The onset of action with chloroprocaine is rapid (usually within 6 to 12 minutes), and the duration of anesthesia, depending upon the amount used and the route of administration, may be up to 60 minutes. Local anesthetics appear to cross the placenta by passive diffusion. However, the rate and degree of diffusion varies considerably among the different drugs as governed by: (1) the degree of plasma protein binding, (2) the degree of lipid solubility, (3) the degree of ionization, and (4) the presence or absence of epinephrine in the anesthetic injection. Thus, the degree of lipid solubility and plasma protein binding may have the lowest fetal/maternal ratios. The extent of placental transfer is also determined by the degree of ionization and lipid solubility of the drug. Lipid soluble, nonionized drugs readily enter the fetal blood stream.

Depending upon the route of administration, local anesthetics are distributed to some extent to all body tissues, with high concentrations found in highly vascularized tissues, such as the liver, lungs, heart, and kidneys. Various pharmacokinetic parameters of the local anesthetics can be significantly altered by the presence of hepatic or renal disease, addition of epinephrine, factors affecting urinary pH, renal blood flow, the route of administration, and the site of the procedure. In vitro plasma half-life of chloroprocaine in adults is 21 ± 2 seconds for males and 25 ± 1 seconds for females. In the intra-plasma half-life in neonates is 43 ± 2 seconds.

Chloroprocaine is rapidly metabolized in plasma by hydrolysis of the ester linkage by pseudocholinesterase. The hydrolytic cleavage results in the formation of diethylaminoethanol and 2-chloro-4-diamozone acid, which inhibits the action of the sulfonamides (see PRECAUTIONS). The kidney is the main excretory organ for most local anesthetics and their metabolites. Urinary excretion is affected by urinary perfusion pressure, the rate of glomerular filtration, and the degree of urine concentration. The kidney is the main excretory organ for most local anesthetics and their metabolites. Urinary excretion is affected by urinary perfusion pressure, the rate of glomerular filtration, and the degree of urine concentration.

Chloroprocaine hydrochloride injection, methylparaben free, contains no sulfites. This product is not stable in the presence of sulfites. The drug is stable in the presence of methylene blue, bilirubin, or hemoglobin, and is not affected by the presence of amylase, lipase, or pseudocholinesterase. The drug is not affected by the presence of plasma from patients with abnormal clotting times.

Pharmacokinetics

The rate of systemic absorption of local anesthetic drugs is dependent upon the following factors: (1) the rate of blood flow to the site of injection, (2) the concentration of drug adjacent to the site of injection, and (3) the concentration of drug in the plasma. The absorption of local anesthetic drugs usually decreases as the severity of the procedure increases. The rate of systemic absorption of local anesthetic drugs is dependent upon the following factors: the body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug. The body's ability to metabolize and excrete the drug.
sion at birth which correlates with high local anesthetic serum levels and usually manifest seizures within six hours. Prompt use of supportive measures combined with forced urinary excretion of the local anesthetic has been used successfully to manage this complication.

Case reports of maternal convulsions and cardiovascular collapse following use of some local anesthetics for paracervical block in early pregnancy (to control labor and to prevent fetal malformation or abortion) suggest that systemic absorption under these circumstances may be rapid. The recommended maximum dose of each drug should not be exceeded. Intraarterial injection of any anesthetic should be avoided, and with frequent aspiration. Allow a 5-minute interval between doses.

There are no data concerning use of chloroprocaine for obstetrical paracervical block when tocolytics of new generation, such as nifedipine, are used. If necessary, nifedipine can be used for the same interval as recommended in the advanced case.

Cardiovascular System Reactions: High doses, or unintended intravascular injection, may lead to high plasma levels and related depression of the myocardium, hypotension, bradycardia, ventricular arrhythmias, and occasionally cardiac arrest. Allergic: Allergic type reactions are rare and may occur as a result of sensitivity to the local anesthetic. These reactions are characterized by signs such as urticaria, pruritis, erythema, anergic dermatitis (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and possibly, anaphylactoid type symptomatology (including severe hypotension). Cross sensitivity among members of the ester-type local anesthetic group has been reported. The usefulness of screening for sensitivity has not been definitely established.

Neurologic: In the practice of caudal and lumbar epidural block, occasional unintentional penetration of the subarachnoid space by the catheter may occur (see PRECAUTIONS). Subsequent adverse observations may depend partially on the amount of drug administered intrathecally. These adverse observations may be related to the magnitude of the subarachnoid injection, which may be only a small fraction of the total dose. Other factors, such as the duration of exposure to high spinal concentration of chloroprocaine injection, may also be involved.

Management of Local Anesthetic Emergencies: The first consideration is prevention, best accomplished by careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each local anesthetic injection. At the first sign of change, oxygen should be administered. The first step in the management of convulsions, as well as under-ventilation or apnea due to unintentional subarachnoid injection of drug solution, consists of immediate attention to the maintenance of a patent airway and assisted or controlled ventilation with oxygen and a delivery system capable of permitting immediate positive airway pressure by mask. Immediately after the institution of these ventilatory measures, the adequacy of the circulation should be evaluated, keeping in mind that drugs used to depress the circulation when administered intravenously. Should convulsions persist despite adequate respiratory support, and if the status of the circulation is judged adequate, an ultra-short acting barbiturate (such as thiopental or thiamylal) or a benzodiazepine (such as diazepam) may be administered intravenously: the clinician should be familiar with the use of these drugs. Supportive treatment of circulatory depression may require administration of intravenous fluids and, when appropriate, a vasopressor drug (such as ephedrine to enhance myocardial contractile force).

If not treated immediately, both convulsions and cardiovascular depression can result in hypoxia, acidosis, bradycardia, arrhythmias and cardiac arrest. Underventilation or apnea due to unintentional subarachnoid injection of local anesthetic solution may produce these same signs and also lead to cardiac arrest if ventilatory support is not instituted. If cardiac arrest should occur, standard cardiopulmonary resuscitation procedures should be followed. Recovery has been reported after prolonged resuscitative efforts.

Intrathecal intubation, employing drugs and techniques familiar to the clinician, is recommended in the initial intubation of oxygen by mask, if difficulty is encountered in the maintenance of a patent airway or if prolonged ventilatory support (assisted or controlled) is indicated.

DOSAGE AND ADMINISTRATION

Chloroprocaine may be administered as a single injection or continuously through the epidural catheter. The dose administered varies with the anesthetic procedure, the vascularity of the tissues, the depth of anesthesia and degree of muscle relaxation required, the duration of surgery and the physical condition of the patient. The smallest dosage and concentration required to produce the desired result should be used. Dosage should be reduced for children, elderly and debilitated patients and patients with cardiac and/or liver disease. The maximum single recommended doses of chloroprocaine in adults are: without epinephrine, 11 mg/kg, not to exceed a maximum total dose of 800 mg; with epinephrine (1:200,000), 14 mg/kg, not to exceed a maximum total dose of 1000 mg. For specific techniques and procedures, refer to standard textbooks.

There have been adverse event reports of cholinergic crisis in patients receiving intravenous infusions of local anesthetics following arthroscopic and other surgical procedures. Chloroprocaine hydrochloride injection is not approved for this use. (See WARNINGS and PRECAUTIONS).

Caudal and Lumbar Epidural Block: In order to guard against adverse experiences sometimes noted following unintended penetration of the subarachnoid space, the following procedure modifications are recommended:

1. Use an adequate test dose (3 mL of chloroprocaine hydrochloride injection 2% or 5 mL of chloroprocaine hydrochloride injection 2.5%) prior to induction of complete block. This test dose should be repeated when the patient is in such a fashion as to have displaced the epidural catheter. Allow adequate time for onset of anesthesia following administration of each test dose.

2. Avoid the rapid injection of a large volume of local anesthetic injection through the catheter. Consider fractional doses, when feasible.

3. In the event of the known injection of a large volume of local anesthetic injection into the subarachnoid space, after suitable resuscitation and if the catheter is in place, consider attempting the recovery of drug by draining a modest amount of cerebrospinal fluid (such as 10 mL) through the epidural catheter.

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

1. Infiltration and Peripheral Nerve Block: Chloroprocaine HCl Injection, USP

<table>
<thead>
<tr>
<th>Anesthetic Procedure</th>
<th>Solution Concentration %</th>
<th>Volume (mL)</th>
<th>Total Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td>3</td>
<td>10 to 20</td>
<td>30 to 60</td>
</tr>
<tr>
<td>Mandibular</td>
<td>3</td>
<td>2 to 3</td>
<td>6 to 12</td>
</tr>
<tr>
<td>Brachial plexus</td>
<td>2</td>
<td>30 to 40</td>
<td>600 to 800</td>
</tr>
<tr>
<td>Digital (without epinephrine)</td>
<td>2</td>
<td>3 to 4</td>
<td>30 to 40</td>
</tr>
<tr>
<td>Pudendal (without epinephrine)</td>
<td>2</td>
<td>10 each side</td>
<td>400</td>
</tr>
<tr>
<td>Paracervical (see also PRECAUTIONS)</td>
<td>1</td>
<td>3 each of 4 sites</td>
<td>up to 120</td>
</tr>
</tbody>
</table>

2. Caudal and Lumbar Epidural Block: For caudal anesthesia, the initial dose is 15 to 25 mL of a 2% or 3% solution. Repeated doses may be given at 40 to 60 minute intervals.

For lumbar epidural anesthesia, 2 to 2.5 mL per segment of a 2% or 3% solution can be used. The usual total volume of chloroprocaine hydrochloride injection is from 15 to 25 mL. Repeated doses 2 to 6 mL, less than the original dose may be given at 40 to 50 minute intervals.

The above dosages are recommended as a guide for use in the average adult. Maximum dosages of all local anesthetics must be individualized and may vary with different clinical situations, the age, weight and the rate of systemic absorption from a particular injection site.

Pediatric Dosage: It is difficult to recommend a maximum dose of any drug for children, since this varies as a function of age and weight. For children over 3 years of age who have a normal or near-normal body mass and normal body development, the maximum dose is determined by the child's age and weight and should not exceed 11 mg/kg (5 mg/lb). For example, in a child of 5 years weighing 52 lbs (23 kg), the dose of chloroprocaine hydrochloride without epinephrine would be 250 mg. Concentrations of 0.1 to 0.5% are suggested for infiltration and 1 to 1.5% for nerve block. In order to guard against systemic toxicity, the lowest effective concentration and lowest effective dose should be used at all times. Some of the lower concentrations for use in infants and smaller children are not available in prepackaged containers; it will be necessary to dilute available concentrations with the amount of 0.9% sodium chloride injection necessary to obtain the required final concentration of chloroprocaine injection.

Preparation of Epinephrine Injections: To prepare a 1:200,000 epi- nephrine-chloroprocaine hydrochloride injection, add 0.1 mL of a 1 to 1000 Epinephrine Injection, USP to 20 mL of Chloroprocaine Hydrochloride Injection, USP.

Chloroprocaine is incompatible with caustic alkalis and their carbonates, soaps, silver salts, iodide and iodines. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. In the event of the known injection of a large volume of local anesthetic injection into the subarachnoid space, after suitable resuscitation and if the catheter is in place, consider attempting the recovery of drug by draining a modest amount of cerebrospinal fluid (such as 10 mL) through the epidural catheter. For example, in a child of 5 years weighing 52 lbs (23 kg), the dose of chloroprocaine hydrochloride without epinephrine would be 250 mg. Concentrations of 0.1 to 0.5% are suggested for infiltration and 1 to 1.5% for nerve block. In order to guard against systemic toxicity, the lowest effective concentration and lowest effective dose should be used at all times. Some of the lower concentrations for use in infants and smaller children are not available in prepackaged containers; it will be necessary to dilute available concentrations with the amount of 0.9% sodium chloride injection necessary to obtain the required final concentration of chloroprocaine injection.

PRECAUTIONS

Chloroprocaine hydrochloride injection is USP, without preservatives and without EDTA, is supplied as follows:

3% solution (NDC 55390-404-20) in 20 mL single dose vials, individually boxed.

2% solution (NDC 55390-403-20) in 20 mL single dose vials, individually boxed.

HOW SUPPLIED Chloroprocaine Hydrochloride Injection, USP, without preservatives and without EDTA, is supplied as follows:

3% solution (NDC 55390-404-20) in 20 mL single dose vials, individually boxed.

2% solution (NDC 55390-403-20) in 20 mL single dose vials, individually boxed.

Keep from freezing. Protect from light. Store at controlled room temperature 15° to 30°C (59° to 86°F).

Manufactured by: Ben Venue Laboratories, Inc. Bedford, OH 44146

Manufactured for: Bedford Laboratories™ Bedford, OH 44146

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