Complete Summary

GUIDELINE TITLE

Calcium channel blocker ingestion: an evidence-based consensus guideline for out-of-hospital management.

BIBLIOGRAPHIC SOURCE(S)

Olson KR, Erdman AR, Woolf AD, Scharman EJ, Christianson G, Caravati EM, Wax PM, Booze LL, Manoguerra AS, Keyes DC, Chyka PA, Troutman WG, American Association of Poison Control Centers. Calcium channel blocker ingestion: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol (Phila) 2005;43(7):797-822. [151 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Calcium channel blocker (CCB) poisoning

Notes:

- This guideline focuses on the ingestion of more than a single therapeutic dose (overdose). Articles that reported adverse effects related to usual therapeutic doses and with therapeutic intent were not included in the review.
- This guideline applies to ingestion of CCBs alone. Co-ingestion of additional substances could require different referral and management recommendation depending on the combined toxicities of the substances.

GUIDELINE CATEGORY

Evaluation
Management
Risk Assessment

CLINICAL SPECIALTY

Emergency Medicine
Family Practice
Internal Medicine
Pediatrics

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Emergency Medical Technicians/Paramedics
Nurses
Pharmacists
Physicians

GUIDELINE OBJECTIVE(S)

To assist U.S. poison center personnel in the appropriate out-of-hospital triage and initial management of patients with suspected ingestions of calcium channel blockers by:

- Describing the process by which a calcium channel blocker ingestion might be managed
- Identifying the key decision elements in managing cases of calcium channel blocker ingestion
- Providing clear and practical recommendations that reflect the current state of knowledge
- Identifying needs for research

TARGET POPULATION

Children under 6 years of age and older children and adults with acute and chronic calcium channel blocker (CCB) ingestion

INTERVENTIONS AND PRACTICES CONSIDERED

Evaluation

1. Assessment of key decision points for triage:
    - Patient intent
    - Time of ingestion and the dose and formulation of specific product
    - Patient's symptoms
    - Underlying medical conditions and any co-ingested drugs

Management

1. Referral to an emergency department
    - Ambulance transport
    - Provision of usual support measures en route to the hospital (e.g., intravenous fluids for hypotension)
    - Intravenous calcium, glucagon, and epinephrine during transport, if available
    - Induction of emesis (considered, but not recommended)
    - Activated charcoal orally if available and no contraindications are present
2. Home observation for asymptomatic patients
3. Follow-up at appropriate intervals

MAJOR OUTCOMES CONSIDERED

- Threshold dose for the development of toxicity after calcium channel blocker ingestion
- Time to onset of effects after overdose
- Signs and symptoms of toxicity

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Literature Search

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

The MEDLINE and PreMEDLINE (1966 to 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 to March 2003, excluding abstracts of meeting presentations), Science Citation Index (1977 to 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 to March 2003). Reactions (1980 to March 2003), the calcium channel poisoning management in POISINDEX, 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 and the reference list of a recent review article 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).

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.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Articles were assigned level-of-evidence scores based on the Grades of Recommendation table developed by the Centre for Evidence-Based Medicine at Oxford University. Single case reports were classified along with case series as level 4.

Levels of Evidence	Description of Study Design
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

Levels of Evidence	Description of Study Design
	became available, but none now die on it)
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
4	Case series, single case reports (and poor quality cohort and case control studies)
5	Expert opinion without explicit critical appraisal or based on physiology or bench research
6	Abstracts

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

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 (see the "Rating Scheme for the Strength of the Evidence" field); 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. The 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 American Association of Poison Control Centers (AAPCC) Web site.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Delphi)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

An expert consensus panel was established to oversee the guideline development process (see Appendix 1 in the original guideline document). 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.

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.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

The rating scheme for the strength of the recommendation (A-D, Z) is directly tied to the level of evidence supporting the recommendation.

Grades of Recommendation	Levels of Evidence
A	1a
	1b
	1c
B	2a
	2b
	2c
	3a
	3b
C	4
D	5
Z	6

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

External review of the second draft was conducted by distributing it electronically to American Association of Poison Control Centers (AAPCC), American Academy of Clinical Toxicology (AACT), and American College of Medical Toxicology (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 (see Appendix 3 in the original guideline document). Comments were submitted via a discussion thread on the AAPCC Web site 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 his 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.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Grades of recommendation (A-D, Z) and levels of evidence (1a-6) are defined at the end of the "Major Recommendations" field.

Note: These recommendations are provided in chronological order of likely clinical use. The grade of recommendation appears in parentheses.

1. Patients with stated or suspected self-harm or the recipient of a potentially malicious administration of a calcium channel blocker (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 in the original guideline document), 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)**.

Definitions:

Grades of Recommendation and Levels of Evidence

Grades of Recommendation	Levels 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
Z	6	Abstracts

CLINICAL ALGORITHM(S)

An algorithm is provided in the Appendix 4 of the original guideline document for the triage of patients with calcium channel blocker ingestions.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate out-of-hospital triage and initial management of patients with suspected ingestions of calcium channel blockers

POTENTIAL HARMS

Not stated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- This guideline is based on an assessment of current scientific and clinical information. The 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.
- 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.

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.

In most of the case reports and case series reviewed, the exact time of ingestion was not reported or was not known, or the time of onset of toxicity can only be estimated as occurring within a range of hours after the suspected ingestion.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Clinical Algorithm

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness
Timeliness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Olson KR, Erdman AR, Woolf AD, Scharman EJ, Christianson G, Caravati EM, Wax PM, Booze LL, Manoguerra AS, Keyes DC, Chyka PA, Troutman WG, American Association of Poison Control Centers. Calcium channel blocker ingestion: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol (Phila) 2005;43(7):797-822. [151 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2005

GUIDELINE DEVELOPER(S)

American Association of Poison Control Centers - Professional Association

SOURCE(S) OF FUNDING

Maternal and Child Health Bureau, Health Resources and Services Administration, U.S. Department of Health and Human Services

GUIDELINE COMMITTEE

Not stated

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

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.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the American Association of Poison Control Centers Web site.

Print copies: Available from the American Association of Poison Control Centers, 3201 New Mexico Avenue NW, Suite 330, Washington, DC 20016

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on October 31, 2005. The information was verified by the guideline developer on November 28, 2005.

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