid solubility and protein binding will result in lower systemic absorption and C_{max} [37]. Therefore, shorter-acting amide drugs such as lidocaine and mepivacaine will be absorbed into the systemic circulation more readily than the long-acting bupivacaine, ropivacaine and levobupivacaine, probably because of binding of the latter to neural and non-neural lipid-rich tissues [15]. Another factor influencing the rate of absorption is the intrinsic vasoactivity of the local anesthetic. Most clinically used local anesthetics cause vasodilation when applied locally, with the exceptions of ropivacaine and levobupivacaine [62,63]. The vasoconstrictive activity of ropivacaine and levobupivacaine results in slower absorption and therefore longer T_{max} values [64,65].

Addition of a vasoconstrictor, such as epinephrine, will counteract the inherent vasodilating effects on the local vasculature of most agents, delaying their systemic absorption. Hyaluronidase is another additive sometimes added to local anesthetics to improve their anesthetic effect by causing depolymerization of interstitial hyaluronic acid and thus increasing the permeability of the tissues; however, it also enhances systemic absorption and the risk of systemic toxicity (see section on Additives later in this chapter).

Some new formulations, such as local anesthetic-loaded liposomes, polylactide microspheres or cyclodextrin inclusion complexes, among others, are designed to cause a slow release of the drug, providing a local depot of local anesthetic, which will significantly decrease systemic absorption and prolong the duration of effect [60,66,67]. When liposome-encapsulated lidocaine was administered epidurally to dogs the C_{max} was lower, while the T_{max} and the duration of effect (170 versus 61 min) were significantly longer compared to regular lidocaine [66]. In sheep, intercostal administration of bupivacaine-dexamethasone microspheres prolonged the duration of the block up to 13 days, with plasma concentrations remaining ten times below the convulsive concentration [68]. Liposome-encapsulated lidocaine has also been administered topically to cats at a dose of 15 mg/kg, which proved to be safe, with C_{max} well below the toxic plasma levels for that species [69]. Administration of different slow-release lidocaine formulations for sciatic nerve block in postoperative pain models in rats produced analgesia from 3 days up to 1 week and inhibited the development of hyperalgesia [70,71].

Distribution

After absorption into the bloodstream, amino-ester local anesthetics are rapidly hydrolyzed by plasma pseudocholinesterases and their distribution into body tissues is limited. Amino-amide local anesthetics are widely distributed into different body organs and tissues. The degree of tissue distribution and binding is normally represented by the pharmacokinetic parameter known as the apparent volume of distribution at steady state (Vd_{ss}), which is usually paralleled by the degree of protein binding [37]. Only the free, active fraction of the drug, and not the protein-bound fraction, governs tissue concentration and degree of entry into the central nervous system [72]. Amide-type local anesthetics bind primarily to α_1-acid glycoprotein (AAG) in the plasma and to a lesser extent to albumin [73,74]. In dogs, increasing concentrations of AAG caused an increase in total serum concentration but a decrease in the free fraction, Vd_{ss}, and elimination half-life of lidocaine [72,75]. Because AAG is an acute phase protein, its circulating levels will be increased during trauma, surgery, cancer or any inflammatory state. Therefore, although the total concentration of local anesthetic in plasma will be greater, reflecting the increase in AAG, the unbound (active) drug fraction will remain similar [37,76].

Amide-type local anesthetics in venous blood undergo first-pass pulmonary uptake, which effectively decreases the plasma concentration of the drug temporarily [77,78]. Consequently, the lungs are able to attenuate the toxic effects after accidental intravenous injections of local anesthetics. In animals with right-to-left cardiac shunts the pulmonary first-pass effect is absent and there is an increased risk of toxicity. The pulmonary uptake of a local anesthetic is mostly dependent on its physicochemical properties, mainly lipid solubility and pKa. More lipid-soluble agents undergo greater pulmonary uptake and those with lower pKa values will have a greater fraction of unionized base form, which is the form that accumulates in the lung [79]. Decreasing blood pH (i.e., acidemia) decreases the degree of pulmonary uptake of local anesthetics, which may contribute to increased plasma concentrations and promote toxicity [77,79]. The rank order of pulmonary uptake in rat lung slices was found to be bupivacaine > etidocaine > lidocaine [79]. Others have also found greater uptake of prilocaine compared to bupivacaine and mepivacaine in isolated perfused rat lungs, with little evidence of pulmonary metabolism [80]. The mean pulmonary uptake of lidocaine after IV administration in dogs has been calculated to be 63.6% [78]. There is evidence of a pulmonary contribution to lidocaine metabolism using rat pulmonary microsomes *in vitro* [81]. After an intravenous bolus injection in rabbits, the pulmonary uptake of levobupivacaine was greater than that of ropivacaine (31% versus 23%) [82].

Local anesthetic agents also distribute rapidly and extensively into milk and muscle at concentrations proportional to those in the bloodstream. Drugs that diffuse most readily into milk are those that are relatively lipophilic, unionized, not strongly protein bound, and with low molecular weights [83]. Following an inverted L nerve block with 100 mL of 2% lidocaine in adult Holstein cows, the lidocaine C_{max} in milk was 300 ng/mL compared with serum C_{max} of 572

ng/mL; T_{max} in milk was 1.75 h compared with serum T_{max} of 0.52 h [57]. The last measurable time of lidocaine detection in milk was 32.5 h with a mean concentration of 46 ng/mL [57]. The current Food Animal Residue Avoidance Database (FARAD) withdrawal recommendations for lidocaine are 24 h for meat and milk, which seem too short based on this study. On the other hand, following caudal epidural administration of 0.22 mg/kg of lidocaine there was no detectable lidocaine concentration present in any serum or milk sample [57]; therefore, a 24 h withdrawal time would be appropriate for this route and dose.

Local anesthetic drugs also cross the placenta and appear in the fetus following administration to the pregnant animal. Ester-linked local anesthetic agents are rapidly metabolized and placental transfer is limited [37]. Amide-linked local anesthetic agents can become 'trapped' in their ionized forms on the more acidotic fetal side of the placenta, and therefore their net transfer across the placenta is increased [84]. In pregnant ewes, as fetal blood pH decreased from 7.35 to 7.10, the fetal-maternal ratio (F:M) for lidocaine increased from 0.76 to 1.21 [84]. Apart from the pH, the degree of local anesthetic binding to both maternal and fetal plasma proteins is also an important determinant of placental transfer of local anesthetics, as only the unbound, free drug crosses the placenta [85]. Since fetal AAG content and binding are less than maternal [86], the F:M of highly protein-bound local anesthetics such as bupivacaine (F:M = 0.36) is lower than less protein-bound drugs such as lidocaine (F:M = 1) [85,87]. The placental transfer of levobupivacaine and ropivacaine is similar to bupivacaine in pregnant ewes [88].

An important consideration when choosing a local anesthetic agent in the pregnant animal is the ability of the neonate to metabolize and excrete the drug after birth. Studies in sheep show that back-transfer of bupivacaine, but not of lidocaine, from the fetus to the mother occurs [85,87]. Lidocaine and its metabolites monoethylglycinexylidide (MEGX) and glycinexylidide (GX) were detected in fetal urine within 1–2 h following intravenous infusion of lidocaine to pregnant ewes [85]. These studies suggest that lidocaine might be a better option in pregnant animals since the fetus/neonate will be able to readily eliminate the drug. They also suggest that if high plasma concentrations of local anesthetic in maternal blood are likely (i.e., large volumes used for local blockade or inadvertent intravenous administration), it would be beneficial to delay delivery in the case of bupivacaine, but there would be no benefit in doing so in the case of lidocaine [85].

Metabolism

Ester-linked local anesthetics are cleared mainly in the blood by non-specific plasma pseudocholinesterases, where they undergo ester hydrolysis. Esterases present in the liver, red blood cells, and synovial fluid also contribute to the clearance of these drugs [89–91]. Among the ester agents, chloroprocaine is cleared most rapidly due to its faster hydrolysis rate. *In vitro* half-lives tend to be very short for the ester-linked drugs, ranging from 11 s for chloroprocaine in human plasma [92] to 9 s and 12 s for procaine in equine whole blood and plasma, respectively [89], and up to several minutes for tetracaine [37]. *In vivo* terminal half-lives are typically longer, probably reflecting slow uptake from the site of administration and/or wide distribution within the body [37,93]. The terminal half-life of procaine in horses after intravenous administration is 50 min with an apparent volume of distribution of 6.7 L/kg [93]. The hydrolysis products of procaine, chloroprocaine, and tetracaine appear to be pharmacologically inactive. Procaine and benzocaine are hydrolyzed to para-aminobenzoic acid (PABA) which may, however, cause rare allergic reactions [37].

Cocaine undergoes ester hydrolysis in plasma and liver, but also *N*-demethylation in the liver to norcocaine, which subsequently undergoes further hydrolysis [91]. Cocaine is rarely used in veterinary medicine, but illegal use in horses or dogs before races to increase performance and delay the time to exhaustion is possible [94]. Procaine also possesses central nervous system stimulatory effects and its use is banned in racehorses [93].

Amide-linked local anesthetics are almost exclusively metabolized in the liver by microsomal enzymes (CYP450). Phase I reactions involve hydroxylation, *N*-dealkylation and *N*-demethylation, followed by Phase II reactions where the metabolites are conjugated with amino acids or glucuronide into less active and inactive metabolites. Clearance values differ among species, but typically the rank order of clearance is prilocaine > etidocaine > lidocaine > mepivacaine > ropivacaine > bupivacaine [37]. In humans, prilocaine is cleared most rapidly, with blood clearance values that exceed liver blood flow, indicating extrahepatic metabolism in this species [37]. Hydrolysis of prilocaine produces orthotoluidine (O-toluidine), a metabolite that oxidizes hemoglobin to methemoglobin [95].

Lidocaine undergoes hydroxylation and *N*-demethylation in the liver. Its two main metabolites are monoethylglycinexylidide (MEGX) and glycinexylidide (GX) in dogs [96], rabbits [97], rats [98], cats [99], horses [100,101], goats [102], and chickens [103], but these metabolites have not been detected in cows [104]. Of these metabolites, especially MEGX has significant activity (approximately 70% that of lidocaine) and could potentially contribute to its toxicity during prolonged intravenous infusions [37,101]. Other amides such as mepivacaine, bupivacaine, and ropivacaine undergo mainly *N*-dealkylation and hydroxylation. These agents produce the less toxic metabolite pipecoloxylidide (PPX) [105]. The *N*-dealkylated metabolite of bupivacaine, *N*-desbutylbupivacaine, is about half as cardiotoxic as bupivacaine, but less toxic to the central nervous system in rat studies [106]. Some amide metabolites are further conjugated to glucuronide before they are eliminated in the urine or bile [107].

Excretion

Local anesthetics are poorly water soluble, which limits renal excretion of the unchanged drug. The hydrolysis metabolites of ester-linked local anesthetics are mainly excreted in urine [108]. Similarly, the metabolites of amide-linked local anesthetics are eliminated in urine or bile. A small portion of amide-type local anesthetics is excreted unchanged in urine (4–7% for lidocaine, 6% for bupivacaine and 16% for mepivacaine in humans; 1.7–2.9% for lidocaine in horses) [109–111].

Factors affecting pharmacokinetics and activity

Patient factors, such as age, may influence the pharmacokinetics of local anesthetics. Absorption of lidocaine from laryngeal spray was higher in dogs less than 20 days of age compared to 2–3-month old puppies [112]. The volume of distribution and the elimination half-life of lidocaine were greater in neonatal lambs compared with adult sheep [113]. In a pharmacokinetic study of lidocaine in puppies, the elimination rate constant from the central compartment (K10) was lower and the elimination half-life longer in 3–16-day old compared with 6-month old puppies [114]. When comparing neonatal lambs with adult sheep, hepatic clearance of lidocaine was similar but renal clearance of unchanged drug was greater in the neonate,

probably due to decreased protein binding, lower urine pH and decreased tubular reabsorption because of higher urine flow rates [113]. Plasma hydrolysis of ester-linked local anesthetics is also affected by age, as observed in human neonates and infants where plasma cholinesterase activity was half that of adults [115]. In geriatric animals, hepatic clearance of local anesthetics may be decreased and half-life increased [116,117].

Increased nerve sensitivity to local anesthetics seems to be present during pregnancy with faster onset of conduction blockade [118]. Acute progesterone treatment had no effect on bupivacaine-induced conduction blockade in the isolated rabbit vagus nerve; therefore, this effect is unlikely to be a direct effect of progesterone on the cell membrane but may involve hormonal effects on protein synthesis [119]. Pregnant ewes were found to clear lidocaine more rapidly, but bupivacaine and ropivacaine more slowly than non-pregnant ewes [120,121]. This difference may be explained by lidocaine's more dependent clearance on hepatic blood flow, which is increased during pregnancy, whereas clearance of bupivacaine and ropivacaine is more dependent on the hepatic enzymatic activity which may be inhibited during pregnancy [37].

Hepatic disease can decrease the rate of metabolism of amide-linked local anesthetics. Plasma pseudocholinesterase activity is also reduced in the presence of liver disease and during pregnancy, which will decrease the rate of hydrolysis of ester-linked local anesthetics [122,123]. In general, standard doses may be administered to animals with hepatic disease for single-dose neural blockade but repeated doses, dosing intervals, and continuous rate infusions need to be adjusted to avoid accumulation and toxicity [37]. A decrease in hepatic blood flow, as can occur during general anesthesia, cardiac disease, or any condition decreasing cardiac output, will decrease hepatic clearance of local anesthetics, especially those more dependent on hepatic blood flow such as lidocaine [37,124]. The Vd_{ss} and clearance (Cl) of intravenous lidocaine were significantly decreased in anesthetized compared to awake horses (0.4 vs 0.79 L/kg and 15 vs 29 mL/kg/min, respectively) [125], and in anesthetized compared to awake cats (1.4 vs 1.9 L/kg and 21 vs 26 mL/kg/min, respectively) [99]. Hepatic clearance of other amide-linked local anesthetics like mepivacaine or bupivacaine is more dependent on activity of hepatic enzymes and the effect of reduced hepatic blood flow is less pronounced.

Renal failure decreases plasma pseudocholinesterase activity by 40% in humans [126]. Amino-amides are excreted mainly as water-soluble metabolites, which may accumulate in animals with renal failure and contribute to central nervous system toxicity if they are active (e.g., MEGX and GX) [124].

Fasting has been shown to decrease hepatic clearance of lidocaine in horses [111]. Gastrointestinal disease (e.g., equine colic) may also affect clearance of amino-amide local anesthetics that depend mainly on hepatic blood flow, like lidocaine, especially if cardiac output is significantly reduced. However, pharmacokinetic parameters of intravenous lidocaine in horses undergoing abdominal surgery for colic are similar to those of healthy, awake horses, with Vd_{ss} and Cl values of 0.7 L/kg and 25 mL/kg/min [127]. It was hypothesized that the cardiac output of the horses included in that study might have been increased, rather than decreased [127].

Interestingly, diabetes mellitus increases hepatic clearance of lidocaine, although the excretion of the metabolite MEGX is impaired [128,129].

Concomitant administration of local anesthetics with other drugs may affect their distribution and elimination kinetics. Drugs that decrease plasma or red cell esterase activity, such as neostigmine or acetazolamide, will prolong half-life of ester-linked local anesthetics [130,131]. When CYP1A2 and CYP3A4 inhibitors, such as erythromycin, are co-administered with amino-amide local anesthetics, their hepatic clearance may decrease [132]. β-Adrenergic receptor blocking drugs reduce liver perfusion and inhibit the activity of hepatic microsomal metabolizing enzymes responsible for the metabolism of amino-amide local anesthetics; hence, greater plasma concentration and decreased elimination will occur when these drugs are co-administered [133].

Co-administration of different classes of local anesthetics may also affect their pharmacokinetic parameters. The rate of hydrolysis of chloroprocaine is reduced by concomitant administration of bupivacaine or etidocaine, but not when it is co-administered with lidocaine or mepivacaine [130,134].

Temperature may also affect the pharmacokinetics and pharmacodynamics of local anesthetics. Lidocaine's ability to block nerve impulses, both *in vitro* and *in vivo,* is potentiated by cooling [135,136]. Conversely, lidocaine uptake by mammalian sciatic nerve is reduced by cooling, with a 45% decrease when the temperature falls from 37°C to 20°C [137]. Some clinical studies in humans have observed an increase in the speed of onset of various types of blocks when the temperature of the local anesthetic solution was increased to 37°C [138–141], although this effect has not been consistent [142,143]. Cooling of the local anesthetic solution increases the pKa and the relative amount of ionized active form, while warming the solution decreases the pKa and increases the amount of non-ionized lipid-soluble form [137]. These pKa changes may explain the increased potency of local anesthetics with cooling and the hastening of onset of action with warming.

Baricity is one of the most important physical properties of local anesthetics during subarachnoid or intrathecal administration as it will affect the distribution and spread of the solution, and therefore impact the characteristics of the block [144]. Baricity of a local anesthetic solution is the calculated ratio of the density of the solution to the density of the cerebrospinal fluid (CSF), both measured at the same temperature, which is normally 37°C. Density is the weight in grams of 1 mL of the solution, and it is inversely related to its temperature [145]. An isobaric solution has a baricity ratio of 1. If the ratio is >1, the solution is hyperbaric, and if it is <1, it is hypobaric. At room temperature, most commercially available local anesthetic solutions are isobaric with respect to the CSF, but when they are warmed to body temperature they become hypobaric [145]. The densities of commercial 2% lidocaine and 0.5% and 0.75% bupivacaine are lower than that of human CSF at 37°C, which makes them relatively hypobaric [146]. Dilution of these solutions with water makes them increasingly hypobaric [146]. When local anesthetics are mixed with dextrose or hypertonic saline, the resulting solution is hyperbaric [145,147]. Neurotoxicity has been observed with hyperbaric bupivacaine when high concentrations and doses are administered intrathecally in dogs (≥10 mg of 1% or 2% bupivacaine in 10% glucose solution), but not with low concentrations and doses (5 mg of 0.5% bupivacaine in 10% glucose solution) [148]. High concentrations and doses of hypobaric bupivacaine (20 mg of 2% bupivacaine in water) were not associated with neurotoxicity when administered intrathecally to dogs [148].

Hypobaric solutions, when injected into the subarachnoid space, will migrate to non-dependent areas, because their density is lower than that of the CSF, while hyperbaric solutions will migrate to dependent areas. This migration allows preferential blockade to occur on the surgical side, with unilateral spinal anesthesia being possible when low doses of local anesthetics are used [149]. Isobaric

solutions will migrate to both sides of the spinal cord, causing bilateral spinal block. In humans, it is reported that unilateral spinal block results in a four-fold reduction of the incidence of clinically relevant hypotension with more stable cardiovascular parameters as compared with conventional bilateral spinal block [150]. Because only small amounts of local anesthetic solution are injected, the extent of spinal block is reduced and the resolution of the sensory and motor blocks is faster [150].

Mixtures of local anesthetic agents with additives such as solvents or vasoconstrictors, or with other drugs such as opioids, may alter the density and baricity of the solution. When 0.125–0.5% bupivacaine solutions are mixed with fentanyl (0.005%), sufentanil (0.005%) or morphine (0.1%) the resultant solutions are hypobaric [151]. The mixture of 2% lidocaine and epinephrine (1:200 000) results in a hyperbaric solution [151].

There is some variation in the density of the CSF among individuals [152]. Density of the CSF may also be influenced by physiologic status of the animal (e.g., density is decreased during pregnancy in humans) [153]. Therefore, there may be some interindividual variation in clinical response to intrathecal solutions, especially with those that are marginally hypo- or hyperbaric [144].

Additives

Epinephrine has been used as an adjunct to local anesthetics for more than a century. The rationale behind its use is that it causes vasoconstriction and therefore decreases the systemic absorption of the local anesthetic agent, which decreases the dose of local anesthetic required and prolongs its duration of effect [154,155]. Decreased systemic absorption also reduces the local anesthetic C_{max}, which decreases the probability of systemic toxicity. Several studies have demonstrated decreased C_{max} of local anesthetics when administered with epinephrine both in peripheral and neuraxial blocks [155–158]. In general, the greatest effects are observed with shorter-acting rather than with longer-acting agents.

In addition to this pharmacokinetic interaction, epinephrine seems to have analgesic effects on its own when administered epidurally or intrathecally by stimulating α_2-adrenergic receptors, thereby inhibiting presynaptic neurotransmitter release from C and Aδ fibers in the substantia gelatinosa of the spinal cord dorsal horn [159–161]. It has also been shown that α_2-adrenergic receptors can modify certain K^+ channels in the axons of peripheral nerves, potentiating the impulse-blocking actions of local anesthetics [162,163]. A later study in rats also showed that local infiltration of epinephrine causes cutaneous anesthesia mediated by activation of local α_1-adrenergic receptors [164]. Therefore, it seems that pharmacokinetic and pharmacodynamic interactions between epinephrine and local anesthetics are responsible for the increased duration and intensity of the block when administered in combination.

A potential concern when epinephrine is co-administered with local anesthetics is a decrease in peripheral nerve or spinal cord blood flow, which could cause nerve or spinal cord ischemia. However, research studies with radiolabeled microspheres in dogs and cats show that epinephrine injected intrathecally causes regional dural vasoconstriction but does not reduce spinal cord or cerebral blood flow [165,166]. This is supported by many years of clinical experience using epinephrine-containing solutions for neuroaxial anesthesia and the absence of observed detrimental effects on spinal cord function [163,167]. *In vitro* studies in rats showed that sciatic nerve blood flow is reduced by injection of lidocaine without epinephrine, but that the reduction is more pronounced when epinephrine (5 μg/mL) is added [168]. However, a more recent *in vivo* rat study using radiolabeled microspheres showed that lidocaine with or without epinephrine (10 μg/mL) does not reduce sciatic nerve or surrounding skeletal muscle blood flow [169]. The authors of this study concluded that mechanisms other than local vasoconstriction might contribute to the prolongation of lidocaine peripheral nerve blockade by epinephrine.

Systemic absorption of epinephrine administered in combination with local anesthetics can also cause cardiovascular effects characterized by an increase in heart rate, stroke volume, and cardiac output, and a decrease in peripheral vascular resistance [170]. A study in humans also showed an improvement of left ventricular diastolic function with epinephrine added to local anesthetics, in contrast with norepinephrine, which impaired it [170]. Excessive plasma concentrations of epinephrine could precipitate tachycardia and arrhythmias.

The recommended concentrations of epinephrine for addition to local anesthetic solutions for clinical use range between 1:400 000 (1 mg/400 mL or 2.5 μg/mL) and 1:200 000 (1 mg/200 mL or 5 μg/mL] [163]. A 1:200 000 concentration can be obtained by adding 0.1 mL of a 1:1000 epinephrine solution (0.1 mg) into 20 mL of local anesthetic solution. Concentrations in excess of 5 μg/mL do not provide any additional decrease in C_{max} and should therefore be avoided in light of the potential for systemic side-effects [37]. Market preparations of local anesthetics that contain epinephrine have lower pH values than do plain or freshly prepared solutions. The lower pH of these epinephrine-containing preparations could potentially decrease the amount of unionized form, thereby slowing the onset of action.

Other vasoconstrictors such as phenylephrine or methoxamine may be added to prolong the duration of the effect of local anesthetics by decreasing their systemic absorption [171]. Some degree of pharmacodynamic interaction may also exist as the infiltration of these α_1-adrenergic receptor agonists caused cutaneous anesthesia in rats [164]. But in contrast with epinephrine, these other agents lack α_2-adrenergic receptor effects and, therefore, potential interactions with local anesthetics mediated by these receptors are not possible. Moreover, phenylephrine, but not epinephrine, caused a significant decrease in sciatic nerve and skeletal muscle blood flow when administered in combination with lidocaine [169], which could potentially cause complications due to nerve ischemia.

Vasoconstrictors should be avoided for blockade of areas with erratic blood supply or without good collateral perfusion (e.g., intravenous regional anesthesia, teat blocks, or large areas of skin) because of the possibility of vasoconstriction-induced tissue ischemia and necrosis.

Phentolamine, a non-selective α-adrenergic receptor antagonist, has been shown to reverse prolonged local anesthetic-induced block when administered in combination with vasoconstrictors [172]. A commercial preparation of phentolamine mesylate (OraVerse®) has been approved for the reversal of soft tissue anesthesia and the associated functional deficits resulting from local dental anesthesia in humans.

Hyaluronidase, an enzyme that depolymerizes hyaluronic acid, the main cement of the interstitium, may be added to local anesthetics to improve tissue penetration and thereby shorten onset and increase spread of the block [173]. Addition of hyaluronidase raises the pH of the anesthetic solution to a slightly more physiologic level, which may contribute to the shortening of onset by increasing the amount of unionized drug. However, local anesthetic C_{max} and the risk of systemic toxicity may also increase. Human and animal studies show diverse results with respect to

improved efficacy. Some human studies show better quality of peribulbar or retrobulbar block and shorter onset of action when hyaluronidase is added at concentrations as low as 3.5 IU/mL to mixtures of 0.5% or 0.75% bupivacaine and 2% lidocaine [174–176], while others show no benefit when hyluronidase is added at concentrations as high as 150 IU/mL to a mixture of 0.75% bupivacaine and 2% lidocaine for peribulbar block [177,178]. Hyaluronidase added to bupivacaine with epinephrine (1:200 000) for brachial plexus block did not increase the speed of onset of anesthesia or reduce the incidence of inadequate nerve block [179]. In a recent study in dogs, the addition of 400 IU of hyaluronidase to 1.06 mg/kg of 0.5% levobupivacaine for lumbosacral epidural block decreased the onset from 15 to five min, but it also decreased the duration of block, while dermatomal spread was unchanged [180]. When used in infiltration anesthesia, hyaluronidase added at 15 IU/mL to 1% lidocaine increased the area of desensitized skin, but pain on injection also increased compared with plain 1% lidocaine [181]. The addition of hyaluronidase to lidocaine for infiltration block does not delay wound healing [182]. The addition of hyaluronidase seems particularly advantageous in ophthalmic blocks, as it has been shown to limit the acute intraocular pressure increase secondary to periocular injection and seems to have a protective effect against local anesthetic-induced myotoxicity resulting in postoperative strabismus [183].

The pH of commercially available local anesthetic solutions is normally acidic to enhance stability and solubility and extend shelf-life [184,185]. Alkalinization of the solution by addition of sodium bicarbonate causes an increase in the amount of local anesthetic in the unionized form, which is the lipid-soluble fraction able to cross the axonal membrane, thereby shortening the onset of the block. The intensity and duration of the block may also increase due to an increase in the transmembrane pH gradient, causing ion trapping of the ionized active form inside the nerve. The efficacy of alkalinization depends on the local anesthetic solution, the site of the block, and the concurrent addition of epinephrine.

Buffering of 1% lidocaine, 1% mepivacaine or 0.5% bupivacaine with sodium bicarbonate for intradermal administration does not affect the onset, extent, and duration of skin anesthesia in humans [186,187]. Addition of bicarbonate to lidocaine for median nerve block in humans increased the rate of motor block without changing the onset or extent of sensory block [188]. Similarly, alkalinization of 1% lidocaine or 0.25% bupivacaine to a pH of 7.4 did not prolong infraorbital nerve block duration in rats [189]. Studies using buffered local anesthetics during epidural anesthesia show controversial results. Some studies show shorter onset of epidural block when 1.5–2% lidocaine, 2% mepivacaine or 0.5% bupivacaine is alkalinized with bicarbonate [190–192], while others show no shortening of onset with buffered 2% lidocaine or 0.5% bupivacaine [193–195]. The alkalinization of 0.75% ropivacaine solution does not decrease sensory or motor block onset, but increases the duration of the epidural block [196]. In femoral and sciatic nerve blocks, the effects of alkalinization on the onset of sensory analgesia and motor block were more evident with 2% mepivacaine, but for brachial plexus axillary block, the greatest effect was observed with 2% lidocaine [192]. Nonetheless, in studies where hastening of block onset occurred with alkalinization, the decrease was less than 5 min when compared with commercial preparations. In addition, it seems that the effect of alkalinization is mainly observed when epinephrine is also added to the solution [197]. Thus, the value of alkalinization of local anesthetics appears debatable as a clinically useful tool to improve anesthesia [15].

Alkalinization has a greater effect when the local anesthetic is administered into an acidic environment, as with intravesicular instillation where the urine is normally acidic. Intravesicular instillation of 5% lidocaine buffered with an equal volume of 8.4% sodium bicarbonate to a pH of 8.0 provided local anesthesia of the bladder submucosa as indicated by the rapid decrease in pain scores in human patients with interstitial cystitis [198]. However, intravesicular administration of alkalinized lidocaine for up to three consecutive days had no apparent beneficial effect on decreasing recurrence rate and severity of clinical signs in cats with obstructive idiopathic lower urinary tract disease [199].

Buffered local anesthetics also have a greater effect when topically administered to the cornea. The corneal permeability of topically applied lidocaine increased when the pH of the solution was buffered from 5.2 to 7.2, with greater concentrations of lidocaine found in the aqueous humor [200,201].

Buffering of the local anesthetic solution with bicarbonate decreases pain on injection when administered subcutaneously and also decreases pain when an epidural catheter is inserted [184,185,202]. Reduction of pain on injection seems to be enhanced by additional warming of the solution to body temperature [202].

The most common dose of sodium bicarbonate used is 0.1 mEq per mL of local anesthetic solution. The addition of bicarbonate may cause precipitation of the solution, especially with bupivacaine and etidocaine when the pH rises above 7.0 [203]. Mepivacaine may also precipitate at a pH above neutral within 20 min [204]. Therefore, it is recommended to use the mixed solution immediately after the addition of sodium bicarbonate.

Carbonation of local anesthetics by adding carbon dioxide (CO_2) is sometimes used to decrease onset and improve quality of the block. Addition of CO_2 to a solution of lidocaine decreased the amount of lidocaine needed to achieve conduction block *in vitro* [205]. This potentiation of local anesthetic block is possibly due to a decreased intracellular pH, causing ion trapping. Carbonated lidocaine administered epidurally shortened the onset and improved the block in humans [206,207]; however, it did not offer any advantage over the hydrochloride salt for caudal epidural anesthesia in horses [208].

The addition of α_2-adrenergic receptor agonist drugs to local anesthetics during regional blocks is being increasingly used in veterinary medicine. Clonidine has been extensively used in humans to prolong the duration of intrathecal, epidural, and peripheral nerve blocks. Meta-analyses and systematic reviews clearly show an analgesic benefit from the addition of clonidine to local anesthetics [209]. In large animals, epidural or intrathecal xylazine has been used in combination with lidocaine since the early 1990s to prolong the analgesic effect [210]. Medetomidine administered either perineurally or systemically (0.01 mg/kg) in combination with mepivacaine for radial nerve block in dogs prolonged the duration of sensory and motor blockade, with residual sensory blockade persisting beyond the observable sedative effects [211]. Dexmedetomidine has been recently introduced as an adjuvant to regional anesthesia in humans and animals. Studies in rats have shown that administration of dexmedetomidine in combination with bupivacaine or ropivacaine enhances sensory and motor blockade in sciatic nerve block without inducing neurotoxicity [212,213]. Clinical studies in humans show a shorter onset, longer duration of sensory and motor block, enhanced block quality, lower pain scores, and decreased systemic opioid requirements when dexmedetomidine is added to bupivacaine or levobupivacaine for various blocks [214–217]. Addition of dexmedetomidine to

lidocaine for intravenous regional anesthesia improved the quality of anesthesia and decreased analgesic requirements, but had no effect on the extent of sensory and motor blockade, or on onset and regression times [218,219].

The increased duration of analgesia caused by adding clonidine or dexmedetomidine to local anesthetics is due to hyperpolarization of C fibers through blockade of the so-called hyperpolarization-activated cation current [220,221]. α-Adrenergic receptors do not seem to be implicated as administration of α-adrenergic receptor antagonists does not reverse the conduction block nor decrease the duration of the block [220–222].

Mixtures of local anesthetics

Local anesthetic mixtures of amino-amide agents consisting of an intermediate acting agent, such as lidocaine or mepivacaine, combined with a long-acting agent, such as bupivacaine, are used in the belief that the combination will provide a shorter block onset and a similar duration than the long-acting agent administered alone. However, these mixtures produce unpredictable and variable clinical results. Clinical studies in humans using a 50:50 mixture of lidocaine or mepivacaine with bupivacaine or ropivacaine for peripheral nerve blocks show a shorter onset of effect, but also a shorter duration of action, compared with the administration of bupivacaine or ropivacaine alone [223–225]. The epidural or intrathecal combination of lidocaine and bupivacaine in cows [226], cats [227], and humans [228–231] produced similar sensory block onset than either agent alone, and the duration was intermediate between the two agents or similar to bupivacaine.

When chloroprocaine, a short onset, short duration of action amino-ester local anesthetic, is administered prior to bupivacaine, the duration of bupivacaine-induced blockade is decreased. This may be due to an inhibitory effect caused by chloroprocaine metabolites on the Na^+ channel receptor site for bupivacaine [232]. Mixing commercial preparations of chloroprocaine and bupivacaine resulted in a pH of 3.6 and nerve blockade with characteristics of a chloroprocaine block [233]. When the pH of the mixture was increased to 5.56, the nerve block resembled that of bupivacaine. Therefore, mixing commercially available solutions of local anesthetics results in unpredictable blockade that will depend on a number of factors including the pH of the final mixture [233]. Furthermore, local anesthetic toxicity of combinations of drugs is additive [234].

Tachyphylaxis

Tachyphylaxis to local anesthetics is defined as a decrease in duration, segmental spread, or intensity of a regional block despite repeated constant dosages [235]. In 1969, Bromage described that repeated injection of a constant dose of epidural lidocaine led to a reduction in both the number of dermatomes blocked and the duration of the block [236]. The incidence of this phenomenon in veterinary medicine is unknown, and probably is largely unrecognized. Tachyphylaxis appears neither to be linked to structural or pharmacologic properties of the local anesthetics, nor to the technique or mode of administration, as it can occur with both ester- and amide-linked local anesthetics and with either neuraxial or peripheral nerve blocks [236–239]. Bromage found that tachyphylaxis to local anesthetics is promoted by longer interanalgesic intervals between injections [236]. If local anesthetic injections were repeated at intervals short enough to prevent return of pain or at intervals with pain of less than 10 min duration, tachyphylaxis did not occur and augmentation of the analgesic effect was noted. Conversely, if the patient experienced pain between local anesthetic administrations for more than 10 min, tachyphylaxis occurred more rapidly.

The mechanisms underlying tachyphylaxis may involve both pharmacokinetic and pharmacodynamic aspects. Suggested pharmacokinetic mechanisms include local edema, increased epidural protein concentration, changes in local anesthetic distribution in the epidural space, a decrease in perineural pH (limiting the diffusion of local anesthetic from the epidural space to binding sites at the Na^+ channel), an increase in epidural blood flow, or an increase in local metabolism (favoring clearance of local anesthetics from the epidural space) [235]. Other factors of pharmacodynamic origin have also been suggested, such as antagonistic effects of nucleotides or increased Na^+ concentration, increased afferent input from nociceptors, or receptor downregulation of Na^+ channels [235]. A human study with repeated injections of epidural lidocaine showed lack of changes in the distribution or rate of elimination of lidocaine from the epidural space [239] and another study in rats failed to show an effect of tissue pH on the development of tachyphylaxis to bupivacaine [237].

Tachyphylaxis to local anesthetics does not result from reduced drug effectiveness at the nerve itself [240], but it seems to be mainly mediated by a spinal site of action [241]. Tachyphylaxis and central hyperalgesia seem to be related, as evidenced by studies in rats, where tachyphylaxis occurred only under conditions where they concurrently developed hyperalgesia in the tested paw [242]. If only non-noxious motor tests were used to test the duration of the block, tachyphylaxis did not occur. Moreover, it has been shown that drugs that prevent hyperalgesia at spinal sites, such as NMDA receptor antagonists [242] and NO-synthase inhibitors [243], prevent the development of tachyphylaxis. Therefore, it seems that a spinal nitric oxide pathway is involved in the development of tachyphylaxis to local anesthetics [241]. Additionally, descending pathways do not seem necessary for the development of tachyphylaxis since it occurs even after spinal cord transection at the tenth thoracic level in rats [241].

Local anesthetic switching has also been proposed when tachyphylaxis to a local anesthetic agent develops. This approach has been successful in humans with cancer-related pain in whom intrathecal morphine and bupivacaine were not effective and substitution of bupivacaine with lidocaine improved analgesia [244].

Specific drugs and clinical uses

Amino-esters

Procaine

This agent has a quick onset and short duration of effect (30–60 min) because of its rapid hydrolysis in blood [15]. Epinephrine may be added to prolong its duration of effect. Its potential for systemic toxicity is minimal, but it occasionally causes allergic reactions due to a hydrolysis metabolite (PABA).

Procaine is used in veterinary medicine for infiltration and nerve blocks at concentrations of 1–2% [245]. It is rarely used for topical anesthesia, as it is not very effective via this route [245]. In humans, it is sometimes administered intrathecally for short procedures [246].

Intravenous procaine is a central nervous system stimulant in horses [93]. Because of this property, and its analgesic effect when used for peripheral nerve blocks, it has been illegally used in racehorses [245]. Procaine is sometimes added to drug formulations (i.e., procaine penicillin) to prolong duration of effect.

Benzocaine
This agent is also a fast-acting and short-lasting local anesthetic, available exclusively for topical anesthesia. It causes methemoglobinemia in several animal species and therefore it is no longer used in clinical practice. Benzocaine is also an anesthetic for fish when added to water [247].

Chloroprocaine
This agent is similar to procaine, with a fast onset and short duration of action (30–60 min). It is available in concentrations of 1% to 3%. It is not widely used in veterinary medicine, but in humans its use has re-emerged for short-duration epidural and intrathecal anesthesia because it is associated with a lower incidence of transient neurologic symptoms compared with lidocaine [248]. It may also be used for local infiltration blocks when a short duration of effect is required.

Tetracaine
Tetracaine is also called amethocaine. It is rarely used in veterinary medicine. In humans it is most commonly used for intrathecal anesthesia because it has a fast onset (3–5 min) and its effect lasts 2–3 h [249]. It is rarely used for other forms of regional anesthesia due to its extremely slow onset and potential for systemic toxicity [249]. It is an excellent topical anesthetic and because of this property it is included in topical anesthetic solutions. However, the absorption of tetracaine from mucous membranes is very rapid and several fatalities have been reported after its use for endoscopic procedures in humans [250]. Human studies have shown that tetracaine topical preparations, including a lidocaine/tetracaine patch (Synera®, Rapydan®), provide faster and better dermal anesthesia than the eutectic mixture of lidocaine and prilocaine (EMLA® cream) [251,252].

Amino-amides
Lidocaine
Lidocaine remains the most versatile and most widely used local anesthetic in veterinary medicine because of its fast onset, moderate duration of effect, and moderate toxicity. It is available as 0.5%, 1%, 1.5%, and 2% solutions. Lidocaine is used for infiltration anesthesia, peripheral nerve blocks, epidural and intrathecal blocks, and intravenous regional anesthesia. The duration of plain lidocaine is approximately 1 h, which can be prolonged up to 3– h with the addition of epinephrine [15]. It is also commonly used topically for laryngeal desensitization before tracheal intubation (2%, 4% or 10% spray solution). For dermal anesthesia it is available in different formulations such as the eutectic mixture with prilocaine (2.5% EMLA® cream), as patches of lidocaine alone (5% Lidoderm®) or mixed with tetracaine (Synera®, Rapydan®).

Lidocaine has numerous non-anesthetic uses when administered intravenously. It is a Class Ib antiarrhythmic drug. It also reduces the requirements for inhalational anesthetics when administered intravenously in different species including dogs [253–255], cats [256], goats [102], horses [257,258], and calves [259]. It is also an analgesic drug for different types of pain when administered systemically, as shown in human patients [260,261] and experimental studies in laboratory animals [262,263]. Administration of intravenous lidocaine (2 mg/kg bolus followed by 0.05 mg/kg/min) produced thermal antinociception in horses [264]. However, it did not affect the thermal threshold in cats (plasma concentrations up to 4.3 μg/mL) [265], or the electrical threshold in dogs (2 mg/kg IV bolus followed by an infusion of up to 0.1 mg/kg/min) [266].

The mechanism by which systemically administered lidocaine produces analgesia is uncertain but is thought to include action at Na^+, Ca^{2+}, and K^+ channels and the NMDA receptor [30–32,34,35]. Lidocaine also possesses anti-inflammatory effects, which may be important in producing analgesia because inflammatory mediators augment neuronal excitability [267]. In addition, some studies show that lidocaine may improve intestinal motility and prevent development of postoperative ileus in horses [268–271], especially in those with reperfusion injury [272].

The disposition of lidocaine after intravenous administration has been described for sheep [113], dogs [96,114,273], cats [99], horses [125], cows [104], and chickens [103] (Table 17.3).

Table 17.3 Pharmacokinetic parameters (mean ± SD) of intravenous lidocaine in domestic species.

	$T_{1/2}$ (min)	Vd_{ss} (L/kg)	Cl (mL/kg/min)
Dog [273]	68.1 ± 10.9	1.38 ± 0.08	27.5 ± 6
Cat [99]	100 ± 28	1.39 ± 0.37	26 ± 2.7
Horse [125]	79 ± 41	0.79 ± 0.16	29 ± 7.6
Cattle [104]	63.6 ± 42	3.3 ± 1.6	42.2 ± 20.5
Sheep [113]	30.9	NA	41.2

$T_{1/2}$ = terminal half-life; Vd_{ss} = apparent volume of distribution in steady state; Cl = total body clearance.

Mepivacaine
This agent has a pharmacologic profile very similar to lidocaine, with a slightly longer duration of effect (up to 2 h), probably because of slightly less intrinsic vasodilatory properties. It is available at concentrations from 0.5% to 2%. Its use in clinical practice is similar to lidocaine, except that it is not routinely used for intravenous regional anesthesia or for obstetric procedures because its metabolism is very slow in the fetus and newborn [249]. Unlike lidocaine, mepivacaine is not an effective topical anesthetic [249]. It is the preferred agent for diagnostic peripheral nerve blocks in horses because of its lower neurotoxicity compared with other local anesthetics [274].

Bupivacaine
This is a highly lipophilic agent, about four times as potent as lidocaine, and with slow onset of action (20–30 min) and a long duration of effect (3–10 h) [249]. It is used in concentrations ranging from 0.125% to 0.75%. Its clinical uses include infiltrative, peripheral nerve, epidural, and intrathecal blocks. Bupivacaine is not used for topical anesthesia and it is not recommended for intravenous regional anesthesia because of its high cardiotoxicity potential. It possesses intrinsic differential blocking properties, especially at low concentrations, and therefore is indicated when sensory blockade accompanied by minimal motor dysfunction is desired.

Levobupivacaine
This is the levoisomer or *S*-enantiomer of bupivacaine, with slightly less cardiotoxic potential than the racemic mixture. Its physicochemical properties and clinical uses are the same as bupivacaine.

Ropivacaine
This agent is structurally related to mepivacaine and bupivacaine, but it is marketed as the pure *S*-enantiomer to reduce the cardiotoxicity associated with the *R*-enantiomer. It is slightly less potent than bupivacaine and is available in concentrations of up to 1%. Its clinical uses are the same as bupivacaine, with similar onset of effect, a marginally shorter sensory blockade (up to 6 h) and a slightly lower degree of motor blockade at equipotent doses [249]. It has a

Table 17.4 Clinically relevant local anesthetic commercial names, indications, and doses.

Local anesthetic	Commercial name	Indications	Doses
Procaine	Novocaine, Procasel, Adrenacaine, Dalocain, Isocain (with epinephrine)	Infiltration Nerve blocks	Maximum 2–4 mg/kg
Lidocaine	Topical: EMLA cream (with prilocaine), Xylocaine, Intubeaze, Lidoderm patches Injectable: Lidocaine HCl, Lignocaine, Xylocaine (some with epinephrine)	Topical (dermal, mucous membranes) Infiltration Nerve blocks Interpleural Epidural Intrathecal[a] Intravenous (IV)	Maximum doses: 6–10 mg/kg (Ca), 3–5 mg/kg (Fe), 6 mg/kg (Eq, Bo, Ov, Cp, Sw) Epidural: 4 mg/kg of 2% sol. (0.2 mL/kg) (Ca, Fe, Ov, Cp, Sw), 6 mL total (Eq, Bo) IV intraoperative: 1–2 mg/kg bolus, 50–100 μg/kg/min (Ca), 25–50 μg/kg/min (Eq, Bo)
Mepivacaine	Carbocaine, Intra-Epicaine, Vetacaine	Infiltration Nerve blocks Interpleural Epidural Intrathecal[a] Intra-articular	Maximum dose: 5–6 mg/kg (Ca, Eq, Bo, Ov, Cp, Sw), 2–3 mg/kg (Fe) Intra-articular: 1–2 mg/kg
Bupivacaine	Marcaine	Infiltration Nerve blocks Interpleural Epidural Intrathecal[a]	Maximum dose: 2 mg/kg (Ca, Eq, Bo, Ov, Cp, Sw), 1–1.5 mg/kg (Fe) Epidural: 1 mg/kg of 0.5% sol. (0.2 mL/kg) (Ca, Fe, Ov, Ca, Sw), 6 mL total (Eq, Bo)
Levobupivacaine	Chirocaine	Infiltration Nerve blocks Interpleural Epidural Intrathecal[a]	Maximum dose: 3 mg/kg (Ca, Eq, Bo, Ov, Cp, Sw), 1.5 mg/kg (Fe) Epidural: 1 mg/kg of 0.5% sol. (0.2 mL/kg) (Ca, Fe, Ov, Cp, Sw), 6 mL total (Eq, Bo)
Ropivacaine	Naropin	Infiltration Nerve blocks Interpleural Epidural Intrathecal[a]	Maximum dose: 3 mg/kg (Ca, Eq, Bo, Ov, Cp, Sw), 1.5 mg/kg (Fe) Epidural: 1 mg/kg of 0.5% sol. (0.2 mL/kg) (Ca, Fe, Ov, Cp, Sw), 6 mL total (Eq, Bo)

[a]Intrathecal dose is 1/10th of epidural dose.
Ca Canine, Fe Feline, Eq Equine, Bo Bovine, Ov Ovine, Cp Caprine, Sw Swine.

biphasic effect on peripheral vasculature, causing vasoconstriction at concentrations below 0.5% and vasodilation at concentrations over 1% (Table 17.4) [275].

Adverse effects

Systemic toxicity

Local anesthetic drugs may cause central nervous system (CNS) and cardiac toxicity at high plasma concentrations. Plasma concentrations are determined by the rate of drug absorption into the systemic circulation, but the most common reason for excessive plasma concentrations is the inadvertent direct intravascular injection of the local anesthetic solution while performing peripheral or neuraxial blocks. Local anesthetics vary considerably in their potency at causing systemic toxic reactions, and generally this potency follows the same rank order as their potency at producing nerve blockade [276]. More lipid-soluble drugs (i.e., bupivacaine) are more potent at causing systemic toxicity than less lipid-soluble agents (i.e., lidocaine or mepivacaine), and the *S*-enantiomers or levoisomers (i.e., levobupivacaine or ropivacaine) are less toxic than the *R*-enantiomers or dextroisomers, or than the racemic mixture of both [277–280].

The dose of a local anesthetic causing systemic toxicity will depend on the route and speed of administration (rapid intravenous administration will be more likely to cause high plasma levels), the species involved, and patient factors (such as acid–base balance, serum potassium levels and whether the animal is under anesthesia).

The clinical incidence of systemic toxicity in domestic animals is unknown. The incidence of systemic toxicity associated with regional anesthetic blocks in humans is estimated to be around 1 in 10 000, with peripheral blocks having the highest incidence (7.5 in 10 000) [281,282].

Central nervous system toxicity

Central nervous system toxic signs follow a progression as the plasma concentration of local anesthetic increases (Fig. 17.5). At low doses, all local anesthetics are effective anticonvulsants, and they also have sedative effects [283]. In conscious, unsedated humans, the initial signs of local anesthetic CNS toxicity include tongue numbness, light-headedness, dizziness, drowsiness, paresthesia of sight and sound, and acute anxiety or even fear of death [284]. In horses, this has been described as alteration in visual function, rapid eye blinking, anxiety, mild sedation, and ataxia [268,269,285]. As the plasma level rises, local anesthetics inhibit inhibitory cortical neurons in the temporal lobe or the amygdala, allowing facilitatory neurons to function in an unopposed fashion, resulting in increased excitatory activity, which first leads to muscle twitching followed by grand mal seizures [276,283]. As the plasma concentration increases further, local anesthetics can inhibit both inhibitory and facilitatory pathways, resulting in CNS depression, unconsciousness, and coma [276,283].

Not all local anesthetics produce signs of aura, such as drowsiness or excitement, before the onset of seizures. With the highly lipophilic, highly protein-bound agents such as bupivacaine, the excitement phase can be brief and mild and the first signs may be bradycardia, cyanosis, and unconsciousness [286].

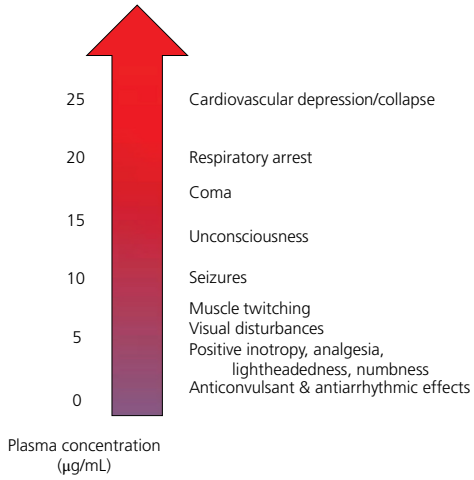

Figure 17.5 Progressive signs of lidocaine systemic toxicity with increasing plasma concentrations. Note: concentrations are approximate and depend on various factors (see text).

Central nervous system toxicity is generally assumed to precede cardiovascular toxicity. This derives from studies in conscious sheep where the doses and plasma drug concentrations associated with cardiovascular collapse (CV, defined as the disappearance of pulsatile blood pressure) and CNS toxicity (signified by the onset of seizures) were calculated as the CV:CNS ratio. Values for the CV:CNS ratio for various local anesthetics in conscious sheep are much greater than 1, supporting this notion [278,287].

In humans, the frequency of seizures and accompanying cardiovascular changes associated with various regional block techniques has been reviewed. There is a significant difference between the rate of seizure development with caudal > brachial plexus > epidural blocks, with no adverse cardiovascular or pulmonary effects occurring during seizures [288].

In conscious dogs, the mean cumulative dose required for convulsive activity was 4 mg/kg for tetracaine, 5 mg/kg for bupivacaine, 8 mg/kg for etidocaine, and 22 mg/kg for lidocaine in one study [9]. In another study, administration of intravenous infusions of lidocaine (8 mg/kg/min), bupivacaine (2 mg/kg/min), or ropivacaine (2 mg/kg/min) caused generalized seizures at an average dose of 21 mg/kg of lidocaine, 4 mg/kg of bupivacaine, and 5 mg/kg of ropivacaine in conscious dogs [289]. The first seizure activity observed with lidocaine toxicity in dogs was tonic extension at an infused dose of 12 mg/kg, followed by running activity after 23 mg/kg, and with tonic-clonic seizures occurring at an infused dose of 33 mg/kg [290]. The plasma concentration of lidocaine causing muscle tremors was 2.7 μg/mL after administration of a total dose of 11.1 mg/kg IV to conscious dogs [291]. The onset of seizures occurred when lidocaine plasma concentrations reached 8.2 μg/mL in another study involving awake dogs [292].

In conscious horses the mean toxic plasma concentration of lidocaine causing muscle fasciculations was determined to be 3.24 μg/mL (range 1.85–4.53 μg/mL), and it did not change regardless of speed of administration [285]. Such plasma concentrations may be achieved during prolonged lidocaine IV infusions of greater than 12 h in postcolic surgery horses [293,294].

In lightly anesthetized and ventilated cats, seizures occurred after administration of 12 mg/kg of lidocaine and 5 mg/kg of bupivacaine given at intravenous infusion rates of 16 mg/kg/min and 4 mg/kg/min, respectively [295]. The CV:CNS toxicity ratio for drug dosage was 4.0 with lidocaine and 4.8 with bupivacaine [295].

In conscious sheep, the doses of infused lidocaine, bupivacaine, and ropivacaine necessary to produce convulsions were 6.8 mg/kg, 1.6 mg/kg, and 3.5 mg/kg, respectively [296]. Therefore, the ratio of the mean convulsant doses (lidocaine/bupivacaine/ropivacaine) was approximately 5:1:2 [296].

There is an inverse relationship between the seizure threshold dose of local anesthetics and the arterial carbon dioxide tension [297]. This may be due to an increase in cerebral blood flow during hypercapnia causing increased delivery of drug to the brain and/or a decrease in plasma protein binding of local anesthetics causing an increase in free drug [298]. Hypoxemia also increases the CNS and cardiovascular toxicity of local anesthetics [299].

Cardiovascular toxicity

At low concentrations, most local anesthetics have an antiarrhythmic effect, but at higher concentrations, they produce cardiac toxicity. Local anesthetics block cardiac Na^+ channels and decrease the maximum rise of Phase 0 of the action potential, leading to a pronounced and evolving inhibition of cardiac conduction [300]. Electrocardiographic changes include prolonged PR and QRS intervals and a prolonged refractory period [300–302]. The cardiovascular effects of local anesthetics are complex and non-linear, involving direct effects on cardiac conduction and contractility and on vascular smooth muscle and also indirect effects mediated by the CNS [276].

All local anesthetics cause myocardial depression with small intravenous doses that cause no overt CNS toxicity [280,303]. At subconvulsant doses, heart rate may increase slightly and the QRS complex may widen, but there are no major effects on blood pressure and cardiac output [280,303]. These effects are mild and rapidly reversed, with no qualitative differences among local anesthetics [280]. At the onset of convulsions, there is a profound sympathetic response associated with all local anesthetics, which reverses the induced myocardial depression causing tachycardia and increased blood pressure and cardiac output [279,280,296]. Convulsant doses of all longer acting local anesthetics cause marked arrhythmias, typically ventricular tachycardia, that may progress to ventricular fibrillation or cardiovascular collapse [279,304]. Supraconvulsant doses of lidocaine cause profound hypotension, bradycardia, decreases in myocardial contractility, respiratory arrest, and ultimately asystole [279,296].

It has been postulated that the CNS toxic effects may be involved in the production of serious cardiotoxicity because of the onset of respiratory failure accompanied by hypoxia, bradycardia, hypercapnia, and acidosis [283].

While all local anesthetics cause direct negative inotropic effects, the shorter acting local anesthetics such as lidocaine and mepivacaine are less arrhythmogenic than the longer acting ones, such as bupivacaine or ropivacaine [279,304]. These differences are caused by differences in the kinetics of binding and unbinding from various ion channels [305,306]. While both shorter and longer acting agents have similar rates of binding to cardiac Na^+ channels, the longer acting agents have slower unbinding rates, hence predisposing to cardiac arrhythmias [276]. The *R*-enantiomers of the more lipophilic local anesthetics have slower unbinding rates than the *S*-enantiomers, thereby making them even more arrhythmogenic [305,306].

No ventricular arrhythmias were observed with cardiotoxic doses of lidocaine in conscious dogs [279]. Ventricular tachycardia with no hemodynamic impairment was observed in only one of eight conscious sheep with lidocaine and one of seven with mepivacaine [304]. In contrast, ventricular arrhythmias occurred in one of six conscious dogs with cardiotoxic doses of ropivacaine and five of six with bupivacaine [279]. Polymorphic ventricular tachycardia accompanied by decreased cardiac output occurred in seven of ten conscious sheep receiving bupivacaine, 4 of 11 with levobupivacaine and 5 of 12 with ropivacaine [304]. Even though the newer local anesthetics ropivacaine and levobupivacaine appear to be less cardiotoxic than bupivacaine (judging by the larger doses tolerated before the onset of serious arrhythmias), they must not be regarded as totally safe [307].

General anesthesia has a substantial impact on toxicity, mortality, and pharmacokinetics of various local anesthetics and distorts pharmacokinetic-pharmacodynamic relationships. In a study in halothane-anesthetized sheep, the pre-existing myocardial depression from halothane was markedly exacerbated by infusions of lidocaine, mepivacaine, prilocaine, bupivacaine, levobupivacaine or ropivacaine [304]. The cardiovascular toxic effects of each local anesthetic were also prolonged in anesthetized sheep compared with conscious sheep, and concurrently, the blood drug concentrations were markedly increased under general anesthesia. However, no serious arrhythmias occurred in any anesthetized sheep. Despite the exaggerated cardiovascular effects of the local anesthetics when the sheep were anesthetized, none of them died, whereas approximately 15% died from fatal cardiac arrhythmias when conscious [304].

As the K^+ gradient across cardiac myocyte membranes is the most important factor in establishing the membrane potential, hyperkalemia can markedly increase local anesthetic toxicity. Under conditions of hyperkalemia (5.4 mEq/L) in dogs, the cardiotoxic doses of both lidocaine and bupivacaine were halved compared to conditions of normokalemia, while the seizure-inducing doses did not change for either agent [308]. Conversely, hypokalemia decreases local anesthetic cardiotoxicity [308].

Treatment of systemic toxicity

When signs of systemic toxicity are noted, the administration of local anesthetic should be discontinued. Treatment of systemic toxicity is primarily supportive (Box 17.1). Oxygenation and ventilation are the main goals. It may be necessary to intubate the trachea and mechanically ventilate the animal to avoid or reverse hypoxemia, hypercapnia, and acidosis, all of which promote toxicity. If grand mal seizures are present, an anticonvulsant drug may be administered. If cardiovascular depression is also present, barbiturates or propofol are not recommended and treatment with a benzodiazepine is preferable.

Box 17.1 Guidelines for treatment of local anesthetic systemic toxicity.

CNS toxicity
1. Intubate trachea, administer O_2 and ventilate.
2. Treat seizures with a benzodiazepine.

Cardiac arrest
1. Start basic cardiopulmonary resuscitation.
2. Administer epinephrine at low doses (≤1 μg/kg IV).
3. AVOID lidocaine, vasopressin, calcium channel blockers, and β-blockers.
4. Administer a 20% lipid emulsion IV.
   - Initial bolus 1.5–4 mL/kg over 1 min.
   - Continue with CRI at 0.25 mL/kg/min for 30–60 min.
   - If non-responsive administer additional boluses of 1.5 mL/kg (up to maximum 7 mL/kg).
   - CRI may be continued at 0.5 mL/kg/h until clinical signs improve (24 h maximum).

Data obtained from references 309 and 319.

Cardiovascular toxicity induced by lidocaine or mepivacaine is usually mild and reversible with the use of positive inotropic drugs and fluid support [15]. Cardiac arrhythmias produced by longer acting local anesthetics such as bupivacaine (i.e., ventricular tachycardia or fibrillation) are usually malignant and refractory to routine treatment. In these cases, cardiopulmonary resuscitation should be immediately instituted and defibrillation initiated if necessary. In humans, the guidelines of the American Society of Regional Anesthesia and Pain Medicine recommend using low doses of epinephrine (<1 μg/kg) and avoiding vasopressin [309]. Calcium channel blockers should not be administered as their cardiodepressant effects are exaggerated [310]. Amiodarone rather than lidocaine is indicated to treat ventricular arrhythmias in this setting [310]. In cases of refractory cardiac arrest, it is recommended to use an intravenous lipid emulsion (i.e., Intralipid® 20%), which has been shown to reverse refractory arrhythmias caused by highly lipophilic local anesthetics in different experimental models [311,312] and in human clinical reports [313–315].

In a rodent model of bupivacaine-induced asystole in animals pretreated with an intravenous lipid solution, the median lethal dose (LD_{50}) of bupivacaine increased by 48% [311]. In a dog model of bupivacaine-induced cardiotoxicity (10 mg/kg IV), cardiopulmonary resuscitation was instituted for 10 min and then dogs received similar volumes of either intravenous saline fluid or a 20% lipid solution (4 mL/kg over 2 min, followed by 0.5 mL/kg/min over 10 min) [312]. Notably, all dogs in the saline control group failed to regain spontaneous circulation and died, while all dogs treated with the lipid solution survived, achieving near baseline blood pressure and heart rate values within 30 min of its administration [312]. Later studies in rats have demonstrated the potential adverse effects of epinephrine administered at high doses during lipid emulsion rescue with a higher incidence of ventricular arrhythmias, hyperlactatemia, hypoxia, acidosis, and pulmonary edema [316,317]. Another study in rats also demonstrated worse outcomes when vasopressin was administered alone or in combination with epinephrine compared with a lipid emulsion [318].

The exact mechanism of action of lipid emulsions is unknown and is likely multifactorial, but it is thought to be related to improved myocardial performance and a 'lipid sink' effect, which postulates that the lipophilic local anesthetic is sequestered into a lipid compartment within the bloodstream [319].

Propofol should not be administered as a substitute for intravenous lipid emulsions as its lipid content is too low (10%) and the large doses required would induce profound cardiovascular depression.

Local toxicity

Neurotoxicity

Exposure of the peripheral or central nervous systems to local anesthetics can cause direct damage, although this complication is rare. Mechanisms of local anesthetic neurotoxicity remain speculative, but some studies suggest injury to Schwann cells, which is time and concentration dependent [320], inhibition of fast axonal transport, disruption of the blood–nerve barrier, decreased neural blood flow with associated ischemia [321], and disruption of cell membrane integrity due to a detergent property of local anesthetics [322].

All local anesthetics are potentially neurotoxic and neurotoxicity parallels anesthetic potency. The *in vitro* rank order of potency for cytotoxicity is procaine ≤ mepivacaine < lidocaine < chloroprocaine < ropivacaine < bupivacaine, based on the LD_{50} for neuronal cells [274]. Neurotoxicity is also related to the concentration of local anesthetic. Clinically relevant concentrations of local anesthetics are considered safe for peripheral nerves [323]. The spinal cord and nerve roots, on the other hand, are more prone to injury [15]. Intrathecal administration of 8% lidocaine, 2% bupivacaine, and 1% tetracaine, but not of 2% chloroprocaine and 2% ropivacaine, caused histopathologic changes in the spinal cord and neurologic deficits in rabbits [324]. The cytotoxic effect of lidocaine and bupivacaine is concentration dependent, with higher concentrations causing death of all cells in culture. In contrast, mepivacaine, ropivacaine, procaine, and chloroprocaine did not kill all cells even at very high concentrations [274].

The effects of local anesthetics on spinal cord blood flow appear to be benign, and do not seem responsible for spinal cord neurotoxicity. Intrathecal administration of lidocaine, mepivacaine, bupivacaine, and tetracaine cause vasodilation and increase spinal cord blood flow, whereas ropivacaine causes vasoconstriction and decreases spinal cord blood flow, with both effects being concentration dependent [63].

The incidence of long-term neurologic injury in human patients undergoing spinal anesthesia is 0-0.02% [282]. Therefore, it seems to be a relatively safe technique in clinical practice if properly performed using clinically appropriate local anesthetic concentrations.

Myotoxicity

Local anesthetics can cause toxicity to skeletal muscle. Experimentally, all local anesthetics have the potential for myotoxicity at clinically relevant concentrations. Myotoxicity is concentration dependent, as observed in a study in rabbits where extraocular muscle injection with 0.75% bupivacaine caused acute myonecrosis and degeneration, compared with only scattered and significantly fewer areas of mild muscle fiber degeneration with 0.38% bupivacaine, and no muscle degeneration observed when the injection was with 0.19% bupivacaine [325]. Bupivacaine seems to be more myotoxic than other local anesthetics as judged by the larger extent of muscle lesions observed [326]. The mechanism of local anesthetic-induced muscle toxicity is likely to be related to dysregulation of intracellular calcium concentration and/or alterations in mitochondrial bioenergetics [327].

In most cases, local anesthetic-induced myonecrosis appears to be regenerative and clinically imperceptible. However, bupivacaine and ropivacaine produced irreversible skeletal muscle damage characterized by calcific myonecrosis observed 4 weeks after peripheral nerve blockade in a study in pigs [326].

Clinically relevant myopathy and myonecrosis have been described in humans after receiving continuous peripheral blocks, infiltration of wound margins, trigger point injections, and peri- and retrobulbar blocks [328].

Chondrotoxicity

Local anesthetics are sometimes injected intra-articularly in clinical practice. Local anesthetic chondrotoxicity has been demonstrated both *in vivo* and *in vitro* in both animal and human cartilage [329–332]. Clinically, chondrolysis has been associated with the use of intra-articular local anesthetic pain pumps in humans [333,334].

The chondrotoxicity exhibited by local anesthetics is time and concentration dependent. *In vitro* bovine chondrocyte viability decreased after just 15 min of exposure to 1% lidocaine, and longer exposures to 1% and 2% lidocaine further reduced chondrocyte viability [330]. Chondrocyte viability was reduced to a larger extent when exposed to 2% lidocaine than to 1% lidocaine [330]. This study also showed that the intact articular surface is not protective against local anesthetic chondrotoxicity [330].

In vitro exposure of equine chondrocytes to 0.5% bupivacaine, 2% lidocaine, or 2% mepivacaine for 30 or 60 min revealed that bupivacaine is the most chondrotoxic of the three local anesthetics and that mepivacaine is the least toxic [331]. Ropivacaine is also significantly less toxic than bupivacaine and lidocaine in both intact human articular cartilage and chondrocyte culture [335,336]. The marked chondrotoxicity exhibited by bupivacaine and lidocaine is mainly due to necrosis rather than apoptosis [331].

In conclusion, evidence suggests that there is a greater risk for chondrolysis with a longer exposure to a higher concentration of local anesthetic, such as with a pain pump, than with a single injection, and that mepivacaine seems to be the least toxic and consequently the preferred drug for intra-articular administration at the present time.

Methemoglobinemia

Methemoglobin (MHb) formation may be induced by certain local anesthetics in several animal species and in humans. Methemoglobin is produced by oxidative damage to the hemoglobin molecule. Specifically, the iron of the heme group is oxidized to the ferric (Fe^{3+}) form. In this state, it cannot bind oxygen (O_2) and therefore blood oxygen-carrying capacity is decreased. The physiologic range of MHb in the blood is 0–2% [337]. Concentrations of MHb of 10–20% are tolerated well, but higher levels are often associated with clinical signs, and levels above 70% may cause death [337]. Oxidative denaturation of hemoglobin can cause Heinz body formation (precipitated hemoglobin or globin subunits), which is irreversible and decreases the lifespan of red blood cells and causes hemolysis.

The local anesthetics more often associated with MHb formation are the ester-type benzocaine and the amide-type prilocaine. Administration of a 2 s spray of benzocaine (estimated dose 56 mg) to the mucous membranes of the nasopharynx of dogs, cats, ferrets, monkeys, rabbits, and miniature pigs induced MHb formation ranging from 3.5% to 38% 15–60 min after administration in more than 95% of the animals tested [338]. In sheep, intranasal administration of topical benzocaine for 2 s caused MHb in half of the animals tested, ranging from 16% to 26%, and a 10 s spray caused MHb levels of up to 50.5% [339,340]. Dermal administration of benzocaine has also been implicated in clinical cases of methemoglobinemia in dogs and cats [341,342]. An *N*-hydroxy metabolite of benzocaine (i.e., O-toluidine) is the likely active MHb-forming substance [339]. Prilocaine has been implicated in cases of methemoglobinemia in mothers and fetuses following epidural administration for labor [343] and following topical administration for dental procedures in humans [337]. Topical lidocaine did not induce MHb formation in sheep or monkeys, but it may be associated with MHb formation in cats and humans [339,344].

When MHb levels are 30% or higher, clinical signs of tissue hypoxia occur including cyanosis, dyspnea, nausea, vomiting, and tachycardia [337,341]. Lethargy, stupor, and shock occur when MHb levels approach 55% [337,342]. Animals with chronic methemoglobinemia may only present with Heinz body anemia and lethargy [342]. Chocolate brown-colored blood together with clinical signs that are not responsive to O_2 therapy are suggestive of methemoglobinemia. Definitive diagnosis is made by measuring the MHb

concentration with co-oximetry or spectrophotometry. Blood smears will reveal the presence of Heinz bodies in the red blood cells.

Traditional first-line therapy of methemoglobinemia consists of slow intravenous administration of 1% methylene blue solution (4 mg/kg in dogs, 1–2 mg/kg in cats) [36]. The action of methylene blue depends on the availability of reduced nicotinamide adenine dinucleotide phosphate (NADPH) within red blood cells [337]. This dose can be repeated in dogs, but caution should be exercised in cats as repeated injections of methylene blue can markedly aggravate subsequent hemolysis without further lowering MHb content [345]. Dextrose should also be administered because it is the major source of reduced nicotinamide adenine dinucleotide (NADH) in red blood cells, which is necessary to form NADPH, which is in turn needed for methylene blue to be effective [337]. In severe cases a blood transfusion may be required.

Toxicosis (Oral ingestion)

Topical preparations containing lidocaine, benzocaine, and tetracaine are found in many prescription and non-prescription products, such as ointments, teething gels, suppositories, and aerosols. These topical local anesthetic preparations can be hazardous if ingested or inappropriately applied to animals. Between 1995 and 1999 the American Society for the Prevention of Cruelty to Animals (ASPCA) Animal Poison Control Center (APCC) consulted on more than 70 cases of local anesthetic toxicosis in a variety of animal species [346]. Benzocaine toxicosis cases reported to the ASPCA APCC involved either ingestion of topical preparations or application of a laryngeal spray before endotracheal intubation. Clinical signs in cats and ferrets with benzocaine toxicosis included varying degrees of vomiting, depression, cyanosis, dyspnea, and tachypnea [346]. Other signs observed with local anesthetic toxicosis in different species include prolonged sedation, vasodilation (leading to hypotension), cardiac arrhythmias, respiratory depression, tremors and seizures, and death [346].

Allergic reactions

Ester-type local anesthetics (e.g., procaine) are associated with a higher incidence of allergic reactions due to a p-aminobenzoic acid (PABA) metabolite. Amide-type agents do not undergo such metabolism and rarely cause allergic reactions. However, preservative compounds (i.e., methylparaben, sodium metabisulfite) used in preparations of amide-type local anesthetics are metabolized to PABA and may cause allergies [347,348]. Therefore, it is recommended that animals known to be allergic to ester-type local anesthetics be treated with a preservative-free amide-type agent [347].

Allergic reactions of dogs and cats treated with amide-type local anesthetics are very rare when compared with humans, which is probably because of their different metabolism and breakdown products [36].

Anaphylactic reactions are characterized by bronchospasm, upper airway edema, vasodilation, increased capillary permeability, and cutaneous wheal and flare [36]. Rapid intervention with airway maintenance, O_2 therapy, epinephrine administration, and volume expansion is essential to avoid a fatal outcome.

References

1 Komai H, McDowell TS. Local anesthetic inhibition of voltage-activated potassium currents in rat dorsal root ganglion neurons. *Anesthesiology* 2001; **94**: 1089–1095.

2 Olschewski A, Hempelmann G, Vogel W, *et al*. Blockade of Na + and K + currents by local anesthetics in the dorsal horn neurons of the spinal cord. *Anesthesiology* 1998; **88**: 172–179.

3 Xiong ZL, Strichartz GR. Inhibition by local anesthetics of Ca2+ channels in rat anterior pituitary cells. *Eur J Pharmacol* 1998; **363**: 81–90.

4 Sugiyama K, Muteki T. Local anesthetics depress the calcium current of rat sensory neurons in culture. *Anesthesiology* 1994; **80**: 1369–1378.

5 Scholz A. Mechanisms of (local) anaesthetics on voltage-gated sodium and other ion channels. *Br J Anaesth* 2002; **89**: 52–61.

6 Hollmann MW, Wieczorek KS, Berger A, *et al*. Local anesthetic inhibition of G protein-coupled receptor signaling by interference with Galpha(q) protein function. *Mol Pharmacol* 2001; **59**: 294–301.

7 Fozzard HA, Lee PJ, Lipkind GM. Mechanism of local anesthetic drug action on voltage-gated sodium channels. *Curr Pharm Des* 2005; **11**(21): 2671–2686.

8 Catterall WA. From ionic currents to molecular mechanisms: the structure and function of voltage-gated sodium channels. *Neuron* 2000; **26**(1): 13–25.

9 Narahashi T, Frazier DT. Site of action and active form of local anesthetics. *Neurosci Res* 1971; **4**: 65–99.

10 Wann KT. Neuronal sodium and potassium channels: structure and function. *Br J Anaesth* 1993; **71**(1): 2–14.

11 Yun I, Cho ES, Jang HO, *et al*. Amphiphilic effects of local anesthetics on rotational mobility in neuronal and model membranes. *Biochim Biophys Acta* 2002; **1564**(1): 123–132.

12 Hille B. Local anesthetics: hydrophilic and hydrophobic pathways for the drug–receptor reaction. *J Gen Physiol* 1977; **69**(4): 497–515.

13 Starmer CF, Grant AO, Strauss HC. Mechanisms of use-dependent block of sodium channels in excitable membranes by local anesthetics. *Biophys J* 1984; **46**(1): 15–27.

14 Huang JH, Thalhammer JG, Raymond SA, *et al*. Susceptibility to lidocaine of impulses in different somatosensory afferent fibers of rat sciatic nerve. *J Pharmacol Exp Ther* 1997; **292**: 802–811.

15 Liu SS, Joseph RS. Local anesthetics. In: Barash PG, Cullen BF, Stoelting RK, eds. *Clinical Anesthesia*, 5th edn. Philadelphia: Lippincott Williams & Wilkins, 2006; 453–471.

16 Stevens RA, Bray JG, Artuso JD, *et al*. Differential epidural block. *Reg Anesth* 1992; **17**: 22–25.

17 Sakura S, Sumi M, Yamada Y, *et al*. Quantitative and selective assessment of sensory block during lumbar epidural anaesthesia with 1% or 2% lidocaine. *Br J Anaesth* 1998; **81**: 718–722.

18 Nathan PW. Observations on sensory and sympathetic function during intrathecal analgesia. *J Neurol Neurosurg Psychiatry* 1976; **39**: 114–121.

19 Gasser HS, Erlanger J. Role of fibre size in the establishment of nerve block by pressure or cocaine. *Am J Physiol* 1929; **88**: 581–591.

20 Gissen AJ, Covino BG, Gregus J. Differential sensitivities of mammalian nerve fibers to local anesthetic agents. *Anesthesiology* 1980; **53**: 467–474.

21 Gokin AP, Philip B, Strichartz GR. Preferential block of small myelinated sensory and motor fibers by lidocaine: in vivo electrophysiology in the rat sciatic nerve. *Anesthesiology* 2001; **95**: 1441–1454.

22 Strichartz G, Pastijn E, Sugimoto K. Neural physiology and local anesthetic action. In: Cousins MJ, Carr DB, Horlocker TT, Bridenbaugh, eds. *Cousins & Bridenbaugh's Neural Blockade in Clinical Anesthesia and Pain Medicine*, 4th edn. Philadelphia: Lippincott Williams & Wilkins, 2009; 26–47.

23 Jaffe RA, Rowe MA. Differential nerve block. Direct measurements on individual myelinated and unmyelinated dorsal root axons. *Anesthesiology* 1996; **84**: 1455–1464.

24 Raymond SA, Steffensen SC, Gugino LD, *et al*. The role of length of nerve exposed to local anesthetics in impulse blocking action. *Anesth Analg* 1989; **68**: 563–570.

25 Fink BR. Mechanisms of differential axial blockade in epidural and subarachnoid anesthesia. *Anesthesiology* 1989; **70**: 851–858.

26 Condouris GA, Goebel RH, Brady T. Computer simulation of local anesthetic effects using a mathematical model of myelinated nerve. *J Pharmacol Exp Ther* 1976; **196**: 737–745.

27 Nakamura T, Popitz-Bergez F, Birknes J, *et al*. The critical role of concentration for lidocaine block of peripheral nerve in vivo. Studies of function and drug uptake in the rat. *Anesthesiology* 2003; **99**: 1187–1197.

28 Waikar SS, Thalhammer JG, Raymond SA, *et al*. Mechanoreceptive afferents exhibit functionally-specific activity dependent changes in conduction velocity. *Brain Res* 1996; **721**: 91–100.

29 Raymond SA. Subblocking concentrations of local anesthetics: effects on impulse generation and conduction in single myelinated sciatic nerve axons in frog. *Anesth Analg* 1992; **75**: 906–921.

30 Olschewski A, Wolff M, Bräu ME, *et al*. Enhancement of delayed-rectifier potassium conductance by low concentrations of local anaesthetics in spinal sensory neurones. *Br J Pharmacol* 2002; **136**: 540–549.

31 Olschewski A, Schnoebel-Ehehalt R, Li Y, *et al*. Mexiletine and lidocaine suppress the excitability of dorsal horn neurons. *Anesth Analg* 2009; **109**: 258–264.

32 Ku WH, Schneider SP. Multiple T-type Ca^{2+} current subtypes in electrophysiologically characterized hamster dorsal horn neurons: possible role in spinal sensory integration. *J Neurophysiol* 2011; **106**: 2486–2498.