For the use of Registered Medical Practitioner of Hospital or a Laboratory only

Atracurium Besylate Injection USP 10mg/ml

COMPOSITION

Each ml contains:

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

CLINICAL PHARMACOLOGY

Pharmacodynamic properties

Pharmacotherapeutic group: muscle relaxants, peripherally acting agents; Other quaternary ammonium components

ATC code: M03AC04

Atracurium besilate 10 mg/ml is a non-depolarising muscle relaxant with medium duration of action.

The active substance, atracurium besilate, interacts specifically with neurophysiological processes at the motor end-plate by competitively displacing acetylcholine from its receptor sites.

As a result of end-plate occupation by atracurium besilate, further depolarisation is inhibited. Subsequently, skeletal muscles are paralysed since stimulation by motor nerves cannot be transmitted to the muscles.

Through inhibition of acetylcholine degradation by means of cholinesterase inhibitors, e.g. neostigmine or edrophonium, an increase of acetylcholine concentration is achieved at all cholinergic synapses. The balance between atracurium besilate (antagonist) and acetylcholine (agonist) is shifted in favour of the latter. As a result, stimulation of the muscle can reoccur.

Paediatric population:

The limited data in neonates from literature reports suggest variability in the time to onset and duration of atracurium in this population as compared to children.

Pharmacokinetic properties

The onset and duration of effect of atracurium besilate are dose-dependent.

In man, following the administration of 0.3 mg atracurium besilate/kg, plasma concentrations of 3 micrograms/ml were measured after 3 minutes.

Atracurium besilate is inactivated by:

1. Hofmann elimination, a non-enzymatic process which occurs at physiological pH and temperature,
2. Ester hydrolysis catalysed by non-specific esterases.

Variations in the blood pH and body temperature in patients within the physiological range will not significantly alter the duration of action of atracurium besilate.

Tests with plasma from patients with low levels of pseudocholinesterase show that the inactivation of atracurium besilate proceeds unaffected.

Plasma protein binding

The plasma protein binding of atracurium besilate is about 82%. Plasma proteins neither influence the rate nor the mode of atracurium besilate catabolism.

Elimination

Elimination half-life for atracurium besilate is 20 to 30 minutes. As the termination of the neuromuscular blocking action of atracurium besilate is not dependent on its hepatic or renal metabolism or excretion, its duration of action, therefore, is unlikely to be affected by impaired renal, hepatic or circulatory function.

When given to laboratory animals, cerebral excitatory effects have been associated with a metabolite of atracurium besilate, laudanosine. Although seizures have been observed in patients in ICUs who were receiving atracurium besilate, they were not attributed in any case to laudanosine or to atracurium besilate, even after weeks of continuous infusion.

The metabolites are present at higher concentrations in intensive care patients with limited renal and/or hepatic function. However, these metabolites have no effect on the muscle relaxant action.

INDICATION AND USAGE

Atracurium Besilate Injection is indicated as an adjunct to general anaesthesia during surgery to relax skeletal muscles, and to facilitate endotracheal intubation and mechanical ventilation. It is also indicated to facilitate mechanical ventilation in intensive care unit (ICU) patients.

CONTRA-INDICATION

Hypersensitivity to the active substance or any of the excipients.

DRUG INTERACTIONS

As with other non-depolarising neuromuscular blocking agents, the magnitude and/or duration of atracurium's effects may be increased as a result of an interaction with the following agents.

Inhalation anaesthetics: atracurium is potentiated by isoflurane, desflurane, sevoflurane and enflurane anaesthesia, and only marginally potentiated by halothane anaesthesia.

Antibiotics: including the aminoglycosides, polymyxins, spectinomycin, tetracyclines, lincomycin, clindamycin and vancomycin.

Anticonvulsants (acute administration only): phenytoin, carbamazepine.

Antiarrhythmic drugs: local anaesthetics such as lidocaine, procainamide, quinidine.

Beta-blockers: propranolol, oxprenolol

Antirheumatic drugs: chloroquine, d-penicillamine

Calcium channel blockers: diltiazem, nicardipine, nifedipine, verapamil.

Diuretics: frusemide, thiazides, acetazolamide and possibly mannitol.

Ganglion blocking agents: trimetaphan, hexamethonium.

Others: dantrolene, parenteral magnesium sulphate, chlorpromazine, steroids, ketamine, lithium salts and quinine.

Rarely, some of the above drugs may aggravate or unmask latent myasthenia gravis or actually induce a myasthenic syndrome. In these situations a consequent increased sensitivity to atracurium would be expected.

The administration of combinations of non-depolarising neuromuscular blocking agents in conjunction with atracurium may produce a degree of neuromuscular blockade in excess of that which might be expected were an equipotent total dose of atracurium administered. Any synergistic effect may vary between different drug combinations.

A depolarising muscle relaxant such as suxamethonium chloride should not be administered to prolong the neuromuscular blocking effects of non-depolarising blocking agents such as atracurium, as this may result in a prolonged and complex block which can be difficult to reverse with anticholinesterase drugs.

The prior use of suxamethonium reduces the onset (to maximum blockade) by approximately 2 to 3 minutes and may increase the depth of neuromuscular blockade induced by atracurium. Therefore, the initial atracurium dose should be reduced and the reduced dose should not be administered until the patient has recovered from the neuromuscular blocking effects of suxamethonium.

The use of intravenous corticosteroids with neuromuscular blocking agents has been reported to antagonise neuromuscular blockades. In addition, prolonged co-administration of these agents may increase the risk and/or severity of myopathy resulting in prolonged flaccid paralysis following discontinuation of the neuromuscular blocking agent. The myopathy is usually reversible with recovery in several months.

The onset of neuromuscular blockade is likely to be lengthened and the duration of blockade shortened in patients receiving chronic anticonvulsant therapy (e.g. carbamazepine, phenytoin). However, if the anticonvulsants are given acutely, the neuromuscular blocking effects may be increased.

In principle, maintaining neuromuscular monitoring until complete reversal of neuromuscular blockade should permit detection of most interactions. Nevertheless, recurrence of neuromuscular blockade may occur, for example, upon treatment with post surgical antibiotics.

WARNINGS AND PRECAUTIONS

Atracurium Besilate Injection should be used only by those skilled in the management of artificial respiration and only when facilities are immediately available for endotracheal intubation and for providing adequate ventilation support, including the administration of oxygen under positive pressure and the elimination of carbon dioxide. The clinician must be prepared to assist or control ventilation, and anticholinesterase agents should be immediately available for reversal of neuromuscular blockade.

Atracurium has no known effect on consciousness, pain threshold, or cerebration. In surgery, it should be used only with adequate general anaesthesia.

In common with other neuromuscular blocking agents, the potential for histamine release exists in susceptible patients during administration of atracurium besilate. Caution should be exercised in patients with a history suggestive of an increased sensitivity to the effects of histamine.

Do not give Atracurium Besilate Injection by intramuscular administration.

Atracurium Besilate Injection has an acid pH and therefore 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 Besilate Injection may be inactivated and a free acid may be precipitated.

When a small vein is selected as the injection site, Atracurium Besilate Injection should be flushed through the vein with physiological saline after injection. When other anaesthetic drugs are administered through the same indwelling needle or cannula as Atracurium Besilate Injection, it is important that each drug is flushed through with an adequate volume of physiological saline.

Atracurium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of non-depolarising agents has been noted. A reduced dosage of atracurium and the use of a peripheral nerve stimulator for assessing neuromuscular blockade is especially important in these patients. Similar precautions should be taken in patients with severe electrolyte disorders.

Atracurium does not have significant vagal or ganglion blocking properties in the recommended dosage range. Consequently, atracurium will not counteract the bradycardia produced by many anaesthetic agents or by vagal stimulation during surgery. Therefore, bradycardia during anaesthesia may be more common with atracurium than with other muscle relaxants.

As with other non-depolarising neuromuscular blocking agents, resistance to atracurium may develop in patients suffering from burns. Such patients may require increased doses of atracurium depending on the time elapsed since the burn injury and the extent of the burn.

Atracurium Besilate Injection should be administered over a period of at least 60 seconds to patients who may be unusually sensitive to falls in arterial blood pressure, for example those who are hypovolaemic.

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

Monitoring of serial creatine phosphokinase (CPK) values should be considered in asthmatic patients receiving high dose corticosteroids and neuromuscular blocking agents in intensive care units.

Special precautions should be taken in patients with known anaphylactic reactions to curares, as cross-reactivity may be possible with this product.

SIDE EFFECTS

Very common	(≥1/10)
Common	(≥1/100 to <1/10)
Uncommon	(≥1/1,000 to <1/100)
Rare	(≥1/10,000 to <1/1,000)
Very rare	(<1/10,000)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Immune system disorders

Very rare: Severe anaphylactic and anaphylactoid reactions including shock, circulatory failure and cardiac arrest have been reported in patients receiving atracurium besilate in conjunction with one or more anaesthetic agents.

Nervous system disorders

Very rare: There have been reports of seizures in patients in ICUs who had been receiving atracurium besilate simultaneously with other pharmacological agents. These patients generally had one or more medical conditions which made them susceptible to seizures (such as brain injury, cerebral oedema, viral encephalitis, hypoxic encephalopathy, uraemia). Even after weeks of continuous infusion, there appears to be no correlation between plasma laudanosine concentration and appearance of seizures in clinical trials.

Cardiac disorders

Common: Tachycardia

Vascular disorders

Common: Mild transient hypotension

Respiratory, thoracic and mediastinal disorders

Common: Bronchospasm, wheezing

Very rare: Laryngospasm

Skin and subcutaneous tissue disorders

Common: Urticaria, skin flushing

Musculoskeletal and connective tissue disorders

Very rare: After prolonged use of atracurium besilate in severely ill ICU patients myasthenia and/or myopathy have been observed. The majority of these patients received concomitant corticosteroids. Causal connection with atracurium besilate therapy is not established.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

It is not recommended to use potentially dangerous machinery or drive a car within 24 hours after full recovery from the neuromuscular blocking action of atracurium.

OVERDOSE

Prolonged muscle paralysis and its consequences are the main signs of overdose.

There is limited experience with atracurium overdosage following parenteral administration. The possibility of iatrogenic overdosage can be minimised by carefully monitoring muscle twitch response to peripheral nerve stimulation. Excessive doses of atracurium are likely to produce symptoms consistent with extensions of the usual pharmacological effects. Overdosage may increase the risk of histamine release and adverse cardiovascular effects, especially hypotension. If cardiovascular support is necessary, this should include proper positioning, fluid administration, and the use of vasopressor agents if necessary. It is essential to maintain a patent airway with assisted positive pressure ventilation until spontaneous respiration is adequate. Full sedation will be required since consciousness is not impaired. The duration of neuromuscular blockade may be prolonged and a peripheral nerve stimulator should be used to monitor recovery. Recovery may be hastened by the administration of an anticholinesterase agent such as neostigmine or pyridostigmine in conjunction with an anticholinergic agent such as atropine, once evidence of spontaneous recovery is present.

DOSAGE & MODE OF ADMINISTRATION

Posology

Use as an adjunct to general anaesthesia

Atracurium Besilate Injection should only be administered by intravenous injection. **Do not give Atracurium Besilate Injection intramuscularly** since this may result in tissue irritation and there are no clinical data to support this route of administration.

To avoid distress to the patient, Atracurium Besilate Injection should not be administered before unconsciousness has been induced.

Atracurium Besilate Injection should not be mixed in the same syringe, or administered simultaneously through the same needle, with alkaline solutions (e.g. barbiturate solutions).

In common with all neuromuscular blocking agents, monitoring of neuromuscular function is recommended during the use of Atracurium Besilate Injection in order to individualise dosage requirements.

Initial bolus doses for intubation

An initial atracurium besilate dose of 0.3 to 0.6 mg/kg (depending on the duration of full block required), given as an intravenous bolus injection, is recommended. This will provide adequate relaxation for about 15 to 35 minutes.

Endotracheal intubation can usually be accomplished within 90 to 120 seconds of the intravenous injection of 0.5 to 0.6 mg/kg. Maximum neuromuscular blockade is generally achieved approximately 3 to 5 minutes after administration. Spontaneous recovery from the end of full block occurs in about 35 minutes as measured by the restoration of the tetanic response to 95% of normal neuromuscular function.

Maintenance doses

Intermittent IV injection: During prolonged surgical procedures neuromuscular blockade may be maintained with atracurium besilate maintenance doses of 0.1 to 0.2 mg/kg. Successive supplementary dosing does not give rise to accumulation of neuromuscular blocking effect.

Use as an infusion: After the initial atracurium bolus dose, neuromuscular blockade may be maintained during prolonged surgical procedures by administering atracurium besilate as a continuous intravenous infusion at a rate of 0.3 to 0.6 mg/kg/hour. The infusion should not be commenced until early spontaneous recovery from the initial atracurium bolus dose is evident.

Atracurium Besilate Injection can be administered by infusion during cardiopulmonary bypass surgery at the recommended infusion rates. Induced hypothermia to a body temperature of 25 to 26°C reduces the rate of inactivation of atracurium, and therefore full neuromuscular block may be maintained with approximately half the original infusion rate at these temperatures.

Reversal of neuromuscular blockade

The neuromuscular blockade induced by atracurium can be reversed with an anticholinesterase agent such as neostigmine or pyridostigmine, usually in conjunction with an anticholinergic agent such as atropine or glycopyrronium to prevent the adverse muscarinic effects of the anticholinesterase. Under balanced anaesthesia, reversal can usually be attempted approximately 20 to 35 minutes after the initial atracurium dose, or approximately 10 to 30 minutes after the last atracurium maintenance dose, when recovery of muscle twitch has started. Complete reversal of neuromuscular blockade is usually achieved within 8 to 10 minutes after administration of the reversing agents.

Rare instances of breathing difficulties, possibly related to incomplete reversal, have been reported following attempted pharmacological antagonism of atracurium 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.

Facilitation of mechanical ventilation in intensive care unit (ICU) patients

After an optional initial bolus dose of 0.3 to 0.6 mg/kg, neuromuscular block may be maintained by administering a continuous atracurium besilate infusion at rates of between 11 and 13 microgram/kg/min (0.65 to 0.78 mg/kg/hr). There may be wide inter-patient variability in dosage requirements and these may increase or decrease with time. Infusion rates as low as 4.5 microgram/kg/min (0.27 mg/kg/hr) or as high as 29.5 microgram/kg/min (1.77 mg/kg/hr) are required in some patients.

The rate of spontaneous recovery from neuromuscular block after infusion of atracurium besilate 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 to 108 minutes has been observed in clinical trials.

Dosage considerations

Use in children: The dosage in children over the age of 1 month is similar to that in adults on a body weight basis, however, large individual variability in the neuromuscular response in paediatric patients indicates that neuromuscular monitoring is essential.

Use in neonates: The use of Atracurium is not recommended in neonates since there are insufficient data available.

Use in the elderly: The standard dose of atracurium may be used in elderly patients, however, it is recommended that the initial dose be at the lower end of the range and it should be administered slowly

Use in patients with reduced renal and/or hepatic function: Standard dosages may be used at all levels of renal or hepatic function, including endstage failure.

Use in patients with cardiovascular disease: In patients with significant cardiovascular disease the initial dose of atracurium should be administered over a period of at least 60 seconds.

Method of Administration

Use only Intravenous injection

PREGNANCY AND LACTATION

Fertility

No fertility data are available

Pregnancy

Atracurium crosses the placenta but there have been no demonstrated adverse effects in the foetus or newborn infant. Animal studies have indicated that atracurium has no adverse effects on foetal development. As with all neuromuscular blocking agents, the use of atracurium in the first three months of pregnancy should be avoided and it should not be used during the second and third trimesters unless clearly necessary.

Atracurium is suitable for maintenance of muscle relaxation during caesarean section as it does not cross the placenta in clinically significant amounts following recommended doses. In an open study, atracurium besilate (0.3 mg/kg) was administered to 26 pregnant women during delivery by caesarean section. No harmful effects were attributable to atracurium in any of the newborn infants, although small amounts of atracurium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following caesarean section during which a neuromuscular blocking agent has been administered.

Anaesthesia during the third trimester of pregnancy exposes the mother to Mendelson syndrome (acid pneumopathy due to gastric acid aspiration). If a muscle relaxant is used at induction of anaesthesia, one should be chosen with a short onset and duration of action and low placental transfer and used in the lowest dose required to induce adequate neuromuscular relaxation. In patients receiving magnesium sulphate, the reversal of neuromuscular blockade may be unsatisfactory and the atracurium dose should be lowered as indicated.

Breastfeeding

Atracurium has a relatively high molecular weight and is highly ionized at physiologic pH, both factors that markedly reduce transfer into milk. In addition, even though milk is slightly more acidic than plasma, any atracurium transferred into milk would be rapidly degraded. Nevertheless, in view of the potential respiratory depressant effect on the neonate, especially if premature, it is recommended that if breastfeeding is started within 24 hours after administration of atracurium, the neonate is closely monitored.

STORAGE CONDITION

Protected from light.

Store in a refrigerator & protect from freezing.

KEEP OUT OF REACH OF CHILDREN

PRESENTATION

2.5ml, 5ml Ampoule packed in cardboard carton along with pack insert.

MANUFACTURED IN INDIA

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