

# Practical Pharmacology in Regional Anesthesia

Jose A. Aguirre • Gina Votta-Velis • Alain Borgeat

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J.A. Aguirre, MD, MSc • A. Borgeat, MD  
 Division of Anesthesiology, Balgrist University Hospital Zurich,  
 Forchstrasse 340, Zurich 8008, Switzerland  
 e-mail: jose.aguirre@balgrist.ch

G. Votta-Velis, MD, PhD (✉)  
 Department of Anesthesia, University of Illinois at Chicago, 1740 W. Taylor Street,  
 Suite 3200W, Chicago, IL 60612, USA

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## Introduction

Local anesthetics are the pharmacologic cornerstone of regional anesthesia producing reversible and complete blockade of neuronal transmission when applied near the axons. Their application results in complete interruption of nerve impulse conduction, allowing abolition of sensation from the area innervated by the corresponding nerves and leading also to motor block. A number of compounds with local anesthetic activity occur in nature such as cocaine, eugenol derived from plants, tetrodotoxin derived from fish species in the family *Tetraodontiformes*, and saxitoxin derived from algae (*dinoflagellates*). The first reported medicinal use of a drug as a local anesthetic occurred in 1884 when Carl Koller used cocaine to anesthetize the eye by topical application.

This chapter describes the basic chemical structure of local anesthetics, the basic receptor pharmacology, and gives an overview over pharmacologic properties of the different drugs. Clinical use, advantages, and side effects are compared. Finally, some clinical pearls are highlighted, and local anesthetic toxicity is described.

## Local Anesthetics

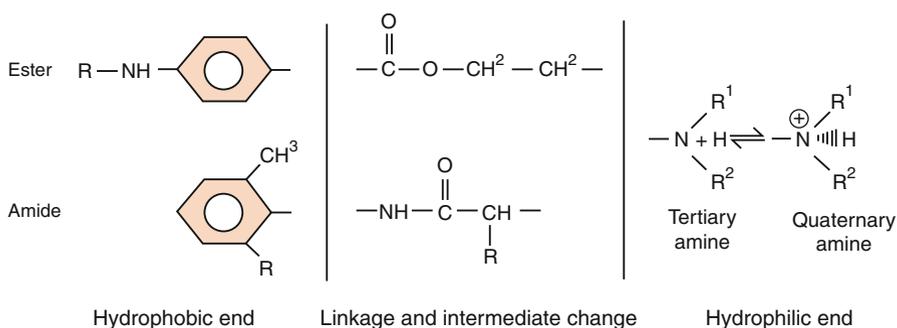
### Chemical Structure

Local anesthetic molecules are comprised of three basic building blocks: a hydrophobic aromatic ring, a hydrophilic tertiary amine, and an intermediate chain connecting the two. Hydrocarbon chain length varies between 6 and 9 Å. The chemical connection between the intermediate chain and the aromatic ring divides local anesthetics in “esters” and “amides” depending on whether the hydrocarbon chain is joined to the benzene-derived moiety by an ester or an amide linkage (Fig. 5.1). The type of linkage is important as it determines how local anesthetics are metabolized. Moreover, this chemical differentiation is clinically relevant because the amides are more stable and have less risk of allergic reaction than the esters (Table 5.1).

### Site of Action and Nerve Conduction

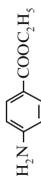
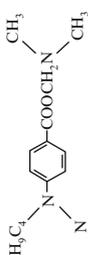
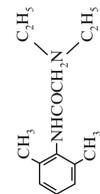
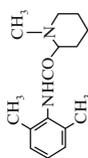
#### Sodium Channel Structure

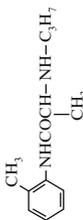
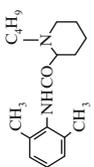
The human sodium channel is a transmembrane protein composed of three subunits forming a voltage-sensitive and sodium-selective channel [1] (Fig. 5.2). Different isoforms are expressed in different tissues (muscle, heart, central nervous system, peripheral nervous system, etc.) [2]. Mutations with different sensitivity to local anesthetics are possible and have been shown in the experimental but not (yet) in clinical setting [3].



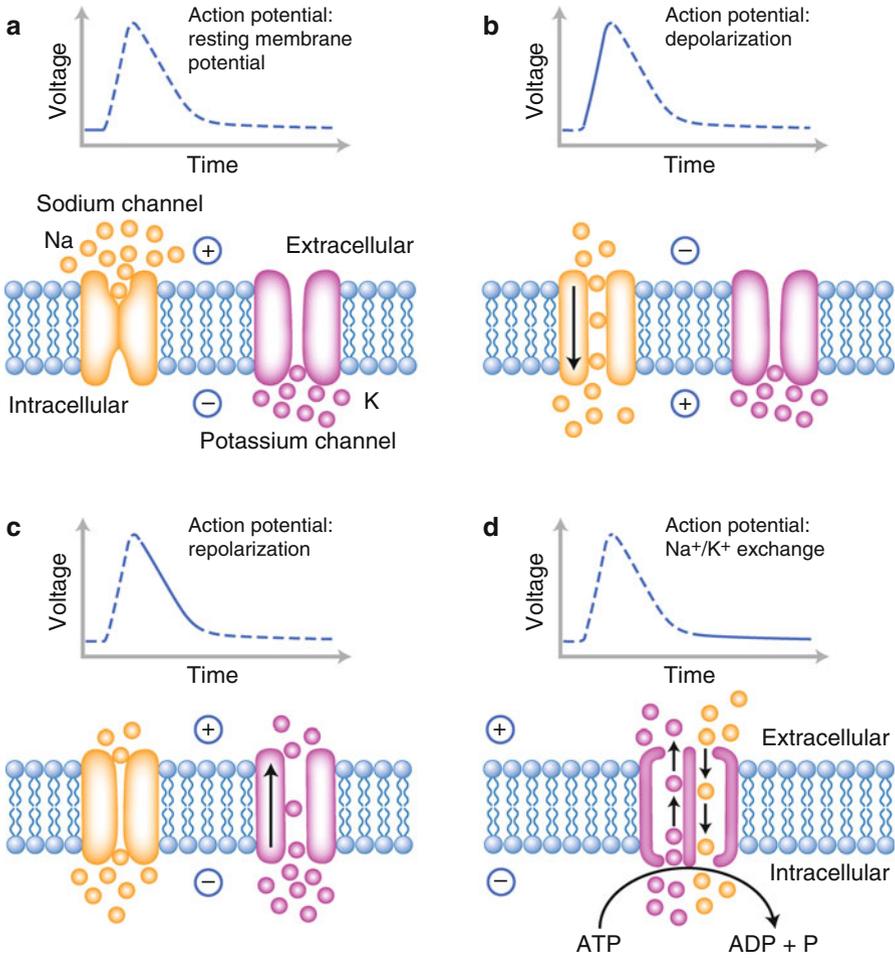
**Fig. 5.1** Typical structure of local ester and amide anesthetic molecules: a practical approach to regional anesthesia. 4th ed; Mulroy Michael F; Wolters Kluwer/Lippincott Williams & Wilkins 2009, Philadelphia; ISBN-13: 978-0-7817-6854-2. p 2

**Table 5.1** Physicochemical properties of local anesthetics: a practical approach to regional anesthesia, 4th ed. Mulroy Michael F; Wolters Kluwer/Lippincott Williams & Wilkins 2009, Philadelphia; ISBN-13:978-0-7817-6854-2, p. 3

Relative in vitro potency						
Drug (brand name)	Type (year introduced)	Chemical structure	Rat sciatic nerve	pK <sub>a</sub>	Partition coefficient <sup>a</sup>	Plasma protein binding
Cocaine	Ester	$\begin{array}{c} \text{CH}_2-\text{CH}-\text{CHCOOCH}_3 \\   \\ \text{NCH}_3-\text{CH} \\   \\ \text{CH}_2-\text{CH}-\text{CH}_2 \end{array}$	-	8.6	-	92
Procaine (Novocaine)	Ester (1905)		1	8.9	1.7	5.8
Benzocaine	Ester (1900)		-	3.5	81	-
Tetracaine (Pontocaine)	Ester (1930)		8	8.5	221	75.6
2-Chloroprocaine (Nesacaine)	Ester (1952)		1	8.7	9.0	NA
Lidocaine (Xylocaine)	Amide (1944)		2	7.72	2.4	64.3
Mepivacaine (Carbocaine, Polocaine)	Amide (1957)		2	7.6	21	77.5

Prilocaine (Citanest)	Amide (1960)		2	7.7	25	55
Ropivacaine (Naropin) (1995)	Amide (1995)		4	8.1	115	95
Bupivacaine (Marcaine, 1963) Sensorcaine) Levobupivacaine (Chirocaine)	Amide (1963)		8	8.1	346	95.6
Etidocaine (Durnest)	Amide (1972)		8	7.74	800	94

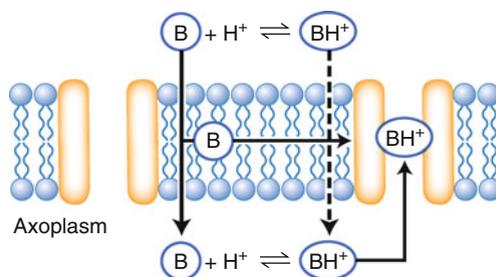
<sup>a</sup>Otanol: buffer pH 7.4



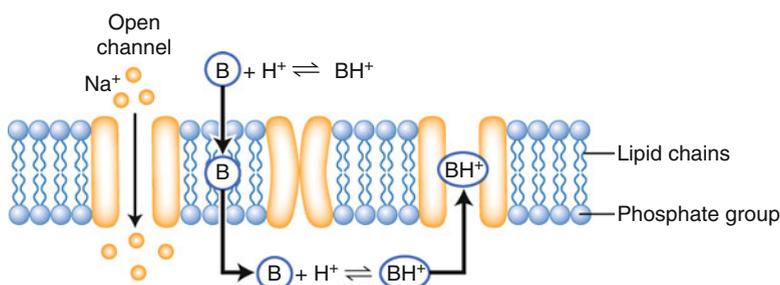
**Fig. 5.2** Sodium and potassium channel function and ion movements during nerve depolarization: a practical approach to regional anesthesia. 4th ed; Mulroy Michael F; Wolters Kluwer/Lippincott Williams & Wilkins 2009, Philadelphia; ISBN-13: 978-0-7817-6854-2. p 6

### Conduction

With electrical excitation of the neuron, a depolarizing stimulus is conducted down an axon. A stimulus of significant magnitude changes the negative resting potential from  $-70$  mV toward  $-55$  mV, the threshold required for complete depolarization: sodium channels in the cell membrane are activated and open permitting  $\text{Na}^+$  ions to



**Fig. 5.3** Model of local anesthetic interaction with the sodium channel. A practical approach to regional anesthesia. 4th ed; Mulroy Michael F; Wolters Kluwer/Lippincott Williams & Wilkins 2009, Philadelphia; ISBN-13: 978-0-7817-6854-2. p 7



**Fig. 5.4** Mechanism of action of local anesthetics. Regional anesthesia. The requisites in anaesthesiology. 1st ed. Rathmell James P, Elsevier Mosby 2004, Philadelphia; ISBN 0-323-02042-9. p.17

move down their electrochemical gradient intracellularly and locally “depolarize” the axonal membrane. This influx of cations rapidly changes the membrane potential to +35 mV. The resultant propagation of voltage change down the axon is defined as the action potential. Local anesthetic molecules traverse the cell membrane and then block the sodium channel from within the cell (Fig. 5.3) blocking propagation of the action along the nerve.

### ***Repolarization***

The sodium channel is inactivated after a few milliseconds by a time-dependent change in conformation closing an inactivation gate (Fig. 5.4). The inactivated state cannot conduct  $\text{Na}^+$  and is not reopened if further stimulated (refractory period). Thereafter, the  $\text{Na}^+$  channel changes further to the closed (resting) state. In this state, it cannot conduct  $\text{Na}^+$  ions, but with a sufficiently strong stimulus, will convert the channel to the open state.

## ***Binding of Local Anesthetics***

Local anesthetics do not bind to a classical “receptor”; it is more a “binding” site which is located within the sodium channel near its intracellular opening [3]. It is, on the one hand, a hydrophobic region to which the hydrophobic part of the local anesthetic molecule “binds,” on the other hand, a hydrophilic region with which the quaternary amine interacts. Any change in amino acid sequence can prevent local anesthetics from being effective.

Action potentials are blocked due to an inhibition of Na<sup>+</sup> movement through the Na<sup>+</sup> channel by a direct blocking or influencing the Na<sup>+</sup> channel conformation.

## **Pharmacodynamics and Physicochemical Properties of Local Anesthetics**

### ***Potency***

The minimal local anesthetic concentration required to produce neural blockade is defined as potency. Lipophilicity correlates in *in vitro* settings well with local anesthetic potency. *In vivo*, this correlation exists but is less stable.

### ***Phasic Block***

The faster a nerve is stimulated, the lower the concentration of local anesthetic is needed to produce a blockade (*in vitro*). This observation is called phasic block or rate-dependent block. Typically, phasic block occurs with more hydrophobic (potent) local anesthetics. They show a greater difference in their binding affinity in dependence of the different channel states compared to the less potent local anesthetics. There is no clear data about phasic block in the *in vivo* model, but phasic block seems to explain why hydrophobic local anesthetics are more cardiotoxic than hydrophilic local anesthetics.

### ***Anesthetic Block in Dependency of Nerve/Axon Exposed***

Axons are classified with respect to their structure (myelinated, unmyelinated), diameter, conduction velocity, and function. The characteristics of local anesthetic blockade vary among different axon types, but the exact role of size, myelination, or function in axonal blockade is, to date, not entirely clear (Table 5.2).

**Table 5.2** Axon classification<sup>a</sup>. A practical approach to regional anesthesia. 4th ed. Mulroy Michael F; Wolters Kluwer/Lippincott Williams & Wilkins 2009, Philadelphia; ISBN-13:978-0-7817-6854-2. p 9

Fiber type	Size (µm)	Function	Local anesthetic sensitivity (in vitro)	Illustrations
<i>A</i>				
<i>α</i>	12–20	Somatic motor, proprioception	++	
<i>β</i>	5–12	Touch, pressure Motor to muscle spindles	++	
<i>γ</i>	3–6	Motor to muscle spindles	+++	
<i>Δ</i>	2–5	Pain, temperature, touch	+++	
<i>B</i>	<3	Autonomic (preganglionic)	++	
<i>C</i>	0.3–1.4	Pain, reflex responses Autonomic (postganglionic)	+	

<sup>a</sup>Human axons are classified by size, presence or absence of myelin, and function, in vitro, small unmyelinated axons are most resistant to local anesthetic blockade, whereas large myelinated axons are the most sensitive. In vivo, however, the sensitivity to local anesthetic block is different for reasons that are not fully understood (See chapter clinical pharmacology of local anesthetics). “+” indicates the relative sensitivity to local anesthetic block.

- Unmyelinated axons: the concentration of local anesthetic required to block conduction of unmyelinated axons decreases with increasing length of nerve exposed to the local anesthetic.
- Myelinated axons: myelin consists of Schwann cell plasma membranes wrapped around axons. There are gaps, called nodes of Ranvier, at fixed intervals between the myelinated areas. Myelination results in much faster conduction velocities because the axonal membrane needs to be only depolarized at the node. This process is called saltatory conduction.
- Unmyelinated axons (C fibers) are in vitro the most resistant to local anesthetic blockade, followed by large ( $A\alpha$ ,  $A\beta$  fibers) and small (B fibers) myelinated axons [4]. Intermediate-size myelinated axons ( $A\delta$ ,  $A\gamma$  fibers) are the easiest axons to block in vitro.

Local anesthetics can gain access to axonal membrane of myelinated axons only at the nodes of Ranvier. In vitro, the  $\text{Na}^+$  channels in approximately three consecutive nodes (0.4–4 mm) need to be blocked for axonal conduction to fail.

### *Acid–Base and $pK_a$*

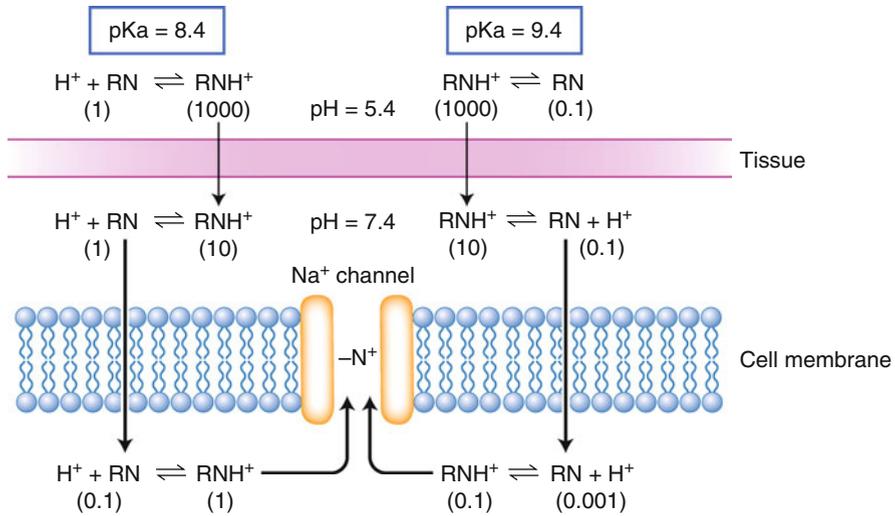
Local anesthetics (except benzocaine) are weak bases ( $pK_a = 7.6\text{--}9.0$ ) that are commercially prepared as an acidic solution, typically at pH 4–5. The  $pK_a$  defines the pH, where half of the drug is ionized (positively charged form, conjugate acid) and half is nonionized (base). The ionized and nonionized forms have different, but important, clinical effects. The nonionized form penetrates the nerve membrane, while the ionized form binds to proteins on the intracellular side of the sodium channel (Fig. 5.5). The percentage of each form present in a solution or in the tissue depends on the pH of the solution or tissue and can be calculated from the Henderson-Hasselbalch equation:

$$pK_a = \text{pH} - \log(\text{base})/(\text{acid}).$$

pH: pH in the solution/tissue;  $pK_a$ : pH at which half the local anesthetic molecules are in the base form and half in the acid form.

The  $pK_a$  of each local anesthetic is unique and measures the tendency of the molecule to accept a proton in the base form or to donate a proton in the acid form. Most local anesthetics have a  $pK_a$  between 7.5 and 9.0.

Sodium bicarbonate can be added to local anesthetic solutions to raise the pH of the solution, thereby increasing the nonionized form. Other factors being similar, local anesthetics with more basic  $pK_a$  have a slower onset of blockade effect due to the lesser amount of nonionized local anesthetic molecules at physiologic pH. This relative lack of the nonionized form impairs local anesthetic movement across the cell membrane and thus delays block onset (Fig. 5.5).



**Fig. 5.5** Effect of ionization on activity. Regional anesthesia. The requisites in anaesthesiology. 1st ed. Rathmell James P, Elsevier Mosby 2004, Philadelphia; ISBN 0-323-02042-9. p.18

### Hydrophobicity

The charged form of all local anesthetics is more hydrophilic than the uncharged form. Hydrophobicity correlates with potency and, to a certain extent, to duration of action: the more hydrophobic the drug, the more potent it is. Hydrophobicity facilitates penetration of the neuronal cell membrane, which accelerates local anesthetic binding to the intracellular portion of the sodium channel.

Adding local anesthetic to a recipient containing two immiscible liquids like an aqueous buffer and a hydrophobic lipid is needed to determine hydrophobicity. The resultant ratio of the concentrations is called the “distribution coefficient” (partition coefficient).

### Protein Binding

One of the most important clinical characteristics of local anesthetics is its duration of action, which correlates with the degree of local anesthetic protein binding (typically to albumin and  $\alpha$ -1-acid-glycoprotein). Binding to plasma protein varies between 5 and 95%. In general, more hydrophobic drugs have higher protein binding. However, plasma protein binding do not correlate necessarily with tissue protein binding.

Normally, short-acting local anesthetics have a fast onset of action, while long-duration local anesthetics have a slower onset of clinical effects. Serum protein binding also protects against drug toxicity because only the free (protein unbound) local anesthetic fraction can induce toxicity. However, once serum proteins are saturated, any additional administration or absorption of local anesthetics rapidly causes toxicity. Therefore, patients show a rapid progression from no signs of local anesthetic toxicity to manifestations of severe toxicity (CNS, cardiac) when highly protein-bound local anesthetics are used inadequately.

Binding to plasma proteins is mainly pH dependent: binding decreases during acidosis due to the decrease of available binding sites in an acidic environment.

## **Metabolism**

Ester local anesthetics are primarily metabolized by ubiquitous plasma cholinesterases (pseudocholinesterase). These enzymes are synthesized by the liver and are found throughout the vascular system and in the cerebrospinal fluid (CSF). They are responsible for the metabolism of numerous drugs of relevance to the anesthesiologist, including ester local anesthetics, succinylcholine, and mivacurium. Because of the widespread distribution of these enzymes, plasma degradation of ester local anesthetics is typically rapid. In contrast, amide local anesthetics undergo degradations by hepatic enzymes and typically have a longer serum half-life.

## **Summary**

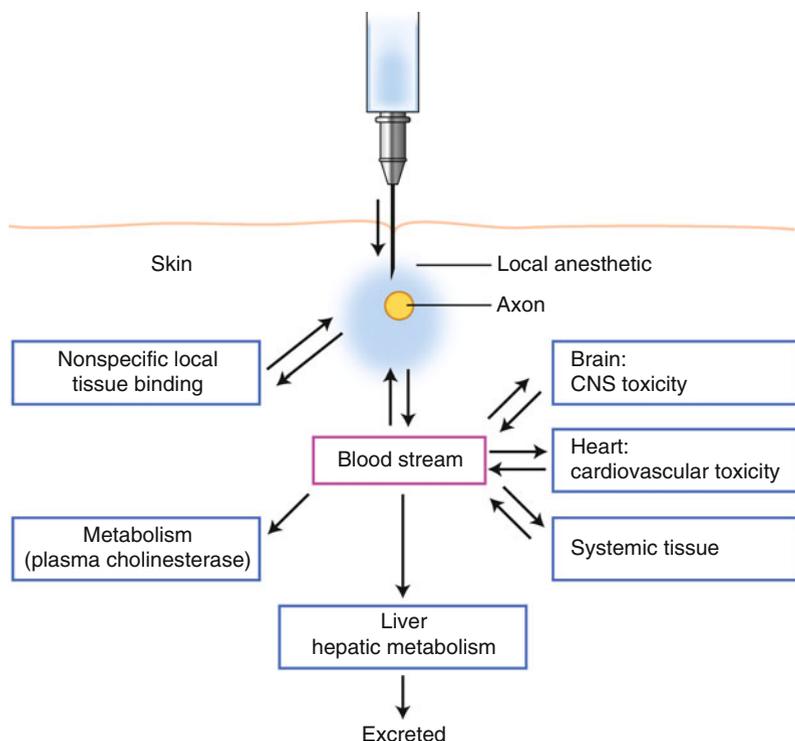
The comprehension of the principles described in this chapter is essential to understand local anesthetic clinical pharmacology. However, one should keep in mind that the clinical setting is much more complicated as there are multiple influencing factors not present in vitro studies.

## **Clinical Pharmacology of Local Anesthetics**

### **Factors Determining Block Quality**

#### ***Block Onset***

The proximity of the injected local anesthetic to the nerve is the most important factor determining block onset; the nearer to the nerve, the shorter the time required to diffuse into the nerve (Fig. 5.6).



**Fig. 5.6** Disposition of sites for local anesthetics following peripheral nerve blocks. A practical approach to regional anesthesia, 4th ed. Mulroy Michael F; Wolters Kluwer/Lippincott Williams & Wilkins 2009, Philadelphia; ISBN-13: 978-0-7817-6854-2. p 12

The total local anesthetic dose and not the volume or concentration determines the onset time, the duration, and the intensity of the nerve block [5].

The choice of the local anesthetic is a crucial issue since hydrophobic agents are more prone to bind to hydrophobic sites on connective tissue compared to hydrophilic drugs. This explains the slower onset of hydrophobic local anesthetics despite their greater potency.

### ***Block Duration***

The main factor influencing block duration is the clearance rate of the local anesthetics.

The choice of local anesthetic greatly influences block duration; hydrophobic local anesthetics have a slower clearance compared to hydrophilic local anesthetics. Moreover, hydrophobic compounds have a higher potency. These two factors are

responsible for a longer-lasting block. Furthermore, local anesthetics show variable vascular effects on local blood vessels. Vasoconstriction will reduce clearance, impairing its transport from the injection site. High concentrations of local anesthetics lead to a vasodilation increasing local blood flow and consequently their own clearance. But with decreasing concentration, vasoconstriction is present reducing clearance and increasing the duration of the block. Individual differences are listed below.

The dose influences duration: larger doses of local anesthetics produce a long-lasting block compared to lower doses. This is explained by the longer time required to clear the higher amount of drug.

### ***Block Potency***

Lipophilicity correlates with potency: the more lipid soluble the local anesthetic, the more potent it is. Lipophilicity facilitates penetration through the cell membrane accelerating thereby the binding of the local anesthetic to the intracellular binding site of the Na<sup>+</sup> channel. Lipophilicity is influenced by the lateral chains of the benzene ring.

## **Individual Local Anesthetics**

Common local anesthetics used in clinical practice and their applications are shown in Table 5.3.

### ***Ester Local Anesthetics***

#### **Cocaine**

Topical mucous membrane applications of cocaine (4% solution) result in very rapid anesthesia and vasoconstriction. At excessive doses, vasoconstrictive properties lead to hypertension, coronary ischemia, and arrhythmias. Mixtures of lidocaine with phenylephrine or oxymetazoline are safer alternatives to cocaine for anesthetizing and vasoconstricting mucous membranes. Attention must be paid not to mix cocaine with other vasoconstrictors (phenylephrine) because of the increased risk of acute myocardial infarction [6].

Cocaine is metabolized in the liver to active metabolites. The half-life is approximately 45 min. If taken together with alcohol, the metabolic pathway is altered, and the highly toxic cocaethylene is produced.

**Table 5.3** Local anesthetic drug clinical doses. A practical approach to regional anesthesia. 4th ed. Mulroy Michael F; Wolters Kluwer/Lippincott Williams & Wilkins 2009, Philadelphia; ISBN-13:978-0-7817-6854-2, p 17

Drug {brand name}	Epidural <sup>f</sup>						Maximum recommended doses					
	Topical <sup>f</sup>			Obstetric <sup>f</sup>			Plain		With epinephrine			
	(%)	Spinal <sup>f</sup> (%)	Surgical <sup>f</sup> (%)	(%)	Obstetric <sup>f</sup> (%)	Peripheral nerve block <sup>f</sup> (%)	Intravenous regional (%)	Total		mg/kg	Total	mg/kg
Cocaine	4	NA	NA	-	NA	NA	NA	200	1.5	-	-	
Benzocaine	5-20	NA	NA	-	NA	NA	NA	-	-	-	-	
<i>Short duration</i>												
Procaine (Novocaine)	NA	10	NI	NI	NI	1	NI	500	-	-	-	
2-Chloroprocaine (nesacaine)	NI	NA	2-3	2-3	1-2	1-2	NI	800	11	1,000	14	
<i>Intermediate duration</i>												
Lidocaine (Xylocaine)	4	5	1.5	1.5	0.5	0.5	0.5	300	4.5	500	7	
Mepivacaine (Carbocaine, Polocaine)	NA	NA	1	NI	1	1	NA	400	-	550	<i>e</i>	
Prilocaine (Citanest)	NA	NA	2-3	NI	1	1	0.5	-	-	500	-	
<i>Long duration</i>												
Ropivacaine (Naropin)	NA	0.5 <sup>b</sup>	0.75, 1 <sup>c</sup>	0.2	0.5	0.5	NA	250	-	250	3	
Bupivacaine (Marcaine, Sensorcaine)	NA	0.5	0.5	0.125 <sup>c</sup>	0.25	0.25	0.25 <sup>b</sup>	175	-	225	3	
		0.5	0.5	0.125 <sup>c</sup>	0.25	0.25	0.5					
				0.5 <sup>e</sup>								

(continued)

Table 5.3 (continued)

Drug {brand name}	Epidural <sup>f</sup>						Maximum recommended doses			
	Topical <sup>f</sup>			Surgical <sup>f</sup>			Plain			
	(%)	Spinal <sup>f</sup> (%)	Obstetric <sup>f</sup> (%)	Peripheral nerve block (%)	Intravenous regional (%)	Total	mg/kg	Total	mg/kg	
Levobupivacaine (Chirocaine)	NA	NA	1	NI	1	NI	300	4	400	6
Etidocaine (Duranest)			1.5							
Tetracaine (Pontocaine)	1-2	1	NA	NA	NA	NA				

Drugs are grouped in general duration of action. Concentrations listed are those recommended for particular application

NA not available, NI not indicated, PDR Physicians' Desk Reference

<sup>a</sup>Produces motor blockade suitable for cesarean delivery

<sup>b</sup>Not approved for this use

<sup>c</sup>For single injection only; lower concentrations should be used for follow-up injections of catheters

<sup>d</sup>Not prepared commercially; must be diluted at time of use

<sup>e</sup>Specific dose for epinephrine-containing solution not identified; this is largest described dose

<sup>f</sup>Preservative free solutions only

The maximum recommended dose of cocaine is 200 mg. Attention must be paid to the use of cocaine for awake fiber-optic nasal intubation: as local anesthetic toxicity is additive, the use of cocaine 4% and lidocaine 4–10% or benzocaine can lead to systemic toxic reaction.

## Procaine

Procaine was the first synthetic local anesthetic used clinically. Unfortunately, procaine combines a short duration and limited tissue penetration. Procaine is still occasionally used for skin infiltration (0.25–1.0%) and short duration (30–45 min) spinal anesthesia (50–100 mg), although discharge readiness may be slightly longer than that seen with equipotent doses of spinal lidocaine. The block after spinal anesthesia is shorter compared to the block induced by lidocaine but has a higher failure rate (inadequate sensory block). On the other hand, less transient neurologic symptoms (TNS) have been reported [7]. Procaine is ineffective when used topically and is not reliable for epidural anesthesia. It is not recommended for peripheral block since it has a very slow onset time paired with a short-acting time. Procaine is metabolized in the plasma by the cholinesterase; its elimination half-life is approximately 8 min.

The 10% solution should be diluted to 5% with dextrose or saline. Procaine is metabolized to *para*-aminobenzoic acid (PABA), which can be associated with allergic reactions.

## 2-Chloroprocaine

Compared to procaine, it has a more rapid onset and slightly longer duration of action. The principal uses of chloroprocaine are in obstetrics and ambulatory anesthesia. It has rapid onset when used for epidural anesthesia and is therefore frequently chosen for urgent forceps or cesarean deliveries. In the 2–3% concentrations, it is also used for spinal anesthesia and peripheral blocks. Like other ester local anesthetics, chloroprocaine is rapidly metabolized by plasma cholinesterase, and with a duration of action between 30 and 60 min, it is a good drug for outpatient procedures. Since serum half-life is approximately 40 s, fetal accumulation and systemic toxicity, in general, are extremely unlikely.

The preservative-free solution should be used for central neuraxial blocks because of the concern regarding potential neurotoxicity.

## Tetracaine

Tetracaine is the longest-acting ester local anesthetic. It is used in spinal and ophthalmic anesthesia and is occasionally used for topical airway anesthesia. The latter application has declined with the recognition that tetracaine has a narrow margin between therapeutic and toxic doses that may lead to serious systemic toxicity after

mucosal application. Metabolism is slower compared to procaine; therefore, the risk of systemic toxicity is greater.

Tetracaine is less chemically stable compared to lidocaine and bupivacaine. This instability may result in an occasional failed spinal anesthetic due to degradation of the local anesthetic during storage.

## **Benzocaine**

Benzocaine was the first developed but not the first clinically used synthetic local anesthetic. Because of its low  $pK_a$  (3.5), it only exists in the uncharged form at physiological pH, and it is hardly soluble in aqueous solutions.

Therefore, it is exclusively used as a topical spray or troche for mucous membranes or for topical application (cream and gel) for dermal hypesthesia.

Methemoglobinemia seems to be observed more frequently when benzocaine is used. This high risk and the difficulty of proper dosage (cream and spray) increase benzocaine potential risk for toxicity.

## ***Amide Local Anesthetics***

### **Lidocaine**

Lidocaine is the most widely used local anesthetic. It combines significant potency, fast onset, intermediate duration, good tissue penetration, and minimal cardiac toxicity. Lidocaine is widely used for infiltration (1–2%), intravenous regional anesthesia (0.5%), peripheral nerve blocks (1 and 1.5%), topical airway (4%), spinal anesthesia (0.2–5%), and epidural anesthesia (2%). It produces moderate vasodilation. The allergic potency is very low.

Lidocaine 5% has been implicated in the occurrence of cauda equina syndrome with the use of small-diameter microcatheters for continuous spinal anesthesia. Spinal microcatheters have since then been withdrawn from the US market. Single-shot spinal anesthesia can be associated with TNS, the etiology of which is uncertain [8, 9].

### **Mepivacaine**

Mepivacaine has similar pharmacokinetic profile to lidocaine, with slightly longer duration and better tissue penetration. Chemically, it is a cyclic tertiary amine like bupivacaine and ropivacaine. It is used primarily for intermediate-duration infiltration, peripheral, epidural, and spinal nerve blocks in Europe. It has a mild vasoconstricting effect which may be responsible for its longer duration compared to

lidocaine. Mepivacaine is not used anymore in obstetric epidural anesthesia since this drug is poorly metabolized in the fetus and neonate and may be responsible for lower neurobehavioral score in the first days of life [10].

### **Prilocaine**

Prilocaine is similar to lidocaine in its clinical profile and is widely used for intravenous regional anesthesia outside the USA. It is the most rapidly metabolized amide local anesthetic. Within the USA, prilocaine was withdrawn from use following several cases of methemoglobinemia. Prilocaine is metabolized to nitro- and ortho-toluidine, which can oxidize hemoglobin to methemoglobin. Prilocaine is mainly used commercially in topical eutectic mixture of local anesthetics (EMLA) cream, as well as in proprietary mixtures of local anesthetics specifically marketed for airway anesthesia. Significant methemoglobinemia has been reported in both of these applications.

### **Etidocaine**

Etidocaine is a derivate of lidocaine. Different chemical changes in the structure make etidocaine very hydrophilic. It is available in the USA as 1, 1.5, or 2% solutions. Thus, it is rarely used in contemporary practice. Its onset is similar to lidocaine, but its high protein binding is similar to bupivacaine, as are its duration of action and cardiac toxicity profile. Clinical potency is similar to that of mepivacaine with 2.5% solutions commonly used in the epidural space and 1% solutions for the performance of peripheral nerve blocks.

### **Articaine**

A structural local anesthetic that has a five-membered-thiophene ring instead of a benzene ring as its hydrophobic tail, articaine 4% is used only as dental local anesthetic and is the second most used local anesthetic for dentistry in the USA since its introduction in 2000. It is popular due to its rapid onset and long duration with a low risk of allergy risk despite its ester side chain attached to the thiophene ring.

### **Bupivacaine**

Bupivacaine was the first long-acting amide local anesthetic. Chemical structure makes bupivacaine significantly more hydrophobic than mepivacaine and lidocaine, slower in onset but of longer duration. Bupivacaine is highly protein bound, which is consistent with long duration and potential for cardiotoxicity. Indeed, the cardiotoxicity of bupivacaine prompted the development of ropivacaine and L-bupivacaine.

Bupivacaine is popular for use in a wide array of applications, including infiltration (0.25%), peripheral nerve blocks (0.375–0.5%), spinal (0.5 and 0.75%), and epidural (0.5 and 0.75%) anesthesia. Because of systemic toxicity, it is not used for IV regional anesthesia.

Bupivacaine has a lower therapeutic index, concerning cardiovascular toxicity compared to lidocaine. Bupivacaine is more slowly absorbed into plasma than lidocaine and produces plasma peak concentrations that are approximately 40% lower.

Clinically used concentrations of bupivacaine vary from 0.05% (epidural continuous infusions for labor analgesia and acute pain management) to 0.5% (spinal anesthesia and peripheral nerve blocks). Peripheral nerve blocks provide sensory block for 4–12 h, sometimes up to 24 h.

The 0.75% concentration is specifically contraindicated for obstetric epidural anesthesia due to concerns about cardiotoxicity. Contemporary epidural anesthesia incorporates use of multihole catheters, test dosing regimens, incremental dosing, and low concentrations of local anesthetic via continuous infusion.

### **Levobupivacaine**

Levobupivacaine is the levorotatory enantiomer of bupivacaine. Commercial bupivacaine is a racemic mixture of both enantiomers (R and S). Levobupivacaine is approximately equivalent to its racemic mixture for its use in regional anesthesia. Cardiac toxicity and CNS studies in animals and healthy volunteers indicated that levobupivacaine is approximately 35% less cardiotoxic compared to racemic bupivacaine [11, 12]. Levobupivacaine is used in the same concentrations, doses, and applications as racemic bupivacaine.

### **Ropivacaine**

Ropivacaine is derived from mepivacaine. Ropivacaine is a long-acting amide local anesthetic which is supplied commercially like levobupivacaine as a single enantiomer. It is available as 0.2, 0.5, 0.75, and 1% solution.

This drug was specifically designed and formulated to minimize cardiotoxicity [13, 14]. At higher concentration (anesthetic), its potency is equivalent to that of bupivacaine [15]. At lower concentration (analgesic), ropivacaine was shown to be 40% less potent than bupivacaine [16]. The clinical experience for peripheral blocks shows that at equivalent doses ropivacaine and bupivacaine produce similar onset and quality of block, but it can be stated that bupivacaine has a significantly longer duration. Ropivacaine is primarily used in epidural anesthesia/analgesia and peripheral nerve block applications. Ropivacaine appears to be approximately 40% less cardiotoxic as compared to racemic bupivacaine in animal models [13]. Ropivacaine produces vasoconstriction at clinically used concentrations for peripheral nerve blocks explaining the little advantage of adding epinephrine to additionally prolong peripheral nerve block or epidural analgesia [17].

## **Adjuvants**

### ***Sodium Bicarbonate***

Theoretically, sodium bicarbonate could fasten the onset time. However, results were not convincing, and actually, the practice of mixing sodium bicarbonate with local anesthetics is rarely used.

### ***Hyaluronidase***

It is used as adjuvant to local anesthetics to breakdown connective tissue in the extracellular matrix and thereby increase drug dispersion through tissue. Except for peribulbar block (sub-Tenon's block), it has been abandoned. Allergic reactions have also been described in this setting.

### ***Vasoconstrictors***

Adding epinephrine leads to vasoconstriction and thereby local blood flow and drug clearance are decreased. This prolongs block duration and decreases local anesthetic plasma concentration following spinal, epidural, and peripheral nerve blocks [18]. Lower peak plasma concentration decreases the risk for toxicity. However, epinephrine does not provide protection if accidental intravascular local anesthetic injection occurs [19].

### ***Clonidine***

Alpha-2-adrenergic agonists are analgesic drugs in their own right and have been shown to inhibit both C fibers and A fibers and to modestly inhibit local anesthetic clearance [20, 21]. When added to local anesthetics, clonidine prolongs sensory block during peripheral, central neuraxial, and intravenous regional anesthesia to a degree comparable to that produced by epinephrine. However, unlike epinephrine, clonidine does not prolong motor block when administered orally, as when added to the intrathecal local anesthetic [22].

### ***Opioids***

When added to short-duration local anesthetics used for spinal anesthesia, short-acting opioids (fentanyl and sufentanil) prolong and intensify sensory block without prolonging motor block or time to void, which is particularly advantageous for

ambulatory spinal anesthesia [23]. However, postanesthesia nausea and vomiting, itching can be a problem [24]. When added to local anesthetics or peripheral nerve block, fentanyl has also been shown to prolong sensory block, but at the expense for significantly slowing onset in some studies [25].

When added to intrathecal local anesthetics, the peak plasma concentrations for sufentanil occur between 20 and 30 min and are greater than what is necessary for postoperative analgesia [14]. This explains the many reports of “early” respiratory depression in mothers [15] and fetal heart rate abnormalities in infants when sufentanil is added to intrathecal local anesthetics for labor analgesia or cesarean section [26].

## Depot Local Anesthetic Preparations

Depot preparations of local anesthetics are interesting because they would allow using long-acting anesthetics without the need for catheters and pumps.

Gels, polymer microspheres, liposomes, and oil-water emulsions have been studied in animal models to produce long-acting anesthetic blocks [27]. To date, clinical convincing results are still lacking.

## Complications of Regional Anesthesia

### *Introduction*

Overall incidence of neuropathy after peripheral nerve block varies from 0 to >5%. Studies which used closed claims databases ranked neuropathy at the second place, with 16% of all claims [28]. In a prospective French study, incidence of major neurologic adverse reactions was estimated at 3.5/10,000 [29]. Peripheral nerve damages following either spinal anesthesia or peripheral nerve blockades represented >50% of severe adverse reactions in this investigation.

Permanent injuries after regional anesthesia are rare [30–32]. Most surveys with large cohorts are retrospective [33, 34] or related to closed claims analysis [35, 36]. Few studies are prospective but focus on specific adverse reactions inducing limitation in their interpretation [29, 37, 38].

The largest recent clinical study was a voluntary reporting model used in France [29]. Data of 158,083 different blocks from 487 anesthesiologists were collected and analyzed. The incidence of serious complications such as central or peripheral nerve injury, seizure, death, etc. was described as 3.5/10,000 blocks. The risk of deaths was shown to be 1/400,000 regional blocks. All but one occurred during spinal anesthesia.

It can be concluded that the incidence of severe complications of regional anesthesia is similar to the one observed after general anesthesia.

## Systemic Toxicity

Systemic toxicity is a significant and potentially dangerous problem [39]. Beside a local toxicity, an increase of the local anesthetic plasma concentration may lead to systemic toxicity, mainly neurologic and cardiovascular ones. Such an increase in local anesthetic plasmatic concentration may be related to inadvertent intravascular injection with a consecutive sudden plasmatic peak of concentration. The most frequent cause of systemic toxicity is related to a high and rapid resorption of local anesthetics through perinervous vessels. Toxicity occurs first in the CNS and then in the cardiovascular system (Fig. 5.7).

### *CNS Toxicity*

The incidence of seizures varies between 0.2 and 1/1,000 cases and according to the anesthetic regional procedure [40, 41]. The clinical manifestation largely depends on the velocity of plasma concentration increment: a slow increase shows clear and reproducible series of typical CNS signs and symptoms. A rapid increase leads to generalized seizures as first clinical manifestation.

Sedatives and hypnotics such as propofol, benzodiazepines, and barbiturates raise seizure threshold and help protecting the CNS [42, 43].

The therapeutic to CNS toxicity ratio is for all local anesthetics, the same indicating that none of them are more or less prone to cause seizures.

The prevention and the treatment of CNS toxicity should be done according to published recommendations [44, 45].

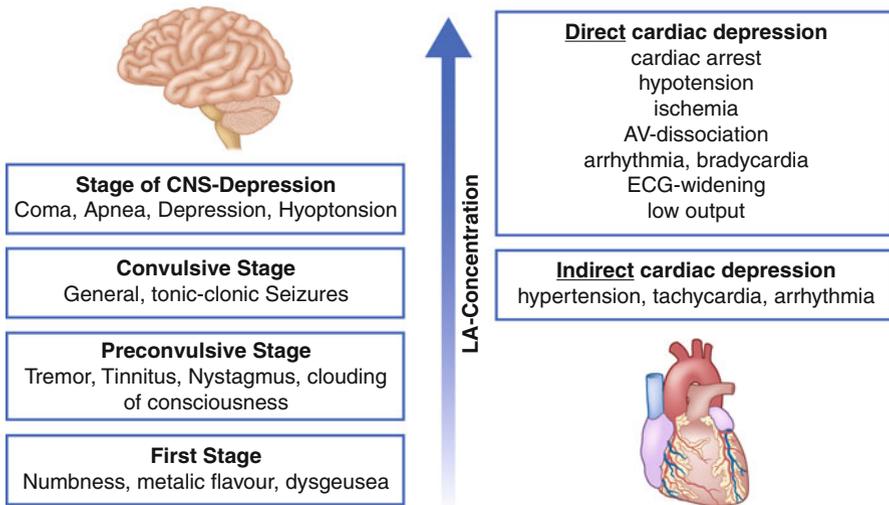


Fig. 5.7 Signs and symptoms of local anesthetics toxicity

**Table 5.4** Classification of nerve injuries

<b>Seddon</b>	
Neuropraxia ( <b>Sunderland 1</b> )	Myelin damage, conduction block
Axonotmesis ( <b>Sunderland 2</b> )	Loss of axonal continuity, endoneurium intact, no conduction
Neurotmesis ( <b>Sunderland 3</b> )	Loss of axonal and endoneurial continuity, perineurium intact, no conduction
( <b>Sunderland 4</b> )	Loss of axonal, endoneurial and perineurial continuity; epineurium intact; no conduction
( <b>Sunderland 5</b> )	Entire nerve trunk separated; no conduction

Based on data from Seddon H, Three types of nerve injury. *Brain* 1943;66:236–88; Sunderland S: A classification of peripheral nerve injuries producing loss of function. *Brain* 1951;74:491–516; and Lundborg G. Nerve injury and repair. Churchill Livingstone; 1988

### ***Cardiac Toxicity***

Estimated incidence of cardiac arrest related to local anesthetics varies between 1.8 and 3.1/10,000 cases [40, 46].

High plasma concentration of local anesthetics is needed to cause significant cardiovascular toxicity. This may occur, when the local anesthetic is injected intravenously, but a quick resuscitation is also possible. The therapeutic/cardiotoxic ratio is lower for hydrophobic local anesthetics (bupivacaine) compared to hydrophilic local anesthetics. Hydrophilic local anesthetics dissociate only after a greater amount of time from their binding sites; therefore, Na<sup>+</sup> channels are blocked when the next depolarization arrives. Cardiac toxicity can manifest as either malignant dysrhythmias (ventricular fibrillation), pulseless electrical activity, or asystolia [19, 42, 47].

Cardiac toxicity should be prevented [45], but in case of patients experiencing signs or symptoms of local anesthetic systemic toxicity (LAST), treatment should be done according to the ASRA guidelines 2010 [44, 48].

Often, the doses of epinephrine in this setting are higher [19, 42, 47, 49]. Intralipid seems to be effective mainly in case of bupivacaine toxicity. A review about models and mechanisms of local anesthetic cardiac toxicity and a review of clinical presentations of local anesthetic systemic toxicity over the last 30 years have recently been published [50, 51].

### ***Prevention of Toxicity***

Toxicity depends on total dose of local anesthetic injected, type of local anesthetic, speed and site of injection, combination with adjuncts, patient's medical history, and concomitant use of other drugs leading to dangerous interactions, particularly with drugs presenting a hepatic metabolism action (hepatic blood flow modification, cytochrome P450 action, etc.). Interactions have been described among local anesthetics

and  $\beta$ -blockers, amiodarone, cimetidine, and volatile agents [52–56]. Calculation of the optimal dose taking into account patient's age, pharmacokinetic and pharmacodynamic interactions with concomitant disease, and other drugs could be probably useful [57]. Development of nerve localization by ultrasonographic technique is thought to help reaching such objectives by limiting the volume of local anesthetic needed to block nerves [58]. However, clinical practice has shown that such a technique cannot always prevent intravascular injection or quick reabsorption [59].

Recently, a good summary about prevention of local anesthetic systemic toxicity (LAST) has been published in a series of articles dealing with LAST [45].

## Local Tissue Toxicity

### *Nerve Injury/Transient Neurologic Syndrome*

Direct nerve injury from local anesthetic is receiving increased scrutiny, particularly with regard to spinal anesthesia [60, 61]. Toxicity can result from either local anesthetics themselves or from additives, preservatives, antiseptics, or the pH of the formulations. The mechanism of local anesthetic-induced neurotoxicity is multifactorial [60, 62]. Direct nerve injury is evident when isolated nerves are exposed to high concentration of local anesthetics, particularly lidocaine and tetracaine. Local anesthetics also change the biologic milieu surrounding neurons, including localized alteration of prostaglandin production, altering ionic permeability and changes in neural blood flow.

Compared with bupivacaine, lidocaine has a significantly greater potential for direct neurotoxicity, particularly when isolated nerves are exposed to high concentrations of lidocaine over long periods of time. Hyperbaric 5% lidocaine and tetracaine have been associated with cauda equina syndrome after continuous spinal anesthesia. In these cases, spinal microcatheters were used to administer supernormal doses (up to 300 mg) of hyperbaric 5% lidocaine. Because spinal microcatheters (25–32 gauge) greatly limit the speed of drug administration, badly distributed local anesthetics presumably pooled near the catheter tip. As a result of the lordotic lumbar spine curvature, higher concentration of lidocaine remained in the lumbosacral cistern [62, 63].

Single-shot spinal anesthesia can cause transient pain (TNS), manifest as back and posterior leg discomfort with radicular symptoms lasting 1–3 days after spinal anesthesia. The etiology of TNS is unclear, but some have speculated that this syndrome represents a form of neurotoxicity. Transient neurologic symptoms occur more frequently with lidocaine than bupivacaine, which may relate to lidocaine's greater neurotoxicity in isolated nerve preparations [36, 64–67]. Additionally, several risk factors (lidocaine, lithotomy position, out-patient status, arthroscopic knee surgery, and obesity) for developing TNS have been identified [64, 65].

## *Needle Trauma*

Recent ultrasonographic data have shown that injections between epineurium and perineurium did not produce significant neural injury [68]. If injection pressure is low (less than 12 psi), intraneural injection does not necessarily result in permanent injury but can lead to severe injury if pressures are high [69].

Studies over the last years have demonstrated that the correlation between needle-nerve proximity and the current necessary to elicit a motor response is poor and not always reliable, despite the high success rate of neurostimulation and its low complication rate [70, 71]. Moreover, also eliciting paresthesia has surprisingly poor correlation with nerve proximity [72, 73]. Case reports of intraneural, intravascular, and other complications despite the use of ultrasound have shown that also this promising technique does not guarantee a complete visualization of the targeted nerve to avoid further complications [74]. The best way to avoid needle-induced nerve trauma is to avoid long bevel needle and perpendicular needle approaches to the nerve.

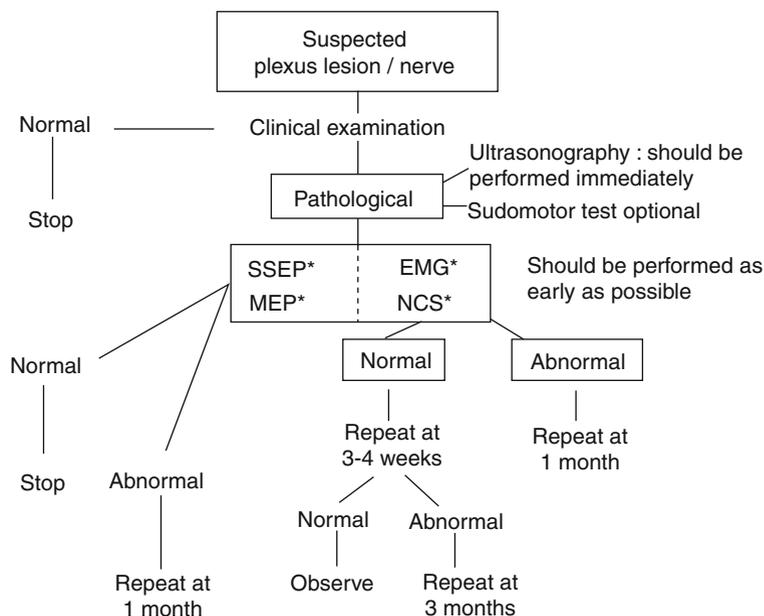
Clinical symptomatology of perimedullary complication following central nervous block is variable. Spinal cord injury can occur even while a patient did not complain of any paresthesia during puncture [75, 76]. Different risk factors have been identified to explain the occurrence of this complication [60]. Epidural hematoma can cause paraplegia following neuraxial anesthesia in patients concomitantly anticoagulated with low-molecular-weight heparin. Other causes of neural injury include positioning injuries, surgical trauma, and injuries related to the use of a limb tourniquet.

Guidelines on management of such complications following both central and peripheral nerve blocks have recently been published by the American Society of Regional Anesthesia [60]. Decision-making algorithms have been proposed to help the clinician in case of neuropathy occurrence [61, 77] (Fig. 5.8).

## *Myotoxicity*

Skeletal muscle toxicity is a rare and uncommon side effect of local anesthetic drugs. Intramuscular injections of these agents regularly result in reversible myonecrosis [78]. The extent of muscle damage is dose dependent and worsens with serial or continuous administration. This problem is probably underestimated as incidence of symptomatic clinical forms is unknown. Experimental studies have concluded that all LA cause muscular damages with concentration use in daily practice. The extent of such damage depends on pharmacological properties of each local anesthetic, dose injected, and site of injection [79].

Animal studies in pigs showed lower mean damage score in muscles exposed to ropivacaine compared to exposure to bupivacaine [80, 81]. Stereospecificity of the drug seems also to play an important role in  $\text{Ca}^{2+}$  metabolism, which has been shown



\* The choice of the examination will be done according to clinical condition and neuro physiologist's recommendations

**Fig. 5.8** Algorithm recommended to be performed in case of suspected plexus/nerve lesion

to be important in myotoxicity [82]. First reports of muscular dysfunction were related to retrobulbar injection of local anesthetics.

Bupivacaine seems to be the most toxic local anesthetic. Phenomena of apoptosis have been described only with bupivacaine but not with other LA [81, 83]. Interactions with the  $\text{Ca}^{2+}$  metabolism seem to be a key pathway and explain most damage [82, 84]. Also, changes in the mitochondrial metabolism induced by local anesthetics have been reported [83, 85, 86]. These effects are less pronounced with ropivacaine, a less lipophilic local anesthetic, compared with bupivacaine on heart cell preparation [87], but this was not shown in rat psoas muscle [88]. A recent study has concluded that mitochondrial bioenergetics alterations with bupivacaine were more severe in young rats compared to adults [89].

### ***Chondrotoxicity***

Complications from the use of pain pumps in orthopedic surgery have recently received considerable interest. Human and animal studies have reported on the chondrotoxicity of intra-articular application of bupivacaine [90–92]. Postarthroscopic glenohumeral chondrolysis is a noninfectious entity associated with factors

including use of radiofrequency tumoral instruments and intra-articular pain pumps that administer bupivacaine [93]. Also, the viability of bovine articular chondrocytes after exposure to corticosteroids alone or with lidocaine in a simulated inflammatory environment was assessed. The results showed a dose-dependent and time-dependent decrease in chondrocyte viability after exposure to methylprednisolone. The combination with lidocaine was toxic, with virtually no cells surviving the treatment [94]. Continuous 0.5% bupivacaine exposure was shown to have a clear detrimental effect on chondrocytes in an in vitro model [95]. There is a growing amount of evidence that intra-articular administration of bupivacaine is chondrotoxic, especially at a higher concentration and with a prolonged exposure. More studies are needed to clarify this issue.

## Allergy

Allergic reactions may occur from preservatives added to some local anesthetics (sulfites and methylparaben). Actual allergic reactions to local anesthetics are quite rare but are more common with ester local anesthetics compared to amides [96]. This is likely due to the breakdown products of ester local anesthetics, such as PABA. There are only a few convincing reports of allergic reactions to preservative-free amide local anesthetics.

If there is a history suggestive of true allergy, it may be worthwhile to perform allergy testing to preservative-free local anesthetics. Measurement of plasma esterase, which is increased in the event of “true” allergy, is useful. Skin testing is often performed to prospectively identify patients with local anesthetic allergy [97].

## Bleeding Complications

This issue deals mainly with neuraxial blocks. Epidural (1:150,000 cases) or intrathecal (1:200,000 cases) hematomas can cause devastating neurologic injury. The increased use of antithrombotic prophylaxis has increased this risk after epidural/spinal anesthesia to 1:1,000–1:10,000. The ASRA has recently reviewed the risks attendant to performance of regional blocks in the anticoagulated patient and refreshed its guidelines [98, 99] which are also to be found in their website ([www.asra.com](http://www.asra.com)). Patients may develop sensory changes, progressive weakness and/or back pain. Confirmatory diagnosis with neuraxial imaging (CT and MRI) must be obtained in conjunction with immediate neurosurgical consultation. If more than 8 h pass between symptom onset and decompression, the likelihood of a full or partial recovery decreases dramatically.

## ***Medicamentous Coagulopathy***

In fully anticoagulated patients (heparin and coumadin), epidural and spinal anesthesia should be avoided unless clear benefit outweighs the added risks.

Recently, the ASRA published new guidelines for regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy [98].

## **Infection**

Infection is a seldom complication in regional anesthesia. Risk factors are indwelling catheters left in place for more than 5 days, immunocompromised patients, catheters in trauma patients, and lack of perioperative antibiotics [30].

## ***Peripheral Nerve Blocks***

Single-shot peripheral nerve blocks have a low risk of infection. The risk of colonization and infection increases when indwelling catheters are used. Despite the high colonization rate (70% primarily *Staphylococcus epidermidis*), clinical evidence of infection is uncommon: less than 3%.

## ***Central Neuraxial Blocks***

Single-shot spinal and epidural anesthesia have a low risk of infection, but this risk seems to be higher than for peripheral nerve blocks. The incidence of meningitis after spinal anesthesia is estimated at less than 1:40,000; the risk of abscess after epidural anesthesia is less than 1:10,000 (Lit 2). Risk factors are the use of indwelling catheters and bacteremia [100].

## **Clinical Pearls**

- Nerve-blocking potency of local anesthetics increases with increasing molecular weight and lipid solubility [101].
- The effectiveness of local anesthetics is influenced by the dose, site of administration, additives, temperature, and pregnancy [101].
- The plasma [101] concentrations of local anesthetics is depending on the injection technique, place of injection, and addition of adjuvants to local anesthetics.

- In laboratory experiments, most local anesthetics will only produce cardiovascular toxicity after the blood concentration has exceeded three times that necessary to produce seizures [50].
- True allergic reactions to preservative-free amide-type local anesthetics are rare [96].
- True anaphylaxis is more common with ester local anesthetics that are metabolized directly to PABA than to amide local anesthetics [96].
- Some patients may react to preservatives, such as methylparaben, used in local anesthetics.
- In contrast to other shorter-acting amide local anesthetics, bupivacaine, levobupivacaine, and ropivacaine have a motor-sparing effect; they produce less motor block for a comparable degree of sensory analgesia.
- It is well accepted that lipid solubility usually goes hand in hand with local anesthetic potency. All things being equal, greater lipid solubility is related to increasing length of the aliphatic chain on the amino ring.
- Intraepidurally administered opioids reduce intraoperative requirements for volatile anesthetics significantly more compared to their intravenous administration. This proves site-specific action in the epidural space.
- Exceeding a total dose of 0.25 mg of epinephrine may be associated with cardiac arrhythmias.
- Adding epinephrine to spinal anesthetics will prolong motor blockade and delay the return of bladder function, thus preventing patients from achieving discharge criteria.
- When clonidine is used in combination with opiates, the analgesic effects are additive, but not synergistic. Thus, patients require a smaller total dose of narcotics and have a decreased incidence of oxygen desaturation with equivalent analgesia.
- Generally, the bigger the size of the nerve fibers, the greater the amount of local anesthetic solution required to block conduction. Thus, fibers of small size are blocked sooner than those of larger diameter.
- The B fibers of the autonomic system constitute an exception of this rule: even though they are myelinated fibers, a minimum concentration of local anesthetic solution is required to produce an effective blockade.
- This explains why the sympathetic blockade is observed before the onset of sensory or motor blockade.
- The onset time of local anesthetic is influenced by the molecules  $pK_a$  (the higher the  $pK_a$ , the slower the onset time of the nerve block in a physiologic environment) and diffusibility [101].
- The ability to cross cell membrane depends on the molecular weight and the liposolubility of the molecule.
- The nonionized form of the molecule is more lipid soluble than the ionized one; therefore, it can cross more readily the cell membrane but diffuses less easily.
- The duration of the action of local anesthetic solutions depends on the protein binding as well as the clearance from the injection site.

- The closer the  $pK_a$  of local anesthetic is to physiologic pH, the shorter the onset time of the nerve block [101].
- Increasing the lipophilicity of local anesthetic increases its potency and toxicity, whereas protein binding is proportional to the duration of action of the local anesthetic.
- Sensory-motor differentiation is based on the different size and myelination of the nerve fibers involved in pain conduction ( $A\delta$  and C) as compared to those involved in motor function ( $A\alpha$ ).
- Postoperative maintenance is best performed with low concentration of a long-acting agent, like 0.2% ropivacaine, 0.125–0.2% levobupivacaine.
- Local toxicity with neurotoxicity primarily occurs in cases of intraneural injection rather than normal applications of clinically relevant concentrations of local anesthetics [102].
- To decrease the risk of nerve injury, utmost care should be taken during nerve localization; excessively high concentrations of local anesthetic and high injection pressures should be avoided [102].
- The larger the fascicle, the greater is the risk of accidental intraneural injection because large fascicles are easily spared by the needle.
- Injections into epineurium or perineural tissue do not result in significant injection resistance.
- When injection is difficult (injection pressures >20 psi), the injection should be stopped because of the risk of intraneural needle position [102].
- It is suggested that nerve stimulation with current intensity of 0.2–0.5 mA (0.1 ms) indicates close needle-nerve placement [103].
- Stimulation with current intensity of  $\leq 0.2$  mA may be associated with intraneural needle placement.
- Motor response to nerve stimulation may be absent even when the needle is inserted intraneurally [68].

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