Dirección: Cra. 53 N° 50-09
Guarne (Antioquia) COLOMBIA.
Teléfono: (574) 550 00 00
Fax: (574) 551 31 34

TECHNICAL DATA SHEET: ODONTOCAINA® 3%
PRFTPT-012

1 GENERAL PRODUCT INFORMATION

Anesthetic Injectable Solutions for Dental Use: MEPIVACAINE Odontocaina® 3% is an anesthetic solution for injection (subcutaneous small volume) for dental use, indicated to produce local anesthesia, applied the techniques by infiltration or nerve block. This product should be used by personnel with professional certification, trained to perform dental procedures.

1.1 Commercial Name and International Nonproprietary Name (INN)

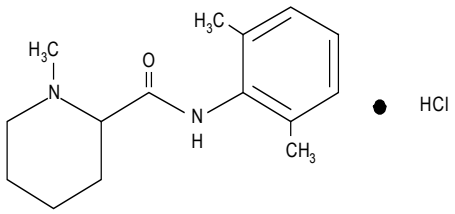
Odontocaína® 3%

2-piperidincarboxamide.
(□)- N-(2,6-dimethylphenil)-1-methyl-monohydrochloride
(□)– 1-methyl-2', 6'-pipecoloxylidide monohydrochloride.

1.2 Molecular Formula, Structural Formula, and/or Empiric Formula of Active Ingredient:

Molecular Formula: $C_{15}H_{22}N_2O$ □ HCl
Molecular Mass: 282.81 g/mol.
Structural Formula:

MEPIVACAINE



2 INFORMATION ABOUT COMPOSITION ELEMENTS

Each dental Cartridge of 1.8 ml.-contains:
Mepivacaine Hydrochloride: 0.054 g
Excipients q.s. a.d.: 1.8 ml

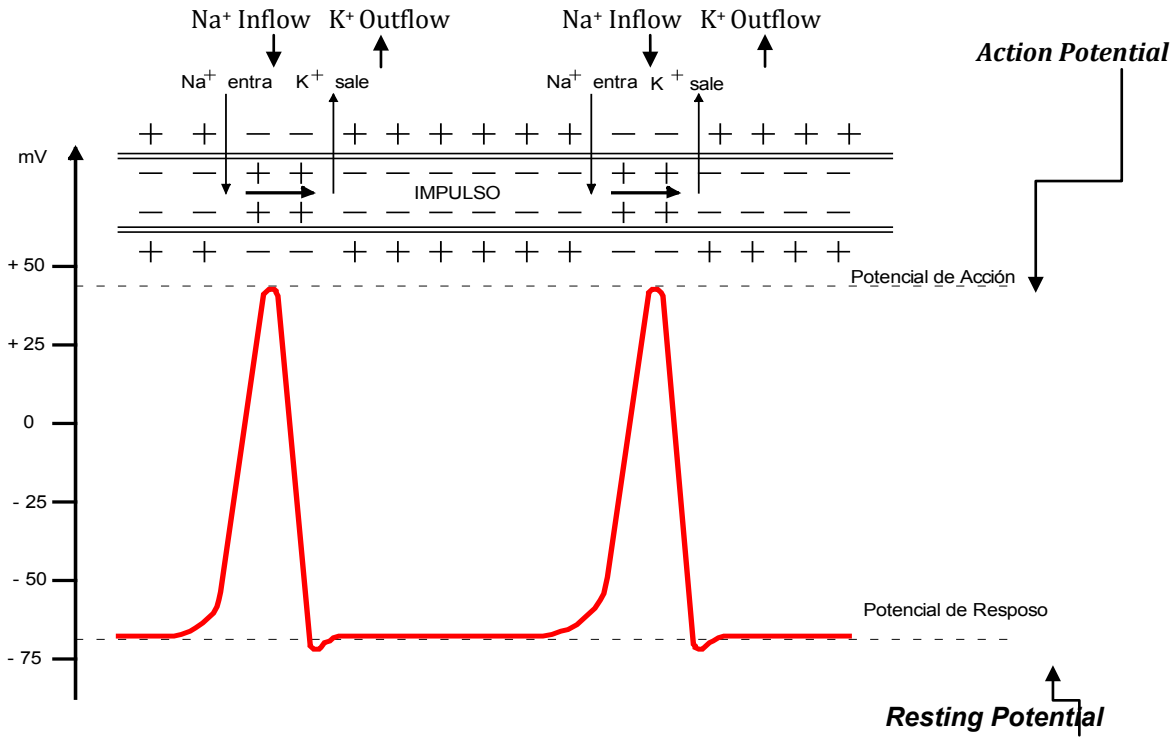
Dirección: Cra. 53 N° 50-09
Guarne (Antioquia) COLOMBIA.
Teléfono: (574) 550 00 00
Fax: (574) 551 31 34

3 PROPERTIES OF THIS PRODUCT

Mepivacaine, a tertiary amino amide-type local anesthetic, appeared for the first time in 1957. It has a medium duration of action and its pharmacological properties are similar to those of Lidocaine. This local anesthetic stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of nerve impulses. (**See Figure nº 1**).

Its onset action is very similar to that of Lidocaine but its duration is a little bit longer (20%) than that of Lidocaine in absence of a vasoconstrictor agent associated with it. Mepivacaine has a slight vasoconstriction action and has no efficacy as a topical anesthetic. In local infiltration, Mepivacaine has no vasodilatation action. High plasma concentrations produced in paracervical blockade lead to uterine vasoconstriction and diminish the blood flow in the uterus. Children and elderly persons tend to be more sensitive to effects of Mepivacaine.

Figure N° 1
Changes in polarity and action potential in the Conduction of impulses by a nervous fiber



Dirección: Cra. 53 N° 50-09
Guarne (Antioquia) COLOMBIA.
Teléfono: (574) 550 00 00
Fax: (574) 551 31 34

3.1 METABOLISM

The amide structure of Mepivacaine is not catabolyzed by plasmatic stearases. This condition makes its metabolism much more restricted and slower than that of ester-type local anesthetics. Its metabolism is mainly hepatic through N-dealkylation and subsequent hydrolysis by amidases microsomal enzymes.

More than 50% of the injected dose of Mepivacaine is metabolized by the bile in the form of metabolites. The most part of metabolized Mepivacaine will probably be reabsorbed by the intestine and excreted later on with urine, because only a very small percentage of this substance has been found in the feces. The kidneys constitute the main excretion route. The most part of this anesthetic and its metabolites are eliminated in approximately 30 hours

More than 16% of the injected dose of Mepivacaine is excreted without change with urine.

It has been observed that hydroxylation and N-desmethylation, two disintoxication reactions, play important roles in the metabolism of this anesthetic. The metabolites of Mepivacaine that have been identified in human adults are: two phenols that are almost exclusively excreted in their glucoronide conjugates, and one N-desmethylated compound (2' 6' – pipecoloxylidide)

4 USES AND APPLICATIONS

Mepivacaine 3% is a local anesthetic used in dentistry to be applied through infiltration or nerve block techniques. This local anesthetic could be the right choice for asthmathic patients as well as in those cases in which the use of a local anesthetic associated to a vasoconstrictor is contra-indicated.

4.1 WARNINGS

Dental professionals who work with local anesthetics must have a deep knowledge of diagnostic methods and the way they can manage local anesthetic emergencies that may happen in the dental office. Facilities for resuscitation, oxygen, and other resuscitation drugs should be available for immediate use when administering local anesthetics.

This anesthetic must not be injected directly into the blood stream.

Slow injection: Excessive pressure during an injection may cause local irritation and postoperative pain. A very rapid injection may also cause necrosis of palate tissues due to the firmness of the ligament on the bone.

To reduce to a minimum the risk of intravascular injections, an aspiration must be made before the injection of the anesthetic solution. If the aspiration contains blood, the needle must be placed on another site where no aspirated blood appears. It must be noted, however, that the absence of blood in the syringe does not guarantee the success of an intravascular injection. This is why a double aspiration is always recommended.

The use of local anesthetics should be avoided if the injection site coincides with an inflamed or abscessed area.

Intravascular injections of small doses of local anesthetics into the head and neck area may produce systemic adverse reactions similar to those observed in cases of inadvertent intravascular injections in higher doses.

In patients with acidosis or hypoxia, the risk and severity of toxic reactions may be increased. Such reactions involve the Nervous Central System (CNS) and the Cardiovascular System. Local anesthetics must be administered with caution in patients suffering from anemia, severe cardiovascular diseases or circulatory dysfunctions of any kind.

4.2 WARNINGS AND CONTRA-INDICATIONS

The safety and efficacy of mepivacaine depend mainly on the following aspects: an appropriate dose, a correct technique, adequate precautionary measures, and emergency procedures.

Facilities for resuscitation, oxygen, and other resuscitation drugs should be available for immediate use.

The dentist should use the lowest possible dose that results in adequate anesthesia, in order to avoid high plasma levels and serious adverse effects.

Dirección: Cra. 53 N° 50-09
Guarne (Antioquia) COLOMBIA.
Teléfono: (574) 550 00 00
Fax: (574) 551 31 34

The administration of repeated doses of mepivacaine may cause significant increase of concentrations of this substance in the blood stream, due to the slow accumulation of this drug and its metabolites. Tolerance to high

concentration levels in the blood plasma can vary from one patient to another. Feeble, elderly, and pediatric patients, as well as patients with acute sickness must be given reduced doses, according to their age and physical condition (See *Dosage and Administration Techniques*).

After each injection of a local anesthetic, the patient's cardiovascular and respiratory functions should be monitored (adequate ventilation) as well as his/her vital signs and consciousness. Symptoms like restlessness, anxiety, tinnitus, dyspnea, blurred vision, tremors, depression or drowsiness must constitute an alert to the dental professional about the possibility of toxicity at the level of the Central Nervous System. The signs and symptoms of depression of the cardio- vascular function are commonly the result of a vasovagal reaction, in particular, if the patient is in upright position. If this situation appears, it is advisable to place the patient in an inclined position (See *Adverse Effects on the Cardiovascular System*).

The depuration of mepivacaine is reduced with the administration of beta-blockers and cimetidine. High concentration levels in the blood plasma may lead to convulsions and cardio-respiratory depression. Benzodiazepines, barbiturates, and volatile anesthetics increase the convulsive threshold. The duration of the anesthetic effect is prolonged with the addition of epinephrine to mepivacaine as well as with alpha 2-agonists (Chlonidine). The alkalization decreases the latency period and increases the anesthetic power. Contrary to ester-type anesthetics, amide-type anesthetics rarely cause allergic reactions.

Mepivacaine 3% should be avoided in spinal anesthesia and in obstetrical anesthesia. The use of this substance to produce paracervical block may lead to bradycardia and fetal acidosis. Special precautions must be taken with patients suffering from dysrhythmias and cardiac blocks. The appearance of toxic levels in the blood plasma may lead to cardiovascular collapse and convulsions, with symptoms characterized by tongue and perioral numbness, metallic taste, restlessness, tinnitus and body tremor.

Circulatory support includes: intravenous solutions (vasopressor agents, intravenous $NaHC0_3$ at 1-2 mEq/kg, intravenous bretilium at 5 mg/kg, electrical cardioversion or defribillation of cardiac dysrhythmias if necessary), and ensure patent airways.

Dirección: Cra. 53 N° 50-09
Guarne (Antioquia) COLOMBIA.
Teléfono: (574) 550 00 00
Fax: (574) 551 31 34

Convulsions can be managed with the following drugs: Sodium Thiopental (1-2 mg/kg, intravenous), Midazolam (20-40 mcg/kg, intravenous) or Diazepam (0.1 mg/kg, intravenous).

The level of sympathic nerve block is proportional to the degree of arterial hypotension after the epidural block. Hydration with crystalloid solutions (10-20

ml/kg of Ringer Solution or saline solution at 0.9%), vasopressor agents (such as ephedrine) and displacement of the uterus to the left (in order to avoid compression of the vena cava) must be some of prophilactic measures or treatments. Atropine must be given in order to avoid bradycardia. Epidural or caudal punctions should be avoided in patients who are in hypovolemic shock or suffering from septicemia, coagulopathies or infection in the punction site.

Local anesthetic Mepivacaine should not be used in the following situations:

Patient's hypersensitivity to this anesthetic (or to amide-type anesthetics);

Patients with hepatic disease (just because amide-type anesthetics are metabolized in the liver; patients with severe hepatic disease, due to their incapacity to normally metabolize local anesthetics and their high risk of presenting high toxic concentrations in their blood plasma;

Patients with kidney disease (because local anesthetics are excreted through kidneys). These patients are also in high risk of presenting high toxic concentrations in their blood plasma;

Patients with A history of troubles in their cardiac rhythm or having suffered cardiac arrests (because the cardiopressor effect of these anesthetics may cause detriment to these patients;

Medical history or predisposition to malignant hyper-rhythmia (because amide-type local anesthetics may contribute to the development of malignant hyper-rhythmia in case of requiring supplementary general anesthesia;

The use of the local anesthetic Mepivacaine should be carefully considered in patients with asthma, diabetes, atherosclerotic troubles, hypertension, hyperthyroidism, and cerebrovascular failure.

The use of the local anesthetic Mepivacaine should be carefully considered if:

There is an inflamed and/or abscessed area around the injection site because this situation may alter the pH in this site and, as a result of this, the anesthetic effect decreases or fails. The plugging capacity of tissues will normally cause a stabilization of pH at the level of the tissue.

Injections into infected areas will sometimes result in incomplete anesthesia because the infected focus produces residual acids that normally reduce the plugging capacity of tissues. An acid pH always reduces the anesthetic power of an injected solution.

4.3 INTERACTIONS WITH DRUGS AND DRUG-RELATED PROBLEMS

If the dentist gives sedatives to reduce the patient's apprehension, the anesthetic dose must be lowered because local anesthetics and sedatives are depressors of the Central Nervous System. This combination may have addictive effects.

From a theoretical point of view, the use of topic Mepivacaine increases the effect of muscle relaxants.

Mepivacaine may alter the results of analytic blood tests: (Biological) increase of Creatinine-Kinase.

No incompatibilities of Mepivacaine with food have been found.

4.4 PREGNANCY AND BREASTFEEDING

Pregnancy: Mepivacaine should be avoided in spinal anesthesia and in obstetrical anesthesia. The use of this substance to produce paracervical block may produce bradycardia and fetal acidosis.

Breastfeeding: The excretion of local anesthetics with human milk is not known. However, since many drugs are excreted jointly with human milk, Mepivacaine should be used with caution in lactating women.

4.5 EFFECTS ON DRIVING SKILLS AND OPERATION OF MACHINERY

Not reported

4.6 ADVERSE DRUG REACTIONS

Adverse drug reactions (ADRs) to Mepivacaine are similar to those produced by other amide-type local anesthetics. These adverse effects are generally produced by high blood plasma concentrations caused by excessive doses, fast

Absorption or inadvertent intravascular injections or may be due to an idiosyncratic hypersensitivity or diminished tolerance to local anesthetics on the part of the patient. Serious adverse effects are generally systemic.

The most commonly reported adverse effects are the following:

Central Nervous System (CNS):

CNS reactions may be excitatory and/or depressant and may manifest as photosensitivity, nervousness, apprehension, euphoria, confusion, vertigo, drowsiness, double or blurred vision, sensations of heat/cold or numbness, tremors, convulsions, loss of consciousness, depression, and respiratory arrest. Excitatory symptoms may be very short-lasting or totally absent. In any case, the first symptom of toxicity may be a sensation of sleepiness followed by loss of consciousness and respiratory arrest.

The sleepiness sensation produced by mepivacaine is usually an early symptom of high concentrations of this anesthetic in the patient's blood plasma as a result of fast absorption of this drug.

Cardiovascular System:

Cardiovascular reactions are usually depressant and may manifest as bradycardia, hypotension, and cardiovascular collapse that may lead to a cardiac arrest.

The signs and symptoms of a cardiovascular depression are commonly due to a vasovagal reaction, particularly, if the patient is in an upright position. Less

frequent symptoms may result from a direct adverse reaction to the local anesthetic.

Failing to recognize premonitory signs such as abundant perspiration, sensation of feebleness or changes in the pulse frequency may lead to a progressive cerebral hypoxia or to a serious cardiovascular catastrophe. An immediate treatment consists in placing the patient in an inclined position and then, to provide him/her with adequate ventilation with oxygen. Supportive treatment of circulatory depression may require administration of intravenous fluids and, when appropriate, a vasopressor (e.g.,ephedrine).as directed by the clinical situation.

Allergic Reactions:

Allergic reactions to mepivacaine are extremely rare. They may be characterized by cutaneous lesions, urticaria, edema or other anaphylactoid reactions. These symptoms must be treated with conventional therapy.

The detection of a patient's sensitiveness by means of superficial cutaneous tests has not revealed to be a safe procedure.

4.7 TREATMENT OF OVERDOSE

Serious emergencies caused by local anesthetics are commonly related to high concentration levels in blood plasma produced during the therapeutic use of the local anesthetic or resulting from excessive doses or inadvertent intravascular injections of the solution of local anesthetic (See *Adverse effects*, *Special Care,* and *Precautions for use*).

Management of Local Anesthetic Emergencies

The first consideration has to do with prevention which is carried out by a constant and careful monitoring of the patient's cardiovascular and respiratory vital signs and his/her state of consciousness after each injection of a local anesthetic. When a first sign of change arrives, oxygen must be provided.

The first step has to do with the treatment of convulsions: The best way is the maintenance of the patient's airway and the provision of assisted or controlled

ventilation with oxygen and to have close at hand an adequate system to immediately provide a positive air pressure, for example, a face mask.

Immediately after these supporting ventilatory measures, the patient's circulation must be evaluated, keeping in mind that anticonvulsive drugs sometimes depress the circulatory system when injected intravenously. Should convulsions persist despite adequate respiratory support, and if the patient's circulatory status permits, small increments of an ultra short-acting barbiturate (such as Sodium Thiopental, 50-100 mg increased, or Thiamilal) or a benzodiazepine (such as Diazepam, 2.5 mg increased) may be administered intravenously every 2 or 3 minutes in order to stop convulsions.

The dental professional should be familiar with the use of local anesthetics combined with anticonvulsant drugs. Supportive treatment of circulatory

depression may require administration of intravenous fluids and, when appropriate, a vasopressor as directed by the clinical situation (e.g., ephedrine).

If convulsions and cardiovascular depression are not treated immediately, they can result in hypoxia, acidosis, bradycardia, arrhythmias, and cardiac arrest. In case of a cardiac arrest, cardiopulmonary resuscitation measures must be instituted.

5 QUALITY ASSURANCE AND CONTROL OF THIS PRODUCT

Odontocaina® 3% is manufactured under the most strict technical and quality controls. Its manufacturing process is carried out in special manufacture areas with environmental, microbiological, and operational controls made by specially trained employees. Raw materials used in this product are previously examined and approved according to requirements of pharmacopeias currently into effect. The control process includes the control of Blister Packing and secondary packaging materials. All raw materials are furnished by qualified providers.

Odontocaina® 3% conforms to all requisites of the United States Pharmacopeia USP 27 in terms of physical appearance and physical properties, contents of active ingredients, and microbiological controls. All these parameters are verified during the different steps of the manufacturing process with the use of high technology

equipment, standardized procedures, areas for special analysis, and specially trained employees

6 INSTRUCTIONS FOR USE

Odontocaína® 3%

Adult Patients:

Localized anesthesia in upper or lower jaw: 54 mg (1.8 ml of solution at 3%)

Infiltration and nerve block in the whole oral cavity: 270 mg (9.0 ml of solution at 3%)

MAXIMUM RECOMMENDED DOSE: Do not exceed 6.6 mg/kg of body weight or 300 mg each dental session.

Children:

Infiltration and nerve block: Do not exceed 6.6 mg/kg of body weight.

In pediatric patients up to 3 years of age, use concentrations between 0.2% and 0.5% of local anesthetic. In pediatric patients of more than 3 years of age and a body weight >13.5 kg, use concentrations between 0.5% and 1.0% of local anesthetic. To obtain these concentrations, dilute the commercial concentration in the amount of sodium chloride at 9% for injections; for nerve block, use concentrations between 0.5% and 1.0%.

The dentist should use the lowest dose of the anesthetic solution that can provide the desired anesthetic effect. The patient should be carefully monitored for possible adverse reactions.

DISINFECTION OF CARTRIDGES

Local anesthetic Cartridges must not be submerged in solutions made of anticorrosive tablets or in solutions of quaternary ammonium salts such as benzalkonium chloride. Some metal ions (e.g. mercury, zinc, cupper) are contained in disinfectant solutions and may be the cause of inflammations after anesthetic procedures. This is why local anesthetic Cartridges should not be submerged into these solutions.

Dirección: Cra. 53 N° 50-09
Guarne (Antioquia) COLOMBIA.
Teléfono: (574) 550 00 00
Fax: (574) 551 31 34

For the chemical disinfection of the Cartridge surface, it is advisable to use isopropylic alcohol at 91% or ethylic alcohol at 70% without denaturalizing agents. Solutions which contain heavy metals are not recommended.

Odontocaina® 3% should not be used if the solution contains a precipitate. Any amount of anesthetic solution that remains in the Cartridge must be discarded.

7 COMMERCIAL PACKAGING SPECIFICATIONS OF THIS PRODUCT

Odontocaina® 3% is marketed in the following types of packaging:

Primary Packaging:

Glass Cartridges: Cylindrical ampoules made of type I- glass (Borosilicate glass).

Plastic Cartridges: Cylindrical ampoules made of virgin polypropylene

Both types of primary packaging have the same sliding plug and top cap: Natural-rubber plug, and metal cap with diaphragm (aluminium and natural rubber)

Secondary Packaging:

Two types of secondary packaging are available:
Blister in cardboard box per 50 Cartridges.
Plastic Box per 50 Cartridges

Dirección: Cra. 53 N° 50-09
Guarne (Antioquia) COLOMBIA.
Teléfono: (574) 550 00 00
Fax: (574) 551 31 34

8 CONSERVATION AND STORAGE CONDITIONS

The injectable solution Odontocaina® 3% must be stored in dry and cool areas. It should be stored at a temperature below 30º C. (111,6°F).