

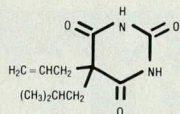
BRIEF SUMMARY Axotal®

Aspirin 650 mg, butalbital 50 mg
(Warning: May be habit forming)

WARNING: May be habit forming.

DESCRIPTION: Each AXOTAL tablet for oral administration contains: butalbital, USP, 50 mg (Warning: May be habit forming) and aspirin, USP, 650 mg.

Butalbital, 5-allyl-5-isobutyl barbituric acid, a white odorless crystalline powder, is a short to intermediate-acting barbiturate. Its molecular formula is $C_{11}H_{16}N_2O_3$ and molecular weight 224.26. The chemical structure of butalbital is:



Indications: AXOTAL is indicated for the relief of the symptom complex of tension (or muscle contraction) headaches.

Contraindications: Hypersensitivity to aspirin or barbiturates. Patients with porphyria.

Precautions: *General*—AXOTAL should be used with caution in patients with certain medical problems, including those with a history of asthma, allergies and nasal polyps. Also, the drug must be prescribed carefully for patients with hemophilia or other bleeding problems, peptic ulcer, renal impairment, or a history of drug abuse or dependence.

Information for Patients—AXOTAL may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

Drug Interactions—Patients receiving narcotic analgesics, antipsychotics, anti-anxiety agents, or other CNS depressants (including alcohol) concomitantly with AXOTAL may exhibit additive CNS depressant effects. When combined therapy is contemplated, the dose of one or both agents should be reduced.

Drugs	Effect
Aspirin with anti-inflammatory agents	Increased ulcerogenic effects
Butalbital with coumarin anticoagulants	Decreased effect of anticoagulant because of increased metabolism resulting from enzyme induction
Butalbital with tricyclic anti-depressants	Decreased blood levels of anti-depressant

Usage in Pregnancy—Adequate studies have not been performed in animals to determine whether this drug affects fertility in males or females, has teratogenic potential or has other adverse effects on the fetus. Although there is no clearly defined risk, experience cannot exclude the possibility of infrequent or subtle damage to the human fetus. AXOTAL should be used in pregnant women only when clearly needed.

Nursing Mothers—The effects of AXOTAL on infants of nursing mothers are not known. Salicylates and barbiturates are excreted in the breast milk of nursing mothers. The serum levels in infants are believed to be insignificant with therapeutic doses.

Pediatric Use—Safety and effectiveness in children below the age of 12 have not been established.

Adverse Reactions: The most frequent adverse reactions are drowsiness and dizziness. Less frequent adverse reactions are lightheadedness and gastrointestinal disturbances including nausea, vomiting and flatulence. Mental confusion or depression can occur due to intolerance or overdosage of butalbital.

Drug Abuse and Dependence: Prolonged use of barbiturates can produce drug dependence, characterized by psychic dependence, and less frequently, physical dependence, and tolerance. The abuse liability of AXOTAL is similar to that of other barbiturate-containing drug combinations. Caution should be exercised when prescribing medication for patients with a known propensity for taking excessive quantities of drugs, which is not uncommon in patients with chronic tension headaches.

Overdosage: The toxic effects of acute overdosage of AXOTAL are attributable mainly to its barbiturate component and, to a lesser extent, aspirin. Symptoms attributable to acute barbiturate poisoning include drowsiness, confusion and coma, respiratory depression, hypertension and shock. Symptoms of salicylate overdosage include central nausea and vomiting, tinnitus and deafness, vertigo and headaches, mental dullness and confusion, diaphoresis, rapid pulse and increased respiration leading to respiratory alkalosis. Treatment consists primarily of management of barbiturate intoxication and the correction of acid-base imbalance due to salicylism. Vomiting should be induced mechanically or with emetics, such as ipecac syrup, in the conscious patient. Gastric lavage may be used if the pharyngeal and laryngeal reflexes are present and if less than 4 hours have elapsed since ingestion. A cuffed endotracheal tube should be inserted before gastric lavage of the unconscious patient and when necessary to provide assisted respiration. Gastric lavage followed by activated charcoal is recommended regardless of time since ingestion. Diuresis, alkalization of the urine, and correction of electrolyte disturbances should be accomplished through administration of intravenous fluids such as 1% sodium bicarbonate in 5% dextrose in water. Meticulous attention should be given to maintaining adequate pulmonary ventilation. Exchange transfusion is most feasible for a small infant while intermittent peritoneal dialysis is useful for cases of moderate severity in adults. Hemodialysis with the artificial kidney is the most effective means of removing salicylate and is indicated for the very severe cases of salicylate intoxication. Hypoprothrombinemia should be treated with intravenous Vitamin K (phytonadione). Methemoglobinemia over 30% should be treated with methylene blue administered slowly intravenously.

Dosage and Administration: One tablet every four hours as needed. Do not exceed 6 tablets per day.

Medication should be taken with food or a full glass of water or milk to lessen gastric irritation caused by aspirin.

How Supplied: Each AXOTAL tablet contains butalbital, USP, 50 mg and aspirin 650 mg.

AXOTAL is available for oral administration as uncoated, white, capsule-shaped tablets coded ADRIA, 130.

Adria® Adria Laboratories
Columbus, OH 43215

AOA

CME quiz discussion

(These discussions relate to the April 1986 JAOA CME quiz.)

1. (b). When both high-molecular-weight dextran and carbon dioxide are used as distending media for hysteroscopy, carbon dioxide is always used first. Dextran is sticky, and unless it is wiped off the instruments after use, it will jam the stopcocks.

2. (a). Congestive heart failure, large left-to-right shunts, or pulmonary arterial hypertension and moderately increased pulmonary vascular resistance are conditions that do not prevent surgical closure in elderly patients with atrial septal defect. However, pulmonary artery pressure equal to systemic pressures with reversed or balanced shunt, or pulmonary vascular resistance greater than 50 percent of systemic vascular resistance are contraindications to surgical repair.

3. (a). A soft systolic murmur is common among patients with atrial septal defect. Also frequently noted is fixed splitting of the second heart sound.

4. (Note—the correct answer was inadvertently omitted from the question.) (b) and (c) were both correct. The criteria for a positive gastrointestinal blood loss scan include increasing activity of an abnormal focus on serial images and changing location of an abnormal focus on serial images.

5. (d). For detection of gastrointestinal hemorrhage, advantages of ^{99m}Tc -Sc-labeled scintigraphy versus angiography include greater sensitivity in detection and the ability to detect intermittent bleeding.

6. (c). The hallmark triad of an angiomyolipoma consists of vascular, fat, and muscle-tissue components.

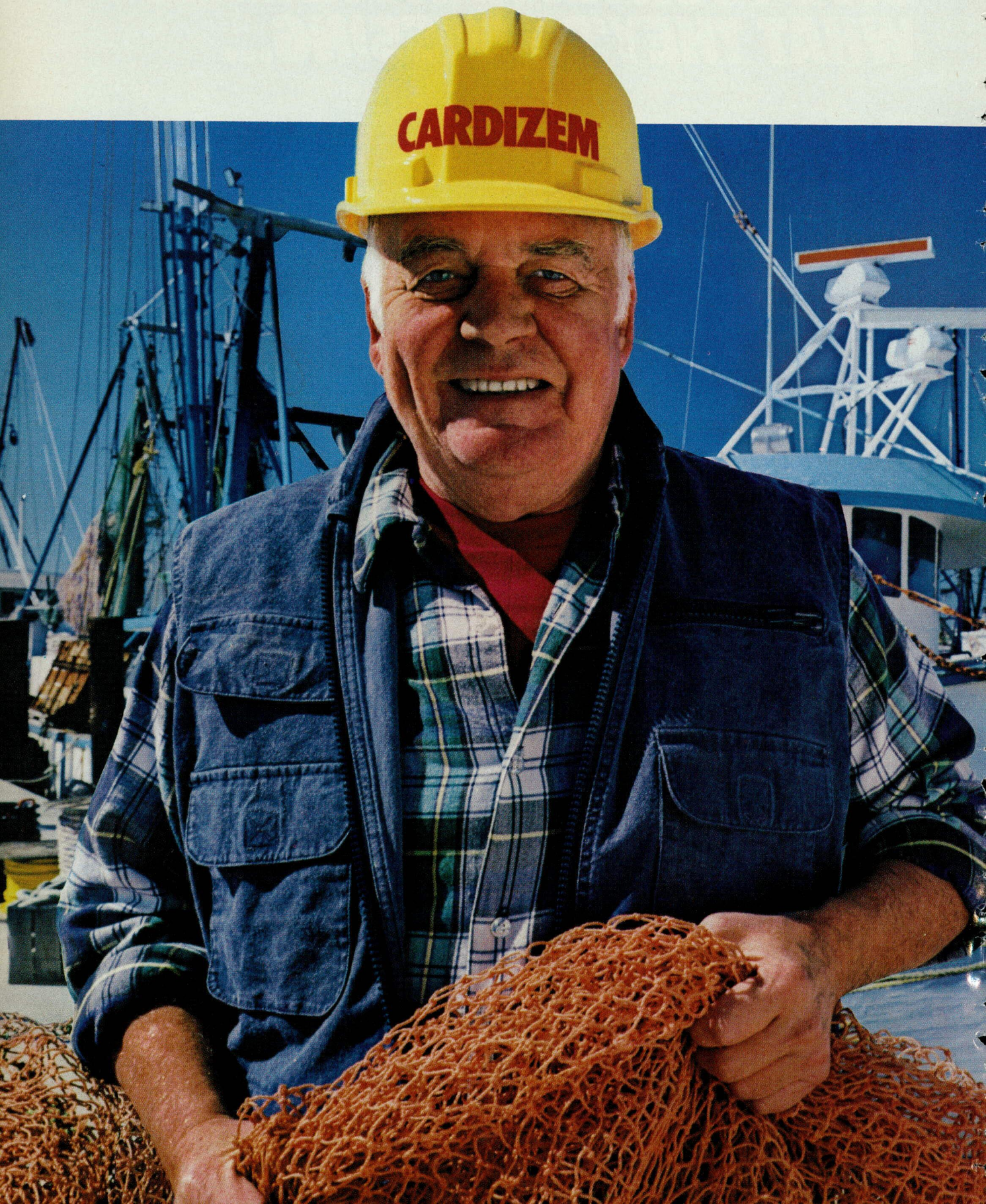
7. (a). Tuberous sclerosis is characterized by bilateral renal involvement.

**GIVE YOUR ANGINA PATIENTS
WHAT THEY'RE MISSING...**



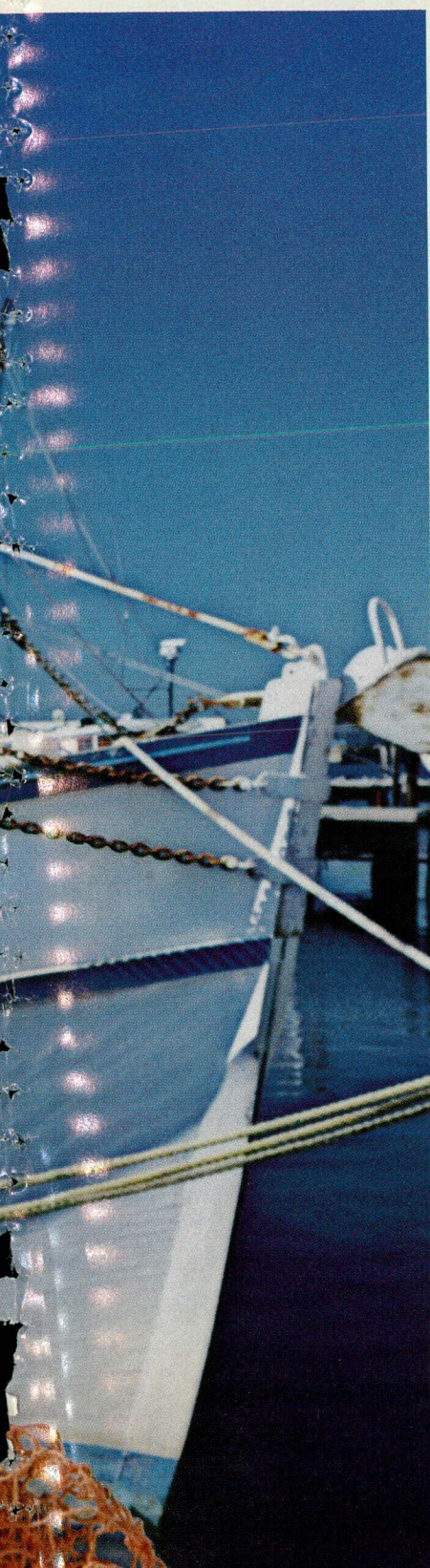
CARDIZEM[®]
diltiazem HCl/Marion

FEWER SIDE EFF



EFFECTS: CARDIZEM[®]

diltiazem HCl/Marion



The lowest incidence of side effects among the calcium channel blockers¹

An exceptionally safe choice for angina patients with coexisting hypertension, diabetes, asthma, or COPD¹⁻³

Proven efficacy when used alone in angina^{1,4-6}

Compatible with both beta-blockers and nitrates⁷

CARDIZEM FOR ANGINA

Please see brief summary of prescribing information on the next page.



CARDIZEM[®] 60 mg tid or qid

diltiazem HCl/Marion

FEWER SIDE EFFECTS IN ANTIANGINAL THERAPY

BRIEF SUMMARY

CARDIZEM[®] (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist).

INDICATIONS AND USAGE

- Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
- Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM 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, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

- Cardiac Conduction.** CARDIZEM 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 (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
- Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
- Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
- Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS AND ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high 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, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy

volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in *in vitro* bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended 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 dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM (diltiazem hydrochloride) in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), AV block (1.1%). In addition, the following events were reported infrequently (less than 1%) with the order of presentation corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradycardia, palpitations, congestive heart failure, syncope.
Nervous System:	Paresthesia, nervousness, somnolence, tremor, insomnia, hallucinations, and amnesia.
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomiting, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivity.
Other:	Polyuria, nocturia.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: erythema multiforme; leukopenia; and extreme elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limited. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
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High-Degree AV Block

Cardiac Failure

Hypotension

Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.

Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics. Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral LD₅₀'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD₅₀'s in these species were 60 and 38 mg/kg, respectively. The oral LD₅₀ in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSEAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 180 to 240 mg/day. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

- Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
- Prophylactic Nitrate Therapy** — CARDIZEM may be safely co-administered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
- Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

CARDIZEM 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1771-49). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1772-49). Each yellow tablet is engraved with MARION on one side and 1772 on the other. Issued 4/1/84

See complete Professional Use Information before prescribing.

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References: 1. *Physicians' Desk Reference*, ed 39. Oradell, NJ, Medical Economics Company Inc, 1985. 2. Cohn PF, Braunwald E. Chronic ischemic heart disease, in Braunwald E (ed): *Heart Disease: A Textbook of Cardiovascular Medicine*, ed 2. Philadelphia, WB Saunders Co, 1984, chap 39. 3. Schroeder JS. Calcium and beta blockers in ischemic heart disease: When to use which. *Mod Med* 1982; 50(Sept):94-116. 4. Subramanian VB. Comparative evaluation of four calcium antagonists and propranolol with placebo in patients with chronic stable angina. *Cardiovasc Rev Rep* 1984; 5:91-104. 5. Schroeder JS, Feldman RL, Giles TD, et al. Multicenter controlled trial of diltiazem for Prinzmetal's angina. *Am J Med* 1982; 72:227-231. 6. Weiner DA, McCabe CH, Cutler SS, et al. The efficacy and safety of high-dose verapamil and diltiazem in the long-term treatment of stable exertional angina. *Clin Cardiol* 1985; 7:648-653. 7. Shapiro W. Calcium channel blockers: Actions on the heart and uses in ischemic heart disease. *Consultant* 1984; 24(Dec):150-159.

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