Chapter 1

Use of Local Anesthetics in Regional Anesthesia and Pain Therapy

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Local anesthetics produce reversible blockage of sodium channels in the nerve cell membrane, thereby interrupting stimulus conduction.

Chemical Structure and Physicochemical Properties [1]

All local anesthetics in common clinical use have three characteristic molecular sections in their chemical structure:

An aromatic residue, which basically determines the lipophilic properties of the agent. Substitutions in the aromatic group allow the pKa and lipid solubility of the substance to be influenced.

An intermediate chain, which in local anesthetics of the ester type (Table 1.1) contains a relatively unstable ester bond (CO–O) that can be broken down hydrolytically by pseudocholinesterases. Local anesthetics of the amide type (Table 1.2) are much more stable, since the amide bond (NH–CO) in their intermediate chain cannot be broken down in plasma. The length of the chain between the aromatic residue and the substituted amino group has an influence on the intensity of effect of the local anesthetic. The agent's protein-binding capacity and lipid solubility can be altered by substitution in the intermediate chain.

A substituted amino group, the protonization of which determines the ratio of the cationic to the basic form. Only the free base is capable of penetrating lipoprotein membranes. However, to be able to affect the nerve membrane, the local anesthetic must be available as a cation. The type of amino group substitution affects the distribution coefficient, the plasma protein binding, and the intensity and duration of the drug's action.

Clinical Significance of the Physicochemical Properties

Local anesthetics differ with regard to their molecular weight, their lipid and water solubility, pKa, and protein-binding characteristics. These factors in turn have a substantial influence on the potency of the drug's local anesthetic effect on the onset of the effect and on its duration (Tables 1.3a and 1.3b).

Local Anesthetic Potency [2]

The combined effect of factors such as protein binding, stereoisomeric structure, and lipophilia determines the potency of a local anesthetic agent. To achieve a blocking effect, the local anesthetic has to diffuse across the cell membrane into the interior of the cell (importance of lipophilia for membrane diffusion) so that, from the cytosol (appropriate hydrophilic properties), it can occupy the sodium channel in its then protonated form (Table 1.4).

A high degree of lipophilia is associated with good membrane permeation, and a high degree of hydrophilia is associated with good solubility in the cytosol. Local anesthetics therefore have to have both of these properties in a favorable ratio.

However, the clinical distinction that is made in local anesthetics between those of mild potency (procaine), medium potency (lidocaine, prilocaine, mepivacaine), and high potency (ropivacaine, bupivacaine, levobupivacaine, etidocaine) does not conform to these correlations in all respects.

The onset of effect in the isolated nerve, at physiological pH, depends on the pKa value of the local anesthetic. The lower this value is, the more local anesthetic base can diffuse toward the membrane receptors, and the shorter the time will be to the onset of the nerve block. Higher concentrations of local anesthetic accelerate onset.

The duration of effect depends on the dosage and concentration of the local anesthetic, its binding to the membrane receptors (protein-binding capacity), and its reabsorption from the tissue into the blood.

Table 1.1 Local anesthetics with an ester bond

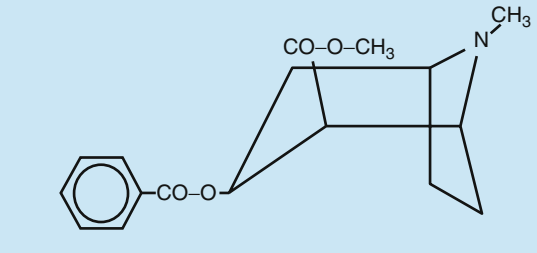
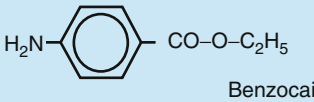
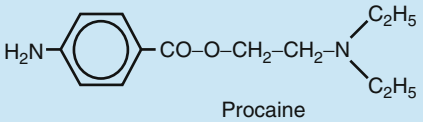
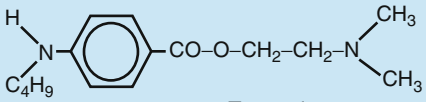
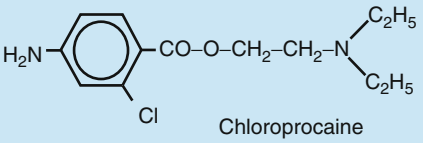
Aromatic residue	Intermediate chain	Substit. amino group	Year introduced
			
Cocaine			1884
			
Benzocaine			1900
			
Procaine			1905
			
Tetracaine			1930
			
Chloroprocaine			1955

Table 1.2 Local anesthetics with an amide bond

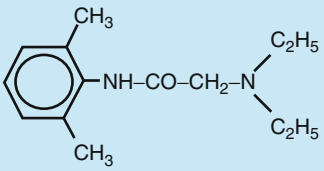
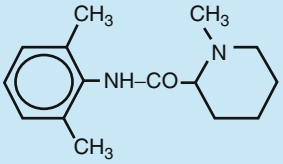
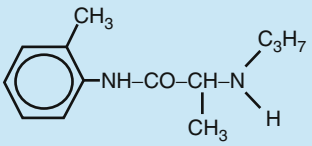
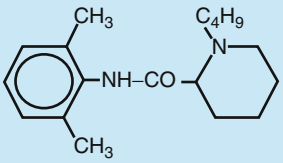
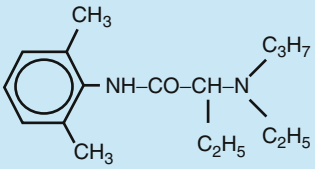
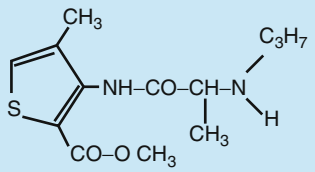
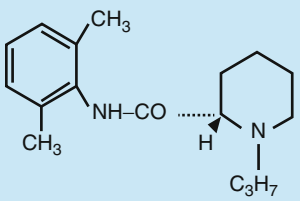
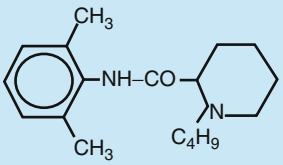
Aromatic residue	Intermediate chain	Substit. amino group	Year introduced
		Lidocaine	1944
		Mepivacaine	1957
		Prilocaine	1960
		Bupivacaine	1963
		Etidocaine	1972
		Carticaine	1974
		Ropivacaine	1996
		Levobupivacaine	2000

Table 1.3a A physicochemical and pharmacological parameters

Agent	Molecular weight	pKa (25°)	Distribution coefficient (lipid/water)	Protein binding (%)	Potency in vitro (isolated nerve)
Procaine	236	8.9	0.02	5.8	1
Lidocaine	220	7.7	2.9	64–70	4
Mepivacaine	234	7.7	0.9	77–80	3–4
Prilocaine	246	7.6	0.8	55	3–4
Bupivacaine	288	8.1	27.5	95	16
Etidocaine	276	7.7	141	95	16
Ropivacaine	274	8.1	9	95	16
Levobupivacaine	288	8.09	27.5	97	16

Table 1.3b Local anesthetic potency and duration of effect

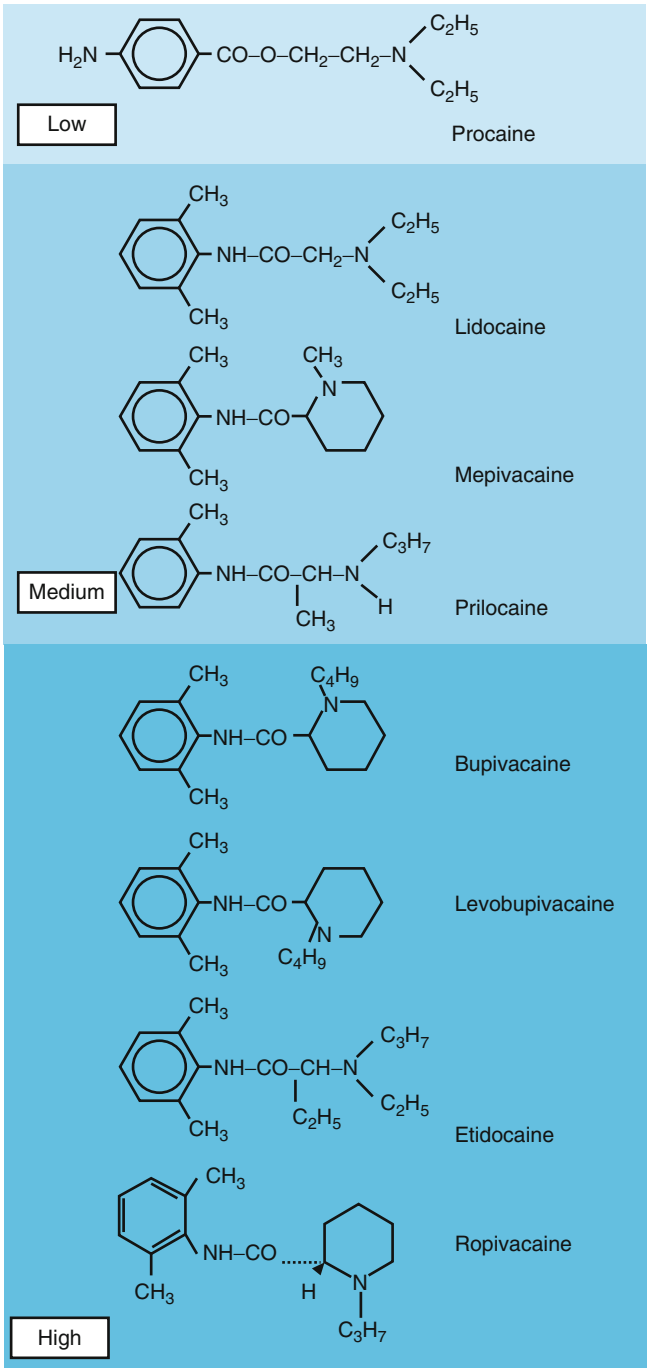
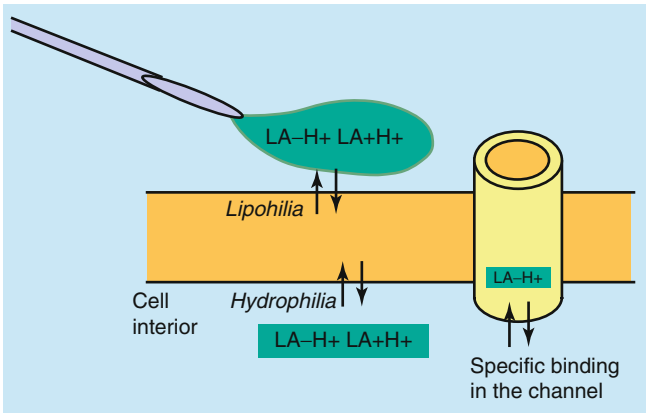


Table 1.4 Chemical requirements of a local anesthetic local anesthetics must combine lipophilic and hydrophilic properties in a favorable ratio with each other hydrophilia, soluble in cytosol; lipophilia, overcoming the cell membrane



Equipotent Concentrations

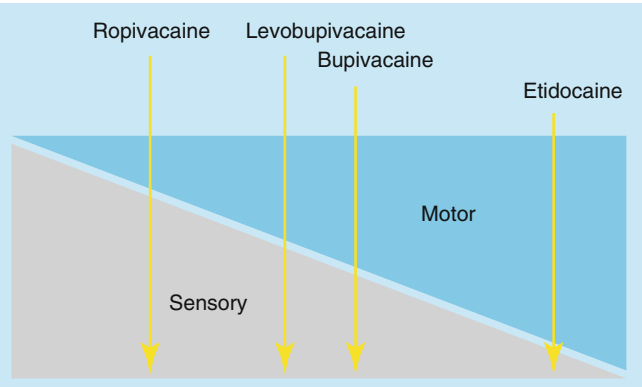
Medium-duration local anesthetics have more or less the same clinical potency (except perhaps for lidocaine—due to stronger vasodilation, this local anesthetic is resorbed more readily from the site of action, and this can affect the duration and intensity of the block).

Equipotent concentrations of long-acting local anesthetics cannot be demonstrated in the same way, since the three local anesthetics mentioned have completely different block profiles: etidocaine (highest lipophilic capacity) produces a mainly motor block, ropivacaine has a mainly sensory effect, and bupivacaine has both motor and sensory effects. Anesthetic concentrations of bupivacaine and ropivacaine are equipotent (one to one).

Block Profile (Table 1.5)

The block profile shows the relation between sensory and motor block. Physicochemical properties determine the block profile. At high anesthetic concentrations—so far as these are toxicologically permissible—the excess quantity of the agent can also block fibers not primarily affected (motor or sensory fibers). On the other hand, the block profile is not altered by low concentrations. A reduced motor block is obtained at the cost of reduced analgesic quality, and this is why opioid supplementation is usually necessary with dilute concentrations of local anesthetic.

Table 1.5 Relative block profile of long-acting local anesthetics



Incompatibility

Local anesthetics can precipitate after dilution with alkaline solutions and should therefore not be diluted with or injected simultaneously with sodium bicarbonate.

Side Effects and Systemic Effects (Tables 1.6 and 1.7)

When assessing the safety and tolerability of a local anesthetic, not only its central nervous system and cardiovascular effects need to be taken into account, but also its allergenic potential and toxic degradation products that may form as it is metabolized.

Table 1.6 Toxicity of clinical dosages of local anesthetics

Local anesthetic	Central nervous system	Heart
Lidocaine	++	+
Mepivacaine	++	+
Prilocaine	+	+/–
Bupivacaine	+++	++++++[a]
Levobupivacaine	++	++++
Ropivacaine	++(+)	+++

[a]Clinical dose can be equivalent to a lethal dose when incorrectly administered

Table 1.7 Symptoms of intoxication due to local anesthetics

Central nervous system	Cardiovascular system
Stimulation phase, mild intoxication	
Tingling of lips, tongue paresthesias, perioral numbness, ringing in the ears, metallic taste, anxiety, restlessness, trembling, muscle twitching, vomiting	Cardiac palpitation, hypertonia, tachycardia, tachypnea, dry mouth
Stimulation phase, moderately severe intoxication	
Excitation phase, moderate toxicity Speech disturbance, dazed state, sleepiness, confusion, tremor, choreoid movements, tonic-clonic cramp, mydriasis, vomiting, polypnea	Tachycardia, arrhythmia, cyanosis and pallor, nausea and vomiting
Paralytic phase, severe toxicity	
Stupor, coma, irregular breathing, respiratory arrest, flaccidity, vomiting with aspiration, sphincter paralysis, death	Severe cyanosis, bradycardia, drop in blood pressure, primary heart failure, ventricular fibrillation, hyposystole, asystole

Systemic Effects

Adverse systemic effects of local anesthetics can occur when their plasma concentration is high enough to affect organs with membranes that can be irritated.

Toxic plasma levels can be reached as a result of:

- Inadvertent intravascular or intrathecal/epidural injection
- Overdosing, particularly in areas with good perfusion and correspondingly high resorption
- Failure to adjust the dosages (mg/kg body weight), particularly in patients with hepatic or renal disease

The severity of intoxication depends on the absolute plasma level, as well as on the strength of the local anesthetic's effect. While anesthetic dosages of short-acting local anesthetics (prilocaine, mepivacaine, lidocaine) can trigger clear CNS symptoms in a range extending to generalized cramp, cardiotoxic reactions are also possible with long-acting local anesthetics. In particular, cases of cardiac arrest have been reported with bupivacaine with comparatively small intravascular injections (50 mg; not treatable in half of the cases).

Cardiac symptoms and cardiac arrest can also occur with ropivacaine after inadvertent intravascular injections. However, these can be treated effectively and only occur at higher dosages. The following sequence of increasing systemic toxicity applies to the most frequently used local anesthetics: procaine < prilocaine < mepivacaine < lidocaine < ropivacaine < levobupivacaine < bupivacaine.

CNS toxicity: Central reactions predominate in terms of frequency and clinical significance. The symptoms of these are listed in Table 1.7 in order of severity and toxicity. For speedy and appropriate treatment, it is important to observe and react immediately when even the preconvulsive signs of CNS intoxication are seen—particularly numbness of the tongue and perioral region.

Cardiovascular toxicity: Toxic effects on the cardiovascular system usually occur after the administration of very high doses. They are seen in the form of conduction disturbances in the autonomic cardiac and vascular nerve fibers, depression of cardiac function, and peripheral vasodilation (Tables 1.6 and 1.7).

Local Anesthetic Systemic Toxicity (LAST) [3–7]

Diagnosing (Table 1.7)

Classic descriptions of LAST depict a progression of subjective symptoms of *CNS excitement* (agitation, auditory changes, metallic taste, or abrupt onset of psychiatric symptoms) followed by seizures or *CNS depression* (drowsiness, coma, or respiratory arrest). Near the end of this continuum, initial signs of *cardiac toxicity* (hypertension, tachycardia, or ventricular arrhythmias) are supplanted by cardiac depression (bradycardia, conduction block, asystole, decreased contractility) [3]. However, there is substantial variation of this classic description, including the following:

- Simultaneous presentation of CNS and cardiac toxicity
- Cardiac toxicity without prodromal signs and symptoms of CNS toxicity

Thus, the practitioner must be vigilant for atypical or unexpected presentation of LAST. The timing of LAST presentation is variable: Immediate (<60 s) presentation suggests intravascular injection of LA with direct access to the brain, while presentation that is delayed 1–5 min suggests intermittent or partial intravascular injection, delayed circulation time, or delayed tissue absorption. Because LAST can present >15 min after injection, patients who receive potentially toxic doses of LA should be closely monitored for at least 30 min after injection.

Caution

The onset of LAST is usually very rapid, following a single LA injection by 50 s or less in half of the cases and occurring before 5 min in ¾ of the cases [3]. The most important first step in improving patient outcome is to have a low threshold for considering the diagnosis (atypical presentation was reported in approximately 40 % of published cases of LAST) [6].

Prevention [6]

Prevention is the most important measure in reducing the frequency and severity of LAST. No single intervention has been identified that can reliably eliminate risk. Central to prevention is limiting the opportunity for intravascular injection or tissue uptake to local anesthetic, which is best accomplished by early detection of intravascular needle or catheter placement.

Local anesthetic dose reduction may be particularly important for those patients thought to be at greater risk of LAST.

Risk Reduction

Local anesthetic blood levels are influenced by the site of injection, and those factors that can increase the likelihood of LAST include:

1. Those patients at extremes of age (<4 months or >70 years).
2. Heart failure, history of ischemic heart disease, and cardiac conduction abnormalities.
3. Metabolic (e.g., mitochondrial) disease.
4. Liver disease.

5. Low plasma protein concentration.
6. Metabolic or respiratory acidosis.
7. Medications that inhibit sodium channels.
   Neither body weight nor body mass index correlates with local anesthetic plasma levels after a specific dose in adults; the correlation is more accurate in children.

Caution

1. Use incremental injection of local anesthetics before and during the injection (after each 4–5 mL—aspiration should be carried out repeatedly, pausing 15–30 s between each injection) observing for signs and querying frequently for symptoms of toxicity between each injection recognizing that there is ~ 2 % false-negative rate for this diagnostic intervention [5].
2. Maintain verbal contact with the patient.
3. Monitor the patient during and after completing the injection, as clinical toxicity can be delayed up to 30 min (or longer after tumescent procedures).

Intravascular Marker

When injecting potentially toxic doses of local anesthetic, use of an intravascular marker is recommended [5]. Although imperfect, intravascular test dosing remains the most reliable marker of intravascular injection. Of the various options described, only fentanyl and epinephrine meet suggested standards for reliability and applicability [4, 6].

Intravascular injection of epinephrine 10–15 μg/mL in adults produces a ≥10-beat HR increase or a ≥15-mmHg SBP increase in the absence of ß-blockade, active labor, advanced age, or general/neuraxial anesthesia. Intravascular injection of epinephrine 0.5 μg/kg in children produces a ≥15-mmHg increase in SBP [8]. Nevertheless, epinephrine test doses are unreliable in the elderly or in patients who are sedated, taking ß-blockers, or anesthetized with general or neuraxial anesthesia. Fentanyl 100 μg produces sedation if injected intravenously in laboring patients [5].

Ultrasound

Ultrasound guidance may reduce the frequency of intravascular injection, but actual reduction of LAST remains unproven in humans.

Recommendations for Treatment of LAST (Table 1.8) [3, 6, 7]

Table 1.8 Recommendation for treatment of LAST

(a)
1. Be prepared. Establish a plan and checklist for managing
2. If signs and symptoms of LAST occur, prompt and effective airway management (ventilate with 100 % oxygen) is crucial to preventing hypoxia and acidosis
▼
3. Immediate treatment of convulsions within 15–30 s of their onset especially correcting hypoxia and acidosis is not associated with cardiac catastrophe [7]
4. Get help
(b)
If seizures occur
1. Benzodiazepines are preferred
2. If benzodiazepines are not readily available,
▼
Small doses of propofol (0.5–1.5 mg/kg) or thiopental (1–2 mg/kg) are acceptable
Although propofol can stop seizures, large doses further depress cardiac function
(c)
▼
If seizures persist despite
Benzodiazepines/small doses of succinylcholine (0.5–1 mg/kg)
(d)
▼
If cardiac arrest occurs
Standard and advanced cardiac life support
Small initial doses of epinephrine (10- to 100-μg boluses in adult) are preferred. There is laboratory evidence that epinephrine can impair resuscitation from LAST and reduce the efficacy of lipid rescue. Therefore, it is recommended to avoid high doses of epinephrine and use smaller doses, for example, 1 μg/kg, for treating hypotension [6]

Caution

1. Avoid vasopressin.
2. Treatment with local anesthetics (lidocaine or procainamide) is not recommended.
3. Avoid calcium channel blockers and beta-adrenergic receptor blockers.
   If ventricular arrhythmias develop, amiodarone is preferred.
4. Alert the nearest facility having cardiopulmonary bypass capability.

Table 1.9 Lipid emulsion therapy

1. 5 mL/kg (lean body mass) 20 % lipid emulsion bolus intravenously over 1 min (ca. 100 mL)
▼
Continuous infusion of 0. 25 mL/kg/min (ca. 18 mL/min; adjust by roller clamp), continued for at least 10 min after circulatory stability is attained
▼
If circulatory stability is not attained, consider giving another bolus and increasing infusion to 0.5 mL/kg/min
Approximately 10 mL/kg lipid emulsion over 30 min is recommended as the upper limit for initial dosing

Lipid Emulsion Therapy (Table 1.9) [7]
Timing of lipid infusion in LAST is controversial. The most reasonable approach is to implement lipid therapy on the basis of clinical severity and rate of progression of LAST.

Dosing [7] (Table 1.9)

Caution
1. Propofol is not a substitute for lipid emulsion.
2. Failure to respond to lipid emulsion and vasopressor therapy should prompt institution of cardiopulmonary bypass.
3. Prolonged monitoring (≥12 h) is recommended after any signs of cardiac toxicity because cardiovascular depression due to LAST can persist or recur after treatment.

Substance-Specific Side Effects [1]

One specific side effect of prilocaine is the increased methemoglobin level caused by the metabolite o-toluidine. Clinically, cyanosis, headache, cardiac palpitation, and vertigo can be expected at methemoglobin levels of 10–20 % and loss of consciousness, shock, and death when the level is 60 % or more. This does not call into question the beneficial toxicological properties of prilocaine, since clinically relevant methemoglobinemia can only occur at dosages of more than 600 mg, which is much more than clinically used doses of mepivacaine or lidocaine. A clinically harmful methemoglobin level can be treated within a few minutes by the intravenous administration of 2–4 mg/kg toluidine blue (or, alternatively, 1–2 mg/kg methylene blue). Because of this specific side effect, prilocaine is not indicated in patients with congenital or acquired methemoglobinemia, in patients who are anemic or have a history of heart disease, in obstetrics (e.g., for pudendal nerve or paracervical block), or in children under the age of 6 months.

Allergenic Potential

There are no reliable data regarding the frequency of allergic reactions after the administration of local anesthetics. There is no doubt that these are extremely rare, although the symptoms can range from allergic dermatitis to anaphylactic shock. Occasional cases of allergic reactions to ester local anesthetics have been reported, and the preservative substances which the various preparations contain (e.g., parabens) and the antioxidant sodium bisulfide in epinephrine-containing solutions are also under discussion as potential causes. In patients with suspected intolerance of local anesthetics, intracutaneous testing with 20 pL of the agent can be conducted.

When the result is positive, subcutaneous provocation tests at increasing dosages (0.1 mL diluted to 1:10,000, 1:1,000, and 1:10; undiluted at 0.1, 0.5, and 1 mL) can be considered. When these tests are being carried out, it is vital to prepare all the necessary safety measures in case of a severe reaction.

Recommended maximum doses without epinephrine, according to specialist information:

Lidocaine	Mepivacaine	Prilocaine
200 mg	300 mg	400 mg

Table 1.10 Functional distinctions between nerve fibers

Fiber type	Function
$A\alpha$	Motor, touch, pressure, depth sensation
$A\beta$	Motor, touch, pressure, depth sensation
$A\gamma$	Regulation of muscle tone
$A\delta$	Pain, temperature, touch
B	Preganglionic sympathetic function
C	Pain, temperature, touch, postganglionic sympathetic function

Table 1.11 Overview of drugs

Drug	Potency	Duration of effect (h)	Toxicity	Half-life	Vdiss
Lidocaine	1	2	1	96′	91
Mepivacaine	1	2–3	1.2	114′	84
Prilocaine	1	2–3	0.5	93′	261

Selection of Suitable Substances for Regional Block

When surgical interventions are being carried out under regional anesthesia, priority must go to shutting off both sensory and motor systems, and knowledge of the expected length of the operation is vital to the choice of anesthetic. The onset of effect and the toxicity of the drug used play important parts, but not decisive ones. In the context of pain therapy, in which the fast-conducting A delta fibers and the slow-conducting C fibers (Table 1.10) are the target of the block, toxicity is much more important than the duration of the effect.

In diagnostic and therapeutic blocks, in which there is a risk of intravascular injection—e.g., in a stellate ganglion block or superior cervical ganglion block—prilocaine should be selected, as it is the medium-duration local anesthetic with the lowest toxicity (mepivacaine and lidocaine are alternatives) (Table 1.11).

Bupivacaine has an important role in regional blocks, being a longer-duration local anesthetic that provides high-quality analgesia and an easily controlled motor block. Its anesthetic potency is about four times that of local anesthetics with medium-duration effects (such as prilocaine). When the lower dosage required in pain therapy than in regional anesthesia is taken into account, bupivacaine can be used for practically all pain therapy procedures in spite of its relatively high toxicity.

Ropivacaine is the most recently introduced long-duration local anesthetic in the amino-amide series. The differential block is even more marked than with bupivacaine, and the drug is associated with much lower CNS toxicity and cardiac toxicity. These characteristics make it particularly suitable for regional anesthesia procedures in which higher dosages or concentrations are required. Ropivacaine provides good-quality analgesia while largely maintaining motor activity (up to 80 % of patients have no measurable motor block on the Bromage scale). At a dosage of 2 mg/mL, the drug is therefore the local anesthetic of choice for epidural obstetric analgesia and for postoperative analgesia (Table 1.5). With its pharmacological profile, ropivacaine is the first local anesthetic with primarily analgesic effects, and it is therefore particularly suitable for pain therapy indications.

Every anesthetist and pain therapy physician who uses anesthetic methods for temporary interruption of stimulus conduction in a ganglion, nerve, or neural plexus should be familiar with the properties and potential applications of the following agents:

Short-Acting Local Anesthetics

Procaine (Novocain®) (Tables 1.1, 1.3a, and 1.3b)

In 1905, Einhorn in Germany succeeded in synthesizing a new local anesthetic, which he called "procaine." Heinrich Braun introduced procaine into clinical practice on the same year, as a 4.5 and 5 % solution.

Class of drug: Local anesthetic of the ester type.
Single threshold dose: 500 mg without epinephrine in adults.
LD_{50} (mouse): 52.2–60.0 mg/kg body weight i.v.
Plasma half-life: <0.14 h.
Latency: Medium.
Duration of effect: 0.5–1 h, depending on the area of application and the concentration used.
Metabolism: Procaine is broken down in plasma by pseudocholinesterase into p-aminobenzoic acid—a naturally occurring component of folic acid synthesis—and into diethylaminoethanol. The metabolites are excreted in the urine or broken down in the liver.
Tolerability and control: Procaine is one of the local anesthetics that have the lowest toxicity. Due to its short half-life, procaine is easily controlled.

Clinical uses: It is not so much its local anesthetic potency that predominates in procaine, but rather its muscle-relaxing properties and vasodilatory effect—which are of primary importance in infiltration therapy and trigger point treatment.
In the therapeutic field, very good results can be obtained with superior cervical ganglion block. However, procaine's high allergenic potency in comparison with amide local anesthetics argues against its use.
Dosage: Procaine is administered at concentrations of 0.5–2 %. Precise dosages are described in the relevant sections of this book.

2-Chloroprocaine (Table 1.1)

2-Chloroprocaine, an ester local anesthetic, is a chlorinated derivative of procaine and is the most rapidly metabolized local anesthetic currently used. Although the potency of chloroprocaine is relatively low, it can be used for epidural anesthesia in large volumes in a 3 % solution because of its low systemic toxicity. The duration of action is between 30 and 60 min. This agent enjoyed its greatest popularity for epidural analgesia and anesthesia in obstetrics because of the rapid onset and low systemic toxicity in both mother and fetus. However, frequent injections are needed to provide adequate pain relief in labor, and it is more usual to establish analgesia with chloroprocaine and then change to a longer-acting agent such as ropivacaine or bupivacaine.

The use of chloroprocaine declined because of reports of prolonged neurological deficit following accidental subarachnoid injection. This toxicity was ascribed to the sodium metabisulfite used in the past as preservative. However, there are no reports of neurotoxicity with newer preparations of chloroprocaine which contain disodium ethylenediaminetetraacetic acid (EDTA) as the preservative. Nevertheless, these preparations are not recommended for intrathecal administration. However, since then, a number of reports of back pain have appeared. The incidence of back pain appears to be related to the large volume (greater than 40 ml) of drug injected. Chloroprocaine has also proved of value for peripheral nerve blocks and epidural anesthesia when the duration of surgery is not expected to exceed 30–60 min.

Tetracaine (Table 1.1)

Tetracaine is a long-acting amino ester. It is significantly more potent and has a longer duration of action than procaine or 2-chloroprocaine. Tetracaine remains a very popular drug for spinal anesthesia in the United States. This drug possesses excellent topical anesthetic properties, and solutions of this agent were commonly used for endotracheal surface anesthesia. Because of its slow onset and high toxicity, tetracaine is rarely used in peripheral nerve blocks.

Medium-Term Local Anesthetics

Lidocaine (Xylocaine®, Lignocaine) (Tables 1.2, 1.3a, 1.3b, 1.6, and 1.11)

Löfgren and Lundqvist in Sweden isolated a new substance in 1943 that was given the working name of "LL 30." It was later renamed "lidocaine." Following extensive pharmacological studies by Goldberg, the first clinical tests in dentistry using lidocaine were carried out in 1947. Torsten Gordh, the father of Swedish anesthesia, carried out the first investigations of lidocaine in humans.

Class of drug: Lidocaine is a medium-duration local anesthetic of the amide type.

Single threshold dose: 200 mg without epinephrine in adults/70 kg body weight. After injection of a maximum dose, subsequent injections should not be given for 90 min. The second dose must not exceed a maximum of half of the first dose.

LD_{50} (mouse): 31.2–62.2 mg/kg body weight i.v.

Plasma half-life: ca. 1.6 h.

Latency: Fast.

Duration of effect: 1–2 h, depending on the area of application and the concentration used.

Metabolism: Lidocaine is metabolized in hepatic microsomes. Only about 3 % of the drug is excreted unchanged via the kidney.

Tolerability and control: Lidocaine is one of the local anesthetics with moderate relative toxicity. It is characterized by a medium-term duration of effect and good distribution characteristics.

Lidocaine causes vasodilation, which may be less than that of procaine. When the medium-duration local anesthetics are compared, the strengths of the associated vasodilatory effects show the following sequence: lidocaine > mepivacaine > prilocaine. Lidocaine is therefore often used with epinephrine.

Clinical uses: Lidocaine is widely used in clinical practice, particularly in neural and segmental therapy. It is also suitable for infiltration anesthesia, for peripheral nerve block, for epidural anesthesia, and for mucosal surface anesthesia (2 % gel, Emla®).

Dosage: Lidocaine is mainly administered as a 0.5–1 % (1.5) % solution. Specific doses are given in the relevant chapters of this book.

Emla® Cream

Emla® (a mixture of 2.5 % lidocaine and 2.5 % prilocaine) is a topical local anesthetic that penetrates intact skin and reaches an anesthetic depth of up to 5 mm. The onset of effect is approximately 1 h. When the effect takes place, the vessels in the skin show vasoconstriction initially, followed by vasodilation when higher concentrations are reached. This form of administration of this local anesthetic mixture has proved particularly useful in pediatric anesthesia before intravenous access placement and for minor surgical procedures on the skin surface.

Lidocaine Plaster

Lidocaine, administered in various forms (i.v., i.m., or transdermally), relieves pain associated with postherpetic neuralgia (PHN) [8–13]. The analgesia is based on the blockade of neuronal sodium channels. However, intravenous administration of lidocaine can lead to plasma concentrations associated with antiarrhythmic effects. Topical application of lidocaine in the form of a gel or plaster avoids high plasma concentrations. This type of lidocaine plaster was developed in the United States, where it has been licensed since 1999 for pain treatment in postherpetic neuralgia (Lidoderm®, Endo Pharmaceuticals Ltd., Chadds Ford, PA). The plaster consists of a soft, stretchable polyester base connected to an adhesive layer that contains 5 % lidocaine. The plaster is 10 × 14 cm in size.

The systemic absorption of lidocaine has been shown in preclinical and clinical studies to be minimal (3 %) in both volunteers and patients with PHN. Treatment with lidocaine plaster has been investigated in comparison with a placebo in three randomized, double-blind clinical studies including a total of 217 patients with PHN [8, 12–14]. A significant reduction in pain intensity and allodynia was observed. Lidocaine plaster therefore represents a treatment option with a relatively low risk of adverse systemic events or drug interactions [15].

In Europe, clinical testing of the plaster for use in postherpetic neuralgia is currently taking place, and its licensing for this indication can be expected within the next 2 or 3 years.

Mepivacaine (Scandicaine®, Mebeverine®) (Tables 1.3a, 1.3b, 1.6, and 1.11)

In 1956, Bo af Ekenstam, a Swedish scientist, developed mepivacaine. It was introduced into clinical practice by K. G. Dhunér in Sweden in 1957.

Class of drug: Mepivacaine is a medium-duration local anesthetic of the amide type.
Single threshold dose without epinephrine in adults (70 kg body weight): 200 mg in the ENT field and 300 mg in other applications.
LD_{50} (mouse): 40.3 ± 3.2 mg/kg body weight i.v.
Plasma half-life: ca. 1.9 h.
Latency: Fast.
Duration of effect: 1–3 h, depending on the area of application and the concentration used.
Metabolism: Mepivacaine is metabolized in the hepatic microsomes.

After intravenous administration, up to 16 % of the agent is excreted unchanged via the kidney. Degradation in the liver mainly produces m-hydroxymepivacaine and p-hydroxymepivacaine. These metabolites are conjugated with glucuronic acid and excreted in the urine. Another metabolite, pipecoloxylidide, collects in bile and passes through the enterohepatic circulation with its degradation products. No 2,6-xylidine is produced when mepivacaine is metabolized, and there is no evidence that either the agent or its metabolites have mutagenic or carcinogenic properties.

Tolerability and control: Mepivacaine is another of the local anesthetics with moderate relative toxicity. It is characterized by a medium-term duration of effect, with good distribution properties and some vasodilatory effect.
Clinical uses: Mepivacaine is the local anesthetic of choice when a medium-duration effect is required for diagnostic and therapeutic blocks in pain therapy—particularly in outpatients. It is suitable for infiltration anesthesia, intravenous regional anesthesia, peripheral nerve block and ganglion block, and epidural anesthesia. Mepivacaine cannot be recommended in obstetrics due to its long elimination half-life in the neonate.
Dosage: Mepivacaine is mainly used as a 1 % (1.5 %) or 0.5 % solution. Specific doses are given in the relevant chapters of this book.

Prilocaine (Xylonest®) (Tables 1.3a, 1.3b, 1.6, and 1.11)

Class of drug: Prilocaine is a medium-duration local anesthetic of the amide type.
Single threshold dose: 400 mg (with or without vasopressor) in adults/70 kg body weight.
LD_{50} (mouse): 62 mg/kg b.w. i.v.
Plasma half-life: ca. 1.5 h.
Latency: Fast.
Duration of effect: 2–3 h, depending on the area of application and the concentration used.
Metabolism: Prilocaine is mainly metabolized in hepatic microsomes, but also in the kidney and lungs. During degradation, the metabolite ortho-toluidine is produced. At doses higher than 600 mg, the body's reduction systems may become exhausted. At doses higher than 800 mg, noticeable methemoglobinemia can be expected (see the section on substance-specific side effects). Fast elimination from the blood leads to low systemic toxicity.
Tolerability and control: Among the amide local anesthetics, prilocaine shows the best ratio between anesthetic potency and toxicity. Due to its high distribution volume and marked absorption in the lungs, plasma levels are significantly lower than those of mepivacaine and lidocaine (by a factor of 2–3). It has a medium-term duration of effect.

Clinical uses: Due to its comparatively low toxicity, prilocaine is particularly suitable for regional anesthesia techniques that require a single injection of a large volume or a high anesthetic dosage. The increasing use of prilocaine (2 % isobaric solution) for spinal anesthesia is relatively new. Comparative studies in recent years have shown good tolerability, while transient neurological symptoms (TNS; see Chap. 41) were observed more often with lidocaine and mepivacaine. Prilocaine—like other medium-duration agents—is not suitable for continuous blocks. Due to the possibility of raised methemoglobin levels, prilocaine should not be used in anemic patients, in children under the age of 6 months, or in obstetrics.

Dosage: Depending on the area of application, a 0.5–2 % solution is used. Specific doses are given in the relevant chapters of this book.

Long-Acting Local Anesthetics

Ropivacaine (Naropin®) (Tables 1.3a, 1.3b, 1.5, and 1.11)

Class of drug: Local anesthetic of the amide type, pure S-enantiomer.

Single threshold dose:

Anesthesia:

Epidural: 0.5–1 %, 200 mg.

Plexus blocks: 0.75 %, 300 mg.

Conduction and infiltration anesthesia: 0.5–0.75 %, 225 mg.

Injection at myofascial trigger points: 0.2 % (1–2 mL per trigger point).

Continuous procedures: 0.2 %, up to 14 mL/h. Increased doses may be required during the early postoperative period—up to 0.375 %, 10 mL/h (maximum 37.5 mg/h). When it is administered over several days, the resulting concentrations are well below potentially toxic plasma levels.

A dosage of 300 mg should be regarded as a guideline value, as this dosage has been confirmed as tolerable by various pharmacological studies.

LD_{50} (mouse): ca. 11.0–12.0 mg/kg b.w. i.v.

Plasma half-life: ca. 1.8 h.

Duration of effect: Epidural anesthesia ca. 7 h (analgesia); ca. 4 h (motor block), 10 mg/mL.

Plexus anesthesia (brachial plexus, lumbosacral plexus): 9–17 h, 7.5 mg/mL.

Infiltration anesthesia: Postoperative analgesia after inguinal herniorrhaphy >7 h (5–23 h), 7.5 mg/mL. Peripheral nerve blocks in pain therapy: 2–6 h (0.2–0.375 mg/mL).

Latency: Medium (decreasing latency at increasing concentrations).

Metabolism: Ropivacaine is metabolized in the liver, mainly through aromatic hydroxylation. Only about 1 % of the drug is excreted unchanged in the urine. The main metabolite is 3-hydroxyropivacaine.

Tolerability: Ropivacaine provides relatively low toxicity for a long-term local anesthetic. Compared with bupivacaine, it has a lower arrhythmogenic potential, and the margin between convulsive and lethal doses is wider. Ropivacaine has more favorable receptor kinetics ("fast in, medium out") in cardiac sodium channels and in comparison with bupivacaine has only slight depressant effects on the energy metabolism of the mitochondria in cardiac muscle cells.

Clinical uses: The first clinical tests were carried out in 1988. Ropivacaine (Naropin®) has been in use since 1996. It is the first local anesthetic with a primary analgesic effect and is therefore of particular interest in pain therapy (postoperative and obstetric, as well as therapeutic blocks).

Ropivacaine is the most comprehensively documented and the most widely approved local anesthetic today. It is the most frequently used long-acting local anesthetic throughout the world. It should be noted that it has been approved, with clinical relevance, for use in continuous therapy for acute pain (epidural and peripheral continuous nerve blocks). Approval for administration in children, including continuous epidural administration, was extended to neonates in 2007. It is the first local anesthetic with primarily analgesic effects and is therefore of particular interest for pain therapy (postoperative and obstetric and therapeutic blocks). In comparison with bupivacaine, it has fewer toxic side effects (CNS and, in particular, cardiac toxicity). High doses are needed before toxic effects develop. CNS symptoms appear well before cardiac symptoms, which in the clinical situation provides time for the local anesthetic injection to be stopped and for early treatment steps to be taken. In an animal model, the chances of successful resuscitation were also found to be better than with bupivacaine (90 % vs. 50 %) [16]. In addition, ropivacaine shows marked differential blocking in epidural analgesia and peripheral blocks. With a good quality of analgesia, up to 80 % of patients have no measurable motor block on the Bromage scale. Epidural combinations (e.g., with sufentanil, dosage range 0.5–1 pg/mL) are possible. In view of the increased use of peripheral blocks and infiltrations at painful trigger points, evidence of higher muscular tissue tolerance in comparison with bupivacaine is also of interest [17]. The relatively low toxicity of ropivacaine means that high concentrations can be given (e.g., 10 mg/mL solution for epidural anesthesia)—providing more intense motor block, a higher success rate, and better-quality analgesia than 0.5 % bupivacaine, for example (Table 1.5 and 1.6).

Dosage: Ropivacaine is administered at concentrations of 2 mg/mL (0.2 %), 7.5 mg/mL (0.75 %), and 10 mg/mL (1 %). Use for continuous epidural infusion has been

approved (Naropin® 2 mg/mL polybag, 100 and 200 mL infusion solution). Cumulative daily doses of up to 675 mg (see specialist information) are well tolerated in adults. Precise information on doses is given in the following chapters.

Levobupivacaine (Chirocaine®) (Tables 1.3a, 1.3b, 1.5, and 1.6)

Class of drug: Local anesthetic of the amide type. A pure S-enantiomer of bupivacaine.
Single threshold dose without epinephrine in adults: 150 mg.
LD_{50} (mouse): 10.6 mg/kg b.w.
Plasma half-life: 80 ± 22 min. Plasma protein binding of levobupivacaine in humans has been assessed in vitro and was more than 97 % at concentrations of 0.1–1.0 pg/mL.
Latency: Medium (between ropivacaine and bupivacaine).
Duration of effect: 8–24 h, depending on the area of application and the concentration used.
Metabolism: Levobupivacaine is extensively metabolized, and unaltered levobupivacaine is not found in the urine or feces. 3-Hydroxylevobupivacaine, one of the principal metabolites of levobupivacaine, is excreted via the urine as a glucuronic acid and sulfate ester conjugate. In vitro studies have shown that levobupivacaine is metabolized via CYP3A4 isoforms and CYP1A2 isoforms into desbutyl levobupivacaine or 3-hydroxylevobupivacaine. The studies showed that the degradation of levobupivacaine and bupivacaine is similar. After intravenous administration of levobupivacaine, the recovery rate within 48 h averaged ca. 95 %, quantitatively measurable in urine (71 %) and feces (24 %). There is evidence of in vivo racemate formation with levobupivacaine.
Tolerability and control: Experimental animal studies have demonstrated a lower risk of CNS and cardiovascular toxicity with levobupivacaine than with bupivacaine. In volunteers, fewer negative inotropic effects were observed after intravenous administration of more than 75 mg levobupivacaine in comparison with bupivacaine. QT interval changes only occurred in a very few cases.
Clinical uses: There is little experience as yet with levobupivacaine in clinical practice. The numbers of published controlled clinical studies are also comparatively small. Available in vitro, in vivo, and controlled patient studies comparing levobupivacaine and bupivacaine have shown similar potency for neural blocks. After epidural administration of levobupivacaine, the same quality of sensory and motor block as with bupivacaine was seen. However, a significant differential block, as provided by ropivacaine, cannot be expected, as the drug has the same degree of lipophilia as bupivacaine. Levobupivacaine has not been approved for use in Germany.
Dosage: 0.125–0.75 %. Precise information on doses is given in the following chapters.

Bupivacaine (Carbostesin®, Marcaine®) (Tables 1.3a, 1.3b, 1.5, and 1.6)

The first clinical studies of a long-acting local anesthetic, bupivacaine, were carried out in 1965/1966.

Class of drug: Local anesthetic of the amide type.
Single threshold dose: 150 mg without epinephrine in adults.
LD_{50} (mouse): 7.8 ± 0.4 mg/kg b.w. i.v.
Plasma half-life: ca. 2.7 h.
Latency: Medium.
Duration of effect: 2.5–20 h, depending on the area of application and the concentration used. A mean duration of effect of 3–6 h can be assumed.
Metabolism: Bupivacaine is broken down in hepatic microsomes at a high rate. The predominant metabolization involves dealkylation to pipecoloxylidide (desbutyl bupivacaine). There is no evidence that either the agent or its metabolites have mutagenic or carcinogenic properties.
Tolerability and control: Bupivacaine is one of the local anesthetics that has a high relative toxicity. Its anesthetic potency is about four times greater than that of mepivacaine. It is characterized by a slower onset of effect and by a long duration of effect.
Clinical uses: Bupivacaine is indicated as a long-duration local anesthetic, particularly for regional anesthesia in the surgical field, in postoperative analgesia, and in therapy for various pain conditions.
It is suitable for infiltration anesthesia, peripheral nerve block, ganglion block and plexus block, as well as all forms of neuraxial anesthesia.
The marked cardiac toxicity of bupivacaine has been known since publications dating from the late 1970s, and severe and fatal adverse effects are still reported. Strict observation of safety standards is therefore of fundamental importance for the safe use of this drug at high doses.
Dosage: Depending on the indication, bupivacaine is administered as a 0.125–0.5 % solution. A 0.75 % solution is still being marketed. Higher concentrations are not required in pain therapy. Specific doses are given in the following chapters.

Examination and Patient Preparation

Before regional anesthesia, the same type of examination of the patient should be carried out as for general anesthesia. Contraindications must be excluded, as well as neurological abnormalities, and when there are relative

contraindications—e.g., hemorrhagic diathesis, stable systemic neurological disease, or local nerve damage—a careful assessment of the risk–benefit ratio needs to be made.

Particular attention needs to be given to anatomical relationships, palpation of the landmarks, and precise localization and marking of the needle insertion point.

To ensure cooperation, the patient should be given detailed information about the aim of the block, its technical performance, and possible or probable paresthesias and their significance. The patient should also be informed about potential adverse effects and complications of the block, and outpatients in particular should be familiarized with guidelines on behavior after anesthesia. The patient information session should be documented using a consent form signed by the patient.

In general, premedication and the administration of sedatives or analgesics should be avoided, particularly in outpatient pain therapy. Constant verbal contact should be maintained with the patient during the block, so that potential side effects or complications can be recognized immediately. In addition, any sedation that is not adjusted individually can lead to respiratory and circulatory complications, which may be mistaken for the early symptoms of local anesthetic toxicity.

Documentation of Treatment

The patient history, including investigations at other centers, and diagnostic results should be documented just as carefully as the preparation, implementation, and success of the block. The checklists and record forms used in our own pain center have been adapted for each individual block technique and are included in the following chapters.

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