Local Anesthetics

Compendium for Local Anesthetics in Dentistry

In cooperation with
Dr. Dr. Rainer Rahn
Dear Dentist,

Low stress and no pain – these are two basic prerequisites for successful dental treatment, both for patients and dentists. Effective and well tolerable products that are used for modern local anaesthesia help to fulfill these prerequisites. The advantages of local anaesthetics are obvious: thanks to their capacity to depress “sensation in a circumscribed area of the body and to depress excitation in nerve endings or an inhibition of the conduction process in peripheral nerves without inducing a loss of consciousness” (Covino et al., 1976), they increase the patients’ feeling of well-being and their compliance to trust their dentists. The dentists, on the other hand, can work more precisely, and the treatment time is shortened.

Local anaesthetics are being used as well with direct as with indirect dental restorations. They are required to present a high intrinsic activity, a rapid onset, and an adequate duration.

With these requirements in mind, 3M ESPE has further developed its state-of-the-art local anaesthetics that have been clinically proven for over 50 years and are well-known and trusted in dental practices throughout the world. Thus, dentists can rely on 3M ESPE’s competence and experience for both the routine-type and the more complex interventions that require a prolonged anaesthesia. Patients, on the other hand, have the benefit of 3M ESPE’s effective, well tolerable and proven local anaesthetic products that help reduce stress and pain during dental treatment.

The goal of the present compendium is to provide a scientific overview of both material handling and technologies to the interested reader. To achieve this, aspects such as neuronal structures, chemistry and pharmacology of local anaesthetics and of vasoconstrictors are highlighted, alongside with dental anaesthetic techniques and clinical aspects such as posology / dosage, adverse effects and precautions for use. The dental background information on function and particularities is provided on 3M ESPE’s solutions for injection Ubistesin™ 1/200000, Ubistesin™ 1/100000, Mepivastesin™, Xylestesin™ A and Pluraject™ aspiration syringe.

Enjoy reading the present compendium and feel free to address any questions to your local 3M ESPE customer service.

Sincerely Yours,

Dr. Rainer Guggenberger
Head of Research & Development, 3M ESPE
1. Introduction ................................................................. 6

2. History of Local Anesthesia ............................................. 7

3. Neuronal Structure .......................................................... 8
   3.1 Neuronal Anatomy .................................................... 8
   3.2 Neurophysiology ................................................... 11

4. Chemistry and Pharmacology of Local Anesthetics .................. 15
   4.1 Chemistry of Local Anesthetics ..................................... 15
   4.2 Physicochemical and Pharmacological Properties ............... 19
   4.3 Pharmacodynamics .................................................. 23
   4.4 Pharmacokinetics .................................................. 33
   4.5 Summary of Pharmacological Data ................................ 38

5. Chemistry and Pharmacology of Vasoconstrictors ............... 39
   5.1 Pharmacology of Vasoconstrictors ................................ 39
   5.2 Categorization of Vasoconstrictors .............................. 39

6. Dental Anesthetic Techniques .......................................... 43
   6.1 Classification of Administration Technique ................. 43
   6.2 Local Anesthesia ................................................ 47

7. Clinical Aspects .......................................................... 55
   7.1 Posology (Dosage) .................................................. 55
   7.2 Adverse Effects and Precautions for Use ...................... 58
   7.3 Physical and Physiological Evaluation of the Patient .......... 65

8. 3M ESPE Products ........................................................ 69

9. References ................................................................. 77
1. Introduction

Fear and pain are two of the main stress factors in connection with dental treatments. For ensuring a successful treatment, it is important to avoid them as far as possible, in order to increase the patient’s compliance and to reach a trusting relationship between dentist and patient.

Local anesthesia creates the necessary conditions for dental treatments free of pain.

Definition of Local Anesthesia

Local anesthesia is defined as a loss of sensation in a circumscribed area of the body caused by a depression of excitation in nerve endings or an inhibition of the conduction process in peripheral nerves without inducing a loss of consciousness. An important feature of local anesthesia is that it produces this loss of sensation without inducing a loss of consciousness. On the one hand, the patient’s sustained ability to cooperate during the intervention facilitates the dental treatment, and on the other hand patients are usually able to leave the dental office immediately after completion of the treatment. Thanks to these major advantages compared to general anesthesia and to the comparatively low rate of complications, local anesthesia is the most common type of anesthesia in dental practice.

Criteria for Local Anesthetics

Thanks to state-of-the-art local anesthetics, local anesthesia has reached a very high safety status. A safe and effective local anesthetic should offer the following characteristics:

• A high intrinsic activity, which ensures complete anesthesia for all dental treatments
• A rapid onset
• An adequate duration of anesthesia, which should range between 30 and 60 minutes for standard dental treatments
• A low systemic toxicity
• No local irritation
• A high efficacy-toxicity ratio
• A low overall incidence of serious adverse effects

Thanks to continuous further developments, today’s state-of-the-art local anesthetics meet these requirements to a large extent.

Literature:
1) Introduction:
3) Brandt B, 1997
5) Covino BG et al. 1976
23) Malamed SF, 2004
32) Spiegelberg F, 2001
2. History of Local Anesthesia

The history of local anesthesia started in 1859, when cocaine was isolated by Nieman. In 1884, the ophthalmologist Koller was the first, who used cocaine for topical anesthesia in ophthalmologic surgery. In 1884, local anesthesia in the oral cavity was first performed by the surgeon Halsted, when he removed a wisdom tooth without pain. However, a number of adverse effects were observed with the clinical use of cocaine. Thus, other local anesthetic agents had to be developed.

In 1905, Einhorn reported the synthesis of procaine, which was the first ester-type local anesthetic agent. Procaine was the most commonly used local anesthetic for more than four decades. In 1943, Löfgren synthesized lidocaine, which was the first “modern” local anesthetic agent, since it is an amide-derivate of diethyl amino acetic acid. Lidocaine was marketed in 1948 and has remained one of the most commonly used local anesthetics in dentistry worldwide, although other amide local anesthetics were introduced into clinical use: mepivacaine 1957, prilocaine 1960, bupivacaine 1963.

In 1969, articaine was synthesized by the chemist Muschaweck and was approved in 1975 as a local anesthetic.

Today, articaine is one of the most commonly used local anesthetics in dentistry in many countries e.g. Germany, Switzerland, Austria, France, Poland, and the Czech Republic.

Figure 1
Jan Victors, “Der Zahnbrecher”
3. Neuronal Structure

3.1 Neuronal Anatomy

Local anesthetics provide pain control by preventing noxious stimuli from reaching the central nervous system. The following review of the anatomy of the peripheral nervous system and the neurophysiology will give you a better understanding of the mode of action, the special pharmacological properties, and even the clinical application of local anesthetic drugs.

The peripheral nervous system conducts sensory information concerning the internal state and external environment of the body to the central nervous system. It is also the primary medium for efferent transmissions from the brain to various effector organs and tissues of the body (e.g., muscles and salivary glands). The neuron is the fundamental unit of the peripheral nervous system.

The Neuron

The neuron is able to transmit signals between the central nervous system and all parts of the body. The neuron is classified into the sensory (afferent) and motor (efferent) neuron.

The sensory neuron, which is able to transmit the sensation of pain, is composed of the cell body, the axon and the dendritic zone. The cell body is responsible for metabolic support of the nerve cell and is not directly involved in nerve transmission. The dendritic zone is an arborization of nerve endings responsive to real or potential tissue damage. An appropriate stimulus (e.g., injury) activates dendritic branches to depolarize and initiate nerve conduction. Incoming signals are relayed from the periphery to the central nervous system by the axon.

Figure 2: Anatomy of Sensory Neuron
Nerve Fibers

The axons of peripheral nerves are supported by a variety of connective tissues. An unmyelinated nerve fiber is surrounded by a single wrapping, the Schwann cell sheath. Groups of unmyelinated fibers share the same Schwann cell sheath. The functional organization of axon and Schwann cell is called “nerve fiber”. The myelin sheath almost completely insulates the axon from the outside. The myelin sheath surrounding a myelinated nerve fiber (A & B fibers) is interrupted at regular intervals by constrictions (nodes of Ranvier). Only at the nodes of Ranvier, the myelinated axon have direct contact to the extracellular space. Due to the insulating properties of the myelin sheath a myelinated nerve is able to conduct impulses much faster than an unmyelinated nerve of equal size.

Individual nerve fibers (axons) are surrounded and also separated from each other by the endoneurium. Groups of axons, the fasciculi, are enclosed in an additional connective tissue sheath called the perineurium. Finally, a number of axonal groups are encased in an external connective tissue sheath, the epineurium. Epineurium, perineurium, and endoneurium are considered anatomical barriers to the diffusion of local anesthetic substances. The physico-chemical properties of individual compounds themselves and the physiological state of the local environment surrounding the nerve fibers determine the rate of diffusion and ultimately the onset of analgesia.

Figure 3: Anatomy of Nerve Fibers

Axon: the efferent appendix of the nerve cell
Endoneurium: covers each nerve fiber
Fasciculi: bundles of 500 to 1000 nerve fibres
Perineurium: covers fasciculi
Epineurium: alveolar connective tissue supporting fasciculi and carrying nutrient vessels
**Trigeminal Nerve**

Essentially, the following cerebral nerves are responsible for the maxillofacial nerve supply:

- Trigeminal nerve (N.V)
- Facial nerve (N. VII)
- Gloss pharyngeal nerve (N. IX)
- Hypoglossal nerve (N. XII)

The trigeminal nerve is a mixed nerve serving the skin of the face, the hard and soft tissues of the mouth, and the mucosal linings of most of the spaces of the head. It conveys the sensations of touch, pressure, pain, and temperature from the oral cavity and also carries the proprioceptive sensations of position, strain, and movement from the masticatory apparatus. The trigeminal nerve also supplies motor stimulation to the muscles of mastication and to several other important muscles in the region. Finally, the trigeminal nerve conveys autonomic fibers (parasympathetic and sympathetic) that control salivary glands.

The trigeminal system includes several distinct intracranial structures. These are the trigeminal ganglion, various sensory and motor nuclei, and tracts with interconnections to other cranial nerve nuclei and higher centers of the brain.

The trigeminal nerve consists of three parts: The ophthalmic division (V1), the maxillary division (V2) and the mandibular division (V3).

**Maxillary Division**

The maxillary nerve (N.V2) leaves the cranial cavity through the foramen rotundum, reaching the fossa pterygopalatine underneath, where it shows the first branching into the palatine nerve, posterior alveolar nerves, zygomatic nerve and anterior alveolar nerves.

Being a strictly afferent nerve, the maxillary nerve supplies the exterior skin in the maxillary region, the mucous membranes of posterior nasal cavity and palate, the gingiva, and the maxillary teeth.

**Mandibular Division**

The mandibular nerve is the largest of the three divisions of the trigeminal nerve. The nerve carries both sensory and motor fibers and leaves the cranium via the oval foramen and divides into a smaller anterior and a larger posterior root. The anterior, mainly motor group only contains one afferent nerve, the buccal nerve.

The posterior root of the mandibular nerve descends and separates into three branches: the auriculotemporal nerve, the lingual nerve and the inferior alveolar nerve.

The mandibular nerve and its branches supply the meatus acusticus ext, the skin of the anterior temple and chin region, the lower lip, the buccal gingiva mesial of the second premolar and between the second premolar and the second molar.
3.2 Neurophysiology

Peripheral nerve fibers carry information to or from the central nervous system in the form of electrical impulses. Known as action potentials, these impulses propagate along the nerve fiber as self-regenerating waves of membrane depolarization. The ability of neurons to initiate and conduct action potentials is based on an asymmetric distribution of ions across the nerve membrane and on variations in permeability of the nerve membrane to these ions.

Electrophysiology and Electrochemistry of Nerve Conduction

Membrane Electrophysiology

Local anesthetic agents exert their primary pharmacological action by interfering with the excitation-conduction process of peripheral nerve fibers and nerve endings. The plasma membrane of the neuronal axon is composed of two layers of lipid molecules (lipid bilayer) acting as a hydrophobic barrier to the passage of molecules. Most ionized molecules are lipid insoluble and thus are not able to diffuse across the membrane. However, selected small electrolytes, such as sodium (Na+), potassium (K+) and other, can traverse the membrane with relative ease because embedded in the membrane proteins (transport proteins), which can promote their movement. Some of these proteins serve as channels through which ions such as Na+ and K+ may flow in relation to their electrochemical gradients. Others provide for the active transport of electrolytes. With respect to nerve conduction, the most important active transport system is the Na+/K+-activated ATP pump (Na+/K+ pump). The Na+/K+ pump provides an asymmetric distribution of Na+ and K+ ions across the nerve membrane with a high concentration of K+ inside the nerve and a high concentration of Na+ in the extracellular fluid. Thus, an electrical gradient would then be established by the unbalanced movements of cations across the plasma membrane.

Resting State

Impulse transmission of nerves is due to changes of the electrophysiological condition at the nerve membrane. Between the inside of the nerve cell and the outside surface of the cell membrane, there is an electrical difference of potential – the membrane or resting potential (-50 – -70 mV), which is due to an unequal ion distribution inside the cell – high concentration of potassium ions – and in the extracellular area – high concentration of sodium ions. The respective anion is mostly chloride. In the resting state, the cell membrane of the nerve cell is largely impermeable to ions.

Figure 5: Ion Distribution and Resting Potential of the Nerve Membrane
Membrane Excitation

**Depolarization** Neuronal excitation is associated with a depolarization and repolarization of the cell membrane. Excitation of a nerve results in an increase in the permeability of the cell membrane to sodium ions. A variety of appropriate stimuli may perturb the nerve membrane and alter the resting potential. Any factor which is able to increase membrane permeability for sodium ions will partially depolarize the membrane and the cytoplasm will become less electronegative with respect to the extracellular fluid. When the potential difference across the cell membrane reaches a critical level (threshold potential), the depolarization becomes self-generating and an extremely rapid rise in sodium permeability induces a rapid influx of sodium ions into the intracellular fluid. The inrushing sodium ions reverse the membrane potential from a negative value to one of approximately +40 mV.

![Figure 6 a: Depolarization](image)

![Figure 6 b: Depolarization](image)

**Repolarization** After completion of the depolarization phase, repolarization begins, and the electrical potential within the cell again becomes progressively more negative with respect to the exterior of the cell until the resting potential is reestablished. A metabolic process begins to reconstitute the original concentration of ions. Active transfer of sodium ions out of the cell and of potassium ions into the cell is based on a pumping mechanism. For moving the ions against their concentration gradient, an energy input is necessary. This energy is provided by the oxidative metabolism of adenosine triphosphate (ATP).
Pain Development

Pain is one of the most commonly experienced symptoms in dentistry. Pain can be described as sharp, burning, cramping or dull.

Pain perception is the physioanatomical process by which pain is received and transmitted by neural structures from the pain perceptors, through the conductive and perceptive mechanisms. Pain receptors are free nerve endings of unmyelinated fibers and are called nociceptors. Pain impulses are conducted into the central nervous system by two different types of nerve fibers classified by size and the speed of impulse conduction. Type A fibers are myelinated and conduct the sharp and well localized pain, Type C fibers are unmyelinated and conduct the slow pain.

To induce any pain, an appropriate stimulus (electrical, thermal, chemical, or mechanical in nature) of sufficient intensity must excite the free nerve endings. If a minimum intensity is reached, the free nerve endings are excited and an impulse is created, which is propagating along the nerve fiber. The impulse, unless otherwise blocked, will continue centrally along the entire course of the nerve with no decrease in speed or intensity.
The trigeminal nerve is the principal sensory nerve of the head region. Any stimulus in the area of the trigeminal nerve is first received by trigeminal fibers and conducted as an impulse via the gasserian ganglion to the brain.

**Toothaches** occur frequently, and in many cases the symptoms are unspecific. There are manifold reasons for toothaches, they are not necessarily specific signals for pathological changes of the dental pulp.

Based on their causes, toothaches are divided into three groups: dentin, pulpal, and periodontal pain.

Originating from dentin injury, dentin pain is caused by exogenic stimuli like mechanical, thermal, or osmotic impulses, for example.

Pulpal pain is independent of exogenic stimuli. This type of toothache is transmitted by C fibers. The pain is dull, and frequently cannot be exactly localized. It is often difficult to distinguish between pulpal pain and neuralgia, as similar to neuralgia, pulpal pain may radiate to the temporal and ophthalmic region.

Periodontal pain is experienced in connection with a total pulpitis leading to periodontitis. It is also referred to as “maxillofacial pain”, as it spreads beyond the area of the tooth.

**Pain Control**

Control or elimination of pain is one of the most important aspects of the dental practice, and in most cases local anesthesia is used. The following alternative techniques are applied less frequently:

Due to considerable additional efforts and high anesthetic risk, conventional intubation anesthesia is only applied with specific indications – e.g. uncooperative patients (children, handicapped patients), as well as extremely fearful patients.

Hypnosis and acupuncture are comparatively rare, as only few dentists know how to apply these methods, and they are not suited for every patient.

Transcutaneous electrical nerve stimulation (TENS) is another alternative based on short DC square pulses of variable intensity (about 5 to 20 mA) applied transcutaneously via an electrode in the area of the nerve. This type of application interrupts the pain conduction. However, as the local anesthetic efficiency is only low, treatment is not always possible completely free of pain.
4. Chemistry and Pharmacology of Local Anesthetics

4.1 Chemistry of Local Anesthetics

Blockade of nerve conduction can be produced by a great variety of chemical structures. For instance, alcohols, many antidepressant, anticonvulsant and antiarrhythmic drugs all have local anesthetic properties. However, local anesthetics, which are clinically useful, are typically composed of an aromatic ring connected to an amino group and a hydrophilic bond.

Chemical Structure

All local anesthetic substances have a common basic chemical structure and are composed of three parts:

- An aromatic group
- An intermediate chain
- A secondary or tertiary amino terminus

Each of these components is an important determinant of anesthetic potency. The aromatic group is responsible for the lipophilic properties on the molecule. The amino terminus confers the water solubility. The intermediate portion of the molecule provides the necessary spatial separation between the hydrophobic and hydrophilic parts of the local anesthetic. In addition, the chemical link serves as a suitable basis for classifying conventional local anesthetics into two groups, the esters (-COO-) and the amides (-NHCO-). The basic differences between the ester and amide compounds are the manner in which they are metabolized and their possible allergic potential.

Figure 8: Chemical Structure of Local Anesthetic Agents
Ester-Type Local Anesthetics

Ester-type local anesthetics are derivates of benzoic acid. The ester derivatives of benzoic acid are hydrolyzed primarily in plasma by the enzyme pseudocholinesterase. The metabolite para-aminobenzoic acid is considered to be responsible for allergic-type reactions. The primary excretory organ is the kidney. Procaine and Tetracaine are the most important ester-type local anesthetics. As modern local anesthetics offer higher efficiency and better compatibility, Procaine is only rarely used in dental medicine, today, and due the unfavorable potency/toxicity ratio, Tetracaine is only used for topical anesthesia.

![Chemical Structure of Procaine and Tetracaine](image)

- **Procaine:**
  Procaine has the highest vasodilating effect of all clinically used local anesthetics.

<table>
<thead>
<tr>
<th>Synthesized</th>
<th>1905</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physicochemical Properties</td>
<td>MW 236, pKₐ value 9.1</td>
</tr>
<tr>
<td>Elimination Half Time</td>
<td>30–50 seconds</td>
</tr>
<tr>
<td>Onset of Action</td>
<td>6–10 minutes</td>
</tr>
<tr>
<td>Duration of Action</td>
<td>Provides no pulpal anesthesia, 15–30 minutes of soft tissue anesthesia</td>
</tr>
<tr>
<td>Potency</td>
<td>1 (with reference to procaine)</td>
</tr>
<tr>
<td>Toxicity</td>
<td>1 (with reference to procaine)</td>
</tr>
<tr>
<td>Effective Dental Concentration</td>
<td>2–4%</td>
</tr>
</tbody>
</table>

  ![Procaine](image)

  Table 1: Procaine (Ref.: 23, 35)

- **Tetracaine:**
  Tetracaine is a potent local anesthetic for topical use.

<table>
<thead>
<tr>
<th>Synthesized</th>
<th>1930</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physicochemical Properties</td>
<td>MW 236, pKₐ value 8.4</td>
</tr>
<tr>
<td>Elimination Half Time</td>
<td>Not relevant, topical application</td>
</tr>
<tr>
<td>Onset of Action</td>
<td>Slow follow. topical application</td>
</tr>
<tr>
<td>Duration of Action</td>
<td>Approx. 45 minutes following topical application</td>
</tr>
<tr>
<td>Potency</td>
<td>Applied topically, 5–8 times more potent than cocaine</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Great potential of systemic toxicity</td>
</tr>
<tr>
<td>Effective Dental Concentration</td>
<td>2%</td>
</tr>
</tbody>
</table>

  ![Tetracaine](image)

  Table 2: Tetracaine (Ref.: 23, 28)
Amide-Type Local Anesthetics

Amide-type local anesthetics consist of a benzene ring or a thiophene ring and an intermediate chain with an amide linkage. Amide-type local anesthetics undergo enzymatic degradation primarily in the liver, except for articaine, which is metabolized in liver and plasma. The primary excretory organ is the kidney. The entry of the first amide-type local anesthetic (lidocaine) into clinical practice transformed dentistry and replaced procaine as the drug of choice for local anesthesia. Compared to procaine, amide type local anesthetics offer a higher efficacy and a better tolerance.

Figure 10: Chemical Structure of Lidocaine, Mepivacaine and Articaine

• Lidocaine:
  Lidocaine was the first non-ester type of local anesthetic compound to be used in dentistry.

<table>
<thead>
<tr>
<th>Synthesized</th>
<th>1943</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physicochemical Properties</td>
<td>MW 234, pKₐ value 7.9, medium lipid solubility, protein binding rate 77% (plasma protein binding 2 µg/ml)</td>
</tr>
<tr>
<td>Elimination Half Time</td>
<td>90–120 minutes</td>
</tr>
<tr>
<td>Onset of Action</td>
<td>2–3 minutes</td>
</tr>
<tr>
<td>Duration of Action</td>
<td>30–60 minutes pulpal anesthesia, 3–5 hours soft tissue anesthesia (depending on vasoconstrictor concentration)</td>
</tr>
<tr>
<td>Potency</td>
<td>4 (with reference to procaine)</td>
</tr>
<tr>
<td>Toxicity</td>
<td>2 (with reference to procaine)</td>
</tr>
<tr>
<td>Effective Dental Concentration</td>
<td>2%</td>
</tr>
</tbody>
</table>

Table 3: Lidocaine (Ref.: 2, 7, 9, 18, 23, 35)
- Mepivacaine:
  Mepivacaine has only mild vasodilating properties and can be used without vasoconstrictor. It is appropriate for patients for whom a vasoconstrictor is not indicated.

<table>
<thead>
<tr>
<th>Synthesized</th>
<th>1957</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physicochemical Properties</td>
<td>MW 246, pKa value 7.6, medium lipid solubility, protein binding rate 78% (plasma protein binding [2 µg/ml])</td>
</tr>
<tr>
<td>Elimination Half Time</td>
<td>114–192 minutes</td>
</tr>
<tr>
<td>Onset of Action</td>
<td>1.5–2 minutes</td>
</tr>
<tr>
<td>Duration of Action</td>
<td>20–40 minutes pulpal anesthesia, 2–3 hours soft tissue anesthesia (without vasoconstrictor)</td>
</tr>
<tr>
<td>Potency</td>
<td>4 (with reference to procaine)</td>
</tr>
<tr>
<td>Toxicity</td>
<td>2 (with reference to procaine)</td>
</tr>
<tr>
<td>Effective Dental Concentration</td>
<td>2% with, 3% w/o vasoconstrictor</td>
</tr>
</tbody>
</table>

Table 4: Mepivacaine (Ref.: 2, 23, 35)

- Articaine:
  Articaine is the only amide-type local anesthetic with a thiophene ring.

<table>
<thead>
<tr>
<th>Synthesized</th>
<th>1969</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physicochemical Properties</td>
<td>MW 284, pKa value 7.8, high lipid solubility, protein binding rate 94% (plasma protein binding [2 µg/ml])</td>
</tr>
<tr>
<td>Elimination Half Time</td>
<td>approx. 20 minutes</td>
</tr>
<tr>
<td>Onset of Action</td>
<td>1–2 minutes</td>
</tr>
<tr>
<td>Duration of Action</td>
<td>45–75 minutes pulpal anesthesia, 2–6 hours soft tissue anesthesia (depending on vasoconstrictor concentration)</td>
</tr>
<tr>
<td>Potency</td>
<td>5 (with reference to procaine)</td>
</tr>
<tr>
<td>Toxicity</td>
<td>1.5 (with reference to procaine)</td>
</tr>
<tr>
<td>Effective Dental Concentration</td>
<td>4%</td>
</tr>
</tbody>
</table>

Table 5: Articaine (Ref.: 2, 7, 17, 18, 23, 27, 35)
4.2 Physicochemical and Pharmacological Properties

Physicochemical characteristics and pharmacological profile are important factors influencing local anesthetic efficacy and toxicity.

**Influence of pKₐ and pH Value**

Local anesthetics are acidic solutions (pH 4 – 6). In solution, local anesthetics exist as uncharged, lipid soluble, free base and charged cationic acid. The base-acid ratio depends on the pH of the solution and of the pKₐ of the specific chemical compound. The pKₐ value is an active-substance specific constant indicating the pH value with equal shares of base and cation. Once injected, the solution has to be buffered in the tissue first (pH 7.4) and the base-acid ratio moves to the free base. The uncharged base is very important for rapid penetration through the nerve membranes, whereas the cationic form is thought to be the most active form at the receptor site. The local anesthetic receptor is not accessible from the external side of the cell membrane.

The relative proportion between uncharged base and charged cation depends on the pKₐ of the local anesthetic and the tissue pH. Dental local anesthetics have a pKₐ value between 7.7 and 9.0. The higher the pKₐ value of a substance, the lower is the portion of free base, and this leads to a slower onset of action. In an acidic tissue pH, e.g. due to an inflammation, the amount of free base is reduced and this may reduce the effectiveness of the local anesthetic.

![Figure 11: pKₐ Value of Local Anesthetic Agents](Ref.: 23)

**Influence of Lipid Solubility**

Lipid solubility of a local anesthetic appears to be related to its intrinsic potency. Increased lipid solubility permits the local anesthetic to penetrate the nerve membrane, which is 90% lipid, more easily. A high lipid solubility correlates with a more rapid onset and a high intrinsic anesthetic activity, but also with a higher systemic toxicity due to a higher affinity to the central nervous system.
**Influence of Protein Binding**

The protein binding rate means the percentage of protein-bound fraction in the blood plasma and reflects the binding of the local anesthetic agent to the lipoprotein membrane. A higher plasma protein binding rate correlates with a higher efficacy and a lower systemic toxicity because it prevents rapid diffusion from the vascular compartment into the tissue. If a local anesthetic reaches the circulation only the non-bound fraction can penetrate the tissue. Articaine has a higher potency in binding to plasma proteins (94%) when compared with lidocaine (77%).

![Protein Binding Rate of Local Anesthetic Agents](image)

*Figure 12: Protein Binding Rate of Local Anesthetic Agents (Ref.: 2, 7)*

**Potency-Toxicity Ratio**

While in principle all local anesthetics work the same way, they offer different specific potencies. The potency is determined by the necessary dose of the local anesthetic in question for reaching a defined reduction of the action potential under certain conditions. The specific potencies of most dental local anesthetics range between 3 and 5 (with reference to procaine).

With reference to procaine, the relative intrinsic activity of articaine is 5 times higher. The relative systemic toxicity is about 1.5 compared to 1 of procaine. The ratio between local anesthetic potency and systemic toxicity of articaine is higher than that of other dental local anesthetics. This means, that articaine has the lowest systemic toxicity in relation to the local anesthetic activity.
Elimination Half Time

An important difference between articaine and the other amide-type local anesthetics is the speed of metabolization. Articaine is metabolized much faster (elimination half time: app. 20 minutes) than other amide-type local anesthetics (elimination half time: 90–210 minutes).
### Summary of Physicochemical and Pharmacological Properties

The table shows the most commonly used local anesthetic agents.

<table>
<thead>
<tr>
<th>Property</th>
<th>Articaine</th>
<th>Lidocaine</th>
<th>Mepivacaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>pKa</td>
<td>7.8</td>
<td>7.9</td>
<td>7.6</td>
</tr>
<tr>
<td>Lipid Solubility</td>
<td>high</td>
<td>medium</td>
<td>medium</td>
</tr>
<tr>
<td>Protein-Binding Rate</td>
<td>94%</td>
<td>77%</td>
<td>78%</td>
</tr>
<tr>
<td>Relative Potency*</td>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Relative Toxicity*</td>
<td>1.5</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Ratio Potency/Toxicity*</td>
<td>3.3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Elimination Half Time</td>
<td>~ 20 min.</td>
<td>90–120 min.</td>
<td>114–192 min.</td>
</tr>
</tbody>
</table>

* Procaine = 1

Table 6: Summary of Physicochemical and Pharmacological Properties
(Ref.: 2, 7, 9, 17, 18, 23, 27, 35)
4.3 Pharmacodynamics

Local anesthetics mainly become effective by a reversible bond to receptors. This bond may lead to a conformation change, triggering an intracellular signal and thus a certain effect. The max. possible effect is reached, when all binding sites are saturated, the required dose being determined by the pharmaceutical substance’s affinity to the receptor.

Mode and Site of Action

Over the years, many theories have been developed to explain how and where local anesthetics work. The most favored theory is the specific receptor theory, which proposes that local anesthetics basically work by reversible bond to specific receptors channels on the sodium. This prevents a massive entry of sodium ions into the nerve cell during depolarization. Depending on the dose, local anesthetics influence the action potential by decreasing the amplitude and reducing the conduction speed. With increasing doses, creation of the action potential is completely prevented.

Local anesthetics reach the site of action by diffusion and only the free base is able to penetrate into the nerve. However, the cationic acid form is responsible for the anesthetic effect. The concentration at the site of action depends on the injected dose, the concentration of the solution, the pKₐ value of the local anesthetic and the pH value of the tissue. Local anesthetics become effective directly at the axon membrane making contact with the receptors located on the membrane inside. Once the local anesthetic has gained access to the receptors, permeability to sodium ions is decreased or eliminated and nerve conduction is interrupted.

Clinical Efficacy

Local anesthetic effect depends on numerous factors, including the concentration and dose of the anesthetic drug, the presence of a vasoconstrictor, the site of injection, and the condition of the patient. The prerequisite for the local anesthetic effect is a sufficient concentration at the site of action, e.g. the nerve fiber. There is a direct relationship between increased concentrations or application of higher doses and an increased local anesthetic effect.
As the volume of injection solution to be applied is limited by the anatomy of the oral cavity, highly concentrated local anesthetic solutions are necessary for reaching a sufficient local anesthetic effect. Thanks to the favorable potency/toxicity ratio, articaine may be applied in a 4% concentration. Most dental local anesthetics are available in 2% or 3% preparations.

Clinical efficacy is determined by:
• Onset, i.e. time until reaching local anesthesia after injection
• Active profile, i.e. duration of complete and incomplete anesthesia with a particular dose and technique
• Duration of anesthesia for therapeutic purposes
• Total duration of anesthesia, i.e. until complete return of sensibility

Onset of Action

One of the important clinical parameters in local anesthesia is the rapidity with which conduction blockade occurs. The onset time is related to the physicochemical properties of the local anesthetic, e.g. a rapid onset correlates with high lipid solubility and low pKₐ.

Basically, all dental local anesthetics offer comparable onset times, which mainly depend on the application technique. After the administration of a local anesthetic, it is distributed through diffusion. The perineurium is the greatest barrier, which most local anesthetics cross quite quickly, however.

• With infiltration anesthesia, the free nerve endings are infiltrated after a few seconds, allowing a quick onset of action
• With nerve block anesthesia, onset of action depends on the duration until overcoming the perineurium barrier. In most cases, complete anesthesia is only reached after 3–5 minutes.
• With intraligament anesthesia, the onset of action is often observed immediately after injection.

Dose Administered

The dose of the anesthetic agent, which is required for sufficient and complete anesthesia, depends on various factors:
• Kind of treatment
• Extension of the area to be anesthetized
• Technique of anesthesia
• Anatomic region
• Pathological changes
• Age and condition of the patient

In a prospective study, the local anesthetic efficacy of different doses of a 2% epinephrine-free articaine solution was examined and compared to that of a 4% articaine solution with epinephrine 1/200,000.

The study was conducted with patients of both sexes and all age groups. Different dental interventions were performed with 391 patients of a dental office:
• restorative treatment
• dental extractions
• endodontic and periodontal interventions.
Doses of 2, 3 or 4 ml of the 2% and 1.5 ml of the 4% articaine solution were injected for local anesthesia. The patients subjectively classified the local anesthetic effect in view of the intervention performed as “complete”, “sufficient”, or “insufficient”. The study shows that local anesthetic efficacy increases with higher doses of the 2% solution and reaches its peak with the 4% solution. This increase is due to the higher proportion of complete anesthesia with a correspondingly lower proportion of incomplete anesthesia, while the proportion of sufficient anesthesia remained constant with different doses. This dose dependent increase in local anesthetic efficacy is explained by the higher volume of active substance reaching the receptor.

In the same study, the anesthetic efficacy of different doses of the 2% and the 4% articaine solution used for infiltration and for nerve block anesthesia were examined. With both techniques, higher efficacy was observed with increasing doses, with the 4% solution reaching the best anesthetic effect. Altogether, infiltration anesthesia resulted in greater differences than nerve block anesthesia.

With infiltration anesthesia, the diffusion path for the local anesthetic through the alveolar bone to the plexus dentalis is relatively long. As from the injection site, the local anesthetic diffuses in all directions, only a certain proportion reaches the site of action. Therefore, increased doses or concentrations allow a better local anesthetic effect, and may compensate an incorrect injection technique.

In contrast to infiltration anesthesia, with nerve block anesthesia this dependency of the local anesthetic effect on dose and concentration of the local anesthetic is less distinct, as here the depot is placed as close as possible to the nerve trunk to be anesthetized. Thanks to the short diffusion path, even low local anesthetic doses allow complete anesthesia, while on the other hand, in case of incorrect injection techniques, even higher doses do not reach sufficient anesthetic effects. Thus, the efficacy of nerve block anesthesia depends on the injection technique rather than on dose or concentration of the local anesthetic.

![Figure 16: Anesthetic Effect of Different Doses of 2% and 4% Articaine Solution (n = 391) (Ref.: 11)](image-url)
Figure 17: Anesthetic Effect of different Doses of 2% and 4% Articaine Solutions with Infiltration Anesthesia (n = 208) (Ref.: 11)

Figure 18: Anesthetic Effect of different Doses of 2% and 4% Articaine Solutions with Nerve Block Anesthesia (n = 183) (Ref.: 11)
Concentration of Local Anesthetic

Local anesthetic efficacy does not only depend on the total dose of the anesthetic agent but also on the concentration of the local anesthetic solution. The degree of anesthesia depends on the molar concentration of the local anesthetic in contact with the nerve fibers, which is correlated to the concentration of the local anesthetic solution and the total dose administered.

In a prospective study the local anesthetic efficacy of epinephrine-free articaine solutions in different concentrations – 2%, 3% and 4% – was compared to a commercial 4% articaine solution with epinephrine 1/200000.

The study was conducted with 400 patients of both sexes and all age groups, with the patients subjectively classifying the local anesthetic effect in view of the intervention performed as “complete”, “sufficient”, or “insufficient”.

The following dental interventions were performed with local anesthesia:
- restorative treatment
- dental extractions
- endodontal and periodontal interventions.

The study shows that the local anesthetic efficacy of the epinephrine-free solution increases with higher concentrations, but the highest efficacy is reached with the solution containing epinephrine.

As described in the paragraph “dose administered”, with infiltration anesthesia the anesthetic effect significantly depends on dose and concentration of the local anesthetic, while with nerve block anesthesia, the correlation between anesthetic efficacy and concentration is less significant, as here injection technique and site are more decisive factors.

Figure 19: Local Anesthetic Potency of Epinephrine-Free Articaine Solutions in Different Concentrations Compared to Articaine 4% with Epinephrine 1/200000 for Dental Interventions (n=400) (Ref.: 29)
Concentration of Vasoconstrictor

Admixture of epinephrine results in a significantly increased local anesthetic efficacy, even at the lower epinephrine concentration of 1/200000. The efficacy of articaine 4% with and without epinephrine (1/200000) was examined in 167 patients undergoing restorative dental treatments.

The local anesthetic efficacy of the epinephrine-free solution was significantly weaker than that of the solution containing epinephrine. Only in 56% of the cases, complete anesthesia was reached compared to 95% with the solution containing epinephrine.
On the other hand, a single-blind randomized comparative study with 120 healthy patients undergoing a caries profunda treatment at a vital maxillary tooth showed that for dental routine interventions, in view of efficacy and duration of anesthesia, a 4% articaine solution with epinephrine 1/100000 does not offer any advantages compared to a 4% articaine solution with epinephrine 1/200000. Thus, higher epinephrine concentrations should only be used for long-term treatments and interventions requiring more intense ischemia, e.g. in endodontic surgery.

### Duration of Action

The duration for therapeutic purposes is defined as the duration of complete anesthesia. The duration of local anesthesia is determined by the local anesthetic’s binding to the axon membrane, and depends on the local anesthetic agent, the dose and concentration of the anesthetic, the vasoconstrictor and the technique of application. The duration of anesthesia is prolonged if epinephrine is added to the solution. The duration of anesthesia is longer in soft tissues than in pulpal tissue.
The average duration of action of 3% mepivacaine without vasoconstrictor used for infiltration anesthesia in pulpal tissue is 20 min, in soft tissue 90 min, if used for nerve block anesthesia in pulpal tissue it is 40 min, in soft tissue 160 min.

The average duration of action of 2% lidocaine + epinephrine used for infiltration anesthesia in pulpal tissue is 60 min, in soft tissue 170 min, if used for nerve block anesthesia in pulpal tissue it is 80 min, in soft tissue 190 min.

The average duration of action of 4% articaine + epinephrine used for infiltration anesthesia in pulpal tissue is 60 min, in soft tissue 170 min, if used for nerve block anesthesia in pulpal tissue it is 90 min, in soft tissue 210 min.

With commercial preparations containing epinephrine, using local infiltration technique, the duration of anesthesia ranges between 40 and 60 minutes in pulpal tissue, reaching up to 170 minutes in soft tissue. Using nerve block anesthesia, the duration ranges between 60 and 90 minutes in pulpal tissue, reaching up to 240 minutes in soft tissue.

![Figure 24: Average Duration of Infiltration Anesthesia (Ref.: 13)](image1)

![Figure 25: Average Duration of Nerve Block Anesthesia (Ref.: 13)](image2)
Comparison of the Clinical Efficacy of Articaine and Lidocaine

1) In a comparative clinical study, the penetration properties and anesthetic efficacy of a 2% lidocaine solution and of a 4% articaine solution were examined and compared. 2 ml each of the 2% lidocaine and the 4% articaine solution were injected, both solutions containing epinephrine 1/200000. The efficacy of the 4% solution was systematically compared to that of the same dose of the lidocaine solution with a weaker concentration. 77 patients were treated with articaine, and 67 patients with lidocaine. Maxillary premolars were extracted after infiltration anesthesia without additional palatal injection and mandibular premolars were extracted after infiltration anesthesia without additional lingual injection.

Whereas after vestibular articaine injection, in 93.5% of the cases all premolars could be extracted, after lidocaine injection, only a rate of 25.4% was reached.

At 74.6%, the rate of failures after application of 2 ml of lidocaine was extremely high, with 50 patients requiring palatal and lingual re-injections. After the application of articaine, re-injections were only necessary in 6.5% of the cases.
Result of the study:

Extraction of maxillary and mandibular premolars after single vestibular injection is possible, with the 4% articaine solution clearly reaching better results than the 2% lidocaine solution.

2) In a further study the clinical efficacy of articaine 4% with epinephrine 1:200000 and lidocaine 2% with epinephrine 1:200000 was compared during restorative dental measures (indirect pulp-capping) and dental extractions (n=120 patients, 1ml anesthetic solution).

Significant differences between lidocaine and articaine were obtained preferentially during treatment of caries (indirect pulp-capping). The anesthetic effects occurred faster with articaine when compared to lidocaine. In addition, the number of patients with additional injections of the anesthetic and the number of patients with residual pain was significantly lower after treatment with articaine 4% with epinephrine 1/200000 compared to those treated with lidocaine 2% with epinephrine 1/200000. However, differences between the anesthetics were not so well-defined in patients undergoing teeth extractions.

Figure 28: Anesthetic Efficacy of Lidocaine 2% and Articaine 4% in Patients undergoing Restorative Measures (indirect Pulp-Capping) and Teeth Extraction (Ref.: 10)

Results:

According to this study the applied dose of 1 ml articaine offers the following advantages over lidocaine:

1. More profound local anesthetic effect during a defined period of time
2. Faster onset of action for indirect cappings
3. Less vestibular re-injections necessary for indirect cappings and molar extractions
4. Less residual pain in connection with indirect cappings and extractions of inflamed teeth.
4.4 Pharmacokinetics

Pharmacokinetics refer to the development of the pharmaceutical substance’s concentration in the organism, which is determined by the combination of resorption, distribution and elimination. The examination of the pharmacokinetics of local anesthetics is important for assessing systemic side effects. The incidence of intoxications depends on the concentration at the organs concerned (e.g. central nervous system, heart), and thus on the concentration in the serum.

Absorption, Distribution, Metabolism, Excretion

After the local anesthetic is injected, it begins to spread through the local tissues, depending on dose and concentration of the solution, injection technique and speed of injection, as well as tissue vascularization.

After the injection, a specific active substance concentration and a certain balance between base and cation is reached at extrafacial sites. This process depends on the local anesthetic’s pKₐ-value as well as on the predominant pH-value in the tissue. This is an important aspect, as the local anesthetic is only able to cross the nerve membrane and thus to reach the site of action in undissociated form (lipophilic base), whereas the cation may become active at the nerve membrane after re-dissociation.

Simultaneously, absorption starts from the site of injection into the vascular compartment. The rate of absorption depends e.g. on the dosage, the pharmacological profile, the presence of a vasoconstrictor and the site of administration.

In the blood, local anesthetics show different extents of protein binding. The local anesthetic, which is not bound to plasma protein, is distributed throughout all body tissues. Highly perfused organs such as the lung and kidneys show higher local anesthetic concentrations than less perfused organs such as muscles. The risk of an intoxication is increased in highly perfused organs. Local anesthetics may cross the placenta barrier, thus reaching the fetal circulation. The local anesthetic’s protein binding rate is a decisive factor for the ratio between the concentrations in fetal and maternal blood.

There are significant differences between ester-type and amide-type local anesthetics in view of their metabolic breakdown. Ester-type local anesthetics are inactivated primarily by hydrolysis. They are preferentially metabolized in the plasma by pseudo cholinesterase. The elimination half times of ester-type anesthetics are quite short and do not exceed 10 minutes.

The metabolism of amide-type local anesthetics is more complex than that of ester-type agents. The liver is the primary organ of metabolism for amid type local anesthetic. The initial reaction is usually N-dealkylation of the tertiary amino terminus. The resultant secondary amine of most amides is susceptible to hydrolysis by hepatic amidase activity. Elimination half time is about 1.5 to over 3 hours.

In contrast to other amide-type local anesthetics, articaine contains a carboxylic ester group. Thus, articaine is inactivated in the liver by less than 10% and mainly by hydrolyzation in the tissue and the blood. Since the hydrolyzation is very fast and starts immediately after injection, about 85 to 90% of administered articaine is inactivated in this way. Main metabolic substance is the nontoxic articainic acid. As the hydrolyzation process is very fast, the elimination half time of articaine is about 20 minutes. Articaine is a high clearance drug with a plasma clearance of approx. 3,500 ml/min.
The kidney is the main excretory organ for local anesthetics and their metabolites. Less than 10% of the local anesthetic agents are excreted unchanged.

The metabolism and elimination of local anesthetics can be significantly influenced by the clinical status of the patient. Hepatic dysfunction will result in an accumulation of the amide-type local anesthetic agents. On the other hand, the rate of hydrolysis of the ester-type local anesthetics is decreased in patients with atypical forms of the enzyme, pseudocholinesterase. A significant impairment of renal function may result in increased blood levels of the anesthetic drug or its metabolites which may cause adverse systemic reactions.

![Figure 29: Absorption, Metabolism and Excretion of Local Anesthetic Agents](image)

**Blood Levels of Local Anesthetics**

Absorption into the bloodstream primarily depends on various factors, e.g. on the dosage, the injection site, and the vasoconstrictor added. Most local anesthetics show a linear relationship between applied dose and max. serum levels, which is important in view of the risk of systemic intoxications.

After single application of a drug, we observe a characteristic development of the serum concentration representing the results of absorption, metabolization, and elimination. Depending on applied dose and resorption conditions, after injection into the mucosa, the graphic representation of the development shows a steep increase until reaching the max. serum concentration ($C_{max}$). The time of reaching the max. serum concentration ($t_{max}$) is mainly determined by the resorption speed. After attaining a peak concentration, the serum concentration shows a decrease corresponding to first order kinetics (exponential function) and described by the elimination half time.

The max. serum concentrations are very important in view of the risk of systemic intoxications. After submucosal injection of a therapeutic dose of 80 mg of articaine or lidocaine – equivalent to one cylindrical cartridge – average maximum serum levels range between 0.5 and 0.8 mg/l. Early signs of central nervous system intoxications are of excitatory nature and normally occur at serum concentrations of > 5 mg/l. Under normal resorption conditions, after single injection of the recommended max. dose of 500 mg of articaine or lidocaine, the max. serum concentrations are not expected to exceed the intoxication threshold. In case of accidental intravasal injections or modified resorption conditions, significantly lower doses may lead to toxic serum concentrations, however.
Serum Levels of Articaine and the Metabolic Substance Articainic Acid

The metabolism of articaine has been studied extensively by determination of blood levels in volunteers and dental patients, using different solutions, doses and performing different techniques.

After submucosal injection, serum levels of articaine increase very fast, with peak levels observed between 10 and 15 minutes after injection. After attaining the peak, serum levels of articaine decrease very fast. 90 minutes after injection, serum levels amount to about 10% of the peak levels. Elimination half time of articaine is within the range of 15 to 20 minutes.

There is a linear relationship between administered dose and resultant peak. This was demonstrated after submucosal administration of higher doses of plain articaine 4% (1.5 ml, 3.0 ml, 6.0 ml, corresponding to 60 mg, 120 mg and 240 mg of articaine) to the upper jaw (vestibular region 14) of 15 healthy volunteers. Independent of the dose, the development of the serum concentration shows a quick increase to the max. value, followed by a quick decrease in concentration.
After submucosal injection of articaine, serum levels of the metabolite articainic acid increase slowly, maximum serum levels can be observed 45 min after injection. There is also a linear relationship between the applied dose of articaine and the maximum serum levels of articainic acid.

**Figure 32:** Concentration-Time Courses of Articainic Acid in the Serum after different Doses of the plain Articaine 4% Solution administered submucosally (Ref.: 3)

Serum Levels of Articaine with and without Epinephrine

Admixture of epinephrine to articaine administered periorally results in changes of the systemic pharmacokinetics of articaine. The curve of the plasma concentrations after administration of articaine 4% with epinephrine 1/200000 and articaine 2% without epinephrine shows a rapid increase to the maximum values which, in the case of the epinephrine-containing articaine 4% solution, is slightly delayed. From this point, the concentration falls off rapidly, specifically in the case of epinephrine-free preparation. Plasma articaine levels cease to be detectable 45 minutes after the injection of articaine 2% and one hour after administration of articaine 4% with epinephrine 1/200000.

**Figure 33:** Serum Concentration-Time Course of Articaine with and without Epinephrine Administration after equal submucosal Administration (80 mg) at the Upper Jaw (Ref.: 38)
Serum Levels of Articaine after Repeated Submucous Injection

In a prospective, double-blind study with 12 healthy volunteers, the serum levels of articaine 4% without epinephrine after repeated injection were determined. Three submucous injections of 2 ml (80 mg) each were administered in periods of 20 min.

The resulting serum levels showed three maximum values after 10, 30, and 50 minutes; at the test end after 90 minutes, a low value was measured.

The study shows that thanks to the short elimination half time and the very high plasma clearance, the risk of accumulation in connection with repeated articaine injections is to be considered low.

![Graph of Serum Levels of Articaine after Repeated Submucous Injection](image)

*Figure 34: Serum Levels of Articaine after Repeated Submucous Injection of 3 x 80 mg in periods of 20 min (Ref.: 25)*

Serum Levels of Articaine versus Lidocaine

The pharmacokinetic parameters of articaine and lidocaine in the systemic blood circulation reflect the peculiarities of the drugs at the site of injection. Plain solutions of articaine and lidocaine (concentration 2%, each at doses of 10 mg, 20 mg and 40 mg) administered to healthy volunteers (n=7) by submucous infiltration in the gingiva of the upper jaw appeared in the blood in measurable concentrations as early as 5 minutes after administration. The maximum serum concentrations of both anesthetics at equal doses were dose-dependent and the peak concentrations of articaine tended to be higher than lidocaine peak concentrations.

With lidocaine, the time until reaching the maximum concentration was slightly prolonged (15–20 minutes) when compared with the same parameter for articaine (10–15 minutes).
4.5 Summary of Pharmacological Data

<table>
<thead>
<tr>
<th>Property</th>
<th>Articaine</th>
<th>Lidocaine</th>
<th>Mepivacaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective Dental Concentration</td>
<td>4%</td>
<td>2%</td>
<td>3% w/o epinephrine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2% with epinephrine</td>
</tr>
<tr>
<td>Onset</td>
<td>1–2 minutes</td>
<td>2–3 minutes</td>
<td>1.5–2 minutes</td>
</tr>
<tr>
<td>Duration</td>
<td>45–75 minutes pulpal anesthesia, 2–6 hours soft tissue dep. on vasoconstrictor concentration</td>
<td>30–60 minutes pulpal anesthesia, 3–5 hours soft tissue anesthesia dep. on vasoconstrictor concentration</td>
<td>20–40 minutes pulpal anesthesia, 2–3 hours soft tissue anesthesia w/o vasoconstrictor</td>
</tr>
<tr>
<td>Metabolism</td>
<td>plasma and liver</td>
<td>liver</td>
<td>liver</td>
</tr>
<tr>
<td>Elim. Half Time</td>
<td>~ 20 min.</td>
<td>90–120 min.</td>
<td>114–192 min.</td>
</tr>
<tr>
<td>Max. Dose with Vasoconstrictor</td>
<td>500 mg</td>
<td>500 mg</td>
<td>500 mg</td>
</tr>
</tbody>
</table>

Table 7: Summary of Pharmacological Data (Ref.: 1, 22, 23, 27)

Figure 35: Maximum Plasma Concentration of Articaine and Lidocaine after submucosal injections of 2% Solutions of Anesthetics (Ref.: 15)
5. Chemistry and Pharmacology of Vasoconstrictors

5.1 Pharmacology of Vasoconstrictors

Most of the local anesthetic agents possess some degree of vasodilating activity, which increases their own uptake into the blood vessels. Particularly in highly perfused regions, this leads to a short duration of the local anesthetic effect, which is insufficient for many interventions. Therefore, local anesthetic preparations often contain a vasoconstrictor.

The vasoconstrictor effect leads to
- a decreased rate of absorption of the local anesthetic into the cardiovascular system
- a lower plasma level of local anesthetic, with lower risk of local anesthetic toxicity
- an increased duration of action and increased depth of anesthesia
- decreased bleeding at the site of local anesthetic administration

5.2. Categorization of Vasoconstrictors

Almost exclusively, catecholamines – epinephrine and norepinephrine – are used as vasoconstrictors, but also felypressin – a synthetic analogue of the polypeptide vasopressin.

Catecholamines

Epinephrine and norepinephrine are sympathomimetic amines. They are the body's own natural agents produced in the adrenal medulla and at the sympathoadrenal nerve ends and acting as transmitter substances in the sympathetic nervous system. Chemically, epinephrine and norepinephrine are catecholamines.

Epinephrine is the most potent and efficient of the vasoconstricting drugs used in dental local anesthetic solutions. Epinephrine as a salt is highly soluble in water. Sodium bisulfite is added normally to epinephrine solution to delay this degradation. Epinephrine can be obtained from a synthetic as well as from a natural source. It is available in concentrations from 1:50000 to 1:20000.

Compared to epinephrine, the addition of norepinephrine as vasoconstrictor bears significant disadvantages, as through contraction of the arterioles it leads to a significant increase in blood pressure. Local vasoconstriction is lower than with epinephrine, while the rate of side effects is nine times higher than that of epinephrine.

Figure 36: Chemical Structure of Epinephrine and Norepinephrine
Mode of Action

Epinephrine and norepinephrine lead to vasoconstriction by activating adrenergic receptors in the vascular musculature. The impact of catecholamines on vessels and other organs is determined by the distribution of the different adrenoreceptors. There are two main types of receptors (α and β), based on the excitatory (usually α) and inhibitory (usually β) effect of catecholamines on smooth muscle. The adrenoreceptors are subdivided into α1 and α2 as well as into β1 (adipocytes, cardiac muscle) and β2 (most other sites).

Catecholamines vary greatly in their relative affinities to different adrenoreceptors. Whereas epinephrine shows an affinity to both α and β, norepinephrine prefers α-receptors. As the distribution of receptor types varies in the different organs, epinephrine and norepinephrine may show different – sometimes even opposed – effects. Epinephrine may have vasoconstricting as well as vasodilating effects.

Figure 37: Systemic Effects of Epinephrine and Norepinephrine

Figure 38: Different Effects of Epinephrine on Blood Vessels
Local Effects

Epinephrine and norepinephrine cause vasoconstriction by stimulating the $\alpha$-receptors located in the walls of the arterioles. The constriction of resistance arterioles and precapillary sphincters is primarily responsible for limiting local blood flow in the injected tissue. This leads to a strong hemostasis reaction in the field of operation. Furthermore, as vasoconstriction slows down the anesthetic evacuation, more molecules remain at the site of action for a longer period of time. This means improvement of the depth of anesthesia as well as a prolonged duration.

![Figure 39: Effects of Epinephrine and Norepinephrine on the Alveolar Mucosa](image)

Systemic Effects

The systemic impact of epinephrine, when added to local anesthetics for dental applications, effects mainly the cardiovascular system. The systemic effects of epinephrine depend on the dose. While low doses make the blood pressure drop, higher doses lead to a rise in (systolic) blood pressure and an increased heart beat frequency with higher contractility. The dose which may cause systemic effects depends on the patient conditions. Severe effects may occur in cardiovascular patients even with low doses of epinephrine.

In contrast to epinephrine, with norepinephrine the $\alpha$-sympathomimetic effects are most important. A general vasoconstriction causes an increased peripheral resistance. Due to a vagoreflexory bradycardia, the increased blood pressure is not accompanied by a higher heart beat frequency.

![Figure 40: Cardiovascular Effects of Epinephrine and Norepinephrine (accord. to Allwood et al) (Ref.: 28)](image)
Pharmacokinetics

Following intraoral injection of a local anesthetic solution, peak plasma levels of epinephrine are usually observed within the first few minutes and then subside over the next 10 to 20 minutes. Most of the catecholamines are absorbed, distributed throughout the body, taken up by extra neuronal tissue and inactivated by the enzyme catechol-o-methyltransferase, which is found in many tissues. The o-methylated product is either excreted in the urine or further metabolized by the enzyme monoamine oxidase. The primary metabolite (vanillylmandelic acid) is then eliminated by the kidney. The metabolic fate of norepinephrine is quite similar to that of epinephrine.

Other Vasoconstrictors

Felypressin is the most commonly used alternative vasoconstrictor. Felypressin is a direct stimulator of vascular smooth muscles and has no direct effects on adrenergic nerve transmission and myocardium. Thus, it is appropriate for patients for whom the application of catecholamines is contraindicated. Felypressin shows some antidiuretic and oxytocic activity. Thus, it is contraindicated during pregnancy. Felypressin is not very active in constricting arterioles and is not nearly as effective as conventional vasoconstrictors. It is usually marketed in combination with 3% prilocaine.

![Chemical Structure of Felypressin](image)

Figure 41: Chemical Structure of Felypressin

Literature: Chemistry and Pharmacology of Vasoconstrictors
4) Burger J, 1995
9) Frenkel G, 1989
16) Kilian H et al, 1973
19) Knoll-Köhler E, 1988
23) Malamed SF, 2004
26) Rohr R, 2000
6. Dental Anesthetic Techniques

6.1. Classification of Administration Techniques

Local anesthesia is indicated for any painful dental procedures (for contraindications please refer to section “Clinical Aspects”). It is the method of choice for producing anesthesia, since it offers a lot of advantages: the patient remains awake and cooperative and may leave the office unescorted. Under normal conditions, the incidence of adverse reactions is very low, the percentage of failures is small and no additional trained personnel is necessary.

The choice of administration technique has to consider the area to be anesthetized, the profoundness of local anesthesia required, duration of local anesthesia, presence of infection, age and condition of the patient and the hemostasis required during treatment.

In dental local anesthesia, we distinguish between the following techniques:

• Topical anesthesia
• Infiltration (supraperiosteal) anesthesia
• Nerve block anesthesia
• Periodontal ligament injection

Topical Anesthesia

Topical anesthesia is defined as the surface application of a local anesthetic to block free nerve endings supplying the mucosal surfaces.

The technique is useful for a variety of procedures and conditions in which only superficial anesthesia is required, including pain relief from dental procedures (e.g. needle insertion, orthodontic band placement, and gingival curettage).

Only substances sufficiently diffusing into the mucosa – e.g. lidocaine or tetracaine – are suitable for topical anesthesia. Topical anesthetics are marketed as pressurized sprays or as a gel or ointment formulation.
Infiltration (Supraperiosteal) Anesthesia

For infiltration anesthesia, the local anesthetic is injected into the submucosa or supraperiosteally in the immediate vicinity of the bone surface. The local anesthetic is distributed in soft tissue and adjacent bones and becomes active at the terminal nerve ends. Onset is after about 3 minutes.

Local infiltration technique is suitable for soft tissue anesthesia and interventions in the areas of maxillary teeth and mandibular incisors and premolars, where the thin bone lamella allows diffusion of the local anesthetic.

Advantages are a high success rate and a technically easy injection. Infiltration anesthesia is usually entirely atraumatic.

The disadvantage is that for use in large areas, multiple needle insertions are necessary, which may lead to the administration of larger volumes of local anesthetic solution, increasing the risk of systemic and local complications.

Figure 43a: Infiltration Anesthesia

Figure 43b: Infiltration Anesthesia (Clinical-Picture)
Nerve Block Anesthesia

For nerve block anesthesia, the local anesthetic solution is deposed within close proximity to a main nerve trunk, ensuring local anesthesia within the supply area of this nerve distal to the injection site.

This technique is used for local anesthesia of the inferior mandibular nerve, the lingual nerve, the buccal nerve, the greater palatine nerve and the nasopalatine nerve.

Nerve block anesthesia is indicated in cases, where no or no sufficient depth of anesthesia is reached with the infiltration technique, for example if the tooth is surrounded by a compact bone layer preventing the local anesthetic from reaching the site of action in sufficient concentration.

Advantages are complete local anesthesia, long duration of action and a comparatively low dose.

Disadvantages are an increased risk of traumatization of the nerve trunk and an accidental intravascular injection of the local anesthetic solution.

Figure 44a: Nerve Block Anesthesia

Figure 44b: Nerve Block Anesthesia (Clinical-Picture)
**Periodontal Ligament Injection**

In periodontal ligament (PDL) technique (= intraligamentary injection), the local anesthetic solution is injected into the desmodontal space. The PDL technique is useful for anesthesia of mandibular molars as an alternative to the nerve block technique. Intraligamentary anesthesia is suited for all interventions limited to one tooth and its desmodont.

Special injection systems are required for controlling the fluid pressure necessary for injection. A total of 0.2 ml of solution is injected at once. The anesthetic effect starts immediately after the injection and ranges between 15 and 20 minutes.

Advantages of this technique are little needle pain, low dose, short duration, limitation of the local anesthesia to one tooth.

Disadvantages are possible desmodont damages followed by biting sensitivity as well as possible bacteremias. Therefore, this technique is contraindicated for patients with increased risk of endocarditis.

*Figure 45a: Periodontal Ligament Injection*  
*Figure 45b: Periodontal Ligament Injection (Clinical Picture)*
6.2 Local Anesthesia

Injection technique depends on the desired dental treatment and the region to be anesthetized, e.g. maxillary or mandibular anesthesia.

Maxillary Anesthesia

Local anesthesia of the maxillary arch involves blocking of one or more of the peripheral nerves of the maxillary division of the trigeminal nerve. For restorative treatment, the superior alveolar nerves must be anesthetized. For dental surgery including periodontal surgery, additional injections to block the nasopalatine and greater palatine nerves are necessary.

The most commonly used method for local anesthesia of maxillary teeth and supporting periodontium is the infiltration technique (supraperiosteal injection). The local anesthetic solution is capable of penetrating the thin cortical plate and the porous maxillar bone and of anesthetizing terminal fibers of the superior dental plexus. The supraperiosteal injection is frequently referred to as infiltration, although more accurately it should be classified as a field block, as some structures may become anesthetized without ever having been exposed to an effective concentration of the local anesthetic.

Injection of local anesthetics into palatal tissue is considered the most uncomfortable of intraoral injection techniques. Palatal injection should be restricted to situations when direct manipulation of palatal mucosa or the underlying bone is performed, including the extraction of teeth, palatal surgery, gingival retraction, or subgingival scaling and curettage.
Maxillary anesthesia can be divided into:

**Infiltration (Supraperiosteal) Anesthesia**

Supraperiosteal injection is the most commonly used method for anesthesia of a single tooth or circumscribed portion of the maxilla.

*Area anesthetized:* For a single tooth a supraperiosteal injection includes the pulp and labial/buccal tissues adjacent to the tooth, depending on the spread of the local anesthetic.

*Indications:* Pulpal anesthesia of the maxillary teeth when treatment is limited to one or two teeth. Soft tissue anesthesia when indicated for surgical procedures in a circumscribed area.

*Advantages:* High success rate, a technically easy injection and usually entirely atraumatic.

*Disadvantages:* Not recommended for use in large areas as multiple needle insertions are needed. The necessity to administer a large volume of local anesthetic solution, increasing the risk to exceed the maximum dose.

*Treatment:* The needle tip is placed under the mucosa adjacent to the periosteum of the alveolar bone overlying the apex of the tooth.
Greater (Anterior) Palatine Nerve Block

For dental procedures treating palatal soft or hard tissue, anesthesia of the hard palate is necessary.

Areas anesthetized: For treatments including the palatal soft tissues distal to the canine. In combination with a nasopalatine block, it will also provide anesthesia of the palatal mucosa adjacent to the canine.

Indications: Restorative procedures on more than two teeth involving palatal soft tissue in the region of the molars and premolars. For pain control during periodontal or oral surgical procedure.

Advantages: Reduced penetration of the needle and volume of solution.

Disadvantages: No hemostasis except in the immediate area of injection. Potentially traumatic.

Treatment: The tip of the needle must be placed close to the foramen, which is located on the lateral aspect of the hard palate, generally opposite the second or third molar. Injection of a small amount of local anesthetic (0.2 ml) is proper for a sufficient anesthesia. If a large amount of anesthetic is used (or its placement is more posterior than usual) and the lesser palatine nerves are blocked, anesthesia of the soft palate, uvula, and tonsilar area will result. In this situation, some patients may misinterpret the loss of sensation in the soft palate as an inability to swallow.
Other Maxillary Local Anesthesia

- Anterior superior (infraorbital) alveolar nerve block is recommended for management of anterior teeth in one quadrant.
- Posterior superior alveolar nerve block is recommended for management of several molar teeth in one quadrant.
- Maxillary nerve block is recommended for extensive buccal, palatal and pulpal management in one quadrant.
Mandibular Anesthesia

Local anesthesia of the mandibular arch involves blocking of one or more of the peripheral nerves of the mandibular division of the trigeminal nerve. The infiltration technique (supraperiosteal injection) ensures sufficient local anesthesia only in incisors, canines and premolars, while molar local anesthesia requires inferior alveolar nerve block. The buccal mucosa can be anesthetized both by supraperiosteal injection or buccal nerve block, lingual mucosa can be anesthetized using lingual nerve block. Buccal and lingual nerve block provides soft tissues anesthesia only. Successful pulpal anesthesia of mandibular teeth is more difficult to achieve due to greater density of the buccal alveolar plate and the wide variation in anatomy.

Mandibular anesthesia can be divided into:

Infiltration (Supraperiosteal) Anesthesia

While the supraperiosteal injection is the most commonly used method for anesthesia of a single tooth of the maxilla, this technique is of limited use for pulpal anesthesia in the adult mandible.

Area anesthetized: For a single-tooth a supraperiosteal injection includes the pulp and labial/buccal tissues adjacent to the tooth, depending on the spread of the local anesthetic.

The anatomic distribution of a single discrete mandibular supraperiosteal injection is quite limited. Soft tissue anesthesia will include the gingiva and adjacent labial mucosa, including a small portion of the lower lip.

If extensive surgery is to be performed on the lower lip, a different technique providing full anesthesia of the mental nerve will be required.

Indications: Most effective in young children and in the anterior region of older children and young adults with a small stature and light bone structure. In adults, the dense cortical bone may effectively prevent the anesthetic from reaching the nerve fibers supplying the teeth.

Advantages: High success rate, a technically easy injection and usually entirely atraumatic.

Disadvantages: Not recommended for use in large areas as multiple needle insertions are needed. The necessity to administer large volume of local anesthetic solution increasing the risk to exceed the maximum dose.

Treatment: The needle tip is placed adjacent to the mandibular periosteum overlying the root tip of the tooth to be anesthetized.
Mandibular Nerve Block (Inferior Alveolar and Lingual Nerve Block)

Inferior alveolar nerve block is the most commonly used nerve block in dentistry and will be routinely performed in dental practice.

**Area anesthetized:** For dental procedures on the mandible from the retromolar region to the midline. When accompanied by a separate buccal nerve block, pain control encompasses the posterior buccal tissues, anterior labial region, and lingual areas to the midline with a single anesthetic procedure.

**Indications:** For bony, periodontal, and pulpal anesthesia of all mandibular molars, premolars, cuspid, and incisors on the side of the injection to the midline.

**Advantages:** A wide area is anesthetized with one injection (quadrant anesthesia).

**Disadvantages:** Higher rate of inadequate anesthesia, high rate of positive aspiration, patient feeling uncomfortable due to lingual and lower lip anesthesia.

**Treatment:** The local anesthetic solution is to be injected into the pterygomandibular space. Depending on the technique, the lingual and/or buccal nerve can be anesthetized at the same time. The tip of the needle has to be placed close to mandibular sulcus just behind the lingula. Within this depression, and partly covered by the lingual, is the mandibular foramen through which the inferior alveolar nerve, artery, and vein pass. After depositing anesthetic solution adjacent to the mandibular foramen to anesthetize the inferior alveolar nerve, the operator withdraws the needle half-way, so that the tip lies about 1 cm anterior to the lingula, where the lingual nerve resides at this height within the pterygomandibular space.
Buccal Nerve Block

During inferior alveolar nerve block the buccal nerve as a branch of the anterior division of the mandibular division of the trigeminal nerve (V3) is not consequently anesthetized.

**Area anesthetized:** Soft tissues and peristeme buccal to the mandibular teeth. The anterior and posterior extent of anesthesia is variable, depending on the distributions of the mental nerve and gingival branch of the posterior superior alveolar nerve.

**Indications:** For anesthesia of the cheek and posterior buccal mucous membranes.

**Advantages:** High success rate and easy technique.

**Disadvantages:** Pain is possible after needle contacting peristeme during injection.

**Treatment:** The nerve can easily be anesthetized by deposing the anesthetic solution close to the nerve as it crosses the anterior border of the ramus.

Figure 51a: Buccal Nerve Block (Clinical Picture)

Figure 51b: Buccal Nerve Block
Mental Nerve Block

The mental nerve is the superficial terminal branch of the inferior alveolar nerve after leaving inferior alveolar canal via the mental foramen.

*Area anesthetized:* Pulpal anesthesia of the mandibular incisors, canine, and variably the first and second premolars and their investing bone and periodontal ligaments. Soft tissue anesthesia includes the facial gingiva and mucosa of these teeth and the lower lip to the midline.

*Indications:* For procedures involving the mandibular incisors, canines and premolars including their investing bone and periodontal ligaments.

*Advantages:* High success rate, easy technique, usually atraumatic.

*Disadvantages:* Hematoma.

*Treatment:* The local anesthetic is to be placed close to mental foramen, which is located below the apex of the mandibular second premolar or just anterior or posterior to it. For successful anesthesia, it is not necessary to inject the local anesthetic into the mandibular foramen.

---

Figure 52a: Mental Nerve Block (Clinical Picture)

Figure 52b: Mental Nerve Block

---

*Literature 6. Dental Anesthetic Techniques*
23) Malamed SF, 2004
26) Roha R, 2000
7. Clinical Aspects

In dentistry the use of drugs is well-established and the use of local anesthetics is necessary whenever painful procedures have to be carried out. Dental local anesthetics have reached a high level of safety, if administered carefully and within recommended dosage limits. However, there’s a risk of undesirable adverse effects whenever a drug is used; this also includes local anesthetics.

In this chapter, systemic and local adverse effects, interactions with other drugs used simultaneously, and potential contraindications are reviewed. In addition, the evaluation of the medical history and clinical status of the patient, risk patient management and maximum and therapeutic doses are considered.

7.1 Posology (Dosage)

Local anesthetic doses are determined according to the necessary effects, taking into consideration maximum or limit doses depending on the weight and possible general diseases of the patients.

Therapeutic Dose

The dosage of local anesthetics depends on the requested effect, the dental application to be performed, and the physical condition of the patient.

The minimum dose necessary for reaching complete anesthesia depends on:
• Type of anesthesia
• Site of injection
• Type of treatment
• Individual algesia of the patient
• Formula of the local anesthetic solution

For infiltration anesthesia, 1.5 – 1.7 ml per tooth and two adjacent teeth, respectively are usually sufficient. For nerve block anesthesia of the inferior alveolar nerve, about 1.0 – 1.7 ml should be injected. Re-injections should range between half of the original dose and the complete original dose. The doses actually required for dental interventions may vary considerably and range between 0.5 and several ml.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extraction of Maxillary Teeth</td>
<td>1.7 ml</td>
</tr>
<tr>
<td>Incision at the Gum</td>
<td>0.1 – 0.2 ml</td>
</tr>
<tr>
<td>Extraction of Mandibular Premolar Teeth</td>
<td>1.7 ml</td>
</tr>
<tr>
<td>Cavity Preparations (per Tooth), Except Mandibular Premolar Teeth</td>
<td>0.5 – 1.7 ml</td>
</tr>
<tr>
<td>Nerve Block Anesthesia of the Mandibular Nerve</td>
<td>1.0 – 1.7 ml</td>
</tr>
</tbody>
</table>

Table 8: Recommended Therapeutic Dose for Ubistesin™ 1/200000 and Ubistesin™ 1/100000 (Ref.: 8)
Maximum Dose of Local Anesthetics

Due to the systemic toxic effects of local anesthetics and vasoconstrictors, maximum or limit doses have to be followed. However, the indicated maximum doses should be considered benchmarks rather than absolute values. It is strongly recommended to use the smallest possible volume of solution which will lead to an effective anesthesia and to evaluate the condition of the patient before any injection.

The recommended max. doses are based on the expected serum concentrations of the substances concerned, the systemic toxic threshold dose, the extrapolation of animal and clinical studies, as well as on the evaluation of reported side effects.

Therefore, under normal conditions no systemic toxic effects have to be expected, if the recommended max. doses are considered. However, due to the patient’s individual range of variation, as well as absorption, distribution, and metabolization of the local anesthetic, toxic reactions may also occur within the so-called safe dosage range. In particular, there is an increased risk in case of quick resorption, accidental intravasal injection, or a reduced threshold dose of the patient.

The doses of local anesthetic drugs are presented in terms of milligrams of drug per unit of body weight.

<table>
<thead>
<tr>
<th>Maximum Dose of Local Anesthetics</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>without</td>
<td>with</td>
</tr>
<tr>
<td></td>
<td>Vasoconstrictor</td>
<td>Vasoconstrictor</td>
</tr>
<tr>
<td>mg/kg</td>
<td>mg/70 kg</td>
<td>mg/kg</td>
</tr>
<tr>
<td>Articaine</td>
<td>4</td>
<td>300</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>4</td>
<td>300</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>4</td>
<td>300</td>
</tr>
</tbody>
</table>

Table 9: Maximum Dose of Local Anesthetic Agents (Ref.: 1)

For healthy adults, the maximum dose of epinephrine as vasoconstricting additive is 200 µg. For patients with coronary heart disease or other serious cardiovascular diseases, the maximum dose is reduced to 40 µg.
Most commercial local anesthetics are combined preparations consisting of a local anesthetic substance and a vasoconstrictor. For both components, different maximum doses are applicable. Therefore, in individual cases, the dose is determined or limited by the local anesthetic or the vasoconstrictor.

The following chart lists the maximum doses of commercial local anesthetics for healthy patients and for patients with coronary heart disease referring to a body weight of 70 kg.

<table>
<thead>
<tr>
<th>Maximum Dose for Healthy Patient with 70 kg BW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Articaine 4% with 1/200000 epinephrine (Ubistesin 1/200000)</td>
</tr>
<tr>
<td>Articaine 4% with 1/100000 epinephrine (Ubistesin 1/100000)</td>
</tr>
<tr>
<td>Mepivacaine 3% (Mepivastesin)</td>
</tr>
<tr>
<td>Lidocaine 2% with 1/80000 epinephrine (Xylestesin A)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Maximum Dose for Cardiovascular Patient with 70 kg BW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Articaine 4% with 1/200000 epinephrine (Ubistesin 1/200000)</td>
</tr>
<tr>
<td>Articaine 4% with 1/100000 epinephrine (Ubistesin 1/100000)</td>
</tr>
<tr>
<td>Mepivacaine 3% (Mepivastesin)</td>
</tr>
<tr>
<td>Lidocaine 2% with 1/80000 epinephrine (Xylestesin A)</td>
</tr>
</tbody>
</table>

Table 10: Maximum Dose for Healthy Patient and Cardiovascular Patient with 70 kg Body Weight (BW) Ref.: 1
7.2 Adverse Effects and Precautions for Use

Adverse effects may occur during or following administration of local anesthetics. Most adverse effects or complications are largely inconsequential, representing more of a temporary inconvenience than a true hazard. Nevertheless, life-threatening systemic reactions may occur in certain situations.

Local reactions can be distinguished from systemic adverse effects related to one of the components of the anesthetic solution.

Local Adverse Effects

Localized responses to anesthetic injections are fairly common. Most individuals, for instance, have experienced mild soreness at one time or another in the area of injection.

Local complications during and after local anesthesia, in addition to those attributed to local anesthetic solutions, may occur. These complications are the result of either the needle insertion or other technical difficulties, which are now discussed in detail.

**Injury of blood vessels**

Injury of blood vessels by the needle is typical for nerve block anesthesia, with a reported incidence of up to 20%. Puncture of blood vessels may also cause hematomas.  
**Measures:** To avoid an unintended intravascular injection, aspiration control must be carried out. A negative aspiration control does not necessarily exclude an intravascular canula position, e.g. needle opening in direct contact with the vascular wall. The aspiration control has to be performed on two levels.

**Injury of nerves**

Injury of nerves by the needle is also typical for nerve block anesthesia, as the local anesthetic is injected in the immediate vicinity of the nerve trunk. Hitting of the nerve usually causes a flashing, very intense pain.  
**Measures:** Needle should be retracted slightly, before the solution is deposited to avoid intraneurval injection.

**Mucosal irritation in palatal area**

The injection might result in a mucosal necrosis, if in an area of fixed mucosa the local anesthetic is applied under high pressure or in excessive doses.  
**Measures:** Injection of the local anesthetic should be done in low doses (about 0.2 ml). Injection pressure should not be too high.

**Self inflicted and accidental injuries**

Local anesthesia is always connected with the risk of injuries caused in the anesthetized area during the treatment, e.g. by rotating instruments. There is also the danger of the patient injuring his lower lip without noticing it – particularly if hot beverages are consumed while the anesthesia is still effective.  
**Measures:** Soft tissue has to be kept away from rotating instruments during dental treatment. The dentist has to inform the patient – especially children – before leaving the dental office not to consume hot beverages until the anesthesia has completely subsided.

**Local infection**

Every injection through the oral mucosa is connected with the risk of germs being carried deep into the tissue and causing infections there. However, normally this risk is low.  
**Measures:** When treating patients with limited physical resistance, a mucosal antiseptic should be applied before the injection.
**Undesired nerve block**

In case of an atypical course of a nerve or incorrect injection technique, the local anesthetic might become effective in the area of a nerve, which was not supposed to be anesthetized. This might also have an impact on motorical nerves, e.g. a high block anesthesia of the alveolaris inferioris nerve might result in a facial paresis.

*Measures:* The accepted techniques and procedures have to be followed closely.

**Systemic Adverse Effects**

Despite of the low systemic toxicity and the high level of safety, adverse effects related to local anesthetics cannot be completely excluded. Systemic effects can be related to one of the components of the solution. They become manifest as intoxication due to relative or absolute overdosage, hypersensitive reaction, or interaction with other pharmaceutical products. Allergic reactions to amide-type local anesthetics are observed very rarely.

Dental local anesthetics offer a relatively large therapeutic index, i.e. the occurring serum concentrations after application of therapeutic doses are significantly below the minimal toxic threshold. It may be stated that adverse effects are primarily caused by an inadvertent intravascular injection or administration into highly vascular sites as caused by an excessive dose (exceeding the max. dose). This is associated with an increasing blood level of local anesthetic agent and vasoconstrictor.

In connection with local anesthesia, frequently unspecific psychogenic reactions are observed, which in individual cases are hard to distinguish from a true intoxication caused by the local anesthetic.

**Possible Systemic Adverse Effects caused by Local Anesthetic Agents**

Local anesthetic substances have unspecific impacts on all nerve cells or neurons, and in high concentrations they may cause side effects beyond the actual site of action. The adverse drug reactions caused by local anesthetics agents essentially involve the central nervous system, because anesthetics easily pass from the peripheral circulation into the brain. In higher doses, also the cardiovascular system is affected.

The manifestation of toxic signs depends on the serum level of the local anesthetic agent. At serum levels below 5 mg/l – that means 500 mg of articaine, lidocaine, or mepivacaine administered – , local anesthetics for dental applications under normal conditions do not cause any toxic signs. Normally, this serum concentration is only reached in children, underweight patients, or in case of accidental intravascular injection.

Early signs of central nervous system intoxications are of excitatory nature and normally occur at serum concentrations of 5 to 10 mg/l, e.g. dizziness, anxiety, confusion, muscular twitching. At serum concentrations of 10 to 15 mg/l, symptoms of CNS intoxication are disorientation, tremor, respiratory depression and seizures, signs of CVS intoxication consist of a cardiovascular instability.

At serum levels of 15 to 20 mg/l, more severe signs of intoxication can be observed, e.g. convulsions, coma and respiratory arrest.

Serum concentrations exceeding 20 mg/l lead to death through respiratory depression and heart failure.

Application of the local anesthetic has to be discontinued immediately, as soon as first signs of intoxication are observed. Mild side effects normally do not require any therapeutic measures, as due to quick resorption and metabolization usually the symptoms only occur temporarily. In case of intoxications with continued symptoms, adequate measures are to be taken (see overdosage).
For treatments of longer durations, in most cases re-injections are necessary. Due to the risk of accumulation, in this case there is an increased risk of intoxication, which is primarily influenced by the speed of metabolism of the local anesthetic. In this context, with a plasma half life of 20 minutes, articaine offers a decisive advantage compared to other acidic amide-type local anesthetics (half lives ranging between 90 and 120 minutes). Thanks to the short elimination half life and the high plasma clearance of articaine, the risk of cumulation is considered very low.

**Possible Systemic Adverse Effects caused by Local Anesthetics**

![Graph showing possible systemic adverse effects caused by local anesthetics](Figure 53: Possible Systemic Adverse Effects caused by Local Anesthetic Agents (Ref.: 28))

**Possible Systemic Adverse Effects caused by Catecholamines**

Most dental local anesthetics contain epinephrine in concentrations between 1:50000 and 1:200000. In case of quick resorption or accidental intravascular injection, even low concentrations may cause side effects. Side effects caused by epinephrine mainly correspond to the pharmacological profile of catecholamines and are primarily due to their β-adrenergic effect. Depending on dose and distribution of specific receptors, catecholamines have different systemic impacts on individual organs and functions.

Adverse drug reactions of catecholamines essentially involve the cardiovascular system. Depending on the dose, catecholamines lead to an increased pulse frequency and cardiac contraction. Depending on the distribution of receptors, there is vascular dilation or contraction.

Side effects caused by epinephrine are especially pallor, anxiety, nervousness, tachycardia, arrhythmia, increased blood pressure, and headaches. Life-threatening side effects include hypertensive crisis, heart attack, cerebral hemorrhage, shock, and ventricular fibrillation.

Epinephrine threshold plasma concentrations for physiological change are in the range of 50 to 450 pg/ml. Adrenalin threshold concentrations for systemic side effects are indicated in the following figure.
Possible Allergic Reactions

Drug allergy may be defined as a specific type of hypersensitivity to a drug or chemical compound. True allergy requires the formation of an antibody to an antigenic substance.

True allergic reaction to amide-type local anesthetic agents are very rare. We have to distinguish between true hypersensitive reactions and pseudoallergic reactions. Pseudoallergic reactions do not show any antigen-antibody reaction, they should rather be considered a consequence of mast cell degranulation or activation of the complement system caused by a pharmaceutical product.

There are no differences between allergic reactions to local anesthetics or their ingredients and allergic reactions to other pharmaceuticals.

The reactions are classified into three severity codes:
• Slight reactions may manifest as cutaneous symptoms, such as reddening of skin, urticaria, pruritus, possibly also agitation and dizziness.
• Medium reactions may manifest as tachycardia and drop in blood pressure, possibly also nausea, vomiting and bellyache.
• The most serious reaction is anaphylactic shock, which may be fatal if untreated.
Management of Overdose

Overdose also belongs to systemic complications, and the dentist should be aware of emergency management.
Undesirable effects (showing an abnormally high concentration of local anesthetic in the blood) may appear either immediately, caused by accidental intravascular injection or abnormal absorption conditions, e.g. in inflamed or intensely vascularized tissue, or later, caused by true overdose following an injection of excessive quantity of anesthetic solution, and manifest themselves as central nervous and/or vascular symptoms.

Emergency management of adverse reactions to local anesthetics and vasoconstrictors depends on the presenting symptoms.
If the reaction is mild and transient, only observation, reassurance of the patient and discontinuation of the procedure are necessary.

With increasing severity of response, oxygen supplementation and support of respiration are vitally important, because inadequate ventilation increases the possibility of seizures and cardiovascular disturbance.
In case of pronounced intoxication, further measures may become necessary, e.g. intravenous fluids or intravenous anticonvulsants (for further information see Summary of Product Characteristics).

<table>
<thead>
<tr>
<th>Local Anesthetic Overdose</th>
<th>Epinephrine Overdose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stop Treatment</td>
<td>Stop Treatment</td>
</tr>
<tr>
<td>Lie Patient Flat</td>
<td>Place Patient Supine or Erect</td>
</tr>
<tr>
<td>Administer Oxygen</td>
<td>Administer Oxygen if not Hyperventilating</td>
</tr>
<tr>
<td>Give Intravenous Fluids</td>
<td>Reassure Patient</td>
</tr>
<tr>
<td>Give Intravenous Anticonvulsants</td>
<td></td>
</tr>
<tr>
<td>Basic Life Support</td>
<td></td>
</tr>
</tbody>
</table>

Table 11: Management of Overdose (Ref.: 24)

Failure of Anesthesia

In dentistry, local anesthesia may not be 100% successful, the reasons being

• anatomical, e.g. variations in the position of nerves and foramina, bone barriers to diffusion, collateral nerve supply
• pathological, e.g. trismus, inflammation
• pharmaceutical, e.g. improper storage may decrease efficacy
• pharmacological, e.g. interactions between certain drugs and local anesthetics
• psychological, e.g sedation should be considered to relax the patient
• technical, e.g. poor technique

Incidence of Adverse Effects

The reported incidence of complications related to dental local anesthesia varies between 0 and 30% – depending on the definition. Complications observed as pallor, unrest, sweating, palpitations and nausea are common manifestations of acute anxiety. The incidence of serious complications of articaine does not exceed 1 in 1 million injections, the mortality rate is about 1 in 100 million injections.
The incidence of serious adverse effects related to dental local anesthesia with articaine is very low even in comparison to analgetic drugs, which are commonly known as harmless. The incidence of serious adverse effects of paracetamol was calculated to be 2 in 1 million applications, of acetylsalicylic acid 16 in 1 million applications. The overall mortality of paracetamol was calculated to be 2 in 100 million applications and of acetylsalicylic acid 160 in 100 million applications.

![Incidence of Adverse Effects](image)

Figure 56: Incidence of Adverse Effects (Ref.: 6, 12, 20, 22, 28, 30, 31)

Interactions of Drugs

If several drugs are taken simultaneously, the efficacy may vary in terms of an increase or reduction. A modified efficacy may be due to different resorption conditions or interactions at the receptor. Interactions between drugs are usually undesirable.

When applying local anesthetics, the following interactions with other drugs should be considered:

The effects of epinephrine may be strengthened or weakened by numerous drugs, particularly by:
- digoxin, digitoxin,
- tricyclic antidepressives, MAO inhibitors,
- antiparkinson drugs, oral antidiabetics,
- non-cardio selective β-blockers,
- methyl dopa and guanethidine,
- certain inhalational anesthetics, such as halothane, may sensitize the heart to catecholamines and therefore induce arrhythmias,
- during treatment with blood coagulation inhibitors the hemorrhagic tendency is increased.

For selecting an appropriate local anesthetic, possible interactions with other drugs must be considered.

Contraindications and Precautions for Use

As the local anesthetics used today normally offer good compatibility, there are only few contraindications and limitations.
Local anesthetics are contraindicated in case of hypersensitivity to one of the components, serious intraventricular conduction defects (AV block), pronounced bradycardia and decompensated cardiac insufficiency, severe hypotension, as well as in patients known to suffer from limited plasma cholinesterase activity (only articaine), hemorrhagic diathesis or inflammation of the injection area.

Epinephrine as vasoconstrictor is contraindicated in case of heart diseases (e.g. instable angina pectoris, recent myocardial infarction, recent by-pass surgery on coronary arteries, refractory arrhythmia, paroxysmal tachycardia, highly frequent absolute arrhythmia, untreated or uncontrolled serious hypertension and decompensated cardiac insufficiency). The combination with MAO inhibitors and tricyclic antidepressives is contraindicated.
7.3 Physical and Physiological Evaluation of the Patient

Patient Evaluation

Before starting any dental therapy, the dentist must evaluate if the patient is able to tolerate the planned procedure physically and psychologically. Therefore, as a general standard of care, the patient has to complete a medical history questionnaire when first visiting the dental office. The information should be updated on a regular basis.

This history should inform the dentist of the following:
1. The patient’s cardiovascular status
2. Any respiratory difficulties
3. Any nervous system disorders
4. Any metabolic deficiencies
5. Any endocrine imbalances
6. The presence of allergies
7. Any hematological pathologies
8. Any iatrogenic conditions
9. Size, age and sex

An example of a medical history questionnaire is attached.

In case of severe ongoing disease, appropriate consultation is strongly recommended to help to estimate the patient's functional reserve and identify specific treatment limitations.

The dentist should depend on this evaluation to determine the following:
1. The patient's general physical and psychological condition
2. The need for a medical consultation
3. The history of any previous unpleasant anesthetic experience
4. The specific drug sensitivities of the patient
5. The need for premedication or intraoperative sedation
6. The time to be allotted for the procedure
7. The technique or method to be used
8. The choice of an anesthetic solution
9. The need and quantity of a vasoconstrictor

A major consideration in the preanesthetic evaluation is whether the patient has a sufficient physical and psychological condition to undergo the proposed procedure. The stress of injection coupled with a subsequent restorative or surgical procedure may occasionally precipitate serious complications in the severely compromised patient.

One of the simplest, most convenient, and most easily remembered methods of assessing the general physical state of a patient is through the classification scheme adopted by the American Society of Anesthesiologists (ASA). This system groups patients into five categories on the basis of overall health. As a general rule, individuals who are in class 1 or 2 can receive routine care, including the use of local anesthetics.

However, some limitations in either the complexity or duration of treatment rendered per appointment may be desirable with individuals in class 2. In addition, some form of anxiety control is often appropriate for patients who are apprehensive about intraoral injections or the proposed treatment. Class 3 patients may also receive local anesthetics, but procedural stress should be strictly limited. In most patients of class 3, the amount of work to be performed is limited. If necessary, vital signs should be monitored during the procedure. Class 4 patients should receive emergency care only under the confines of a hospital.

Special consideration of the evaluation before treatment enables the dentist to exactly determine the patient’s ability to tolerate the stress associated with the planned dental procedure.
**Risk Patient**

Despite the high safety of dental local anesthesia, some patients bear an increased risk of adverse effects: children and aging patients, pregnant women and patients suffering from general diseases. Anamnestic incidence of general diseases and risk factors in dental patients vary between 1 and over 20%.

**Aged Patient**

In contrast to young patients, most aged patients are characterized by reduced metabolism, multimorbidity, and reduced mental adaptability. When treating aged patients, please consider that special aging processes influence pharmacokinetics and -dynamics, and that aged patients frequently suffer from general diseases. With increasing age, the key elimination organs liver and kidney show a reduced performance. Therefore, metabolism and elimination of drugs may be reduced and delayed. Thus, cumulation of drugs may be possible if repeated injection is performed. In aging patients, local anesthetics with a fast metabolization should be used. Articaine is the only amide-type local anesthetic inactivated through unspecific esterases in plasma and tissue, which offering an activity largely independent of age. Therefore, the risk of delayed metabolization due to age is considered low. Furthermore it has to be considered that aging patients often take medications possibly interacting with local anesthetics or vasoconstrictors.

**Children**

Of particular interest in the selection of a local anesthetic and the amount to be administered is the patient's age and size. When administering these agents to children, one must reduce the amount injected according to the individual's size and/or age.

Since the individual dosage limit depends on the body weight, most true overdoses of local anesthetics in dentistry occur in young children. For example, the maximum dose of articaine for a child of 10 kg is calculated to be 70 mg, which is equivalent to one cartridge. To avoid adverse reactions in children, the maximum dose must not be exceeded. Please also consider that – if applied – the dose of the topical anesthetic has to be added to the injected dose. For children, a local anesthetic agent with high anesthetic potency and low systemic toxicity must be used. Articaine offers a favorable potency/toxicity ratio.

As in most cases, children are afraid of the pending injection, they should be informed appropriately about the pain to be expected. The anesthetic solution has to be applied slowly, and the dentist should be prepared for possible defense reactions pain causes in children.

**Pregnant Women**

Although certain drugs administered during pregnancy may be potentially hazardous to the fetus, clinical experience suggests that the risk in using local anesthetics during pregnancy is to be considered low.

Local anesthetic drugs appear to pass the placenta by passive diffusion and enter the fetal blood stream. However, the rate and degree of diffusion vary considerably between specific agents and appear to be inversely correlated to the degree of plasma-protein-binding. Prilocaine shows the highest umbilical vein/maternal blood ratio (1.00 – 1.08) and lowest plasma-protein-binding capacity (55%). On the other hand, the UVM ratio of articaine is about 0.3 and this agent is approximately 94% protein-bound. Lidocaine and Mepivacaine occupy an intermediate position both in terms of placental transmission (UVM ratio 0.52 – 0.71) and protein-binding (64 – 77%). Fetal plasma-protein binding of local anesthetic agents is approximately 50% less than in maternal blood, so that more unbound drug is present in the fetus.
Systemic toxicity of local anesthetics is inversely correlated to the protein binding and the elimination half time of the agent. Articaine has a high protein binding rate and a fast metabolization in comparison to other local anesthetics. In pregnant women, epinephrine may induce abortion in higher doses – especially in the first trimester. Thus, concentration of epinephrine added to the local anesthetics should be as low as possible.

**Medically compromised Patients**

The selection of a local anesthetic for intraoral injection must include considerations of efficacy, safety, and individual patient and operative needs. The risk of adverse effects related to local anesthetics and vasoconstrictors may be increased in patients suffering from general diseases.

**Cardiovascular Disorders**

Epinephrine may cause adverse effects in patients with various diseases:
- In patients suffering from heart failure, epinephrine may cause acute decompensation of heart failure.
- With coronary heart disease, there is an increased risk of angina pectoris attack, myocardial infarction.
- With hypertension, angina pectoris attack, myocardial infarction, or stroke may occur.
- An increased risk of heart failure or ventricular fibrillation exists in patients with cardiac arrhythmias.
- Stroke may occur in patients suffering from cerebrovascular disorders.

In patients suffering from severe cardiovascular diseases, epinephrine should be avoided or administered in low doses. Thus, for patients suffering from severe cardiovascular disorders, local anesthetics with an epinephrine concentration of 1/200000 seem to be preferable.

In patients suffering from cardiovascular disorders, articaine should be used only after careful consideration of the benefit-risk-ratio. These patients may show a reduced ability to balance the functional changes in connection with the prolongation of the AV conduction caused by articaine.

**Convulsive Disorders**

Convulsive disorders are characterized by a loss of consciousness, involuntary muscle movements, and disturbances of the autonomic nervous system. Epileptic, grand mal and petit mal, disorders are phenomena due to a variety of causes and occurring at indefinite times. However, a good history should inform the dentist of the type of seizure and frequency of occurrence. Convulsive disorders should always be of concern to the dentist since they may alter the selection of drugs and the pain control methods used.

In patients suffering from convulsive disorders, convulsibility may be increased by local anesthetics, depending on the dose administered. In those patients, local anesthetics should only be applied in low doses and a single injection. If a higher dose is required, it should be administered by fractioned injection. In this case, the local anesthetic should posses a high protein binding rate and a fast metabolization, e.g. articaine.
Hepatic Disorders

Amide type local anesthetics are largely degraded in the liver, and interruption of their metabolism in case of pronounced liver disease may permit toxic amounts of the drug to accumulate in the systemic circulation. In contrast to other amide-type local anesthetics, articaine is hydrolyzed mainly by non specific cholin-esterases in the tissues and in the blood serum. A minor part is metabolised in the liver.

Due to this special pathway of metabolization, articaine may be used in patients suffering from hepatic disorders as the risk of accumulation can be considered lower. Nevertheless, articaine must be used with particular caution in the event of severe impairment of the hepatic function.

Diabetic Disorders

Diabetes is a common condition affecting about 2% of the population. It is caused by a disorder of carbohydrate metabolism resulting from insulin deficiency or ineffectiveness. Most diabetic patients know of their condition and thus will give the information on the history. The most important information concerns the severity of the diabetes. Patients controlling their diabetes strictly by diet should not present any problems to the dentist. The choice of a local anesthetic will be of less importance than the amount of vasoconstrictor used. The vasoconstrictor should be kept at a minimum because of related cardiovascular conditions.

However, if the patient requires large doses of insulin daily, the possibility of diabetic coma or insulin shock should be considered.

In patients with diabetes disorders, the concentration of epinephrine in local anesthetics should not exceed 1/200000.

Literature 7. Clinical Aspects

1) Arzneimittelkommission der Deutschen Ärzteschaft (Drug Commission of the German Medical Association), 1985
2) Arzneimittelkommission der Deutschen Ärzteschaft (Drug Commission of the German Medical Association), 1985
3) Brandt B, 1997
4) Daubländor M et al, 1997
5) 3M ESPE. Ubistesin 1/200000 Solution for injection/Ubistesin 1/100000 Solution for injection, Summary of Product Characteristics
6) 3M ESPE. Ubistesin 1/200000 Solution for injection/Ubistesin 1/100000 Solution for injection, Summary of Product Characteristics
7) Ihl-Beste W, 1998
8) Langmann MJS et al, 1993
9) Lipp M, 1992
10) Meecham JG, 2002
11) Malamed SF, 2004
12) Malamed SF, 2004
13) Rahn R, 2000
14) Rahn R, 2000
15) Rahn R, 2001
8. 3M ESPE Products

Even using local anesthetics with articaine and epinephrine as active substance there are some differences between the products of different manufacturers. 3M ESPE is synthesizing its own articaine and has experience with the production of this pharmaceutical products over more than 50 years.

Special Safety Aspects of Ubistesin

There is a well designed packaging system for all 3M ESPE’s Local Anesthetics.

Cartridge

3M ESPE manufactures all its local anesthetics cartridges with a very thin silicon layer on the inner side of the cartridge.

The production process: After unpacking, the cartridges are first washed in order to get rid of any potential glass splinters or particles. Siliconisation of the inner side is done by spraying an aqueous silicone oil emulsion into the empty carpule. This substantially eases the gliding of the stopper. The siliconized cartridges are then transported into a hot air tunnel where the silicone film is fixed onto the inner side of the carpule through high temperature. After passing the hot air tunnel, the cylinders are filled with the anesthetic solution under laminar flow conditions.

The silicone coated inner side of the cylindrical glass ampoules enables a gentle, smooth injection. Out of this, the reduced injection force onto the plunger enables a soft gliding of the plunger and thus makes the application easier for the patient and the doctor.
Packaging

Security Foil

Most of the manufacturers print all required information regarding the local anesthetics onto the glass of the carpule with an etching technique.

3M ESPE is one of the few manufacturers which uses a security foil for labeling. Similar to laminated glass used in car windshields, a safety foil protects the cartridge from splintering. If unvisable tiny cracks occur in the carpule and if in addition high pressure is applied, e.g. in intraligamentry injection and the carpule bursts the security foil will hold possible splinters together.

![Figure 59: 3M ESPE Cartridges with Security Foil](image1)

![Figure 60: Cartidges without Security Foil](image2)

Metall Tin

Safety is very important for 3M ESPE. Therefore, 3M ESPE packs its local anesthetics cartridges in tins to help to avoid any damage during the supply chain of its product.

The example shows an orginal tin after a transport accident. NOT a single cartridge was broken due to the metal tin.

![Figure 61: Damaged Tin unbroken, ALL Cartridges remained](image3)

However, protection against damage is not the only advantage of the metal tin: The tin also provides the dentist in its daily work in order to store 3M ESPE local anesthetics.
**Ubistesin™ 1/200000 (Ubistesin)**

For routine-type interventions

- Contains 4% articaine with epinephrine 1/200000 as a vasoconstrictor
- Contains only sulfite as a stabilizer (max 0.31 mg)
- Suitable for adults and children over the age of 4 years
- Average duration of action: 45 minutes pulpal anesthesia and 120 – 240 minutes soft tissue anesthesia; onset period of 1–3 minutes
- Recommended maximum dose: 7 mg/kg body weight (500 mg for a 70 kg patient) for healthy adults, which is equivalent to 12.5 ml of Ubistesin™ 1/200000 (7 cartridges)
- For more details please refer to the instructions for use

---

**Ubistesin™ 1/100000 (Ubistesin forte)**

For more complex interventions requiring prolonged anesthesia

- Contains 4% articaine with epinephrine 1/100000 as a vasoconstrictor
- Contains only sulfite as a stabilizer (max 0.31 mg)
- Suitable for adults and children over the age of 4 years
- Average duration of action: 75 minutes pulpal anesthesia and 120 – 240 minutes soft tissue anesthesia; onset period of 1–3 minutes
- Recommended maximum dose: 7 mg/kg body weight (500 mg for a 70 kg patient) for healthy adults, which is equivalent to 12.5 ml of Ubistesin™ 1/100000 (7 cartridges)
- For more details please refer to the instructions for use
Mepivastesin™

For simple, routine-type interventions in risk patients

- Contains 3% mepivacaine
- Contains no sulfite as stabilizer and no epinephrine as vasoconstrictor; thus it is particularly suited for patients where the use of sulfite or epinephrine is contraindicated
- Suitable for adults and children
- Average duration of action: 20 – 40 minutes pulpal anesthesia and 45 – 90 minutes soft tissue anesthesia; onset period of 1–3 minutes
- Recommended maximum dose: 4 mg/kg body weight (300 mg for a 70 kg patient) for healthy adults, which is equivalent to 10 ml of Mepivastesin™ (5.5 cartridges)
- For more details please refer to the instructions for use

Xylestesin™- A

For routine-type interventions

- Contains 2% lidocaine with epinephrine 1/80000 as a vasoconstrictor
- Contains only sulfite as a stabilizer (max 0.31 mg)
- Suitable for adults and children
- Average duration of action: 30 – 60 minutes pulpal anesthesia and 120 – 180 minutes soft tissue anesthesia; onset period of 1–3 minutes
- Recommended maximum dose: 7 mg/kg body weight (500 mg for a 70 kg patient) for healthy adults; due to the addition of epinephrine 1/80000 the maximum dose of 20 ml of Xylestesin™- A (11.5 cartridges) must not be exceeded.
- For more details please refer to the instructions for use
Pluraject™ 2

• Aspiration Syringe for 1.8 ml cylindrical glass ampoules with perforated stoppers
• For use with dental injection needles with metric and inch thread
• Manual aspiration (active) and self-aspiration (passive) possible
• Lightweight and compact for better handling
• Easy loading and unloading of ampoules thanks to flip mechanism
## 3M ESPE Local Anesthetics
### Summary of Product Characteristics

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Solution for Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Usbiesin</em> 1/100 000</td>
<td>40 mg/ml + 10 micrograms/ml</td>
</tr>
<tr>
<td><em>Usbiesin</em> 1/200 000</td>
<td>40 mg/ml + 5 micrograms/ml</td>
</tr>
<tr>
<td><em>Usbiesin</em> 1/400 000</td>
<td>40 mg/ml + 2.5 micrograms/ml</td>
</tr>
</tbody>
</table>

### Undesirable effects

**Due to articaine, the following adverse effects can occur**

- **Cardiovascular disorders**
  - Decrease in heart rate, hypotension.
  - Drop in blood pressure, cardiac impulse conduction disorders, bradycardia, asystolia, cardiovascular arrest.

**Due to epinephrine, the following undesirable effects can occur**

- **Cardiovascular disorders**
  - Tachypnea, then bradypnea, which could lead to apnoea.

**Allergic reactions**

- **Very rare (< 1/10,000)**
  - One may observe manifestation of hypersensitivity to articaine as rash, pruritus edema, pruritus, and erythema as well as nausea, diarrhea, wheezing or anaphylaxis.

**Respiratory, thoracic and mediastinal disorders**

- **Very rare (< 1/10,000)**
  - Tachypnea, then bradypnea, which could lead to apnoea.

- **Very rare (< 1/10,000)**
  - One may observe manifestation of hypersensitivity to articaine as rash, pruritus edema, pruritus, and erythema as well as nausea, diarrhea, wheezing or anaphylaxis.

**Nervous system disorders**

- **Very rare (< 1/10,000)**
  - Heat sensation, sweating, tremor, muscle twitching, tonic-clonic seizures, coma and respiratory paralysis.

**Cardiovascular disorders**

- **Very rare (< 1/10,000)**
  - Heat sensation, sweating, tremor, muscle twitching, tonic-clonic seizures, coma and respiratory paralysis.

**Due to epinephrine, the following undesirable effects can occur**

- **Cardiovascular disorders**
  - *Rare (1/10,000 to < 1/1,000)*
  - *Very rare (< 1/10,000)*
  - *Rare (< 1/10,000 to < 1/1,000)*

**Due to sulphite, the following undesirable effects can occur in very rare cases**

- **Allergic reactions or hypersensitivity reactions, particularly in bronchial asthmatics, which are manifested as vomiting, diarrhoea, wheezing, acute asthma attack, clouding of consciousness or shock.**

### Contraindications

- **Usbiesin must not be used in**
  - children under 4 years of age (< 20 kg)
  - patients with a history of hypersensitivity to the active substances, sodium sulphite (E221) or to any of the other excipients,
  - patients with haemorrhagic diatheses – increased bleeding risk particularly with nerve block anaesthesia
  - **Due to articaine, Usbiesin must not be used in the event of:**
    - known allergy or hypersensitivity to local anaesthetics of the amide type
    - patients who are known to have a deficiency in plasma cholinesterase activity, also drug-induced forms,
    - severe, untreated or uncontrolled excitation and conduction disorders of the heart (e.g. grade II and III AV block, pronounced bradycardia),
    - acutely decompensated heart failure,
    - severe hypotension,
    - injection into an inflamed area because of treatment failure due to reduced penetration of articaine into the inflamed area.

**Due to epinephrine, Usbiesin must not be used in the event of:**

- **Heart diseases such as:**
  - unstable angina pectoris
  - recent myocardial infarction
  - recent coronary artery bypass surgery
  - refractory arrhythmias and paroxysmal tachycardia or high-frequency, continuous arrhythmia
  - untreated or uncontrolled severe hypertension
  - untreated or uncontrolled congestive heart failure
  - concomitant treatment with monoamine oxidase (MAO) inhibitors or tricyclic antidepressants
  - Usbiesin is not allowed to be used in acra of extremities.

**Due to sulphite, Usbiesin must not be used in the event of:**

- **Allergy or hypersensitivity to sulphite,
  - severe bronchial asthma.

Usbiesin can provoke acute allergic reactions with anaphylactic symptoms (e.g. bronchoospasm).

### Therapeutic indications

**Usbiesin 1/100 000**

- Local anaesthesia (infiltration and nerve-block anaesthesia) in dentistry.
- *Usbiesin 1/100 000* is especially indicated for complicated procedures requiring prolonged anaesthesia.

**Usbiesin 1/200 000**

- Local anaesthesia (infiltration and nerve-block anaesthesia) in dentistry during minor procedures.

**Usbiesin 1/400 000**

- *Usbiesin 1/400 000* is a solution for injection exclusively used in dentistry for infiltration and nerve-block anaesthesia during routine procedures with a duration up to 30 min, such as uncomplicated extractions and cavity and crown stump preparations.

**Usbiesin is indicated in adults and children over 4 years**

### Composition

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Solution for Injection Contains:</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Usbiesin</em> 1/100 000</td>
<td>Active substances: Articaine hydrochloride 40 mg + Epinephrine (Adrenaline) 10 micrograms (as hydrochloride)</td>
</tr>
<tr>
<td><em>Usbiesin</em> 1/200 000</td>
<td>Active substances: Articaine hydrochloride 40 mg + Epinephrine (Adrenaline) 5 micrograms (as hydrochloride)</td>
</tr>
<tr>
<td><em>Usbiesin</em> 1/400 000</td>
<td>Active substances: Articaine hydrochloride 40 mg + Epinephrine (Adrenaline) 2.5 micrograms (as hydrochloride)</td>
</tr>
</tbody>
</table>

**Excipients:**

- Sodium chloride
- Water for injections
- Hydrochloric acid 14%
- Sodium sulphite (E 221) 0.6 mg
- Sodium hydroxide solution 9% for adjusting the pH-value

### Preparation

**3M ESPE Local Anesthetics**

41453 Neuss, Germany

3M Deutschland GmbH
Carl-Schurz-Straße 1
41453 Neuss, Germany

Januar 2012

Information shortened. For further details please refer to the Instructions for Use.

Date of revision of the text: Usbiesin 1/100 000, 1/200 000, 1/400 000 Januar 2012

3M Deutschland GmbH
Carl-Schurz-Straße 1
41453 Neuss, Germany
3M ESPE Local Anesthetics
Summary of Product Characteristics

MEPIVASTE SIN™
Active ingredient: Mepivacaine hydrochloride

Composition
1 ml solution for injection contains:
Active substance:
Mepivacaine hydrochloride 30 mg
Excipients:
Sodium chloride, water for injections

Therapeutic indications
Infiltration anaesthesia and nerve-block in dentistry
MEPIVASTE SIN is indicated for simple extractions as well as cavity and stump preparations
MEPIVASTE SIN is especially suitable for patients to whom vasoconstricting additives are contraindicated

Contraindications
MEPIVASTE SIN is not allowed to be used in:
– children below 4 years of age (approx. 20 kg body weight)
Due to mepivacaine, MEPIVASTE SIN is not allowed to be used in the event of:
– known allergy or hypersensitivity to local anaesthetics of the amide type
– severe impairment of the nervous impulses and conduction system of the heart (e.g. grade II and III AV block, pronounced bradycardia)
– acutely decompensated cardiac insufficiency
– severe hypotension

Pregnancy and lactation
Pregnancy
There are no clinical studies regarding the application of mepivacaine hydrochloride during pregnancy. Animal studies have not provided adequate insights in view of possible effects of mepivacaine hydrochloride on pregnancy, embryofetal development, childhood and postnatal development
Mepivacaine hydrochloride passes the placental barrier and reaches the unborn child
As compared to other local anaesthetics, when using mepivacaine during the first trimester of pregnancy an increased risk of malformations cannot be excluded; during early pregnancy mepivacaine should only be used, if no other local anaesthetics are available

Lactation
It is unknown in which doses mepivacaine hydrochloride reaches the breast milk. If its application is necessary during lactation, breastfeeding may be resumed after about 24 hours

Undesirable effects
Due to mepivacaine, the following side effects can occur from the use of MEPIVASTE SIN:
Milder central nervous symptoms involve metallic taste, tinnitus, dizziness, nausea, vomiting, restlessness, anxiety, initial increase in respiratory rate
More severe symptoms are dizziness, confusion, tremor, muscle twitching, tonicospastic spasms, coma and respiratory paralysis
Severe cardiovascular episodes are seen in the form of a drop in blood pressure, asauecence, bradycardia, cardiovascular arrest

Allergic reactions to mepivacaine are extremely rare

PRESCRIPTION
Information shortened. For further details please refer to the instructions for use

Date of revision of the text:
January 2012

XYLESTESIN™-A

Composition
1 ml solution for injection contains:
Active substance:
Lidocaine hydrochloride 20 mg
(R)-Epinephrine hydrochloride 0.015 mg
equivalent to 0.0125 mg base
Excipients:
Sodium sulphite max. 0.6 mg
(R)-Epinephrine hydrochloride 0.015 mg
Sodium chloride, Water for injections

Therapeutic indications
Infiltration anaesthesia and nerve-block in dentistry

Contraindications
Due to lidocaine, XYLESTESIN-A cannot be used in the event of:
– known allergy or hypersensitivity to local anaesthetics of the amide type
– severe impairment of the nervous impulses and conduction system of the heart (e.g. grade II and III AV block, pronounced bradycardia)
– acutely decompensated cardiac insufficiency (acute cardiac output)
– severe hypotension (very low blood pressure)

Due to epinephrine, XYLESTESIN-A also cannot be used in the event of:
– pteroylglutamic acid or hyperglycaemia, continuous arrhythmia
– pronounced coronary insufficiency
– severe hypertension (high blood pressure)
– thyrotoxicosis (hyperactivity of the thyroid)
– narrow-angle glaucoma
– decompensated diabetic metabolic condition
– phaeochromocytoma
– concurrent treatment, or treatment during the past 14 days, with tricyclic antidepressants or monamine oxidase (MAO) inhibitors

WARNING:
XYLESTESIN-A must not be used in persons who are allergic or hypersensitive to sulphite, as well as in persons with severe bronchial asthma. In these persons, XYLESTESIN-A can provoke acute allergic reactions with anaphylactic symptoms (e.g. bronchospasm)

Undesirable effects
Due to lidocaine, the following side effects can occur from the use of XYLESTESIN-A:
Milder central nervous symptoms involve metallic taste, tinnitus, dizziness, nausea, vomiting, restlessness, anxiety, initial increase in respiratory rate
More severe symptoms are dizziness, confusion, tremor, muscle twitching, tonicospastic spasms, coma and respiratory paralysis
Severe cardiovascular episodes are seen in the form of a drop in blood pressure, asauecence, bradycardia, cardiovascular arrest

Allergic reactions to lidocaine are most rare

Undesirable effects which can occur due to epinephrine:
Severe cardiovascular episodes are seen in the form of a drop in blood pressure, asauecence, bradycardia, cardiovascular arrest

SPECIAL WARNINGS:
Due to the content of anhydrous sodium sulphite, allergic reactions or hypersensitivity reactions can ensue in isolated cases, particularly in bronchial asthmatics, which are manifested as vomiting, diarrhoea, wheezing, acute asthma attack, clouding of consciousness or shock

PRESCRIPTION
Information shortened. For further details please refer to the instructions for use

Date of revision of the text:
January 2012
Dear patient,

Please answer the following questions regarding your general medical history (anamnesis) in order to enable us to select the appropriate drugs and therapies for your treatment. The provided information will be treated confidentially. Please do not hesitate to ask me any questions you may have.

Patient’s Name and Address: __________________________________________________________________________________________________________________________________________

Patient’s Birthday: ___________________________________________________________________________________________________________________________________________

Patient’s Insurance: _________________________________________________________________________________________________________________________________________________

Doctor’s Name and Address: __________________________________________________________________________________________________________________________________________

Date/Signature: ___________________________________________________________________________________________________________________________________________________

Do you suffer or have you suffered under one of the following diseases? Yes No

<table>
<thead>
<tr>
<th>Disease</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Allergies (which)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Seizure Disorder (epilepsy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Respiratory Diseases (which)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Blood Coagulation Problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Diabetes (which type)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Glaucoma (increased eye pressure)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 Hematological Diseases (diseases of blood-producing organs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 Cardiovascular Diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.1 Cardiac Insufficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.2 Coronary Heart Disease/Angina Pectoris</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.3 Heart Attack</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.4 Cardiac Arrhythmia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.5 Cardiac Pacemaker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.6 Valvular Defect/Replacement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.7 Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.8 Hypotension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.9 Anemia of CNS/Apoplexus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 Infectious Diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.1 Hepatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.2 Acquired Immune Deficiency Syndrome (AIDS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 Hepatic Diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 Gastro-Intestinal Diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Renal Diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.1 Chronic Renal Insufficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.2 Dialysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 Osteoporosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 Rheumatoid Arthritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 Thyroid Diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 Tumors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17 Previous Surgery? (which)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 Are you afraid of the treatment?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19 Are you pregnant?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 Do you take medications? (which)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
9. References

1) Arzneimittelkommission der Deutschen Ärzteschaft: Lokalanästhetika, Dtsch Ärztebl, 82, 100, 1985
8) 3M ESPE Ubistesin® 1/200000 Injektionslösung/3M ESPE Ubistesin® 1/100000 Injektionslösung: kombinierte Gebrauchsanweisung und Fachinformation, 2005
18) Knoll-Köhler E.: Sicherheit bei der Lokalanästhesie I: Pharmakologie lokalanästhetische Substanzen; Phillip J 1, 33, 1988
20) Langmann MJS. et al: Risks of bleeding peptic ulcer associated with individual non-steroid anti-inflammatory drugs; Gastroenter, 105, 1078, 1993
26) Pilz G.: Klinische Vergleichsstudie zur Wirkung von Articain und Lido-cain; In Frenkel G
27) Oertel R. et al: Clinical Pharmacokinetics of Articain ; Clin Pharm 33, 6, 1997
ZWR 103 Jahrg., Nr. 12, 1994
Zahnärztliche Welt, 109, 677, 2000
Oralchr J, 1,33, 2001
32) Spiegelberg F.: Untersuchung der Serum-Konzentration von Articain und Lido-cain bei
submuköser Injektion bei älteren Patienten. Med Diss Frankfurt 2001
33) Strasser K. et al: Placenta-Passage von Carticain (Ultracain®), einem neuen Lokal-
34) Strichartz GR.: Local Anesthetics, Springer Verlag Berlin Heidelberg, 1987
35) USP DI.: Anesthetics (Parenteral-Local). The United States Pharmacopeial Convention I,
editor. USP DI® Drug Information for the Health Care Professional. 24rd Ed., Taunton
(US), Micromedex, 2004
36) Van Oss G. et al: Clinical effects and pharmacokinetics of articaine acid in one volunteer
after intravenous administration; Pharm Weekbl [Sci] 10 (6) 284, 1988
37) Vogt M.: Verträglichkeit von niedrigdosiertem Articain und Lido-cain bei intravenöser
Applikation; Med Diss Frankfurt, 1994
38) Vogt R.: Pharmacokinetik von Articain (Ultracain) mit und ohne Adrenalinzusatz 1:200000
bei intraoral Lokalanästhesie; Med.Diss. Frankfurt, 1993