PRODUCT MONOGRAPH

GEN-DILTIAZEM CD
(Diltiazem Hydrochloride)

120 mg, 180 mg, 240 mg and 300 mg Controlled Delivery Capsules

Antihypertensive Agent - Antianginal Agent

Genpharm Inc
85 Advance Road
Etobicoke ON
M8Z 2S6

Date of Preparation
June 8, 2004

Control # 092046

PRODUCT MONOGRAPH

Gen-Diltiazem CD

(Diltiazem hydrochloride)
Once a day controlled delivery capsules
Mfr. Standard

120 mg, 180 mg, 240 mg, and 300 mg

Antihypertensive Agent - Antianginal Agent

ACTION AND CLINICAL PHARMACOLOGY

Gen-Diltiazem CD capsules are a formulation of diltiazem hydrochloride, which is a calcium ion influx inhibitor (calcium entry blocker or calcium ion antagonist).

Mechanism of Action
The therapeutic effect of this drug is believed to be related to the specific cellular action of selectively inhibiting transmembrane influx of calcium ions into cardiac muscle and vascular smooth muscle. The contractile processes of these tissues are dependent upon the movement of extracellular calcium into the cells through specific ion channels. Diltiazem blocks transmembrane influx of calcium through the slow channel without affecting to any significant degree the transmembrane influx of sodium through the fast channel. This results in a reduction of free calcium ions available within cells of the above tissues. Diltiazem does not alter total serum calcium.

Angina:
The precise mechanism by which diltiazem relieves angina has not been fully determined but it is believed to be brought about largely by its vasodilator action.

In angina due to coronary spasm, diltiazem increases myocardial oxygen delivery by dilating both large and small coronary arteries and by inhibiting coronary spasm at drug levels which cause little negative inotropic effect. The resultant increases in coronary blood flow are accompanied by dose dependent decreases in systemic blood pressure and

decreases in peripheral resistance.

In angina of effort it appears that the action of diltiazem is related to the reduction of myocardial oxygen demand. This is probably caused by a decrease in blood pressure brought about the reduction of peripheral resistance and of heart rate.

Hypertension:

The antihypertensive effect of diltiazem is believed to be brought about largely by its vasodilatory action on peripheral blood vessels with resultant decrease in peripheral vascular resistance.

Hemodynamic and Electrophysiologic Effects

Diltiazem produces antihypertensive effects both in the supine and standing positions. Resting heart rate is usually slightly reduced. During dynamic exercise, increases in diastolic pressure are inhibited while maximum achievable systolic pressure is usually unaffected. Heart rate at maximum exercise is reduced.

Studies to date, primarily in patients with normal ventricular function, have shown that cardiac output, ejection fraction and left ventricular end-diastolic pressure have not been affected.

Chronic therapy with diltiazem produces no change, or an increase, in circulating plasma catecholamines. However, no increased activity of the renin-angiotensin-aldosterone axis has been observed. Diltiazem inhibits the renal and peripheral effects of angiotensin II.

In an intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods by approximately 20%. Chronic oral administration of diltiazem in doses up to 540 mg per day has resulted in small increases in PR interval. Second degree and third degree AV block have been observed (see WARNINGS). In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Pharmacokinetics

Diltiazem is well absorbed from the gastrointestinal tract and is subject to an extensive

first-pass effect giving absolute bioavailability (compared to intravenous dosing) of about 40)%. Therapeutic blood levels appear to be in the 50-200 ng/mL range and the plasma elimination half-life (beta-phase) following single or multiple drug administration is approximately 3.5 to 6.0 hours. In vitro human serum binding studies revealed that 70 to 80% of diltiazem is bound to plasma proteins. Diltiazem hydrochloride undergoes extensive hepatic metabolism in which only 2-4% of the drug appears unchanged in the urine and 6-7% appears as metabolites. The metabolic pathways of diltiazem hydrochloride include – and O-demethylation (via cytochrome P-450), deacetylation (via plasma and tissue esterases), in addition to conjugation (via sulfation and glucuronidation). In vitro studies have demonstrated that CYP 3A4 is the principal CYP isoenzyme involved in N-demethylation. The major metabolite, desacetyl diltiazem, is present in the plasma at levels 10-20% of the parent drug and is 25-50% as potent as diltiazem in terms of coronary vasodilation.

Diltiazem hydrochloride controlled delivery (once-a-day) capsules:
When compared to a regimen of Diltiazem tablets at steady-state, more than 95% of drug is absorbed from the Diltiazem CD formulation A single 360 mg dose of the capsule results in detectable plasma levels within 2 hours and peak plasma levels between 10 and 14 hours. When Diltiazem CD taken with a high fat content breakfast, the extent of diltiazem absorption was not affected but was delayed. Dose-dumping does not occur. The apparent elimination half-life after single or multiple dosing is 5 to 8 hours. A departure from linearity similar to that seen with Diltiazem tablets and Diltiazem SR capsules is observed. As the dose of Diltiazem CD capsules is increased from a daily dose of 120 mg to 240 mg, there is an increase in the area under the curve (AUC) of 2.7 times. When the dose is increased from 240 mg to 360 mg there is an increase in AUC of 1.6 times.

A study which compared patients with normal hepatic function to liver cirrhosis patients noted an increase in half-life and a 69% increase in bioavailability in the hepatically impaired patients. A single dose study in patients with severely impaired renal function showed no difference in the half-life of diltiazem as compared to patients with normal renal function. (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Summary tables of the comparative bioavailability studies

Table 1

Parmacokinetic parameters for the Comparative bioavailability study of Genpharm Inc. and HMR Canada Inc. (Cardizem® CD) diltiazem HCl extended release (CD) capsule following administration of a single, oral 300 mg dose under fasting conditions.

Parameter	Geometric Mean and Arithmetic Mean (CV)		Ratio of Geometric Means (%) (CI)
	Gen-Diltiazem CD	Cardizem CD	
	300 mg	300 mg	
AUC_T (ng.h/mL)	2374.7 2676.0 (46%)	2324.9 2632.1 (44.8%)	102%
AUC_I (ng.h/mL)	2456.5 2761.6 (46.8%)	2417.3 2734.3 (45.3%)	102%
C_{MAX} (ng/mL)	127.52 139.32 (39.2%)	102.33 132.54 (40.9%)	106%
T_{MAX} (h)	10.317 (50.1%)	8.850 (52.0%)	--
T½ (h)	6.8295 (44.2%)	7.4600 (35.9%)	--

Table 2

Parmacokinetic parameters for the Comparative bioavailability study of Genpharm Inc., and HMR Canada Inc. (Cardizem® CD) diltiazem HCl extended release (CD) capsule following administration of a single, oral 300 mg dose under fed conditions.

Parameter	Geometric Mean and Arithmetic Mean (CV)		Ratio of Geometric Means (%) (CI)
	Gen-Diltiazem CD	Cardizem CD	
	300 mg	300 mg	
AUC_T (ng.h/mL)	2519.6 2690.7 (41.9%)	2290.6 2435.0 (34.4%)	110%
AUC_I (ng.h/mL)	2572.9 2746.0 (41.5%)	2343.8 2492.3 (34.3%)	110%
C_{MAX} (ng/mL)	136.17 143.93 (40.0%)	124.30 131.12 (36.3%)	110%
T_{MAX} (h)	12.417 (36.4%)	13.375 (53.8%)	--
T½ (h)	5.3777 (14.7%)	5.2797 (17.3%)	--

Table 3

Parmacokinetic parameters for the Comparative bioavailability study of Genpharm Inc., and HMR Canada Inc. (Cardizem® CD) diltiazem HCl extended release (CD) capsule following a multiple dose administration of a 300 mg dose under fasting conditions.

Parameter	Geometric Mean and Arithmetic Mean (CV)		Ratio of Geometric Means (%) (CI)
	Gen-Diltiazem CD	Cardizem CD	
	300 mg	300 mg	
AUC_T (ng.h/mL)	3176.7 3393.8 (39.5%)	3061.5 3349.2 (40.6%)	104%
AUC_I (ng.h/mL)	--	--	--
C_{MAX} (ng/mL)	218.00 232.84 (40.5%)	218.24 236.18 (37.5%)	100%
T_{MAX} (h)	8.340 (52.4%)	6.720 (43.8%)	--
T½ (h)	--	---	--
C_{MIN} (ng/ml)	71.11 83.77 (54.0%)	72.39 84.00 (54.7%)	98%
Fluctuation (%)	109.53 (28.1%)	113.78 (21.9%)	--

INDICATIONS AND CLINICAL USE

Angina

1. Gen-Diltiazem CD (Once-a-day) Capsule is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta-blockers and/or organic nitrates or who cannot tolerate those agents.

2. Gen-Diltiazem CD (Once-a-day) Capsule may be tried in combination with beta-blockers in chronic stable angina patients with normal ventricular function. When such concomitant therapy is introduced, patients must be monitored closely (See WARNINGS).

3. Since the safety and efficacy of CD capsules in the management of unstable or vasospastic angina has not been substantiated, use of the formulation for these indications is not recommended.

Hypertension

Gen-Diltiazem CD capsule is indicated for the treatment of mild to moderate essential hypertension. Diltiazem Hydrochloride CD should normally be used in those patients in whom treatment with diuretics or beta-blockers has been ineffective, or has been associated with unacceptable adverse effects.

Gen-Diltiazem CD capsule can be tried as an initial agent in those patients in whom the use diuretics and/or beta-blockers is contraindicated, or in patients with medical conditions in which these drugs frequently cause serious adverse effects.

Safety of concurrent use of Gen-Diltiazem CD with other antihypertensive agents has not been established.

CONTRAINDICATIONS

Diltiazem HCl is contraindicated:

1. In patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker;

2. In patients with second or third degree AV block;

3. In patients with known hypersensitivity to diltiazem;

4. In patients with severe hypotension (less than 90 mm Hg systolic);

5. In myocardial infarction patients, who have left ventricular failure manifested by pulmonary congestion;

6. In pregnancy and in women of child-bearing potential. Fetal malformations and adverse effects on pregnancy have been reported in animals. In repeated dose studies a high incidence of vertebral column malformations were present in the offspring of mice receiving more than 50 mg/kg of diltiazem HCl orally.

In the offspring of mice receiving a single oral dose of 50 or 100 mg/kg on day 12 of gestation, the incidence of cleft palate and malformed extremities was significantly higher. Vertebral malformations were most prevalent when they received the drug on day 9. In rats, a significantly higher fetal death rate was present when 200 and 400 mg/kg were given orally on days 9 to 14 of gestation. Single oral dose studies in rats resulted in a significant incidence of skeletal malformations in the offspring of the group receiving 400 mg/kg on day 11. In rabbits, all pregnant dams receiving 70 mg/kg orally from day 6-18 of gestation aborted; at 35 mg/kg, a significant increase in skeletal malformations was recorded in the offspring (See REPRODUCTION STUDIES).

WARNINGS

Cardiac Conduction

Diltiazem prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second-or third-degree AV block (6 of 1208 patients or 0.5%).

First degree AV block was observed in 5.8% of patients receiving [v] CD (see ADVERSE REACTIONS).

Concomitant use of diltiazem with agents known to affect cardiac conduction (such as beta-blockers, digitalis or amiodarone) may result in additive effects on cardiac conduction (see Precautions, Drug Interactions).

Congestive Heart Failure

Because diltiazem has a negative inotropic effect **in vitro** and it affects cardiac conduction, the drug should only be used with caution and under careful medical

supervision in patients with congestive cardiac failure. (see also CONTRAINDICATIONS).

Use with Beta-blockers

The combination of diltiazem and beta-blockers warrants caution since in some patients additive effects on heart rate, AV conduction, blood pressure or left ventricular function have been observed. Close medical supervision is recommended.

Generally, diltiazem should not be given to patients with impaired left ventricular function while they receive beta-blockers. However, in exceptional cases when, in the opinion of the physician, concomitant use is considered essential, such use should be instituted gradually in a hospital setting.

Diltiazem gives no protection against the dangers of abrupt beta-blocker withdrawal and such withdrawal should be done by the gradual reduction of the dose of beta-blocker.

Hypotension

Since diltiazem lowers peripheral vascular resistance, decreases in blood pressure may occasionally result in symptomatic hypotension. In patients with angina or arrhythmias using antihypertensive drugs, the additional hypotensive effect of diltiazem should be taken into consideration.

Patients with Myocardial Infarction

Use of immediate release diltiazem at 240 mg per day started 3 to 15 days after a myocardial infarction was associated with an increase in cardiac events in patients with pulmonary congestion, and no overall effect on mortality. Although there has not been a study of diltiazem hydrochloride SR or Diltiazem hydrochloride CD in acute myocardial infarction reported, their use may have effects similar to those of immediate release diltiazem in acute myocardial infarction.

Acute Hepatic Injury

In rare instances, significant elevations in alkaline phosphatase, CPK, LDH, SGOT, SGPT and symptoms consistent with acute hepatic injury have been observed. These reactions have been reversible upon discontinuation of drug therapy. Although a causal

relationship to diltiazem has not been established in all cases, a drug induced hypersensitivity reaction is suspected (see ADVERSE REACTIONS). As with any drug give over prolonged periods, laboratory parameters should be monitored at regular intervals.

PRECAUTIONS

Dermatological Events

Dermatological events (see Adverse Reactions) may be transient and may disappear despite continued use of diltiazem. However, skin eruptions progressing to erythema multiform and/or exfoliate dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Impaired Hepatic or Renal Function

Diltiazem should be used with caution in patients with renal or hepatic impairment. Because diltiazem is extensively metabolized by the liver and excreted by the kidney and in bile. The monitoring of laboratory parameters of renal or hepatic function is recommended and cautious dosage titration are recommended in patients with impaired hepatic or renal function. (See ADVERSE REACTIONS).

Nursing Mothers

Diltiazem has been reported to be excreted in human milk. One report with oral diltiazem suggests that concentrations in breast milk may approximate serum levels. Since diltiazem safety in newborns has not been established, it should not be given to nursing mothers.

Pediatric Use

The safety and effectiveness of diltiazem in children has not yet been established.

Use in the Elderly

Administration of diltiazem to elderly patients (over or equal to 65 years of age) requires caution. The incidence of adverse reactions is approximately 13% higher in this group. Those adverse reactions which occur more frequently include: peripheral edema,

bradycardia, palpitation, dizziness, rash and polyuria. Therefore, particular care in titration is advisable (see DOSAGE AND ADMINISTRATION).

Drug Interactions

Due to the potential for additive effects, caution and careful titration are warranted in patients receiving diltiazem concomitantly with other agents know to affect cardiac contractility and/or conduction.

Cytochrome P450 System

As with all drugs, care should be exercised when treating patients with multiple medications. Calcium channel blockers undergo biotransformation by the cytochrome P450 system. Coadministration of diltiazem with other drugs which follow the same route of biotransformation may result in altered bioavailability. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, and especially in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered diltiazem to maintain optimum therapeutic blood levels.

Drugs known to be inhibitors of the cytochrome P450 system include: azole antifungals, cimetidine, cyclosporine, erythromycin, quinidine, warfarin.

Drugs known to be inducers of the cytochrome P450 system include: phenobarbital, phenytoin, rifampin.

Drugs known to be biotransformed via P450 include: benzodiazepines, flecainide, imipramine, propafenone, terfenadine, theophylline.

Amiodarone:

Severe conduction system abnormalities including heart block of varying degree, sinus arrest and a low cardiac output state of life threatening severity have been reported following concomitant use of diltiazem and amiodarone. These drugs may also have additive effects on cardiac conduction and contractility.

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 channel blockers should be titrated carefully.

Benzodiazepines:

Diltiazem significantly increases peak plasma levels and the elimination half-life of triazolam and midazolam.

Beta-blockers:

The concomitant administration of diltiazem with beta adrenergic blocking drugs warrants caution and careful monitoring. Such an association may have an additive effect on heart rate, on AV conduction or on blood pressure (See WARNINGS). Appropriate dosage adjustments may be necessary. A study in five normal subjects showed that diltiazem increased propranolol bioavailability by approximately 50%.

Calcium Antagonists

Limited clinical experience suggests that in certain severe conditions not responding adequately to verapamil or to nifedipine, using diltiazem in conjuction with either of these drugs may be beneficial.

Carbamazepine:

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

Cimetidine:

A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1 week course of cimetidine at 1200 mg per day and a single dose of oral diltiazem 60 mg. Ranitidine produced smaller, nonsignificant increases. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and

discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Cyclosporine:

Concomitant administration of diltiazem and cyclosporine has resulted in an increase in cyclosporine concentrations. 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 15% to 48% was necessary to maintain cyclosporine through concentrations similar to those seen prior to the addition of diltiazem. If these agents are to be administered concurrently, cyclosporine concentrations should be monitored, especially when diltiazem therapy is initiated, adjusted or discontinued. Downward titration of cyclosporine dose may be necessary. The effect of cyclosporine on diltiazesm plasma concentrations has not been evaluated.

Digitalis:

Diltiazem and digitalis glycosides may have an additive effect in prolonging AV conduction. In clinical trials, concurrent administration of diltiazem and digoxin have resulted in increases in serum digoxin levels with prolongation of AV conduction. This increase may result from a decrease in renal clearance of digoxin. Patients on concomitant therapy, especially those with renal impairment, should be carefully monitored. The dose of digoxin may need downward adjustment.

Lovastatin:

In a ten-subject study, coadministration of diltizem (120 mg bid, diltiazem SR) with lovastatin resulted in a 3-4 times increase in mean lovastin AIC and C_{max} versus lovastatin alone; no change in pravastatin AUC and C_{max} was observed during diltiazem coadministration. Diltiazem plasma levels we not significantly affected by lovastatin or pravastatin.

Rifampin:

Administration of diltiazem with rifampin markedly reduced plasma diltiazem concentrations and the therapeutic effect of diltiazem.

Short and Long-acting Nitrates:
Diltiazem may be safely co-administered with nitrates, but there have been few controlled studies to evaluate the antianginal effectiveness of this combination.

ADVERSE REACTIONS

(See also OVERALL Diltiazem CD SAFETY PROFILE)

Angina:
The safety of Diltiazem CD, (diltiazem hydrochloride), administered at doses up to 360 mg a day, was evaluated in 365 patients with chronic stable angina treated in controlled and open-label clinical trials. Adverse events were reported in 21.1% of patients, and required discontinuation in 2.2% of patients.
The most common adverse effects reported were: first degree AV block (5.8%), dizziness (3.0%), headache (3.0%), asthenia (2.7%), bradycardia (2.5%), and angina pectoris (1.6%).

The following percentage of adverse effects, divided by system, was reported:

Cardiovascular:
First degree AV block (5.8%), bradycardia (2.5%), angina pectoris (1.6%), peripheral edema (1.4%), palpitations (1.1%), and ventricular extrasystoles (0.8%).

Central Nervous System:
Dizziness (3.0%), headache (3.0%), asthenia (2.7%), insomnia (1.1%), nervousness (0.8%).

Gastrointestinal:
Nausea (1.4%), diarrhea (0.5%).

Dermatological:
Rash (0.8%).

Other:
Amblyopia (0.5%).

The following additional adverse effects have occurred with an incidence of less than 0.5% in clinical trials; bundle branch block, ventricular tachycardia, ECG abnormality, supraventricular extrasystoles, chest pain, syncope, postural hypotension, paresthesia, tremor, depression, mental confusion, impotence, abdominal pain, constipation, GI disorder, epistaxis, nuchal rigidity, myalgia.

Hypertension:
A safety evaluation was carried out in controlled studies in 378 hypertensive patients treated with diltiazem hydrochloride CD at doses up to 360 mg a day. Adverse effects were reported in 30.7% of patients and required discontinuation of therapy in 2.1%.
The most common adverse effects were: headache (8.7%); edema (4.0%); bradycardia (3.7%); dizziness (3.4%); ECG abnormality (2.9%); asthenia (2.6%); and first degree AV block (2.1%).

The following percentage of adverse effects, divided by system, was reported:

Cardiovascular:
Edema peripheral (4.0%), bradycardia (3.7%), ECG abnormalities (2.9%), first degree AV block (2.1%), arrhythmia (1.6%), vasodilation (flushing) (1.6%), bundle branch block (0.8%), cardiomegaly (0.5%), hypotension (0.5%).

Central Nervous System:
Headache (8.7%), dizziness (3.4%), asthenia (2.6%), somnolence (1.3%), nervousness (1.1%).

Gastrointestinal:
Constipation (1.3%), dyspepsia (1.3%), diarrhea (0.6%).

Laboratory Tests:
SGPT increase (0.8%).

Other:
Leukopenia (1.1%), Nocturia (0.5%).

The following additional adverse effects have occurred with an incidence of less than 0.5% in clinical trials: systolic murmur, supraventricular extrasystoles, migraine, tachycardia, increased appetite, increase in weight, albuminuria, bilirubinemia, hyperuricemia, thirst, insomnia, vertigo, nausea, pruritus, rash, increased perspiration, polyuria amblyopia, tinnitus, and elevations in creatine kinase, alkaline phosphatase, and SGOT

Overall Diltiazem CD safety profile:
In clinical trials of diltiazem hydrochloride tablets, diltiazem hydrochloride SR capsules and diltiazem hydrochloride CD capsules involving over 3300 patients, the most common adverse reactions were headache (4.6%), edema (4.6%), dizziness (3.5%), asthenia (2.7%), first-degree AV block (2.4%), bradycardia (1.7%), flushing (1.5%), nausea (1.4%), rash (1.2%), and dyspepsia (1.0%).

In addition, the following events were reported with a frequency of less than 1.0%.

Cardiovascular:
Angina, arrhythmia, bundle branch block, tachycardia, ventricular extrasystoles, congestive heart failure, syncope, palpitations, AV block (second-or-third-degree), hypotension, ECG abnormalities.

Dermatological:
Petechiae, pruritus, photosensitivity, urticaria.

Gastrointestinal:
Anorexia, diarrhea, dysgeusia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see WARNINGS), vomiting, weight increase, thirst, constipation.

Nervous System:
Amnesia, depression, gait abnormality, nervousness, somnolence, hallucinations, paresthesia, personality change, tinnitus, tremor, abnormal dreams, insomnia.

Other:

Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, sexual difficulties, nasal congestion, nocturia, osteoarticular pain, impotence, dry mouth, polyuria, hyperuricemia.

Post-Marketing Surveillance:

The following postmarketing events have been reported infrequently in patients receiving diltiazem hydrochloride: acute generalized exenthematous pustulosis, allergic reactions, alopecia, asystole, erythema multiforme (including Stevens-Johnson syndrome, toxic epidermal necrolysis), exfoliative dermatitis (see Precautions), extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, detached retina, increased bleeding time, leukopenia, myopathy, purpura, retinopathy, and thrombocytopenia.

Isolated cases of angioedema have been reported. Angioedema may be accompanied by breathing difficulty. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A number of well-documented cases of generalized rash, some characterized as leukocytoclastic vasculitis, have been reported. However, a definite cause and effect relationship between these events and diltiazem hydrochloride therapy is yet to be established.

SYMPTOMS AND TREATMENT OF OVERDOSE

There have been reports of diltiazem overdose in amounts ranging from < 1 g to 18 g. In cases with a fatal outcome, the majority involved multiple drug ingestion.

Events observed following diltiazem overdose included bardycardia, hypotension, heart block and cardiac failure.

The effectiveness of intravenous calcium administration to reverse the pharmacological effects of diltiazem overdose has been inconsistent. In a few reported cases, overdose with calcium channel blockers associated with hypotension and bradycardia that was initially refractory to atropine became more responsive to atropine after the patients received intravenous calcium. In some cases intravenous calcium has been administered

(1 g calcium chloride or 3 g calcium gluconate) over 5 minutes, and repeated every 10-20 minutes as necessary. Calcium gluconate has also been administrated as a continuous infusion at a rate of 2 g per hour for 10 hours. Infusions of calcium for 24 hours or more may be required. Patients should be monitored for signs of hypercalcemia.

In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. Limited data suggest that plasmapheresis or charcoal hemoperfusion may hasten diltiazem elimination. The following measures may be considered:

Bradycardia
Administer atropine. If there is no response to vagal blockade, 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
Administer fluids and vasopressors (e.g., dopamine or noradrenaline).
Actual treatment and dosage should depend on the severity of the clinical situation.

DOSAGE AND ADMINISTRATION

Angina
Dosages for the treatment of angina should be adjusted to each patient's needs, starting with a dose of 120 mg to 180 mg once daily. Individual patients may respond to higher doses of up to 360 mg once daily. When necessary, titration should be carried out over a 7 to 14 day period. Patients controlled on diltiazem alone or in combination with other medications may be safely switched to Gen-Diltiazem CD capsules at the nearest

equivalent total daily dose. Subsequent titration to higher or lower doses may be necessary and should be initiated as clinically warranted.

There is limited experience with doses above 360 mg, however, the incidence of adverse reactions increases as the dose increases with first degree AV block, dizziness, and sinus bradycardia bearing the strongest relationship to dose. Therefore, doses greater than 360 mg are not recommended.

Hypertension

Dosage should be individualized depending on patient's tolerance and responsiveness to Gen-Diltiazem CD capsules. When used as monotherapy, usual starting doses are 180 to 240 mg once daily, although some patients may respond to 120 mg once daily. Maximum antihypertensive effect is usually observed after approximately 2 to 4 weeks of therapy; therefore, dosage adjustments should be scheduled accordingly. The usual dosage range studied in clinical trials was 240 to 360 mg once daily.

A maximum daily dose of 360 mg once daily should not be exceeded.

The dosage of Gen-Diltiazem CD capsules or concomitant antihypertensive agents may need to be adjusted when adding one to the other. See WARNINGS and PRECAUTIONS regarding use with beta-blockers.

Hypertensive patients controlled on diltiazem hydrochloride SR alone or in combination with other antihypertensive agents may be safely switched to Gen-Diltiazem CD capsules at the same total daily dose. Subsequent titration to higher or lower doses may be necessary and should be initiated as clinically warranted.

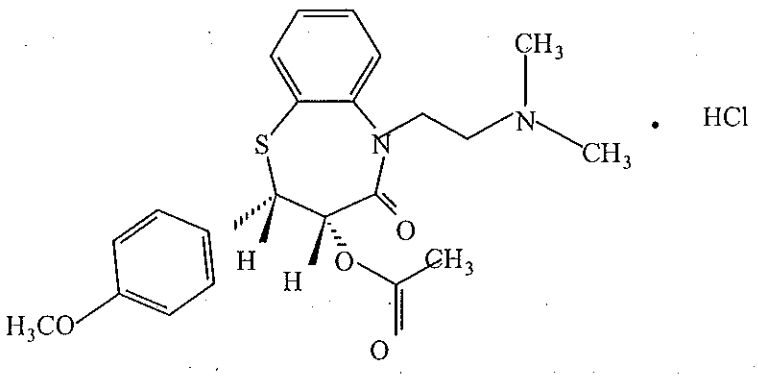
Gen-Diltiazem CD capsules should not be chewed or crushed.

PHARMACEUTICAL INFORMATION

Drug Substance Name: **Diltiazem Hydrochloride**

Chemical Name: 1,5-benzothiazepin-4(5H)one, 3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride, (+)-cis-.

Structural Formula:



Molecular Formula: $C_{22}H_{26}N_2O_4S.HCl$

9

Molecular Weight: 450.98

Description: The compound is a white crystalline substance or powder having a bitter taste. Diltiazem is considered freely soluble in water, methanol or chloroform, slightly soluble in absolute ethanol and barely soluble in benzene.

Composition: Gen-Diltiazem CD once-a-day controlled delivery capsules contain Diltiazem hydrochloride and the following non-medicinal ingredients: sugar spheres, ethylcellulose, polysorbate, acetyltributyl citrate, talc, eudragit, and magnesium stereate. The gelatin capsules contain: gelatin, FD&C blue #1, titanium dioxide, and black iron oxide (300 mg only).

Storage Recommendations: Preserve in tight containers between 15° - 30°C

SUPPLIED

Gen-Diltiazem CD 120 mg gelatin capsules are light turquoise blue opaque; radially imprinted "G" on body with "DIL 120" on cap; containing off-white round pellets. Supplied in bottles of 30, 100, 500 and 1000 capsules.

Gen-Diltiazem CD 180 mg gelatin capsules are light turquoise blue opaque/ light blue opaque; radially imprinted "G" on body with "DIL 180" on cap; containing off-white round pellets. Supplied in bottles of 30, 100, 500 and 1000 capsules.

Gen-Diltiazem CD 240 mg gelatin capsules are light blue opaque; radially imprinted "G" on body with "DIL 240" on cap; containing off-white round pellets. Supplied in bottles of 30, 100, 500 and 1000 capsules.

Gen-Diltiazem CD 300 mg capsules are light gray opaque/light blue opaque; radially imprinted "G" on body with "DIL 300" on cap; containing off-white round pellets. Supplied in bottles of 30, 100, 500 and 1000 capsules.

PHARMACOLOGY

In Vitro Observations

Initial experimental work revealed that diltiazem was a coronary and peripheral vasodilator. Subsequent work substantiated that diltiazem's smooth muscle relaxant effect, as well as negative inotropic effect, resulted from the drug's ability to block excitation-contraction coupling by inhibiting slow calcium channel conduction. In a muscle bath study with isolated human coronary artery segments obtained at the time of cardiac transplantation, diltiazem produced nearly complete relaxation of potassium-contracted segments.

Studies in various experimental models have confirmed the negative inotropic effect of diltiazem. At low doses (1.1×10^{-7}M) diltiazem caused a reduction in contractile force of guinea pig papillary muscle with no demonstrable effect on the action potential. However, at higher concentrations (1.1×10^{-5}M) both a decrease in contractile tension and a lowering of maximum dp/dt were seen.

Studies done in isolated perfused rat hearts showed that diltiazem (10^{-6}M) decreases contractility without affecting action potential duration or resting membrane potential. In several experimental models it has been shown that the concentration of diltiazem required to produce smooth muscle relaxation and vasodilation is significantly less than the concentration required to produce a negative inotropic effect.

In Vivo Observations

Experiments in both open and closed chest dog models indicate that diltiazem increases coronary blood flow and reduces coronary vascular resistance. Intravenous diltiazem (100 μg/kg) increased coronary blood flow by 90%, with a predominant effect on large coronary arteries and collaterals. Increase in coronary blood flow has also been shown following diltiazem administration in both the epicardial and subendocardial regions in ischemic and non ischemic models. There was also a dose-related decrease in mean aortic pressure and systemic vascular resistance with an increase in stoke volume and cardiac output. No significant change was noted in determinants of LV function such as LVEDP or LV dP/dT. The reduction in blood pressure that is seen with diltiazem is due

to a direct vasodilatory effect on the blood vessels and is not mediated by sympathetic alpha receptor blockade, beta receptor stimulation, or ganglionic blockade. Diltiazem has been shown to inhibit the pressor responses induced by norepinephrine and angiotensin II.

In animal studies, the negative inotropic effect of diltiazem appears to be offset by its ability to decrease afterload and induce a mild reflex adrenergic response.

TOXICOLOGY

Acute Toxicity

Route	Animal	Sex	LD_{50} mg/kg	LD_{50} 95% Confidence Limits (mg/kg)
Oral	mice rats	M&F M&F	415 - 700 560 - 810	(343 - 736) (505 - 1004)
s.c.	mice	M&F	260 - 550	(220 - 672)
i.p.	mice rats	M&F M&F	187 211	(165 - 211) (155 - 287)
i.v	mice rats	M&F M&F	58 - 61 38 - 39	(52 - 69) (34 - 44

Toxic effects appeared rapidly and toxicity included reduction of spontaneous activity, ptosis, piloerection, ataxia, loss of muscle tone and loss of righting reflex. Gross autopsy of animals who died as well as the survivors revealed no abnormalities

Tolerance was evaluated in rabbits and dogs. Dogs received oral doses of 12.5, 25, 50, 100 mg/kg. Ataxia, disorientation, decreased activity, diuresis and mydriasis were noted at 25 mg/kg. In addition, heavy sedation and emesis were seen at 50 mg/kg. At 100 mg/kg, convulsions occurred and one of the two animals died. Rabbits received 100,

200, 300, 400 mg/kg. The major symptoms were decreased activity, increased respiration, salivation and opisthotonos. One of the two rabbits died at 300 mg/kg and the two rabbits in the 400 mg/kg group died.

Subacute Toxicity

In rats, oral doses of 10, 20, 50, 100, 250 or 500 mg/kg/day of diltiazem were administered for 28 or 30 days. The relative liver weights of animals receiving 250 mg/kg/day and 500 mg/kg/day were increased. Microscopic examination revealed drug related degeneration of hepatic and renal cells in the highest dose group.

When the drug was given to rats intraperitoneally at 25 mg/kg/day for 30 days, hepatic and renal cell degeneration was seen. Macular hyaloid degeneration of the heart also was seen in 50% of the rats in this study.

Thirty day subacute studies in dogs revealed hepatic and renal cell degeneration when diltiazem was given at doses of 25 mg/kg/day orally and 5 mg/kg/day intravenously. Two dogs out of 5 receiving 50 mg/kg/day orally, died.

Chronic Toxicity/Carcinogenicity

In mice, diltiazem was administered at doses of 5, 15 or 30 mg/kg/day for a period of 21 months in females. Because of a lower survival, males were terminated at 20 months. Gross and histopathological examination failed to reveal any treatment related increase in the incidence of either neoplastic or other toxic lesions.

Rats received 6.25, 25 or 100 mg/kg/day of diltiazem for 24 months. An additional group received 200 mg/kg for 12 months. Treatment was terminated at 23 months in females receiving 100 mg/kg because of the low survival. Females had increased weight gain at 100 and 200 mg/kg, food consumption was increased among both sexes at these dose levels. Organ weight data revealed a significant increase in liver weight for rats of both sexes given 200 mg/kg. Microscopic evaluation revealed some evidence of dose dependent hepatic cytoplasmic vacuolization in rats treated with doses of 100 and 200 mg/kg/day and killed at 12 months. At 24 months, there were similar findings in control and treated animals. There was no increase in the incidence of neoplastic or other toxic lesions in rats treated with diltiazem.

Diltiazem was administered orally to dogs for 12 months at doses of 5, 10, 20 mg/kg/day. A dose related suppression of body weight gain became noticeable after 6 months.

Mutagenicity

No mutagenic changes were observed in the recombination test and two Ames reverse mutagenicity assays.

REPRODUCTION STUDIES

Results in mice

Route	Doses mg/kg	Time of administration during gestation	Findings in the offspring
oral	10, 25, 50, 100, 200, 400	Day 7 to day 12	High incidence of vertebral column malformations when more than 50 mg/kg was administered
oral	Single doses of 12.5, 25, 50, 100, 200	One of days 7 to 14	Cleft palate and malformation of extremities or trunk were significantly higher when 50 or 100 mg/kg was administered on day 12. Vertebral malformations were most prevalent when 50 or 100 mg/kg was administered on day 9.
intra-peritoneal	0.2, 3.1, 6.3, 12.5, 25	Day 7 to day 12	Fetal mortality greatly increased when 12.5 mg/kg or more was administered. No teratogenic effect was demonstrated.
intra-peritoneal	Single dose of 3.1, 6.3 12.5, 25, 50	One of days 5 to 16	Brachydactyly and hematoma in the extremities when 50 mg/kg was administered on day 13. Vertebral column malformations from the thoracid to coccygeal level and malformations of the ribs were observed when a dose of 25 mg/kg or greater was administered on day 9.

Results in rats

Route	Doses mg/kg	Time of administration during gestation	Findings in the offspring
oral	10, 50, 100, 200, 400	Day 9 to day 14	No teratogenic effect. High fetal death rate when 200 & 400 mg/kg was administered.
oral	10, 30, 100	Day 6 to 15	No teratogenic effect.
oral	Single doses of 300, 400, 600	On one of days 9 to 14	Significant incidence of skeletal malformations involving vertebrae & sternebrae when 400 mg/kg was administered on day 11. General edema, short or absent tail was observed when 600 mg/kg was administered on day 12.
intra-peritoneal	0.2, 2.0, 20, 40, 80	Day 9 to 14	Brachydactyly and hematoma in the front paw and tail and a high fetal mortality rate were observed when 80 mg/kg was administered.
Intra-peritoneal	80	Day 9 to 11	Vertebral anomalies.
Intra-peritoneal	80	Day 12 to 14	Bracydactyly, hematoma of the front paw and tail deformities and high fetal mortality rate.
Intra-peritoneal	Single dose of 80	One of days 9 to 14	Fetal mortality increased on day 11 reached 100% on day 12 and decreased thereafter. Limb and tail deformities were induced when 80 mg/kg was administered on day 13 & 14. Vertebral column deformities were induced when 80 mg/kg was administered on day 11.
	Single doses of 40	One of days 11 to 14	No teratogenic effect

Results in Rabbits

Route	Doses mg/kg	Time of administration during gestation	Findings in the offspring
oral	17.5, 35, 70	Day 6 to day 18	Significant increase in skeletal malformations occurred when 35 mg/kg was administered. All pregnant dams aborted between days 21 and 25 of gestation when 70mg/kg was administered.
Intra-peritoneal	6.3, 12.5, 25	Day 7 to 16	Fetal mortality greatly increased at 12.5 mg/kg and reached 100% at 25 mg/kg and reached 100% at 25 mg/kg. Skeletal defects and external malformations were induced when 12.5 mg/kg was administered. Their incidence was not statistically significant due to the low number of surviving fetuses.

In fertility studies female rats received doses of 12.5, 25, 50 and 100 mg/kg p.o. In the 100 mg/kg group there was a reduction in the number showing a positive mating. However, the overall pregnancy rates and the average pre-coital time were comparable.

In peri-and post-natal studies, rats received diltiazem in doses of 10, 30 or 100 mg/kg/day from day 14 of gestation through day 21 post partum. Diltiazem was associated with a reduction in early individual weights and survival rates of the pups. At 100 mg/kg/day dystocia was evident. Retinal and tongue malformations were more frequent in the offspring of the 30 and 100 mg/kg/day group.

BIBLIOGRAPHY

4. Anderson JL, et al: Comparative effects of diltiazem, propranolol and placebo on exercise performance using radionuclide ventriculography in patients with symptomatic coronary artery disease: Results of a double-blind, randomized, crossover study. Am Hear J 1984;107(4):698-706.

5. André-Fouet X, et al: Diltiazem vs propranolol: A randomized trial in unstable angina. Circulation 1981;64:IV-293.

6. Bourassa MG et al: Hemodynamics and coronary flow following diltiazem administration in anesthetized dogs and in humans. Chest 1980;78:224-230.

7. Cassagnes J, et al: Traitement du syndrome de menace par le diltiazem. Thérapie 1980;35:465-473.

8. Eimer, M and Carter, BL: Elevated serum carbamazepine concentrations following diltiazem initiation. Drug Intelligence and Clinical Pharmacy 1987;21:340-342.

9. Feldman RL, et al: Short and long-term responses to diltiazem in patients with variant angina, Am J Cardiol 1982;49:554-559.

10. Frishmen WH, et al: Comparison of hydrochlorothazide and sustained-release diltiazem for mild to moderate systemic hypertension. Am J Cardiol 1987;59(6):615-623.

11. Hossack KF, et al. Divergent effects of diltiazem in patients with exertional angina. Am J Cardiol 1982;49:538-546.

12. Hossack KF, et al: Efficacy of diltiazem in angina of effort: A multicenter trial. Am J Cardiol 1982;49:567-572

13. Hung J, et al: The effect of diltiazem and propranolol, alone and in combination, on exercise performance and left ventricular function in patients with stable effort angina: A double-blind, randomized, and placebo-controlled study. Circulation 1983;68:560-567.

14. Ishikawa T, et al: Atrioventricular dissociation and sinus arrest induced by oral diltiazem. N Engl J Med 1983;309:1124-1125.

15. Jacobs MB: Diltiazesm and akathisia. Ann Int Med 1983;99:794-795.

16. Josephson MA, et al: Hemodynamic and metabolic effects of diltiazem during coronary sinus pacing with particular reference to left ventricular ejection fraction. Am J Cardiol 1985;55:286-290.

17. Massie B, et al: Diltiazem and propranolol in mild to moderate essential hypertension as monotherapy or with hydrochlorothiazide. Ann Intern Med 1987;107:150-157.

18. Moser, M et al: Comparative effects of diltiazem and hydrochlorothiazide in blacks with systemic hypertension. Am J Cardiol 1985;56(16):10H-104H.

19. Moss AJ, eet al: The effect of diltiazem on mortality and reinfarction after myocardial infarction: The Multicenter Diltiazem Postinfarction Trial Research Group. N Engl J Med 1988;319:385-392.

20. Nicolas G, et al: Le traitement de l'angor instable par le diltiazem. À propos de 61 observations. Ann Cardiol Angeiol (Paris) 1981;30:289-292.

21. Pool PE, et al: Long-term efficacy of diltiazem in chronic stable angina associated with atherosclerosis: Effect on treadmill exercise. Am J Cardiol 1982;49:573-577.

22. Pool PE, et al: Diltiazem as monotherapy for systemic hypertension: A multicenter, randomized, placebo-controlled trial. Am J Cardiol 1986;57:212-217.

23. Rameis H, et al: The diltiazem-digoxin interaction. Clin Pharmacol Ther 1984;36:183-189.

24. Reboud JP: Accidents au cours de l'association diltiazem bêta-bloquants. Presse médicale 1984;13;1396.

25. Schroeder JS, et al: Multiclinic controlled trial of diltiazem for Prinzmetal's angina. Am J Med 1982;72:227-232.

26. Schroeder JS, et al: Diltiazem for long-term therapy of coronary arterial spasm. Am J Cardiol 1982;49:533-537.

27. Strauss WE, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. Am J Cardiol 1982;49:560-566.

28. Swartz SL: Endocrine and vascular responses in hypertensive patients to long-term treatment with diltiazem. J Cardiovasc Pharmacol 1987;9(4):391-395.

29. Szlachcic J, et al: Diltiazem versus propranolol in essential hypertension: Responses of rest and exercise blood pressure and effects on exercise capacity. Am J Cardiol 1987;59:393-399.

30. Taeymans Y, et al: A prospective randomized study of propranolol vs diltiazem in patients with unstable angina. Am J Cardiol 1982;49:896 (Abstract).

31. Tilmant PY et al: Detrimental effect of propranolol in patients with coronary arterial spasm countered by combination with diltiazem. Am J Cardiol; 1983;52:230-233.

32. Valantine, H, et al: Cost containment: coadministration of diltiazem with cyclosporine afte heart transplantation. J Heart Lung Transplantation 1992;11:1-7.

33. Waters DD, et al: Provocative testing with ergonovine to assess the efficacy of treatment with nifedipine, diltiazem and verapamil in variant angina. Am J Cardiol 1981;48:123-130.

34. Weir MR, et al: Sustained-release diltiazem compared with atenolol monotherapy for mild to moderate systemic hypertension. Am J Cardiol 1987;60:361-411.

35. Winship, LC eet al; The effect of ranitidine and cimetidine on single-dose diltiazem pharmacokinetics. Pharmacotherapy 1985;5:16-19.

36. Zawada ET, et al: Renal-metabolic consequences of antihypertensive therapy with diltiazem versus hydrochlorothiazide. Miner Electrolyte Metab 1987;13(2):72-77.

37. Zelis RR, et al: The pharmacokinetics of diltiazem in healthy American men. Am J Cardiol 1982;49:529-532.