Regional Nerve Block in Anesthesia and Pain Therapy: General Consideration

1

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Regional Nerve Blocks and Infiltration Therapy in Clinical Practice

General Consideration

Regional anesthesia means the interruption of impulse conduction in the nerves using specific, reversibly acting drugs (local anesthetics). This interruption of impulse conduction can be carried out in every region of the body in which the nerves are accessible for external injection.

The indications for regional anesthesia include:

1. Clinical anesthesia

   Particularly in the fields of traumatology, orthopedics, urology, and gynecology, as well as in large-scale abdominal surgery with continuous procedures for epidural or spinal anesthesia.
2. Obstetrics

   The use of regional anesthesia especially neuraxial anesthesia will be discussed in detail in Chap. 42.
3. Postoperative analgesia

   There is no postoperative analgesia procedure that is more appropriate than regional anesthesia. This field also includes the classic indications for a combination of local anesthetics with opioids or other substances. Optimal patient care can only be achieved using a multimodal approach (effective pain therapy, early mobilization, early enteral nutrition, and emotional and psychological care). Effective pain therapy (e.g., with catheter analgesia procedures) plays a central role here, as it can substantially reduce the perioperative stress response (Fig. 1.1).
4. Pain therapy

   In 1979, a commission set up by the International Association for the Study of Pain (IASP) defined pain as "... an unpleasant sensory and emotional experience, linked to actual or potential tissue damage". Since then, the definition of pain is recently revised. Acute pain is caused by stimulation of pain receptors. This stimulation is transient and sets in motion biologically useful protective mechanisms. Ideally, pain can be relieved by treating

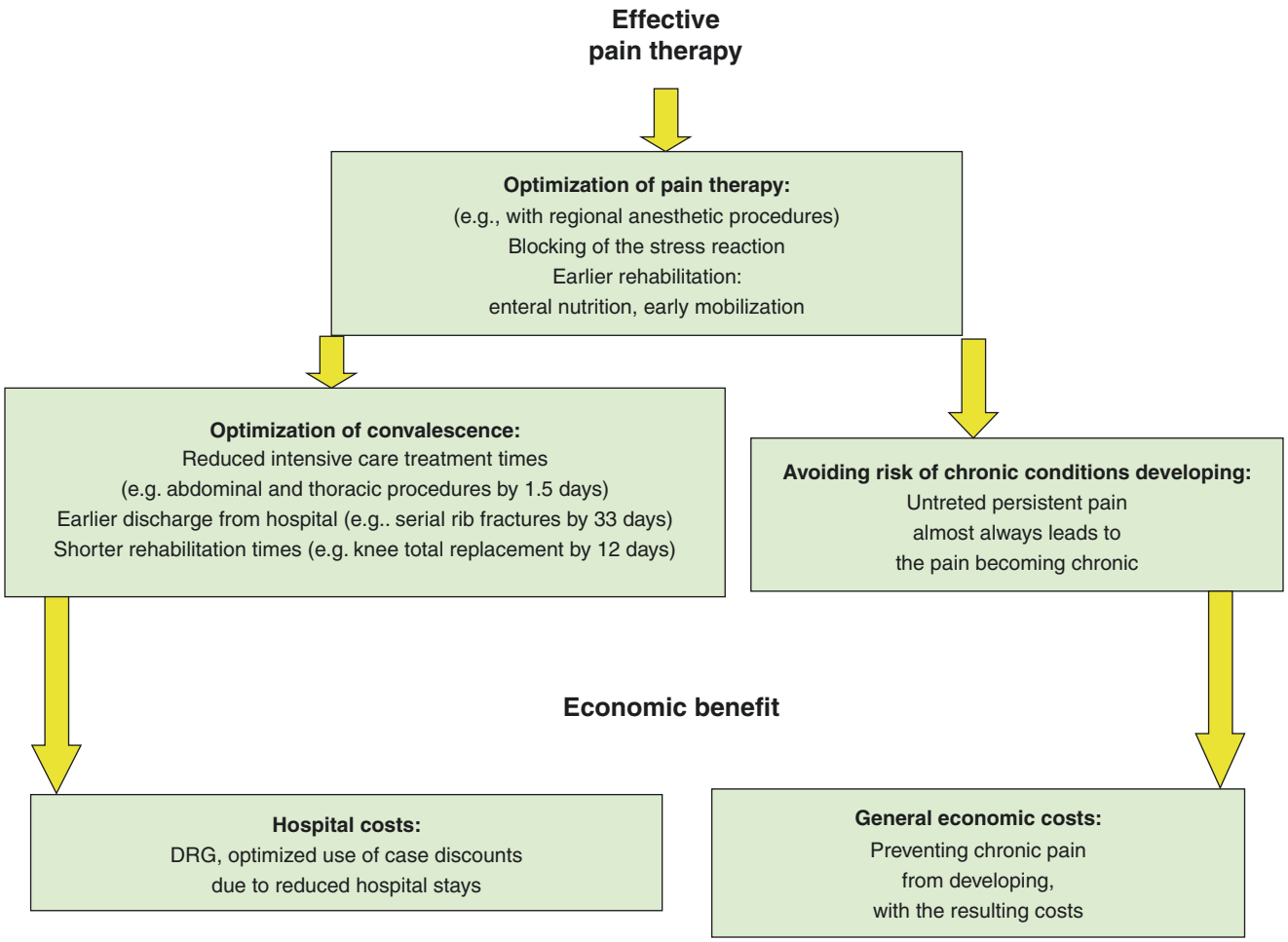


Fig. 1.1 Importance of effective pain therapy as part of a multimodal approach to treatment

the cause. Chronic pain is regarded as a pathological response on the part of the body. The relief of pain should be viewed as a "human right." In this context, there are a significant number of patients who will not obtain effective pain relief without access to potent neural blockade techniques.

It arises due to constant stimulation of nociceptive afferents, or can develop as neuropathic pain after injury or damage to the peripheral nociceptive system. Chronic pain can often lead to alterations in patient's living habits, physical abilities, and personality, and requires a coordinated interdisciplinary approach. This in turn presupposes a clear diagnosis, based on a full general history and pain history, physical examination and functional assessment of the patient's musculature, locomotor apparatus, autonomic nervous system, and neurological and angiological situation.

In addition to medical treatment for pain, nerve blocks have a firmly established place in pain therapy—alongside physical and manual procedures, neurological and neurosurgical methods, physiotherapy and the psychosocial management of patients. In quantitative terms, regional anesthesia procedures play only a minor part in the management of chronic pain, but qualitatively they can produce very good results when used with the correct indications.

Nerve Blocks in Surgery and Pain Therapy

The application of the anesthesiology methods described in the subsequent chapters of this book for temporary interruption of stimulus conduction in a nerve or nerve plexus requires the use of strictly established indications and the implementation of a coordinated therapeutic approach. In principle, these blocks can be administered for surgery, diagnosis, prognosis, and therapy (Table 1.1).

Surgical blocks are administered with high-dose local anesthetics for targeted isolation of a specific body region in order to carry out an operation.

Diagnostic blocks using low-dose local anesthetics are appropriate for the differential diagnosis of pain syndromes. They allow the affected conduction pathways to be recognized and provide evidence regarding the causes of the pain. Diagnostic blocks can also be used to clarify the question of whether the source of the pain is peripheral or central.

Prognostic blocks allow predictions to be made regarding the potential efficacy of a longer-term nerve block, neurolysis or surgical sympathectomy. They should also be used to prepare the patient for the effects of a permanent block.

Therapeutic blocks are used in the treatment of a wide variety of pain conditions. Typical examples of these are post-traumatic and postoperative pain, complex regional pain syndrome (CRPS) types I and II (reflex sympathetic dystrophy and causalgia), joint mobilization, postherpetic neuralgia, and tumor pain.

Table 1.1 Important rules to observe when administering regional anesthesia or therapeutic nerve blocks

Before the block
Patient
1. Preoperative information
– Explain the procedure
– Discuss potential side effects and complications
–Advise the patient about what to do after the procedure
– Document the discussion
2. Determine the patient's neurological status
– Exclude neurological abnormalities
3. Exclude contraindications
4. Avoid premedication in outpatients (particularly in blocks in which there is an increased risk of intravascular injection—e.g., stellate ganglion or superior cervical ganglion)
Anatomy, complications, side effects
1. With rarely used regional blocks, the anatomic and technical aspects should always be studied again beforehand
2. Detailed knowledge of potential complications and side effects of a regional block and how to avoid them
3. Ability to control potential complications and side effects
4. Select the correct block techniques
5. Manual skill and good training on the part of the anesthetist
Preparation
1. Ensure optimal positioning of the patient
2. Always secure intravenous access
3. Check that emergency equipment is complete and fully functioning
4. Added vasopressors are contraindicated in pain therapy
5. Observe sterile precautions
Safety standards when injecting larger doses of local anesthetics
1. Carry out aspiration tests before and during the injection
2. Administer a test dose
3. Inject local anesthetics in incremental doses (several test doses)
4. Maintain verbal contact with the patient
5. Cardiovascular monitoring
6. Keep careful notes of the block

Nerve Blocks and Chronic Pain

A *multimodal treatment approach* to chronic pain is essential for successful treatment. The use of nerve blocks as part of this approach presupposes that the following steps have been taken:

1. Careful analysis of the pain.
2. Correct diagnosis and establishment of the indication.
3. Assessment of the pain chronicity stage.
4. Well-selected patient groups.

Important preconditions for the application of nerve blocks in chronic pain include:

1. A good knowledge of anatomy.
2. Attention to and control of potential side effects and complications.
3. Choice of the correct block techniques.
4. Manual skill and good training on the part of therapist.

The most important tasks facing us include conducting more double-blind, randomized and well-controlled studies on the use of nerve blocks in chronic pain conditions, and developing a consistent standard for carrying out nerve blocks. The answers to two questions need to be found:

1. Selection criteria to identify which patients are suitable for nerve blocks.
2. The number of nerve blocks to be used in the treatment of chronic pain.

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—for example, 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 (Table 1.1).

Informed Consent

To ensure cooperation, the patient should be given simple, short 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.

*Do not discuss only serious and major risks of the procedure, but also benefits and expected results of the proposed regional anesthetic procedure. The consent process has to be used as a simultaneous education of the patient

Safety Measures

It is important that a number of safety measures are taken to ensure the most suitable regional anesthesia technique is performed for the correct patient. These measures include obtaining patient consent, checking all equipment and drugs, ensuring appropriate monitoring and performance of a correct surgical site check. Once the regional block is performed, it is vital to accurately document the procedure in detail (Table 1.1).

In general, premedication and the administration of sedatives or analgesics should be avoided 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.

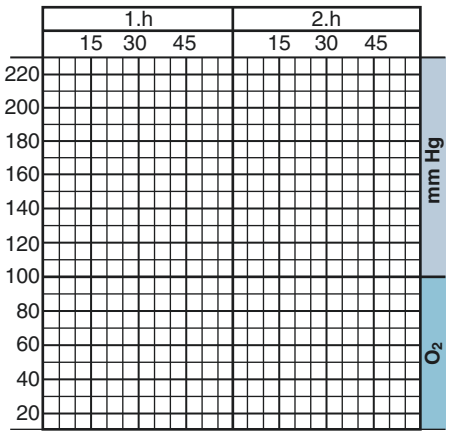
The checklists and record forms used in our Institution have been adapted for each individual block technique. Samples of record and checklists, for example, stellate ganglion block, neuraxial block, or peripheral nerve block are shown in Figs. 1.2, 1.3, and 1.4.

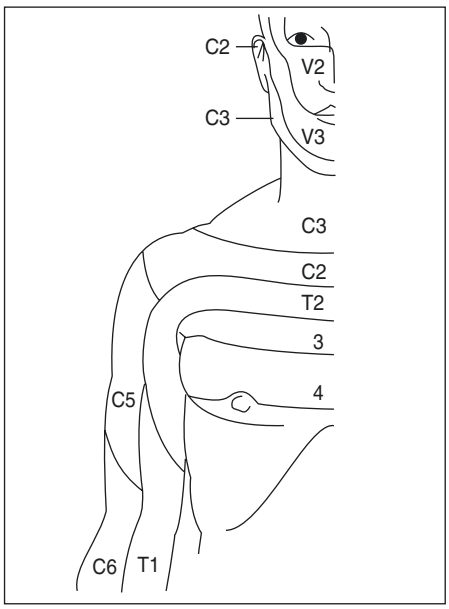
This comprehensive list has pertinent information including purpose of the block, position and approach, type of local anesthetics used, and complications that might arise. Such standardized recommendations are useful for the purpose of medicolegal documentation and conducting retrospective studies on complications. Paper records are increasingly being replaced with electronic medical record-keeping systems. Legibility and ability to correct errors are advantages to the e-block note. Another useful aspect of regional nerve block documentation is the recording of an ultrasound image or video clip, to be stored in the patient's chart.

Technical Requirements

Carrying out temporary nerve blocks and regional anesthetic procedures in surgery and pain therapy requires the appropriate basic technical equipment and experience in the use of all of the instruments concerned. The conditions for patient positioning, the aseptic conditions required, and the syringes, needle types, and other supplies needed are discussed alongside the individual block techniques described in this book. Complete and properly functioning equipment must be available both for primary care and in case of adverse events and complications, as well as treatment monitoring.

Record and checklist





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Cervicothoracic ganglion (stellate ganglion)

Block no. ☐ Right ☐ Left

Name: _____ Date: _____

Diagnosis: _____

Premedication: ☐ No ☐ Yes _____

Purpose of block: ☐ *Diagnostic* ☐ *Therapeutic*

Needle: ☐ *22 G* ☐ *40 mm long* ☐ *50 mm long*

i.v. access: ☐ *Yes*

Monitoring: ☐ *ECG* ☐ *Pulse oximetry*

Ventilation facilities: ☐ *Yes (equipmet checked)*

Emergency equipment *(drugs):* ☐ *Checked*

Patient: ☐ *Informed*

Position: ☐ *Supine* ☐ *Neck extended*

Approach: ☐ *Paratracheal* ☐ *C6* ☐ *C7*
☐ *Ultrasound - guided*
☐ *Transducer* ☐ *Linear*
☐ *In plane* ☐ *Out of plane*

Local anesthetic: _____ *ml* _____ *%* _____

Test dose: _____ *ml*

Addition to
Injection solution: ☐ *No* ☐ *Yes* _____

Patient's remarks during injection:
☐ *None* ☐ *Pain* ☐ *Paresthesias* ☐ *Warmth*

Nerve region _____ _____ _____

Objective block effect after 15 min:
☐ *Cold test* ☐ *Temperature measurement right* ____ *°C left* ____ *°C*

Horner's syndrome: ☐ *Yes* ☐ *No*

Segment affected: ☐ *C2* ☐ *C3* ☐ *C4* ☐ *C5* ☐ *T* ____

Monitoring after block: ☐ *< 1 h* ☐ *> 1 h*
Time of discharge _____

Complications: ☐ *None*
☐ *Yes (intravascular, epidural, subarachnoid injection, other)* _____

Side effects: ☐ *None*
☐ *Yes (recurrent laryngeal nerve, phrenic nerve, vagus* _____

Subjective effects of the block: *Duration:* _____
☐ *None* ☐ *Increased pain*
☐ *Reduced pain* ☐ *Relief of pain*

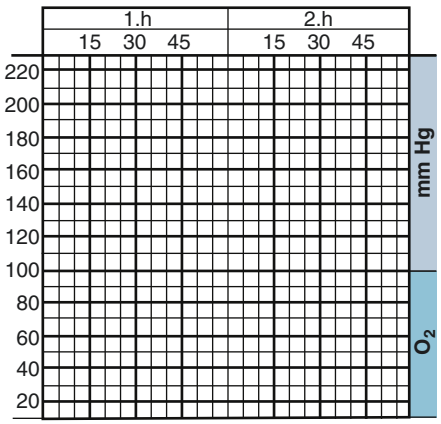
VISUAL ANALOG SCALE

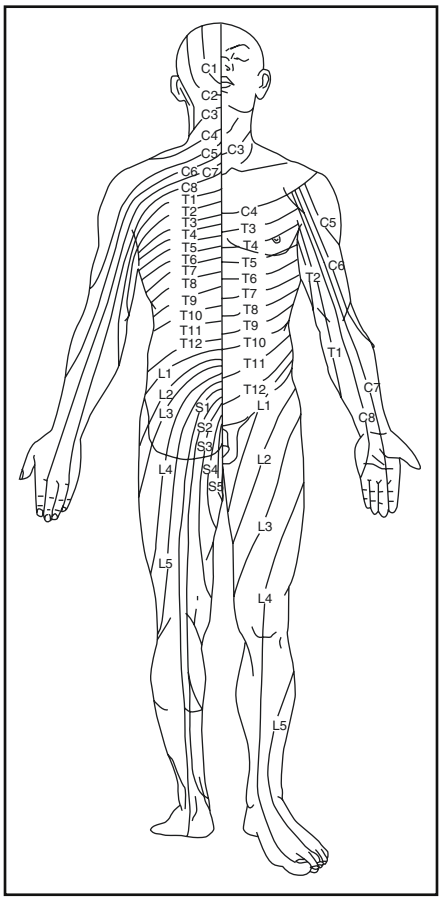
0 10 20 30 40 50 60 70 80 90 100

Special notes:
_____
_____
_____

Fig. 1.2 Checklist and record for cervicothoracic ganglion block. (Courtesy of Danilo Jankovic with permission)

Record and checklist





Lumbar epidural anesthesia

Name: _____ Date: _____

Diagnosis: _____

Premedication: ☐ No ☐ Yes _____

Neurological abnormalities: ☐ No ☐ Yes _____

Purpose of block: ☐ *Surgical* ☐ *Therapeutic* ☐ *Diagnostic*

Needle: ☐ *Tuohy G*___ ☐ *Other* ___

i.v. access, infusion: ☐ *Yes*

Monitoring: ☐ *ECG* ☐ *Pulse oximetry*

Ventilation facilities: ☐ *Yes (equipment checked)*

Emergency equipment (drugs): ☐ *Checked*

Patient: ☐ *Informed*

Position: ☐ *Lateral decubitus* ☐ *Sitting*

Access: ☐ *Median* ☐ *Paramedian*

Injection level: ☐ *L3/L4* ☐ *Other* _____

Injection technique: ☐ *Loss of resistance* ☐ *Other* _____

☐ *Ultrasound guided* ☐ *Transducer* ☐ *Curved* ☐ *Linear*

Approach: ☐ *In plane* ☐ *Out of plane*

Epidural space: ☐ *Identified*

Aspiration test: ☐ *Carried out*

Test dose: _____ Epinephrine added: ☐ *Yes* ☐ *No*

Check on sensorimotor function after 5 min: ☐ *Carried out*

Abnormalities: ☐ *No* ☐ *Yes*_____

Injection:

☐ Local anesthetic: _____ *mL* _____ *%*
(incremental)

☐ Addition: _____ µg/mg

Patient's remarks during injection:

☐ *None* ☐ *Pain* ☐ *Paresthesias* ☐ *Warmth*

Duration and area: _____

Objective block effect after 20 min:

☐ *Cold test* ☐ *Temperature measurement before*_____ °C *after* _____ °C

☐ *Sensory: L* _____ *T*_____

☐ *Motor*

Complications:

☐ *None* ☐ *Pain*
☐ *Radicular symptoms* ☐ *Vasovagal reactions*
☐ *BP drop* ☐ *Dural puncture*
☐ *Vascular puncture* ☐ *Intravascular injection*
☐ *Massive epidural anesthesia* ☐ *Total spinal anesthesia*
☐ *Subdural spread* ☐ *Respiratory disturbance*
☐ *Drop in body temperature* ☐ *Muscle tremor*
☐ *Bladder emptying disturbances* ☐ *Postdural puncture headache*
☐ *Back pain* ☐ *Neurological complications*

Special notes:

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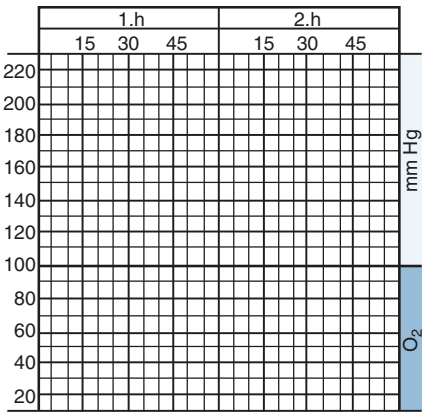
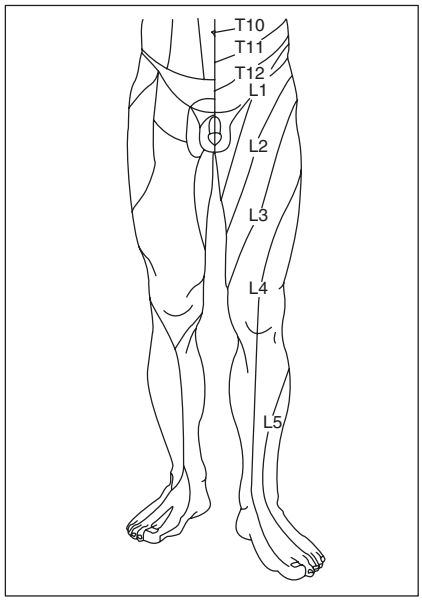
Fig. 1.3 Checklist and record for lumbar epidural anesthesia. (Courtesy of Danilo Jankovic with permission)

Record and checklist





Lumbosacral plexus and individual nerves in the plexus

Block no. ☐ Right ☐ Left

Name: _____ Date: _____

Diagnosis: _____

Premedication: ☐ No ☐ Yes

Neurological abnormalities: ☐ No ☐ Yes _____

Purpose of block: ☐ Surgical ☐ Diagnostic ☐ Therapeutic

Needle: G____ Length _____ cm ☐ 15° ☐ 30° ☐ Other

i.v. access: ☐ Yes

Monitoring: ☐ ECG ☐ Pulse oximetry

Ventilation facilities: ☐ Yes (equipment checked)

Emergency equipment (drugs): ☐ Checked

Patient: ☐ Informed (behavior after block)

Position: ☐ Prone ☐ Lateral recumbent ☐ Sims-Position ☐ Sitting

Injection: ☐ Inguinal "3-in-one" block ☐ Dorsal psoas compartment block

☐ *Sciatic nerve* ☐ *Femoral nerve* ☐ *Lateral cutaneous nerve of thigh*

☐ *Obturator nerve* ☐ *Ilioinguinal nerve / hypogastric nerve*

Location technique: ☐ Electrostimulation ☐ Other

☐ *Ultrasound- guided* ☐ *Transducer* ☐ *Linear* ☐ *Curved*

Approach: ☐ *In-plane* ☐ *Out of plane*

Plexus (nerve): ☐ *Located* ☐ *Aspiration test* ☐ *Test dose*

Injection:

Local anesthetic: _____ *mL* _____ *%*

(in incremental doses)

☐ *Inguinal "3-in-one" block* ____ *mL* ☐ *Dorsal psoas compartmt. block* ____ *mL*

☐ *Sciatic nerve* ____ *mL* ☐ *Femoral nerve* ____ *mL* ☐ *Lateral cutaneous nerve of thigh* ___ *mL* ☐ *Obturator nerve* ___ *mL* ☐ *Ilioinguinal nerve/hypogastric nerve* ___ *mL*

☐ Addition to LA _____ *µg/mg*

Patient's remarks during injection:

☐ None ☐ Paresthesias ☐ Warmth ☐ Pain (intraneural position?)

Nerve area: _____

Objective block effect after 15 min:

☐ Cold test ☐ Temperature measurement before ____°C after ____°C

☐ Sensory ☐ Motor

Monitoring after block: ☐ < 1 h ☐ > 1 h

Time of discharge: _____ ☐ Sensorimotor function checked

Complications:

☐ None ☐ Intravascular injection ☐ Signs of intoxication

☐ Hematoma ☐ Neurological complications ☐ Other

Subjective effects of the block: Duration: _____

☐ None ☐ Increased pain ☐ Reduced pain ☐ Relief of pain

VISUAL ANALOG SCALE

0 10 20 30 40 50 60 70 80 90 100

Special notes:

With permission from Danilo Jankovic

Fig. 1.4 Checklist and record for peripheral nerve block. (Courtesy of Danilo Jankovic with permission)

Accessories for Primary Care

Emergency Equipment (Figs. 1.5, 1.6, and 1.7)
- Intubation and ventilation equipment.
- Oxygen source (breathing apparatus).
- Ventilation bag with two masks (large, medium).
- Guedel tubes nos. 3, 4, 5.
- Wendel tubes nos. 26–32.
- Endotracheal tubes nos. 28–36.
- Tube clamp, blocker syringe (10 mL).
- Laryngoscope with batteries (replacement batteries and replacement bulbs), spatula.
- Magill forceps, mouth wedge, 1 tube 2% lidocaine gel.
- Suction device.
- Infusion equipment.
- Two sets of infusion instruments.
- Five plastic indwelling catheters.
- Syringes (2 mL, 5 mL, 10 mL), plaster, gauze bandages.
- Infusion solutions.
- 1 bottle each of Ringer's solution, plasma expander, 8.4% sodium bicarbonate (100 mL).

Defibrillator
- Drugs for emergency treatment.

When blocks are being administered, a sedative (midazolam), a vasopressor (phenylephrine or ephedrine), and a vagolytic (glycopyrrolate) should be available for immediate injection. Lipid emulsion 20% should be available in the presence of local anesthetic systemic toxicity.

Anesthetic Machine

For neuraxial anesthesia, ganglion blocks, intravenous regional anesthesia, and plexus anesthesia, an anesthesia trolley with facilities for intubation is also required (Fig. 1.8).

Monitoring
- Electrocardiogram (ECG).
- Pulse oximeter (Fig. 1.9).

Fig. 1.5 Emergency equipment

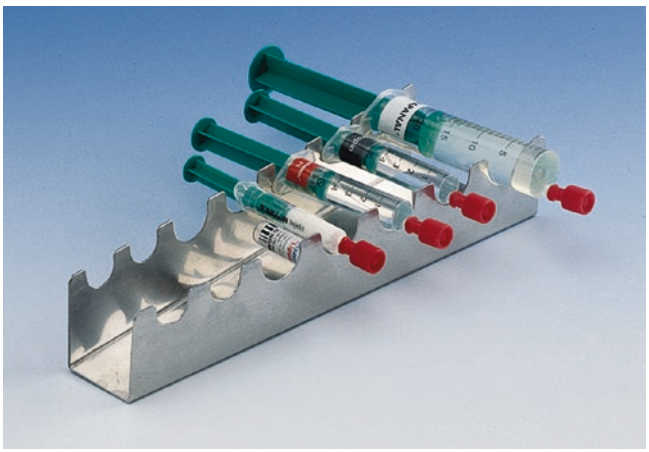


Fig. 1.6 Emergency drugs

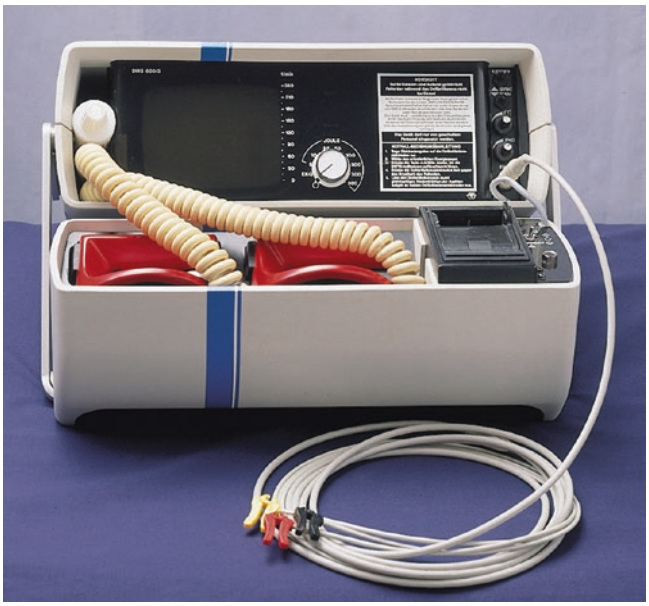


Fig. 1.7 Defibrillator

Peripheral Nerve Stimulator

Peripheral nerve stimulation is a valuable aid in clinical practice and has considerable advantages in combination with an atraumatic catheter technique (Fig. 1.10). A full chapter on the electric stimulation for perioperative use will be discussed in Chap. 3.

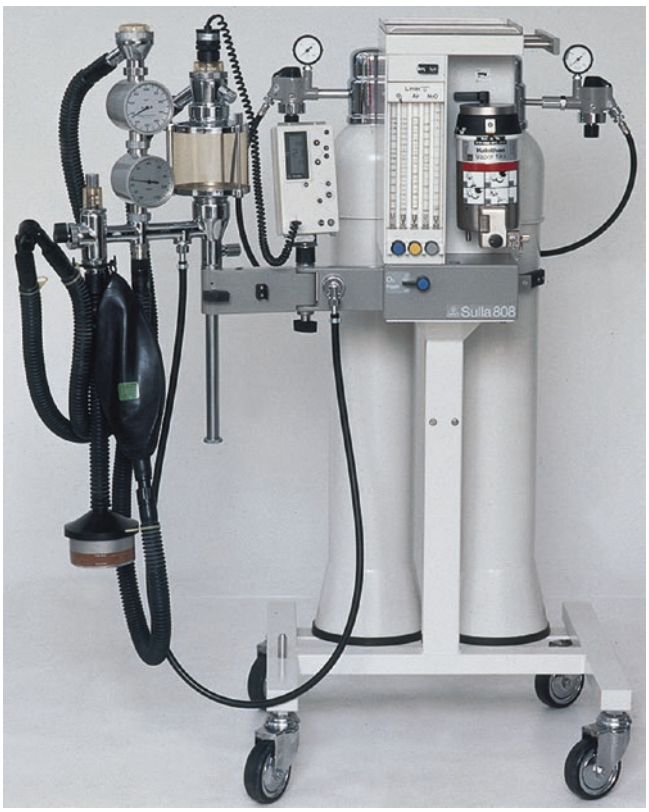


Fig. 1.8 Anesthetic machine

Fig. 1.9 ECG and pulse oximeter

Ultrasound

In the last two decades, the field of regional anesthesia, and in particular peripheral nerve blockade, has entered an unprecedented renaissance. This renaissance is due primarily to the widespread introduction of ultrasound-guided regional anesthesia (Fig. 1.11). The ability to visualize the anatomy of interest, the needle–nerve relationship, and the spread of the local anesthetic has resulted in significant growth of interest in and use of peripheral, sympathetic, and neuraxial blocks.

Fig. 1.10 Peripheral nerve stimulator

The basic principle of applying ultrasound in regional anesthesia is discussed in detail in Chap. 2.

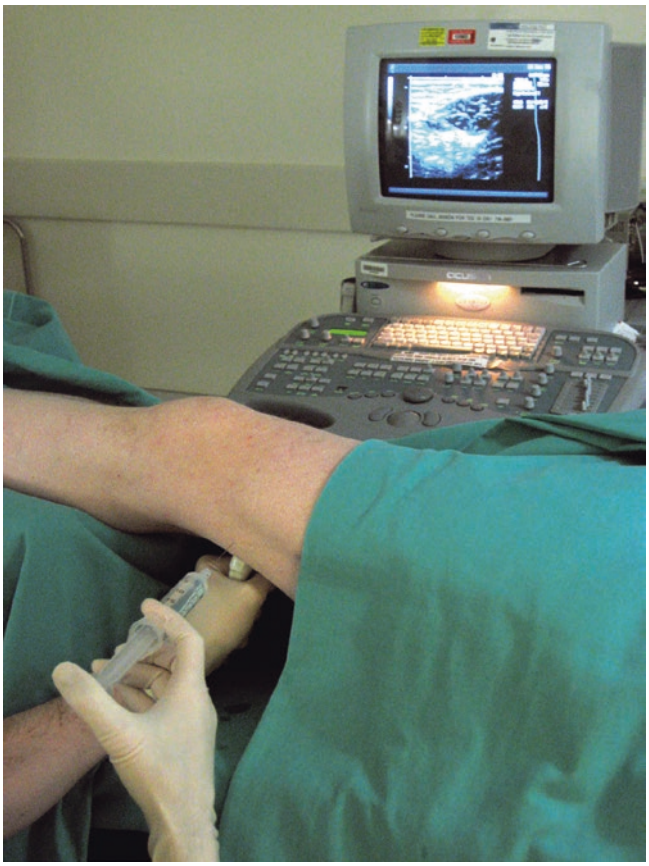


Fig. 1.11 Ultrasound machine

Use of Local Anesthetic in Regional Anesthesia and Pain Therapy

General Consideration

Local anesthetics produce anesthesia by inhibiting the excitation of nerve endings or by blocking conduction in peripheral nerves. Cocaine, a compound indigenous to the Andes Mountains, West Indies, and Java, was the first anesthetic to be discovered and is the only naturally occurring local anesthetic; all others are synthetically derived. Cocaine was introduced into Europe in the 1800s following its isolation from coca beans. Sigmund Freud, the noted Austrian psychoanalyst, used cocaine on his patients and became addicted through self-experimentation.

Local anesthetics block voltage-gated sodium channels thereby interrupting the initiation and transmission of nerve impulses in axons. Based on this mechanism of action, local anesthetics provide a wide variety of biologic actions, both desirable and unwanted, and have side effects through other mechanisms. Currently available local anesthetics are of two chemical classes: aminoesters and aminoamides. Aminoesters are metabolized primarily by plasma esterases, and aminoamides are metabolized primarily by hepatic cytochrome P450-linked enzymes. The knowledge of their pharmacology is important for safe and optimal use of this group of drugs. The principal systemic toxicities of local anesthetics involve the heart (including atrioventricular conduction block, arrhythmias, myocardial depression, and cardiac arrest) and the brain (including agitation, lethargy, seizures, and generalized central nervous system depression). Local anesthetics are directly toxic to nerve at the concentrations supplied in commercial solutions. Intraneural concentrations during regional anesthesia are generally, but not always, less

than a threshold for toxicity because of local vascular removal, and dilutional effects due to spread of solutions through tissues and into nerve. Hence, injection into a constrained tissue space increases the risk for local toxicity. Optimal use of local anesthetics in regional anesthesia requires an understanding of the individual patient's clinical situation, the location, intensity, and duration of regional anesthesia and analgesia required, anatomic factors affecting deposition of drugs near nerves, proper drug selection and dosing, and repeated assessment of clinical effects after administration of a local anesthetic. Local anesthetics are increasingly being used as postoperative infusions and via both local and systemic administration for the management of chronic pain.

Chemical Structure and Physicochemical Properties

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.

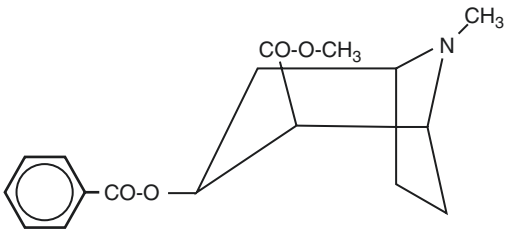
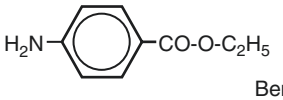
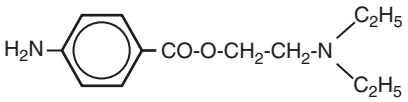
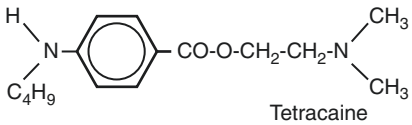
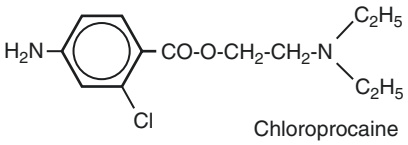
An intermediate chain, which in local anesthetics of the ester type (Table 1.2) contains a relatively unstable ester bond (CO–O) that can be broken down hydrolytically by pseudocholinesterases. Local anesthetics of the amide type (Table 1.3) are much more stable, since the amide bond (NH–CO) in their 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 1.4a and 1.4b).

Table 1.2 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

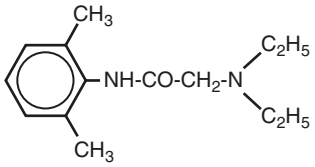
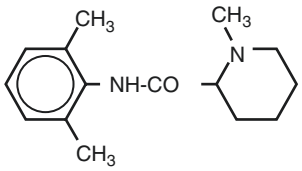
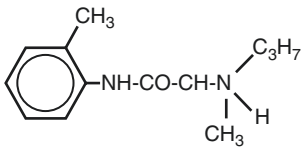
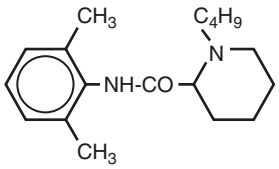
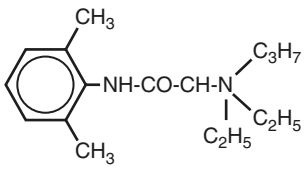
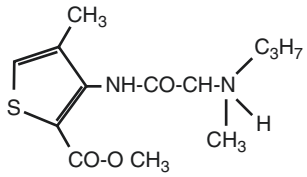
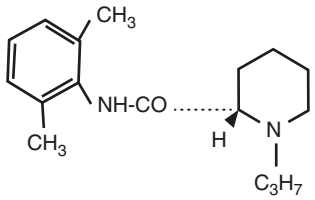
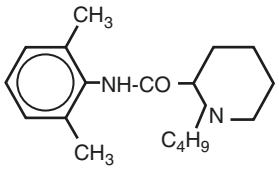
Local Anesthetic Potency

The combined effect of factors such as protein binding, stereoisomeric structure, and lipophilia determine 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 (Fig. 1.12).

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

Table 1.3 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

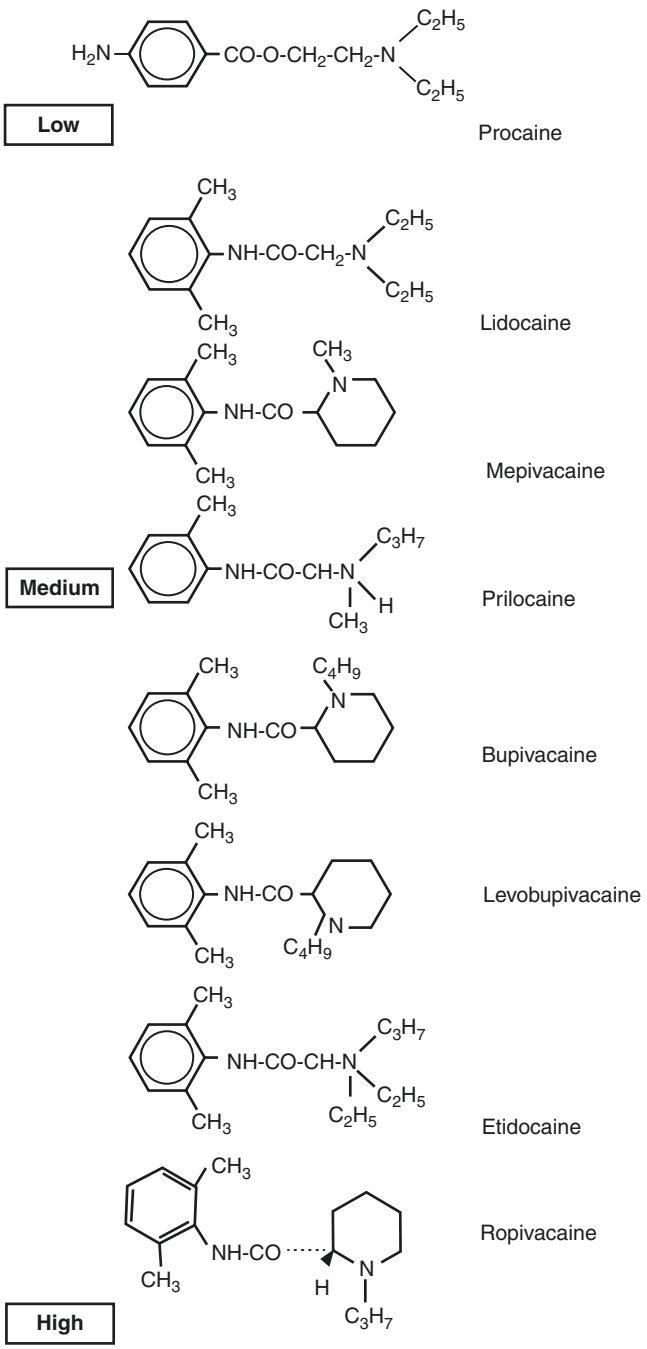
potency (lidocaine, prilocaine, mepivacaine), and high potency (ropivacaine, bupivacaine, levobupivacaine, etidocaine) does not conform to these correlations in all respects.

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

Table 1.4a Physicochemical and pharmacological parameters

Agent	Molecular weight	p*K*a (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 1.4b Local anesthetic potency and duration of effect



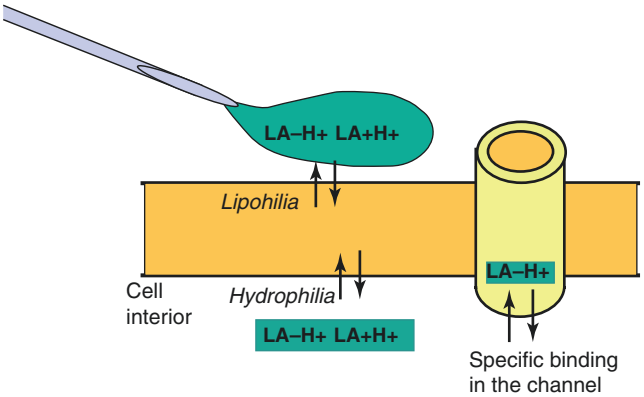


Fig. 1.12 Chemical requirements of a local anesthetic. Local anesthetics must combine lipophilic and hydrophilic properties in a favorable ratio with each other. Hydrophilia = soluble in cytosol, lipophilia = overcoming the cell membrane. (Reprinted with permission from Dr. Danilo Jankovic)

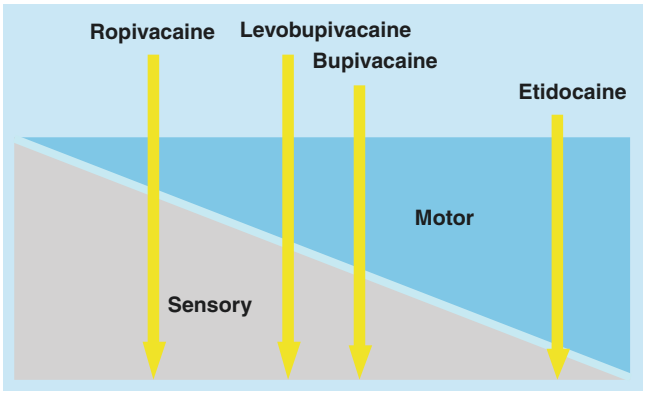


Fig. 1.13 Relative block profile of long-acting local anesthetics

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.

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

The block profile shows the relation between sensory and motor block (Fig. 1.13). 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.

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

When assessing the safety and tolerability of a local anesthetic, account needs to be taken not only of its central nervous and cardiovascular effects, but also of its allergenic potential and of toxic degradation products that may form as it is metabolized (Tables 1.5 and 1.6).

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

Table 1.5 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 1.6 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

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 1.6 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 1.5 and 1.6).

A detailed discussion of local anesthetic systemic toxicity (LAST) can be found in Chap. 5 of this book.

Table 1.7 Functional distinctions between nerve fibers

Fiber type	Function
^{A}a	Motor, touch, pressure, depth sensation
^{A}|3	Motor, touch, pressure, depth sensation
N Ay	Regulation of muscle tone
^{A}s	Pain, temperature, touch
B	Preganglionic sympathetic function
C	Pain, temperature, touch, postganglionic sympathetic function

Substance-Specific Side Effects

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, 1:1000, and 1:10; undiluted at 0.1 mL, 0.5 mL, 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.

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 1.7) 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—for example, 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 or lidocaine are alternatives) (Tables 1.7 and 1.8).

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 (Fig. 1.13). 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

Cocaine (Table 1.2)

The pioneering work of Koller (1857–1944) on the anesthetic effect of cocaine (10–20%) in the context of ophthalmic surgery was the historical starting point for local and regional anesthesia (11 September, 1884). Cocaine occurs naturally in the leaves of the coca shrub and is ester of benzoic acid. Currently, cocaine is used primarily to provide topical anesthesia of the upper respiratory tract (see Chap. 7; Regional Anesthesia for Airway) and in nasal block of pterygopalatine ganglion (see Chap. 9; Deep Block of Trigeminal Nerve).

Procaine (Novocaine®) (Tables 1.2, 1.4a, and 1.4b)

In 1905, Einhorn in Germany succeeded in synthesizing a new local anesthetic, which he called "procaine." Heinrich Braun introduced procaine into clinical practice 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.

Table 1.8 Overview of drugs

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

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 1.2)

2-Chloroprocaine, an ester local anesthetic, is a chlorinated derivative of procaine and is 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.

Medium-Term Local Anesthetics

Lidocaine (Xylocaine®, Lignocaine) (Tables 1.3, 1.4a, and 1.4b)

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. Thorsten 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.

Mepivacaine (Scandicaine®, Meaverine®) (Tables 1.3, 1.4a, and 1.4b)

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, 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, pipecolylxylidide, 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 for epidural anesthesia. Mepivacaine cannot be recommended in the 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 1.3, 1.4a, and 1.4b)

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; Neuraxial Anesthesia and Analgesia for Surgery) 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, 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 1.3, 1.4a, and 1.4b)

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 analgetic 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 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 analgetic 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%). 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. 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 (Tables 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 1.3, 1.4a, and 1.4b)

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 number of published controlled clinical studies is 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 1.3, 1.4a, and 1.4b)

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 pipecolylxylidide (desbutylbupivacaine). 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.

Tetracaine (Table 1.2)

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.

Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy

General Consideration

Performing neuraxial anesthesia in patients receiving antithrombotic drugs remains an *individual risk-benefit analysis*. In particular, the patient's individual risk of thromboembolic and ischemic complications as a result of interrupting the anticoagulation must be taken into account. Guidelines on neuraxial anesthesia and anticoagulants aim to assist anesthesiologists to facilitate decisions for or against neuraxial blockades. Compliance with the *substance-specific time interval* allows puncture within lowest anticoagulant blood levels. The current ASRA guidelines for the placement of epidural and spinal catheters *differentiate* between *interventional pain procedures* and *perioperative regional anesthesia* blocks.

Pain-specific procedural guidelines are important because the technical and anatomical considerations for pain interventions are significantly different than for peripheral regional anesthesia. The spectrum of interventional spine and pain procedures is far broader than that for regional anesthesia, with diverse targets and objectives.

Classification of Interventional Pain Procedures According to the Potential Risk of Serious Bleeding is based on the guideline published by American Society of Regional Anesthesia (ASRA) in 2018 (second edition) (Narouze et al.).

Pain procedures vary from minimally invasive procedures with high-risk targets (e.g., spinal cord stimulation trial and implant, intrathecal catheter and pump implant, vertebral augmentation epiduroscopy) to intermediate-risk procedures (e.g., interlaminar ESIs, transforaminal ESIs, cervical facet MBNB and RFA, intradiscal procedures, sympathetic blocks, trigeminal ganglia blocks) and to low-risk peripheral nerve

blocks (e.g., peripheral nerve blocks, trigger point injections including piriformis injection, sacroiliac joint injection, peripheral nerve stimulation trial and implant).

It is strongly recommended a *shared assessment*, *risk stratification*, and *management decision* in conjunction with the treating physician(s) for those patients with higher bleeding risk profiles, *especially when taking concomitant antiplatelet medications*, advanced patient *age,* advanced *liver or renal disease,* or prior *history of abnormal bleeding* exist.

Those important parameters have to be considered before procedure:

- The *degree of invasiveness* (low or intermediate risk or high-risk procedures)
- The *reason* for *anticoagulants utilization*
- *Concomitant* medication
- Significant *spinal abnormalities*
- The *vascular anatomy* surrounding the target area
- The *potential sequelae* associated with *perioperative bleeding*

Anatomical Considerations for Hematoma Development in Spinal and Non-spinal Areas

The risk of formation of *interspinal hematoma* after administration of neuraxial injections is increased in patients who *received anticoagulant therapy* or have a *coagulation disorder*, *technical difficulties* in the performance of the neuraxial procedures due to anatomic abnormalities of the spine, and *multiple* or *bloody punctures.* Although most cases of *spinal hematoma* have a *multifactorial etiology*, certain anatomical features may pose higher risks secondary to the anatomy and vascular supply of that specific spinal location.

It is important for interventional pain physicians to apply *knowledge of spinal and epidural anatomy* during preprocedural planning. *Other locations* associated with significant undesirable vascularity include the *target ganglia* (cervical, lumbar sympathetic, and celiac plexus). *Radiological imaging* should be reviewed prior to performing *interventional spine and pain procedures* in order to assess for *central* and *foraminal stenosis, disc herniations* that compromise canal diameter, *ligamentum flavum hypertrophy*, *epidural fibrosis*, and previous surgical *scarring,* which can alter the level of procedural difficulty.

Plexus and Peripheral Blockade in the Anticoagulant Patient

For patients undergoing *peri-neuraxial, deep plexus,* or *deep peripheral* block, ASRA recommends similar guideline as for the neuraxial techniques.

For patients undergoing *neural plexus or peripheral nerve techniques,* ASRA recommends management (performance, catheter maintenance, and catheter removal) based on site compressibility, vascularity, and consequences of bleeding should it occur.

Chronic Pain and Stress as a Hypercoagulable State

Chronic psychosocial stress causes a *hypercoagulable state*, as reflected by increased procoagulant molecules (fibrinogen or coagulation factor VII), reduced fibrinolytic capacity, and increased platelet activity. *Chronic stress* increases many stress hormone levels. Catecholamine and cortisol surges may underlie the hypercoagulability observed with chronic psychological distress. As *chronic pain* frequently coexists with *mental stress*, characterized by a *hypercoagulable state*, *chronic pain patients* may be at increased risk of coronary or cerebrovascular events after discontinuation of protective antiplatelet and anticoagulant medications.

Consider

- *Do not perform* a *neuraxial* or *deep plexus block* in patients on *more than one antiplatelet drug!*
- *Avoid traumatic puncture* (multiple needle and lead insertions-trauma).
- As a rule of thumb, a time interval of *two half-lives* between last (prophylactic) administration and neuraxial puncture is considered as an *adequate safety margin*. In *renal insufficiency* or *"therapeutic" anticoagulation*, the time interval should be *extended* to *four to five half-lives.*

Specific Recommendations for Pain Management and Regional Anesthesia in Patients Utilizing Anticoagulants or Antiplatelet Agents

The following are the recommendations for the management of anticoagulants, antiplatelet agents, and thrombolytic in patients receiving either regional anesthesia or pain management. All those recommendations are based on the two guidelines published by American Society of Regional Anesthesia (ASRA) in 2018 (second edition).

Antiplatelet Medication

Nonsteroidal Anti-inflammatory Drugs (NSAIDs) Including Aspirin

Aspirin

Aspirin is effective at inhibiting platelet activation, platelet aggregation, and thrombosis. Aspirin is rapidly absorbed

from the gastrointestinal tract, with peak levels occurring approximately *30 min* following ingestion, resulting in significant platelet inhibition at *1 h*. Aspirin, within *1 h* after ingestion, results in greater than *90%* in thromboxane levels. The *average life span* of a platelet is *7–10 days*. *Each day*, approximately *10%* of the circulating platelet pool is replaced (at *5–6 days*, approximately *50%*). Zisman et al. demonstrated that in most ASA-treated patients platelet function recovers *4 days* after drug discontinuation.

Non-ASA NSAIDs

Non-steroidal anti-inflammatory drugs inhibit prostaglandin production by inhibiting cyclooxygenase (COX). These drugs may be discontinued without negatively affecting cardiac and cerebral function.

Interventional Pain Management

For *interventional pain high-risk procedures* consideration should be given to discontinue these medications. Each NSAID can be discontinued based on its *specific half-life* (e.g., *discontinuation time = 5 half-lives/h*: Diclofenac, Ketorolac *(1 days)*; Ibuprofen, Indomethacin *(2 days)*; Naproxen, Meloxicam *(4 days)*; Piroxicam *(10 days)*.

Similar to regional anesthesia guidelines, aspirin may be continued when the procedure is low-risk pain procedure (consider concomitant drugs).

If ASA is being taken for *primary prophylaxis*, ASA discontinuation is recommended for high-risk procedures and certain intermediate-risk procedures with heightened risk of perioperative bleeding (e.g., interlaminar cervical ESIs and cervical ganglia) *(6 days*). If ASA is being taken for *secondary prophylaxis*, ASA discontinuation is recommended for high-risk elective pain procedures *(6 days)* and low or intermediate-risk procedures *(4 days).*

Regional Anesthetic Management

In *perioperative settings*, *NSAIDs (including Aspirin)* alone appear to represent no added significant risk of the development of spinal hematoma in patients having spinal or epidural anesthesia. There are no specific concerns as to the timing of single injection or catheter techniques in relationship to the dosing of NSAIDs, postoperative monitoring, or the timing of neuraxial catheter removal. Caution is suggested in the performance of neuraxial techniques if the concurrent use of other medications (other antiplatelet agents, oral anticoagulants, unfractionated heparin and low molecular weight heparin) affect clotting mechanisms in the early postoperative period because of the increased risk of bleeding complications. *Careful preoperative assessment* of the patient to identify alterations of health that might contribute to bleeding is crucial (history of easy bruising/excessive bleeding, female sex, and increased age). The evidence suggests that aspirin and non-steroidal anti-inflammatory drugs alone pose only a small increased risk but that in combination with other drugs affecting coagulation, there may be more significant risk.

P2Y12 Inhibitors: Thienopyridine Derivates (Ticlopidine, Clopidogrel, Ticagrelor, Cangrelor)

Thienopyridine, such as ticlopidine and clopidogrel, is a class of selective, irreversible adenosine diphosphate (ADP) receptor/P2Y12 inhibitors used for their antiplatelet activity.

The recommended intervals of discontinuation and resumption of the thienopyridines for regional anesthesia procedures and interventional pain management are based on the two guidelines published by American Society of Regional Anesthesia (ASRA) in 2018 (second edition).

Clopidogrel (Plavix®) (Oral, Irreversible Inhibition)[1]

Regional Anesthetic Management

Discontinuation time: (*5–7 days)*[2]
Restart: (*24 h).*
Time after puncture/catheter manipulation or removal: *after catheter removal*.

Interventional Pain Management

Discontinuation time:
High- and intermediate-risk procedures: *(7 days)* (footnote 2)
Low-risk procedures: No (risk-benefit assessment)[3]
Restart: (*12–24 h).*

Ticlopidine (Ticlid®) (Oral, Irreversible Inhibition) (Footnote 1)

Regional Anesthetic Management

Discontinuation time: (*10 days).*
Restart: (*24 h).*
Time after puncture/catheter manipulation or removal: *after catheter removal.*

Interventional Pain Management

Discontinuation time: (*10 days).*
Restart: (*24 h).*

[1]The antiplatelet effect is not immediate. *Neuraxial catheters* may be maintained for *1–2 days* provided a loading dose of the antiplatelet agent is not administered.

[2]In patients with high risk of thromboembolic events or for trial of SCS: a 5 day discontinuation is recommended (e.g., a "bridge" therapy with low molecular weight heparin). After an intervention, the usual daily dose (75 mg) of clopidogrel can be started 12 h later.

[3]Risk-benefit assessment: higher bleeding risk profiles, concomitant antiplatelet medications, advanced patient age, advanced liver or renal disease, or prior history of abnormal bleeding exist.

Prasugrel (Efient®) (Oral, Irreversible Inhibition)[4]

Regional Anesthetic Management
Discontinuation time: (*7–10 days).*
Restart: (*24 h).*
Time after puncture/catheter manipulation or removal: (*6 h).*

Interventional Pain Management
Discontinuation time:
High- and intermediate-risk procedures: (*7–10 days).*
Low-risk procedures: No (Risk-benefit assessment) (footnote 3)
Restart: (*24 h*).

Ticagrelor (Brilique®) (Oral, Reversible Inhibition) (Footnote 4)

Regional Anesthetic Management
Discontinuation time: (*5–7 days).*
Restart: (*24 h).*
Time after puncture/catheter manipulation or removal: (*6 h).*

Interventional Pain Management
Discontinuation time:
High- and intermediate-risk procedures: (*5 days*).
Low-risk procedures: No (Risk-benefit assessment) (footnote 3)
Restart: (*24 h*).

***Cangrelor* (Intravenous Direct, Reversible Inhibition; Onset: 2.6–3.3 min; Offset: 60–90 min)**

Interventional Pain Management
Discontinuation time:
High- and intermediate-risk procedures: (*3 h).*
Low risk procedures: No (Risk-benefit assessment (footnote 3)).
Restart: (*24 h).*

Older Anticoagulants

Warfarin and Acenocoumarol

The oral anticoagulants exercise their pharmacological action by inhibiting ϒ-carboxylation of the vitamin K-dependent coagulation factors (II, VII, IX, and X) and proteins C and S. Warfarin is difficult to dose, because it has narrow therapeutic index and wide interpatient dosing variability, with genetic factors accounting for a large proportion of the variations in dose requirements. Monitoring of anticoagulation is performed with the INR. In Europe, acenocoumarol is the most commonly used drug in this group, whereas in the United States warfarin is used.

The recommended intervals of discontinuation and resumption of the *older anticoagulants* for regional anesthesia procedures and interventional pain management are based on the two guidelines published by American Society of Regional Anesthesia (ASRA) in 2018 (second edition).

Regional Anesthetic Management

- The anticoagulant therapy must be *stopped (ideally 5 days prior* to the planned procedure), and *INR normalized* prior to initiation of neuraxial block *(INR ≤ 1.4)*.
- The performance of neuraxial anesthesia or removal of epidural catheters *within 24 h* of initial warfarin intake is probably safe.
- In patients receiving an initial dose of warfarin *prior to surgery*, the *INR* should be checked *prior to neuraxial block* if the first dose was given *more than 24 h earlier* or a *second dose* of oral anticoagulant has been administered.
- Caution should be used when performing neuraxial techniques in patients recently *discontinued from chronic warfarin therapy*. Consider *increased sensitivity* to warfarin (e.g., age > 65, female sex, weight, liver, cardiac, renal disease).
- ASRA recommends *against the concurrent use of medication* that affects other components of clotting mechanisms (e.g., aspirin, NSAIDs, thienopyridines, UFH, and LMWH).
- *Neurologic testing* should be performed routinely during epidural (neuraxial) analgesia for patients on warfarin therapy.

The *indwelling catheters* may be maintained with caution, based on INR and duration of warfarin therapy. As a thromboprophylaxis with warfarin is initiated, ASRA suggests that *neuraxial catheters be removed* when the *INR is <1.5.* In patients with an INR of >3, ASRA recommends that the warfarin be held or reduced in patients with indwelling neuraxial catheters and the neurologic assessment be continued for at least 24 h following catheter removal.

Interventional Pain Management

Warfarin

Discontinuation time:
High- and intermediate-risk procedures: (*5 days*); Normal INR (≤1.2).
Low-risk procedures: No (Risk-benefit assessment[5]).
Restart: (*6 h).*

[4]*Neuraxial catheters* should *not be maintained with prasugrel or ticagrelor* because of the *rapid onset*. *Thienopyridine therapy* may be resumed *immediately* after needle placement/ catheter removal, provided a loading dose of the drugs is not administered. If *loading dose* is administered, ASRA suggests a time interval of *6 h* between catheter removal and administration.

[5]Risk-benefit assessment: higher bleeding risk profiles, concomitant antiplatelet medications, advanced patient age, advanced liver or renal disease, or prior history of abnormal bleeding exist.

Acenocoumarol
Discontinuation time:
High- and intermediate-risk procedures *(3 days);* Normal INR (≤1.2);
Low-risk procedures: No (Risk-benefit assessment (footnote 5));
Restart: (*24 h).*

Heparin

Intravenous Unfractionated Heparin (IV UFHs)

Unfractionated heparin inactivates thrombin (factor IIa), factor Xa, and factor IXa. The anticoagulant effect of IV heparin is immediate. Heparin has a *half-life of 1.5–2 h,* and its therapeutic effect *ceases 4–6 h* after its administration.

Subcutaneous Unfractionated Heparin (SC UFHs)

The anticoagulant effect of low-dose, BID subcutaneous heparin (5000 U every 8–12 h) is through heparin-mediated inhibition of activated factor Xa. After subcutaneous injection of heparin, maximum anticoagulation is observed in *40–50* min, which dissipates within *4–6 h.*

Enoxaparin (Lovenox®, Clexane®)

Low-molecular-weight heparins (LMWH)[6] are used for both prophylaxis and treatment of arterial and venous thromboembolism (VTE). The biochemical and pharmacologic properties of LMWH differ from those of UFH. Most relevant are the prolonged half-life and irreversibility with protamine. Anti-factor Xa levels peak 3–5 h after administration. The elimination half-life of LMWH is 3–6 h. LMWH exhibits a dose-dependent antithrombotic effect that is assessed by the anti-factor activity level. The recovery of anti-factor Xa activity after subcutaneous injection of LMWH approaches 100%. The plasma *half-life* of the LMWHs ranges from *2 to 4 h* after an *intravenous* injection and *3 to 6 h* after *subcutaneous* injection.

The recommended intervals of discontinuation and resumption of the *Intravenous Unfractionated Heparin*, *Subcutaneous Unfractionated Heparin,* and *Enoxaparin (LMWH)* for interventional pain management and regional anesthesia:

Interventional Pain Management

Intravenous Unfractionated Heparin (UFHs)
Discontinuation time:
High-, intermediate- and low-risk procedures: (*6 h); (24 h* especially if it was bloody).
Restart: *minimum > (2 h)* after pain procedure.

Subcutaneous Unfractionated Heparin (UFHs)
Discontinuation time:
High-risk procedures: (*24 h)* (INR normalization).
Intermediate-risk procedures: (*6 h)* (BID or TID dosing).
Restart: (*6–8 h);*
Low-risk procedures (No; Risk-benefit assessment); Restart > *(2 h).*

Enoxaparin (LMWH)
Discontinuation time:
High-/intermediate-low risk procedures:
Prophylactic dose (30 mg BID or 40 mg once d.) (*12 h).*
Therapeutic dose (1 mg/kg BID or 1.5 mg/kg once d.) (*24 h).*
Restart:
Low risk: (*4 h*).
High/intermediate risk procedures
Prophylactic dose: (12–24 h). (Laboratory tests: Platelets during treatment for >5 days).
Therapeutic dose: low-risk procedures: (*4 h)*; intermediate/high-risk procedures:(*12–24 h).*
(Laboratory tests: Platelets during treatment for >5 days);

Consider
- *Concomitant drugs* that affect hemostasis (e.g., antiplatelet, NSAIDs, other anticoagulants) should be used with extreme caution in patients on LMWH.

Regional Anesthetic Management

IV Heparin (UHFs) **(for prophylaxis, ≤15,000 IU/and for treatment)**
Discontinuation time: (*4–6 h).*
Time after puncture/catheter manipulation or removal: (*4–6 h).*
Restart: (*1 h*).
(Laboratory tests: Platelets during treatment for >5 days, aPTT, ACT, platelets)
Consider increased risk:
<1 h between the administration of heparin and lumbar puncture, *traumatic needle placement* or *bloody tap*.
Concomitant use of other anticoagulants, avoid neuraxial techniques in patients with *other coagulopathies.*

SC Heparin (UHFs)
- Low dose (e.g., 5000 U BID or TID).
  Discontinuation time: (*4–6 h*).
  Time after puncture/catheter manipulation or removal: (*4–6 h* after last heparin dose); Restart: *(1 h).*

[6]Although the LMWHs constitute a relatively homogenous pharmacological group, the most studied and referenced drug is *Enoxaparin*; there are different commercial preparations on the market that share common characteristics but that also possess different clinical and pharmacological properties and must be regarded as *similar but not equal drugs*.

- Higher dose[7] (e.g., 7500–10,000 U BID or daily dose ≤20,000 U).
  Discontinuation time: *(12 h).*
  Time after puncture/catheter manipulation or removal: *(12 h).*
  Restart: *(1 h).*
  (Laboratory tests: Coagulation status).
- Therapeutic dose(e.g., >10,000 U per dose or >20,000 U total daily dose). Discontinuation time*:(*24 h*).*
  Time after puncture/catheter manipulation or removal: *(24 h)*.
  Restart: *(1 h).*
- ASRA guidelines of regional anesthesia considered mini-dose BID subcutaneous heparin not a contraindication to neuraxial injections.

Enoxaparin (LMWH)
Discontinuation time:

- *Prophylactic dose*[8]: *(12 h).*
  Time after puncture/catheter manipulation or removal:
  – Twice daily dose*:(>12 h following day).*
  – Single daily dose: (a) first day*:(>12 h after)*; (b) second day: *(24 h after the first dose)*.
- *Therapeutic dose*[9]: *(24 h).*
  Time after puncture/catheter manipulation or removal: *(24 h* after non-high-bleeding risk surgery); *(48–72 h* after high-bleeding risk surgery).
  Indwelling neuraxial catheters be removed: *(4 h* prior to the first postoperative dose and *(24 h* after needle/catheter placement*)*.

Consider

- LMWH should not be given ≤*2 h after epidural catheter removal.*
- *Risk-benefit assessment* (risk of thrombosis versus risk of bleeding).
- ASRA recommends *against concomitant antiplatelet or oral anticoagulant medications* that affect hemostasis.
- *The presence of blood during needle/catheter placement* does not necessitate postponement of surgery. *The initiation of LMWH should be delayed for 24 h postoperatively.*
- Routine monitoring of the anti-factor Xa level *is not recommended.*

In patients administered a dose of LMWH *2 h preoperatively* (general surgery patients), ASRA recommends *against neuraxial techniques.*

[7] *The safety of indwelling neuraxial catheters* in patients receiving doses >5000 U or > 15,000 U of UFH/day has not been established. The risk and benefits be assessed on an individual basis (neurologic monitoring).

[8] Enoxaparin 30 mg BID or 40 mg /once d.

[9] *Enoxaparin 1 mg/kg every 12 h;* Dalteparin 120 U/kg every 12 h, 200 U/kg every 12 h; Tanzaparin 175 U/ kg day.

New Anticoagulants

Anti-Factor Xa Agents Fondaparinux (Arixtra®)

Fondaparinux (Arixtra®) is a synthetic anticoagulant that selectively inhibits factor Xa. The drug is *100% bioavailable*, attains *maximum concentration* within *1.7 h* of administration, and has a *half-life of 17–21 h*. Its extended half-life allows *once-daily* dosing. It is usually administered *6 h after surgery.* Fondaparinux is recommended as an antithrombotic agent after major orthopedic surgery and as initial treatment of pulmonary embolism.

The recommended intervals of discontinuation and resumption of fondaparinux for pain management and regional anesthesia management:

Interventional Pain Management

Fondaparinux (1 × 2.5 mg/day)
Discontinuation time:
High-/intermediate-risk procedures: *(4 days).*
Low-risk (Risk-benefit assessment *(2 days = 2 half-life*, for more conservative approach).
Restart: High-/intermediate-risk procedures: *(24 h);* Low-risk procedures: *(6 h).*

Regional Anesthetic Management

Fondaparinux (1 × 2.5 mg/day)
Discontinuation time: *(36–42 h).*
Time after puncture/catheter manipulation or removal: *(6–12 h).*
(Laboratory tests: Anti-factor Xa (<0.1 U/mL)

- *Based on the sustained and irreversible antithrombotic effect, early postoperative dosing, and the spinal hematoma reported during initial clinical trials, ASRA recommends that until further clinical experience is available performance of neuraxial techniques should occur under conditions used in clinical trials (single needle pass, atraumatic needle placement, avoidance of indwelling neuraxial catheters).*

New (or Direct) Oral Anti-Factor Xa Agents (Dabigatran, Rivaroxaban, Apixaban, Edoxaban)

These drugs are at least as effective anticoagulants as the vitamin K antagonists but seem to be safer in terms of bleeding, have a rapid onset of action and a short half-life, and are devoid of the need for routine laboratory monitoring. Do not require serial coagulation monitoring and are safer, partly because of their short half-lives.

Dabigatran (Pradaxa®)

Dabigatran etexilate is a direct thrombin inhibitor that blocks the interaction of thrombin with different substances. It acts independently of anti-thrombin. Dabigatran is highly dependent (>80%) on renal excretion. The bioavailability after oral dabigatran etexilate is 7.2%, and peak plasma concentrations

are attained 1.5–3 h after intake of prodrug. The half-life of dabigatran is 12–17 h (28 h in severe renal disease).

Rivaroxaban (Xarelto®)

Rivaroxaban, a direct factor Xa inhibitor, has a rapid onset of action. Peak plasma concentrations are observed within 2.5–4 h, and maximum inhibition of factor Xa (up to 68%) occurs 3 h after dosing. Factor Xa Inhibition occurs for 12 h or 24–48 h when higher doses are given in the elderly. The half-life of Rivaroxaban is 5.7–9.2 h and can be as long as 13 h in elderly patients secondary to the age-related decline in renal function.

Apixaban (Eliquis®)

Apixaban is rapidly absorbed, attaining peak concentrations in 1–2 h. The half-life of apixaban is 13.5 ± 9.9 h after a single 20 mg dose, and 15.2 ± 8.5 h after a single 5 mg dose, and 11.7 ± 3.3 after multiple 5 mg doses.

Edoxaban (Lixiana®)

Edoxaban is indicated for the prevention of stroke in patients with atrial fibrillation and for treatment of deep venous thrombosis and pulmonary embolism.

Maximum concentration is attained in 1–2 h; it is 60% bioavailable and 50% of the drug is excreted by the kidneys. Its half-life is 8.75–14 h.

The recommended intervals of discontinuation and resumption of new oral anti-coagulants for pain management and regional anesthesia management:

Interventional Pain Management

Dabigatran(Pradaxa®)
Discontinuation time:
High-/intermediate-risk procedures *(4 days);* end-stage of renal disease *(5–6 days);*
Low-risk procedures (Risk-benefit assessment—more conservative approach *(2 days = 2 half-lives).*
Restart: *(24 h); Risk of VTE (12 h).*

Rivaroxaban (Xarelto®)
Discontinuation time:
High-/intermediate-risk procedures: *3 days (65 h).*
Low-risk procedures (Risk-benefit assessment—more conservative approach *(2 days = 2 half-lives).*
Restart: *(24 h)*; *Risk of VTE (12 h).*

Apixaban(Eliquis®)
Discontinuation time:
High-/intermediate-risk procedures: *3 days (75 h).*
Low-risk procedures (Risk-benefit assessment—more conservative approach *(2 days = 2 half-lives).*
Restart: *(24 h); Risk of VTE (12 h).*

Edoxaban(Lixiana®)
Discontinuation time:
High-/intermediate-risk procedures: *3 days (70 h).*
Low-risk procedures (Risk-benefit assessment—more conservative approach *(2 days = 2 half-lives).*
Restart: *(24 h);* Risk of VTE *(12 h).*

Regional Anesthetic Management

Dabigatran: **(110/220 OD[10] 150 mg BID[11])**
Time before puncture/catheter manipulation or removal: *72 h (3 days)–120 h (5 days)*[12]
Time after puncture/catheter manipulation or removal: *(6 h).*
(Laboratory tests: a PTT, ECT, TT)

Consider:

- With *unanticipated administration with indwelling catheter*, dabigatran dosing be held for *34–36 h* or the dTT or ECT assessed before catheter removal.
- *Avoid performance* of neuraxial blocks in patients with *CrCl of <30 mL/min.*
- Age > 65, hypertension, concomitant antiplatelet medication.

Rivaroxaban

- (≤10 mg/day).
  Time before puncture/catheter manipulation or removal: *(22–26 h).*
  Time after puncture/catheter manipulation or removal: *(6 h).*
- (2 × 15 mg/day or 1 × 20 mg/day).
  Time before puncture/catheter manipulation or removal: *44–65 h (3 days).*
  Time after puncture/catheter manipulation or removal: *(6 h).*
  (Laboratory tests: Anti-factor Xa, standardized for specific agent)

Consider

- With *unanticipated administration with indwelling catheter*, ASRA recommends that rivaroxaban dosing be held for 22–26 h before or an anti-factor Xa assay calibrated to rivaroxaban be assessed before the catheter is removed.

Apixaban

- *(2 × 2.5 mg/day).*
  Time before puncture/catheter manipulation or removal: *(26–30 h).*
  Time after puncture/catheter manipulation or removal *(6 h).*

[10] Prophylactic dose for joint replacement.

[11] Risk reduction or treatment for VTE or PE; RA-regional anesthesia procedure including manipulation or removal of catheter.

[12] *72 h (3 days)* (CrCl ≥80 mL/min); *96 h (4 days)* (CrCl 50–79 mL/min); *120 h (5 days)* (CrCl 30–49 mL/min) (ASRA).

- *(2 × 5 mg/day).*
  Time before puncture/catheter manipulation or removal: *40–75 h (3 days).*
  Time after puncture/catheter manipulation or removal *(6 h).*
  (Laboratory: Anti-factor Xa, standardized for specific agent)

Consider

- With *unanticipated administration with indwelling catheter*, ASA recommend that apixaban dosing be held for 26–30 h or an anti-factor Xa assay calibrated to apixaban before the catheter is removed.

Edoxaban

- *(≤30 mg/day).*
  Time before puncture/catheter manipulation or removal: *(20–28 h).*
  Time after puncture/catheter manipulation or removal: (*6–7 h).*
- *(≤60 mg/day).*
  Time before puncture/catheter manipulation or removal: *40–70 h (3 days).*
  Time after puncture/catheter manipulation or removal: (*6–7 h).*

Consider

With *unanticipated administration with indwelling catheter*, ASRA recommends that edoxaban dosing be held for 20–28 h or an anti-factor Xa assay calibrated to edoxaban before the catheter is removed.

Thrombolytic Agents

Thrombolytic agents convert plasminogen and thrombin to plasmin, the enzyme that causes fibrinolysis. Cases of spontaneous spinal hematoma have been reported in patients on thrombolytic therapy. There are also cases of spinal hematoma in patients who had neuraxial procedures and had subsequent thrombolytic therapy.

Recommended Management of Thrombolytic for Interventional Pain Management

- Interventional pain management should *be avoided* in patients who just received fibrinolytic agents.
- If an intervention has to be performed, a *minimum of 48 h* between discontinuation of a thrombolytic agent and a neuraxial injection is probably safe. Longer intervals, that is, *72 h,* should be considered for *high-risk* surgical pain procedures.
- In *emergency situations* wherein a thrombolytic needs to be administered after a spine pain intervention, the *pain service* should preferably be informed.
- If the patient has a neuraxial catheter or SCS lead, the device can be left in place. Fibrinogen levels can be determined and the *device removed after 48 h* or after a minimum of the two half-lives of the drug has elapsed.

Recommended Management of Thrombolytic for Regional Anesthetic Management

- *Avoid performance of neuraxial block* in patients who have received fibrinolytic and thrombolytic drugs. Guidelines detailing original *contraindications* to thrombolytic drugs suggest *avoidance of these drugs for 10 days following puncture* of noncompressible vessels.
- In patients *scheduled* to receive thrombolytic therapy, guidelines suggests that the patient be *queried and medical record reviewed* for a recent history of lumbar puncture, spinal or epidural anesthesia, or ESI to allow appropriate monitoring.
- Data are not available to clearly outline the length of time neuraxial puncture should be avoided after discontinuation of these drugs. However, a *48 h* time interval and documentation of normalization of clotting studies (including fibrinogen) are suggested.
- In those patients *who have received neuraxial blocks* at or near the time of fibrinolytic / thrombolytic therapy, ASRA recommends that *neurological monitoring* should be considered for an appropriate interval.
- There is no definitive recommendation for *removal of neuraxial catheters* in patients who *unexpectedly received* fibrinolytic and thrombolytic therapy during a neuraxial catheter infusion. ASRA recommends the measurement of fibrinogen level.

Conclusion

The management of anticoagulants or antiplatelet agents in the perioperative period is based on their pharmacokinetics and pharmacodynamic profile. Understanding clinical indications for the drugs will make an anesthesiologist more aware of the risks of discontinuation. Several new oral anticoagulants offer oral routes of administration, simple dosing regimen, efficacy with less bleeding risks, reduced requirement for clinically monitoring. Due to safety concerns of bleeding risks, guidelines and recommendations have been designed to reduce patient morbidity/mortality during regional anesthesia. Patient-specific factors and surgery-related issues should be considered to improve patient-oriented outcomes.

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