Complete Summary

GUIDELINE TITLE

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

BIBLIOGRAPHIC SOURCE(S)

Wax PM, Erdman AR, Chyka PA, Keyes DC, Caravati EM, Booze L, Christianson G, Woolf A, Olson KR, Manoguerra AS, Scharman EJ, Troutman WG. Beta-blocker ingestion: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol (Phila) 2005;43(3):131-46. PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE
METHODOLOGY - including Rating Scheme and Cost Analysis
RECOMMENDATIONS
EVIDENCE SUPPORTING THE RECOMMENDATIONS
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
QUALIFYING STATEMENTS
IMPLEMENTATION OF THE GUIDELINE
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY
DISCLAIMER

SCOPE

DISEASE/CONDITION(S)

Beta-blocker poisoning

Note: This guideline applies to ingestion of beta-blockers 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 beta-blockers by:

- Describing the process by which a beta-blocker ingestion might be managed
- Identifying the key decision elements in managing cases of beta-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 with acute and chronic beta-blocker exposure
- Older children and adults with acute and chronic beta-blocker exposure

INTERVENTIONS AND PRACTICES CONSIDERED

Evaluation

1. Assessment of key decision points for triage:
    - Patient intent
    - Patient symptoms
    - Underlying medical conditions and other medications used
    - Estimated dose and formulation of specific beta-blocker ingested

Management

1. Referral and transportation to an emergency department
2. Home observation for asymptomatic patients with unintentional beta-blocker ingestion and low-dose exposure
3. Gastrointestinal decontamination with activated charcoal

Note: Ipecac syrup and intravenous glucagon were considered but not recommended

4. Follow-up calls for up to 12 to 24 hours

MAJOR OUTCOMES CONSIDERED

- Dose-toxicity relationship in children and adults
- Time of onset of toxicity after overdose in children and adults
- Effectiveness of out-of-hospital treatments

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 February 2003) using adrenergic beta-antagonists (exploded as a Medical Subject Heading [MeSH] term) with the subheadings poisoning (po) or toxicity (to), limited to humans.

The MEDLINE and PreMEDLINE (1966 to February 2003) databases were searched using a list of 42 beta-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 February 2003, excluding abstracts of meeting presentations), Science Citation Index (1977 to February 2003), Database of Abstracts of Reviews of Effects (accessed February 2003), Cochrane Database of Systematic Reviews (accessed February 2003), and Cochrane Central Register of Controlled Trials (accessed February 2003). A similar search was conducted in EMBASE (1990 to March 2003). MEDLINE was searched again for all articles describing beta-blocker use in children from 1 through 5 years of age. Reactions (1980 to March 2003), the beta-blocker poisoning management in POISINDEX, and the bibliographies of recovered articles were reviewed to identify previously undiscovered articles. Furthermore, North American Congress of Clinical Toxicology abstracts published in the Journal of Toxicology-Clinical Toxicology (1995 to 2003) were reviewed for original human data. The chapter bibliographies in four current major toxicology textbooks 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 beta-blocker poisoning or any deaths from beta-blocker poisoning in children. These cases were abstracted for use by the panel.

Criteria Used to Identify Applicable Studies

The recovered citations were entered into an EndNote library and duplicate entries were eliminated. The abstracts of these articles were reviewed, looking specifically for those that dealt with 1) estimations of mg/kg or ingested doses with or without subsequent signs or symptoms, and 2) management techniques that might be suitable for out-of-hospital use (e.g., gastrointestinal decontamination). Articles excluded were those that didn't meet either of the preceding criteria, didn't add new data (e.g., some reviews, editorials), or that described inpatient-only procedures (e.g., dialysis).

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 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

Data Extraction Process

All articles that were retrieved from the original search were reviewed by a single abstractor. Each article was assigned a level of evidence score from 1 to 6 (see the "Rating Scheme for the Strength of the Evidence" field); the complete paper was reviewed for original human data regarding the toxic effects of beta-blockers, or original human data directly relevant to the out-of-hospital management of patients with beta-blocker toxicity or overdose. Relevant data (e.g., dose of beta-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 evidence table is available at http://www.aapcc.org/DiscGuidelines/BetaBlockerEvidenceTable.pdf

The completed 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 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 beta-blockers in acute pediatric ingestions reported to cause toxicity). These were also forwarded to the author and guideline panel members. A written summary of the data was created and distributed by the abstractor. Copies of all of the abstracted articles were made available for reading by the panel members on a secure American Association of Poison Control Centers (AAPCC) website.

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 published cost analysis was 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). Comments were submitted via a discussion thread on the AAPCC web site or privately through email 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.

1. Patients with stated or suspected self-harm or who are the victims of a potentially malicious administration of beta-blocker should be referred to an emergency department immediately. This referral should be guided by local poison center procedures. In general, this should occur regardless of the dose reported **(Grade D)**.
2. 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 of the following amounts (whichever is lower) warrants consideration of referral to an emergency department: (see Table 5 in the original guideline document)
    - An amount that exceeds the usual maximum single therapeutic dose or
    - An amount equal to or greater than the lowest reported toxic dose.

    Ingestion of any excess dose of any beta-blocker in combination with a calcium channel blocker or the ingestion of any excess dose by an individual with serious underlying cardiovascular disease (e.g., end-stage cardiomyopathy) also warrants referral to an emergency department **(Grade C)**.

3. Do not induce emesis. Consider the oral administration of activated charcoal if it is available and no contraindications are present. However, do not delay transportation in order to administer charcoal **(Grade A)**.
4. Asymptomatic patients who ingest more than the referral dose should be sent to an emergency department if the ingestion occurred within 6 hours of contacting the poison center for an immediate-release product other than sotalol, within 8 hours of contacting the poison center for a sustained-release product and 12 hours if they took sotalol **(Grade C)**.
5. Ambulance transportation is recommended for patients who are referred to emergency departments because of the potential for life-threatening complications of beta-blocker overdose. Provide usual supportive care en route to the hospital, including intravenous fluids for hypotension **(Grade D)**
6. Depending on the specific circumstances, follow-up calls should be made to determine outcome at appropriate intervals for up to 12 to 24 hours based on the judgment of the poison center staff **(Grade D)**.
7. Asymptomatic patients who are referred to healthcare facilities should be monitored for at least 6 hours after ingestion if they took an immediate-release preparation other than sotalol, 8 hours if they took a sustained-release preparation, and 12 hours if they took sotalol. Routine 24-hour admission of an asymptomatic patient who has unintentionally ingested a sustained-release preparation is not warranted **(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 Appendix 4 of the original guideline document for the triage of patients with beta-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 beta-blockers
- Reduced over- and under-referral to healthcare facilities

POTENTIAL HARMS

Not stated

QUALIFYING STATEMENTS

- This guideline has been developed for the conditions prevalent in the U.S. While the toxicity of beta-blockers is not expected to vary in a clinically significant manner in other nations, the out-of-hospital conditions could be much different. Some beta-blockers available outside the U.S. are not currently marketed in the U.S. These beta-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.
- 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 health professionals providing care, considering all of the circumstances involved.

Limitations of the Published Data

Overall, the level 4 data were extremely difficult to interpret and summarize for a number of reasons. The case reports and case series varied widely in the level of clinical detail presented and the cases themselves varied widely in the severity and clinical effects of poisoning and in the timing, combination, dose, and routes of various treatments used.

The lack of precision in dose reporting is a major limitation of this data analysis. The estimates that were used are subject to many assumptions and guesswork. Data for amount ingested are often inaccurate or incomplete. The history may be 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 record the dose taken as the worst-case scenario in order to provide a wide margin of safety. Tablet counts from bottles are often unreliable. The suspect tablets might be simply missing, with only a possibility that it was ingested. In most case reports and case series the histories of beta-blocker exposure were not independently verified or confirmed by laboratory testing. Poor correlation between reported estimated doses and subsequent serum concentrations or toxicity has been documented for children with unintentional ingestions of other drugs, such as acetaminophen, for which quantitative laboratory confirmation is routine.

For the purpose of these analyses the expert consensus panel concentrated on cases of beta-blocker-only overdoses. Even when the authors present a history of beta-blocker-only toxicity, the lack of analytical confirmation of the presence of the beta-blocker and the lack of analytical confirmation of the absence of other possible confounding drugs, such as calcium channel blockers, weakens the data culled from these case reports and case series. In addition, an unrecognized underlying medical condition might decrease a patient's tolerance to a particular dose.

In most of the case reports and case series reviewed the exact time of ingestion was not reported or was not known. The time of onset of toxicity usually can only be estimated as occurring within a range of hours after the suspected ingestion. The unclear time interval from ingestion to onset of toxicity is confounded by a lack of definition of consequential toxicity. For instance, after a beta-blocker overdose the development of mild drowsiness in a child could indicate toxicity onset or could represent the approach of nap time.

Another problem encountered was a lack of data on a number of potentially important prehospital interventions and approaches. Studies on prehospital gastrointestinal decontamination of patients with beta-blocker toxicity have not been performed. Likewise, studies on the use of glucagon and other pressor agents to treat beta-blocker toxicity in the prehospital setting have not been reported.

Even the rather straightforward issue of determining the most appropriate mode of transport to an emergency department for the patient with beta-blocker toxicity has not been studied. Given the potential for serious toxicity, expeditious transport by emergency medical services (EMS) might be the most appropriate approach.

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)

Wax PM, Erdman AR, Chyka PA, Keyes DC, Caravati EM, Booze L, Christianson G, Woolf A, Olson KR, Manoguerra AS, Scharman EJ, Troutman WG. Beta-blocker ingestion: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol (Phila) 2005;43(3):131-46. PubMed

ADAPTATION

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

DATE RELEASED

2005 Mar 30

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 Pharmaceuticals.

There are no other potential conflicts of interest reported by the panel members or authors 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 27, 2005. The information was verified by the guideline developer on November 28, 2005.

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