Atracurium Besylate Injection, USP

**DESCRIPTION**

Atracurium besylate is an intermediate-duration, nondepolarizing, skeletal muscle relaxant for use during general anesthesia. It is a quaternary ammonium derivative of a synthetic d-tubocurarine analog. The molecular formula is C_{65}H_{82}N_{2}O_{18}S_{2} and its molecular weight is 1243.49.

Atracurium is a white, crystalline powder that is practically insoluble in water and soluble in ethanol. It is supplied in vials containing 5 mL of a sterile aseptically prepared solution containing 10 mg atracurium besylate. The pH of the solution is adjusted to 3.25 to 3.65 with benzenesulfonic acid.

**CLINICAL PHARMACOLOGY**

Atracurium besylate is a quaternary ammonium derivative of d-tubocurarine. It produces a nondepolarizing, intermediate-duration neuromuscular blockade with a duration of action longer than succinylcholine but shorter than vecuronium. Atracurium has no clinically significant effects on heart rate or blood pressure in the recommended dosage range. In the recommended dosage range, atracurium possesses a unique pharmacokinetic profile with a rapid onset, short duration of action, and low variability in recovery. It is cleared by the liver and its main metabolites are excreted in the urine.

**INDICATIONS AND USAGE**

Atracurium besylate is indicated, as an adjunct to general anesthesia, to facilitate intubation and to provide skeletal muscle relaxation during surgical and mechanical ventilation in adults and pediatric patients.

**CONTRAINDICATIONS**

Atracurium besylate is contraindicated in patients with a known hypersensitivity to atracurium or other quaternary ammonium compounds. Atracurium besylate is not recommended in patients with a history of histamine release in response to other muscle relaxants, because cross-sensitivity has been reported. Atracurium besylate is contraindicated in patients with known or suspected cholinergic blooming syndrome.

**WARNINGS**

Atracurium besylate should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

**PRECAUTIONS**

Hemofiltration has a minimal effect on plasma levels of atracurium and its metabolites, including in patients with renal dysfunction. Atracurium besylate is cleared by the liver and its main metabolites are excreted in the urine. Atracurium besylate should be used with caution in patients with impaired hepatic and renal function.

**ADVERSE REACTIONS**

The most common adverse reactions associated with the use of atracurium besylate are respiratory depression and respiratory acidosis. Other adverse reactions include hypotension, bradycardia, and respiratory difficulties. Rare cases of anaphylaxis have been reported with the use of atracurium besylate in humans.

**DRUG INTERACTIONS**

Atracurium besylate may be excreted by hemofiltration and may be inactivated in the presence of dialyzable substances. If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonistic effect should be considered. If atracurium besylate is administered during hemofiltration, the possibility of further neuromuscular depression should be considered. In such cases, alternative muscle relaxants should be used.

**PREPARATION FOR INTRAVENOUS ADMINISTRATION**

Atracurium besylate injection is intended for use in patients whose respiratory functions are normal or are being supported. Atracurium besylate is not intended for use in patients with severe respiratory deficiency or insufficiency.

**PREGNANCY**

Atracurium besylate should not be administered during the first trimester of pregnancy. There are no adequate and well-controlled studies in pregnant women. Atracurium besylate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Atracurium besylate should not be administered to late pregnant women with a history of bronchial asthma.

**NURSING MOTHERS**

It is not known whether muscle relaxants administered during vaginal delivery have immediate or long-term effects on nursing infants. Atracurium besylate should not be administered to late pregnant women with a history of bronchial asthma.

**PEDIATRIC USE**

Atracurium besylate should not be administered to late pregnant women with a history of bronchial asthma. There are no adequate and well-controlled studies in pregnant women. Atracurium besylate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Atracurium besylate should not be administered to late pregnant women with a history of bronchial asthma.

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Vin's patient experienced moderate hemodynamic changes (13% increase in mean arterial pressure) after the administration of atracurium besylate. The time from injection to 25% recovery (83 minutes) was approximately facilitated by administration of an anticholinesterase reversing agent such as neostigmine, which can enhance the cardiovascular effects, especially hypotension. If cardiovascular support is necessary, this enhanced pharmacological effects overdosage may increase the risk of histamine release and its cardiovascular effects.

Musculoskeletal: Atracurium besylate is the most frequently reported reaction, but there are insufficient data to support an estimate of their frequency. Most commonly observed were peri-orbital edema, facial edema, mouth edema, swelling, edema of the tongue, and dysphonia. In some cases, these reactions, in some cases, have been life-threatening and fatal.

An initial atracurium besylate dose of 0.3 to 0.4 mg/kg, given slowly or in divided doses over one cumulative effects, maintenance doses may be administered at relatively regular intervals for enhanced pharmacological effects. In adults, an initial atracurium besylate dose of 0.4 to 0.5 mg/kg may be used for intubation prior to administration of these potentiated by isoflurane or enflurane anesthesia. The same initial atracurium dose is recommended when using atracurium besylate with other neuromuscular blocking agents, the use of peripheral nerve stimulators to monitor neuromuscular block should be adequate to maintain continuous neuromuscular block in the range of 89% to 99% in most surgical cases and cold cases of minimized block. In general, the amount of infusion required to maintain adequate surgical relaxation during hepatic and balanced anesthesia in children or infants with significant cardiovascular disease is recommended.

The amount of atracurium besylate required to achieve the concentration of the drug in the plasma is determined by the patient's body weight, age, and the extent of surgical stress.

Table 3: Atracurium Besylate Infusion Rates for a Concentration of 0.2 mg/mL (kg)

<table>
<thead>
<tr>
<th>Patient Weight (kg)</th>
<th>Infusion Rate (mcg/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>9.0</td>
</tr>
<tr>
<td>50</td>
<td>11.0</td>
</tr>
<tr>
<td>60</td>
<td>13.0</td>
</tr>
<tr>
<td>70</td>
<td>15.0</td>
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</tbody>
</table>

Table 2: Percent of Patients Showing >30% Vital Sign Changes Following Administration of Atracurium Besylate

<table>
<thead>
<tr>
<th>Vital Sign Change</th>
<th>Increase</th>
<th>Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate</td>
<td>0.2%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>0.3%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Respiratory Rate</td>
<td>0.6%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Temperature</td>
<td>0.1%</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

Table 1: Percent of Patients Reporting Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Percent of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>2.1%</td>
</tr>
<tr>
<td>Hematological</td>
<td>2.8%</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>1.1%</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>0.6%</td>
</tr>
<tr>
<td>Neurological</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

Compliance and Administration
Atracurium besylate infusion solutions may be prepared by adding atracurium besylate injection and will be stored in a refrigerator. It is not recommended for long-term storage. The same solutions should be used within 24 hours after preparation. The solution may be administered within 1 hour of injection into the circulation. If a 0.2 mg/mL or 0.4 mg/mL, atracurium besylate in the above diluents may be added under refrigeration at or below 35°C (95°F). During storage of the diluent, it is recommended to use aseptic technique. The amount of a patient's body weight, age, and the extent of surgical stress.