DISCLAIMER

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Diltiazem Hydrochloride Injection
0.5% (5 mg/mL)

The molecular formula is C_{22}H_{26}N_{2}O_{4}S\cdot HCl.

Diltiazem Hydrochloride Injection is a clear, colorless, sterile, nonpyrogenic solution. Its pH range is 3.7 to 4.1.

Pharmacokinetics
Diltiazem is extensively metabolized by the liver and excreted by the kidneys and in bile. The drug should be used with caution in patients with impaired renal or hepatic function (see PRECAUTIONS, Drug Interactions). If high-dose AV block occurs in sinus rhythm, intravenous diltiazem should be discontinued and appropriate supportive measures instituted (see OVERDOSAGE).

1. Cardiac Conduction. Diltiazem prolongs AV nodal conduction and refractoriness that may result in second- or third-degree AV block or sinus bradycardia. Concomitant use of diltiazem with agents known to affect cardiac conduction may result in additive effects (see PRECAUTIONS, Drug Interactions). If high-dose AV block occurs in sinus rhythm, intravenous diltiazem should be discontinued and appropriate supportive measures instituted (see OVERDOSAGE).

2. Congestive Heart Failure. Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, in vivo 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 improvement in cardiac output. Administration of diltiazem to patients with severe ventricular dysfunction treated with diltiazem hydrochloride injection. As such, the initial use of diltiazem hydrochloride injection should be, if possible, as described above.

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 atrial fibrillation or atrial flutter may be accompanied by a potential life-threatening increase in heart rate associated with the Wolff-Parkinson-White syndrome or short PR syndrome. Unless otherwise contraindicated, appropriate vagal maneuvers should be attempted prior to administration of diltiazem hydrochloride injection.

4. Atrium-Ventricular Conduction. Rapid conduction of paroxysmal supraventricular tachycardia (PSVT) to sinus rhythm. This includes all reentrant supraventricular tachycardia (SVT) mechanisms. In patients with atrial fibrillation or flutter associated with an accessory bypass tract such as in Wolff-Parkinson-White (WPW) syndrome or short PR syndrome. Unless otherwise contraindicated, appropriate vagal maneuvers should be attempted prior to administration of diltiazem hydrochloride injection.

5. Atrioventricular Node. Atrioventricular conduction is not altered by therapeutic concentrations of digoxin, phenytoin, hydrochlorothiazide, indomethacin, phenytoin sodium, propranolol, salicylic acid, tobutamide, or warfarin.

6. 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. Unless otherwise contraindicated, appropriate vagal maneuvers should be attempted prior to administration of diltiazem hydrochloride injection.

7. Patients with ventricular tachycardia. Administration of other calcium channel blockers to patients with wide complex tachycardia, i.e., >200 beats/minute, has resulted in hemodynamic deterioration and/or sudden death. It is important that an accurate pretrial diagnosis distinguishes wide complex QRS tachycardia of supraventricular origin from that of ventricular origin prior to administration of diltiazem hydrochloride injection.

W W W

The prolongation of PR interval correlated significantly with plasma diltiazem concentration in normal volunteers using the Sigmoidal E_max model. Changes in heart rate, systolic blood pressure, and diastolic blood pressure did not correlate with diltiazem plasma concentration in normal volunteers. Reduction in mean arterial pressure correlated linearly with diltiazem plasma concentration in a group of hypertensive patients.

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 at 20% to 40%.

Pharmacokinetics and Metabolism
Diltiazem is a single optical isomer injection in healthy male volunteers, diltiazem hydrochloride appears to obey linear pharmacokinetics over a dose range of 10.5 to 21 mg. The plasma elimination half-life is approximately 3.4 hours. The apparent volume of distribution of diltiazem hydrochloride 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 for 15 mg/h for 24 hours, diltiazem systemic clearance averaged 42 L/h and 31 L/h, respectively.

Based on the results of pharmacokinetic studies in healthy volunteers administered different oral diltiazem hydrochloride formulations, constant rate intravenous infusions of diltiazem hydrochloride at 3, 5, 7, and 11 mg/h are predicted to produce steady-state plasma diltiazem concentrations equivalent to 120-, 200-, 400-, and 600-mg total daily oral doses of diltiazem hydrochloride tablets or capsules.

After oral administration, diltiazem hydrochloride undergoes extensive metabolism in man by deacetylation, N-demethylation, and O-demethylation via cytochrome P-450 (oxidative metabolism) in addition to conjugation. Metabolites N-monomethyldiltiazem, desacetyl diltiazem, desacetyl-N-monomethyldiltiazem, desacetyl-O-demethyldiltiazem, and desacetyl-N-O-demethyldiltiazem have been identified in human urine. Following oral administration, 2% to 4% of the unchanged diltiazem appears in the urine. Drugs which induce or inhibit hepatic microsomal enzymes may alter diltiazem disposition.

Following intravenous administration of diltiazem hydrochloride, however, plasma concentrations of N-monomethyldiltiazem and desacetyldiltiazem, two principal metabolites found in plasma after oral administration, are typically not detected. These metabolites are observed, however, following 24 hour constant rate intravenous infusion. Total radioactivity measurement following short intravenous administration in healthy volunteers suggests the presence of other unidentified metabolites which attain higher concentrations than 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.

Diltiazem hydrochloride is 70% to 80% bound to plasma proteins. In vitro studies suggest alpha-, alpha-glycoprotein binds approximately 40% of the drug at clinically significant concentrations. Albumin appears to bind approximately 30% of the drug. Only a small fraction of diltiazem is present in cerebrospinal fluid. It is not clear whether diltiazem binding is not altered by therapeutic concentrations of digoxin, phenytoin, hydrochlorothiazide, indomethacin, phenytoin sodium, propranolol, salicylic acid, tobutamide, or warfarin.

Diltiazem is extensively metabolized by the liver and excreted by the kidneys and in bile. The drug should be used with caution in patients with impaired renal or hepatic function (see WARNINGS). High intravenous dosages (4.5 mg/kg/h) administered to dogs resulted in significant bradycardia and alterations in AV conduction. In subacute and
chronic dog and rat studies designed to produce toxicity, high oral doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver, which were reversible when the drug was discontinued. In dogs, oral doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatologic events progressing to erythema multiforme and/or exfoliative dermatitis have been infrequently reported following oral diltiazem. Therefore, the potential for these dermatologic reactions exists following exposure to intravenous diltiazem. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interactions

Due to potential for additive effects, caution is warranted in patients receiving diltiazem hydrochloride injection concomitantly with other agent(s) known to affect cardiac contractility and/or SA or AV node conduction (see WARNINGS).

As with all drugs, care should be exercised when treating patients with multiple medications. Diltiazem hydrochloride is excreted primarily by the liver; however, some pharmacokinetic drug-drug interaction studies have not been conducted with single intravenous injection or constant rate intravenous infusion, coadministration of diltiazem hydrochloride with other agents which primarily undergo the same route of biotransformation may result in competitive inhibition of metabolism.

Digitalis. Intra cardiac diltiazem has been administered to patients receiving either intravenous or oral digitalis therapy. The combination of the two drugs was well tolerated without serious adverse effects. However, since both drugs affect AV node conduction, patients should be monitored for excessive slowing of the heart rate and/or AV block.

Beta-blockers. Intra cardiac 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. 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 (see CONTRAINDICATIONS). 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 is displaced from its binding sites by diltiazem.

Anesthesics. The depression of cardiac contractility, conductivity, and automatically 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.

Cyclosporine. A pharmacokinetic interaction between diltiazem and cyclosporine has been observed during studies involving renal and cardiac transplant patients. In renal and cardiac transplant recipients, a reduction of cyclosporine dose ranging from 10% to 48% was necessary to maintain cyclosporine trough concentrations similar to those seen prior to the addition of diltiazem hydrochloride injection. If these agents are to be administered concurrently, cyclosporine concentrations should be monitored, especially when diltiazem therapy is initiated, adjusted or discontinued.

The effect of cyclosporin on plasma cyclosporine concentrations has not been evaluated.

Carbamazepine. Concurrent administration of oral diltiazem with carbamazepine has been reported to result in elevated plasma levels of carbamazepine (by 40 to 72%), resulting in toxicity in some cases. Patients receiving these drugs concurrently should be monitored for a potential drug interaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day, and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vivo in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy

Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of oral doses ranging from 15% to 48% was necessary to maintain cyclosporine trough concentrations similar to those seen prior to the addition of diltiazem hydrochloride injection. If these agents are to be administered concurrently, cyclosporine concentrations should be monitored, especially when diltiazem therapy is initiated, adjusted or discontinued.

Due to potential for additive effects, caution is warranted in patients receiving diltiazem hydrochloride injection concomitantly with other agents primarily undergo the same route of biotransformation may result in competitive inhibition of metabolism.

Dermatologic events progressing to erythema multiforme and/or exfoliative dermatitis have been infrequently reported following oral diltiazem. Therefore, the potential for these dermatologic reactions exists following exposure to intravenous diltiazem. Should a dermatologic reaction persist, the drug should be discontinued.

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician. Diltiazem does not appear to be removed by peritoneal or hemodialysis. Limited data suggest that plasmaapheresis or charcoal hemoperfusion may hasten diltiazem elimination following overdose.

The intravenous LD50 in mice and rats were 60 to 38 mg/kg, respectively. The toxic dose in man is not known.

DOSEAGE 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 (30 mg is a reasonable dose for the average patient). 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 (25 mg is a reasonable dose for the average patient). 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 continuous reduction of the heart rate (up to 24 hours) in patients with atrial fibrillation or atrial flutter, an intravenous infusion of diltiazem hydrochloride injection 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 injection. The recommended initial infusion rate of diltiazem hydrochloride injection 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 pharmacokinetics. 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, DSW, or DSW/0.45% NaCl. Mix thoroughly. Use within 24 hours. Keep refrigerated until use. Use within 24 hours. 0.9% saline may be appropriate for some patients.

Diltiazem hydrochloride injection is supplied for use with commonly used intravenous fluids at a maximal concentration of 1 mg diltiazem hydrochloride per milliliter. Diltiazem hydrochloride injection was found to be physically compatible and chemically stable in the following parenteral solutions for at least 24 hours when stored in glass or polyvinyl chloride (PVC) bags at controlled room temperature 15° to 30°C (59° to 86°F) or under refrigeration 2° to 8°C (36° to 46°F).

Manufactured by: Akorn, Inc.
Lake Forest, IL 60045

1404-379 Diltiazem DH00N R4-14 DH00N R4-14 Diltiazem 5/5/14 11:39 AM Page 2