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β-BLOCKER AND CALCIUM CHANNEL BLOCKER TOXICITY

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Patients accidentally or intentionally poisoned with cardiovascular drugs represent a growing population of seriously ill individuals who seek medical attention in the emergency department. This article focuses on β-adrenergic receptor blocker (β-blockers) and calcium channel blocker (CCBs) drugs, two important classes of cardiovascular drugs that account for approximately 44% of all cases of cardiovascular drug poisonings reported to the American Association of Poison Control Centers. The most recent AAPCC data[114] for 1992 includes more than 5300 cases for each of these classes with 16 deaths attributed to β-blockers and 38 deaths to CCBs. For β-blockers, this represents a 5% annual increase in total cases since 1988.[112, 113, 115, 116] The increase is more dramatic for CCBs, with the number of reported cases increasing more than fourfold since 1987 (Fig. 1).[3, 113, 115–117] Although these increases may be apparent because of improved data collection, expanding use of these drugs is more likely the cause.[133, 152] Traditional indications for prescribing β-blockers and CCBs include treatment of hypertension, angina pectoris, and arrhythmias. In addition, β-blockers are used in the management of conditions causing cardiac outflow obstruction and play an increasingly important role in reducing mortality in the postmyocardial infarction patient.[19, 182] Noncardiovascular applications of both drug classes are expanding. CCBs are prescribed for chronic pain syndromes such as migraine headache and pelvic pain, and even chronic psychiatric diseases such as schizophrenia.[211] Noncardiac uses of β-blockers include treatment of essential tremors, pheochromocytoma, glaucoma, anxiety, and migraine headaches.[62] Both types of drug are used in the elderly, who are more vulnerable to the toxic effects of medication errors.[1, 32, 41] As use in such patient populations expands, toxic exposures are likely to increase.[3, 41]

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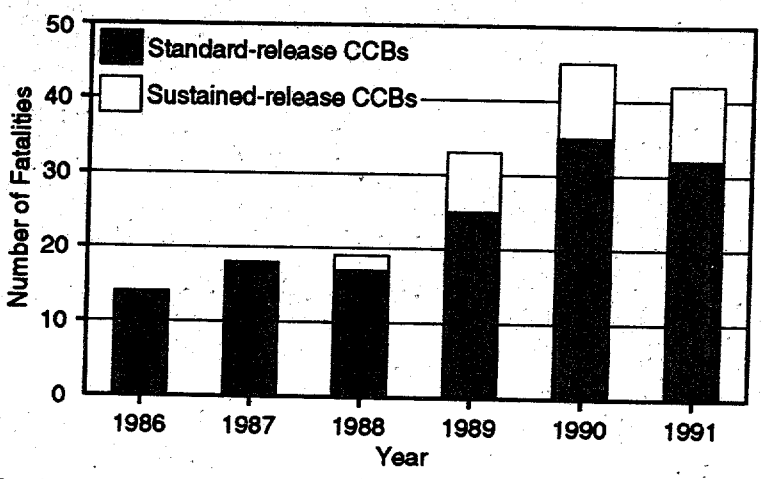


Figure 1. Fatalities from calcium channel antagonists, 1986–1991. (Data from references 112, 113, 115–117.)

CALCIUM CHANNEL BLOCKERS

Review of Calcium-Induced Muscle Contraction and the Effects of CCBs

CCBs antagonize the entry of extracellular calcium into cardiac and smooth muscle cells. CCBs do not affect skeletal muscle that does not require extracellular calcium for contraction.[50, 78, 139, 183, 200] In cardiac myocytes, calcium normally enters the cell through invaginations in the cell membrane termed the t-tubules, proceeding down a 10,000-fold concentration gradient.[26, 33, 78, 94, 95] Upon entering the cytosol, calcium participates in many mechanical, electrical, and biochemical reactions. One of the most critical roles of calcium is in excitation-contraction. When calcium enters the myocyte, the sarcoplasmic reticulum is signaled by both calcium and intermediary proteins to release its stores of calcium.[96, 185] These pools of calcium may then bind to troponin C, which releases the inhibitory effect of tropomyosin, allowing actin and myosin to interact and produce myocardial contraction.[50, 94, 142, 189] Calcium also participates in the gradual depolarizing upstroke during phase four of the action potential in the sinus node and atrial conducting tissue. Calcium currents are also crucial to normal A-V conductance; thus their antagonism slows A-V conductance, producing P-R interval lengthening on surface ECG.[38, 96, 130, 134, 200, 222] In smooth muscle cells, calcium combines with calmodulin. This complex increases the activity of myosin light-chain kinase, an enzyme that phosphorylates myosin, resulting in increased smooth muscle contraction and increased peripheral vascular resistance.[10, 50, 95]

Pharmacology of CCBs

All CCBs produce clinical toxicity by binding to the dihydropyridine (DHP) receptor (Fig. 2), which, in part, comprises the L-type calcium channel. The initial amount of calcium allowed into smooth or cardiac muscle cells during depolarization depends on the proportion of L-type channels on the cell surface that are open. The proportion of open channels is decreased by CCB binding[2, 33, 52, 58, 78] and increased by β-adrenergic stimulation, which leads to phosphorylation of

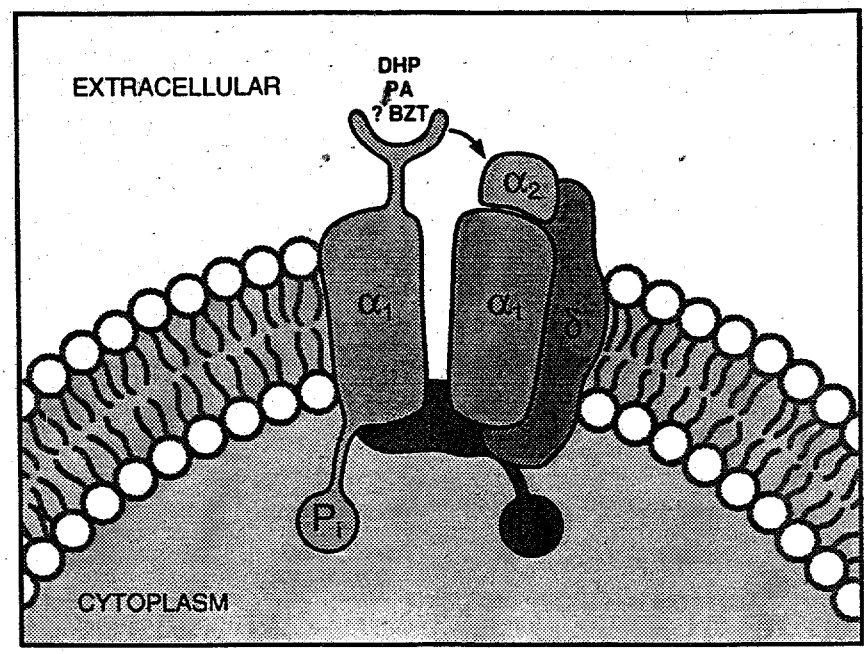


Figure 2. Schematic representation of the voltage-sensitive L-type Ca^{2+} channel. DHP, PA, BZT represents putative site for dihydropyridine, phenylalkylamine, and benzothiazepine binding, leading to hypothetical "closure" *(arrow)* of the ionophore.

the channel at the α_1-subunit[37, 79, 81, 166, 167, 189] (Fig. 2). In cardiac tissue, the opening of channels is a primary step in initiating excitation-contraction (Fig. 3). Thus, toxic manifestations of any CCB result from effects at the DHP receptor. Various excitable tissues contain DHP subtypes with differing affinities for each class of CCB, producing composite physiologic responses that vary slightly for each CCB (Table 1).

CCBs are classified into three classes according to structure (see Table 1), and each class demonstrates slight differences in pharmacologic activity as a result of receptor-binding characteristics.[143] The first group is the phenylalkylamines whose prototype is verapamil.[5, 140] Verapamil produces more profound cardiac conduction defects and equal reductions in systemic vascular resistance versus the other CCBs on a milligram per kilogram basis.[96, 140] Thus, verapamil is more likely than other CCBs to produce a symptomatic decrease in blood pressure, heart rate, and cardiac output. Diltiazem (a benzothiazepine) produces equal reductions in cardiac conduction and contraction compared with verapamil in experiments using isolated atrial and ventricular myocardium from various species.[50, 96, 134, 140, 171, 200] However, diltiazem improves cardiac index and pulmonary capillary wedge pressure in patients with existing cardiac failure, in contrast to verapamil which generally worsens these parameters.[67, 103, 128] When compared with equimolar doses of verapamil, diltiazem decreases systemic vascular resistance to a similar degree.[2, 140, 152] Nifedipine, the prototype DHP, preferentially binds to vascular smooth muscle and predominantly decreases systemic and coronary vascular resistance.[23, 96, 134, 171] In human, animal, and ex vivo heart preparations, therapeutic doses of DHPs actually improve A-V conduction.[23, 96, 134, 152] Additionally, DHPs (with the exception of amlodipine) produce reflex increases in heart rate by the unloading of baroreceptors, resulting in net increases in the indices of myocardial contractility 20 to 30 minutes after initial

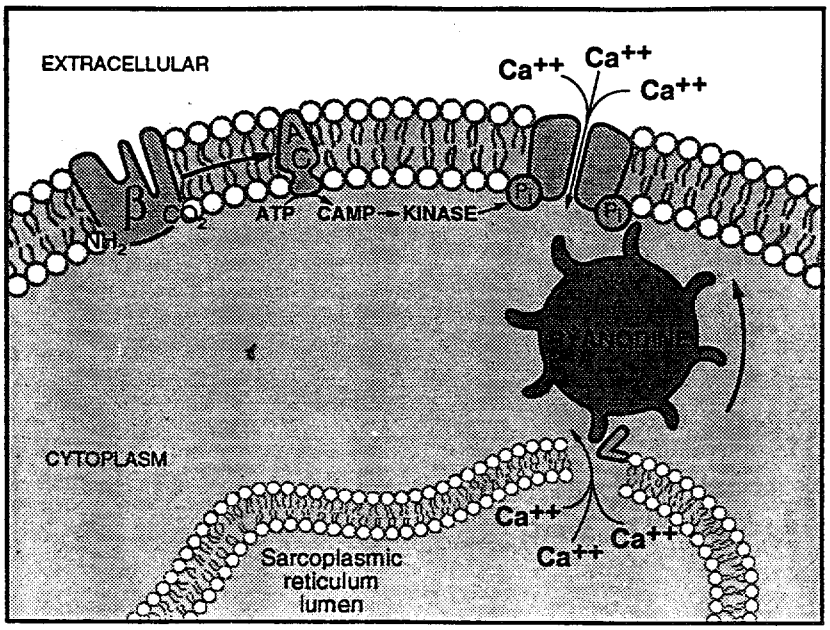
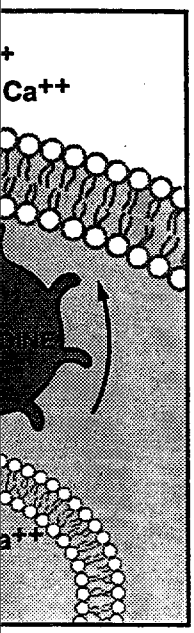


Figure 3. Schematic, simplified overview of Ca^{2+} homeostasis during myocardial contraction. β = β-adrenergic receptor, which when stimulated, increases (through G-protein coupling, not shown) adenylate cyclase activity (AC), leading to activation of kinases which phosphorylate the L-channel, increasing Ca^{2+} entry. Ryanodine = ryanodine receptor that couples plasmellemal Ca^{2+} currents to the sarcoplasmic reticulum, allowing release of intracellular pools of Ca^{2+}.

Table 1. MAJOR CALCIUM CHANNEL BLOCKERS AND PHARMACOLOGIC CHARACTERISTICS

Class	Phenylalkylamines	Benzothiazepines	Dihydropyridines
Prototype	Verapamil	Diltiazem	Nifedipine
Hours to peak plasma concentration (NR/SR)	1.5/5–7	2–3/6–11	0.5/5
Half-life (range in hours)	3–7/10–12	3–5/6–7	2–5/5–7
In massive overdose (hours)	10–12	8–9	7–8
Volume of distribution (L/kg)	4.0	5.0	1.2
Predominant excretion route	(1) Hepatic (2) Renal	Hepatic	Renal
Active metabolite?	Yes (20%)	Yes (25–50%)	No
Heart rate*	−10%	−15%	+10%
Systemic vascular resistance*	−10%	−10%	−20%
A-V nodal conduction velocity*	−20%	−25%	+10%

Data from references 5, 56, 57, 74, 122, 123, 140, 152.
NR = normal release; SR = sustained release.
*In therapeutic doses; % are vs. baseline.



ring myocardial contrac-
(through G-protein coup-
vation of kinases which
ryanodine receptor that
allowing release of intra-

ACOLOGIC

es	Dihydropyridines
	Nifedipine
	0.5/5
	2–5/5–7
	7–8
	1.2
	Renal
	No
	+10%
	−20%
	+10%

absorption of drug in near-therapeutic doses. Occasionally an increase in arterial blood pressure occurs.[36] However, with severe nifedipine toxicity, cardiac contractility is reduced and bradycardia with conduction delays follow within the next 30 minutes.[75, 134, 176, 212]

Metabolism and Pharmacokinetics

All standard CCB preparations are rapidly absorbed from the gastrointestinal tract with onset of action occurring within 30 minutes.[5, 6, 152] Verapamil and most DHPs are extensively protein bound, whereas diltiazem is not. Verapamil and diltiazem undergo first-pass hepatic metabolism and both have large volumes of distribution (Vd). Verapamil is *N*-dealkylated to norverapamil, which possesses 15% to 20% of verapamil's pharmacologic activity[91] and is renally excreted.[5, 123, 152] Thus, complete elimination of verapamil requires both intact hepatic and renal function.[136] Diltiazem is deacylated to deacetyldiltiazem, which has one-half the potency of the parent compound and undergoes biliary excretion.[74, 89] Nifedipine is 80% excreted in the urine and has a much lower Vd than the other CCBs (45 L in adults). Amlodipine is a recently FDA-approved DHP that is unique compared with other DHPs because it causes less reflex tachycardia and has a longer plasma half-life (30 to 50 hours).[4]

β-BLOCKERS

Mechanism of Toxicity

A review of β-adrenergic receptor activity may facilitate understanding of the mechanism of toxicity and the mechanism of action for various treatments for β-blocker poisoning.

Binding of catecholamines to β-receptors ultimately results in increased cytosolic calcium, which enhances excitation-contraction coupling of the cell. This can be described in steps beginning with binding of the catecholamine to the β-receptor. Upon binding, the G-protein complex in the cell membrane is phosphorylated. The phosphorylated protein provides energy for adenyl cyclase to catalyze cAMP formation within the cell (Fig. 3). cAMP acts as a cytosolic messenger to stimulate protein kinases within the membrane of the sarcoplasmic reticulum, thereby releasing calcium. Phosphodiesterase then hydrolyzes the cAMP.[15, 198]

The clinical expression of this process depends on the location of the receptor. There are at least two β-receptors, the β_1 subunit located in the myocardium, kidney, and eye, and the β_2 subunit found in adipose tissue, pancreas, liver, and both smooth and skeletal muscle. β_1 stimulation produces increases in chronotropy and inotropy in the heart, as well as increases in renin secretion by the kidney and aqueous humor production in the anterior chamber of the eye. Excitement of β_2 receptors relaxes smooth muscle in blood vessels, bronchial tree, intestinal tract, and uterus. Additionally, β_2 activation prepares for increased metabolic demands by stimulating lipolysis, glycogenolysis, and insulin release.[81]

Blockade of β-receptors results in decreased cAMP[62] with a resultant blunting of the metabolic, chronotropic, and inotropic effects of endogenous or exogenous catecholamines. However, this blunted response to catecholamines alone does not fully explain the severity of clinical manifestations often encountered in β-blocker toxicity. The fact that toxicity can be induced in catecholamine-depleted

experimental models[40, 107] suggests that alternative or additional mechanisms contribute to toxicity.

The effects of β-blockers on ion homeostasis, commonly referred to as membrane stabilization, are not fully understood. β-blockers may impede sodium entry via myocardial fast inward sodium channels, thus slowing phase zero of the action potential. This results in a prolonged QRS duration on the electrocardiogram. Several β-blocking drugs are known to have some membrane stabilizing ability (Table 2),[60] which is not evident with typical therapeutic doses but may occur with high concentrations (1 to 3 mg/kg of propranolol in experimental animals).[71, 146] Thus, membrane stabilization may contribute to toxicity in the patient who has ingested a large amount of β-blocker drug. The contribution of disturbances in calcium homeostasis by β-blockers has not been fully investigated. Propranolol, acebutolol, and practolol inhibit ATPase-independent calcium uptake into sarcoplasmic reticulum and mitochondria.[45, 147] The resulting excess cytosolic calcium theoretically may alter resting membrane potential by stimulating the calcium-dependent potassium channel, thereby making the cell more difficult to depolarize. In an experiment studying the effect of various calcium concentrations in the perfusate of isolated rat hearts during induction of β-blocker cardiotoxicity, high levels of calcium were found to be protective.[107]

Another potential mechanism is centrally mediated cardiotoxicity. A central event was suggested in a rat model comparing intravenous versus intracerebral administration of β-blockers. At similar plasma concentrations, central administration produced more respiratory depression and hypotension compared with the intravenous route.[108] Evidence from experimental models using isolated neuronal preparations indicates that propranolol produces direct, local anesthetic properties on the nerve cells by inhibiting calcium currents.[13, 14]

Essential Pharmacology and Kinetics

More than 20 β-blockers are available, each of which differs slightly in pharmacologic properties (selectivity for β-adrenoreceptors, intrinsic sympathomimetic activity, and membrane stabilizing activity) (Table 3) and pharmacoki-

Table 2. β-BLOCKER PHARMACOLOGIC PROFILE

Agent	β_1 Selective	Partial Agonist	Membrane Stabilization
Acebutolol	Yes	Yes	Yes
Atenolol	Yes	No	No
Esmolol	Yes	No	No
Labetolol	No	Yes	No
Metoprolol	Yes	No	No
Nadolol	No	No	No
Oxprenolol	No	Yes	Yes
Pindolol	No	Yes	Yes
Propranolol	No	No	Yes
Sotalol	No	No	No
Timolol	No	No	No

Adapted from Frishman W, Jacob H, Eisenberg E, et al: Appraisal and reappraisal of cardiac therapy: Clinical pharmacology of the new beta-adrenergic blocking drugs: Part 8. Self-poisoning with beta-adrenoreceptor blocking agents: Recognition and management. Am Heart J 98:798, 1979; with permission.

Table 3. β-BLOCKER PHARMACOKINETIC PROPERTIES

Agent	Absorption (%)	Protein Binding (%)	Onset of Action (hours)	Volume of Distribution (L/kg)	Elimination/ Half-life (hours)	Lipophilic
Acebutolol	70	25	1–3	3	Renal/3–4	Moderate
Atenolol	50	<5	2–4	0.6–1.1	Renal/6–9	Weak
Esmolol	NA	55	5 min	3.4	Blood esterase 9 min	Weak
Labetolol	90	50	1–3	5.1–9.4	Hepatic/3–4	Weak
Metoprolol	90	12	1–2	5.6	Hepatic/3–4	Moderate
Nadolol	30	30	3–4	1.8–2	Renal/14–24	Weak
Oxyprenolol	90	80	1–2	1.2	Hepatic/2–3	Moderate
Pindolol	90	57	1¼	1.2–2	Renal/3–4	Moderate
Propranolol	90	93	1–1½	3.4–6	Hepatic/3–4	High
Sotalol	70	0	2–3	0.23–0.7	Renal/9–10	Weak
Timolol	90	10	1–2	1.3–3.6	Renal/4–5	Weak

Data from references 60, 80, 172, 208.
NA = not applicable.

netic properties (bioavailability, protein binding, volume of distribution, lipid solubility, route of metabolism, and elimination half-life) (Table 4). Despite recognition that drugs in overdose amounts may not follow the known pharmacology or pharmacokinetics associated with therapeutic doses, the known properties of β-blockers will still be useful in making general predictions of drug behavior in acute ingestion and in evaluating the potential usefulness of various therapies.

Pharmacokinetic characteristics important to the clinician include rate and completeness of drug absorption, lipid solubility, volume of distribution (Vd) and type of preparation. Absorption of normal release (NR) β-blockers is rapid with peak effect in 1 to 4 hours.[208] Agents with high lipid solubility, such as propranolol, should penetrate the blood brain barrier better than the water soluble agents, thereby displaying a greater degree of central nervous system toxicity. The utility of therapeutic modalities such as extracorporeal elimination can be predicted from the degree of plasma protein binding, Vd, and lipid solubility. For those β-blockers that have a Vd greater 1.0 L/kg and high lipid solubility, dialysis would not be expected to be clinically useful.

The pharmacologic differences between drugs may influence expression of toxicity. Acebutolol, atenolol, esmolol, and metoprolol are β_1-selective agents. Because they act predominantly on the β_1 receptor, therapeutic use of these drugs

Table 4. TREATMENT PRIORITIES FOR CCBs & β-BLOCKERS

CCB	β-Blocker
Calcium bolus (10 mL of 10% solution) followed by infusion (20–50 mg/kg per hour)	Glucagon bolus (3.5–5 mg) followed by infusion (1–5 mg per hour)
Epinephrine infusion (1 μg/kg per minute) and titrate	Epinephrine infusion (1 μg/kg/min) and titrate
Glucagon bolus (3.5–5.0 mg) followed by infusion (1–5 mg per hour)	or
Amrinone infusion (5 μg/kg per minute) and titrate	Isoproterenol infusion (2 μg/min) and titrate
Electrical pacing	Amrinone infusion (5 μg/kg per minute) and titrate
	Electrical pacing

is less likely to produce peripheral vasoconstriction, bronchospasm, and disturbances in glucose homeostasis that result from β_2 inhibition. However, with acute ingestion of large amounts of drug, selectivity may be lost.[61, 129] Several β-blockers have partial agonist activity (Table 2) such that while they block the β-receptor to catecholamines, they simultaneously, weakly stimulate the receptor. This partial agonist activity may have a protective effect in overdose. Propranolol, and to a lesser extent acebutolol, labetolol, oxprenolol, and pindolol, can inhibit myocardial sodium channels in addition to β-receptors, thus making these drugs potentially more toxic.

CLINICAL MANIFESTATIONS OF β-BLOCKER AND CCB TOXICITY

General

The β-blocker or CCB intoxicated patient may present with a spectrum of severity of illness, ranging from asymptomatic to cardiovascular collapse with hallmark myocardial depression and hypotension. The severity of toxicity is determined by a number of factors including the amount and characteristics of the drug ingested, underlying health of the patient, coingestants, and delay until treatment. The majority of serious cases result from ingestion of verapamil, the most toxic of the CCBs, and propranolol, the most frequently reported β-blocker. Patients with congestive heart failure are clearly more susceptible to CCB myocardial depression and are more likely to demonstrate symptoms of CCB toxicity than age-matched patients with normal left ventricular function.[30, 67, 103, 128] Older patients are more sensitive to CCB toxicity: CCBs of all classes are likely to produce exaggerated depression of cardiac function and conduction in senescent isolated rat hearts and in elderly human subjects.[36, 88, 89, 103, 163, 164, 174, 175] Toxic ingestions of NR preparations typically produce symptoms within 2 hours for all CCB classes, although maximal toxicity may not occur for 6 to 8 hours.[74, 75, 84, 102, 187, 192, 221] In acute ingestion of NR β-blockers, symptoms typically develop within 1 to 3 hours after ingestion, though onset may range from 15 minutes to 10 hours.[29, 60, 111, 132, 144, 149, 181, 184, 208] A delay in onset of symptoms may occur due to factors such as drug formulation and coingestants. Sustained release (SR) preparations, which are available for all classes of CCBs and some β-blockers, represent an increasing toxic threat in all age groups (Fig. 1).[113, 115–117, 164] These SR preparations can produce significant toxicity with onset of symptoms delayed more than 6 hours postingestion in 10% of CCB cases[9, 112, 113, 115–117, 164, 221] and more than 12 hours in one case.[190] Although not specifically reported for long-acting β-blocker preparations, delay in onset of clinical illness should be anticipated based on experience with other SR formulations such as CCBs[164] and lithium.[28] Co-ingested drugs that decrease gastrointestinal motility, such as opioids and anticholinergics, may delay absorption and hence peak drug effect. Co-ingestants and certain metabolic alterations may increase the toxic effects of CCBs (Table 5).

Calcium Channel Blockers

Each of the three classes of CCBs can produce a slightly varied presentation depending on the time since ingestion and the amount ingested, but the major threat to life is always myocardial depression and hypotension. Nifedipine pro-