

# UTAH TOX UPDATE

A PUBLICATION OF THE  
UTAH POISON CONTROL CENTER

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## Calcium Channel Blocker Toxicity and Treatment Issues

### Introduction

Calcium antagonists are a diverse group of chemicals that include over ten drugs currently on the US market. They are classified by structure and include the diphenylalkylamines (verapamil), benzothiazepines (diltiazem) and dihydropyridines (nifedipine, amlodipine, felodipine, isradipine, nicardipine, nimodipine, and nisoldipine). Bepridil is a calcium antagonist that does not fit into the current classifications. Current indications for these agents include the treatment of hypertension, angina, arrhythmias, SVT, subarachnoid hemorrhage, migraine headaches, Raynaud's syndrome, congestive heart failure and congestive cardiomyopathy. Calcium antagonists are the most common cardiovascular drug involved in poison exposures reported to the Toxic Exposure Surveillance System (TESS).<sup>1</sup> Of the more than 9,000 cardiovascular drug exposures reported to TESS in 1997, 61% involved adults, 52% were treated in a health care facility, 77% were unintentional and 3% resulted in a major effect or fatal outcome.

### Pharmacology

Calcium antagonists block the movement of calcium into cell membranes through inhibition of the voltage-sensitive L-type calcium channels.<sup>2</sup> In doing so, calcium antagonists affect vascular smooth muscle tone, myocardial contractility, automaticity and atrioventricular conduction. The dihydropyridine class (nifedipine) is unique in that they have greater selectivity for vascular smooth muscle than the myocardium.<sup>2,3</sup> This vascular selectivity results in potent peripheral vasodilation, a subsequent reflex-adrenergic discharge that causes increased oxygen demand and reflex tachycardia. In therapeutic doses, bepridil has shown arrhythmogenic potential related to an increased QT and QTc interval.<sup>4</sup>

Drug interactions play a key role in the development of adverse events and toxicity. Significant interactions may occur in patients taking other drugs with myocardial depressant properties. Some of the calcium antagonists, particularly diltiazem, are metabolized through the cytochrome P-450 isozymes. Important interactions may occur with other drugs metabolized via this route, such as cimetidine/ranitidine, erythromycin and quinidine.

### Toxic Effects

Toxic manifestations of calcium antagonists include myocardial depression, hypotension, syncope, lethargy, dizziness, seizures, altered mental status and noncardiogenic pulmonary edema.<sup>5,6</sup> Specific presentations depend somewhat upon the class of calcium channel blocker ingested. For example, during the first 30 minutes of a nifedipine overdose, patients may initially present with tachycardia and normal blood pressure, followed later by hypotension and bradycardia.<sup>7</sup> In contrast, patients overdosing on diltiazem or verapamil may present with nausea, vomiting, metabolic acidosis and hyperglycemia (blocks insulin release).<sup>6,8</sup> Varying degrees of AV block have been reported, especially with verapamil. Patients may present asymptomatic but can rapidly develop cardiovascular collapse. The differential diagnosis includes beta-blocker, cardiac glycoside, clonidine intoxication and medical conditions.

Certain conditions may exacerbate a calcium channel blocker overdose. Elderly patients and those with congestive heart failure are at increased risk for toxicity due to increased sensitivity to myocardial depression. Concomitant beta-adrenergic blockade may blunt autonomic reflexes and response to exogenous catecholamines.

### Treatment

Adequate airway management is essential because mental status may rapidly deteriorate. For this reason, ipecac should be avoided due to increased risk of aspiration. Gastric lavage may be beneficial if the patient presents within one to two hours of ingestion, but should be used cautiously due to potential vagal stimulation. Activated charcoal should be given to all patients with adequate bowel sounds. Due to delayed absorption, more than one dose of charcoal may be of value with ingestion of extended-release products. Whole bowel

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irrigation is another gut decontamination option, especially when extended-release preparations are involved. However, the presence of whole tablets in the stool does not necessarily mean absorption has been inhibited. Currently, there is at least one product on the market (Procardia XL®) in which the tablet remains intact and is excreted in the feces.<sup>4</sup> Calcium antagonists are highly protein bound. Therefore, hemodialysis is not likely to be effective at enhancing elimination.

All patients ingesting immediate-release preparations should be monitored for a minimum of eight hours after ingestion. Many of the calcium antagonists are available in an extended-release preparation. For some of these preparations, onset of action and time to peak concentrations are markedly delayed compared to immediate-release preparations. These patients should be observed for 24 hours. Symptomatic patients should be admitted to ICU. An ECG should be obtained upon presentation and repeated frequently (q 1-2 hours for 8 hours) until stable. Only asymptomatic patients who have ingested immediate-release preparations and have a normal (or unchanged) ECG at eight hours should be discharged to home.

Calcium antagonists affect myocardial contractility and heart rate. Specific therapy is directed to improve contractility, increase heart rate and improve perfusion. No one agent has been consistently effective in the treatment of severe intoxication. Hypotension should be initially treated with a crystalloid fluid bolus if pulmonary edema is not present.

Atropine is considered the drug of choice for the treatment of symptomatic bradycardia. It may be used initially to increase heart rate in mild to moderate calcium antagonist poisoning, but it is usually ineffective in the treatment of severe calcium channel blocker overdoses.

Calcium is a logical therapeutic option and is the initial pharmacological agent used by many clinicians. A bolus of 1-2 g (10-20 mL 10%) calcium chloride plus a continuous infusion of 20-40 mg/kg/hr (0.2-0.4 mL/kg/hr 10%) calcium chloride may improve hypotension, conduction abnormalities and cardiac contractility. A continuous infusion is preferred over repeated boluses because sustained increases in extracellular calcium can only be provided through a continuous infusion. Calcium is not always effective in improving hemodynamic parameters.<sup>9</sup> Moreover, calcium boluses can cause various adverse effects such as nausea, vomiting, confusion, thrombophlebitis, lethargy, cardiac conduction defects with bradycardia and increased oxygen consumption resulting in angina. Severe hypercalcemia, although rare, has been reported.<sup>10</sup> Calcium concentrations should be determined every two hours to monitor for hypercalcemia. If a cardiac glycoside is a co-ingestant, intracellular calcium may already be elevated and additional calcium may worsen the cardiac glycoside toxicity unless Digibind™ has already been given. If a therapeutic

benefit is not noted after an adequate trial of calcium, catecholamine therapy should be considered.

Dopamine is effective in increasing blood pressure and heart rate, and has been successfully used to treat ingestions of all three classes of calcium channel blockers.<sup>5</sup> An epinephrine continuous infusion may also be effective in improving hemodynamic parameters. Like calcium administration, vasopressors are not always effective.

Glucagon may improve cardiac contractility and increase heart rate by acting through stimulation of adenylate cyclase and the resultant increase in intracellular concentrations of cyclic adenosine monophosphate (cAMP). Animal studies of verapamil overdose show that glucagon can increase heart rate and arterial blood pressure as well as decrease the PR interval.<sup>11</sup> A reasonable initial dose is 2-5 mg IV over 30-60 seconds for an adult and 50 mg/kg in children. This may be repeated in five minutes if no response is seen. Responders should have a continuous infusion begun that consists of the initial "response dose" given per hour. In preparing glucagon for administration, the diluent provided by the manufacturer should be avoided due to the presence of phenol as a preservative.

Phosphodiesterase inhibitors (amrinone) inhibit the breakdown of cAMP that may prolong the action of intracellular calcium. In canine studies of calcium channel blocker toxicity, amrinone improved cardiac function.<sup>5</sup> Amrinone should be used with caution as it may upregulate dihydropyridine receptors that may lead to increased L-channel blockade.<sup>5</sup>

Transvenous or external cardiac pacing can be used when pharmacological means of increasing heart rate fail. Intra-aortic balloon pump has been used with success.

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## UPCC News

### Stable Funding

After years of unpredictable and unstable funding, the Utah Poison Control Center (UPCC) finally achieved stable funding. During the 1998 legislative session, the Utah Legislature passed Senate Bill 221, Emergency Services Telephone Charge, sponsored by Senator David H. Steele. Senate Bill 221 stabilized the funding of the UPCC by including the UPCC in the 911 telephone surcharge. The new funding has allowed the UPCC to carry out its full mission by addressing education needs in addition to the telephone hotline.

### What's New?

The UPCC now has a board certified medical toxicologist on-site two days a week. E. Martin Caravati, MD, MPH, ACMT, the UPCC's Associate Medical Director achieved board certification in medical toxicology last fall. Our Medical Director, Douglas E. Rollins, MD, PhD, and/or Dr. Caravati are on-call 24 hours a day and available for a direct consultation.

Pati Comes, BS, has recently joined the UPCC as the Outreach Poison Education Provider. Pati comes to the UPCC from the Utah Department of Health. She will be involved in conducting a community needs assessment and developing education programs to target high risk populations.

### CSPI Exam

There is more good news! Three of our Specialists in Poison Information (SPI) took and passed the Certified Specialist in Poison Information (CSPI) examination in May of this year. Currently, 75% of the UPCC's specialists in poison information are CSPI's. The CSPI Exam is administered by the American Association of Poison Control Centers (AAPCC), and it tests a specialist's knowledge base and problem solving skills regarding management of poison exposures. The exam covers drugs, household products, biologicals (venomous bites, food poisoning and plants), pesticides, chemicals and metals. Candidates for the examination must be a registered nurse or pharmacist currently employed as a SPI and have at least one year (2,000 hours) of experience and handled at least 2,000 human poison exposure telephone consultations. To maintain certification, the examination must be passed every seven years. In order for a poison control center to remain certified by the American Association of Poison Control Centers, at least 50% of the SPI's must be certified.

## Fatality Report

In each issue of UTOX Update, we will present a poisoning fatality from published abstracts. These fatalities will highlight the clinical course, the toxicology of the substance and the critical management issues of the fatality. This issue features a death as the direct effect from the overdose of a calcium channel blocking agent.

Sixty-one deaths attributed to calcium channel blockers were reported to the AAPCC's Toxic Exposure Surveillance System (TESS) in 1998.<sup>1</sup> Calcium channel blockers accounted for 7.9% of all fatalities reported and 0.7% of all calcium channel blocker exposures resulted in death. This demonstrates the potential seriousness of these poisonings. Thirty-four fatalities involved verapamil, 11 diltiazem, 9 nifedipine, 6 amlodipine, and 1 unknown calcium channel blocker.

Case: A 38-year-old male who ingested up to 90 diltiazem 300 mg extended-release tablets and presented to the emergency department (ED) five hours after ingestion lethargic with a blood pressure of 130/91 mmHg and a heart rate of 90 bpm. After two hours in the ED he developed complete heart block and an idioventricular rhythm. Whole bowel irrigation was begun and he was given dopamine, norepinephrine and calcium gluconate infusions. He became more awake and seemed to improve but then his urine output decreased and he developed an ileus. Less than 24 hours after admission, he experienced cardiorespiratory arrest and died.<sup>2</sup>

This case demonstrates that patients who ingest an extended-release product may present without any evidence of cardiovascular toxicity but can later develop serious effects. Whole bowel irrigation and multi-dose charcoal may be indicated for extended-release medications. Cardiac pacemaker and intra-aortic balloon pump may be required in severe calcium channel blocker toxicity.

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