PRODUCT MONOGRAPH

[Pr]BRETYLIUM TOSYLATE INJECTION USP

50 mg/mL

Antiarrhythmic

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Date of preparation: July 4, 2007
Date of revision:

Control No: 115036

Bretylium Tosylate Injection USP
50 mg/mL

THERAPEUTIC CLASSIFICATION

Antiarrhythmic

ACTIONS AND CLINICAL PHARMACOLOGY

Bretylium, a quaternary ammonium compound is an adrenergic neuron blocking agent.

It suppresses ventricular fibrillation and ventricular arrhythmias. The mechanisms of the antifibrillatory and antiarrhythmic actions of bretylium are not established.

Bretylium selectively accumulates in sympathetic ganglia and their postganglionic adrenergic neurons where it inhibits norepinephrine release by depressing adrenergic nerve terminal excitability.

Catecholamine stores are not depleted by bretylium and parenteral administration of the drug results in initial release of norepinephrine from the adrenergic postganglionic nerve terminals. Subsequently, bretylium blocks the release of norepinephrine in response to neuron stimulation.

Reports indicate that the drug has a positive inotropic effect on the myocardium but it is not yet certain that the effect is direct or mediated by catecholamine release.

Peripheral adrenergic blockade regularly causes orthostatic hypotension but has less effect on supine blood pressure.

The plasma half-life of bretylium is 5 to 10 hours. In 4 normal volunteers who were given a single 4 mg/kg dose of IV bretylium, the half-life averaged 7.8 hours.

Bretylium is eliminated intact by the kidneys. Seventy to 80% is excreted unchanged in the urine within 24 hours and an additional 10% excreted over the next 3 days.

It is unknown whether bretylium crosses the placenta, but it does not cross the blood-brain barrier.

The concentration of bretylium in plasma has not been correlated with the intensity of its antiarrhythmic action and cannot be used to guide individualization of dosage.

INDICATIONS AND CLINICAL USE

Bretylium Tosylate Injection USP may be of value as a last resort in life-threatening ventricular arrhythmias, principally ventricular tachycardia and fibrillation, which are resistant to conventional antiarrhythmic drug treatment.

Bretylium Tosylate Injection USP should be used only in intensive care units in hospitals, where facilities for monitoring and treating patients with serious cardiac arrhythmias are available.

Following administration of bretylium, there may be a delay of 20 minutes to as long as 6 hours before the onset of action. Quick acting drugs like lidocaine or procainamide remain the treatment of choice in patients with serious ventricular arrhythmias. If these continue and reoccur despite treatment with lidocaine or any other antiarrhythmic agent, bretylium may be of value in restoring sinus rhythm.

CONTRAINDICATIONS

There is no evidence that prophylactic administration of Bretylium Tosylate Injection USP confers clinical benefit in patients with recent but uncomplicated myocardial infarction. In such patients the use of Bretylium Tosylate Injection USP may lead to unpredictable cardiovascular effects. Therefore, this drug should not be used to prevent the development of arrhythmias in patients with recent myocardial infarction.

WARNINGS

Hypotension

Administration of Bretylium Tosylate Injection USP regularly results in postural hypotension, subjectively recognized by dizziness, lightheadedness, vertigo and faintness. Some degree of hypotension is present in about 50% of patients while they are supine. Hypotension may occur at doses lower than those needed to suppress arrhythmias.

The hypotensive effect of Bretylium Tosylate Injection USP should be especially borne in mind during anesthesia.

Patients should be kept in the supine position until tolerance to the hypotensive effect of Bretylium Tosylate Injection USP develops. Tolerance occurs unpredictably but may be present after several days.

Hypotension with supine systolic pressure greater than 75 mm Hg need not be treated unless there are associated symptoms. If supine systolic pressure falls below 75 mm Hg, an infusion of dopamine or norepinephrine may be used to raise blood pressure. When catecholamines are administered, a dilute solution should be employed and blood pressure monitored closely because the pressor effects of the catecholamines are enhanced by Bretylium Tosylate Injection USP. Volume expansion with blood or plasma and correction of dehydration should be carried out where appropriate.

Transient Hypertension and Increased Frequency of Arrhythmias
Due to the initial release of norepinephrine from adrenergic post-ganglionic nerve terminals by Bretylium Tosylate Injection USP, transient hypertension or increased frequency of premature ventricular contractions and other arrhythmias may occur in some patients. Such arrhythmias have been observed especially in persons receiving inotropic catecholamines.

Concomitant Use with Digitalis Glycosides
The initial release of norepinephrine caused by Bretylium Tosylate Injection USP may aggravate digitalis toxicity. When a life-threatening cardiac arrhythmia occurs in the digitalized patient, Bretylium Tosylate Injection USP should be used only if the etiology of the arrhythmia does not appear to be digitalis toxicity and other antiarrhythmic drugs are not effective. Simultaneous initiation of therapy with digitalis glycoside and Bretylium Tosylate Injection USP should be avoided.

Patients with Fixed Cardiac Output
In patients with fixed cardiac output, as with severe aortic stenosis or severe pulmonary hypertension, Bretylium Tosylate Injection USP should be avoided since severe hypotension may result from a fall in peripheral resistance without a compensatory increase in cardiac output. If survival is threatened by the arrhythmia, bretylium tosylate may be used but vasoconstrictive catecholamines should be given promptly if severe hypotension occurs.

Geriatrics
The elderly may require dosage modification due to altered renal clearance rates.

Use in Pregnancy
The safety of Bretylium Tosylate Injection USP in human pregnancy has not been established. However, as the drug is intended for use only in life-threatening situations, it may be used in pregnant women when its benefits outweigh the potential risk to the fetus.

Use in Children
The safety and efficacy of this drug in children has not been established. Bretylium Tosylate Injection USP has been administered to a limited number of pediatric patients, but such use has been inadequate to fully define a proper dosage and limitations for use.

PRECAUTIONS

Since rapid intravenous administration may cause severe nausea and vomiting, Bretylium Tosylate Injection USP should be diluted in dextrose and infused slowly. However, where immediate life-threatening ventricular arrhythmia exists, as in ventricular fibrillation, bretylium should then be given as rapidly as possible.

Impaired Renal Function

Bretylium Tosylate Injection USP is excreted principally *via* the kidney, and dosage should be reduced in patients with impaired renal function.

Sinus Bradycardia

The administration of Bretylium Tosylate Injection USP may aggravate sinus bradycardia and therefore should be used with caution in patients with this condition.

Drug Interactions

Patients should be carefully observed when Bretylium Tosylate Injection USP is used in combination with drugs such as quinidine, procainamide and propranolol. A significantly prolonged A-V transmission time and aggravation of preexisting A-V block may occur.

ADVERSE REACTIONS

Postural hypotension and supine hypotension have been the most frequently reported adverse reactions, usually within the first hour of therapy (see **WARNINGS**).

Nausea and vomiting occurred in about 3% of patients, primarily when Bretylium Tosylate Injection USP was administered rapidly by the intravenous route.

Vertigo, dizziness, lightheadedness and syncope, which sometimes accompanied postural hypotension, were reported in about 7 patients in 1 000.

Bradycardia, increased frequency of premature ventricular contractions, transitory hypertension, initial increase in arrhythmias (see **WARNINGS**), precipitation of anginal attacks, and sensation of substernal pressure have also been reported in a small number of patients, approximately 1-2 patients in 1 000.

Renal dysfunction, diarrhea, abdominal pain, hiccups, erythematous macular rash, flushing, hyperthermia, confusion, paranoid psychosis, emotional lability, lethargy, general tenderness, anxiety, shortness of breath, diaphoresis, nasal stuffiness and mild conjunctivitis have been reported in about 1 patient in 1 000. The relationship of Bretylium Tosylate Injection USP administration to these reactions has not been clearly established.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The symptoms are blurred vision, headache, nausea, hypotension and circulatory failure. The treatment should be symptomatic.

DOSAGE AND ADMINISTRATION

Bretylium Tosylate Injection USP is to be used clinically only for treatment of life-threatening ventricular arrhythmias under constant electrocardiographic monitoring. Since there is a delay in onset of its antiarrhythmic action, Bretylium Tosylate Injection USP is not to be considered or used as a replacement for rapidly-acting antiarrhythmic agents currently in use. The clinical use of Bretylium Tosylate Injection USP is for short-term only. Patients should either be kept supine during the course of Bretylium Tosylate Injection USP therapy or be closely observed for postural hypotension. The optimal dose schedule for parenteral administration of Bretylium Tosylate Injection USP has not been determined. There is comparatively little experience with dosages greater than 30 mg/kg/day although such doses have been used without apparent adverse effects. The following dosage schedule is proposed:

For Immediately Life-threatening Ventricular Arrhythmia, as in Ventricular Fibrillation:
Administer **undiluted** Bretylium Tosylate Injection USP (50 mg/mL) at a dosage of 5 mg/kg of body weight by rapid intravenous injection. Other usual cardiopulmonary resuscitative procedures, including electrical cardioversion, should be employed prior to and following the injection in accordance with good medical practice. If ventricular fibrillation persists, the dosage may be increased to 10 mg/kg and repeated at 15-30 minute intervals until a total dose of not more than 30 mg/kg of body weight has been given.

Other Ventricular Arrhythmias
Intravenous Use: Bretylium Tosylate Injection USP must be **diluted** as follows before intravenous administration. Using aseptic technique, dilute contents of 10 mL vial containing 500 mg bretylium tosylate to a minimum of 50 mL with Dextrose Injection USP or Sodium Chloride Injection USP. Diluted solution must be used within 24 hours from the time of preparation. The diluted solution should be inspected visually for discolouration, haziness, particulate matter and leakage prior to administration. Discard unused portion.

Administer the diluted solution at a dosage of 5-10 mg bretylium tosylate per kg of body weight by intravenous infusion over a period greater than 8 minutes. More rapid infusion may cause nausea and vomiting. A second dose may be given in 1 to 2 hours if the arrhythmia persists.

For Intramuscular Injection: Inject 5-10 mg **undiluted** Bretylium Tosylate Injection USP per kg of body weight. Dosage may be repeated in 1-2 hours if the arrhythmia persists. Thereafter, maintain with the same dosage every 6-8 hours.

When injected intramuscularly not more than 5 mL should be given in one site and injection sites should be varied since repeated intramuscular injection into the same site may cause atrophy and necrosis of muscle tissue, fibrosis, vascular degeneration and inflammatory changes. Care should be taken not to inject directly into or near a major nerve.

Maintenance Dosage
The diluted Bretylium Tosylate Injection USP solution should be administered by intermittent bolus infusion or by constant infusion. The solution must be used within 24 hours.

Intermittent Infusion: Infuse the diluted solution at a dose of 5-10 mg Bretylium Tosylate Injection USP per kg body weight over a period greater than 8 minutes every 6 hours. More rapid infusion may cause nausea and vomiting.

Constant Infusion: Infuse the diluted solution at a dosage of 1-2 mg Bretylium Tosylate Injection USP per minute.

Dosage of Bretylium Tosylate Injection USP should be reduced and discontinued in 3 to 5 days under electrocardiographic monitoring. Other appropriate antiarrhythmic agents should be substituted if indicated.

INSTRUCTIONS FOR DILUTION

Using aseptic technique, dilute contents of 10 mL vial containing 500 mg bretylium tosylate to a minimum of 50 mL with Dextrose Injection USP or Sodium Chloride Injection USP. Diluted solution must be used within 24 hours from the time of preparation. The diluted solution should be inspected visually for discolouration, haziness, particulate matter and leakage prior to administration. Discard unused portion.

AVAILABILITY OF DOSAGE FORMS

Each mL contains: bretylium tosylate 50 mg, sodium hydroxide and/or hydrochloric acid to adjust pH and water for injection.

Bretylium Tosylate Injection USP 50 mg/mL is available in 10 mL single use amber vials, boxes of 5.

Store between 15 and 30°C. Protect from light.

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

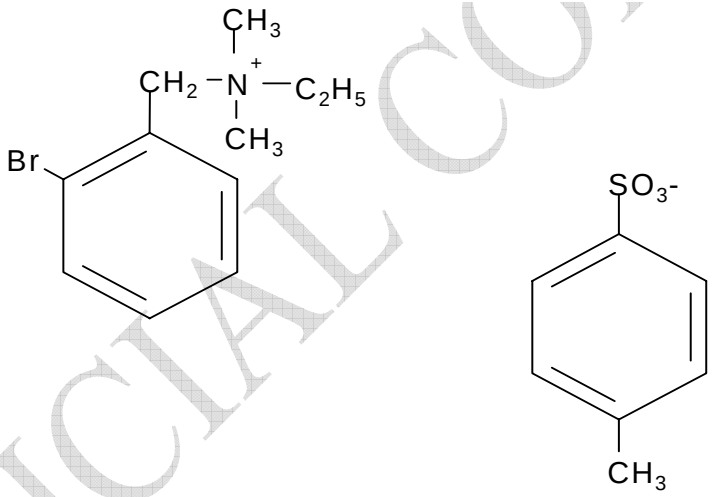
Proper Name: Bretylium tosylate

Chemical Name: (*o*-Bromobenzyl)ethyldimethylammonium *p*-toluenesulfonate.

Molecular Formula: $C_{18}H_{24}NO_3SBr$

Molecular Weight: 414.36

Structural Formula:



Description: Bretylium tosylate is a white to off-white, free-flowing, fine powder, very deliquescent and almost odourless. It is very soluble in water and alcohol, and almost insoluble in ether and ethylacetate.

PHARMACOLOGY

Bretylium exerts moderate to potent antiarrhythmic and antifibrillatory effects in many animal models. It is extremely effective in raising the ventricular fibrillation threshold to electrical stimulation in normal coronary artery ligated dogs and in protecting against hypothermia-induced fibrillation.

Bretylium initially has a sympathomimetic effect because of displacement of norepinephrine from adrenergic nerve terminals. It subsequently inhibits adrenergic neuronal responses by preventing release of norepinephrine from peripheral postganglionic sympathetic nerve fibres. The effector organ is able to respond to exogenous or endogenous non-neuronal catecholamines. Bretylium does not block release of catecholamines from the adrenal medulla. The net effects of the drug are similar to those seen following postganglionic sympathectomy. Bretylium depresses both excitatory and inhibitory responses evoked by electrical stimulation of peripheral sympathetic nerves.

The drug is slowly accumulated in sympathetic ganglia and their postganglionic nerve trunks, reaching concentrations that are as much as 20 times greater than in parasympathetic ganglia or cholinergic nerve trunks. These accumulated concentrations are temporally related to the adrenergic neuron blocking action.

Moderate to large intravenous doses of bretylium (3-10 mg/kg) in dogs and cats increased heart rate, blood pressure, and nictitating membrane activity; in general, these effects were mild and short-lasting. Bretylium has weak diuretic and MAO-inhibiting activity, and has a strong local anæsthetic effect at nerve terminals.

Bretylium is widely distributed in the body, showing a strong affinity of drug to the tissues and is eliminated by active urinary secretion and by biliary excretion.

TOXICOLOGY

Acute Toxicity

Species	Route	LD_{50} (mg/kg)	
		Male	**Female**
Mouse	IV	13.1	15.1
	IM	66.6	61.0
	IP	49.0	53.9
Rat	IV	17.9	16.7
	IM	166.3	84.2
	IP	152.6	62.2
Rabbit	IV	27 - 33.1	
	IM	144 - 173	
Dog	IV	35 - 50	
	IM	> 100	

Sub-Chronic Toxicity

Rats receiving 0, 2.5, 5 and 10 mg/kg exhibited diarrhea and dose-related tremors, but no deaths were seen. Hematology, serum chemistries, and urinalysis were all unremarkable.

Dogs receiving 0, 6.25, 12.5 and 25 mg/kg/day IV for 28 days showed dose-related sympathomimetic effects, salivation, erythema, incontinence, prostration, and lethargy. Two male high dose dogs died. Hematology, clinical chemistries, urinalyses, organ weights, and histopathologies were unremarkable.

BIBLIOGRAPHY

1. Bacaner MB. Treatment of ventricular fibrillation and other acute arrhythmias with bretylium tosylate. Am J Cardiol 1968; 21: 530-43.

2. Bernstein JG, Koch-Weser J. Effectiveness of bretylium tosylate against refractory ventricular arrhythmias. Circulation 1972; 55: 1024-34.

3. Castle L. Therapy of ventricular tachycardia. Am J Cardiol 1984; 54: 26A-33A.

4 Cohen HC, Gozo EG, Langendorf R, et al. Response of resistant ventricular tachycardia to bretylium: relation to site of ectopic focus and location of myocardial disease. Circulation 1973; 47: 331-40.

5. Dhurandhar RW, Teasdale SJ, Mahon WA. Bretylium tosylate in the management of refractory ventricular fibrillation. C.M.A.J 1971; 105: 161-5.

6. Duff HJ, Roden DM, Yacobi A, et al. Bretylium: relations between plasma concentrations and pharmacologic actions in high-frequency ventricular arrhythmias. Am J Cardiol 1985; 55: 395-401.

7. Garrett ER, Green JR, Bialer M. Bretylium pharmacokinetics and bioavailabilities in man with various doses and modes of administration. Biopharm Drug Dispos 1982; 3: 129-64.

8. Holder DA, Sniderman AD, Fraser G, Fallen EL. Experience with bretylium tosylate by a hospital cardiac arrest team. Circulation 1977; 55: 541-4.

9. Josselson J, Narang PK, Adir J, et al. Bretylium kinetics in renal insufficiency. Clin Pharmacol Ther 1983; 33: 144-50.

10. Kamath BL, Gibson TP, Look ZM, et al. Pharmacokinetics of bretylium in dogs and the effect of hemoperfusion on elimination. J Pharm Sci 1982; 71: 1294-6.

11. Kamath BL, Stampfli HF, Lai C-M, Yacobi A. Pharmacokinetics of [^{14}C] bretylium tosylate in rats. J Pharma Sci 1981; 70: 667-9.

12. Romhilt DW, Bloomfield SS, Lipicky RJ, et al. Evaluation of bretylium tosylate for the treatment of premature ventricular contractions. Circulation 1972; 45: 800-7.

13. Sanna G, Arcidiacono R. Chemical ventricular defibrillation of the human heart with bretylium tosylate. Am J Cardiol 1973; 32: 982-7.

14. Bretylium Tosylate Injection. Medical Officer's Review of NDA 17-954. F.O.I. Services, 1978.

15. Bretylium Tosylate Injection. Pharmacologist's Review of NDA 17-954. F.O.I. Services, 1977.