PRODUCT MONOGRAPH

TRACRIUM®

(Atracurium besylate)

10 mg/mL Injection

Intravenous Skeletal Neuromuscular Blocking Agent

AbbVie Corporation
8401 Trans Canada Highway
St-Laurent (QC) CANADA H4S 1Z1

DATE OF PREPARATION:
November 1, 2012

DATE OF LATEST REVISION:

DATE OF REVISION:

Control No. 158344

PRODUCT MONOGRAPH

NAME OF DRUG

TRACRIUM®

(Atracurium Besylate Injection)

THERAPEUTIC CLASSIFICATION

Intravenous Skeletal Neuromuscular Blocking Agent

ACTIONS AND CLINICAL PHARMACOLOGY

TRACRIUM (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.

INDICATIONS AND CLINICAL USE

TRACRIUM (atracurium besylate) is indicated, as an adjunct to general anesthesia, 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 to assess degree of muscle relaxation.

CONTRAINDICATIONS

TRACRIUM (atracurium besylate) is contraindicated in patients known to have a hypersensitivity to atracurium.

Use of atracurium from multiple-dose vials containing benzyl alcohol as a preservative is contraindicated in patients with a known sensitivity to benzyl alcohol.
In newborn infants (children less that one month of age), benzyl alcohol has been associated with

an increased incidence of neurological and other complications which are, sometimes, fatal. Atracurium from multiple-dose vials containing benzyl alcohol should not be used in newborn infants.

WARNINGS

TRACRIUM (atracurium besylate) 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 INTRAMUSCULARLY.

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

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

TRACRIUM 10 mL multiple-dose 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.

TRACRIUM 5 mL vials do not contain benzyl alcohol.

PRECAUTIONS

Histamine Release

Although atracurium is a less potent histamine releaser that d-turbocurarine or metocurine, the possibility of substantial histamine release with consequent bronchospasm or anaphylaxis in sensitive individuals must be considered. Special caution should be exercised in administering TRACRIUM (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.

Use in 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.

Use in 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 that a forceps delivery will be necessary may increase.

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 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 a nursing woman.

Use in 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 diseases 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° to 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 anesthetic agents or vagal stimulation.

Malignant Hyperthermia

Multiple factors in anesthesia practice are suspected of triggering malignant hyperthermia (MH), a potentially fatal hypermetabolic state of skeletal muscle. Halogenated anesthetic 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 anesthesia. Reports of MH have been rare in cases in which atracurium besylate has been used. In studies of MH-susceptible animals (swine) and in a clinical study of MH-susceptible patients, atracurium did not trigger this syndrome.

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 non-depolarizing 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 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 metabolites that may accumulate during days to weeks of atracurium administration in ICU patients. Concentrations of metabolites are higher in ICU patients with abnormal renal and/or hepatic function. These metabolites do not contribute to neuromuscular block.

Laudanosine, a major biologically active metabolite of atracurium 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 or other agents. These patients usually had predisposing causes (such as head trauma, cerebral edema, hypoxic encephalopathy, viral encephalitis, uremia). 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 T_1 OR TO THE FIRST TWITCH. IF NO RESPONSE IS ELICITED, INFUSION ADMINISTRATION SHOULD BE DISCONTINUED UNTIL A RESPONSE RETURNS.

The effects of hemodialysis, hemoperfusion and hemofiltration on plasma levels of atracurium and its metabolites are unknown.

Drug Interactions

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

Other 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

TRACRIUM (atracurium besylate) was well tolerated and produced few adverse reactions during extensive clinical trials and as observed in clinical practice. 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.

Observed in Controlled Clinical Studies

In 27 studies including 875 patients, atracurium besylate was discontinued in one patient (who required treatment for bronchial secretions). Six other patients required treatment for adverse reactions attributable to the drug (wheezing in one, hypotension in five). Of the five patients who required treatment for hypotension, three had a history of significant cardiovascular disease. The overall incidence rate for clinically important adverse reactions, therefore, was 7 in 875 or 0.8%. The table below includes all adverse reactions reported attributable to atracurium besylate during clinical trials with 875 patients.

Percent of Patients Reporting Adverse Reactions

Adverse Reaction	Initial Dose (mg/kg) (Total = 875 Patients)			
	0.00 to 0.30 n=485	0.31 to 0.40 n=236	0.46 to 0.50 n=127	≥0.56 n=27
Skin Flush	0.8%	5.5%	15.0%	26.0%
Erythema	0.4%	0.0%	2.4%	0.0%
Itching	0.4%	0.0%	0.0%	0.0%
Wheezing/Bronchial Secretions	0.2%	0.0%	0.8%	0.0%
Hives	0.2%	0.0%	0.0%	0.0%

Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. The following table summarizes the incidences of substantial

vital sign changes noted during atracurium besylate clinical trials with 530 patients in whom these parameters were assessed.

Percent of Patients with Vital Sign Changes (ASA 1 and 2)*					
Vital Sign Change		**Initial Dose (mg/kg)**			
		0.00 to 0.30 n=365	0.36 to 0.40 n=124	0.50 n=20	≥0.60 n=21
Mean Arterial Pressure					
Decrease	≥40%	0.3%	0.0%	10.0%	5.0%
Decrease	≥30%	1.1%	0.0%	15.0%	15.0%
Decrease	≥20%	2.5%	2.4%	15.0%	30.0%
Increase	≥20%	7.4%	7.3%	5.0%	0.0%
Increase	≥30%	1.9%	3.2%	0.0%	0.0%
Increase	≥40%	0.8%	1.6%	0.0%	0.0%
Heart Rate					
Decrease	≥40%	0.3%	0.0%	0.0%	0.0%
Decrease	≥30%	0.8%	0.0%	0.0%	0.0%
Decrease	≥20%	3.0%	1.6%	0.0%	5.0%
Increase	≥20%	4.9%	4.0%	5.0%	10.0%
Increase	≥30%	1.6%	2.4%	5.0%	5.0%
Increase	≥40%	1.4%	1.6%	0.0%	0.0%

* American Society of Anesthesiologists Classification of Physical Status:
1. A normal healthy patient
2. A patient with a mild systemic disease.

In a small group of patients with cardiovascular disease (n = 34) the changes in vital signs were more predominant, even at the lower doses.

Patients with Cardiovascular Disease with Vital Sign Changes			
Vital Sign Change		**Initial Dose (mg/kg)**	
		0.00 to 0.30 n=18	**0.36 to 0.40 n=16**
Mean Arterial Pressure			
Decrease	≥40%	0	1 (6.3%)
Decrease	≥30%	2 (11.1%)	6 (37.5%)
Decrease	≥20%	7 (38.9%)	11 (68.8%)
Increase	≥20%	0	2 (12.5%)
Increase	≥30%	0	0
Heart Rate			
Decrease	≥30%	0	0
Decrease	≥20%	2 (11.0%)	1 (6.3%)
Increase	≥20%	2 (11.0%)	0
Increase	≥30%	0	0

Three large prospective postmarketing 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.

Observed in Clinical Practice

Based on initial clinical practice experience in approximately 11 million patients who received atracurium besylate, spontaneously reported adverse reactions were uncommon (0.006%). The following adverse reactions are among the most frequently reported, but there are insufficient data to support an estimate of their incidence:

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**). There have been some reports of muscle weakness and/or myopathy following prolonged use of muscle relaxants in severely ill patients in the ICU. Most patients were receiving concomittant corticosteroids. These events have been seen infrequently in association with atracurium besylate and a causal relationship has not been established.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There has been limited experience with TRACRIUM (atracurium besylate) overdosage. 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.

Three pediatric patients (3 weeks, 4 and 5 months of age) unintentionally received doses of 0.8 mg/kg to 1.0 mg/kg. The time to 25% recovery (50 to 55 minutes) following these doses, which were 5 to 6 times the ED_{95} dose, was moderately longer than the corresponding time observed following doses 2.0 to 2.5 times the atracurium besylate ED_{95} dose in infants (22 to 36 minutes). Cardiovascular changes were minimal. Nonetheless, the possibility of cardiovascular changes must be considered in the case of overdose.

An adult patient (17 years of age) unintentionally received an initial dose of 1.3 mg/kg. The time from injection to 25% recovery (83 minutes) was approximately twice that observed following maximum recommended doses in adults (35 to 45 minutes). The patient experienced moderate hemodynamic changes (13% increase in mean arterial pressure and 27% increase in heart rate) which persisted for 40 minutes and did not require treatment.

DOSAGE AND ADMINISTRATION

To avoid distress to the patient, TRACRIUM (atracurium besylate) 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 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 ED_{95}), 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 anesthesia. 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, enflurane, sevoflurane or desflurane anesthesia. 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 anesthesia, 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 anesthetic 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 anesthesia, slightly longer under isoflurane enflurane, sevoflurane or desflurane. Higher doses (up to 0.2 mg/kg) permit maintenance dosing at longer intervals.

Children

No dosage adjustments are required for pediatric patients two 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 anesthesia. 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 anesthesia, 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 besylate 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 anesthesia. Further reductions may be desirable with the use of potent inhalation anesthetics. 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 should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit.

Use by Infusion

After administration of a recommended initial bolus dose of atracurium besylate (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 μg/kg/min may be required to rapidly counteract the spontaneous recovery of neuromuscular function. Thereafter, a rate of 5 to 9 μg/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 anesthesia. Occasional patients may require infusion rates as low as 2 μg/kg/min or as high as 15 μg/kg/min.

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

TRACRIUM Infusion Rates

for a Concentration of 0.2 mg/mL						
Patient Weight (kg)	Drug Delivery Rate (μg/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

TRACRIUM Infusion Rates for a Concentration of 0.5 mg/mL						
Patient Weight (kg)	Drug Delivery Rate (μg/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

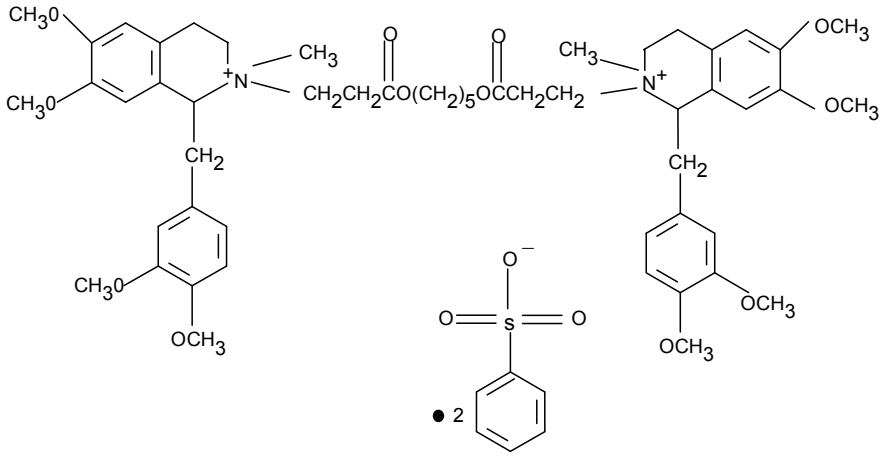
Drug Substance

Trade Name: TRACRIUM

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: $C_{65}H_{82}N_2O_{18}S_2$

Molecular Weight: 1243.49

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 in chloroform, soluble in water, and practically insoluble in diethyl ether. The melting point is 85° to 90° C.

Composition

TRACRIUM Injection is a sterile, non-pyrogenic aqueous solution. The pH of the solution is adjusted to between 3.0 and 3.8 with benzenesulfonic acid.

5 mL Single Use Vials

Each vial contains 50 mg atracurium besylate and water for injection.

10 mL Multiple-Dose Vials

Each vial contains 100 mg atracurium besylate, 0.9% benzyl alcohol added as a preservative, and water for injection.

Stability and Storage Recommendations

TRACRIUM slowly loses potency with time at the rate of approximately 6% per year under refrigeration (2°to 8°C). Rate of loss in potency increases to approximately 5% per month at 25°C. TRACRIUM Injection **should be stored under refrigeration (2° to 8°C)** to preserve potency. PROTECT FROM FREEZING. TRACRIUM is stable for up to 14 days at room temperature up to 25°C, without significant loss of potency.

TRACRIUM for Continuous Infusions

Infusion solutions may be prepared by admixing TRACRIUM injection with an appropriate diluent such as 5% Dextrose Injection USP, 0.9% Sodium Chloride Injection USP, or 5% Dextrose and 0.9% Sodium Chloride Injection USP. Solutions containing 0.2 mg/mL or 0.5 mg/mL TRACRIUM in these diluents may be stored either under refrigeration or at room temperature 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 TRACRIUM has been demonstrated to occur more rapidly in Lactated Ringer's solution than in 0.9% Sodium Chloride 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. Visually inspect prior to administration.

AVAILABILITY OF DOSAGE FORMS

5 mL Single Use Vials: Each 5 mL vial of TRACURIUM Injection contains 50 mg atracurium besylate. Packages of 10.

10 mL Multiple-Dose Vials: Each 10 mL vial of TRACRIUM Injection contains 100 mg atracurium besylate and the following non-medicinal ingredient: 0.9% benzyl alcohol. Packages of 10.

PHARMACOLOGY

Animal Pharmacology

TRACRIUM (atracurium besylate) antagonizes the neurotransmitter action of acetylcholine by competitively binding with cholinergic receptor sites on the motor endplate. The pharmacodynamics of atracurium has been established in a number of *in vitro* and *in vivo* models.

Atracurium abolished responses to electrical stimulation in an isolated chick nerve-muscle preparation at bath concentrations of 0.5 to 1.0 μg/mL without producing an initial contracture.

Blockade was antagonized by the anticholinesterase drugs, physostigmine and edrophonium.

In anesthetized, ventilated cats, beagle dogs and rheusus monkeys, intravenous administration of atracurium blocked single twitch and tetanic responses of the gastrocnemius muscle elicited by electrical simulation of the sciatic nerve.

The doses estimated to produce 50% reductions in single twitches and tetanic contractions are summarized in Table 6:

Table 6
The Estimated doses to produce 50% reductions in single twitches and tetanic contractions.

	Mean Estimated 50% Paralyzing Dose (mg/kg) ± SEM	

Species	n	Single Twitch	Tetanic Response
Cat	6	0.129 ± 0.008	0.095 ± 0.005
Dog	4	0.080 ± 0.007	0.050 ± 0.002
Monkey	7	0.124 ± 0.002	0.083 ± 0.008

Atracurium was more potent in the dog than the other two species, but subsequent clinical studies showed that the results in cats and monkeys were more predictive of the human response. In all three species, full blockade was observed at doses of 0.25 to 0.50 mg/kg. Maximal effects occurred within about 0.5 to 4 minutes with these doses and were reversible by approximately 30 to 60 minutes after treatment. Atracurium neuromuscular blockade was antagonized by neostigmine and edrophonium, and its effects on cardiovascular parameters and autonomic functions (both sympathetic and parasympathetic) were minimal.

Comparisons with other neuromuscular blocking agents in cats indicated that atracurium is much less potent than dimethyl tubocurarine, pancuronium and alcuronium; equipotent with tubocurarine; and several times more potent than gallamine and fazadinium.

The plasma t½ of an intravenously administered dose of atracurium (0.3 mg/kg) in the cat was determined to be approximately 20 minutes (which is similar to the t½ in man), and the AUC was approximately 29,000 ng/mL/min.

In vitro and animal studies demonstrated that atracurium is inactivated in plasma by two non-oxidative mechanisms: enzymatic ester hydrolysis and a purely chemical degradation process called, Hoffmann elimination.

In studies in cats using carbon-14 radiolabeled atracurium, elimination of parent compound from the plasma was independent of liver and kidney function, although the products of atracurium breakdown were largely excreted in bile and, to a lesser extent, in urine. Less than 1% of the administered radioactivity was recovered in expired air. Clearance from plasma was more rapid for unchanged drug than the metabolites. Approximately 65 to 70% of the administered radioactivity was recovered in bile and urine within five hours, and up to 90% was recovered within seven hours.

Whole-body autoradiography in the rat revealed that carbon-14 radiolabeled atracurium did not enter the central nervous system.

Human Pharmacology

Atracurium besylate is a nondepolarizing skeletal neuromuscular blocking agent.

The ED_{95} (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 anesthesia) 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 anesthetics. 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 anesthesia, 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 anesthesia, 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 anesthesia, 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* studies which have shown that the drug 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. 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 (totaling > 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 hemodynamic 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 Toxicity

Acute intravenous LD_{50} values for TRACURIUM in non-ventilated male and female albino mice and male Wistar rats were 1.9, 2.01, and 1.31 mg/kg, respectively. The LD_{50} 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 LD_{50} of subcutaneously administered drug was 282.8 mg/kg in the rat. The subcutaneous LD_{50} value for male Wistar rats was also 282.8 mg/kg. These deaths occurred 45 to 120 minutes after injection and were preceded by tremors, ptosis, loss of reflexes and respiratory failure.

Subacute Toxicity

Atracurium besylate was intravenously administered in sufficient doses to maintain paralysis for four hours to groups of beagle dogs (2/sex/group) twice weekly for 3 weeks (6 total doses). For each treatment, the dogs were anesthetized, mechanically-ventilated and received either an initial atracurium injection of 0.3 mg/kg, followed by supplemental doses of 0.05 mg/kg every five minutes for four hours, or and initial dose of 0.9 mg/kg, plus 0.15 mg/kg every five minutes for four hours. The smaller doses produced ful full paralysis, whereas the larger doses represented three-fold excesses. All dogs survived and no consistent adverse effects, including untoward hemotologic, clinical chemical or histopathologic changes, were observed. Evaluations that were intended to monitor changes in general appearance and behaviour, clinical signs, ophthalmology, electrocardiography, hematology, clinical chemistry, urinalysis, gross pathology and histopathology revealed no treatment-related effects.

Intravenous administration of 0.6 mg/kg atracurium produced full paralysis in six pregnant cats, yet no effect was observed on the respiratory activity of their fetuses, and atracurium could not be detected in the fetal blood. These results suggest that the drug did not cross the placenta. There is evidence, though, that limited placental transfer occurs in rats. Direct intravenous or intraperitoneal administration of 0.6 mg/kg to cat fetuses had no effect on their respiration, suggesting that the neonate is relatively resistant to the pharmacologic activity of atracurium.

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 groups of nonventilated New Zealand White pregnant rabbits (17 to 21 rabbits/group) on days 6 through 18 of gestation. Doses administered were 0.15 mg/kg once daily or 0.10 mg/kg twice daily. Dams treated with atracurium briefly exhibited signs associated with the drug's pharmacological effect, e.g., dyspnea, at both dose levels. 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%.

Post-implantation losses were increased in rabbits treated with 0.15 mg/kg/day, and increased incidence of fetal visceral and skeletal anomalies were found at one or both dosages when compared to a group of untreated controls.

Mutagenicity

Atracurium besylate was found 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 μg/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 strain of 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.

Evidence of histamine release (i.e., a fall in arterial blood pressure which was partially ameliorated by blockade of histamine receptors) was seen in dogs only after a relatively large intravenous dose of atracurium, 2.0 mg/kg.

No histologic evidence of local irritation was observed when a 25 mg/mL solution of atracurium was repeatedly injected into the cephalic veins of three dogs and retained there by gentle proximal pressure for one minute. Injection of a half-milliliter of a 10 mg/mL atracurium solution into dogs' longissimus dorsi muscle produced little or no muscular irritation, but mild perivenous irritation was observed in two of four dogs when a half-milliliter of the 10 mg/mL solution was injected in the region of a saphenous vein.

Guinea pigs treated intradermally every other day for 20 days with a solution of atracurium and challenged two weeks later exhibited no evidence of sensitization.

Atracurium was non-mutagenic in an Ames test using *Salmonella typhimurium* strains TA-1535, -1537, -1538, -98 and -100, in the presence and absence of metabolic activation. It was also non-

mutagenic in a rat bone marrow cytogenicity assay, while positive responses were observed in the mouse lymphoma test.

Studies in the cat and dog indicated that atracurium breakdown products, including laudanosine, a major degradation product that caused seizures in dogs at relatively high plasma levels, lack either neuromuscular or cardiovascular activity in amounts that would normally be expected to result from clinical doses of atracurium.

The results of interaction studies in cats revealed that the action of atracurium is enhanced by d-tubocurarine, halothane, gentamycin, neomycin and polymyxin, and antagonized by adrenaline and suxamethonium. Pretreatment with suxamethonium did not affect the subsequent block by atracurium.

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.

REFERENCES

1. Atkinson RS, Rushman GB, Lee JA: A Synopsis of Anaesthesia. Bristol: Wright, 1987; 282.

2. Attia RR, Grogono AW, Domer FR: Practical Anesthetic Pharmacology. Norwalk: Appleton-Century-Crofts, 1987; 96.

3. Basta SJ, Ali HH, Savarese JJ, Sunder N, Gionfriddo M, Cloutier G, Lineberry C, Cato AE: Clinical pharmacology of atracurium besylate (BW 33A): A new non-depolarizing muscle relaxant. Anesth Analg 1982; 61(9):723-29.

4. Basta SJ, Savarese JJ, Ali HH, Moss J, Gionfriddo M: Histamine-releasing potencies of atracurium besylate (BW 33A), metocurine, d-tubocurarine. Anesthesiology 1982; 57(3):A261 (Abstract).

5. Beemer GH, Dennis WL, Platt PR, Bjorksten AR, Carr AB: Adverse reactions to atracurium and alcuronium - A prospective surveillance study. Br J Anaesth 1988; 61:680-4.

6. Bell PF, Mirakhur RK, Clarke RS: Dose-response studies of atracurium, vecuronium, and pancuronium in the elderly. Anesthesia 1989; 44:925-927.

7. Bevan DC, Bevan JC, Donati F. Muscle Relaxants in Clinical Anesthesia. Chicago: Year Book Medical Publishers, 1988; 307.

8. d'Hollander AA, Luyckx C, Barvais L, De Ville A: Clinical evaluation of atracurium besylate requirement for a stable muscle relaxation during surgery: Lack of age-related effects. Anesthesiology 1983; 59:237-240.

9. Flynn PJ, Frank M, Hughes R: Evaluation of atracurium in caesarian section using train-of-four responses. Anesthesiology 1982; 57(3):A286 (Abstract).

10. Goat VA, Yeung ML, Blakeney C, Feldman SA: The effect of blood flow upon the activity of gallamine triethiodide. Br J Anaesth 1976; 48:69-73.

11. Gramstad L, Lilleaasen P, Minsaas B: Onset time and duration of action for atracurium, Org NC45 and pancuronium. Br J Anaesth 1982; 54(8):827-30.

12. Griffiths RB, Hunter JM, Jones RS: Atracurium infusions in patients with renal failure on an ITU. Anaesthesia 1986; 41:375-381.

13. Gwinnutt CL, Eddleston JM, Edwards D, Pollard BJ: Concentrations of atracurium and laudanosine in cerebrospinal fluid and plasma in three intensive care patients. Br J Anaesth 1990; 65:829-832.

14. Harrison GA, Junius F: The effect of circulation time on the neuromuscular action of suxamethonium. Anaesth Intensive Care 1972; 1:33-40.

15. Hunter JM, Jones RS, Utting JE: Use of the muscle relaxant atracurium in anephric patients: preliminary communication. J R Soc Med 1982; 75:336-40.

16. Jick H, Andrews EB, Tilson HH, Pfanschmidt M, Branche C, Walker AB, Lawson DH: Atracurium - A post-marketing surveillance study: methods and U.S. experience. Br J Anaesth 1989; 62:590-595.

17. Kalli I, Meretoja OA: Infusion of atracurium in neonates, infants and children. Br J Anaesth 1988; 60:651-654.

18. Katz RL, Stirt J, Murray AL, Lee C: Neuromuscular effects of atracurium in man. Anesth Analg 1982; 61(9):730-34.

19. Kent AP, Parker CJ, Hunter JM: Pharmacokinetics of atracurium and laudanosine in the elderly. Br J Anaesth 1989; 63:661-666.

20. Kitts JB, Fisher DM, Canfell PC, Spellman MJ, Coldwell JE, Heier T, Fahey MR, Miller RD: Pharmacokinetics and pharmacodynamics of atracurium in the elderly. Anesthesiology 1990; 72:272-275.

21. Lawson DH, Paice GM, Glavin RJ, Andrews EB, Branche C, Tilson H, Jick H: Atracurium - A post-marketing surveillance study: U.K. study and discussion. Br J Anaesth 62:596-600, 1989.

22. Lowry KG, Mirakhur RK, Lavery, GG, Clarke RS: Vecuronium and atracurium in the elderly: a clinical comparison with pancuronium. Acta Anesthesiol Scand 1985; 29:405-408.

23. Parker CJR, Jones JE, Hunter JM: Disposition of infusions of atracurium and its metabolite, laudanosine, in patients in renal and respiratory failure in an ITU. Br J Anaesth 1988; 61/5:531-540.

24. Payne JP, Hughes R: Evaluation of atracurium in anaesthetized man. Br J Anaesth 1981; 53:45-54.

25. Ramsey FM, White PA, Stullken EH, Allen LL, Roy RC: Neuromuscular and hemodynamic effects of atracurium during enflurane anesthesia. Anesthesiology 1982; 57(3):A254 (Abstract).

26. Ridley SA, Hatch DJ: Post-tetanic count and profound neuromuscular blockade with atracurium infusion in paediatric patients. Br J Anaesth 1988; 60:31-25.

27. Rupp SM, Fahey MR, Miller RD: Neuromuscular blocking effects of atracurium during N2O-fentanyl or isoflurane anesthesia. Anesthesiology 1982; 57(3):A257 (Abstract).

28. Schaer H, Baasch K, Nasschi R: Comparative clinical investigations of vecuronium, atracurium, and pancuronium in elderly subjects. Anaesthesist 1984; 33:543-7.

29. Tilson HH, Weakly JN, Lineberry CG, Cato AE: Adverse Drug Experiences - Postmarketing of TRACRIUM, 1983-1986. J Clin Res Drug Dev 1988; 2:89-99.

30. Varin F, Ducharme J, Théorêt Y, Besner JG, Bevan DR, Donati F: Influence of extreme obesity on the body disposition and neuromuscular blocking effect of atracurium. Clin Pharmacol Ther 1990; 48:18-25.

31. Wadon AJ, Dogra S, Anand S: Atracurium infusions in the intensive care unit. Br J Anaesth 1986; 58:64-67.

32. Werner MU, Nielsen HK, Jensen AG, Lybecker H: Atracurium in the intensive care unit. Acta Anaesthesiol Scand 1987; 31:200.

33. Weinstein JA, Matteo RS, Ornstein E, Schwartz AE, Goldstaff M, Thal G: Pharmacodynamics of vecuronium and atracurium in the obese surgical patient. Anesth Analg 1988; 67:1149-1153.

34. Yate PM, Flynn PJ, Arnold RW, Weatherly BC, Simmonds RJ, Dopson T: Clinical experience and plasma laudanosine concentrations during the infusion of atracurium in the intensive therapy unit. Br J Anaesth 1987; 59:211-217.