Complete Summary

GUIDELINE TITLE

Diphenhydramine and dimenhydrinate poisoning: an evidence-based consensus guideline for out-of-hospital management.

BIBLIOGRAPHIC SOURCE(S)

Scharman EJ, Erdman AR, Wax PM, Chyka PA, Caravati EM, Nelson LS, Manoguerra AS, Christianson G, Olson KR, Woolf AD, Keyes DC, Booze LL, Troutman WG. Diphenhydramine and dimenhydrinate poisoning: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol (Phila) 2006;44(3):205-23. PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

Diphenhydramine and dimenhydrinate poisoning

Notes:

- This guideline applies to unintentional exposures or exposures that are the results of errors following therapeutic use. Exposures resulting from intentional abuse or self-harm will all require referral to an emergency department for evaluation.
- This guideline applies to ingestion or dermal application of diphenhydramine or the ingestion of dimenhydrinate alone. Co-ingestion of additional

substances could require different referral and management recommendations 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 a suspected ingestion of diphenhydramine or dimenhydrinate or a dermal exposure to diphenhydramine by:

- Describing the process by which an ingestion of or dermal exposure to diphenhydramine or the ingestion of dimenhydrinate might be managed
- Identifying the key decision elements in managing cases of diphenhydramine ingestion/dermal exposure or cases of dimenhydrinate 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 ingestion of diphenhydramine and dimenhydrinate and dermal exposure to diphenhydramine

INTERVENTIONS AND PRACTICES CONSIDERED

Evaluation

1. Assessment of key decision elements for triage:
    - Patient intent

- Patient's age
- Dose and formulation of the product ingested and other co-ingestants
- Time since ingestion
- Patient's symptoms

Management

1. Referral to an emergency department
    - Ambulance transport
    - Physostigmine
2. Skin decontamination with water and soap for chronic dermal exposure
3. Intravenous sodium bicarbonate and benzodiazepine administration by emergency medical services (EMS) if appropriate
4. Home observation
5. Follow-up

MAJOR OUTCOMES CONSIDERED

- Time to onset of effects after overdose
- Toxic threshold doses of diphenhydramine and dimenhydrinate
- Signs and symptoms of toxicity
- Effectiveness of out-of-hospital treatments for diphenhydramine or dimenhydrinate overdose

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 2004) using diphenhydramine or dimenhydrinate as Medical Subject Heading (MeSH) terms with the subheadings poisoning (po) or toxicity (to), limited to humans. A second MEDLINE search (1966 to March 2004) located all diphenhydramine or dimenhydrinate articles that identified patients from 1 through 5 years of age.

The MEDLINE and PreMEDLINE (1966 to March 2004) databases were searched using diphenhydramine or dimenhydrinate as textwords (title, abstract, MeSH term, CAS registry) plus either poison* or overdos* or intox*, limited to humans. This same process was repeated in International Pharmaceutical Abstracts (1970-March 2004, excluding abstracts of meeting presentations), Science Citation Index (1977-March 2004), Database of Abstracts of Reviews of Effects (accessed March 2004), Cochrane Database of Systematic Reviews (accessed March 2004), and the Cochrane Central Register of Controlled Trials (accessed March 2004). Reactions

(1980-March 2004), the diphenhydramine poisoning management in Poisindex, and the bibliographies of recovered articles were reviewed to identify previously undiscovered articles. Furthermore, North American Congress of Clinical Toxicology (NACCT) abstracts published in the Journal of Toxicology Clinical Toxicology (1995-2003) were reviewed for original human data. The chapter bibliographies in four 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 (1985-2002) for deaths resulting from diphenhydramine or dimenhydrinate poisoning. 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 could potentially provide: (1) estimations of mg/kg or ingested doses with or without subsequent signs or symptoms, (2) estimations of time to symptom onset, (3) information regarding management techniques that might be suitable for out-of-hospital use (e.g., gastrointestinal decontamination). Articles excluded were those that did not meet any of the preceding criteria, did not 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

Levels of Evidence	Description of Study Design
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 search were reviewed by a single abstractor. Each article was examined for original human data regarding the toxic effects of diphenhydramine or dimenhydrinate or original human data directly relevant to the out-of-hospital management of patients with diphenhydramine or dimenhydrinate overdose. Relevant data (e.g., dose of diphenhydramine, 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/guidelines%20tables/diphenhydramine%20evidence%20table.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 significant foreign language articles and have their crucial information extracted, translated, and tabulated. A written summary of the data was created and distributed by the abstractor. 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.

Criteria Used to Evaluate Studies and Assign Levels of Evidence

The 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 (see the "Rating Scheme for the Strength of the Evidence" field). Single case reports were classified along with case series as level 4.

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 of 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 record of accomplishment 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). 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 her 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.

Recommendations

1. All patients with suicidal intent, intentional abuse, or in cases in which a malicious intent is suspected (e.g., child abuse or neglect) should be referred to an emergency department **(Grade D)**.
2. In patients without evidence of self-harm, abuse, or malicious intent, poison center personnel should elicit additional information including the time of the ingestion or dermal exposure, determination of the precise dose ingested, and the presence of co-ingestants **(Grade D)**.
3. Patients experiencing any changes in behavior other than mild drowsiness or mild stimulation should be referred to an emergency department. Examples of moderate to severe symptoms that warrant referral include (but are not limited to) agitation, staring spells, inconsolable crying, hallucinations, abnormal muscle movements, loss of consciousness, seizures, or respiratory depression **(Grade D)**.
4. For patients referred to the emergency department, transportation via ambulance should be considered based on several factors including the condition of the patient and the length of time it will take the patient to arrive at the emergency department **(Grade D)**.

Diphenhydramine

5. If the patient has no symptoms, and more than 4 hours have elapsed between the time of ingestion and the call to the poison center, referral to an

emergency department is not recommended. For dermal exposures, if the patient has no symptoms and it has been more than 8 hours since the diphenhydramine was thoroughly removed from the skin, referral to an emergency department is not recommended **(Grade D)**.

6. Patients with acute ingestions of less than a toxic dose, or chronic exposures to diphenhydramine with no or mild symptoms, can be observed at home with instructions to call the poison center back if symptoms develop or worsen. The poison center should consider making a follow-up call at approximately 4 hours after ingestion **(Grade D)**.

Acute Exposures in Children Less than 6 Years of Age

7. Children less than 6 years of age who ingest at least 7.5 mg/kg should be referred to an emergency department **(Grade D)**.

Acute Exposures in Patients 6 Years of Age and Older

8. Patients ingesting at least 7.5 mg/kg or 300 mg (whichever is less) should be referred to an emergency department **(Grade D)**.

Dimenhydrinate

9. If the patient has no symptoms, and more than 6 hours has elapsed between the time of ingestion and the call to the poison center, referral to an emergency department is not recommended **(Grade D)**.
10. Patients with acute ingestions of less than a toxic dose, or chronic exposures to dimenhydrinate with no or mild symptoms, can be observed at home with instructions to call the poison center back if symptoms develop or worsen. The poison center should consider making a follow-up call at approximately 6 hours after ingestion **(Grade D)**.

Acute Exposures in Children Less than 6 Years of Age

11. Children ingesting at least 7.5 mg/kg should be referred to an emergency department **(Grade D)**.

Acute Exposures in Patients 6 Years of Age and Older

12. Patients ingesting at least 7.5 mg/kg or 300 mg (whichever is less) should be referred to an emergency department for evaluation **(Grade D)**.

Other Out-of-Hospital Management

13. For oral exposures, do not induce emesis. Because of the potential for diphenhydramine or dimenhydrinate to cause loss of consciousness or seizures, activated charcoal should not be administered at home or en route to an emergency department **(Grade D)**.
14. For chronic dermal exposures, skin decontamination (with water or soap and water) should be attempted prior to transporting a patient to an emergency department unless hallucinations, loss of consciousness, seizures, and/or arrhythmias are already present. In this circumstance, transportation should

not be delayed and emergency medical services (EMS) personnel should attempt skin decontamination en route to the emergency department **(Grade D)**.

15. Intravenous sodium bicarbonate may be administered by EMS personnel if QRS widening (QRS >0.10 msec) is present and if authorized by EMS medical direction expressed by written treatment protocol or policy, or direct medical oversight **(Grade D)**.
16. Physostigmine should be reserved for administration in a hospital. The lack of literature describing its use in the prehospital setting and the limited literature describing its efficacy and safety in patients with diphenhydramine toxicity preclude its use in the out-of-hospital setting **(Grade D)**.
17. Benzodiazepines may be administered by EMS personnel if agitation or seizures are present and if authorized by EMS medical direction expressed by written treatment protocol or policy, or direct medical oversight **(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 diphenhydramine or dimenhydrinate poisoning.

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 diphenhydramine and dimenhydrinate or a dermal exposure to diphenhydramine

POTENTIAL HARMS

Adverse effects of pharmacological agents (i.e., physostigmine or benzodiazepines) used in the management of diphenhydramine toxicity

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- This guideline has been developed for the conditions prevalent in the US. While the toxicities of diphenhydramine and dimenhydrinate are not expected to vary in a clinically significant manner in other nations, the out-of-hospital conditions could be much different. 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 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. This guideline does not substitute for clinical judgment.

Dose

- The evaluation of doses in out-of-hospital management is limited to an estimation based on the patient's history and the assessment of the product and its packaging (when available for evaluation). The estimated dose of diphenhydramine or dimenhydrinate for an acute ingestion is determined by multiplying the number of units ingested by the size of each unit. If precise data for the ingestion are unknown or unclear (package size, unit size, number of units ingested), poison centers in the United States typically utilize a method in which the maximum potential dose is calculated. For example, if the actual dose ingested cannot be determined, the amount of the diphenhydramine or dimenhydrinate product that is missing is multiplied by the concentration of the formulation.

- When the mg/kg dose or a child's weight was not included in an article, the mg/kg dose was estimated by the use of pediatric growth charts. The 95th percentile weight was used for a particular age and sex. When the sex of the child was not stated, the weight for boys was used. This approach errs on the side of estimating a lower mg/kg dose. Estimated mg/kg doses are italicized throughout the guideline whenever they are presented.

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)

Scharman EJ, Erdman AR, Wax PM, Chyka PA, Caravati EM, Nelson LS, Manoguerra AS, Christianson G, Olson KR, Woolf AD, Keyes DC, Booze LL, Troutman WG. Diphenhydramine and dimenhydrinate poisoning: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol (Phila) 2006;44(3):205-23. PubMed

ADAPTATION

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

DATE RELEASED

2005 Aug 26

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

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

There are no 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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