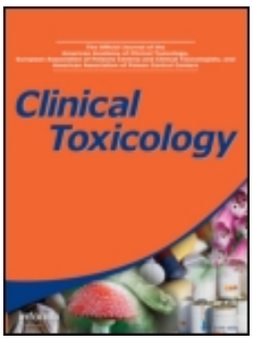

Clinical Toxicology

ISSN: 1556-3650 (Print) 1556-9519 (Online) Journal homepage: http://www.tandfonline.com/loi/ictx20

Calcium Channel Blocker Ingestion: An Evidence-Based Consensus Guideline for Out-of-Hospital Management

Kent R. Olson M.D., Andrew R. Erdman M.D., Alan D. Woolf M.P.H. M.D., Elizabeth J. Scharman Pharm.D., Gwenn Christianson M.S.N., E. Martin Caravati M.P.H. M.D., Paul M. Wax M.D., Lisa L. Booze Pharm.D., Anthony S. Manoguerra Pharm.D., Daniel C. Keyes M.P.H. M.D., Peter A. Chyka Pharm.D. & William G. Troutman Pharm.D.

To cite this article: Kent R. Olson M.D., Andrew R. Erdman M.D., Alan D. Woolf M.P.H. M.D., Elizabeth J. Scharman Pharm.D., Gwenn Christianson M.S.N., E. Martin Caravati M.P.H. M.D., Paul M. Wax M.D., Lisa L. Booze Pharm.D., Anthony S. Manoguerra Pharm.D., Daniel C. Keyes M.P.H. M.D., Peter A. Chyka Pharm.D. & William G. Troutman Pharm.D. (2005) Calcium Channel Blocker Ingestion: An Evidence-Based Consensus Guideline for Out-of-Hospital Management, Clinical Toxicology, 43:7, 797-822, DOI: 10.1080/15563650500357404

To link to this article: http://dx.doi.org/10.1080/15563650500357404

Published online: 19 Aug 2009.

Clinical Toxicology, 43:797–822, 2005

ISSN: 0731-3810 print / 1097-9875 online
DOI: 10.1080/15563650500357404

Taylor & Francis
Taylor & Francis Group

PRACTICE GUIDELINE

Calcium Channel Blocker Ingestion: An Evidence-Based Consensus Guideline for Out-of-Hospital Management

Kent R. Olson, M.D., Andrew R. Erdman, M.D., Alan D. Woolf, M.D., M.P.H., Elizabeth J. Scharman, Pharm.D., Gwenn Christianson, M.S.N., E. Martin Caravati, M.D., M.P.H., Paul M. Wax, M.D., Lisa L. Booze, Pharm.D., Anthony S. Manoguerra, Pharm.D., Daniel C. Keyes, M.D., M.P.H., Peter A. Chyka, Pharm.D., and William G. Troutman, Pharm.D.

American Association of Poison Control Centers, Washington, District of Columbia, USA

In 2003, U.S. poison control centers were consulted after 9650 ingestions of calcium channel blockers (CCBs), including 57 deaths. This represents more than one-third of the deaths reported to the American Association of Poison Control Centers' Toxic Exposure Surveillance System database that were associated with cardiovascular drugs and emphasizes the importance of developing a guideline for the out-of-hospital management of calcium channel blocker poisoning. The objective of this guideline is to assist poison center personnel in the appropriate out-of-hospital triage and initial management of patients with suspected ingestions of calcium channel blockers. An evidence-based expert consensus process was used to create this guideline. This guideline applies to ingestion of calcium channel blockers alone and is based on an assessment of current scientific and clinical information. The expert consensus panel recognizes that specific patient care decisions may be at variance with this guideline and are the prerogative of the patient and the health professionals providing care, considering all of the circumstances involved. The panel's recommendations follow. The grade of recommendation is in parentheses. 1) All patients with stated or suspected self-harm or the recipient of a potentially malicious administration of a CCB should be referred to an emergency department immediately regardless of the amount ingested (Grade D). 2) Asymptomatic patients are unlikely to develop symptoms if the interval between the ingestion and the call is greater than 6 hours for immediate-release products, 18 hours for modified-release products other than verapamil, and 24 hours for modified-release verapamil. These patients do not need referral or prolonged observation (Grade D). 3) Patients without evidence of self-harm should have further evaluation, including determination of the precise dose ingested, history of other medical conditions, and the presence of co-ingestants. Ingestion of either an amount that exceeds the usual maximum single therapeutic dose or an amount equal to or greater than the lowest reported toxic dose, whichever is lower (see Table 5), would warrant consideration of referral to an emergency department (Grade D). 4) Do not induce emesis (Grade D). 5) Consider the administration of activated charcoal orally if available and no contraindications are present. However, do not delay transportation in order to administer charcoal (Grade D). 6) For patients who merit evaluation in an emergency department, ambulance transportation is recommended because of the potential for life-threatening complications. Provide usual supportive care en route to the hospital, including intravenous fluids for hypotension. Consider use of intravenous calcium, glucagon, and epinephrine for severe hypotension during transport, if available (Grade D). 7) Depending on the specific circumstances, follow-up calls should be made to determine outcome at appropriate intervals based on the clinical judgment of the poison center staff (Grade D).

Keywords Calcium channel blockers; Calcium entry blockers; Calcium antagonists; Poison control centers/standards; Prehospital; Poisoning; Practice guidelines

INTRODUCTION

Ingestion of a calcium channel blocker (CCB) is a potentially lethal event. In 2003, U.S. poison control centers were consulted after 9650 ingestions of CCBs. Of these, 4834 patients (50%) were evaluated in healthcare facilities, 1481 (15%) experienced major or moderate toxicity, and 57 died. This represents more than one-third of the deaths reported to the American Association of Poison Control Centers' Toxic Exposure Surveillance System (TESS) database that were associated with cardiovascular drugs (1).

The evaluation of possible CCB poisoning has medical, economic, and social costs. Because the toxic doses overlap with the upper therapeutic range for many of these drugs, poison control centers frequently recommend hospital evaluation after any CCB exposure. Moreover, because most CCBs

Guidelines for the Management of Poisoning. Supported in full by Cooperative Agreement 8 U4BH500084 between the American Association of Poison Control Centers and the Maternal and Child Health Bureau, Health Resources and Services Administration, Department of Human Services.

Address correspondence to American Association of Poison Control Centers, 3201 New Mexico Ave., NW, Suite 330, Washington, DC 20016, USA; E-mail: info@aapcc.org

are formulated as modified-release products that might have delayed onsets of symptoms, prolonged observation of asymptomatic patients is widely practiced (2). Finding a child with an open medicine container that might have contained just one tablet of a CCB is often followed by overnight hospital observation. Patients taking CCBs therapeutically might unintentionally take second doses of their own medications and could be at risk for toxicity if they have underlying heart disease or if the amount of drug in each dosage unit is large. Many such patients are also taking other cardiodepressant drugs that might have additive effects on heart rate or contractility. Thus, poison control center triage of unintentional CCB ingestion is usually based on a low threshold for hospital referral, with transportation often occurring by ambulance. The potential costs of EMS transportation, emergency department evaluation, aggressive gastrointestinal decontamination (including whole bowel irrigation for sustained-release products), and intensive care unit observation are potentially enormous, especially considering that most patients develop no symptoms as a result of an exposure (3). A review of poison control center management protocols and medical toxicology textbooks suggests that the threshold for triage after acute unintentional CCB ingestion varies widely (see below).

Background and Definitions

Calcium channel blockers (also known as calcium antagonists or calcium entry blockers) are used widely for the treatment of a variety of disorders including hypertension, angina pectoris, coronary artery spasm, supraventricular arrhythmias, and migraine headache. Ten calcium channel blockers are currently marketed in the U.S. (amlodipine, bepridil, diltiazem, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, and verapamil). These drugs block the entry of calcium through cellular membrane voltage-sensitive calcium channels. In vascular tissue, this results in arterial smooth muscle relaxation. In the heart, CCBs inhibit depolarization of cells in the sinoatrial and atrioventricular nodes and depress contractility. At doses used clinically, nifedipine and other dihydropyridines (amlodipine, felodipine, isradipine, nicardipine, and nimodipine) are relatively selective vasodilators and do not usually affect nodal conduction or contractility; however, in overdose this distinction can be lost (4,5). Patients with pre-existing cardiac dysfunction (e.g., congestive heart failure, cardiomyopathy, conduction disorders) could have pronounced effects. Combination of CCBs with other negative inotropes (e.g., β-blockers) can produce additive toxicity (6).

Toxicity from CCBs can occur as a result of a single acute ingestion, which could be unintentional or intentional, or with repeated or therapeutic use. An acute exposure might involve unintentional ingestion of a second therapeutic dose in a patient already on the drug, unintentional ingestion of someone else's therapeutic dose in a patient naïve to CCBs, unintentional ingestion by a child, or intentional ingestion with suicidal intent.

This guideline focuses on the ingestion of more than a single therapeutic dose (overdose). Therapeutic doses of CCBs can sometimes cause adverse effects in both adults and children—some idiosyncratic and some dose-dependent. Articles that reported adverse effects related to usual therapeutic doses and with therapeutic intent were not included in the review.

For the purpose of this guideline, age groups are defined as 1) children under 6 years of age and 2) older children and adults. The older age group is much more likely to attempt self-harm and to conceal an ingestion. Acute exposures are defined as those occurring over a period of no more than 8 hours, and chronic exposures are those that occur over a period of 8 or more hours. The term out-of-hospital is defined as the period before a patient reaches a healthcare facility.

Intended Users of the Guideline

The intended users of this guideline are personnel in U.S. poison centers. This guideline has been developed for the conditions prevalent in the U.S. While the toxicity of calcium channel blockers is not expected to vary in a clinically significant manner in other nations, the out-of-hospital conditions could be much different. Some calcium channel blockers are not currently marketed in the U.S. These calcium channel blockers are not addressed in this document. This guideline should not be extrapolated to other settings unless it has been determined that the conditions assumed in this guideline are present.

Objective of This Guideline

The objective of this guideline is to assist poison center personnel in the appropriate out-of-hospital triage and initial management of patients with suspected ingestions of calcium channel blockers by

1. describing the process by which a calcium channel blocker ingestion might be managed,
2. identifying the key decision elements in managing cases of calcium channel blocker ingestion,
3. providing clear and practical recommendations that reflect the current state of knowledge, and
4. identifying needs for research.

This guideline applies to ingestion of calcium channel blockers alone. Co-ingestion of additional substances could require different referral and management recommendations depending on the combined toxicities of the substances.

This guideline is based on an assessment of current scientific and clinical information. The expert consensus panel recognizes that specific patient care decisions may be at variance with this guideline and are the prerogative of the patient and the health professionals providing care, considering all of the circumstances involved.

METHODOLOGY

The methodology used for the preparation of this guideline was developed after reviewing the list of key elements of guidelines described by Shaneyfelt et al. (7). An expert consensus panel was established to oversee the guideline development process (Appendix 1). The American Association of Poison Control Centers (AAPCC), the American Academy of Clinical Toxicology (AACT), and the American College of Medical Toxicology (ACMT) appointed members of their organizations to serve as panel members. To serve on the expert consensus panel, an individual had to have an exceptional track record in clinical care and scientific research in toxicology, board certification as a clinical or medical toxicologist, significant U.S. poison center experience, and be an opinion leader with broad esteem. Two specialists in poison information were included as full panel members to provide the viewpoint of the end-users of the guideline.

Literature Search

The National Library of Medicine's MEDLINE database was searched (1966–March 2003) using calcium channel blockers (exploded as a MeSH term) with the subheadings poisoning or toxicity, limited to humans. A second MEDLINE search (1966–October 2003) located all calcium channel blocker articles that included patients from 1 through 5 years of age.

The MEDLINE and PreMEDLINE (1966–February 2003) databases were searched using a list of 23 calcium channel blockers as textwords (title, abstract, MeSH term, CAS registry) plus either poison* or overdos* or tox*, limited to humans. This same process was repeated in International Pharmaceutical Abstracts (1970–March 2003, excluding abstracts of meeting presentations), Science Citation Index (1977–March 2003), the Database of Abstracts of Reviews of Effects (accessed March 2003), the Cochrane Database of Systematic Reviews (accessed March 2003), and the Cochrane Central Register of Controlled Trials (accessed March 2003). A similar search was conducted in Excerpta Medica Database (EMBASE, 1990–March 2003). Reactions (1980–March 2003), the calcium channel poisoning management in POISINDEX (8), and the bibliographies of recovered articles were reviewed to identify previously undiscovered articles. Furthermore, NACCT abstracts published in the Journal of Toxicology–Clinical Toxicology (1995–2003) were reviewed for original human data. The chapter bibliographies in four current major toxicology textbooks (9–12) and the reference list of a recent review article (13) were reviewed for citations of additional articles with original human data. Finally, the Toxic Exposure Surveillance System (TESS) maintained by the American Association of Poison Control Centers was searched for deaths resulting from unintentional calcium channel blocker poisoning or any deaths from calcium channel blocker poisoning in children (for the years 1985–2002). These cases were abstracted for use by the panel.

Article Selection

The recovered citations were entered into an EndNote® library and duplicate entries were eliminated. The abstracts of the remaining articles were reviewed, looking specifically for those that dealt with estimations of mg/kg or ingested doses with or without subsequent signs or symptoms, and management techniques that might be suitable for out-of-hospital use (e.g., gastrointestinal decontamination). Articles excluded were those that did not meet either of the preceding criteria, didn't add new data (e.g., some reviews, editorials), and some that exclusively described inpatient-only procedures (e.g., dialysis).

Data Extraction

All articles that were retrieved from the search were reviewed by a single abstractor. Each article was assigned a level-of-evidence score from 1 to 6 using the rating scheme developed by the Centre for Evidence-Based Medicine at Oxford University (Appendix 2); the complete paper was then reviewed for original human data regarding the toxic effects of calcium channel blockers or original human data directly relevant to the out-of-hospital management of patients with calcium channel blocker toxicity or overdose. Relevant data (e.g., dose of calcium channel blocker, resultant effects, time of onset of effects, therapeutic interventions or decontamination measures given, efficacy or results of any interventions, and overall patient outcome) were compiled into a table and a brief summary description of each article was written. This full evidence table is available at http://www.aapcc.org/DiscGuidelines/CCB%20evidence%20table.pdf. The complete table of all abstracted articles was then forwarded to the panel members for review and consideration in developing the guideline. Every attempt was made to locate significant foreign language articles and have their crucial information extracted, translated, and tabulated. In addition to this evidence table, several brief sub-tables were generated that included all of the articles and data relating to a particular topic (e.g., dose of calcium channel blockers in acute pediatric ingestions reported to cause toxicity). These were also forwarded to the primary author and guideline panel members. Copies of all of the articles were made available for reading by the panel members on a secure AAPCC website.

California Poison Control System Data

The primary author (KO) reviewed data from the California Poison Control System's Visual Dotlab database, including narrative case notes, for cases of calcium channel blocker exposure for the years 2000 through 2003. The cases were reviewed for information about dose, time of onset, and outcome.

Guideline Writing and Review

A guideline draft was prepared by the primary author. The draft was submitted to the expert consensus panel for comment. Using a modified Delphi process, comments from the expert consensus panel members were collected, copied into a table of comments, and submitted to the primary author for response. The primary author responded to each comment in the table and, when appropriate, the guideline draft was modified to incorporate changes suggested by the panel. The revised guideline draft was again reviewed by the panel and, if there was no strong objection by any panelist to any of the changes made by the primary author, the draft was prepared for the external review process. External review of the second draft was conducted by distributing it electronically to AAPCC, AACT, and ACMT members and the secondary review panel. The secondary review panel consisted of representatives from the federal government, public health, emergency services, pediatrics, pharmacy practice, and consumer organizations (Appendix 3). Comments were submitted via a discussion thread on the AAPCC website or privately through e-mail communication to AAPCC staff. All submitted comments were stripped of any information that would identify their sources, copied into a table of comments, and reviewed by the expert consensus panel and the primary author. The primary author responded to each comment in the table and their responses and subsequent changes in the guideline were reviewed and accepted by the panel. Following a meeting of the expert consensus panel, the final revision of the guideline was prepared.

REVIEW OF CURRENT PRACTICE

Recommended Therapeutic Doses of Calcium Channel Blockers

Because calcium channel blockers have a low toxic-to-therapeutic dose ratio, and serious effects have been reported at doses only slightly above those used for therapy, the panel reviewed currently available recommendations for therapeutic dosing. Table 1 presents recommended doses of common calcium channel blockers for children and adults.

TABLE 1
Summary of therapeutic doses of CCBs

Drug	Lowest single therapeutic dose	Maximum single therapeutic dose	Maximum daily dose
Amlodipine	Adult: 2.5 mg	10 mg	10 mg
	Child: 0.05 mg/kg	0.3 mg/kg	0.6 mg/kg or 10 mg
Bepridil	Adult: 200 mg	300 mg	300–400 mg
	Child: Not reported	Not reported	Not reported
Diltiazem	Adult: 30 mg	120 mg	360–540 mg
	SR prep: 60 mg	SR prep: 360 mg	
	CD, XR prep: 120 mg	CD, XR prep: 540 mg	
	Child: 0.5 mg/kg	1 mg/kg	3.5 mg/kg
Felodipine	Adult: 2.5 mg	10 mg	10–20 mg
	Child: 0.05 mg/kg	0.3 mg/kg	0.6 mg/kg or 10 mg
Isradipine	Adult: 2.5 mg	20 mg	20 mg
	Child: 0.05 mg/kg	0.1 mg/kg	0.8 mg/kg or 20 mg
Nicardipine	Adult: 20 mg	40 mg	120 mg
	SR prep: 30 mg	SR prep: 60 mg	
	Child: not reported	Not reported	Not reported
Nifedipine	Adult: 10 mg	30 mg	180 mg
	CC, XL prep: 30 mg	CC, XL prep: 120 mg	
	Child: 0.2 mg/kg	1 mg/kg	3 mg/kg up to 180 mg
Nimodipine	Adult: 60 mg	Not reported	Not reported
	Child: not reported	Not reported	Not reported
Nisoldipine	Adult: 10 mg	30 mg	60 mg
	Child: not reported	Not reported	Not reported
Verapamil	Adult: 40–80 mg	Adult: 120 mg	480–720 mg
	SR prep: 120 mg	SR prep: 480 mg	
	Child: 0.5 mg/kg	Child: 2.5 mg/kg	8 mg/kg up to 480 mg

From Refs. (14–17).

Current Poison Control Center Practices

During the preparation of this guideline, the panel investigated poison center referral patterns for calcium channel blocker ingestions. All U.S. poison centers were invited by the AAPCC to provide copies of any protocols or operational guidelines for calcium channel blocker ingestion. Twenty-eight poison centers responded but 14 of these stated they did not have a specific guideline for calcium channel blockers. Fourteen guidelines were received (see Table 2). All 14 advised healthcare facility (HCF) referral for a suspected suicidal ingestion. Nine guidelines recommended HCF referral after ingestion of any amount of a CCB. Of these nine, one specified ''any SR preparation,'' one commented that it is ''prudent to send most small children in,'' and one advised referral to an HCF for all CCB ingestions by children. The other five PCC guidelines did not specifically distinguish pediatric from adult exposures or immediate-release vs. modified-release products.

Seven of the PCC guidelines described threshold HCF referral amounts for CCB ingestions by children. However, these varied widely. For example, one center advised HCF referral for pediatric ingestion of more than 80 mg immediate-release (IR) verapamil, of any amount of a modified-release (SR) verapamil, and of any amount of any nifedipine preparation. Another center had a lower threshold for verapamil (2.5 mg/kg) and a higher threshold for nifedipine (1 mg/kg). The latter PCC's guideline indicated that death had been reported after a single 10-mg nifedipine. Another PCC uses the ''lowest pediatric therapeutic dose'' as a threshold, and refers the guideline user to ''pediatric dosing books.''

TABLE 2
Summary of CCB Guidelines from 14 U.S. Poison Control Centers

Drug	Threshold for children	Comments
Amlodipine	Any amount	8 PCCs
	>0.2 mg/kg	2 PCCs
	2.5 mg (smallest tablet)	1 PCC
	>''lowest pediatric therapeutic dose''	Specific mg not listed
	>''maximum therapeutic dose''	Specific mg not listed
Diltiazem	Any amount	7 PCCs
	>80 mg IR	1 PCC
	>1 mg/kg	1 PCC
	>2 mg/kg	1 PCC
	>2.5 mg/kg IR or >3 mg/kg SR	1 PCC
	>3 mg/kg SR	1 PCC
	>30 mg (smallest tablet)	1 PCC
	>''lowest pediatric therapeutic dose''	Specific mg not listed
	>''maximum therapeutic dose''	Specific mg not listed
Felodipine	Any amount	8 PCCs
	>0.4 mg/kg	1 PCC
	>2.5 mg (smallest tablet) or >5 mg*	1 PCC
Nifedipine	Any amount	8 PCCs
	>0.25 mg/kg	1 PCC
	>1 mg/kg	1 PCC
	>1.25 mg/kg IR or SR	1 PCC
	>10 mg (smallest tablet)	1 PCC
	>''lowest pediatric therapeutic dose''	Specific mg not listed
	>''maximum therapeutic dose''	Specific mg not listed
Verapamil	Any amount	7 PCCs
	>80 mg IR	1 PCC
	>5 mg/kg or >40 mg (1–5 yr old) or >80 mg (>5 yr old)	1 PCC
	>8 mg/kg IR or >10 mg/kg SR	1 PCC
	>40 mg (smallest tablet)	1 PCC
	>''lowest pediatric therapeutic dose''	Specific mg not listed
	>''maximum therapeutic dose''	Specific mg not listed

*Conflicting referral doses in this PCC's guideline.

Recommendations for adults with unintentional ingestion or ingestion of an extra dose were also variable and were specifically addressed by only seven of the 14 PCCs. One advised referral for ingestion of more than the maximum therapeutic adult dose. Three PCCs allowed home observation for a double dose of one's own medicine but added qualifiers that would override the amount taken, such as the caller is alone, is having symptoms, has underlying cardiac disease, or takes other medicines that might contribute to an adverse reaction. One of these three PCCs also suggested that the caller contact the patient's own physician to decide on HCF referral.

Seven PCCs recommended a specific period of observation in an HCF, with range of 6–8 hours for immediate-release and 16–24 hours for modified-release products. Three of these PCCs specifically recommended 24 hours of observation or longer for SR products.

Review of Medical Toxicology Textbooks

A review of textbooks revealed similar variation in recommendations—two texts provide no dose guidelines for HCF referral (10,11) while others recommend any dose greater than the usual therapeutic dose (18), any dose of two to three times the normal dose (19), or various specific doses varying from 5 mg/kg (12) to 720 mg (9) for diltiazem, and similar variations for other calcium channel blockers.

Review of TESS and California Poison Control System Data

During the 18-year period 1985–2002, TESS received reports of 235 deaths involving CCB poisoning. There were 15 cases in which death occurred as a result of acute unintentional ingestion, therapeutic error, or misuse; and the estimated dose of CCB was recorded on the abstract. These cases are summarized in Table 3. The lowest reported fatal dose of immediate-release diltiazem in an adult was 360 mg and for modified-release diltiazem it was 240–360 mg. An 11-month-old child died after ingesting 40 mg of immediate-release nifedipine. A 7-day-old child died after receiving 25 mg verapamil. Doses between 360 and 540 mg were associated with death in three adults. An 84-year-old woman with hypertension treated with lisinopril and verapamil died after

TABLE 3
TESS CCB fatalities 1985–2002*

Drug	Age and sex	Amount ingested	Summary
Diltiazem (IR)	38 yr F	360 mg	Patient with pulmonary hypertension given 60 mg/hr orally for 6 hr.
Diltiazem (IR)	45 yr F	720 mg	Patient with chronic pulmonary hypertension in a study got 60 mg orally every hour for 12 hr.
Diltiazem (IR)	65 yr M	2160 mg	CCB given instead of antibiotic.
Diltiazem (SR)	76 yr F	240–360 mg	Patient with chronic renal failure and diabetes started on CCB for hypertension. Took 120 mg BID for 2–3 doses, arrived with HR 30/min, BP 70/p.
Diltiazem (SR)	80 yr F	240 QID for 72 hrs	Therapeutic error over 72 hrs.
Diltiazem (SR)	86 yr F	960–1440 mg	Mistook for vitamins, one dose.
Nifedipine (IR)	11 mo M	40 mg	Cardiopulmonary arrest in ER.
Nifedipine (SR)	3 yr M	120 mg	Unintentionally given 2 SR nifedipine 60 mg instead of acetaminophen.
Verapamil (SR)	7 day M	25 mg	Dose administration accident. Cardiorespiratory arrest at 8 hr.
Verapamil (SR)	64 yr F	360–540 mg	Chronic end-stage renal failure on dialysis, took 2–3 extra verapamil 180 SR.
Verapamil (SR)	28 yr M	480 mg	Took one extra 240 mg for migraines, presented with chest pain, heart block, deteriorated to ARDS and acute renal failure. Tox (+) for cocaine.
Verapamil (SR)	84 yr F	480 mg	Patient with congestive heart failure and hypertension also on lisinopril unintentionally took a second 240 dose 1 hr after first dose.
Verapamil (SR)	56 yr M	2400 mg	Taken over 3–4 hr for ''chest pain''
Verapamil (SR)	58 yr F	2400 mg	Took 10×240 mg over 12 hr (misuse)

*Unintentional or therapeutic error or misuse; oral; acute; and dose recorded.

TABLE 4
2000–2003 CPCS CCB data coded as major effect or death

Drug	Age and sex	Amount ingested	Summary
Diltiazem (CR)	80 yr F	240 mg	Hospice patient chewed instead of swallowed CR—died
Diltiazem (SR)	75 yr F	1240 mg	Took 5 capsules by mistake instead of potassium. Bradycardia but no hypotension.
Verapamil	58 yr F	1080 mg	Unintentionally took 6×180 mg thinking they were vitamins. Hypotension, bradycardia
Verapamil	69 yr F	640 mg	Therapeutic error, not described. Hypotension, bradycardia, heart block
Verapamil (SR)	48 yr F	1920 mg	Took for the first time, 2 tablets TID, found next AM after 8 tablets used, with hypotension and bradycardia
Verapamil (SR)	58 yr M	360 mg	Took usual 240 mg dose for migraine then took additional 120 mg, came to ER a few hr later with pallor, dizzy, BP 92/60, HR 41/min with junctional rhythm.
Verapamil (SR)	68 yr M	1000 mg	Took 1000 mg during the course of the day, presented with HR 40/min (also had anterolateral MI).
Verapamil (SR)	69 yr F	480 mg	Took 2×240 mg instead of 1.5 tablets. Hypotension, bradycardia
Verapamil (SR)	85 yr F	480 mg	Might have taken a second dose of 240 mg. Hypotensive and bradycardic

she accidentally took a second dose of her 240-mg modified-release verapamil 1 hour after her usual dose.

Data recorded in the California Poison Control System database for 2000–2003 were reviewed (obtained through an internal study by the lead author), and cases coded ''Major Effect'' or ''Death'' are summarized in Table 4. In addition, all pediatric exposures to any calcium channel blocker reported to the CPCS during 2002 and 2003 were reviewed individually. There were no pediatric cases coded as ''Major Effect'' or ''Death.'' The only fatal case involved diltiazem 240 mg (controlled-release) that was chewed instead of swallowed (this case occurred in 2003 and is not the same as case 5 in Table 3). Three adults had significant cardiovascular effects after ingesting only mildly supratherapeutic doses of verapamil. A 58-year-old man took his usual dose (240 mg SR) for a migraine headache, then took an additional 120 mg and presented to an emergency department with dizziness, junctional bradycardia, and hypotension. A 69-year-old woman took two 240-mg verapamil SR tablets instead of 1.5 tablets and developed hypotension and bradycardia.

Benson et al. (20) analyzed 2002–2003 TESS data in children under 6 years of age involving unintentional ingestions of amlodipine (as a single agent ingestion) in which estimated doses were recorded. Of 679 cases, estimated amounts ingested ranged from 0.25 to 200 mg. Clinically significant symptoms were recorded for 3.5% of 346 children who ingested between 2.5 and 5 mg, 3.8% of 183 children who ingested between 5 and 10 mg, and 11% of 73 children who were thought to have ingested more than 10 mg. No children ingesting less than 2.5 mg had significant symptoms.

REVIEW OF THE MEDICAL LITERATURE

Dose of CCBs Resulting in Toxicity

Acute Supratherapeutic Ingestion in Patients 6 Years of Age and Older

No level 1, 2, or 3 studies were found evaluating the threshold dose for the development of toxicity in adults or children 6 years of age and older with acute CCB exposures.

A large number of case reports and case series with dose-toxicity information were found (level 4). The cases in which the exposure dose was known (or estimated) and reported are summarized in Table 5. In the vast majority of cases it was impossible to gauge the accuracy of the estimated dose. Cases in which the exposure dose was either not reported or unknown are not included in the summary but can be found in the full evidence table. Cases in which β-blockers were co-ingested are also not included in Table 5 because it was felt that the similarity and synergism between the clinical effects of β-blockers and CCBs would make it difficult to determine the contribution of each drug. Cases of CCB and β-blocker co-intoxication are included in the full evidence table.

Acute Supratherapeutic Ingestion in Patients Less Than 6 Years of Age

No level 1, 2, or 3 studies were found evaluating the threshold dose for the development of toxicity in children less than 6 years of age with acute CCB exposures.

A few case reports and two multi-year retrospective chart reviews (level 4) were identified with dose-toxicity information. The results are summarized in Table 6. Combined

TABLE 5
Acute supratherapeutic CCB ingestion in patients 6 years of age and older

Drug	Dose (mg)	Coingestions*	Effect severity	Onset†	Laboratory confirmation?	Reference
Amlodipine	30	None	Severe	NR	N	(21)
	50–100	Alcohol	Mod	NR	Y	(22)
	70	Benzodiazepine	Death	<2.5 hr	Y	(23)
	140 (2 mg/kg)	Mefenamic acid	Death	2 hr	Y	(24)
	300	Nitrendipine (600 mg), ACE inhibitor	Severe	<4.5 hr	N	(25)
Diltiazem	145 mg IV	None	Severe	20 min from infusion onset	N	(26)
		360=smallest toxic dose; 600=smallest dose resulting in CV				(27)
		420=smallest toxic dose in this 1-yr prospective series				(2)
	630	None	Mod	<several hr	N	(28)
		720=smallest toxic dose in this 2-yr chart review				(29)
	900	Alcohol	Severe	3.5 hr	Y	(30)
	1200	Dipyridamole	Severe	3.5 hr	N	(31)
	1200	Alcohol	Moderate	<1 hr	N	(32)
	1200	NT	Mild	NT	NT	(33)
	~1500	NR	Severe	NR	Y	(34)
	1620	None	Death	NR	Y	(35)
	1800	None	Mod	NR	Y	(36)
	1800	Tilidine	Severe	<4 hr	N	(37)
	2460	NT	NT	NT	NT	(38)
	3000	Enalapril	Mod	NR	N	(39)
	4200	Sulindac	Severe	<2 hr	Y	(40)
	4200 (68 mg/kg)	Benzodiazepine, alcohol	Severe	<2 hr	Y	(41)
	4800 (67 mg/kg)	None	Severe	<2 hr	Y	(42)
	5880	Alcohol	Severe	NR	Y	(43)
	6000	Spironolactone, clorazepate	Mod	<5 hr	N	(32)
	7200	Benzodiazepine	Severe	<2 hr	N	
	9000	None	Severe	<2.5 hr	Y	(44)
	10,800	None	Severe	<2 hr	Y	(45)
SR Diltiazem	700	None	Mild	Nadir of CV function was at 14 hr	Y	(46)
	1020	None	Severe	<8 hr	Y	(47)
	1800–3600	Isosorbide, alcohol	Severe	Minimal symptoms at 6 hr; deteriorated at 24 hr	N	(48)
	2400	Ibuprofen	Severe	<12 hr	N	(49)
	7200	None	Severe	<3.5 hr	Y	(50)
	14,940 (150 mg/kg)	None	Severe	<4 hr	Y	(51)
Gallopamil	7000	None	Severe	<2 hr	Y	(52)

Nicardipine	260=smallest toxic dose causing non-CV effects in patients >12 y.o.; 600=smallest toxic dose causing significant CV effects; 1800=smallest lethal dose					(53)
Nifedipine	50	None	Mild	NR	N	(39)
	50=smallest toxic dose in this 1-yr prospective series					(2)
	100–400=smallest toxic dose in patients >12 y.o.					(53)
	200=smallest toxic dose in this 2-yr chart review					(29)
	200–250	Alcohol	Severe	<1 hr	Y	(54)
	280	None	Mod	<4 hr	Y	(55)
	300	Alcohol	Severe	NR	N	(56)
	900 (11 mg/kg)	Furosemide	Mod	<1.5 hr	N	(57)
	900	Possible tricyclic antidepressant	Severe	NR	N	(58)
	4200	None	Severe	<1 hr	Y	(59)
SR Nifedipine	<180 mg	Clonidine	Mod	CNS <2 hr; hypotension at 4 hr	N	(60)
	200–400=smallest toxic dose in patients >12 y.o. in this French series					(53)
	350	None	Severe	<6 hr	N	(61)
	600	Acetaminophen	Severe	~4.5 hr	Y	(62)
	2400–3000	Alcohol	Severe	NR	Y	(63)
	<2700	None	Severe	CNS on admission; BP dropped at 6 hr	N	(64)
	3600	Crack cocaine	Severe	<3 hr	Y	(65)
Nitrendipine	600	Amlodipine (300 mg), ACE inhibitor	Severe	<4.5 hr	N	(25)
Verapamil	160=smallest toxic dose in this 4-yr retrospective review					(39)
	720=smallest toxic dose from 1-yr prospective series					(2)
	800	Alcohol	Severe	NR	N	(65)
	≥1200	None	Severe	<18 hr	Y	(66)
	1200=smallest toxic dose in this series of 6 patients					(67)
	1600	None	Severe	NR	N	(68)
	1800	Ibuprofen, Fioricet	Severe	<5 hr	Y	(69)
	2000	None	Mod	<2 hr	N	(70)
	2160	Alcohol	Severe	<3 hr	N	(71)
	2400	None	Severe	<5 hr	N	(72)
	2400 (32 mg/kg)	Alcohol	Severe	<2 hr	Y	(73)
	2400 (30 mg/kg)	Alcohol	Severe	<2.5 hr	Y	(74)
	2400	NT	Severe	NT	NT	(75)
	2400	None	Severe	<3 hr	Y	(76)
	2400	None	Severe	<2.5 hr	N	(77)
	2400	None	Severe	<2 hr	N	(78)
	3000	None	Severe	<2.5–3 hr	Y	(79)
	3200	None	Severe	NR	Y	(80)

TABLE 5
Continued

Drug	Dose (mg)	Coingestions*	Effect severity	Onset†	Laboratory confirmation?	Reference
Verapamil	3200	None	Severe	<3 hr	N	(81)
	3200	None	Vomiting and ulcers	Several hr	N	(82)
	3200	Alcohol	Severe	<2 hr	Y	(83)
	3200	Amoxicillin, dipyridamole, trimethoprimsulfamethoxazole	Severe	NR	Y	(84)
	3200–4800	None	Death	<1 hr	Y	(85)
	3600	None	Severe	<1.5 hr	Y	(86)
	4000 (89 mg/kg)	None	Severe	<2 hr	Urine qualitative positive	(87)
	4000	None	Severe	<1–2 hr	Y	(83)
	4160	None	Death	1.5 hr	Y	(88)
	4800	Alcohol	Death	<1 hr	Y	(85)
	4800	None	Severe	<1 hr	Y	(89)
	4800	Alcohol, allopurinol	Severe	<1 hr	N	(90)
	5600	Aspirin, codeine, potassium	Severe	<1.25 hr	N	(91)
	6400	None	Severe	<7 hr	N	(66)
	6400	Alcohol	Severe	<1 hr	N	(92)
	6400–7200	Benzodiazepine	Severe	<1–2 hr	N	(66)
	6800	None	Severe	<2.5 hr	N	(93)
	8000 (83 mg/kg)	None	Severe	~45 min	Y	(94)
	8000	Benzodiazepine	Severe	~2 hr	N	(95)
	8000 (135 mg/kg)	None	Severe	<5 hr	N	(96)
	9600	None	Death	2–3 hr	N	(97)
	9600 (171 mg/kg)	None	Severe	<2–3 hr	Y	(74)
	16,000 (200 mg/kg)	None	Severe	<50 min	Y	(94)
	24,000	None	Severe	<2.5 hr	N	(98)
SR Verapamil	720	None	Severe	<1 hr	Blood qualitative positive	(99)
		960=smallest toxic adult dose in 2-yr review				(29)
	1200–2400 (24–48 mg/kg)	Smoked phencyclidine piperdine 24 hr before ingestion	Severe	12 hr	Urine qualitative positive	(100)
	30 mg/kg over 6 hr	None	Severe	30 min after last dose	Y	(101)

2400	NT	Death	NT	NT	(102)
2640	None	Mild	7–8 hr	N	(103)
2880	BZD	Severe	NR	Y	(104)
3500	None	Severe	NR	Y	(39)
3500	Acetaminophen, pseudoephedrine, tetracycline	Severe	<2 hr=CNS 16 hr=hypotension	Y	(105)
53 mg/kg	None	Severe	NR	N	(85)
55 mg/kg	Hydrochlorothiazide	Severe	<3 hr	Y	(101)
4800	None	Severe	<6 hr	N	(106)
4800	None	Mild	20 hr	Y	(105)
71 mg/kg	None	Severe	NR	Y	(101)
6000	None	Severe	~8–9 hr	N	(107)
7200	None	Severe	<3 hr	Y	(108)
7200	None	Severe	Had ECG findings on presentation; BP dropped 6 hr later	N	(109)
7200	None	Severe	NR	N	(110)
7200	Alcohol	Mild	<1 hr	Y	(111)
7200	Acetaminophen	Severe	<7 hr	N	(107)
7200	Sertraline, benzodiazepine, diphenhydramine	Severe	NR	Y	(112)
7200–9600	None	Death	<8 hr	Y	(113)
7200–9600	None	Severe	<9 hr	Y	(114)
8160	Enalapril, indomethacin	Severe	<12 hr	N	(102)
8640	None	Severe	<5 hr	N	(85)
12,000	None	Death	Several hr	N	(115)
15,000–20,000	None	Severe	<24 hr	Y	(105)
16,800	NT	Severe	NT	NT	(116)
18,000	None	Mild	2 hr	N	(109)
24,000	Aspirin	Severe	<10 hr	N	(117)

NR=not reported.

NT=not fully translated.

*Cases with β-blocker coingestions are not included in this table (see full evidence for details).

†Maximal time of onset (in some cases, effects might have begun earlier); ''<'' means that symptoms were present on admission but might have begun earlier.

TABLE 6
Acute supratherapeutic CCB ingestion in patients less than 6 years of age

Agent	Dose (mg)	Coingestions	Effect severity	Onset*	Laboratory confirmation	Reference
Amlodipine	0.4 mg/kg=lowest toxic dose in this 6-yr chart review				(3)	
Diltiazem	180	NT	''Hypotension''	12 hr	NT	(28)
Isradipine	2.5	None	Mod	<30 min	N	(118)
Nicardipine	1.25 mg/kg=lowest toxic dose in this 6-yr chart review				(3)	
Nifedipine	20 (4 mg/kg)	None	Severe	20 min	N	(119)
	200=lowest toxic dose in children (age not specified) in this 2-yr review				(29)	
	800 (70 mg/kg)	None	Severe	<20–30 min	N	(120)
	2.8 mg/kg=lowest toxic dose in this 6-yr chart review				(3)	
SR Nifedipine	10	None	Death	NR	Y	(121)
	30	None	Min	45 min	N	(122)
	<200	None	Death	NR	Y	(121)
	2.7 mg/kg=lowest toxic dose in this 6-yr chart review				(3)	
Verapamil	400	None	Severe	45 min	N	(123)
SR Verapamil	1440 (106 mg/kg)	None	Death	3 hr	Y	(118)
	12 mg/kg=lowest toxic dose in this 6-yr chart review				(3)	

NR=not reported.

*Maximal time of onset (in some cases, effects might have begun earlier); ''<'' means that symptoms were present on admission but might have begun earlier.

β-blocker/CCB exposures were not summarized nor were cases in which the dose was not known or reported.

Chronic Supratherapeutic Ingestion in Patients 6 Years of Age and Older

No level 1, 2, or 3 studies were found regarding chronic (over 8 or more hours) supratherapeutic CCB ingestions by older children and in adults. Several level 4 reports were reviewed with chronic dose-toxicity information, however. These are summarized in Table 7.

Chronic Supratherapeutic Ingestion in Patients Less Than 6 Years of Age

No data were found regarding chronic (over 8 or more hours) supratherapeutic CCB ingestions in children less than 6 years of age.

Time to Onset of Effects After Overdose

The time to onset of effects was recorded for each article because it was felt that this information might be useful in creating the guideline. Specifically, how long after ingestion an asymptomatic patient might be judged unlikely to develop toxicity and, therefore, safe to observe at home; the recommended mode of prehospital transportation; and when to schedule poison control center follow-up calls.

Clinical effects were defined as any sign, symptom, or laboratory/electrocardiographic finding consistent with CCB toxicity. It is important to note that the actual onset of effects likely occurred earlier than reported in many cases because the patients presented to HCFs well into the course of their poisonings. Therefore, the times recorded in the summary tables are estimates of the maximum possible delay to onset of symptoms. In addition, the tables refer only to the time of first

TABLE 7
Chronic supratherapeutic CCB ingestion in patients 6 years of age and older

Agent	Dose	Coingestions	Effect severity	Onset	Laboratory confirmation?	Reference
Amlodipine	100 mg over 24 hr	None	Severe	NA	Y	(124)
Verapamil	480 mg daily	Cimetidine, alcohol	Mod	NA	Y	(119)
	200 mg three times daily for 3 days	NR	Severe	NR	Y	(120)
SR Verapamil	3600 mg over 14 hr	None	Severe	NR	N	(121)

effect onset and do not give information on the time-to-peak effects or the total duration of effects. Time-to-peak effects varied and were difficult to discern and summarize in a useful format based solely on the level 4 reports available. However, it was noted that in several instances of overdose with modified-release (SR) products, patients deteriorated clinically many hours into the course of their poisoning (46,48,63,64, 101,103,105,107,109). In many such cases, there were mild clinical or electrocardiographic signs of toxicity early on, but in others these clues were either not reported or not clearly evident.

Acute Supratherapeutic Ingestion in Patients 6 Years of Age and Older

There were no level 1, 2, or 3 studies investigating the time to onset of clinical effects after CCB overdose in adults. A number of individual case reports and case series (level 4) listed information on time to onset of clinical effects. Time-to-effect onset is shown in Table 8 when it was known (or estimated) by the authors of the report. Cases in which β-blockers and calcium channel blockers were co-ingested are not included because it was felt that, given the similarity and synergism between the clinical effects of β-blockers and CCBs, it would be difficult to derive meaningful data when the two were combined.

Acute Supratherapeutic Ingestion in Patients Less Than 6 Years of Age

There were no level 1, 2, or 3 studies investigating the time to onset of clinical effects after CCB overdose in children less than 6 years of age. Several level 4 reports were reviewed that contained information on onset of effects. Their data are tabulated in Table 9.

Potential Out-of-Hospital Treatments

There were no studies that looked specifically at out-of-hospital decontamination measures. The articles were therefore reviewed for information regarding those decontamination measures evaluated in-hospital that could reasonably be expected to be instituted in an out-of-hospital setting. These were limited to activated charcoal administration and induction of emesis with syrup of ipecac.

Activated Charcoal

One level 1b article was found with information on the efficacy of activated charcoal after CCB ingestion. It was a randomized, controlled trial in healthy volunteers and found that 25 g activated charcoal given immediately after the ingestion of 10 mg amlodipine reduced amlodipine absorption by 99% compared to untreated controls. The same dose of activated charcoal given 2 hours later reduced absorption by about half and, when given 6 hours after ingestion, there was no significant reduction in absorption (131).

The rest of the data on activated charcoal are presented as level 4 data—a large number of case reports and series in which it was used (see full evidence table). It was not possible to detect any benefit or lack of benefit from charcoal administration in such cases. However, no significant detrimental effects were reported with its use.

Emesis Induction

No level 1, 2, or 3 studies were found regarding the utility of emesis induction for patients with CCB overdoses.

Several level 4 articles reported the use of ipecac syrup or other forms of induced emesis in patients with CCB overdose, but in most cases there were either no tablet fragments returned or the results of emesis induction were not reported (2,30,36,39,54,88,89,122). Only one level 4 report was found in which the authors reported the use of ipecac syrup to be successful in retrieving tablet fragments (95). No reports of adverse outcomes associated specifically with the use of emesis after calcium channel blocker ingestion were found.

Other Treatments

There were no level 1, 2, or 3 studies that addressed the efficacy of any other treatments for CCB overdose. The data were limited to case reports and a few case series (level 4). There were very few papers that specified a treatment as being performed out-of-hospital or in-hospital. Hence, the articles were reviewed for any interventions that might potentially be instituted in an out-of-hospital setting (i.e., atropine, dobutamine, dopamine, epinephrine, calcium, glucagon, insulin, pacing), and the resultant information is compiled in Table 10, which lists the various interventions reported for reversing the major cardiovascular manifestations (e.g., hypotension, bradycardia, conduction abnormalities) of CCB toxicity. Other treatments that were mentioned in the articles as being potentially beneficial but that would not likely be available to, or practicable for, U.S. out-of-hospital personnel are not listed in the table. These include dexamethasone (81), methylscopolamine (91), metaproterenol (66,139), 4-aminopyridine (134), amrinone (96,138), angiotensin II (25), theophylline (139), enoxamine (73), and vasopressin (112). General supportive care measures (e.g., airway management measures, fluids, anticonvulsants, bicarbonate) might have been beneficial in some cases but were difficult to evaluate and are not specifically addressed in the table or this summary. Treatments aimed at treating the non-cardiovascular complications of CCB overdose (e.g., seizures, hyperglycemia, acidosis, renal failure) are also not addressed here. However, all interventions used, their effect, and the context in which they were used are described in the full evidence table.

For each reported intervention, an attempt was made to assess its efficacy based on information about the patient's

TABLE 8
Onset of effects in acute supratherapeutic CCB ingestion in patients 6 years of age and older

Drug	Onset	Coingestants	Laboratory confirmation?	Reference
Amlodipine	2 hr	Mefenamic acid	Y	(24)
	<2.5 hr	BZD	Y	(23)
	<4.5 hr	Nitrendipine, ACE inhibitor	N	(25)
Diltiazem	<2 hr	Benzodiazepine, alcohol	Y	(41)
	<2 hr	None	Y	(42)
	<2 hr	None	Y	(45)
	<2 hr	Sulindac	Y	(40)
	<2.5 hr	None	Y	(44)
	3.5 hr	Alcohol	Y	(30)
	3.5 hr	Dipyridamole	N	(31)
	<Several hr	None	N	(28)
	1.5–15 hr in a retrospective review (from translated abstract)			(28)
SR Diltiazem	<3.5 hr	None	Y	(50)
	<4 hr	None	Y	(51)
	<6–7 hr	None	N	(125)
	6 hr—minimal symptoms present 24 hr—severe deterioration	Isosorbide, alcohol	N	(48)
	<8 hr	None	Y	(47)
	<12 hr	Ibuprofen	N	(49)
	14 hr	None	Y	(46)
Gallopamil	<2 hr	None	Y	(52)
Nifedipine	<1 hr	None	Y	(59)
	<1 hr	Alcohol	Y	(54)
	<1.5 hr	Furosemide	N	(57)
	<4 hr	None	Y	(55)
SR Nifedipine	<2 hr—CNS effects 4 hr—BP drop	Clonidine	N	(60)
	<3 hr	Crack cocaine	Y	(65)
	~4.5 hr	Acetaminophen	Y	(43)
	Several hr	None	N	(64)
	<6 hr	None	N	(25)
Nitrendipine	<4.5 hr	Amlodipine, angiotensin converting enzyme inhibitor	N	(25)
Verapamil	~45 min	None	Y	(94)
	<50 min	None	Y	(94)
	<1 hr	Alcohol	N	(92)
	<1 hr	None	Y	(89)
	<1 hr	Allopurinol, alcohol	N	(90)
	<1 hr	Alcohol	Y	(85)
	<1–2 hr	None	Y	(83)
	<1–2 hr	None	Y	(126)
	<1–2 hr	Benzodiazepine	N	(66)
	1.25 hr	Codeine, aspirin, potassium	N	(91)
	<1.5 hr	None	Y	(86)
	<1.5 hr	None	Y	(88)

	<2 hr	Alcohol	Y	(83)
	<2 hr	Alcohol	Y	(74)
	<2 hr	None	N	(71)
	<2 hr	None	N	(78)
	<2 hr	None	Urine qualitative +	(87)
	~2 hr	Benzodiazepine	N	(95)
	2–3 hr	None	N	(97)
	<2–3 hr	None	Y	(74)
	<2.5 hr	None	N	(98)
	<2.5 hr	None	N	(77)
	<2.5 hr	None	N	(93)
	<2.5 hr	Alcohol	Y	(75)
	<2.5–3 hr	None	Y	(79)
	<3 hr	None	N	(127)
	<3 hr	None	Y	(76)
	<3 hr	None	N	(81)
	<5 hr	None	N	(96)
	<5 hr	None	N	(73)
	<5 hr	Ibuprofen, Fiorcet	Y	(70)
	Several hrs	None	N	(82)
	<Some hrs	Ethanol	N	(66)
	<7 hr	None	N	(66)
	<18 hr	None	Y	(67)
SR Verapamil	<1 hr	Alcohol	Y	(111)
	<1 hr	None	Urine qualitative +	(99)
	<2 hr CNS—effects 16 hr—hypotension	Acetaminophen, pseudoephedrine, tetracycline	Y	(105)
	2 hr	None	N	(109)
	<3 hr	None	Y	(108)
	<3 hr	Hydrochlorothiazide	Y	(101)
	<5 hr	None	N	(85)
	<6 hr	None	N	(106)
	Several hr	None	N	(115)
	<7 hr	Acetaminopen	N	(107)
	7–8 hr	None	N	(103)
	<8 hr	None	Y	(113)
	~8–9	None	N	(107)
	<9 hr	None	Y	(114)
	<10 hr	Aspirin	N	(117)
	<12 hr	Enalapril, indomethacin	N	(103)
	12 hr	Smoked phencyclidine piperidine cigarettes 24 hr prior	Urine qualitative +	(100)
	20 hr	None	Y	(105)
	<24 hr	None	Y	(105)
	<24–36	None	Y	(128)
All IR CCBs	All with CCB toxicity from IR CCBs developed symptoms within 6 hr			(2)
All SR CCBs	10% of patients who developed toxicity did so between 6–12 hr			(2)

TABLE 9
Onset of effects in acute supratherapeutic CCB ingestion in patients less than 6 years of age

Drug	Onset	Coingestants	Laboratory confirmation?	Reference
Diltiazem	12 hr	NT	NT	(27)
Isradipine	<30 min	None	N	(118)
Nifedipine	<20–30 min	None	N	(120)
	20 min	None	N	(119)
SR Nifedipine	45 min	None	N	(122)
	16 hr	None	N	(129)
Verapamil	45 min	None	N	(123)
SR Verapamil	3 hr	None	Y	(130)
All IR CCBs	0.5–3 hr onset in a 6-yr chart review of IR CCB ingestions			(3)
	All with CCB toxicity from IR CCBs developed symptoms within 6 hr			(2)
All SR CCBs	1–14 hr onset of symptoms in a 6-yr chart review of SR CCB ingestions			(3)
	10% of patients who developed toxicity did so between 6–12 hr			(2)

NT = not fully translated.

response, the temporal relationship of any effects, the consequences of either withdrawing or repeating the intervention, any evidence of a dose-response relationship, and the overall physiologic plausibility of the intervention. Clinical responses were grouped into one of four categories: effective (++), partially effective (+), not effective (0), or detrimental (−). Effective interventions were those that fully reversed all of the major cardiovascular manifestations of CCB toxicity. Partially effective interventions only partly reversed the negative cardiovascular manifestations of toxicity, fully reversed only one aspect of cardiovascular toxicity (e.g., heart rate or blood pressure), or only reversed cardiovascular toxicity in combination with other agents or interventions. Interventions in the not effective category had no appreciable clinical effect. Included in this group are treatments after which the patient continued to deteriorate clinically consistent with the course of CCB intoxication. Interventions were deemed detrimental if they caused a clinical deterioration that could not otherwise be attributed to the usual course of CCB toxicity alone. If the response to an intervention was not reported in an article, the article was not included in the summary table. The same intervention in the same patient can appear in more than one category of efficacy, if, for example, it was unsuccessful at one dose or time but successful at another. In addition, just because a therapy appears in the effective category does not mean it was the only therapy given throughout the patient's course. It indicates that, to the best that could be ascertained, it was the only therapy associated with the patient's clinical recovery at that time. Other measures, particularly supportive measures, could either have been ongoing or were not specifically listed by the authors.

In reviewing the evidence, it became clear that no intervention was reliably effective alone, although insulin/dextrose shows promise (145) and glucagon animal data are encouraging (146). In the majority of cases, combinations of agents were necessary to provide hemodynamic support. Some agents seemed to work for some patients but not others. Of note, there were several reports of patients surviving CCB overdoses with supportive measures alone, both adults (22,33,71,147,148) and children (118,129). In many of these cases, however, the underlying toxicity appears to have been comparatively mild.

Limitations of the Published Data

The case reports and case series varied widely in the extent of clinical detail presented, and the cases varied widely in the severity and clinical effects of poisoning; the timing, combination, dose, and routes of various treatments used; and in a number of other patient- or context-specific factors.

Data for the amount ingested are often inaccurate or incomplete. The history is frequently obtained from an intoxicated patient or an emotionally stressed or elderly caregiver. Parents might underestimate or overestimate the ingested dose because of denial or anxiety. Poison center staff often use the worst-case scenario to estimate an ingested dose in order to provide a wide margin of safety. In most case reports and case series the history of exposure was not independently verified or confirmed by laboratory testing. Poor correlation between reported estimated doses and subsequent concentrations or toxicity has been documented for children with unintentional ingestions of other drugs, such as acetaminophen, for which quantitative laboratory confirmation is routine (149–151).

In most of the case reports and case series reviewed, the exact time of ingestion was not reported or was not known, or

TABLE 10
Treatments used in reported cases of CCB poisoning and their relative efficacy

	Relative efficacy* and references			
Treatment	−	0	+	++
Atropine		(31, 34, 41, 42, 58,67,75,76, 88, 90, 93, 98, 101,104,105, 109, 113, 115, 117, 121†, 125–127, 130†, 132–135)	(2) (29% with increased HR), 23–24†, 30, 39, †, 40, 51, 60, 78, 85†, 92, 110, 114, 120, 121†, 125, 132, 136–140	36
Calcium		(21, 23, 25, 30, 31, 36, 40–42, 49–52, 56–59, 61–64, 70, 73, 75–77, 84, 88, 90, 93, 94, 96–99, 101, 104, 107, 109, 113, 115, 121†, 125–127, 130†, 133, 135)	(2) (64–80% responded with increased HR, conduction, or BP), (23, 24, 26, 29, 39, 124‡), (7/11 responded), (40, 44, 45, 48–50, 55, 57–60, 66, 67, 69, 75, 78, 81, 84, 85‡, 87, 89, 94, 101, 103, 106–108, 110, 112–115, 117, 120,121‡, 130†, 134, 135,137–141)	(43, 54, 65, 79, 80, 95, 111, 132, 142, 143)
Dobutamine		(21, 47, 50, 52, 67, 88, 94, 113, 125, 135)	(44, 48, 90, 101, 104–106, 112, 124, 126, 139, 144)	
Dopamine		(21, 25, 31, 40–42, 47, 50–52, 58, 61, 67, 77, 88, 94, 96, 99, 101, 109, 112,113, 115, 119†, 121†, 130†, 125,126, 128, 133)	(2, 23, 26, 30, 34, 40, 41, 43–45, 49, 58–60, 63, 66, 75, 76, 84, 85‡, 87, 89, 93, 94, 100,104–108, 110, 112–115, 117, 120, 123†, 124, 135, 137, 139–141, 144)	56, 66, 70, 107
Epinephrine		(23, 34, 50, 51, 88, 94, 99, 105, 109, 113, 115, 119†, 121†, 130†, 127, 143)	(23,24) (temporary effect), (31, 41, 48, 49, 51, 52, 75,98, 105, 115, 121, 121†,‡, 135, 139,140)	(42, 77, 99) (temp)
Glucagon		(21, 42, 48, 50–51, 67, 84, 94, 99, 101, 109, 119†, 121†, 125, 127)	(2, 23, 60, 85‡, 94, 101, 106, 108, 117, 124, 138, 139	(26, 57, 64, 104)
Insulin+/−dextrose			(101)	(21, 101, 119)†
Isoproterenol		(34, 42, 76, 84, 96, 97, 130†, 128, 135	(2) (2 of 3 had increased HR), (31, 45, 66, 67, 85‡, 87, 90, 96, 98, 106, 108, 113–115, 126, 134, 137, 140)	(136)
Pacing	(TV) 51	(TV/TC) 94	(TV/TC) (42, 88, 125)	(TV) (28, 85, 104)‡
TV=transvenous		(TV) 74, 75, 105, 130†, 133, 139	(TV) (2) (in this series 2/4 patients had capture), (31, 34, 48, 52, 62, 66, 76, 83, 90, 96–98, 106,108,109,113–115, 126, 140, 143)	
TC=transcutaneous		(TC) 121†	(TC) (117)	

*++ = effective at restoring CV toxicity to normal; + = partially effective (e.g., improved CV function but did not completely restore it to normal, only restored one parameter to normal, or restored CV status to normal only in conjunction with other treatments); 0=not effective (e.g., no temporal improvement was noted); −=detrimental (e.g., caused potentially significant deterioration that would not have been expected based on the course of β-blocker poisoning alone)

† Pediatric cases.

‡ Temporary effect.

the time of onset of toxicity can only be estimated as occurring within a range of hours after the suspected ingestion.

CONCLUSIONS

Key Decision Points for Triage

The expert consensus panel chose to emphasize the importance of information that would be needed in order to make a sound triage decision for the patient with a calcium channel blocker ingestion. These variables include the patient's intent, the time of the ingestion, the patient's symptoms or underlying medical condition, the dose and formulation of the specific product ingested, and any co-ingested drugs. The panel agreed that in each case the judgment of the specialist in poison information, with the assistance of their medical consultant or pre-approved policies, might override any specific recommendation.

Patient Intent

The expert consensus panel concluded that all patients with a suicidal intent or in which a malicious intent was suspected (e.g., child abuse or neglect) should be transported expeditiously by EMS to an emergency department. Patients without these characteristics are candidates for consideration of out-of-hospital management of their ingestion.

Time Since Ingestion

The panel concluded that asymptomatic patients are unlikely to develop symptoms if the interval between the ingestion and the call is greater than 8 hours for immediate-release products, 12–24 hours for most modified-release products, and 24 hours for modified-release verapamil.

Patient's Symptoms or Underlying Medical Condition

The expert consensus panel concluded that referral to an emergency department should be considered for any patient who is experiencing symptoms that might be reasonably related to the CCB (e.g., dizziness, syncope, generalized weakness, shortness of breath), with severe underlying cardiovascular disease (e.g., end-stage cardiomyopathy), or on multiple cardiovascular medicines that could have additive cardiodepressant effects with the dose of CCB taken. The

TABLE 11
Maximum single dose, lowest reported toxic dose, and longest reported delay in onset of toxicity for CCBs

Drug	Maximum recommended single therapeutic dose	Lowest reported toxic oral dose	Longest reported delay to onset of toxicity
Amlodipine	Adult: 10 mg	Adult: 30 mg	2–4.5 hr
	Child: 0.3 mg/kg	Child: 0.4 mg/kg	N/A
Bepridil	Adult: 300 mg	N/A	N/A
	Child: N/A	N/A	N/A
Diltiazem	Adult: 120 mg (IR)	Adult: 360 mg (IR)	3.5–5 hr (IR)
	360 mg (SR)	700 mg (SR)	<12 hr (SR)*
	540 mg (XR, XT)		
	Child: 1 mg/kg	Child: 180 mg (unknown product)	12 hr
Felodipine	Adult: 10 mg	N/A	N/A
	Child: 0.3 mg/kg	N/A	N/A
Isradipine	Adult: 20 mg	N/A	N/A
	Child: 0.1 mg/kg	Child: 2.5 mg/kg resulted in moderate toxicity	<30 min
Nicardipine	Adult: 40 mg (IR)	Adult: 260 mg (non-CV toxicity)	N/A
	60 mg (SR)	600 mg (significant CV toxicity)	
	Child: 20 mg	Child: 1.25 mg/kg	N/A
Nifedipine	Adult: 30 mg (IR)	Adult: 50 mg (IR)	<4 hr (IR)*
	120 mg (SR)	200 mg (SR)	<6 hr (SR)*
	Child: 1 mg/kg	Child: 2.8 mg/kg	20–30 min
		4 mg/kg (severe)	
		10 mg (SR) [death]	
Nimodipine	Adult: 60 mg	N/A	N/A
	Child: N/A	N/A	N/A
Nisoldipine	Adult: 30 mg	N/A	N/A
	Child: N/A	N/A	N/A
Verapamil	Adult: 120 mg (IR)	Adult: 160 mg (IR)	<18 hr* (IR)
	480 mg (SR)	720 mg (SR)	<24 hr (SR)
	Child: 2.5 mg/kg	Child: 12 mg/kg	45 min (IR)
			3 hr (SR)

*The use of the ''<'' symbol indicates that the estimated time of the onset of symptoms is based on the reported time of arrival of the patient to medical care, and the actual delay to onset of symptoms is not known with certainty.

importance of each of these variables can be difficult to judge in a telephone conversation so a low threshold for emergency department evaluation is considered prudent. Symptomatic patients should be transported by EMS.

Dose and Formulation of the Specific Drug Taken

The estimation of dose is based largely on the patient's history and the type of product and its packaging (when available for evaluation). If precise data for the ingestion are unknown or unclear (package size, unit size, number of units ingested), poison centers in the United States often utilize a method in which the maximum potential dose is calculated. For example, if the actual dose ingested cannot be ascertained, the amount of the drug product that is missing from the container is multiplied by the dosage unit or concentration of the formulation. Modified-release products often contain larger amounts of a drug but their rate of absorption could be much slower and toxicity might be delayed.

For asymptomatic patients with an acute, unintentional ingestion of a CCB, the panel concluded that home observation might be allowable for very small exposures. However, the panel recognized that a definite threshold dose for toxicity, based on a confirmed history of exposure, has not been reported. After a thorough review of published case reports, recommended therapeutic dosage regimens, current poison control center practice, and expert experience, the panel concluded that ingestion of either of the following amounts (whichever is lower) should warrant consideration of referral to an emergency department (Table 11):

- An amount that exceeds the usual maximum single therapeutic dose; or
- An amount equal to or greater than the lowest reported toxic dose

This recommendation applies to both patients who are naïve to the specific calcium channel blocker and to patients currently taking calcium channel blockers who take extra doses. The panel recognized that the decision to send a patient to a hospital for monitoring is made on a case-by-case basis, taking into account the reliability of the caller's history, underlying medical illness, concomitant use of other medications (e.g., β-blockers) that could have additive cardiodepressant effects, and other variables. It also recognized that the thresholds chosen for this guideline are more conservative than some current poison center protocols and less conservative than others. Prospective studies might provide more definitive data and could result in adjustments of the recommended threshold doses.

Duration of Observation for Asymptomatic Patients

The expert consensus panel concluded that onset and duration of toxicity could be affected by several variables, including the specific type of pharmaceutical product (liquid, tablet, modified-release formulation), the total quantity ingested, and co-ingestants, as well as gastrointestinal decontamination measures such as activated charcoal. After a careful review of the case reports and observational studies summarized in Tables 8 and 9, and considerable discussion, the panel recommends that the duration of observation of an asymptomatic patient be at least 6 hours for immediate-release products, 18 hours for modified-release products other than verapamil, and 24 hours for modified-release verapamil. Patients who are asymptomatic after these intervals are unlikely to subsequently develop symptoms.

Potential Out-of-Hospital Management

Gastrointestinal Decontamination

The expert consensus panel concluded that out-of-hospital gastrointestinal decontamination offered potential benefit, but the risks and overall benefit to the patient were difficult to determine. Inducing emesis with ipecac syrup was concluded to carry the risk of pulmonary aspiration of gastric contents if the patient became hypotensive or lost consciousness and is not supported by sufficient evidence of benefit to warrant its use. Moreover, ipecac syrup would likely delay or prevent the use of alternative, potentially more effective treatments and it might induce a vagal stimulus that could further depress heart rate. Activated charcoal was determined to be a useful treatment that could be administered orally in the prehospital setting, although its effectiveness and risks have not been evaluated in the prehospital setting. Also, the panel agreed that transportation to an emergency department should not be delayed in order to attempt charcoal administration.

Specific Pharmacological Therapy

The expert consensus panel concluded that although the available literature on in-hospital management of CCB poisoning supports the use of intravenous calcium, glucagon, and epinephrine, which are often available to paramedics, no studies were found addressing the effectiveness or safety of these drugs for the out-of-hospital treatment of CCB-induced hypotension and bradycardia.

RECOMMENDATIONS

These recommendations are provided in chronological order of likely clinical use. The grades of recommendation appear in parentheses.

1. Patients with stated or suspected self-harm or the recipient of a potentially malicious administration of a CCB should be referred to an emergency department immediately. This activity should be guided by local poison center procedures. In general, this should occur regardless of the dose reported (Grade D).
2. Asymptomatic patients are unlikely to develop symptoms if the interval between the ingestion and the call is greater than 6 hours for immediate-release products, 18 hours for modified-release products other than verapamil, and

24 hours for modified-release verapamil. These patients do not need referral or prolonged observation (Grade D).
3. Patients without evidence of self-harm should have further evaluation, including determination of the precise dose ingested, history of other medical conditions, and the presence of co-ingestants. Ingestion of either an amount that exceeds the usual maximum single therapeutic dose or an amount equal to or greater than the lowest reported toxic dose, whichever is lower (see Table 11), would warrant consideration of referral to an emergency department (Grade D).
4. Do not induce emesis (Grade D).
5. Consider the administration of activated charcoal orally if available and no contraindications are present. However, do not delay transportation in order to administer charcoal (Grade D).
6. For patients who merit evaluation in an emergency department, ambulance transportation is recommended because of the potential for life-threatening complications. Provide usual supportive care en route to the hospital, including intravenous fluids for hypotension. Consider use of intravenous calcium, glucagon, and epinephrine for severe hypotension during transport, if available (Grade D).
7. Depending on the specific circumstances, follow-up calls should be made to determine outcome at appropriate intervals based on the clinical judgment of the poison center staff (Grade D).

These recommendations are summarized in Appendix 4.

IMPLICATIONS FOR RESEARCH

A large-scale prospective study of unintentional CCB ingestions is needed, with a careful attempt to confirm the estimates of the doses taken, the specific formulations, CCB serum concentrations, the presence or absence of underlying illnesses, the use of other medications, the presence or absence of symptoms, the times of onset of any toxicities, the durations of medical observation, and outcomes. Given the low incidence of serious toxicity after unintentional ingestion, especially in children, a multi-center and multi-year study will be needed.

An additional need is better correlation between the estimated ingested dose, clinical symptoms, and serum concentrations of the CCB in patients with serious overdoses.

Prehospital use of calcium, glucagon, insulin/dextrose, epinephrine, and other measures should be studied.

DISCLOSURES

Dr. Booze's husband is employed by AstraZeneca. Dr. Erdman is currently employed by AstraZeneca but was not when this guideline was written. There are no other potential conflicts of interest reported by the expert consensus panel or project staff regarding this guideline.

APPENDIX 1

Expert Consensus Panel Members

Lisa L. Booze, Pharm.D.
Certified Specialist in Poison Information
Maryland Poison Center
University of Maryland School of Pharmacy
Baltimore, Maryland

E. Martin Caravati, M.D., M.P.H., F.A.C.M.T., F.A.C.E.P.
Professor of Surgery (Emergency Medicine)
University of Utah
Medical Director
Utah Poison Center
Salt Lake City, Utah

Gwenn Christianson, R.N., M.S.N.
Certified Specialist in Poison Information
Indiana Poison Center
Indianapolis, Indiana

Peter A. Chyka, Pharm.D., F.A.A.C.T., D.A.B.A.T.
Professor, Department of Pharmacy
University of Tennessee Health Science Center
Memphis, Tennessee

Daniel C. Keyes, M.D., M.P.H.
Medical Director
Pine Bluff Chemical Demilitarization Facility
Associate Professor, Southwestern Toxicology Training Program
Dallas, Texas

Anthony S. Manoguerra, Pharm.D., D.A.B.A.T., F.A.A.C.T.
Professor of Clinical Pharmacy and Associate Dean
School of Pharmacy and Pharmaceutical Sciences
University of California San Diego
Former Director, California Poison Control System, San Diego Division
San Diego, California

Kent R. Olson, M.D., F.A.C.E.P., F.A.A.C.T., F.A.C.M.T.
Medical Director
California Poison Control System, San Francisco Division
Clinical Professor of Medicine and Pharmacy
University of California, San Francisco
San Francisco, California

Elizabeth J. Scharman, Pharm.D., D.A.B.A.T., B.C.P.S., F.A.A.C.T.
Director, West Virginia Poison Center
Professor, West Virginia University School of Pharmacy, Department of Clinical Pharmacy
Charleston, West Virginia

Paul M. Wax, M.D., F.A.C.M.T.
Managing Director
Banner Poison Center
Professor of Clinical Emergency Medicine
University of Arizona School of Medicine
Phoenix, Arizona

Alan D. Woolf, M.D., M.P.H., F.A.C.M.T.
Director, Program in Environmental Medicine
Children's Hospital, Boston
Associate Professor of Pediatrics
Harvard Medical School
Boston, Massachusetts

APPENDIX 2

Grades of Recommendation and Levels of Evidence

Grade of recommendation	Level of evidence	Description of study design
A	1a	Systematic review (with homogeneity) of randomized clinical trials
	1b	Individual randomized clinical trials (with narrow confidence interval)
	1c	All or none (all patients died before the drug became available, but some now survive on it; or when some patients died before the drug became available, but none now die on it).
B	2a	Systematic review (with homogeneity) of cohort studies
	2b	Individual cohort study (including low quality randomized clinical trial)
	2c	''Outcomes'' research
	3a	Systemic review (with homogeneity) of case-control studies
	3b	Individual case-control study
C	4	Case series, single case reports (and poor quality cohort and case control studies)
D	5	Expert opinion without explicit critical appraisal or based on physiology or bench research
	6	Abstracts

APPENDIX 3

Secondary Review Panel Organizations

Ambulatory Pediatric Association
American Academy of Breastfeeding Medicine
American Academy of Emergency Medicine
American Academy of Pediatrics
American Association for Health Education
American College of Clinical Pharmacy
American College of Emergency Physicians
American College of Occupational and Environmental Medicine
American Public Health Association
American Society of Health-System Pharmacists
Association of Maternal and Child Health Programs
Association of Occupational and Environmental Clinics
Association of State and Territorial Health Officials
Canadian Association of Poison Control Centres
Centers for Disease Control and Prevention—National Center for Injury Prevention and Control
Consumer Federation of America
Consumer Product Safety Commission
Department of Transportation
Emergency Medical Services for Children
Emergency Nurses Association
Environmental Protection Agency
European Association of Poisons Control Centres and Clinical Toxicologists
Food and Drug Administration
National Association of Children's Hospitals and Related Institutions
National Association of Emergency Medical Services Physicians
National Association of Emergency Medical Technicians
National Association of School Nurses
National Association of State Emergency Medical Services Directors
National Safe Kids Campaign
Teratology Society
World Health Organization International Programme on Chemical Safety

APPENDIX 4

Algorithm for Triage of Calcium Channel Blocker Ingestions

Is self-harm, suicidal or malicious intent suspected?	YES → Refer to emergency department.
NO ↓	
Is patient symptomatic? (e.g., weak, dizzy, syncopal)	YES → Refer to emergency department.
NO ↓	
Has more than 6 hr (immediate-release product), 18 hr (modified-release other than verapamil) or 24 hr (modified-release verapamil) passed since the ingestion?	YES → Toxicity unlikely to occur. No referral or treatment is needed.
NO ↓	
Does patient have significant underlying cardiovascular disease, or is he/she taking a ß-blocker or another cardiodepressant drug?	YES → Refer to emergency department or consult medical director or on-call medical toxicologist.
NO ↓	
Is the home situation of concern? (e.g., patient lives alone or family/caregiver seems unreliable)	YES → Refer to emergency department.
NO ↓	
Unable to estimate maximum amount ingested?	YES → Refer to emergency department.
NO ↓	
Maximum total possible dose:	
Amlodipine: Adult >10 mg Child >0.3 mg/kg	YES → Refer to emergency department.
Bepridil: Adult >300 mg Child: any amount	YES → Refer to emergency department.
Diltiazem: Adult >120 (IR or chewed SR), 360 (SR), or 540 (XR, XT) Child >1 mg/kg	YES → Refer to emergency department.
Felodipine: Adult >10 mg Child >0.3 mg/kg	YES → Refer to emergency department.
Isradipine: Adult >20 mg Child >0.1 mg/kg	YES → Refer to emergency department.
Nicardipine: Adult >40 mg (IR or chewed SR) or 60 mg (SR) Child ≥1.25 mg/kg	YES → Refer to emergency department.
Nifedipine: Adult >30 mg (IR or chewed SR) or 120 mg (SR) Child: any amount	YES → Refer to emergency department.
Nimodipine: Adult >60 mg Child any amount	YES → Refer to emergency department.
Nisoldipine: Adult: >30 mg Child: any amount	YES → Refer to emergency department.
Verapamil: Adult >120 mg (IR or chewed SR) or 480 mg (SR) Child >2.5 mg/kg	YES → Refer to emergency department.
NO → Observe at home.	

REFERENCES

1. Watson WA, Litovitz TL, Klein-Schwartz W, Rodgers GC Jr, Youniss J, Reid N, Rouse WG, Rembert RS, Borys D. 2003 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am J Emerg Med 2004; 22:335–404.
2. Ramoska EA, Spiller HA, Winter M, Borys D. A one-year evaluation of calcium channel blocker overdoses: toxicity and treatment. Ann Emerg Med 1993; 22:196–200.
3. Belson MG, Gorman SE, Sullivan K, Geller RJ. Calcium channel blocker ingestions in children. Am J Emerg Med 2000; 18:581–586.
4. Goodman & Gilman's the Pharmacological Basis of Therapeutics. 10th ed.. Hardman JG, Limbird LE, eds. New York: McGraw-Hill, 2001.
5. Pearigen PD, Benowitz NL. Poisoning due to calcium antagonists. Experience with verapamil, diltiazem and nifedipine. Drug Safety 1991; 6:408–430.
6. Kerns W II, Kline J, Ford MD. Beta-blocker and calcium channel blocker toxicity. Emerg Med Clin North Am 1994; 12:365–390.
7. Shaneyfelt TM, Mayo-Smith MF, Rothwangl J. Are guidelines following guidelines? The methodological quality of clinical practice guidelines in the peer-reviewed medical literature. JAMA 1999; 281:1900–1905.
8. Poisindex System. Klasco RK, ed. Thomson Micromedex: Greenwood Village, CO, edition expires March 2003.
9. Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning. 2nd ed. Ellenhorn MJ, ed. Baltimore: Williams & Wilkins, 1997.
10. Ford MD, Delaney KA, Ling LJ, Erickson T. Clinical Toxicology. Philadelphia: WB Saunders, 2000.
11. Goldfrank's Toxicologic Emergencies. 7th ed. Goldfrank LR, Flomenbaum NE, Lewin NA, Howland MA, Hoffman RS, Nelson LS, eds. New York: McGraw-Hill, 2002.
12. Clinical Management of Poisoning and Drug Overdose. 3rd ed. Haddad LM, Shannon MW, Winchester JF, eds. Philadelphia: WB Saunders, 1998.
13. Salhanick SD, Shannon MW. Management of calcium channel antagonist overdose. Drug Safety 2003; 26:65–79.
14. Nelson Textbook of Pediatrics. 17th ed. Behrman RE, Kliegman RM, Jenson HB, eds. Philadelphia: WB Saunders, 2004.
15. The Science and Practice of Pediatric Cardiology. 2nd ed. Garson A, Bricker JT, Fisher DJ, Neish SR, eds. Baltimore: Williams & Wilkins, 1998.
16. The Harriet Lane Handbook: A Manual for Pediatric House Officers. 16th ed. Philadelphia: Mosby, 2002.
17. USP DI. Drug Information for the Health Care Professional. 24th ed. Englewood, CO: Thomson Micromedex, 2004.
18. Poisoning & Drug Overdose. 4th ed. Olson KR, ed. New York: McGraw-Hill, 2004.
19. Medical Toxicology. 3rd ed. Dart RC, ed. Philadelphia: Lippincott, Williams & Wilkins, 2003.
20. Benson BE, Spyker DA, Troutman WG, Watson WA. TESS-based amlodipine dose-response in pediatric exposures. J Toxicol Clin Toxicol 2004; 42:753–754 [abstract].
21. Boyer EW, Shannon M. Treatment of calcium channel blocker intoxication with insulin infusion. N Engl J Med 2001; 344:1721–1722.
22. Stanek EJ, Nelson CE, DeNofrio D. Amlodipine overdose. Ann Pharmacother 1997; 31:853–856.
23. Koch AR, Vogelaers DP, Decruyenaere JM, Callens B, Verstraete A, Buylaert WA. Fatal intoxication with amlodipine. J Toxicol Clin Toxicol 1995; 33:253–256.
24. Cosbey SH, Carson DJ. A fatal case of amlodipine poisoning. J Anal Toxicol 1997; 21:221–222.
25. Tovar JL, Bujons I, Ruiz JC, Ibanez L, Salgado A. Treatment of severe combined overdose of calcium antagonists and converting enzyme inhibitors with angiotensin II. Nephron 1997; 77:239.
26. Mahr NC, Valdes A, Lamas G. Use of glucagon for acute intravenous diltiazem toxicity. Am J Cardiol 1997; 79:1570–1571.
27. Lambert H, Weber M, Renaud D. Intoxications aiguës par diltiazem (DTZ). Bilan des Centres Anti-Poisons Français. J Toxicol Clin Exp 1990; 10:229–242.
28. Fang CC, Tsai LM. Hematologic complications of diltiazem overdose. Am Heart J 1993; 126:1017–1018.
29. Ramoska EA, Spiller HA, Myers A. Calcium channel blocker toxicity. Ann Emerg Med 1990; 19:649–653.
30. Roberts D, Honcharik N, Sitar DS, Tenenbein M. Diltiazem overdose: pharmacokinetics of diltiazem and its metabolites and effect of multiple dose charcoal therapy. J Toxicol Clin Toxicol 1991; 29:45–52.
31. Oliver TB, Awunor-Renner C. Isoprenaline infusion and right ventricular pacing in severe diltiazem poisoning. N Z Med J 1992; 105:483.
32. Jaeger A, Sauder P, Bianchetti G, Kopferschmitt J, Dahlet M, Tritsch L, Flesch F. Intoxications aiguës par le diltiazem: étude cinétique et hémodynamique. J Toxicol Clin Exp 1990; 10:243–248.
33. Garcia del Pozo JM, Siquier B, Vicens C. Intento de autólisis con diltiacem. Rev Esp Cardiol 1991; 44:355–357.
34. Snover SW, Bocchino V. Massive diltiazem overdose. Ann Emerg Med 1986; 15:1221–1224.
35. Darmanaden R, Kienlen J, Rouve MB. One case of fatal poisoning by diltiazem. Therapie 1992; 47:80–81.
36. Jakubowski AT, Mizgala HF. Effect of diltiazem overdose. Am J Cardiol 1987; 60:932–933.
37. Buffet M, Ostermann G, Raclot P, Bertault R, Rambourg MO, Jaussand M, Journe B, Seys GA. Cinétique du diltiazem au cours d'un surdosage volontaire. Presse Med 1984; 13:1338. <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=6233565&query_h1=1>.
38. Gibelin P, Maccario M, Lapalus P, Morand P. Intoxication volontaire par le diltiazem. Presse Med 1984; 13:745.
39. Howarth DM, Dawson AH, Smith AJ, Buckley N, Whyte IM. Calcium channel blocking drug overdose: an Australian series. Human Exp Toxicol 1994; 13:161–166.
40. Erickson FC, Ling LJ, Grande GA, Anderson DL. Diltiazem overdose: case report and review. J Emerg Med 1991; 9:357–366.
41. Fauville JP, Hantson P, Honore P, Belpaire F, Rosseel MT, Mahieu P. Severe diltiazem poisoning with intestinal pseudo-obstruction: case report and toxicological data. J Toxicol Clin Toxicol 1995; 33:273–277.
42. Henderson A, Stevenson N, Hackett LP, Pond SM. Diltiazem overdose in an elderly patient: efficacy of adrenaline. Anaesth Intensive Care 1992; 20:507–510.
43. Ferner RE, Odemuyiwa O, Field AB, Walker S, Volans GN, Bateman DN. Pharmacokinetics and toxic effects of diltiazem in massive overdose. Human Toxicol 1989; 8:497–499.
44. Connolly DL, Nettleton MA, Bastow MD. Massive diltiazem overdose. Am J Cardiol 1993; 72:742–743.
45. Malcolm N, Callegari P, Goldberg J, Strauss H, Caillé G, Vezina M, Spenard J. Massive diltiazem overdosage: clinical and pharmacokinetic observations. Drug Intell Clin Pharm 1986; 20:888. <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=3780429&query_h1=2>.
46. Morimoto S, Sasaki S, Kiyama M, Hatta T, Moriguchi J, Miki S, Kawa T, Nakamura K, Itoh H, Nakata T, Takeda K, Nakagawa M. Sustained-release diltiazem overdose. J Hum Hypertens 1999; 13:643–644. <http://ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10482975&query_h1=3>.
47. Satchithananda DK, Stone DL, Chauhan A, Ritchie AJ. Unrecognized accidental overdose with diltiazem. Br Med J 2000; 321:160–161.

48. Isbister GK. Delayed asystolic cardiac arrest after diltiazem overdose; resuscitation with high dose intravenous calcium. Emerg Med J 2002; 19:355–357.
49. Cimpello LB, Craig S, Lawrence E, Baker MD. A calcium channel blocker and ibuprofen overdose. Curr Opin Pediatr 1998; 10:303–307.
50. Luomanmaki K, Tiula E, Kivisto KT, Neuvonen PJ. Pharmacokinetics of diltiazem in massive overdose. Ther Drug Monit 1997; 19:240–242.
51. Williamson KM, Dunham GD. Plasma concentrations of diltiazem and desacetyldiltiazem in an overdose situation. Ann Pharmacother 1996; 30:608–611.
52. Frese JH, Rohland L, Schulz M, Schmoldt A. Intoxikation mit gallopamil. Dtsch Med Wochenschr 1988; 113:770–772.
53. Droy JM, Daridon E, Leroy J, Massari P. Intoxications aiguës par nicardipine et nifédepine. Etude multicentrique. J Toxicol Clin Exp 1990; 10:249–256.
54. Welch RD, Todd K. Nifedipine overdose accompanied by ethanol intoxication in a patient with congenital heart disease. J Emerg Med 1990; 8:169–172.
55. Schiffl H, Ziupa J, Schollmeyer P. Clinical features and management of nifedipine overdosage in a patient with renal insufficiency. J Toxicol Clin Toxicol 1984; 22:387–395.
56. Whitebloom D, Fitzharris J. Nifedipine overdose. Clin Cardiol 1988; 11:505–506.
57. Walter FG, Frye G, Mullen JT, Ekins BR, Khasigian PA. Amelioration of nifedipine poisoning associated with glucagon therapy. Ann Emerg Med 1993; 22:1234–1237.
58. Herrington DM, Insley BM, Weinmann GG. Nifedipine overdose. Am J Med 1986; 81:344–346.
59. Lam YM, Tse HF, Lau CP. Continuous calcium chloride infusion for massive nifedipine overdose. Chest 2001; 119:1280–1282.
60. Fant JS, James LP, Fiser RT, Kearns GL. The use of glucagon in nifedipine poisoning complicated by clonidine ingestion. Pediatr Emerg Care 1997; 13:417–419.
61. Cavagnaro F, Aglony M, Rios JC, Paris E. A suicide attempt with an oral calcium channel blocker. Vet Hum Toxicol 2000; 42:99–100.
62. Ferner RE, Monkman S, Riley J, Cholerton S, Idle JR, Bateman DN. Pharmacokinetics and toxic effects of nifedipine in massive overdose. Human Exp Toxicol 1990; 9:309–311.
63. Wax PM. Intestinal infarction due to nifedipine overdose. J Toxicol Clin Toxicol 1995; 33:725–728.
64. Papadopoulos J, O'Neil MG. Utilization of a glucagon infusion in the management of a massive nifedipine overdose. J Emerg Med 2000; 18:453–455.
65. Haddad LM. Resuscitation after nifedipine overdose exclusively with intravenous calcium chloride. Am J Emerg Med 1996; 14:602–603.
66. Immonen P, Linkola A, Waris E. Three cases of severe verapamil poisoning. Int J Cardiol 1981; 1:101–105.
67. Crump BJ, Hot DW, Vale JA. Lack of response to intravenous calcium in severe verapamil poisoning. Lancet 1982; 2:939–940.
68. Sauder P, Kopferschmitt J, Dahlet M, Tritsch L, Flesch F, Siard P, Manz JM, Jaeger A. Les intoxications aiguës par le vérapamil. A propos de 6 cas. Revue de la littérature. J Toxicol Clin Exp 1990; 10:261–270. <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=2262922&query_h1=4>.
69. Gutierrez H, Horgensen M. Colonic ischemia after verapamil overdose. Ann Intern Med 1996; 124:535.
70. Leesar MA, Martyn R, Talley JD, Frumin H. Noncardiogenic pulmonary edema complicating massive verapamil overdose. Chest 1994; 105:606–607.
71. Candell J, Valle V, Soler M, Rius J. Acute intoxication with verapamil. Chest 1979; 75:200–201.
72. Lapostolle F, Bourdain F, Adnet F, Benaissa A, Muszynski J, Baud F. Intoxication aiguë par le vérapamil. Proposition d'une stratégie de prise en charge therapeutique. Ann Fr Anesth Reanim 2000; 19:607–610.
73. Link A, Hammer B, Weisgerber K, Bohm M. Therapie der verapamil-intoxikation mit noradrenalin und dem phosphodiesterasehemmer enoximon. Dtsch Med Wochenschr 2002; 127:2006–2008.
74. Kuhlmann U, Schoenemann H, Muller T, Keuchel M, Lange H. Plasmapheresis in life-threatening verapamil intoxication. Artif Cells Blood Substit Immobil Biotechnol 2000; 28:429–440.
75. Buckley CD, Aronson JK. Prolonged half-life of verapamil in a case of overdose: implications for therapy. Br J Clin Pharmacol 1995; 39:680–683.
76. Enyeart JJ, Price WA, Hoffman DA, Woods L. Profound hyperglycemia and metabolic acidosis after verapamil overdose. J Am Coll Cardiol 1983; 2:1228–1231.
77. Chimienti M, Previtali M, Medicia A, Piccinini M. Acute verapamil poisoning: successful treatment with epinephrine. Clin Cardiol 1982; 5:219–222.
78. da Silva OA, de Melo RA, Jorge Filho JP. Verapamil acute self-poisoning. Clin Toxicol 1979; 14:361–367.
79. Woie L, Storstein L. Successful treatment of suicidal verapamil poisoning with calcium gluconate. Eur Heart J 1981; 2:239–242.
80. Perkins CM. Serious verapamil poisoning: treatment with intravenous calcium gluconate. Br Med J 1978; 2:1127.
81. Moroni F, Mannaioni PF, Dolara A, Ciaccheri M. Calcium gluconate and hypertonic sodium chloride in a case of massive verapamil poisoning. Clin Toxicol 1980; 17:395–400.
82. Miller ARO, Ingamells CJ. Gastrointestinal hemorrhage associated with an overdose of verapamil. Br Med J 1984; 288:1346.
83. Kivisto KT, Neuvonen PJ, Tarssanen L. Pharmacokinetics of verapamil in overdose. Human Exp Toxicol 1997; 16:35–37.
84. Watling SM, Crain JL, Edwards TD, Stiller RA. Verapamil overdose: case report and review of the literature. Ann Pharmacother 1992; 26:1373–1378.
85. Brass BJ, Winchester-Penny S, Lipper BL. Massive verapamil overdose complicated by noncardiogenic pulmonary edema. Am J Emerg Med 1996; 14:459–461.
86. Oe H, Taniura T, Ohgitani N. A case of severe verapamil overdose. Jpn Circ J 1998; 62:72–76.
87. Kuo MJ, Tseng YZ, Chen TF, Fong DE. Verapamil overdose and severe hypocalcemia. J Toxicol Clin Toxicol 1992; 30:309–311.
88. Minella RA, Schulman DS. Fatal verapamil toxicity and hypokalemia. Am Heart J 1991; 121:1810–1812.
89. Spurlock BW, Virani NA, Henry CA. Verapamil overdose. West J Med 1991; 154:208–211.
90. Watson NA, FitzGerald CP. Management of massive verapamil overdose. Med J Aust 1991; 155:124–125.
91. de Faire U, Lundman T. Attempted suicide with verapamil. Eur J Cardiol 1977; 6:195–198.
92. Croker JR, Vaile JH. Management of massive verapamil overdose. Med J Aust 1991; 155:728.
93. McMillan R. Management of acute severe verapamil intoxication. J Emerg Med 1988; 6:193–196.
94. Horowitz BZ, Rhee KJ. Massive verapamil ingestion: a report of two cases and a review of the literature. Am J Emerg Med 1989; 7:624–631.
95. Coaldrake LA. Verapamil overdose. Anaesth Intensive Care 1984; 12:174–175.
96. Goenen M, Col J, Compere A, Bonte J. Treatment of severe verapamil poisoning with combined amrinone-isoproterenol therapy. Am J Cardiol 1986; 58:1142–1143.
97. van der Meer J, van der Wall E. Fatal acute intoxication with verapamil. Neth J Med 1983; 26:130–132.
98. Jain SC, Bharadwaj RP, Shukla RK, Ahmad M, Mathur SP. Severe hypotension and bradycardia after suicidal consumption of 100 tablets of verapamil: a case report. Indian Heart J 1982; 34:175–176.
99. Sporer KA, Manning JJ. Massive ingestion of sustained-release

verapamil with a concretion and bowel infarction. Ann Emerg Med 1993; 22:603–605.
100. Tom PA, Morrow CT, Kelen GD. Delayed hypotension after overdose of sustained release verapamil. J Emerg Med 1994; 12:621–625.
101. Yuan TH, Kerns WP II, Tomaszewski CA, Ford MD, Kline JA. Insulin-glucose as adjunctive therapy for severe calcium channel antagonist poisoning. J Toxicol Clin Toxicol 1999; 37:463–474.
102. Mayer U, Buhl N, Sachs H, Sigel H. Tödliche vergiftung mit verapamil in retard-form. Therapeutische überlegungen. Dtsch Med Wochenschr 1985; 110:1293–1296.
103. Spiller HA, Meyers A, Ziemba T, Riley M. Delayed onset of cardiac arrhythmias from sustained-release verapamil. Ann Emerg Med 1991; 20:201–203.
104. Doyon S, Roberts JR. The use of glucagon in a case of calcium channel blocker overdose. Ann Emerg Med 1993; 22:1229–1233.
105. Buckley N, Dawson AH, Howarth D, Whyte IM. Slow-release verapamil poisoning. Use of polyethylene glycol whole-bowel lavage and high-dose calcium. Med J Aust 1993; 158:202–204.
106. Quezado Z, Lippmann M, Wertheimer J. Severe cardiac, respiratory, and metabolic complications of massive verapamil overdose. Crit Care Med 1991; 19:436–438.
107. Sami Karti S, Ulusoy H, Yandi M, Güdüz A, Koşucum M, Erol K, Ratip S. Non-cardiogenic pulmonary œdema in the course of verapamil intoxication. Emerg Med J 2002; 19:458–459.
108. Ori Y, Korzets A, Caneti M, Weinstein T, Chagnac A, Salman H, Malachi T, Gafter U. Lymphocytic intracellular calcium in a patient with complicated verapamil overdose. Am J Med Sci 2000; 319:63–67. <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10653445&query_h1=5>.
109. Barrow PM, Houston PL, Wong DT. Overdose of sustained-release verapamil. Br J Anaesth 1994; 72:361–365.
110. Shah AR, Passalacqua BR. Case report: sustained-release verapamil overdose causing stroke: an unusual complication. Am J Med Sci 1992; 304:357–359.
111. Krick SE, Gums JG, Grauer K, Cooper GR. Severe verapamil (sustained-release) overdose. DICP 1990; 24:705–706.
112. Vadlamudi L, Wijdicks EF. Multifocal myoclonus due to verapamil overdose. Neurology 2002; 58:984.
113. MacDonald D, Alguire PC. Case report: fatal overdose with sustained-release verapamil. Am J Med Sci 1992; 303:115–117.
114. Kozlowski JH, Kozlowski JA, Schuller D. Poisoning with sustained-release verapamil. Am J Med 1988; 85:127.
115. Hofer CA, Smith JK, Tenholder MF. Verapamil intoxication: a literature review of overdoses and discussion of therapeutic options. Am J Med 1993; 95:431–438.
116. Hagege A, Masquet C, Beaufils P, Slama R. Intoxication massive par le vérapamil à libération prolongée. Arch Mal Coeur Vaiss 1990; 83:1745–1747.
117. Ashraf M, Chaudhary K, Nelson J, Thompson W. Massive overdose of sustained-release verapamil: a case report and review of literature. Am J Med Sci 1995; 310:258–263.
118. Spiller HA, Ramoska EA. Isradipine ingestion in a two-year-old child. Vet Hum Toxicol 1993; 35:233.
119. Boyer EW, Duic PA, Evans A. Hyperinsulinemia/euglycemia therapy for calcium channel blocker poisoning. Pediatr Emerg Care 2002; 18:36–37.
120. Wells TG, Graham CJ, Moss MM, Kearns GL. Nifedipine poisoning in a child. Pediatrics 1990; 86:91–94.
121. Lee DC, Greene T, Dougherty T, Pearigen P. Fatal nifedipine ingestions in children. J Emerg Med 2000; 19:359–361.
122. Brayer AF, Wax P. Accidental ingestion of sustained release calcium channel blockers in children. Vet Hum Toxicol 1998; 40:104–106.
123. Passal DB, Crespin FH. Verapamil poisoning in an infant. Pediatrics 1984; 73:543–545.
124. Adams BD, Browne WT. Amlodipine overdose causes prolonged calcium channel blocker toxicity. Am J Emerg Med 1998; 16:527–528.
125. Proano L, Chiang WK, Wang RY. Calcium channel blocker overdose. Am J Emerg Med 1995; 13:444–450.
126. Orr GM, Bodansky HJ, Dymond DS, Taylor M. Fatal verapamil overdose. Lancet 1982; 2:1218–1219.
127. Li Saw F, Hee FL, Lip GY. Case report: fatal verapamil overdosage despite intensive therapy and use of high dose intravenous calcium. J Hum Hypertens 1996; 10:495–496.
128. Rankin RJ, Edwards IR. Overdose of sustained release verapamil. N Z Med J 1990; 103:165.
129. Kardevandian E, Marcus S. Accidental ingestion of sustained release calcium channel blockers in children. Vet Hum Toxicol 1998; 40:237–238.
130. Hendren WG, Schieber RS, Garrettson LK. Extracorporeal bypass for the treatment of verapamil poisoning. Ann Emerg Med 1989; 18:984–987.
131. Laine K, Kivisto KT, Laakso I, Neuvonen PJ. Prevention of amlodipine absorption by activated charcoal: effect of delay in charcoal administration. Br J Clin Pharmacol 1997; 43:29–33.
132. Bonechi F, Brandinelli Geri A, Maioli M, Ieri A. Avvelenamento da verapamile a scopo suicida. Descrizione di un caso. G Ital Cardiol 1993; 23:69–72.
133. Rosansky SJ. Verapamil toxicity—treatment with hemoperfusion. Ann Intern Med 1991; 114:340–341.
134. ter Wee PM, Kremer Hovinga TK, Uges DR, van der Geest S. 4-Aminopyridine and haemodialysis in the treatment of verapamil intoxication. Human Toxicol 1985; 4:327–329.
135. Kalman S, Berg S, Lisander B. Combined overdose with verapamil and atenolol: treatment with high doses of adrenergic agonists. Acta Anaesthesiol Scand 1998; 42:379–382.
136. Samniah N, Schlaeffer F. Cerebral infarction associated with oral verapamil overdose. J Toxicol Clin Toxicol 1988; 26:365–369.
137. Humbert VH Jr, Munn NJ, Hawkins RF. Noncardiogenic pulmonary edema complicating massive diltiazem overdose. Chest 1991; 99:258–259.
138. Wolf LR, Spadafora MP, Otten EJ. Use of amrinone and glucagon in a case of calcium channel blocker overdose. Ann Emerg Med 1993; 22:1225–1228.
139. Holzer M, Sterz F, Schoerkhuber W, Behringer W, Domanovits H, Weinmar D, Weinstabl C, Stimpfl T. Successful resuscitation of a verapamil-intoxicated patient with percutaneous cardiopulmonary bypass. Crit Care Med 1999; 27:2818–2823. <http://ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10628632&query_h1=6>.
140. Romano MJ, Gaylor A, Sang CJ. Life-threatening isradipine poisoning in a child. Pharmacotherapy 2002; 22:766–770.
141. Hattori VT, Mandel WJ, Peter D. Calcium for myocardial depression from verapamil. N Engl J Med 1982; 306:238.
142. Lipman J, Jardine I, Roos C, Dreosti L. Intravenous calcium chloride as an antidote to verapamil-induced hypotension. Intensive Care Med 1982; 8:55–57.
143. Luscher TF, Noll G, Sturmer T, Huser B, Wenk M. Calcium gluconate in severe verapamil intoxication. N Engl J Med 1994; 330:718–720.
144. Passeron D, Peschaud JL. Intoxication aiguë par la nicardipine. J Toxicol Clin Exp 1990; 10:257–259.
145. Shepherd G, Klein-Schwartz W. High-dose insulin therapy for calcium-channel blocker overdose. Ann Pharmacother 2005; 39:923–930.
146. Bailey B. Glucagon in beta-blocker and calcium channel blocker overdoses: a systematic review. J Toxicol Clin Toxicol 2003; 41:595–602.
147. Robles NR, Garcia Diaz MC, Fernandez Mora G, Sanchez Casado E. Intoxicación por verapamilo de liberación lenta en un enfermo urémico. Med Clin (Barc) 1992; 99:741–742.

148. Jaeger A, Berton C, Sauder P, Kopferschmitt J. Toxicité des inhibiteurs calcique. J Toxicol Clin Exp 1990; 10:219–228.
149. Rumack BH. Acetaminophen overdose in young children. Treatment and effects of alcohol and other additional ingestants in 417 cases. Am J Dis Child. 1984 May; 138(5):428–433.
150. Gee P, Ardagh M. Paediatric exploratory ingestions of paracetamol. N Z Med J 1998; 111:186–188.
151. Caravati EM. Unintentional acetaminophen ingestion in children and the potential for hepatotoxicity. J Toxicol Clin Toxicol 2000; 38:291–296.