For the use only of a registered medical practitioner or a hospital or a laboratory

℞ Atracurium Besylate Injection IP

AMERICAN
Atranium

For I.V. Use only.

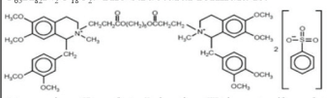
Composition:-

Each ml Contains:-

Atracurium Besylate	IP	10 mg
Water for Injection	IP	q.s

Description

Atracurium Besylate Injection IP is an intermediate-duration, non-depolarising, skeletal muscle relaxant for intravenous administration. Atracurium Besylate Injection IP is chemically unique, and is designated as 2, 2'-(3, 11-dioxo-4, 10-dioxatridecamethylene)-bis-(2-methyl-1,2,3,4- tetrahydropapaverinium benzenesulfonate). It has a molecular weight of 1243.49, and its empirical formula is $C_{65}H_{82}N_2O_{18}S_2$. The structural formula is:



Atracurium Besylate Injection IP is a sterile solution in water. Each ml contains 10 mg atracurium besylate. The pH is adjusted to 3.2-3.7 with benzenesulfonic acid.

PHARMACOLOGY

Non-depolarising agents antagonise the neurotransmitter action of acetylcholine by binding competitively with cholinergic receptor sites on the motor end-plate. This antagonism is inhibited and neuromuscular block reversed, by acetylcholinesterase inhibitors such as neostigmine, edrophonium and pyridostigmine.

The duration of neuromuscular blockade produced by Atracurium Besylate Injection IP is approximately one third to one half the duration seen with d-tubocurarine and pancuronium at equipotent doses. As with other non-depolarising neuromuscular blockers, the time to onset of paralysis decreases and the duration of maximum effect increases with increasing doses.

The ED95 (dose required to produce 95% suppression of the muscle twitch response) averages 0.23 mg/kg. An initial Atracurium Besylate Injection IP dose of 0.4 to 0.5 mg/kg generally produces maximum neuromuscular blockade within 3 to 5 minutes of injection, with suitable intubation conditions within 2 to 2.5 minutes. Recovery from neuromuscular blockade (under balanced anaesthesia) can be expected to begin approximately 20 to 35 minutes after injection. Recovery to 25% of control is achieved approximately 35 to 45 minutes after injection, and recovery is usually 95% complete 60 to 70 minutes after injection. The neuromuscular blocking action of Atracurium Besylate Injection is enhanced in the presence of potent inhalation anaesthetics. Isoflurane and enflurane increase the potency of Atracurium Besylate Injection and prolong neuromuscular blockade by approximately 35%; however, halothane's potentiating effect (approximately 20%) is marginal (see DOSAGE AND ADMINISTRATION section).

Repeat administration of maintenance doses of Atracurium Besylate Injection has no cumulative effect on the duration of neuromuscular blockade; therefore, doses can be administered at relatively regular intervals with predictable results. After an initial dose of 0.4 to 0.5 mg/kg under balanced anaesthesia, the first maintenance dose (suggested maintenance dose is 0.08 to 0.10 mg/kg) is generally required within 20 to 45 minutes, and subsequent maintenance doses are usually required at approximately 15 to 25 minute intervals. Repeated bolus dosing with atracurium does not give rise to prolongation of the neuromuscular blocking effect. This is reflected in the lack of accumulation.

Once recovery from Atracurium Besylate Injection's neuromuscular blocking effects begins, it proceeds more rapidly than recovery from d-tubocurarine, alcuronium and pancuronium. Regardless of Atracurium Besylate Injection dose, the time from start of recovery (from complete block) to complete recovery, as measured by restoration of the tetanic response to 95% of normal, is approximately 30 minutes under balanced anaesthesia, and approximately 40 minutes under halothane, enflurane or isoflurane. Repeated doses have no cumulative effect on recovery rate.

Reversal of neuromuscular blockade produced by Atracurium Besylate Injection can be achieved with an anticholinesterase agent such as neostigmine, edrophonium, or pyridostigmine, in conjunction with an anticholinergic agent such as atropine. Under balanced anaesthesia, reversal can usually be attempted approximately 20 to 35 minutes after an initial Atracurium Besylate Injection dose of 0.5 to 0.6 mg/kg, or approximately 10 to 30 minutes after 0.08 to 0.10 mg/kg maintenance dose, when recovery of muscle twitch has started. Complete reversal is usually accomplished within 8-10 minutes of the administration of reversing agents. There have been few reports of recurarization following reversal of Atracurium Injection induced neuromuscular blockade, a finding consistent with the rapid elimination of Atracurium Besylate Injection.

The pharmacokinetics of Atracurium Besylate Injection in man is essentially linear within the 0.3 to 0.6 mg/kg dose range. The elimination half-life is approximately 20 minutes. THE DURATION OF NEUROMUSCULAR BLOCKADE PRODUCED BY ATRACURIUM INJECTION DOES NOT CORRELATE WITH PLASMA PSEUDOCHOLINESTERASE LEVELS AND IS NOT ALTERED BY THE ABSENCE OF RENAL FUNCTION. This is consistent with the results of *in vitro* studies which have shown that Atracurium Besylate Injection is inactivated in plasma via two nonoxidative pathways: ester hydrolysis,

catalyzed by nonspecific esterases; and Hofmann elimination, a nonenzymatic chemical process which occurs at physiological pH and body temperature. The rate of Hofmann elimination, which is the principal route of elimination for Atracurium Besylate Injection is increased at a higher pH or at higher temperatures and reduced at a lower pH or lower temperatures. Some placental transfer occurs in humans.

Variations in the blood pH and body temperature of the patient within the physiological range will not significantly alter the duration of action of Atracurium Besylate Injection.

Tests with plasma from patients with low levels of pseudocholinesterase show that the inactivation of Atracurium Besylate Injection proceeds unaffected. The termination of the neuromuscular blocking action of Atracurium Besylate Injection is not dependent on hepatic or renal function. Its duration of action, therefore, is unlikely to be affected by impaired renal, hepatic or circulatory function.

The elimination half-life of atracurium is approximately 20 minutes, and the volume of distribution is 0.16 Uks. Atracurium is 82% bound to plasma proteins.

Radiolabel studies demonstrated that Atracurium Besylate Injection undergoes extensive degradation in cats, and that neither kidney nor liver plays a major role in its elimination. Biliary and urinary excretions were the major routes of excretion of radioactivity (totalling 90% of the labelled dose within 7 hours of dosing), of which Atracurium Besylate Injection represented only a minor fraction. The metabolites in bile and urine were similar, including products of Hofmann elimination and ester hydrolysis. A major metabolite is laudanosine which has the potential to accumulate in patients with end-stage liver failure who have received atracurium by infusion for several days to weeks. Laudanosine does not possess any neuromuscular blocking activity; CNS activating properties have been demonstrated in animals. Laudanosine is probably metabolised in the liver and is also cleared to a relatively small extent through the kidney. Accumulation is more likely in patients with hepatic and renal failure.

Plasma histamine levels were increased by 15% in a dose-dependent way with initial Atracurium Besylate Injection doses up to 0.5 mg/kg, and haemodynamic changes were minor within this dose range. Histamine levels increased by 92% following 0.6 mg/kg of Atracurium Besylate injection and were shown to correlate with a transient (5 minutes) decrease in blood pressure and a brief (2 to 3 minutes) episode of skin flushing. While these effects are of little clinical significance in most patients, the possibility of substantial histamine release at recommended doses in sensitive individuals or in patients in whom substantial histamine release would be especially hazardous (e.g. patients with significant respiratory or cardiovascular disease) must be considered.

It is not known whether the prior use of other non-depolarising neuromuscular blocking agents has any effect on the activity of Atracurium Besylate Injection. The prior use of suxamethonium decreases by approximately 2 to 3 minutes the time to maximum blockade induced by Atracurium Besylate Injection, and may increase the depth of blockade.

Atracurium Besylate Injection has no direct effect on intra-ocular pressure, and is therefore suitable for use in ophthalmic surgery.

Precautions:

In common with all the other neuromuscular blocking agents Atracurium Injection paralyses the respiratory muscles as well as other skeletal muscles but has no effect on consciousness. Atracurium Injection should be administered only with adequate anaesthesia or sedation/analgesia in the ICU and only by those skilled in the management of artificial respiration and only when facilities are instantly available for endotracheal intubation and for providing adequate ventilation of the patient, including the administration of oxygen under positive pressure and the elimination of carbon dioxide. The clinician must be prepared to assist or control respiration and anticholinesterase reversal agents should be immediately available.

Atracurium Injection has the potential to cause histamine release. Anaphylactic and anaphylactoid reactions have been reported and have sometimes been life-threatening. For this reason it is essential that appropriate resuscitative equipment be immediately available. Caution should be exercised in administering atracurium injection to patients with a history suggestive of an increased sensitivity to the effects of histamine.

Do not give atracrium by intramuscular administration.

Atracurium Injection is hypotonic and must not be administered into the infusion line of a blood transfusion.

Atracurium Injection has no known effect on consciousness, pain threshold, or cerebration.

Atracurium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g. barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Atracurium Injection may be inactivated and a free acid may be precipitated.

Caution should also be exercised when administering atracurium to patients who have shown hypersensitivity to other neuromuscular blocking agents since cross-sensitivity between neuromuscular blocking agents has been reported

Dosage and Administration

To avoid distress to the patient, Atracurium Injection should not be administered before unconsciousness has been induced. Atracurium Injection should not be mixed in the same syringe, or administered simultaneously through the same needle, with alkaline solutions (e.g. barbiturate solutions).

Atracurium Injection should be administered intravenously. DO NOT GIVE ATRACURIUM INJECTION INTRAMUSCULARLY. Intramuscular administration of Atracurium injection may result in tissue irritation and there is no clinical data to support this route of administration.

Bolus doses for intubation and maintenance of neuromuscular blockade

Use in adults:

The initial dosage for adults ranges from 0.3 to 0.6 mg/kg (depending on the duration of full block required) and will provide adequate relaxation for 15 to 35 minutes.

A Atracurium Injection dose of 0.5 to 0.6 mg/kg (2.2 to 2.6 times the ED95), given as an intravenous bolus injection provides suitable conditions for non-emergency intubation in 2 to 2.5 minutes in most patients which is comparable to other drugs of this class. Maximum neuromuscular blockade is achieved approximately 2 to 5 minutes after injection. Complete neuromuscular blockade generally lasts 20 to 35 minutes under balanced anaesthesia. Recovery to 25% of control is achieved approximately 35 to 45 minutes after injection, and recovery is usually complete 60 to 70 minutes after injection.

Atracurium Injection is potentiated by isoflurane or enflurane anaesthesia. The same initial Atracurium Injection dose of 0.5 to 0.6 mg/kg may be used for intubation prior to administration of these inhalation agents; however, if Atracurium Injection is first administered under steady state of isoflurane or enflurane, the initial Atracurium injection dose may be reduced by approximately one-third, i.e. 0.3 to 0.4 mg/kg, to adjust for the potentiating effects of these anaesthetic agents. With halothane, which has only a marginal (approximately 20%) potentiating effect on Atracurium Injection, smaller dosage reductions may be considered.

Atracurium Injection doses of 0.08 to 0.10 mg/kg are recommended for maintenance of neuromuscular blockade during prolonged surgical procedures. The first maintenance dose will generally be required 20 to 45 minutes after the initial Atracurium Injection injection, but the need for maintenance doses should be determined by clinical criteria. Because Atracurium Injection lacks cumulative effects, maintenance doses may be administered at relatively regular intervals for each patient, ranging approximately from 15 to 25 minutes under balanced anaesthesia, slightly longer under isoflurane or enflurane. Higher Atracurium Injection doses (up to 0.2 mg/kg) permit maintenance dosing at longer intervals.

Use in children:

No Atracurium Injection dosage adjustments are required for paediatric patients two years of age or older. A Atracurium Injection dose of 0.4 mg/kg is recommended as the initial dose for paediatric patients aged 1 month to 2 years of age under halothane anaesthesia. Maintenance doses may be required with slightly greater frequency in infants and children than in adults.

Safety and efficacy in children younger than one month have not been established.

In common with all neuromuscular blocking agents monitoring of neuromuscular function is recommended, particularly during long-term use, in order to individualise dosage requirements.

Special considerations:

Atracurium Injection may be used at standard dosage at all levels of renal or hepatic function, including end stage failure.

Atracurium Injection may be used at standard dosage in elderly patients. It is recommended, however, that the initial dose be at the lower end of the range and that it be administered slowly.

An initial Atracurium Injection dose of 0.3 to 0.4 mg/kg, given slowly or in divided doses over one minute, is recommended for patients with significant cardiovascular disease (an increased incidence of hypotensive episodes has been seen in these patients) and for patients with any history (e.g. anaphylactoid reactions or asthma) suggesting a greater risk of histamine release.

Dosage reductions must be considered also in patients with neuromuscular disease, severe electrolyte disorders, or carcinomatosis in which potentiation of neuromuscular blockade or difficulties with reversal have been demonstrated. There has been no clinical experience with Atracurium Injection in these patients, and no specific dosage adjustments can be recommended.

An initial Atracurium Injection dose of 0.3 to 0.4 mg/kg is recommended following the use of suxamethonium for intubation under balanced anaesthesia. Further reductions may be desirable with the use of potent inhalation anaesthetics. The patient should be permitted to recover from the effects of suxamethonium prior to Atracurium Injection administration.

Reversal:

Reversal of neuromuscular blockade produced by Atracurium Injection can be achieved with an anticholinesterase such as neostigmine in conjunction with an anticholinergic agent such as atropine. Under balanced anaesthesia, reversal can usually be attempted approximately 20 to 35 minutes after the initial Atracurium Injection dose or approximately 10 to 30 minutes after a maintenance dose, when recovery of muscle twitch has started. Complete reversal is usually accomplished within 8 to 10 minutes of the administration of reversing agents. Rare instances of breathing difficulties, possibly related to incomplete reversal, have been reported following attempted pharmacological antagonism of Atracurium Injection induced neuromuscular blockade. As with other agents in this class, the tendency for residual neuromuscular block is increased if reversal is attempted at deep levels of blockade or if inadequate doses of reversal agents are employed.

Use as an Infusion:

An initial bolus dose of 0.3 to 0.6 mg/kg of Atracurium Injection can be used to maintain neuromuscular block during long surgical procedures by administration as a continuous infusion. An initial infusion rate of 9 to 10 µg/kg/min may be required to restore adequate neuromuscular block. Thereafter, a rate of 5 to 9 µg/kg/min should be adequate to maintain continuous neuromuscular block in the range of 89 to 99% in most paediatric and adult patients under balanced anaesthesia. Occasional patients may require infusion rates as low as 2 µg/kg/min or as high as 15 µg/kg/min.

Longer term use in Intensive Care Unit (ICU) Patients:

There is only limited information on the efficacy and safety of long-term (median duration approximately 90 hours) intravenous atracurium infusion to facilitate mechanical ventilation in the ICU (n=58).

After an optional initial bolus dose of Atracurium Injection of 0.3 to 0.6 mg/kg, Atracurium injection can be used to maintain neuromuscular block by administering a continuous infusion at rates of between 11 and 13 µg/kg/min (0.65 - 0.78 mg/kg/hr). However, there is wide inter-patient variability in dosage requirements. Dosage requirements may change with time. Infusion rates as low as 4.5 µg/kg/min (0.27 mg/kg/hr) or as high as 29.5 µg/kg/min (1.77 mg/kg/hr) are required in some patients.

The rate of spontaneous recovery from neuromuscular block after infusion of Atracurium Injection in ICU patients is independent of the duration of administration. Spontaneous recovery to a train-of-four ratio >0.75 (the ratio of the height of the fourth to the first twitch in a train-of-four) can be expected to occur in approximately 60 minutes. A range of 32-108 minutes has been observed in clinical trials.

Limited information is available on the plasma levels or clinical consequences of atracurium metabolites that may accumulate during days to weeks of atracurium administration in ICU patients. Laudanosine, a major biologically active metabolite of atracurium without neuromuscular blocking activity, produces transient hypotension and, in higher doses, cerebral excitatory effects (generalised muscle twitching and seizures) when administered to several animal species. Although seizures have been seen in ICU patients receiving atracurium, definite causality has not been attributable to laudanosine or atracurium. Thesepatients usually had predisposing causes (such as cranial trauma, cerebral oedema, hypoxic encephalopathy, viral encephalitis, and uraemia).

Monitoring:

In common with all neuromuscular blocking agents continuous monitoring of neuromuscular function is recommended during the use of Atracurium Injection in order to individualise dosage requirements which may be variable over time.

Pregnancy

Use in Pregnancy: (Category C)

Atracurium has been shown to cross the placenta to a limited degree although the transfer of metabolites may be greater. Animal studies of teratogenic potential are limited to a single study in which pregnant rabbits received subcutaneous doses of 0.15 mg/kg once daily or 0.1 mg/kg twice daily during the period of organogenesis. There was no clear evidence of teratogenic activity at these doses, which are less than those used clinically, although there was some indication of fetotoxicity manifest as slight increases in the incidences of minor skeletal and visceral anomalies. There are no adequate and well controlled studies in pregnant women. In common with all neuromuscular blocking agents, Atracurium Injection should be used in pregnant women only if in the opinion of the physician, the potential benefit outweighs any potential risk to the foetus.

Warnings:-

Atracurium should be used only by those skilled in airway management and respiratory support. Equipment and personnel must be immediately available for endotracheal intubation and support of ventilation, including administration of positive pressure oxygen. Adequacy of respiration must be assured through assisted or controlled ventilation. Anticholinesterase reversal agents should be immediately available.

Do not give atracurium besylate Injection by intramuscular administration.

Atracurium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia.

Atracurium besylate injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, atracurium may be inactivated and a free acid may be precipitated.

Atracurium besylate injection 10 ml multiple dose vials contain benzyl alcohol. In neonates, benzyl alcohol has been associated with an increased incidenceof neurological and other complications which are sometimes fatal. Atracurium besylate injection 5 ml single use vials do not contain benzyl alcohol (see PRECAUTIONS: Pediatric Use).

Storage:-

Store protect from light at temperature between 2° to 8°C. Do not freeze.

Improper Storage may deteriorate the product

Medicine: - Keep out of reach of children.

Presentation:- Each pack contain 10 mg/ml of Atracurium Besylate Injection in a Clear ampoule/vial.

Manufactured by:

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