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

8021511-805

DILZEM® I.V.

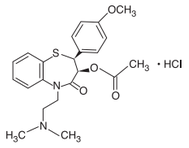
(Diltiazem Hydrochloride Injection 5 mg/ml; 5 ml vial)

COMPOSITION

Each ml contains :
Diltiazem Hydrochloride I.P. 5.0 mg
Water for injection I.P. q.s.

DESCRIPTION

Diltiazem Hydrochloride is a calcium ion influx inhibitor (slow channel blocker or calcium channel antagonist). Diltiazem hydrochloride is a white, crystalline powder or small crystals which is freely soluble in *chloroform*, in *methanol*, in *water* and in *formic acid*; sparingly soluble in *ethanol*; insoluble in *ether* and Chemically is *s*-2,3,4,5-tetrahydro-5-(2-dimethylaminoethyl)-2-(4-methoxyphenyl)-4-oxobenzo[b]thiazepin-3-yl acetate monohydrochloride. It has a molecular weight of 451.0. The molecular formula is $C_{22}H_{26}N_2O_4S,HCl$ and the chemical structure is :



Dilzem injection is a clear, colorless, sterile, nonpyrogenic solution. It has a pH range of 3.7 to 4.1.
Dilzem injection is for direct Intravenous bolus injection and continuous intravenous infusion.

CLINICAL PHARMACOLOGY

Mechanisms of Action

Diltiazem inhibits the influx of calcium (Ca^{2+}) ions during membrane depolarization of cardiac and vascular smooth muscle. The therapeutic benefits of diltiazem in supraventricular tachycardias are related to its ability to slow AV nodal conduction time and prolong AV nodal refractoriness. Diltiazem exhibits frequency (use) dependent effects on AV nodal conduction such that it may selectively reduce the heart rate during tachycardias involving the AV node with little or no effect on normal AV nodal conduction at normal heart rates.
Diltiazem slows the ventricular rate in patients with a rapid ventricular response during atrial fibrillation or atrial flutter. Diltiazem converts paroxysmal supraventricular tachycardia (PSVT) to normal sinus rhythm by interrupting the reentry circuit in AV nodal reentrant tachycardias and reciprocating tachycardias, e.g., Wolff-Parkinson-White syndrome (WPW).
Diltiazem prolongs the sinus cycle length. It has no effect on the sinus node recovery time or on the sinoatrial conduction time in patients without SA nodal dysfunction. Diltiazem has no significant electro-physiologic effects on tissues in the heart that are fast sodium channel dependent, e.g., His-Purkinje tissue, atrial and ventricular muscle, and extranodal accessory pathways. Like other calcium channel antagonists, because of its effect on vascular smooth muscle, diltiazem decreases total peripheral resistance resulting in a decrease in both systolic and diastolic blood pressure.

Hemodynamics

In patients with cardiovascular disease, diltiazem administered intravenously in single bolus doses, followed in some cases by a continuous infusion, reduced blood pressure, systemic vascular resistance, the rate-pressure product, and coronary vascular resistance and increased coronary blood flow. In a limited number of studies of patients with compromised myocardium (severe congestive heart failure, acute myocardial infarction, hypertrophic cardiomyopathy), administration of intavenous diltiazem produced no significant effect on contractility, left ventricular end diastolic pressure, or pulmonary capillary wedge pressure. The mean ejection fraction and cardiac output/index remained unchanged or increased. Maximal hemodynamic effects usually occurred within 2 to 5 minutes of an injection. However, in rare instances, worsening of congestive heart failure has been reported in patients with preexisting impaired ventricular function.

Pharmacodynamics

In patients with atrial fibrillation and atrial flutter, a significant correlation was observed between the percent reduction in HR and plasma diltiazem concentration using the Sigmoidal E_{max} model. Based on this relationship, the mean plasma diltiazem concentration required to produce a 20% decrease in heart rate was determined to be 80 ng/mL. Mean plasma diltiazem concentrations of 130 ng/mL and 300 ng/mL were determined to produce reductions in heart rate of 30% and 40%.
Following administration of one or two Intravenous bolus doses of Dilzam Injection, response usually occurs within 3 minutes and maximal heart rate reduction generally occurs in 2 to 7 minutes. Heart rate reduction may last from 1 to 3 hours. If hypotension occurs, it is generally short-lived, but may last from 1 to 3 hours.
A 24-hour continuous Infusion of Diltiazem hydrochloride Injection in the treatment of atrial fibrillation or atrial flutter has been reported to maintain at least a 20% heart rate reduction during the infusion in 83% of patients. Upon discontinuation of Infusion, heart rate reduction may last from 0.5 hours to more than 10 hours (median durartion 7 hours). Hypotension, If it occurs, may be similarly persistent.

Pharmacokinetics and Metabolism

Following a single intravenous injection in healthy male volunteers, diltiazem appears to obey linear pharmacokinetics over a dose range of 10.5 to 21.0 mg. The plasma elimination half-life is approximately 3.4 hours. The apparent volume of distribution of diltiazem is approximately 305 L. Diltiazem is extensively metabolized in the liver with a systemic clearance of approximately 65 L/h.
After constant rate intravenous infusion to healthy male volunteers, diltiazem exhibits nonlinear pharmacokinetics over an infusion range of 4.8 to 13.2 mg/h for 24 hours. Over this infusion range, as the dose is increased, systemic clearance decreases from 64 to 48 L/h while the plasma elimination half-life increases from 4.1 to 4.9 hours. The apparent volume of distribution remains unchanged (360 to 391 L). In patients with atrial fibrillation or atrial flutter, diltiazem systemic clearance has been found to be decreased compared to healthy volunteers. In patients administered bolus doses ranging from 2.5 mg to 38.5 mg, systemic clearance averaged 36 L/h. In patients administered continuous infusions at 10 mg/h or 15 mg/h for 24 hours, diltiazem systemic clearance averaged 42 L/h and 31 L/h, respectively.
Diltiazem is 70% to 80% bound to plasma proteins. In vitro studies suggest alpha$_1$-acid glycoprotem binds approximately 40% of the drug at clinically significant concentrations. Albumin appears to bind approximately 30% of the drug, while other constitutents bind the remaining bound fraction. Competitive in vitro ligand binding studies have shown that diltiazem binding is not altered by therapeutic concentrations of digoxin, phenytoin, hydrochlorothiazide, indomethacin, phenyl- butazone, propranolol, salicyclic acid, tolbutamide, or warfarin. N-monodesmethyl diltiazem and desacetyldiltiazem, two principal metabolites found in plasma after oral administration, are typically not detected. These metebolites are observed, however, following 24 hour constant rate intravenous infusion. Total radioactivity measurement following short IV administration in healthy volunteers suggests the presence of other unidentified metabolites which attain higher concentrations then those of diltiazem and are more slowly eliminated; half life of total radioactivity is about 20 hours compared to 2 to 5 hours for diltiazem.

INDICATIONS AND USAGE

Diltiazem Hydrochloride Injection is indicated for the following :

1. ***Atrial Fibrillation Or Atrial Flutter.*** Temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter. It should not be used in patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in Wolff-Parkinson-White (WPW) syndrome or short PR syndrome.
2. ***Paroxysmal Supraventricular Tachycardia.*** Rapid conversion of paroxysmal supraventricular tachycardias (PSVT) to sinus rhythm. This includes AV nodal reentrant tachycardias and reciprocating tachycardias associated with an extranodal accessory pathway such as the WPW syndrome or short PR syndrome. Unless otherwise contraindicated, appropriate vagal maneuvers should be attempted prior to administration of Diltiazem Hydrochloride Injection. The use of Diltiazem Hydrochloride Injection for control of ventricular response in patients with atrial fibrillation or atrial flutter or conversion to sinus rhythm in patients with PSVT should be undertaken with caution when the patient is compromised hemodynamically or is taking other drugs that decrease any or all of the following: peripheral resistance, myocardial filling, myocardial contractility, or electrical impulse propagation in the myocardium.

For either indication and particularly when employing continuous intravenous infusion, the setting should include continuous monitoring of the ECG and frequent measurement of blood pressure.

A defibrillator and emergency equipment should be readily available.

DOSAGE AND ADMINISTRATION

Direct Intravenous Single Injections (Bolus)

The initial dose of Diltiazem Hydrochloride injection should be 0.25 mg/kg actual body weight as a bolus administered over 2 minutes. If response is inadequate, a second dose may be administered after 15 minutes. The second bolus dose of Diltiazem Hydrochloride injection should be 0.35 mg/kg actual body weight administered over 2 minutes. Subsequent intravenous bolus doses should be individualized for each patient. Patients with low body weights should be dosed on a mg/kg basis. Some patients may respond to an initial dose of 0.15 mg/kg, although duration of action may be shorter. Experience with this dose is limited.

Continuous Intravenous Infusion

For continued reduction of the heart rate (up to 24 hours) in patients with atrial fibrillation or atrial flutter, an intravenous infusion of diltiazem hydrochloride may be administered. Immediately following bolus administration of 20 mg (0.25 mg/kg) or 25 mg (0.35 mg/kg) diltiazem hydrochloride injection and reduction of heart rate, begin an intravenous infusion of diltiazem hydrochloride. The recommended initial infusion rate of diltiazem hydrochloride is 10 mg/h.
Some patients may maintain response to an initial rate of 5 mg/h. The infusion rate may be increased in 5 mg/ h increments up to 15 mg/h as needed, if further reduction in heart rate is required. The infusion may be maintained for up to 24 hours.
Diltiazem shows dose-dependent, non-linear pharma-cokinetics. Duration of infusion longer than 24 hours and infusion rates greater than 15 mg/h have not been studied. Therefore, infusion duration exceeding 24 hours and infusion rates exceeding 15 mg/h are not recommended.

Dilution: To prepare diltiazem hydrochloride injection for continuous intravenous infusion, aseptically transfer the appropriate quantity (see chart) of diltiazem hydrochloride injection to the desired volume of either Normal Saline, D5W, or D5W/0.45% NaCl. Mix thoroughly. Use within 24 hours. Keep refrigerated until use.

Diluent Volume	Quantity of Diltiazem HCl Injection to Add	Final Concentration	Administration Dose*	Infusion Rate
100 mL	125 mg (25 mL) Final Volume 125 mL	1 mg/mL	10 mg/h 15 mg/h	10 mL/h 15 mL/h
250 mL	250 mg (50 mL) Final Volume 300 mL	0.83 mg/mL	10 mg/h 15 mg/h	12 mL/h 18 mL/h
500 mL	250 mg (50 mL) Final Volume 550 mL	0.45 mg/mL	10 mg/h 15 mg/h	22 mL/h 33 mL/h

* 5 mg/h may be appropriate for some patients.

CONTRAINDICATIONS

Diltiazem Hydrochloride Injection is contraindicated in :

1. Patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker.
2. Patients with second-or third-degree AV block except in the presence of a functioning ventricular pacemaker.
3. Patients with severe hypotension or cardiogenic shock.
4. Patients who have demonstrated hypersensitivity to the drug.
5. Intravenous diltiazem and intravenous beta-blockers should not be administered together or in close proximity (within a few hours).
6. Patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in WPW syndrome or short PR syndrome.
   As with other agents which slow AV nodal conduction and do not prolong the refractoriness of the accessory pathway (e.g., verapamil, digoxin), in rare instances patients in atrial fibrillation or atrial flutter associated with an accessory bypass tract may experience a potentially life-threatening increase in heart rate accompanied by hypotension when treated with Diltiazem Hydrochloride Injection. As such, the initial use of Diltiazem Hydrochloride Injection should be, if possible, in a setting when monitoring and resuscitation capabilities, including DC cardio-version/defibrillation, are present.
7. Patients with ventricular tachycardia. Administration of other calcium channel blockers to patients with wide complex tachycardia (QRS > 0.12 seconds) has resulted in hemodynamic deterioration and ventricular fibrillation. It is important that an accurate pretreatment diagnosis distinguish wide complex QRS tachycardia of supraventricular origin from that of ventricular origin prior to administration of Diltiazem Hydrochloride Injection.

WARNINGS

1. ***Cardiac Conduction.*** Diltiazem prolongs AV nodal conduction and refractoriness that may rarely result in second- or third-degree AV block in sinus rhythm. Concomitant use of diltiazem with agents known to affect cardiac conduction may result in additive effects. If high-degree AV block occurs in sinus rhythm, intravenous diltiazem should be discontinued and appropriate supportive measures instituted.
2. ***Congestive Heart Failure.*** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function and in patients with a compromised myocardium, such as severe CHF, acute MI, and hypertrophic cardiomyopathy, have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Administration of oral diltiazem in patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission is contraindicated. Experience with the use of Diltiazem Hydrochloride Injection in patients with impaired ventricular function is limited. Caution should be exercised when using the drug in such patients.
3. ***Hypotension.*** Decreases in blood pressure associated with Diltiazem Hydrochloride Injection therapy may occasionally result in symptomatic hypotension (3.2%). The use of intravenous diltiazem for control of ventricular response in patients with supraventricular arrhythmias should be undertaken with caution when the patient is compromised hemodynamically. In addition, caution should be used in patients taking other drugs that decrease peripheral resistance, intravascular volume, myocardial contractility or conduction.
4. ***Acute Hepatic Injury.*** In rare instances, significant elevations in enzymes such as alkaline phosphate, LDH, SGOT, SGPT, and other phenomena consistent with acute
   hepatic injury have been noted following oral diltiazem. Therefore, the potential for acute hepatic injury exists following administration of intravenous diltiazem.

Ventricular Premature Beats (VPBs). VPBs may be present on conversion of PSVT to sinus rhythm with Diltiazem Hydrochloride Injection. These VPBs are transient, are typically considered to be benign, and appear to have no clinical significance.

DRUG INTERACTIONS

Anesthetics. The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.
Beta-blockers. Intravenous diltiazem has been administered to patients on chronic oral beta-blocker therapy. The combination of the two drugs was generally well tolerated without serious adverse effects. If intravenous diltiazem is administered to patients receiving chronic oral beta-blocker therapy, the possibility for bradycardia, AV block, and/or depression of contractility should be considered. Oral administration of diltiazem with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. In vitro, propranolol appears to be displaced from its binding sites by diltiazem.
Digitalis. It has been reported that the combination of Intravenous diltiazem with either intravenous or oral digitalis therapy were well tolerated without serious adverse effects. However, since both drugs affect AV nodal conduction, patients should be monitored for excessive slowing of the heart rate and/or AV block.

USE IN PREGNANCY, LACTATION AND CHILDREN

Pregnancy

Pregnancy Category C
Reproduction studies have been conducted in mice, rats and rabbits. Administration of oral doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended oral antianginal therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human oral antianginal dose or greater. There are no well-controlled studies in pregnant women; therefore, use diltiazem in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Diltiazem is excreted in human milk. One report with oral diltiazem suggests that concentrations in breast milk may approximate serum levels. If use of diltiazem is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Adverse events reported in controlled and uncontrolled clinical trials were generally mild and transient. Hypotension was the most commonly reported adverse event during clinical trials. Asymptomatic hypotension occurred in 4.3% of patients. Symptomatic hypotension occurred in 3.2% of patients. When treatment for hypotension was required, it generally consisted of administration of saline or placing the patient in the Trendelenburg position. Other events reported in at least 1% of the diltiazem-treated patients were injection site reactions (eg, itching, burning) 3.9%, vasodilation (flushing) 1.7%, and arrhythmia (junctional rhythm or isorhythmic dissociation) 1.0%. Side effects with rare incidence include-atrial flutter, AV block, bradycardia, chest pain, congestive heart faliure, sinus pause, sinus node dysfunction, syncope, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia, pruritus, constipation, elevated SGOT or alkaline phosphatase, nausea, vomitting, dizziness, paresthesia. ambiyopia, asthenia, dyspnea, edema, headache and hyperuricemia. Although not observed in clinical trials with Dilzem injection, other reactions associated with oral diltiazem may occur.

OVERDOSAGE

Overdose experience with Diltiazem Hydrochloride is limited. In the event of overdose or exaggerated response, appropriate supportive measures should be employed. The following measures may be considered :
Bradycardia : Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockage, administer isoproterenol cautiously.
High-Degree AV Block : Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure: Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension: Vasopressors (e.g. dopamine or levarterenol bitartrate).
In a few reported cases, overdose with calcium channel blockers has been associated with hypotension and bradycardia, initially refractory to atropine but becoming more responsive to this treatment when the patients received large doses (close to 1 gram/hour for more than 24 hours) of calcium chloride.
The intravenous LD50's in mice and rats were 60 and 38 mg/kg, respectively. The toxic dose in man is not known. Charcoal hemoperfusion has been used successfully as an adjunct therapy to hasten drug elimination.
Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

STORAGE

Store under refrigeration between 2°C to 8°C.
Do not allow to freeze may be stored at room temperature for upto 1 month.
Destroy after 1 month if stored at a room temperature.

PRESENTATION

Dilzem® I.V. available in a 5 ml glass vial.

Marketed by :

torrent PHARMA

TORRENT PHARMACEUTICALS LTD.
Torrent House, Off Ashram Road,
Ahmedabad-380 009, INDIA

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