PRODUCT MONOGRAPH

4% Citanest® Plain Dental
Prilocaine Hydrochloride Injection, USP
(40 mg/mL)

Local Anesthetic

Sponsor:
Dentsply Canada, Ltd.
161 Vinyl Court
Woodbridge ON L4L 4A3

DATE OF REVISION:
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Control#: **187346**

PRODUCT MONOGRAPH

NAME OF DRUG

4% Citanest® Plain Dental
Prilocaine Hydrochloride Injection, USP
(40 mg/mL)

THERAPEUTIC CLASSIFICATION

Local Anesthetic for Infiltration and Nerve Block

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

4% Citanest® Plain Dental stabilizes the neuronal membrane and prevents the initiation and transmission of nerve impulses thereby, effecting local anesthetic action. Local anesthetics of the amide type are thought to act within sodium channels of the nerve membrane.

Onset of Action

When used for infiltration anesthesia in dental patients, 4% Citanest® Plain Dental has a rapid onset time of approximately 2-3 minutes and duration of approximately 1- 1½ hours for soft tissue anesthesia. 4% Citanest® Plain Dental has a short duration for operative anesthesia of approximately 15 minutes.

When used for mandibular block anesthesia, 4% Citanest® Plain Dental requires 5 minutes or more to take full effect. The duration of soft tissue anesthesia is approximately 2½ hours while operative anesthesia has a duration of 1- 1½ hours.

Hemodynamics

Prilocaine, like other local anesthetics, may also have effects on excitable membranes in the brain and myocardium. If excessive amounts of drug reach systemic circulation rapidly, symptoms and signs of toxicity will appear, emanating from the central nervous and cardiovascular systems.

Central nervous system toxicity (see SYMPTOMS AND TREATMENT OF OVERDOSAGE) usually precedes the cardiovascular effects since it occurs at lower plasma concentrations. Direct effects of local anesthetics on the heart include slow conduction, negative inotropism and eventually cardiac arrest.

Pharmacokinetics and Metabolism

Prilocaine is between 40-55% protein bound in plasma, mainly to alpha-acid glycoprotein.

Prilocaine redistributes rapidly from the blood and has a large apparent distribution volume of between 190-260 L. The terminal elimination half-life of Prilocaine is 1.6 h.

Prilocaine readily passes the placenta and free plasma concentrations are similar in both fetus and mother. In the presence of fetal acidosis, plasma concentrations may be slightly higher in the fetus due to ion trapping. Information concerning the elimination half-life of Prilocaine in neonates is not available.

Prilocaineis metabolized in both the liver and the kidney and is excreted via the kidney. It is not metabolized by plasma esterases.

In the liver, Prilocaine is primarily metabolized by amide hydrolysis to o-toluidine and N-propylamine. o-Toluidine is subsequently hydroxylated to 2-amino-3-hydroxytoluene and 2amino-5-hydroxytoluene, metabolites which are believed to be responsible for the occurrence of methemoglobinemia (see CONTRAINDICATIONS).

Only a small proportion of Prilocaine (<5%) is excreted unchanged in the urine. *In vitro* and animal studies have shown metabolism of Prilocaine by lung and kidney tissues.

INDICATIONS

4% Citanest® Plain Dental is indicated in dentistry for the production of local anesthesia by infiltration or nerve block.

CONTRAINDICATIONS

Patients with a known history of hypersensitivity to local anesthetics of the amide type or to other components of the solution. Patients with congenital or idiopathic methemoglobinemia.

Local anesthetics should not be used in severe shock or heart block. They should not be used when there is inflammation or sepsis in the region of the proposed injection.

WARNINGS

LOCAL ANESTHETICS SHOULD ONLY BE EMPLOYED BY CLINICIANS WHO ARE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF DOSE-RELATED TOXICITY AND OTHER ACUTE EMERGENCIES THAT MIGHT ARISE FROM THE BLOCK TO BE EMPLOYED AND THEN ONLY AFTER ENSURING THE IMMEDIATE AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY EQUIPMENT AND THE PERSONNEL NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES (see also ADVERSE REACTIONS and PRECAUTIONS). DELAY IN PROPER MANAGEMENT OF DOSE-RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE, AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST AND POSSIBLY, DEATH.

To minimize the likelihood of intravascular injection, aspiration should be performed before the local anesthetic solution is injected. If blood is aspirated, the needle must be repositioned until no return of blood can be elicited by aspiration. Note, however, that the absence of blood in the syringe does not assure that intravascular injection will be avoided.

PRECAUTIONS

The safety and effectiveness of 4% Citanest® Plain Dental depends on proper dosage, correct technique, adequate precautions and readiness for emergencies. Standard textbooks should be consulted for specific techniques and precautions for various dental anesthetic procedures.

Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use (see WARNINGS and SYMPTOMS AND TREATMENT OF OVERDOSAGE). THE LOWEST DOSAGE THAT RESULTS IN EFFECTIVE ANESTHESIA SHOULD BE USED TO AVOID HIGH PLASMA LEVELS AND SERIOUS ADVERSE EFFECTS. INJECTIONS SHOULD BE MADE SLOWLY, WITH FREQUENT ASPIRATIONS BEFORE AND DURING THE INJECTION TO AVOID INTRAVASCULAR INJECTION.

Repeated doses of 4% Citanest® Plain Dental may cause significant increases in blood levels with each repeated dose because of slow accumulation of the drug or its metabolites. Tolerance to elevated blood levels varies with the status of the patient. Debilitated, elderly patients, acutely ill patients and children should be given reduced doses commensurate with their age and physical condition. 4% Citanest® Plain Dental should also be used with caution in patients with epilepsy, impaired cardiac conduction, bradycardia, and impaired hepatic function.

Because amide-type local anesthetics such as Prilocaine are metabolized by the liver, these drugs, especially repeat doses, should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at greater risk of developing toxic plasma concentrations. Prilocaine should also be used with caution in patients with impaired cardiovascular function since they may be less able to compensate for functional changes associated with the prolongation of A-V conduction produced by these drugs.

Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness should be performed after each local anesthetic injection. It should be kept in mind at such times that restlessness, anxiety, incoherent speech, lightheadedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness,

blurred vision, tremors, twitching, depression or drowsiness may be early warning signs of central nervous system toxicity.

Many drugs used during the conduct of anesthesia are considered potential triggering agents for familial malignant hyperthermia. It has been shown that the use of amide local anesthetics in malignant hyperthermia is safe. However, there is no guarantee that neural blockade will prevent the development of malignant hyperthermia during surgery. It is also difficult to predict the need for supplemental general anesthesia. Therefore a standard protocol for the management of malignant hyperthermia should be available.

4% Citanest® Plain Dental should be used with caution in persons with known drug sensitivities. Patients allergic to para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to Prilocaine.

Methemoglobinemia

A few instances of cyanosis have been reported following the administration of more than 400 mg of Prilocaine. It would be necessary to inject five cartridges of 4% Citanest® Plain Dental to produce an average methemoglobin value of 1%. Since methemoglobin values of less than 20% generally do not produce any clinical symptoms of hypoxia, the routine use of 4% Citanest® Plain Dental for normal dental procedures should not be associated with any side effects related to methemoglobinemia. The usual clinical signs of methemoglobinemia are cyanosis of the nail beds and lips. Although the possibility of methemoglobinemia occurring in dental patients is extremely rare, it should be remembered that methemoglobinemia can be treated easily and reversed rapidly by the use of 1-2 mg/kg body weight of methylene blue administered intravenously over a 5 minute period. (see ADVERSE REACTIONS and SYMPTOMS AND TREATMENT OF OVERDOSAGE).

Caution should be exercised when administering 4% Citanest® Plain Dental concomitantly with other medications which are potential producers of methemoglobin (e.g. sulfonamides, antimalarials, and certain nitric compounds).

Use in the Head and Neck Area

Small doses of local anesthetics injected into the head and neck area, including retrobulbar, dental and stellate ganglion blocks, may produce adverse reactions caused by inadvertent injection to an artery. These reactions may be similar to systemic toxicity seen with unintentional intravascular injections of larger doses. Inadvertent injections into an artery can cause cerebral symptoms even at low doses. Confusion, convulsions, respiratory depression and/or respiratory arrest, and cardiovascular stimulation or depression leading to cardiac arrest have been reported. Patients receiving these blocks should have their circulation and respiration monitored and be constantly observed.

Drug Interactions

See also under Methemoglobinemia.

Prilocaine should be used with caution in patients receiving other agents structurally related to amide-type local anesthetics, since the toxic effects are additive.

If sedatives are employed to reduce patient apprehension, they should be used in reduced doses, since local anesthetic agents, like sedatives, are central nervous system depressants which in combination may have an additive effect.

Information for Patients

The patient should be informed of the possibility of temporary loss of sensation and muscle function following infiltration or nerve block injections. The patient should be advised to exert caution to avoid inadvertent trauma to the lips, tongue, cheek mucosa of soft palate when these structures are anesthetized. The ingestion of food should therefore be postponed until normal function returns. The patient should be advised to consult the dentist if anesthesia persists, or if a rash develops.

Use in Pregnancy

The safe use of 4% Citanest® Plain Dental has not been established with respect to possible adverse effects upon fetal development. Careful consideration should be given to this fact before administering this drug in pregnancy. No specific disturbances to the reproductive process have so far been reported, e.g. no increased incidence of malformations or other direct or indirect harmful effects on the fetus.

Methemoglobinemia in the neonate has been reported after the administration of Prilocaine to the mother in doses exceeding 600 mg.

Nursing Mothers

Prilocaine may enter the breast milk, but in such small quantities that there is generally no risk of affecting the infant at therapeutic dose levels.

ADVERSE REACTIONS

Adverse experiences following the administration of Prilocaine are similar in nature to those observed with other amide local anesthetic agents. These adverse experiences are, in general, dose-related and may result from high plasma levels caused by overdosage, rapid absorption, or inadvertent intravascular injection, or may result from a hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient. Such reactions are systemic in nature and involve the central nervous system and/or the cardiovascular system.

Reactions to 4% Citanest® Plain Dental are very rare in the doses used in dental procedures. Psychogenic reactions to anticipation of or during the dental procedures, are however, common and may mimic the symptoms of a generalized systemic reaction to local anesthetics.

Serious adverse experiences are generally systemic in nature. The following types are those most commonly reported:

Central Nervous System

CNS manifestations are excitatory and/or depressant and may be characterized by circumoral paresthesia, lightheadedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, hyperacusis, tinnitus, blurred vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest. The excitatory manifestations may be very brief or may not occur at all, in which case the first manifestation of toxicity may be drowsiness merging into unconsciousness and respiratory arrest.

Drowsiness following the administration of Prilocaine is usually an early sign of a high Prilocaine plasma level and may occur as a consequence of rapid absorption.

Cardiovascular System

Cardiovascular manifestations are usually depressant and are characterized by bradycardia, hypotension, arrhythmia, and cardiovascular collapse, which may lead to cardiac arrest.

Allergic

Allergic reactions are characterized by cutaneous lesions, urticaria, edema, or in the most severe instances, anaphylactic shock. Swelling and persistent paresthesia of the lips and oral tissues have been reported after blocking the inferior alveolar nerve. Allergic reactions of the amide type are extremely rare and may occur as a result of sensitivity either to the local anesthetic agent or to other components in the formulation.

Neurologic

The incidence of adverse neurological reactions, e.g. persistent neurological deficit, associated with the use of local anesthetics is very low. Neurological reactions may be dependent upon the particular drug used, the route of administration and the physical status of the patient. Many of these effects may be linked to the injection technique, with or without a contribution by the drug. Neurological

reactions following regional nerve blocks have included persistent paresthesia and sensory disturbances.

Methemoglobinemia

Cyanosis due to the formation of methemoglobin may occur after the administration of 4% Citanest® Plain Dental. The repeated administration of 4% Citanest® Plain Dental, even in relatively small doses, can lead to clinically overt methemoglobinemia.

The conversion of hemoglobin to methemoglobin is caused by the prilocaine metabolite, o-toluidine, which has a long half-life and tends to accumulate, and in turn, its conversion to 4- and 6-hydroxytoluidine. Methemoglobin has risen to clinically significant levels in patients receiving high doses of prilocaine. Cyanosis occurs when the methemoglobin concentration in the blood reaches 10-20g/L (6-12% of the normal hemoglobin concentration). Methemoglobin oxidizes only slowly back to hemoglobin, but this process can be greatly accelerated by giving methylene blue intravenously (see SYMPTOMS AND TREATMENT OF OVERDOSAGE).

The reduction in the oxygen-carrying capacity in normal patients is marginal; hence cyanosis is usually symptomless. However, in severely anemic patients it may cause significant hypoxemia. It is important to rule out other more serious causes of cyanosis such as acute hypoxemia and/or heart failure. In using the recommended adult dosage of 4% Citanest® Plain Dental, 1-2 mL (corresponding to 40-80 mg prilocaine hydrochloride), the occurrence of methemoglobinemia in dental practice appears remote. However, gross overdosage in dental practice has been reported to cause methemoglobinemia.

Note: Even low concentrations of methemoglobin may interfere with pulse oximetry readings, indicating a false low oxygen saturation.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Patient Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Patient Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Since prilocaine is the least toxic of the amino-amide anesthetics, it is particularly useful in situations when high dosage may be needed. This advantage, however, should be weighed against the risk of causing methemoglobinemia.

Acute emergencies are, in general, dose-related and may result from high plasma levels caused by excessive dosage, rapid absorption (i.e. rate of increase of plasma concentration) or unintentional intravascular injection, or may result from hypersensitivity or diminished tolerance on the part of the patient.

Acute Systemic Toxicity

CNS reactions are excitatory or depressant and may be characterized by nervousness, tinnitus, twitching, euphoria, drowsiness, blurred or double vision, dizziness, convulsions, unconsciousness and possibly respiratory arrest. The excitatory reactions may be very brief or may not occur at all, in which case the first manifestation of toxicity is drowsiness merging into unconsciousness and even respiratory arrest.

Cardiovascular reactions are depressant and may be characterized by hypotension, myocardial depression, bradycardia and possibly cardiac arrest. Signs and symptoms of depressed cardiovascular function may commonly result from a vasovagal reaction, particularly if the patient is in an upright position. Less commonly, they may occur as a direct effect of the drug. Failure to recognize premonitory signs such as sweating, a feeling of faintness, changes in pulse or sensorium, may result in progressive cerebral hypoxia and seizure or serious cardiovascular collapse.
Cardiovascular effects are usually only seen in the most severe cases and are generally preceded by signs of toxicity in the central nervous system.

Acidosis or hypoxia in the patient may increase the risk and severity of toxic reactions. Such reactions involve the central nervous system and the cardiovascular system.

Treatment of Acute Toxicity

The immediate treatment of acute systemic toxicity is as follows:

a) Put the patent in a supine position. Raise the legs 30°-45° above the horizontal level.

b) Ensure a patient airway. If ventilation is inadequate, ventilate the patient, with oxygen if available. This is important since toxicity increases with acidosis.

c) The treatment of convulsions consists of ensuring a patent airway and arresting convulsions. Should convulsions persist despite adequate ventilation, 5-15 mg diazepam or 50-200 mg thiopental should be administered intravenously to arrest the convulsions. Since this treatment may also depress respiration, the means of mechanically supporting or controlling ventilation should be available.

d) Supportive treatment of circulatory depression may require the administration of intravenous fluids and, when appropriate, a vasopressor (e.g. ephedrine 5-10 mg i.v. and repeated, if necessary, after 2-3 min), as governed by the clinical situation.

e) If the patient is unresponsive and the carotid pulse rate is totally absent, start external cardiac massage and mouth to mouth resuscitation.

Treatment of Acute Methemoglobinemia

If clinical methemoglobinemia occurs, it can be rapidly treated by a single intravenous injection of a 1% methylene blue solution, 1mg/kg body weight, over a 5 minute period. Cyanosis will disappear in about 15 minutes. This dose should not be repeated as methylene blue in high concentrations acts as a hemoglobin oxidant.

For management of a suspected drug overdose, contact your regional Poison Control Centre

DOSAGE AND ADMINISTRATION

The dosage of 4% Citanest® Plain Dental varies and depends on the area of the oral cavity to be anesthetized, the vascularity of the oral tissues and the technique of anesthesia. The total dose must be adjusted to the age, size and physical status of the patient. The lowest dosage that results in effective local anesthesia should be administered. Injections should be made slowly with careful aspiration before and intermittently during injection to avoid inadvertent intravascular injection, which may have toxic effects. For specific techniques and procedures of a local anesthesia in the oral cavity, refer to standard textbooks.

4% Citanest® Plain Dental is recommended for use in maxillary infiltration anesthesia for procedures lasting approximately 15 minutes. 4% Citanest® Plain Dental is therefore especially suited to short procedures in the maxillary anterior teeth. For long procedures, or those involving maxillary posterior teeth where soft tissue numbness is not troublesome to the patient, 4% Prilocaine Hydrochloride formulations that contain epinephrine is recommended.

4% Citanest® Plain Dental is also recommended for those dental procedures in which it is desirable to use a local anesthetic that does not contain a vasoconstrictor agent, e.g., in those patients for whom vasoconstrictor agents are not indicated.

Adults: For most routine dental procedures, initial dosages of 1-2 mL of 4% Citanest® Plain Dental (40-80 mg prilocaine hydrochloride) will usually provide adequate infiltration or major nerve block anesthesia. No more than 400 mg (10 mL) should be administered per procedure.

Children: In children under ten years of age it is rarely necessary to administer more than one-half cartridge (0.9-1 mL or 36-40 mg prilocaine hydrochloride) of 4% Citanest® Plain Dental per procedure.

Due to the specific need for bone penetration, dental local anesthetics contain high concentrations of active drug, e.g. 40 mg/mL prilocaine hydrochloride for4% Citanest® Plain Dental. A combination of high pressure induced by the use of a dental cartridge system and a rapid rate of injection may lead to complications (see SYMPTOMS AND TREATMENT OF OVERDOSAGE) even after the injection of small amounts of local anesthetic. This is due to the high concentration, especially following accidental intravascular injection, when the injected drug could travel in a retrograde manner along the vessel and, in cases of intra-arterial injection in the head and neck area, reach the brain without the same degree of dilution than occurs with an intravenous injection.

Aspiration is recommended since it reduced the possibility of intravascular injection, thereby keeping the incidence of side effects and anesthetic failures to a minimum.

For best results, it is important that cartridges be used with a syringe of appropriate size.

Each cartridge contains 1.8 mL of anaesthetic with 72 mg of Prilocaine hydrochloride.

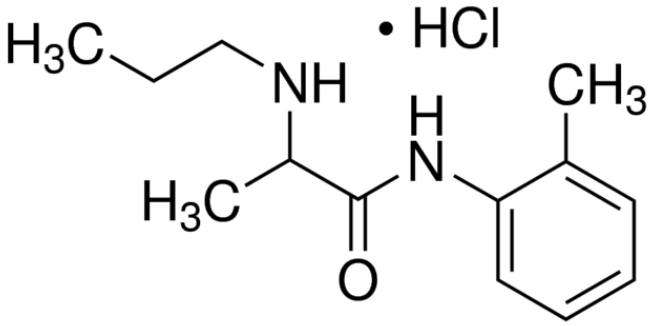
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Prilocaine hydrochloride

Chemical Name: propanamide, N-(2-methylphenyl)-2-(propylamine)-, monohydrochloride

Structure Formula:



Molecular Formula: $C_{13}H_{20}N_2OHCl$

Molecular Weight: 256.77 g/mol

Description: Prilocaine hydrochloride is an amide-type local anesthetic. It is a white, odourless crystalline powder freely soluble in water and alcohol, very slightly soluble in chloroform, slightly soluble in acetone and practically insoluble in ether. Prilocaine hydrochloride has a melting range between 166-169°C.

Dosage Form

4% Citanest® Plain Dental is sterile, aqueous, isotonic solution.

Composition (mg/mL):

	4% Citanest® Plain Dental
Prilocaine hydrochloride	40 mg
Water for injection	q.s.
Sodium hydroxide and/or hydrochloric acid to adjust pH	6.0 – 7.0

4% Citanest® Plain Dental is **filled under nitrogen.**

Sterilization, Storage and Technical Procedures:

Cartridges should not be autoclaved, because the rubber plunger will typically be extruded thus compromising container integrity.

If disinfection of the cartridge is desired, its immersion should be avoided due to the risk of undesirable effects on the rubber membrane and aluminum cap, and the risk of contamination of the solution. Disinfection of the rubber membrane or the entire dental cartridge should be accomplished by wiping it with a cotton pledget that has been moistened with a disinfectant. Isopropyl alcohol (91%) or ethyl alcohol (70%) is recommended. Many commercially available brands of rubbing alcohol, as well as solutions of ethyl alcohol not of USP grade, contain denaturants which are injurious to rubber and therefore are not to be used.

Quaternary ammonium salts, such as benzalkonium chloride, are electrolytically incompatible with aluminum. Cartridges which are sealed with aluminum caps should not be immersed in any solution containing these salts.

Anti-rust tablets usually contain sodium nitrate or other similar agents which may be capable of releasing metal ions from syringes, needles and aluminum sealed cartridges. Accordingly, cartridges should not be kept in such solutions.

To avoid leakage of solutions during injection, be sure to penetrate the center of the rubber diaphragm perpendicularly with the needle when loading the syringe. An off-center penetration produces an oval shaped puncture that allows leakage around the needle.

Cracking of glass cartridges is most often the result of an attempt to use a cartridge with an extruded plunger. An extruded plunger loses its lubrication and can be forced back into the cartridge only with difficulty. Cartridges with extruded plungers should be discarded.

In order to avoid traumatic nerve injuries leading to paresthesia in conjunction with dental nerve block, an atraumatic technique should be used. Dental cartridge systems may generate high pressures during injection, however, injected local anesthetics may travel in a retrograde manner along a nerve in cases of intraneural injection. If an accidental traumatic nerve injury has occurred, epinephrine, if present in the anesthetic solution, may aggravate the local neurotoxicity by decreasing the intraneural blood circulation. In order to minimize the risk of intraneural injection as well as fascicular injuries, the needle should always be withdrawn a little if paresthesia is elicited during injection. Furthermore, a short-beveled needle should be considered for regional blocks (in which case a topical anesthetic may be used to reduce the pain of needle insertion), while a sharper (i.e. long-beveled) needle can still be recommended for infiltration.

4% Citanest® Plain Dental should be stored at room temperature (15-30° C).

4% Citanest® Plain Dental is preservative free and for single use only. Discard unused portion.

Store cartridges in the outer carton.

AVAILABILITY OF DOSAGE FORMS

4% Citanest® Plain Dental is available in 1.8 mL glass dental cartridges, packed 50 per box.

PHARMACOLOGY

Prilocaine is a local anesthetic of the amide type with a potency and duration similar to lidocaine.

Prilocaine was found to be as effective as lidocaine in sciatic nerve blocks in rats, in blocking the sneeze reflex in rabbits, and in anesthetic potency on the rabbit cornea. With low concentrations of epinephrine, the duration of the nerve block is more prolonged with lidocaine than with prilocaine. On the other hand, without vasoconstrictors, prilocaine provides a longer duration of nerve block than does lidocaine.

Metabolic studies indicate that prilocaine is broken down in the liver much more rapidly than lidocaine. In addition, the serum concentrations of prilocaine following intravenous injections decreased at a much greater rate than lidocaine in both human and animal studies.

One of the metabolites of prilocaine is o-toluidine. This substance has been found to produce methemoglobin both *in vitro* and *in vivo*. However, in vivo, o-toluidine apparently is formed from the metabolic degradation of prilocaine with the resultant formation of methemoglobin. Studies in experimental animals and man indicate that, in general, a dose-response relationship exists between the total dose of prilocaine administered as a single injection and the amount of methemoglobin formed. Doses of 8 mg/kg administered intravenously in cats and 600 mg administered into the peridural space in man were required to produce statistically significant amounts of methemoglobin.

TOXICOLOGY

The toxicity of prilocaine, expressed as the LD_{50}, is approximately 60% that of lidocaine in laboratory animals as determined by intravenous, intraperitoneal and subcutaneous routes of administration. In addition, tolerance studies conducted with human subjects revealed that prilocaine, administered intravenously in doses of 200-400 mg, results in a lower incidence and a milder form of toxic symptoms than equivalent doses of lidocaine.

Two studies of the effects of prilocaine on reproduction and fetal development have been carried out in animals. In one study, doses of prilocaine of 10 and 30 mg/kg were injected subcutaneously each day for 8 months in male and female rats. During the 8 months, the rats were mated three times and the resultant litters were examined. The study revealed no teratogenic effects of prilocaine and no adverse effects on the number of litters produced on the average weight of pups at birth, on the average weight of pups surviving to weaning age, nor on the distribution of sex. In the third littering

the average number of pups per litter at birth was lower in the group treated with a high dose of prilocaine than in the control group. In all three litterings, the survival of pups in some of the treated groups was less than in their corresponding control groups. Adjustments in the experimental procedure indicated that these differences in survival were at least partially due to experimental artifacts.

In the other study, the effects of prilocaine on organogenesis and fetal development were investigated in the rat. Doses ranging from 100 to 300 mg/kg were injected intramuscularly into pregnant rats from day 7 to day 13 post coitum. On the twenty-first gestational day the fetuses were examined. No external or skeletal malformations were observed and no significant differences were observed in the number of living and dead fetuses among the treated and control groups. The mean fetal weights in the treated groups were, however, less than that of the control groups. In addition, hydronephrosis was observed in approximately 1% of the fetuses derived from treated mothers, but in none of the fetuses of the control groups. This latter observation was not statistically significant.

Chronic oral toxicity studies of ortho-toluidine, a metabolite of prilocaine, in mice (150-4800 mg/kg) and rats (150-800 mg/kg) have shown that ortho-toluidine is a carcinogen in both species. The lowest dose corresponds to approximately 50 times the maximum amount of ortho-toluidine to which a 50 kg subject would be expected to be exposed following a single injection (8 mg/kg) of prilocaine.

o-Toluidine (0.5 μg/mL) showed positive results in *Escherichia coli* DNA repair and phage-induction assays. Urine concentrates from rats treated with o-toluidine (300 mg/kg, orally) were mutagenic to *Salmonella typhimurium* with metabolic activation. Several other tests, including reverse mutations in five different *Salmonella typhimurium* strains with or without metabolic activation; and single strand breaks in DNA of V79 Chinese hamster cells, were negative.

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