

PRODUCT MONOGRAPH

Pr ATRACURIUM BESYLATE INJECTION

10 mg/mL

Skeletal Neuromuscular Blocking Agent

Sandoz Canada Inc.
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Date of Revision: March 25, 2013

Control no.: 161881

Pr **ATRACURIUM BESYLATE INJECTION**
10 mg/mL

THERAPEUTIC CLASSIFICATION

Skeletal Neuromuscular Blocking Agent

ACTIONS AND CLINICAL PHARMACOLOGY

Atracurium besylate is a nondepolarizing, intermediate-duration, skeletal neuromuscular blocking agent. Nondepolarizing agents antagonize the neurotransmitter action of acetylcholine by binding competitively to 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 is approximately one-third to one-half the duration seen with d-tubocurarine, metocurine and pancuronium at equipotent doses. As with other nondepolarizing neuromuscular blockers, the time to onset of paralysis decreases and the duration of maximum effect increases with increasing atracurium besylate doses.

The pharmacokinetics of atracurium besylate in man are 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 does not correlate with plasma pseudocholinesterase levels and is not altered by the absence of renal function.

INDICATIONS AND CLINICAL USE

Atracurium Besylate Injection is indicated, as an adjunct to general anaesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation. It can be used most advantageously if muscle twitch response to peripheral nerve stimulation is monitored.

CONTRAINDICATIONS

Atracurium besylate is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS

Atracurium Besylate Injection should be used 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. Do not give Atracurium Besylate Injection intramuscularly.

Atracurium besylate has no known effect on consciousness, pain threshold, or cerebation. It should be used only with adequate anaesthesia.

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. In such mixtures, the resultant pH may cause inactivation of the drug and precipitation of the free acid.

Atracurium Besylate Injection 10 mL multidose vials contain benzyl alcohol. Benzyl alcohol has been associated with an increased incidence of neurological and other complications in newborn infants which are sometimes fatal.

PRECAUTIONS

Histamine Release

The possibility of substantial histamine release with consequent bronchospasm or anaphylaxis in sensitive individuals must be considered. Special caution should be exercised in administering atracurium besylate to those patients in whom substantial histamine release would be especially hazardous (e.g. patients with clinically significant cardiovascular disease) and in patients with any history (e.g. severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute. Limited clinical experience indicates that mean arterial pressure decreases in a substantial percentage of patients with a history of cardiovascular disease even at these doses.

Pregnancy

Atracurium besylate has been shown to be potentially teratogenic at up to half the human dose when given to nonventilated rabbits by the subcutaneous route at sub-paralyzing doses (see TOXICOLOGY: Teratology). Therefore, atracurium besylate should not be used during pregnancy unless, in the opinion of the physician, the potential benefits outweigh the unknown hazards.

Obstetrics

It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility may increase that a forceps delivery will be necessary.

In an open study, atracurium besylate has been administered (0.3 mg/kg) to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to the drug in any of the newborn infants, although small amounts were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean

section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and the atracurium besylate dose should be lowered as indicated.

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 atracurium besylate is administered to nursing women.

Children

Safety and effectiveness in children below the age of 1 month have not been established.

Patients with Special Diseases and Conditions

Atracurium besylate may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular disease in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis.

The safety of atracurium besylate has not been established in patients with bronchial asthma.

Obesity

Ideal body weight should be considered in dosage calculations for obese patients with appropriate attention to the attendant risk of underdosing. Severe obesity may pose airway or ventilatory problems before, during, or after the use of nondepolarizing neuromuscular blockers.

Hypothermia

Hypothermia (25 - 28°C) has been associated with a decreased requirement for nondepolarizing neuromuscular blocking agents.

Cardiovascular Effects

Since atracurium besylate has no clinically significant effects on heart rate at the recommended dosage range, it will not counteract the bradycardia produced by many anaesthetic agents or vagal stimulation.

Malignant Hyperthermia

Multiple factors in anaesthesia practice are suspected of triggering malignant hyperthermia (MH), a potentially fatal hypermetabolic state of skeletal muscle. Halogenated anaesthetic agents and succinylcholine are recognized as the principal pharmacologic triggering agents in MH-susceptible patients; however, since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anaesthesia. Reports of MH have been rare in cases in which atracurium besylate has been used.

Burns

Resistance to nondepolarizing neuromuscular blocking agents may develop in burn patients. Increased doses of nondepolarizing muscle relaxants may be required in burn patients and are

dependent on the time elapsed since the burn injury and the size of the burn.

Electrolyte Abnormalities

Electrolyte abnormalities may antagonize or potentiate the action of neuromuscular blocking agents. For example, hyperkalemia has been reported to antagonize nondepolarizing agents, while hypokalemia has been associated with an enhancement of their activity.

The action of neuromuscular blocking agents may be enhanced by magnesium salts administered for the management of toxemia of pregnancy.

Long-Term Use in Intensive Care Unit (ICU)

There is only limited information available on the efficacy and safety of long-term (days to weeks) intravenous atracurium besylate infusion to facilitate mechanical ventilation in the ICU. These data suggest that dosage requirements show wide interpatient variability and may decrease or increase with time.

When there is a need for long-term mechanical ventilation, the benefits-to-risk ratio of neuromuscular blockade must be considered.

Little information is available on the plasma levels or clinical consequences of atracurium besylate metabolites that may accumulate during days to weeks of atracurium besylate administration in ICU patients. Laudanosine, a major biologically active metabolite of atracurium besylate without neuromuscular blocking activity, produces transient hypotension and, in higher doses, cerebral excitatory effects (generalized muscle twitching and seizures) when administered to several species of animals. There have been rare reports of seizures in ICU patients who have received atracurium besylate or other agents. These patients usually had predisposing causes (such as head trauma, cerebral edema, hypoxic encephalopathy, viral encephalitis, uraemia). There are insufficient data to determine whether or not laudanosine contributes to seizures in ICU patients.

Whenever the use of atracurium besylate or any neuromuscular blocking agent is contemplated in the ICU, it is recommended that neuromuscular transmission be monitored continuously during administration with the help of a nerve stimulator. Additional doses of atracurium besylate or any other neuromuscular blocking agent should not be given before there is a definite response to T₁ or to the first twitch. If no response is elicited, infusion administration should be discontinued until a response returns.

The effects of haemodialysis, haemoperfusion and haemofiltration on plasma levels of atracurium and its metabolites are unknown.

Sensitivity/Resistance

Anaphylaxis

Anaphylactic reactions can occur following the administration of neuromuscular blocking agents. These reactions have in some cases been life-threatening and fatal. Due to the potential severity of these reactions, the necessary precautions, such as immediate availability of appropriate emergency treatment, should be taken. Precautions should also be taken in those individuals who have had previous anaphylactic reactions to other neuromuscular blocking agents since cross-reactivity

between neuromuscular blocking agents has been reported in this class of drugs.

DRUG INTERACTIONS

Atracurium besylate is potentiated by isoflurane and by enflurane anaesthesia, and marginally potentiated by halothane (see DOSAGE AND ADMINISTRATION).

Drugs which may enhance the neuromuscular blocking action of atracurium besylate include: certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide and quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonistic effect should be considered.

The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth of neuromuscular blockade induced by atracurium besylate. Atracurium besylate should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

ADVERSE REACTIONS

Atracurium besylate was well tolerated and produced few adverse reactions during clinical trials and post-marketing surveillance. Most adverse reactions were suggestive of histamine release. Fully developed anaphylactic or anaphylactoid reactions have been reported, and in rare instances these were severe (e.g., cardiac arrest). Skin flush and decreases in mean arterial pressure were the most common reactions seen in the recommended dose range. The incidences of decreases in mean arterial pressure were substantially increased in patients with a history of cardiovascular disease.

Three large prospective post-marketing surveillance studies have been reported, tabulating the incidence of adverse reactions associated with atracurium besylate; they did not uncover any new events attributable to the drug.

The following adverse reactions are among the most frequently reported:

General:	Allergic reactions (anaphylactic or anaphylactoid responses) which, in rare instances, were severe (e.g. cardiac arrest).
Musculoskeletal:	Inadequate block, prolonged block.
Cardiovascular:	Hypotension, vasodilatation (flushing), tachycardia, bradycardia.
Respiratory:	Dyspnea, bronchospasm, laryngospasm.
Integumentary:	Rash, urticaria, reaction at injection site.

There have been rare reports of seizures in ICU patients following long-term infusion of atracurium to support mechanical ventilation. There are insufficient data to define the contribution, if any, of atracurium and/or its metabolite laudanosine. (See PRECAUTIONS: Long-Term Use in the Intensive Care Unit).

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect

Call toll-free at 1-866-234-2345

Complete a Canada Vigilance Reporting Form and:

- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

Symptoms and Treatment

The possibility of limited iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation. Excessive doses can be expected to produce enhanced pharmacological effects. Overdosage may increase the risk of histamine release and cardiovascular effects, especially hypotension. If cardiovascular support is necessary, this should include proper positioning, fluid administration, and the use of vasopressor agents if necessary. The patient's airway should be assured, with manual or mechanical ventilation maintained as necessary. A longer duration of neuromuscular blockade may result from overdosage and a peripheral nerve stimulator should be used to monitor recovery. Recovery may be facilitated by administration of an anticholinesterase-reversing agent such as neostigmine, edrophonium, or pyridostigmine, in conjunction with an anticholinergic agent such as atropine or glycopyrrolate.

DOSAGE AND ADMINISTRATION

To avoid distress to the patient, Atracurium Besylate Injection should not be administered before

unconsciousness has been induced. It should not be mixed in the same syringe, or administered simultaneously through the same needle, with alkaline solutions (e.g., barbiturate solutions).

Atracurium Besylate Injection should be administered intravenously. **DO NOT GIVE ATRACURIUM BESYLATE INTRAMUSCULARLY:** Intramuscular administration may result in tissue irritation and there are no clinical data to support this route of administration.

The use of a peripheral nerve stimulator to monitor muscle twitch suppression and recovery will permit the most advantageous use of the drug and minimize the possibility of overdosage.

Bolus Injections For Intubation And Maintenance Of Neuromuscular Blockade

Adults

A dose of 0.4 to 0.5 mg/kg (1.7 to 2.2 times the ED₉₅), given as an intravenous bolus injection, is the recommended initial dose for most patients. With this dose, good or excellent conditions for nonemergency intubation can be expected in 2 to 2.5 minutes in most patients, with maximum neuromuscular blockade being achieved approximately 3 to 5 minutes after injection. Clinically effective 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 95% complete 60 minutes after injection.

Atracurium besylate is potentiated by isoflurane or enflurane anaesthesia. The same initial dose of 0.4 to 0.5 mg/kg may be used for intubation prior to administration of these inhalation agents; however, if atracurium besylate is first administered under steady state isoflurane or enflurane anaesthesia, the initial dose may be reduced by approximately one-third, i.e. to 0.25 to 0.35 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 besylate, smaller dosage reductions may be considered.

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 Besylate Injection, but the need for maintenance doses should be determined by clinical criteria. Because atracurium besylate 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 doses (up to 0.2 mg/kg) permit maintenance dosing at longer intervals.

Children

No dosage adjustments are required for pediatric patients 2 years of age or older. A dose of 0.3 to 0.4 mg/kg is recommended as the initial dose for infants (1 month to 2 years of age) under halothane anaesthesia. Maintenance doses may be required with slightly greater frequency in children than in adults.

Reversal

Reversal of neuromuscular blockade produced by atracurium besylate can be achieved with an anticholinesterase agent such as neostigmine, edrophonium, or pyridostigmine, in conjunction with an anticholinergic agent such as atropine or glycopyrrolate. Under balanced anaesthesia, reversal

can usually be attempted approximately 20 to 35 minutes after an initial dose of 0.4 to 0.5 mg/kg, or approximately 10 to 30 minutes after a 0.08 to 0.10 mg/kg 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 incidences of breathing difficulties, possibly related to incomplete reversal, have been reported following attempted pharmacologic 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.

Special Considerations

An initial dose of 0.3 to 0.4 mg/kg, given slowly or in divided doses over one minute, is recommended for adults or children with significant cardiovascular disease (an increased incidence of hypotensive episodes has been seen in these patients) and for adults or children with any history (e.g., severe 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 besylate in these patients, and no specific dosage adjustments can be recommended.

No atracurium besylate dosage adjustments are required for patients with renal disease.

An initial dose of 0.3 to 0.4 mg/kg is recommended for adults following the use of succinylcholine 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 succinylcholine prior to atracurium besylate administration. Insufficient data are available for recommendation of a specific initial atracurium besylate dose for administration following the use of succinylcholine in children and infants.

As with other parenteral drug products, Atracurium Besylate Injection should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Use by Infusion

After administration of a recommended initial bolus dose of Atracurium Besylate Injection (0.3 to 0.5 mg/kg), a diluted solution can be administered by continuous infusion to adults and children aged 2 or more years for maintenance of neuromuscular blockade during extended surgical procedures.

Long-term intravenous infusion to support mechanical ventilation in the intensive care unit has not been studied sufficiently to support dosage recommendations (see PRECAUTIONS: Long-Term use in Intensive Care Unit).

Infusion should be individualized for each patient. The rate of administration should be adjusted according to the patient's response as determined by peripheral nerve stimulation. Accurate dosing is best achieved using a precision infusion pump.

Infusion should be initiated only after evidence of spontaneous recovery from the bolus dose. An initial infusion rate of 9 to 10 mcg/kg/min may be required to rapidly counteract the spontaneous recovery of neuromuscular function. Thereafter, a rate of 5 to 9 mcg/kg/min should be adequate to maintain continuous neuromuscular blockade in the range of 89 to 99% in most pediatric and adult patients under balanced anaesthesia. Occasional patients may require infusion rates as low as 2 mcg/kg/min or as high as 15 mcg/kg/min.

The neuromuscular blocking effect of atracurium besylate administered by infusion is potentiated by enflurane or isoflurane and, to a lesser extent, by halothane. Reduction in the infusion rate of atracurium besylate should, therefore, be considered for patients receiving inhalation anaesthesia. The rate of infusion should be reduced by approximately one-third in the presence of steady-state enflurane or isoflurane anaesthesia; smaller reductions should be considered in the presence of halothane.

In patients undergoing cardiopulmonary bypass with induced hypothermia, the rate of infusion required to maintain adequate surgical relaxation during hypothermia (25 to 28°C) has been shown to be approximately half the rate required during normothermia.

Spontaneous recovery from neuromuscular blockade following discontinuation of infusion may be expected to proceed at a rate comparable to that following administration of a single bolus dose.

The amount of infusion solution required per minute will depend upon the concentration of atracurium besylate in the infusion solution, the desired dose and the patient's weight. The following tables, Table 1 and Table 2, provide guidelines for delivery in mL/hr (equivalent to microdrops/min when 60 microdrops = 1 mL) of drug solutions in concentrations of 0.2 mg/mL (20 mg in 100 mL) or 0.5 mg/mL (50 mg in 100 mL) with an infusion pump or a gravity flow device.

As with all parenteral products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discolouration or leakage prior to administration, whenever solution and container permit.

Table 1: Atracurium Besylate Infusion Rates for a Concentration of 0.2 mg/mL

Patient Weight (kg)	Drug Delivery Rate (mcg/kg/min)					
	5	6	7	8	9	10
	Infusion Delivery Rate (mL/hr)					
30	45	54	63	72	81	90
35	53	63	74	84	95	105
40	60	72	84	96	108	120
45	68	81	95	108	122	135
50	75	90	105	120	135	150
55	83	99	116	132	149	165
60	90	108	126	144	162	180
65	98	117	137	156	176	195
70	105	126	147	168	189	210
75	113	135	158	180	203	225
80	120	144	168	192	216	240
90	135	162	189	216	243	270
100	150	180	210	240	270	300

Table 2: Atracurium Besylate Infusion Rates for a Concentration of 0.5 mg/mL

Patient Weight (kg)	Drug Delivery Rate (mcg/kg/min)					
	5	6	7	8	9	10
	Infusion Delivery Rate (mL/hr)					
30	18	22	25	29	32	36
35	21	25	29	34	38	42
40	24	29	34	38	43	48
45	27	32	38	43	49	54
50	30	36	42	48	54	60
55	33	40	46	53	59	66
60	36	43	50	58	65	72
65	39	47	55	62	70	78
70	42	50	59	67	76	84
75	45	54	63	72	81	90
80	48	58	67	77	86	96
90	54	65	76	86	97	108
100	60	72	84	96	108	120

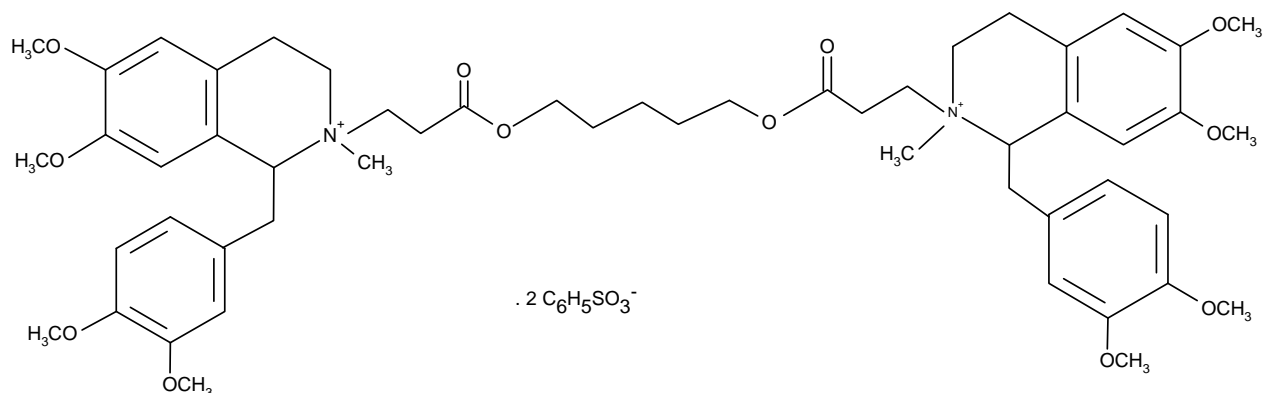
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Atracurium besylate

Chemical Name: 2,2'-[Pentamethylenebis (oxycarbonylethylene)]bis-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium) dibenzenesulfonate

Structural Formula:



Molecular Formula: C₆₅H₈₂N₂O₁₈S₂

Molecular Weight: 1243.51

Description: Atracurium besylate is a complex molecule containing four sites at which different stereochemical configurations can occur. The symmetry of the molecule, however, results in only ten instead of sixteen possible different isomers. The manufacture of atracurium besylate results in these isomers being produced in unequal amounts but with a consistent ratio. Those molecules in which the methyl group attached to the quaternary nitrogen projects on the opposite side to the adjacent substituted benzyl moiety predominate by approximately 3:1.

Atracurium besylate is a white to pale yellow powder. It is freely soluble in acetonitrile and chloroform, soluble in water, and practically insoluble in diethyl ether. It has a pH (1% aqueous solution) of 5.0 - 7.0 and a melting point range of 85-90°C.

DOSAGE FORMS AND COMPOSITION

Atracurium Besylate Injection is a sterile aqueous solution, with the pH of the solution adjusted to 3.4 - 3.7 with benzenesulfonic acid.

10 mL Multidose Vials: Each mL contains atracurium besylate 10 mg in water for injection, with benzyl alcohol 0.9% v/v as preservative and benzenesulfonic acid to adjust pH.

STORAGE AND STABILITY

Store between 2 - 8 °C. Protect from freezing. Protect from light.

Atracurium Besylate for Continuous Infusions

Infusion solutions may be prepared by admixing Atracurium Besylate Injection with an appropriate diluent such as 5% Dextrose Injection USP or 0.9% Sodium Chloride Injection USP. Solutions containing 0.2 mg/mL or 0.5 mg/mL atracurium besylate in these diluents may be stored under refrigeration for 24 hours without significant loss of potency. Infusion solutions should be used within 24 hours of preparation. Unused solutions should be discarded.

Spontaneous degradation of atracurium besylate has been reported to occur more rapidly in Lactated Ringer's solution, therefore, it is recommended that Lactated Ringer's Injection USP not be used as a diluent in preparing solutions for infusion.

Care should be taken during admixture to prevent inadvertent contamination. As with all parenteral products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration or leakage prior to administration, whenever solution and container permit.

PACKAGING

Atracurium Besylate Injection, 10 mg/mL, is available in multidose amber vials of 10 mL, boxes of 10.

DETAILED PHARMACOLOGY

Atracurium besylate is a nondepolarizing skeletal neuromuscular blocking agent.

The ED₉₅ (dose required to produce 95% suppression of the muscle twitch response) averaged 0.23 mg/kg. An initial dose of 0.4 to 0.5 mg/kg generally produces complete neuromuscular blockade within 3 to 5 minutes of injection, with good or excellent 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 approximately

60 to 70 minutes after injection.

The neuromuscular blocking action of atracurium besylate is enhanced in the presence of potent inhalation anaesthetics. Isoflurane and enflurane increase its potency and prolong neuromuscular blockade by approximately 35%; however, halothane's potentiating effect (approximately 20%) is marginal (see DOSAGE AND ADMINISTRATION).

Repeatedly administered maintenance doses have no cumulative effect on the duration of neuromuscular blockade; therefore, doses can be administered at 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.

Once recovery from the neuromuscular blocking effects begins, it proceeds more rapidly than recovery from d-tubocurarine, metocurine, and pancuronium. Regardless of dose, the time from start of recovery (from complete block) to complete (95%) recovery 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 can be achieved with an anticholinesterase agent such as neostigmine, edrophonium, or pyridostigmine, in conjunction with an anticholinergic agent such as atropine or glycopyrrolate. Under balanced anaesthesia, reversal can usually be attempted approximately 20 to 35 minutes after an initial dose of 0.4 to 0.5 mg/kg, or approximately 10 to 30 minutes after a 0.08 to 0.10 mg/kg 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 incidences of breathing difficulties, possibly related to incomplete reversal, have been reported following attempted pharmacologic 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.

The pharmacokinetics of atracurium besylate in man are 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 the drug 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* and *in vivo* studies which have shown that the drug is inactivated in plasma via two nonoxidative pathways: ester hydrolysis, catalysed by nonspecific esterases; and Hofmann elimination, a nonenzymatic chemical process which occurs at physiological pH. Some placental transfer occurs in humans.

Radiolabel studies demonstrated that atracurium besylate undergoes extensive degradation in cats, and that neither kidney nor liver plays a major role in its elimination. Biliary and urinary excretion were the major routes of excretion of radioactivity (totalling > 90% of the labelled dose within 7 hours of dosing), of which the drug represented only a minor fraction. The metabolites in bile and urine were similar, including products of Hofmann elimination and ester hydrolysis.

Histamine release and haemodynamic changes are minimal with initial atracurium besylate doses up to 0.4 mg/kg. A moderate histamine release following 0.6 mg/kg has been shown to correlate with a transient (<5 minutes) decrease in blood pressure and a brief (2 to 3 minutes) episode of skin flushing. This is of little clinical significance in most patients; however, the possibility of substantial histamine release in sensitive individuals or in patients in whom substantial histamine release would be especially hazardous (e.g., patients with significant cardiovascular disease) must be considered.

It is not known whether the prior use of other nondepolarizing neuromuscular blocking agents has any effect on the activity of atracurium besylate. The prior use of succinylcholine decreases by approximately 2 to 3 minutes the time to maximum blockade induced by the drug, and may increase the depth of blockade. Atracurium besylate should be administered only after a patient recovers from succinylcholine-induced neuromuscular blockade.

TOXICOLOGY

Acute

The LD₅₀ of intravenously administered atracurium besylate in the mouse and rat were approximately 1.95 mg/kg and 1.31 mg/kg, respectively. Deaths occurred within 2 minutes and were caused by respiratory paralysis. The LD₅₀ of subcutaneously administered drug was 2.82 mg/kg in the rat. Tremors, ptosis, loss of reflexes and respiratory failure preceded death which occurred 45 to 120 minutes after subcutaneous injection.

Subacute

Atracurium besylate was intravenously administered to anaesthetized and ventilated dogs twice weekly for 3 weeks (6 total doses). Initial bolus of 0.3 mg/kg or 0.9 mg/kg were followed by regular additional doses for a 4-hour period. Evaluations that were intended to monitor changes in general appearance and behaviour, clinical signs, ophthalmology electrocardiography, haematology, clinical chemistry, urinalysis, gross pathology and histopathology revealed no treatment-related effects.

Subcutaneously administered atracurium besylate was studied in the nonventilated monkey and rat. Maximum tolerated (non-lethal) doses were given 2 to 4 times daily for 4 weeks in monkeys and once daily for 14 days in rats. In the monkey, no drug-related effects were noted other than those attributable to neuromuscular blockade. In the rat, inflammatory reaction at the site of injection was noted at necropsy and confirmed histologically, possibly explaining increased leukocyte and plasma potassium values. These were considered related to injection site damage or hypoxia and acidosis related to neuromuscular blockade.

Teratology

Atracurium besylate was administered subcutaneously to nonventilated New Zealand White rabbits on days 6 through 18 of gestation. Doses administered were 0.15 mg/kg once daily and 0.10 mg/kg twice daily. Lethal respiratory distress occurred in two 0.15 mg/kg animals and in one 0.10 mg/kg animal, with transient respiratory distress or other evidence of neuromuscular blockade occurring in 10/19 and in 4/20 of the 0.15 mg/kg and 0.10 mg/kg animals, respectively. There was an increased incidence of certain spontaneously occurring anomalies or variations in one or both treated groups

when compared with the control group. In addition, bilobed bladder was observed in 1/60 fetuses at the mid-dose and in 3/67 at the high dose. It is noted that in the literature the reported spontaneous incidence of bilobed bladder in the New Zealand White rabbit is lower than 0.01%.

Mutagenicity

Atracurium besylate was reported to be reproducibly mutagenic in the L5178Y/TK +/- mouse lymphoma assay both in the presence and absence of metabolic activation.

Negative results were obtained in the Ames Salmonella assay at concentrations up to 1000 mcg/mL, and in the rat bone marrow cytogenicity assay performed at sub-paralyzing doses.

Special Studies

Atracurium besylate was tested for its ability to excite malignant hyperthermia in susceptible Pietrain pigs. Intravenous doses of 2.5 or 10.0 mg/kg showed no evidence of malignant hyperthermia. After the effects of the drug were reversed, malignant hyperthermia was induced in all pigs using other agents.

Atracurium besylate had no effect on the respiration of neonatal kittens delivered by cesarean section from dams given 0.1 or 0.6 mg/kg doses. It was not detected in blood samples of the neonatal kittens, indicating a lack of placental transfer. No convincing suppression of respiration was seen in cesarean-delivered kittens injected intravenously with the drug in spite of blood levels that were 10 to 50 times those associated with complete respiratory paralysis in dams.

Minimal evidence of irritancy was seen in dogs treated intravenously, intramuscularly or perivenously with 10 mg/mL or 25 mg/mL aqueous solutions.

In vitro studies of the effects of atracurium besylate on human blood indicated little likelihood of marked effects on blood at drug/blood ratios to be experienced clinically.

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