PRODUCT MONOGRAPH

NESACAINE® - CE

(chloroprocaine hydrochloride injection)

AstraZeneca Standard

Local Anesthetic

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NAME OF DRUG

NESACAINE® - CE
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THERAPEUTIC CLASSIFICATION

Local Anesthetic for Infiltration and Regional Nerve Block

ACTION

Mechanism of Action

NESACAINE (chloroprocaine hydrochloride) stabilizes the neuronal membrane and prevents the initiation and transmission of nerve impulses, thereby effecting local anesthetic action.

Onset of Action

The onset of action is rapid (usually within 6 to 12 minutes). The duration of anesthesia depends on the procedure and the amount used, but could last up to 60 minutes.

Pharmacokinetics and Metabolism

Chloroprocaine is rapidly hydrolyzed in plasma by pseudocholinesterase. This hydrolysis results in the formation of β-diethylaminoethanol and 2-chloro-4-aminobenzoic acid which inhibits the action of sulfonamides. See PRECAUTIONS.

Solutions of NESACAINE do not injure nervous tissue and are not irritating to other tissues in the recommended concentrations.

INDICATIONS AND CLINICAL USE

NESACAINE (chloroprocaine hydrochloride) is indicated for the production of local anesthesia by infiltration and regional nerve block, including caudal and epidural blocks. Any unused portion should be discarded. NESACAINE should not be used for spinal anesthesia.

CONTRAINDICATIONS

NESACAINE (chloroprocaine hydrochloride) is contraindicated in patients hypersensitive (allergic) to drugs of the PABA ester group.

Although central nervous system disease is generally considered a contraindication to caudal or epidural nerve block, it is not a contraindication to peripheral nerve block. Pathologic changes of the vertebral column may make epidural puncture impossible or inadvisable.

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 WHICH MIGHT ARISE FROM THE BLOCK TO BE EMPLOYED, AND THEN ONLY AFTER ENSURING THE IMMEDIATE AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY RESUSCITATIVE EQUIPMENT, AND THE PERSONNEL RESOURCES 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.

Reports of Irreversible Chondrolysis with Intra-articular Infusions of Local Anesthetics Following Surgery: Intra-articular infusions of local anesthetics following arthroscopic and other surgical procedures is an unapproved use, and there have been post-marketing reports of irreversible chondrolysis in patients receiving such infusions. The majority of reported cases of irreversible chondrolysis have involved the shoulder joint; cases of gleno-humeral irreversible chondrolysis have been described in pediatric and adult patients following intra-articular infusions of local anesthetics with and without epinephrine for periods of 48 to 72 hours. The time of onset of symptoms, such as joint pain, stiffness and loss of motion can be variable, but may begin as early as the 2nd month after surgery. Currently, there is no effective treatment for irreversible chondrolysis; patients who experienced irreversible chondrolysis have required additional diagnostic and therapeutic procedures and some required arthroplasty or shoulder replacement. **NESACAINE (chloroprocaine hydrochloride) should not be used for post-operative intra-articular infusion** (See DOSAGE AND ADMINISTRATION).

Use of Vasopressors with Ergot-Type Oxytoctic Drugs: Vasopressors should not be used in the presence of ergot-type oxytocic drugs, since a severe persistent hypertension may occur.

Avoiding Intravascular Injection: To avoid intravascular injection, aspiration should be performed before the anesthetic solution is injected. The needle must be repositioned until no blood return can be elicited. However, the absence of blood in the syringe does not guarantee that intravascular injection has been avoided.

Use for Obstetrical Paracervical Block Anesthesia: There are no data concerning use of NESACAINE for obstetrical paracervical block when toxemia of pregnancy is present or when fetal distress or prematurity is anticipated in advance of the block; such use is, therefore, not recommended. The following information should be considered by clinicians who select NESACAINE for obstetrical paracervical block anesthesia:

1. Fetal bradycardia (generally a heart rate of less than 120 per minute for more than 2 minutes) has been noted by electronic monitoring in about 5% to 10% of the cases (various studies) where initial total doses of 120 mg to 400 mg of NESACAINE were employed. The incidence of bradycardia, within this dose range, might not be dose related.

2. Fetal acidosis has not been demonstrated by blood gas monitoring around the time of bradycardia or afterwards. These data are limited and are generally restricted to non-toxemic cases where fetal distress or prematurity was not anticipated in advance of the block.

3. No intact chloroprocaine and only trace quantities of a hydrolysis product, 2-chloro-4-aminobenzoic acid have been demonstrated in umbilical cord arterial or venous plasma following properly administered paracervical block with chloroprocaine.

4. The role of drug factors and non-drug factors associated with fetal bradycardia following paracervical block are unexplained at this time.

PRECAUTIONS

The safety and effectiveness of NESACAINE (chloroprocaine hydrochloride) injections depend upon proper dosage, correct technique, adequate precautions and readiness for emergencies.

The lowest dosage that results in effective anesthesia should be used to avoid high plasma levels and serious undesirable systemic side effects. Tolerance varies with the status of the patient. Debilitated patients, elderly patients, acutely ill patients and children should be given reduced doses commensurate with their age and physical status.

Solutions containing vasoconstrictors should be used cautiously in the presence of disease which may adversely affect the patient's cardiovascular system.

Since ester-type local anesthetics are hydrolyzed by plasma cholinesterase produced by the liver, chloroprocaine should be used cautiously in patients with hepatic disease.

INJECTIONS SHOULD ALWAYS BE MADE SLOWLY AND WITH FREQUENT ASPIRATIONS TO AVOID INADVERTENT RAPID INTRAVASCULAR ADMINISTRATION WHICH CAN PRODUCE SYSTEMIC TOXICITY.

Chloroprocaine hydrochloride should be employed cautiously in persons with known drug allergies or sensitivities.

Injection of solutions containing epinephrine (see DOSAGE and ADMINISTRATION section) in areas where the blood supply is limited (i.e., ears, nose, digits, etc.) or when peripheral vascular disease is present should be used cautiously.

Drug Interactions

Serious cardiac arrhythmias may occur if preparations containing a vasopressor are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichloroethylene, or other related agents. The para-aminobenzoic acid metabolite of chloroprocaine inhibits the action of sulfonamides. Therefore, NESACAINE should not be used in any condition in which a sulfonamide drug is being employed.

In obstetrics, if vasoconstrictor drugs are used either to correct hypotension or are added to the local anesthetic solution, the obstetrician should be warned that some oxytocic drugs may cause severe persistent hypertension and even rupture of a cerebral blood vessel may occur during the post-partum period.

Solutions containing vasoconstrictors, particularly epinephrine and norepinephrine, should be used with extreme caution in patients receiving certain antidepressants, such as MAO inhibitors and tricyclic compounds, since severe prolonged hypertension may occur.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term studies in animals to evaluate carcinogenic potential and reproduction studies to evaluate mutagenesis or impairment of fertility have not been conducted with chloroprocaine.

Usage in Pregnancy

Safe use of chloroprocaine hydrochloride has not been established with respect to adverse effects upon fetal development. This fact should be carefully considered before administering this drug to women of child-bearing potential, particularly during early pregnancy. This does not preclude the use of the drug at term for obstetrical analgesia. Adverse effects on the fetus, course of labour, or delivery have rarely been observed when proper dosage and proper technique have been employed.

Labour and Delivery

Local anesthetics rapidly cross the placenta, and when used for epidural, paracervical, pudendal or caudal block anesthesia, can cause varying degrees of maternal, fetal and neonatal toxicity.

The incidence and degree of toxicity depend upon the procedure performed, the type and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus and neonate involve alterations of the central nervous system, peripheral vascular tone and cardiac function.

Maternal hypotension has resulted from regional anesthesia. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient's legs and positioning her on her left side will help prevent decreases in blood pressure. The fetal heart rate should also be monitored continuously, and electronic fetal monitoring is highly advisable.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when chloroprocaine is administered to a nursing mother.

ADVERSE REACTIONS

Systemic

Systemic adverse reactions result from high plasma levels due to rapid absorption, inadvertent intravascular injection or excessive dosage. Hypersensitivity, idiosyncrasy, or diminished tolerance (as in patients with plasma cholinesterase deficiency) are other causes of reactions. Reactions due to overdosage (high plasma levels) are systemic and involve the central nervous system and the cardiovascular system.

Central Nervous System

These are characterized by excitation and/or depression. Restlessness, anxiety, dizziness, tinnitus, blurred vision or tremors may occur, possibly proceeding to convulsions. However, excitement may be transient or absent, with depression the first manifestation of an adverse reaction. This may quickly be followed by drowsiness merging into unconsciousness and respiratory arrest.

Cardiovascular System

High doses or unintended intravascular injection may cause depression of the myocardium manifested by an initial episode of hypotension and bradycardia and even cardiac arrest.

Allergic

Allergic reactions are rare and may occur as a result of sensitivity to chloroprocaine and are characterized by cutaneous lesions, urticaria, edema and anaphylactoid type symptomatology. These allergic reactions should be managed by conventional means. The detection of potential sensitivity by skin testing has not been fully established.

Neurologic

In the practice of epidural block, occasional inadvertent penetration of the subarachnoid space by the catheter may occur. The subsequent reactions depend on the amount of drug administered subdurally and may include, among others, spinal block of varying magnitude, loss of bowel and bladder control, loss of perineal sensation and sexual function. Persistent neurological deficit of some lower spinal segments with slow recovery (several months) has been reported in rare instances. (See DOSAGE AND ADMINISTRATION, CAUDAL AND

EPIDURAL BLOCK). Backache and headache have also been noted following lumbar epidural or caudal block.

OVERDOSAGE

Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use of local anesthetics or to unintended subarachnoid injection of local anesthetic solution (see ADVERSE REACTIONS, WARNINGS, and PRECAUTIONS).

Treatment of Systemic Reactions

Treatment of a patient with toxic manifestations consists of assuring and maintaining a patent airway and supporting ventilation with oxygen and assisted or controlled ventilation (respiration) as required. This usually will be sufficient in the management of most reactions. Should a convulsion persist despite ventilatory therapy, small increments of anticonvulsive agents may be given intravenously, such as a benzodiazepine (e.g. diazepam), or ultra-short acting barbiturate (e.g. thiopental or thiamylal), or a short-acting barbiturate (e.g. pentobarbital or secobarbital). Cardiovascular depression may require circulatory assistance with intravenous fluids and/or vasopressors (e.g. ephedrine) as dictated by the clinical situation.

If not treated immediately, both convulsions and cardiovascular depression can result in hypoxia, acidosis, bradycardia, arrhythmias and cardiac arrest. If cardiac arrest should occur, standard cardiopulmonary resuscitative measures should be instituted. Recovery has been reported after prolonged resuscitative efforts.

DOSAGE AND ADMINISTRATION

The lowest dose needed to provide effective anesthesia should be administered. As with all local anesthetics, the dosage varies and depends upon the area to be anesthetized, vascularity of the tissues, number of neuronal segments to be blocked, individual tolerance and the technique employed.

Dosages should be reduced for children, elderly or debilitated patients, and in patients with cardiac and/or liver disease. For specific techniques and procedures, refer to standard textbooks.

There have been adverse event reports of irreversible chondrolysis in patients receiving intra-articular infusions of local anesthetics following arthroscopic and other surgical procedures. NESACAINE (chloroprocaine hydrochloride) is not approved for this use (see WARNINGS).

Preparation of Epinephrine Solution

To prepare a 1:200,000 epinephrine-chloroprocaine hydrochloride solution add 0.1 mL of a 1:1,000 Epinephrine Injection USP to 20 mL of NESACAINE. Please consult package insert text for epinephrine for contraindications, warnings and precautions.

As a guide for some routine procedures, suggested doses are given below:

1. INFILTRATION AND NERVE BLOCK:

Local Infiltration: Quantity depends on the concentration of NESACAINE, the site to be infiltrated and the discretion of the operator.

Nerve Blocks:

Type of Block	Volume (mL)	Concentration	Total Dose (mg)
mandibular	2-3	2%	40-60
infraorbital	0.5-1	2%	10-20
brachial plexus	30-40	2%	600-800
pudendal block for obstetrics	10 mL each side	2%	400

2. CAUDAL AND EPIDURAL BLOCK:

Caudal Anesthesia: The initial dose is 15 to 25 mL of NESACAINE 2%. This volume should not be exceeded. Repeated doses may be given at 40 to 60 minute intervals.

Epidural Anesthesia: The recommended total volume of NESACAINE for the main dose in epidural anesthesia is 15 to 25 mL, and this volume should not be exceeded. Furthermore, a local anesthetic agent other than NESACAINE, such as XYLOCAINE® Parenteral Solution for infiltration and nerve block, should be used for skin and needle tract infiltration. Repeated doses 2 to 6 mL less than the original dose may be given at 40 to 50 minute intervals.

There have been post-marketing reports of irreversible chondrolysis in patients receiving post-operative intra-articular infusion of local anaesthetics. NESACAINE is not approved for this use (see WARNINGS).

In order to guard against possible adverse reactions resulting from inadvertent penetration of the subarachnoid space, the following procedures are recommended:

1. Use of an adequate (in the case of NESACAINE, approximately 5 mL of 2%) test dose prior to induction of complete block. This test dose should be repeated if the patient is moved in such a fashion as to have displaced the epidural catheter. At least 5 minutes should elapse after each test dose prior to proceeding further.

2. Injection of a large, single therapeutic dose through a catheter should be avoided; instead, repeated fractional doses are advocated.

3. In the event of the known injection of a large volume of NESACAINE into the subarachnoid space, an appropriate amount of cerebrospinal fluid (such as 10 mL) should be withdrawn through the catheter or by separate lumbar puncture.

MAXIMUM DOSAGES

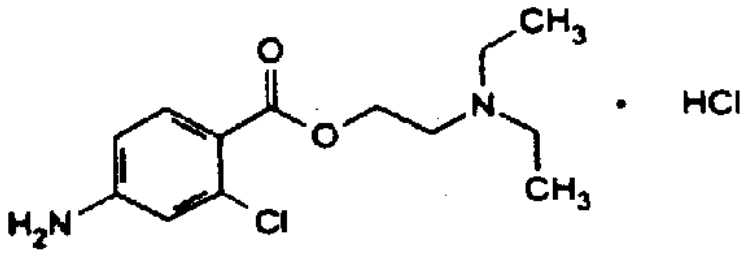
Adults

The maximum single recommended doses of NESACAINE (chloroprocaine hydrochloride) in adults are: without epinephrine, 11 mg/kg body weight, not to exceed 800 mg; with epinephrine (1:200,000), 14 mg/kg body weight, not to exceed 1000 mg.

For caudal and lumbar epidural anesthesia, a total of 25 mL of solution should not be exceeded.

PHARMACEUTICAL INFORMATION

The active ingredient in NESACAINE is chloroprocaine hydrochloride which is chemically designated as: 2-(diethylamino)ethyl-4-amino-2-chlorobenzoate mono hydrochloride. It has the following structural formula:



The molecular formula is $C_{13}H_{19}ClN_2O_2 \cdot HCl$. The molecular weight is 307.22.

Non-medicinal Ingredients

20 mL vials (2%)
sodium chloride water for injection hydrochloric acid and/or sodium hydroxide to adjust pH 2.7-4.0

Sterilization, Storage and Technical Procedures

As with other anesthetics having a free aromatic amino group, NESACAINE solutions are slightly photosensitive and may become discoloured after prolonged exposure to light. It is recommended that these vials be stored in the original outer containers, protected from direct sunlight. Discoloured solution should not be administered. If exposed to low temperatures, NESACAINE may deposit crystals of chloroprocaine hydrochloride, which will redissolve with shaking when returned to room temperature. The product should not be used if it contains undissolved material.

Nesacaine solutions should not be resterilized by autoclaving. Sterilization of vials with ethylene oxide is not recommended, since absorption through the closure may occur.

Chloroprocaine is incompatible with caustic alkalis and their carbonates, soaps, silver salts, iodine and iodides.

Keep from freezing. Protect from light. Store at controlled room temperature: 15-30°C.

AVAILABILITY

NESACAINE (chloroprocaine hydrochloride) 2% solution is available in 20 mL single use vials.

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