



Diphenhydramine and Dimenhydrinate Poisoning: an Evidence-Based Consensus Guideline for Out-of-Hospital Management

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PRACTICE GUIDELINE

Diphenhydramine and Dimenhydrinate Poisoning: an Evidence-Based Consensus Guideline for Out-of-Hospital Management*

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In 2003, there were 28,092 human exposures to diphenhydramine reported to poison centers in the US. A related drug, dimenhydrinate, is a less frequent cause of poisonings. Between January 2000 and June 2004, there were 2,534 reported dimenhydrinate ingestions in children less than 6 years of age. An evidence-based expert consensus process was used to create this guideline. Relevant articles were abstracted by a trained physician researcher. The first draft was created by the primary author. The entire panel discussed and refined the guideline before distribution to secondary reviewers for comment. The panel then made changes based on the secondary review comments. The objective of this guideline is to assist 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. 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. The panel's recommendations for dermal or oral exposures to diphenhydramine or oral exposures to dimenhydrinate follow. The grade of recommendation is in parentheses: 1) All patients with suicidal intent, intentional abuse, or in cases in which a malicious intent is suspected (e.g., child abuse or neglect)

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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 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). 5) If the patient has no symptoms, and more than 4 hours have elapsed between the time of diphenhydramine ingestion and the call to the poison center, referral to an emergency department is not recommended. For dermal exposures to diphenhydramine, 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 of diphenhydramine, or chronic exposures to diphenhydramine and 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). 7) Children less than 6 years of age who ingest at least 7.5 mg/kg of diphenhydramine should be referred to an emergency department (Grade D). 8) Patients 6 years of age and older who ingest at least 7.5 mg/kg or 300 mg of diphenhydramine (whichever is less), should be referred to an emergency department (Grade D). 9) If the patient has no symptoms, and more than 6 hours have elapsed between the time of dimenhydrinate 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 of dimenhydrinate, or chronic exposures to dimenhydrinate and 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). 11) Children less than 6 years of age ingesting at least 7.5 mg/kg of dimenhydrinate should be referred to an emergency department (Grade D). 12) Patients 6 years of age and older ingesting at least 7.5 mg/kg or 300 mg of dimenhydrinate (whichever is less), should be referred to an emergency department for evaluation (Grade D). 13) Following oral exposures of diphenhydramine or dimenhydrinate, 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 en route to an emergency department (Grade D). 14) For chronic dermal exposures of diphenhydramine, skin decontamination (with water or soap and water) should be attempted prior to transporting a patient to an emergency department unless moderate to severe symptoms are already present. In this circumstance, transportation should not be delayed, and 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 (Grade D). 16) Physostigmine should be reserved for administration in a hospital (Grade D). 17) Benzodiazepines may be administered by EMS personnel if agitation or seizures are present, and if authorized by EMS medical direction (Grade D).

Keywords diphenhydramine/poisoning; dimenhydrinate/poisoning; poison control centers/standards; practice guidelines

INTRODUCTION

Scope of the Problem and Importance of the Guideline

According to the American Association of Poison Control Center's Toxic Exposure Surveillance System (TESS), there were 28,092 human exposures to diphenhydramine reported to poison centers in the US in 2003; 11,355 (40.4%) of which were evaluated in a healthcare facility. Children less than 6 years of age accounted for 12,089 (43.0%) of all reported diphenhydramine exposures. There were six cases with fatal outcomes in 2003 in which diphenhydramine was apparently the only substance ingested (1). A review of all fatalities reported to TESS from 1985 through 2002 found 48 deaths in which diphenhydramine was the only drug reported to be ingested. The age range for these fatalities was 2 months to 86 years. Seven of these patients were 3 years of age or younger (2).

Despite the frequency of diphenhydramine exposure, there is little consensus among poison centers as to when patients who have been exposed to diphenhydramine should be referred to healthcare facilities (Table 1). Of the 17 centers responding to a request from the expert consensus panel for guidelines in 2004, six had no triage guidelines for diphenhydramine. For the 11 centers with guidelines, the range of diphenhydramine doses requiring hospital referral was 5–17 mg/kg. Appropriate

TABLE 1
Current Diphenhydramine and Dimenhydrinate Guidelines Used by 11 Poison Centers in the United States, 2004

Poison Center	Emergency Department Referral Doses			
	Diphenhydramine <6 years of age	Diphenhydramine ≥6 years of age	Dimenhydrinate <6 years of age	Dimenhydrinate ≥6 years of age
A	17 mg/kg average dose reported to cause symptoms	25 mg/kg stated to be fatal	N/A	N/A
B	≥10 mg/kg	N/A	N/A	N/A
C	>10 mg/kg	20 to 40 mg/kg stated to be fatal	N/A	N/A
D	>10 mg/kg	Notes 1 gram may cause seizures	N/A	N/A
E	>10 mg/kg	Not delineated by age	N/A	N/A
F	≥7.5 mg/kg	N/A	N/A	N/A
G	>7.5 mg/kg	>7.5 mg/kg	N/A	N/A
H	5–7.5 mg/kg syrup of ipecac >7.5 mg/kg refer	5–7.5 mg/kg syrup of ipecac >7.5 mg/kg refer	50 mg dimenhydrinate stated to be equivalent to 25 mg diphenhydramine	50 mg dimenhydrinate stated to be equivalent to 25 mg diphenhydramine
I	>7 mg/kg	>7 mg/kg	N/A	N/A
J	>5 mg/kg if diphenhydramine citrate, multiple dose by 0.66 to convert to diphenhydramine dose	>5 mg/kg	Multiply amount ingested by 0.555 to convert to diphenhydramine dose	Multiply amount ingested by 0.555 to convert to diphenhydramine dose
K	≤2 yr, >100 mg 3–4 yr, >125 mg ≥5 yr, >150 mg	N/A	N/A	N/A

referral is critical as diphenhydramine ingestion can result in severe toxicity including hallucinations, seizures, cardiac arrhythmias, and death.

A related drug, dimenhydrinate, is a less frequent cause of poisonings. Between January 2000 and June 2004, there were 2,534 dimenhydrinate ingestions in children less than 6 years of age reported to TESS. A moderate effect was recorded in 17 cases and a major effect was recorded in three cases. Between 1985 and 2002 there was one dimenhydrinate-associated death reported to TESS (an intentional ingestion by a 19-year-old). Of the 17 poison centers that supplied guideline information for diphenhydramine, only two reported triage guidelines for dimenhydrinate. Although dimenhydrinate exposures are less common, dimenhydrinate is being considered as part of this guideline because it contains diphenhydramine as its primary active ingredient.

Background

Diphenhydramine, an ethanolamine, is an antagonist of the histamine H₁ receptor and has anticholinergic properties. It is found in a variety of nonprescription products as the sole active ingredient or combined with other ingredients for the treatment of colds, allergies, and insomnia. It is available without a prescription as non-chewable, chewable, orally disintegrating tablets, capsules, and as a liquid. For topical use, it is available as a cream, non-aerosol spray, stick, lotion, and gel. The majority of products contain diphenhydramine hydrochloride. Diphenhydramine is also available as a citrate salt; however, this salt form of diphenhydramine is only found in multi-ingredient products (3). For the products that contain diphenhydramine citrate, 65.8% of the diphenhydramine citrate dose is equivalent to diphenhydramine hydrochloride. All doses in this guideline refer to diphenhydramine hydrochloride. Recently, diphenhydramine became available as a tannate salt. The manufacturer states that this salt form reduces the risk of side effects because of altered absorption characteristics. This statement could not be confirmed and there have been no case reports published involving the ingestion of diphenhydramine tannate. In addition, unlike diphenhydramine citrate, a dose conversion between diphenhydramine hydrochloride and diphenhydramine tannate is not available. Therefore, doses of diphenhydramine tannate and diphenhydramine hydrochloride will be assumed to be equivalent for the purposes of this guideline.

Signs and symptoms observed following diphenhydramine overdose are anticholinergic in nature and can include dry mucous membranes, decreased bowel sounds, mydriasis, flushed skin, hyperthermia, drowsiness, tachycardia, hallucinations, and seizures. Death has resulted from seizures and/or cardiac arrhythmias. Cardiac arrhythmias are similar to those following an overdose of other drugs with class Ia antiarrhythmic properties, and result from the blockade of fast sodium channels (4).

Dimenhydrinate is an ethanolamine antihistamine used for the prevention and treatment of motion sickness. It is available in non-chewable and chewable tablets, and as a liquid (3). Dimenhydrinate contains a diphenhydramine moiety and is sometimes described as the “chlorotheophylline salt of diphenhydramine.” According to the official USP monograph, dimenhydrinate is composed of 53–55.5% diphenhydramine and 44–47% 8-chlorotheophylline (5). Information on how dimenhydrinate is metabolized is lacking. Dimenhydrinate might have depressant effects on labyrinthine function, while the drug’s antiemetic effects are most likely due to the diphenhydramine component (3).

Definition of Terms

For the purposes of this analysis, age groups are defined as: 1) children less than 6 years of age and 2) older children and adults. The term “out-of-hospital” is defined as the period before a patient reaches a healthcare facility. An acute exposure is defined as any number of ingestions/applications that occur within an 8-hour period. To be consistent with TESS definitions, a chronic exposure is any number of ingestions/applications over a period of greater than 8 hours (AAPCC TESS Manual 2002).

Intended Users of the Guideline

The intended users of this guideline are personnel in US poison centers. 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 applies to unintentional exposures or exposures that are the result of errors following therapeutic use. Exposures resulting from intentional abuse or self-harm will all require referral to an emergency department for evaluation. The patient’s intent is determined by explicitly asking the caller the reason for the exposure, in addition to considering information such as the patient’s age and the internal consistency of the history. The likelihood of self-harm is much greater in adolescents and adult patients.

Objective of the 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 a suspected ingestion of diphenhydramine, or dimenhydrinate or a dermal exposure to diphenhydramine by: 1) describing the process by which an ingestion of or dermal exposure to diphenhydramine or the ingestion of dimenhydrinate might be managed, 2) identifying the key decision elements in managing cases of

diphenhydramine ingestion/dermal exposure or cases of dimenhydrinate 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 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.

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.

METHODOLOGY

The methodology used for the preparation of this guideline was developed after reviewing the key elements of practice guidelines (6,7). 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 record of accomplishment in clinical care and scientific research in toxicology, board certification as a clinical or medical toxicologist, significant US 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 2004) using diphenhydramine or dimenhydrinate as MeSH terms with the subheadings poisoning (po) or toxicity (to), limited to humans. A second MEDLINE search (1966–March 2004) located all diphenhydramine or dimenhydrinate articles that identified patients from 1 through 5 years of age.

The MEDLINE and PreMEDLINE (1966–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 (8), 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 (9101112) 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, and 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).

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 AAPCC website.

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 (Appendix 2). Single case reports were classified along with case series as level 4.

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 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 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.

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 US 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 (13). 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.

Time Since Ingestion

Ascertaining the time since ingestion is useful in evaluating the potential for toxicity and determining the need for healthcare referral, and the duration of observation in the hospital setting. Taking into consideration the time since ingestion can help the poison center personnel determine if the patient needs referral to a healthcare facility. Once the time of peak effect has passed, an asymptomatic patient with an unintentional ingestion might not require referral to a healthcare facility just because the dose exceeded a critical threshold.

EVALUATION OF LITERATURE

Diphenhydramine: Acute Oral Exposures in Children Less than 6 Years of Age

The maximum recommended therapeutic dosage of diphenhydramine for children less than 6 years of age is 5 mg/kg/day to a maximum of 75 mg per day in divided doses every 6 hours (14).

The review of the literature found no level 1b articles (randomized trials) that investigated a toxic threshold dose for diphenhydramine in children less than 6 years of age, nor were there any level 2b or 3b studies (cohort, case-control studies) with dose-response information in children. However, multiple level 4 or 6 articles (case reports, case series, or their abstracts) were found with dose-response information. Specifically, 19 level 4 articles described 27 cases of the ingestion of diphenhydramine alone in children from 9 weeks to 3.5 years of age (15–33). The lowest amount of diphenhydramine reported to cause death in a child less than 6 years of age was 62.5 mg (11.6 mg/kg) unintentionally given to a 9-week-old infant (16). The lowest dose resulting in severe toxicity (seizures, respiratory arrest, arrhythmias) was 100–150 mg (10–15 mg/kg) ingested by a 13-month-old (23).

Death was reported in a 15-month-old at 33 mg/kg who received an additional 12 mg IV (0.8 mg/kg) in an emergency department (20), a 2-year-old at 39 mg/kg (18), and an 18-month-old girl (weight not reported) who ingested 600 mg (45.5 mg/kg). In the fatality reported by Aaron (a 2.5-year-old), dose information was not provided (15). Doses were not available for six of the seven childhood deaths reported to TESS between 1985 and 2002; the seventh death was published by Baker et al. (16). Doses were also not available for four of the five fatalities reported by Baker et al. (16), a fatality reported

by Wyngaarden and Seevers (33), or for the fatality reported by Lindsay et al. (26).

Hyperactivity, irritability, ataxia, aphasia, and seizures were reported in a 34-month-old who ingested 4 mg/kg (28). Starr and Rankin (30) described an 18-month-old with an ingestion of 15–25 mg/kg that resulted in coma and convulsions. Seizures occurred in a 3-year-old at a dose of 51–58 mg/kg (33). Duerfeldt (19) reported a 3-year-old who ingested 51.5–59 mg/kg and developed seizures and multiple episodes of respiratory depression. It is unknown if the 3-year-old reported by Duerfeldt and the 3-year-old reported in the literature review/case series by Wyngaarden and Seevers are the same child.

In the majority of published cases, patient weights were not provided so mg/kg doses could only be estimated. In one such case, an 18-month-old girl developed hyperthermia, coma, and seizures followed by a stroke that caused residual neurological deficits at a dose of 350 mg (26 mg/kg) (27). In another case, an 18-month-old girl developed poor coordination, purposeless movement of her head and extremities, and absent abdominal and patellar reflexes after ingesting 200 to 300 mg (15 to 23 mg/kg) (17). Severe toxicity (hallucinations, seizures, dysrhythmias, and/or coma) developed in a 20-month-old (sex not reported) who ingested 500 mg (35 mg/kg) (21), a 2.5-year-old girl who could have ingested as much as 500 mg diphenhydramine (31 mg/kg) (25), and a 2.5- to 3-year-old girl who ingested 850 mg (51 mg/kg) (33). However, a 32-month-old (sex not reported) who ingested 450 mg (27 mg/kg) only developed “excitation” that was treated with phenobarbital and resolved the next day (33). Herlitz and Lindberg (22) described an 11-month-old boy who accidentally received 150 mg of diphenhydramine (12.5 mg/kg), resulting in seizures. The next evening, and again 3 weeks later, the same dose was received; seizures followed both overdoses.

A description of how the ingested dose was determined or verified was not provided in the published articles. However, to verify that diphenhydramine was the drug ingested, confirmatory serum concentrations were documented in eight cases (16,20,24,26,31). Tissue concentrations were reported in two cases (15,32), and a gastric washing concentration was documented in one case (33). Attempts by the authors to correlate measured concentrations with the reported amounts ingested were not made.

Toxic doses published in Poisindex (8) are regularly used by Specialists in Poison Information to determine triage criteria. The sole source for the published toxic dose of 17 mg/kg diphenhydramine in the Poisindex diphenhydramine monograph is an abstract (level 6) by Zavitz et al. (34). The abstract was never published as a peer-reviewed article. This abstract described a prospective collection of 184 diphenhydramine or dimenhydrinate ingestions in patients up to 18 years of age from seven poison centers. The mean age was 5.2 years; no median or range was provided. The history was thought to be reliable in 58% of the cases. Fifty-three of the 184 cases were dimenhydrinate ingestions. However, the number of diphenhydramine

products recorded is 169. As 53 dimenhydrinate cases plus 169 diphenhydramine cases would equal 222 cases, and only 184 cases were evaluated, it is unclear whether the unaccounted for 38 cases were excluded or included a combination of both drugs. The abstract reported that the mean ingested dose in symptomatic cases was 17.3 mg/kg; no dose range or median was provided. The way in which dimenhydrinate doses were converted to diphenhydramine doses is unknown. No age-associated data are reported for the 50 symptomatic patients. Symptoms reported included central nervous system depression, tachycardia, and mild hypertension (undefined).

In the published cases, initial symptom onset (drowsiness, agitation, abnormal muscle movements) following oral exposure occurred as early as less than 30 minutes after ingestion in four cases (18,19,23,27), and in 30 minutes to less than 4 hours in nine cases (15,21,24,25,31,33). In the case described by Chitwood and Moore (17), the child was admitted to an emergency department 6 hours after ingestion; the time after ingestion that symptoms began was not stated. In the remaining 13 cases, the time to symptom onset was not reported.

In a published case of an adverse reaction to diphenhydramine in a 4-year-old, the child received a 25 mg dose with a second 25 mg dose given 7 hours later. Within 2 hours of the second dose, torticollis, posturing of the right limbs, slurred speech, and confusion developed. Symptoms improved in 8 hours and were gone in 18 hours (35).

Diphenhydramine: Acute Exposures in Patients 6 Years of Age and Older

The therapeutic dosage for adolescents and adults is 25–50 mg every 4–6 hours, to a maximum of 400 mg per day (36).

There were no level 1 studies specifically investigating a toxic threshold dose for acute diphenhydramine toxicity. There were, however, nine level 1b studies (individual randomized clinical trials) that were reviewed in which therapeutic doses (ranging from 37.5 to 75 mg) of diphenhydramine were administered to generally healthy volunteers of varying ages (37–45). No serious toxicity was noted in these studies. In one case report, a dose of 25 mg in a 26-year-old man resulted in agitation, confusion and paranoia; the reaction recurred when 50 mg was taken the following night. He had no underlying medical or psychiatric conditions; the only other medication taken was acetaminophen (46).

A cohort study (level 2b) attempted to establish a dose-response relationship for diphenhydramine through analysis of multiple diphenhydramine poisoning cases reported to one poison center in Switzerland. The study was divided into two parts, a retrospective portion and a prospective portion, with 232 and 50 cases, respectively. The age range for the retrospective portion was 15–75 years and for the prospective portion it was 16–45 years. In the retrospective portion, doses as low as 300 mg were reported to cause what the author defined as moderate toxicity (hallucinations), and doses as low as 1000 mg

were noted to cause what the author defined as severe toxicity (delirium/psychosis, seizures, coma). In the prospective portion, doses as low as 500 mg were associated with moderate toxicity (agitation, confusion, hallucinations, and/or ECG changes described as minor prolongation of QTc, ST-T changes, first-degree AV block, or left bundle branch block), and doses as low as 1000 mg were associated with severe toxicity. There was no correlation between age and symptom severity. Times to symptom onset were not reported (47).

A case series (level 4) included 136 patients admitted to a single hospital or reported to one poison center over a 3-year period with the ingestion of diphenhydramine alone. The age range was 14 to more than 60 years. In the 29 cases managed at the hospital (all intentional ingestions), diphenhydramine concentrations were determined. No other drugs were detected in gastric contents and/or urine samples. The doses, when known, ranged from 300 mg to over 5 g. The dose was not reported in the one fatality that occurred. Unfortunately, no attempt was made to correlate the amount ingested with symptoms. The authors did not find a correlation between plasma concentrations and the "frequency and extent" of symptoms (48).

There were 29 cases identified in 20 level 4 or 6 articles (4,33,49–66). The lowest dose resulting in hallucinations was 500 mg in a 16-year-old (60). In the case reported by Clark and Vance (4), the ingestion of 750 mg by a 17-year-old resulted in seizures and QRS widening, while in the case reported by Jones et al. (54), the ingestion of 750 mg by a 24-year-old resulted in hallucinations, hypertension, and anticholinergic symptoms. The time to onset of symptoms was less than 30 minutes in three cases (4,33,62), less than 1 hour in four cases (56,65), less than 2 hours in one case (60), and less than 3 hours in one case (51). In the other two cases in which a time was provided, the victims were found with severe symptoms from less than 6 hours to less than 15 hours after ingestion; therefore, it is unknown when their symptoms first appeared (57,66).

Diphenhydramine: Dystonic Reactions

There were seven reported cases (level 4) of acute dystonic reactions occurring after therapeutic doses of diphenhydramine in adults (35,67,69). Jones and Lal (68) described a 50-year-old woman who took 150 mg of diphenhydramine over a 20-minute period for sleep. She developed choreoathetoid movements of upper and lower extremities, writhing movements of the trunk and pelvis, repetitive blinking, and buccolingual and tongue movements. Brait and Zagerman (67) reported that a 19-year-old woman who received an intramuscular dose of diphenhydramine developed spasm of the sternocleidomastoid and platysmus muscles and laryngospasm within an hour of the injection. A 66-year-old woman who received 50 mg of intravenous diphenhydramine developed diffuse tremors, dyskinesia, swallowing difficulties, trismus, dysarthria, motor incoordination, and rigidity. Her symptoms resolved in 45 minutes (69).

Etzel (35) described a 45-year-old woman who ingested 25 mg of diphenhydramine to treat an allergic reaction and received an intravenous dose of 25 mg 30 minutes later for additional therapy. The symptoms occurred within 2 minutes of the injection and included tightness of the throat and jaw, trismus, dysarthria, tremors of the upper extremities and a fixed downward stare. Etzel also documented three other previously reported cases of acute dystonic reactions in adults (ages 19–66 years; 50 mg doses given to two patients, unknown dose given to the third). Symptoms in these three cases included trismus, dysarthria, torticollis, difficulty swallowing, diffuse tremors, limb stiffening, and extensor posturing of the neck. The usual onset was described as being rapid with resolution over several hours.

Diphenhydramine: Rhabdomyolysis

There were eight published cases (level 4) of rhabdomyolysis following diphenhydramine overdose (31,50,53,56,66,70). All patients had elevated creatinine kinase (CK) levels and evidence of renal injury, except for the cases described by Stucka et al. (31) (CK elevated at 4505 U/L and SCr 0.4 mg/dL) and Viertel et al. (66) (CK elevated at 58,000 U/L and SCr 1.1 mg/dL). In the case published by Frankel et al. (70), ingestion of doxylamine could not be excluded. In five cases, other causes for rhabdomyolysis were absent (e.g., lack of seizures, severe agitation, severe electrolyte disturbances or acidosis, or the use of physical restraints) (31,50,56,71). In the case reported by Emadian et al. (50), the patient's temperature on admission was 39.1°C. The temperatures on admission were documented in three of the other four cases and were reported to be 37.6, 37.1, and 37.2°C (31,56). Four of the five cases were adults (50,56,71) and one was a 23-month-old (31). Anticholinergic symptoms present in these cases included tachycardia, mydriasis, and dry skin and mucous membranes. Anticholinergic symptoms were not reported in the case by Hampel et al. (71). The dose ingested in the case reported by Viertel et al. (66) was 1500 mg; the amounts ingested in the remaining cases were not reported.

Diphenhydramine: Chronic Exposures in Children Less than 6 Years of age

Chronic Oral Exposure

There were no level 1 studies (randomized clinical trials) specifically investigating a chronic toxic threshold dose for diphenhydramine. There was one level 1b study in which 50 children ranging in age from 23 months to 12 years were given doses of 1 mg/kg nightly for sleep for 1 week. "Mild drowsiness" developed in only one patient (age unknown, assumed to be "daytime" drowsiness as the drug was being used for sleep but the effect was not described by author) (72).

There were four cases involving chronic oral exposure reported in the literature (level 4). A 3-year-old boy developed

restlessness, with arm flexion and extension, and increased muscle tone after being given an undetermined quantity of diphenhydramine and phenylpropanolamine cold syrup for 2 days (73). A 3.5-year-old boy developed inappropriate behavior, slurred speech, muscular twitching, spastic movements, urinary incontinence, and hyperreflexia. He had received 50 mg of diphenhydramine twice daily for 3–4 days. Symptoms began after he was given an extra 100 mg dose (74). A neonate developed apnea, bradycardia, and poor tone and respiratory effort after being delivered by caesarian section from a mother who had ingested 25 mg of diphenhydramine every 4 hours for weeks prior to delivery (75). Another neonate developed probable diphenhydramine withdrawal (“generalized tremulousness” and diarrhea) on day 5 of life after maternal use of 150 mg daily (76).

Chronic Dermal Exposure

Pharmacokinetic data describing the extent of absorption of diphenhydramine through intact skin are not available. It would be expected that absorption through non-intact skin would be greater, although the extent to which absorption would be increased is not known.

There were nine cases involving dermal exposure of diphenhydramine (77–83) and 11 cases of combined dermal and oral exposure (77–79,84–86). In all cases (level 4), diphenhydramine was being used to treat the itching associated with *Varicella* rash and was applied to broken skin. None of the case descriptions provided specific information on the amount of diphenhydramine applied per application, a measured body surface area to which the drug was applied, a measure of the percentage of body surface area the drug was applied to that was not intact, or an indication as to whether the child was bathed between applications. Therefore, the precise dose that was absorbed could not be quantified. Confirmatory diphenhydramine serum concentrations were obtained in all but five of the 20 cases of chronic toxicity (74,78,80,83,85). In one of these five cases, diphenhydramine was detected by a drug screen (83). There was one death among the 20 cases, which was determined at autopsy to be the result of the patient’s underlying medical condition (80). The other cases resulted in moderate toxicity including symptoms described as bizarre behavior, delirium, abnormal muscle movements, and visual and auditory hallucinations in addition to other anticholinergic symptoms. In all cases, the first symptom noted by the caregivers was irritability or altered behavior. The duration of exposure was recorded for 12 of the 20 cases and ranged from 1 to 6 days (77–80,83,85,86). Symptoms cleared within 8–48 hours following cessation of oral therapy and removal of the diphenhydramine from the skin by washing.

Diphenhydramine: Chronic Exposures in Patients 6 Years of Age and Older

There were no level 1 articles specifically investigating a chronic toxic threshold dose for diphenhydramine. There were,

however, two clinical trials (level 1b) in which adult volunteers developed potentially dose-related adverse effects after receiving chronic doses of diphenhydramine. In the first, doses of 100–200 mg diphenhydramine given over 16 hours were associated with symptoms including constipation, drowsiness, and mild anticholinergic effects (87). No serious toxicity was noted in any volunteer. The second study was a randomized, controlled trial of diphenhydramine for sleep among 50 children ranging in age from 23 months to 12 years given doses of 1 mg/kg diphenhydramine nightly at bedtime for 1 week. As reported in the previous section that described this same study, toxicity was noted in only one patient (age not reported) and the effect was noted only as “mild drowsiness” (assumed to be daytime drowsiness) (72).

There was one level 2b study; a prospective, unblinded, controlled trial in which 10 children aged 6–11 years with various psychiatric disorders were treated with diphenhydramine 200–800 mg daily (88). Doses greater than 450 mg daily were associated with “toxicity” but the exact symptoms were not described.

There were 15 cases in 14 level 4 or 6 articles with some dose-response information (33,85,89–100). However, three of these cases were dermal exposures (89,93,97) and one was a combined dermal/oral exposure (85); therefore, the dose could not be quantified accurately for these cases. Of the remaining cases, there were seven in which the amount of diphenhydramine exceeded the 400 mg maximum oral daily dose for adults (33,90,92,95,96,99). Of these, one was abuse of diphenhydramine at 750 mg/day (95) and another was abuse at 800 mg twice daily (92). Wyngaarden and Seevers (33) reported that a 28-year-old ingested 1500 mg over 60 hours and developed psychosis. There were two reported cases of diphenhydramine abuse by 18-year-old women who each ingested 2000 mg over 48 hours. One developed hallucinations and agitation and the other had altered judgment (33,90). The largest dose ingested for abuse purposes was 2500 mg/day (99). In the only one of these eight cases that did not involve intentional abuse of diphenhydramine, a 28-year-old man was given 2200 mg inadvertently over 5 days. He developed nervousness, hallucinations, and tremor (96).

In four cases, toxicity occurred at doses that were less than the maximum recommended dose (91,94,98,100) and symptoms were severe in two. A 26-year-old woman was started on 50 mg of diphenhydramine three times daily for seborrheic dermatitis. After 300 mg had been given, she developed palpitations, malaise, and dimmed vision. After the next dose, she was found pale, cold, and pulseless; her blood pressure was unmeasurable. Several days after she recovered, she was again given 300 mg and the symptoms returned (palpitations, dim vision, nausea, malaise, disorientation, “excitation,” “pale skin,” and “weak pulse”). Diphenhydramine was discontinued and she recovered (94). A 43-year-old man developed vasculitis and toxic encephalitis following chronic ingestion of 100–400 mg daily; his symptoms reappeared after rechallenge with the same dose (91).

Dimenhydrinate: Acute Exposures in Children Less than 6 Years of Age

The therapeutic dosage of dimenhydrinate is 5 mg/kg/day in divided doses every 6 hours (14).

There were no level 1, 2, or 3 studies specifically investigating a toxic threshold dose for dimenhydrinate in children. There were six cases reported in four level 4 or 6 articles with some dose-response information (33,101–103). The smallest amount of dimenhydrinate reported to cause toxicity (two episodes of apnea) was 8 mg given rectally to a 2-month-old; however, important details may be missing as this was a case reported to the authors as a personal communication. The same authors also reported two 1-month-old twins born prematurely (35 weeks gestation) who developed apnea and a prolonged QTc after the rectal administration of 40 mg (13 mg/kg) dimenhydrinate (103). Wyndgaarden and Seevers (33) reported a 22-month-old who died following a dose of 700 mg; no weight was given (47 mg/kg) and no evidence was given to confirm the dose. Dose information was not provided for the remaining two cases involving a 4-year-old and a 4-month-old (102). Toxicity in these cases included ataxia and hallucinations (101) and seizures, agonal respirations, and arrhythmias (102). Serum concentrations were only reported for one of these six cases (102).

The time to onset of symptoms after rectal administration was less than 6 hours in two of the cases reported by Wolf et al. (103). The time to symptom onset of symptoms following dimenhydrinate ingestion was less than 4.5 hours in the case reported by Wyndgaarden et al. (33), and less than 6 hours in the case reported by Farrell et al. (102). Time to symptom onset was not reported for the other published cases.

Dimenhydrinate: Acute Exposures in Patients 6 Years of Age and Older

The therapeutic dosage is 50 to 100 mg every 4 to 6 hours to a maximum of 400 mg per day (3).

There were no level 1, 2, or 3 studies specifically investigating a toxic threshold dose for dimenhydrinate in patients 6 years of age and older. There were 16 cases (level 4) that involved ingestion of dimenhydrinate alone reported in six level 4 or 6 articles (104–109). The only case that was unintentional was a 42-year-old who developed anticholinergic toxicity from postoperative administration of dimenhydrinate; no dose information was provided (107). Malcolm and Miller (106) reported that two adults who ingested dimenhydrinate for recreational purposes developed euphoria and hallucinations. One of the adults ingested 16 50-mg tablets (800 mg) and one ingested 16 tablets of unknown strength. The two never sought treatment and the description of symptoms was based on self-reports. Brown and Sigmundson (104) described an 18-year-old who had “disappointing” results with 500 mg dimenhydrinate so he ingested 900–1250 mg. He developed marked anticholinergic symptoms, hallucinations, difficulty speaking and swallowing, and he became violent. In one case series, five girls

ingested 500–750 mg and three girls ingested 750 mg to get high. The girls were aged 14 to 17 years. They developed mild tachycardia, ataxia, and feelings of being “spaced out.” One of the girls who ingested 750 mg reported hallucinations (108). In a case series of three teenagers who regularly abused dimenhydrinate, a 17-year-old stated that he ingested 500–750 mg at a time (an unknown number of times) to get high over a 2-year period. In the second case, another 17-year-old reported that “many times” she ingested 250–350 mg at a time for a “cheap high”. The dose was not specified for the 18-year-old in the third case (105). There is one published death following an intentional overdose with 5000 mg (109). In the case reported by Winn and McDonnell (109), symptoms began within 30 minutes of the ingestion. Time to onset of symptoms was not reported in the other published cases.

Dimenhydrinate: Chronic Exposures in Children Less than 6 Years of Age

There were no level 1, 2, or 3 studies specifically investigating a toxic threshold dose for chronic dosing of dimenhydrinate in young children. All three reported cases of chronic dimenhydrinate exposures in children less than 6 years of age are reported as personal communications (level 5). A 4-week-old developed seizures, opisthotonus, respiratory failure, anuria, and bowel atonia after receiving 24 mg rectally over 2 days. A 28-day-old given 21 mg dimenhydrinate rectally over 10 hours developed urinary retention. In the remaining case, a 2-month-old given 4 mg orally over 3 days (three doses of 1.37 mg) was reported to be “apathetic” and had extrapyramidal symptoms (103).

Dimenhydrinate: Chronic Exposures in Patients 6 Years of Age and Older

There were no level 1, 2, or 3 studies specifically investigating a toxic threshold dose for chronic dosing of dimenhydrinate in this age group. One level 1b study evaluated the effectiveness of dimenhydrinate for motion sickness. Dimenhydrinate 100 mg every 12 hours for two doses was mixed with 50 mg of caffeine. Dry mouth, vertigo, and gait disturbances were reported among the 16 adult volunteers (110). In the three cases of regular abuse described by Gardner and Kutcher (105), withdrawal symptoms were reported to include lethargy, anhedonia, and depression.

There is one reported case of a dystonic reaction following therapeutic doses of dimenhydrinate (25 mg/day for 3 days) given to an 11-year-old (111).

POTENTIAL OUT-OF-HOSPITAL TREATMENTS

Gastrointestinal Decontamination

Ipecac Syrup

There are no studies or case reports evaluating the use of ipecac syrup following diphenhydramine or dimenhydrinate

overdose. Because these drugs can cause drowsiness and seizures, this management option would not be recommended.

Activated Charcoal

Guay et al. (43) studied the adsorption of diphenhydramine by activated charcoal *in vitro* and *in vivo* with a three-way crossover trial in six volunteers (level 1b). Volunteers were given diphenhydramine 50 mg. Following this dose, one group received 50 g of activated charcoal within 5 minutes, one group received 50 g of activated charcoal 60 minutes after the dose, and a control group received no activated charcoal. The absorption of diphenhydramine was evaluated by evaluating multiple blood samples. Although a trend for a reduction in diphenhydramine absorption was noted for the 60-minute group (12.3% reduction), statistical significance was not achieved. The 5-minute group did demonstrate a statistically significant reduction in absorption (94.8%). Activated charcoal did not accelerate elimination of diphenhydramine.

Eyer and Sprenger (112) gave a charcoal-sorbitol suspension to five volunteers 2 minutes after the administration of diphenhydramine 50 mg. The absorption of diphenhydramine was decreased by 28%. Less than 2% of diphenhydramine was absorbed when the diphenhydramine and charcoal-sorbitol were given concurrently.

No studies were found regarding the use of activated charcoal following dimenhydrinate overdose.

Cathartics

Eyer and Sprenger (112) reported that sorbitol at acidic and neutral pH *in vitro* decreased the adsorption of diphenhydramine by activated charcoal by 19%. No evidence was found supporting the use of cathartics in diphenhydramine or dimenhydrinate poisoning. As whole bowel irrigation is not used as an out-of-hospital procedure for the management of poisonings, it is not discussed in this guideline.

Physostigmine

There are no level 1, 2, or 3 studies investigating the efficacy or safety of intravenous physostigmine following diphenhydramine overdose.

There is one case series (level 4) that retrospectively reviewed the charts of 52 patients with anticholinergic poisoning who were treated with physostigmine, benzodiazepines, or both in an emergency department or intensive care unit. Forty-five (86%) patients received physostigmine; 26 of them received physostigmine as the sole therapy. Diphenhydramine was the ingested drug in 24 (46%) of the 52 cases. However, the results were not broken down by ingested substance. Therefore, of the 96% of patients in whom agitation was reversed and the 87% of patients in whom delirium was reversed, it is not known how many of the non-responders had ingested diphenhydramine. Adverse effects were noted in five patients (11%) who received physostigmine alone or in

combination with a benzodiazepine and included diaphoresis, emesis, diarrhea, and bradycardia. Complications were noted in eight patients (18%) who received physostigmine alone or in combination with a benzodiazepine and included rhabdomyolysis, aspiration pneumonia, endotracheal intubation, and ethanol withdrawal syndrome. In the two patients with rhabdomyolysis, physostigmine was the sole agent given. Since a breakdown by ingested agent was not provided, it is unknown how many of the patients with adverse effects or complications had ingested diphenhydramine. In patients receiving benzodiazepines, side effects were noted in four (15%), and 10 (38%) developed complications. Based on these findings, the authors concluded that physostigmine was safer and more effective than benzodiazepines for the management of agitation and delirium in patients with anticholinergic toxicity (113).

There are eight published cases and abstracts (levels 4 and 6) in which physostigmine was used in a hospital setting for management of diphenhydramine exposure (20,56–58,61, 62,95,114,115). The abstract (level 6) by Reisdorf et al. (115) just reported that physostigmine was used twice in the 11,663 cases evaluated. Padilla and Pollack (95) documented the effectiveness of physostigmine following a diphenhydramine overdose by a 31-year-old. Two milligrams were given initially, which resulted in an improvement in mental status; a repeat dose of 1 mg was required 90 minutes later with similar results. Prior to physostigmine administration, tachycardia and altered mental status were present; significant agitation and cardiac arrhythmias were absent. Khosla et al. (56) reported that physostigmine administration (dose not reported) resulted in a “dramatic” improvement in mental status when given following a diphenhydramine overdose in a 29-year-old with anticholinergic symptoms (dry secretions, heart rate 131/minute, decreased bowel sounds). Köppel et al. (57) reported its use in a 14-year-old. Symptoms of anticholinergic toxicity disappeared within minutes after the administration of 2 mg physostigmine, recurred 8 hours later, and disappeared after a second 2-mg dose. Bangh and Roberts (114) reported that a 20-year-old pregnant woman became less tachycardic and more coherent after 1 mg of physostigmine was administered. Mild anticholinergic delirium and sedation recurred 1 hour later. The heart rate of the fetus also decreased. Rinder et al. (62) reported its use (1-mg with a repeat 1-mg dose given 10 minutes later), however the other multiple medications given preclude evaluation of its effectiveness (diazepam, phenobarbital, pancuronium). Payne et al. (61) reported that physostigmine was not effective (dose not reported) when administered to a 29-year-old with seizures, metabolic acidosis, and a widened QRS interval. In two cases with fatal outcomes, physostigmine was administered without significant improvement being seen. In the case reported by Krenzelok et al. (58), 2 mg with a repeat dose of 1 mg was administered to a 14-year-old presenting with respiratory depression, asystole followed by arrhythmias, and possible seizure activity. Goetz et al. (20) described a

15-month-old who was having seizures and arrhythmias prior to administration of 0.7 mg physostigmine. Therefore, the effectiveness of physostigmine for the management of diphenhydramine toxicity was only documented in four of the eight published cases (56,57,95,114).

Borkenstein et al. (116) reported a case in which 0.5 mg physostigmine was administered to a 4-year-old with hallucinations following a dimenhydrinate overdose. The child's symptoms resolved. Matschiner et al. (107) reported its use following postoperative administration of dimenhydrinate. A physostigmine dose of 0.5 mg was also reported in the one published dimenhydrinate fatality; the patient had arrhythmias before and after administration and multiple other medications were given (109).

Other Treatments

Sodium Bicarbonate

Diphenhydramine has quinidine-like effects on myocardial conduction. As sodium bicarbonate is used to manage the cardiac toxicity caused by other medications with class Ia antiarrhythmic properties, its use following diphenhydramine overdose has been proposed (4).

There are seven cases in four published level 4 articles (4,58,59,65) and two published level 6 abstracts (52,63) describing the use of sodium bicarbonate in adults to treat cardiac arrhythmias following diphenhydramine overdoses. The QRS narrowed to normal values in four cases (4,52,65) and minimally narrowed (from 162 to 151 msec following sodium bicarbonate) or remained unchanged in three cases (59,63,65). In the fatality reported by Krenzelok et al. (58), the change in QRS interval following sodium bicarbonate administration was accompanied by correction of acidosis (initial pH 6.77).

There is one published case of the administration of sodium bicarbonate following an overdose of dimenhydrinate. A 4-month-old had a narrowed QRS complex (62 msec) 25 minutes after sodium bicarbonate was administered. The initial QRS interval was not reported; the child was reported to have had a junctional tachycardia with left bundle branch block (102).

Dermal Decontamination

Following chronic dermal toxicity in seven cases, improvement began after decontamination of the skin to remove applied diphenhydramine (77,79,82,84). The other reported cases of dermal toxicity did not specifically state that the diphenhydramine was removed from the skin.

CONCLUSIONS

Key Decision Points for Triage

The panel chose to emphasize the importance of information that would be needed in order to make a sound triage decision for the patient with the ingestion of a product containing

diphenhydramine or dimenhydrinate, or a dermal exposure to a product containing diphenhydramine. These variables include the patient's intent, the time since the ingestion, the patient's symptoms, the dose and formulation of the product ingested, and other co-ingestants. The expert consensus panel agreed that in each case, the judgment of the specialist in poison information or the poison center medical director might override any specific recommendation from this guideline.

Patient Intent

The panel concluded that 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. Patients without these characteristics are candidates for consideration of out-of-hospital management of their ingestion.

Diphenhydramine

Minimum Toxic Dose of Diphenhydramine in Children Less Than 6 Years of Age

There is little information in the literature to adequately define a minimum acute toxic dose for patients less than 6 years of age. Many of the case reports only confirm that large single ingestions cause either severe toxicity, which can be successfully treated, or death. The strength of the evidence in the abstract by Zavitz et al. (34) was considered to be insufficient to support managing children with ingestions up to 17 mg/kg at home. Although seizures were reported with a dose of 4 mg/kg (28), the panel felt that this case appeared to be an outlier, as this would be the equivalent of less than or equal to 50 mg in the majority of children less than 2 years of age; a dose that all 11 of the poison centers providing guidelines currently manage at home. Excluding the case by Reyes-Jacang (28), the lowest dose reported to cause severe toxicity (seizures, respiratory arrest, arrhythmias) was 10–15 mg/kg (23), and a death was reported with 11.6 mg/kg (16). The panel noted that six of the 11 poison centers submitting guidelines used a dose of greater than 7.5 mg/kg as their referral dose (an additional center uses greater than or equal to 7.5 mg/kg). The panel concluded that doses of 7.5 mg/kg or more of diphenhydramine merited emergency department referral.

With only two cases (not involving neonatal exposure) of chronic oral diphenhydramine toxicity in patients less than 6 years of age, a chronic toxic dose could not be determined. It is clear, however, that the combination of oral diphenhydramine therapy and dermal application of diphenhydramine to non-intact skin places patients less than 6 years of age at risk for toxicity. A dose of topical diphenhydramine that would be expected to cause toxicity cannot be determined from the case reports. In the absence of an established toxic dose (from chronic oral and/or dermal exposure), the panel concluded that any patient 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.

Dystonias have been documented with therapeutic doses. Patients experiencing dystonias should be referred to an emergency department.

Minimum Toxic Dose of Diphenhydramine in Patients 6 Years of Age and Older

The doses reported to cause acute toxicity in the publications by Radovonovic et al. and Köppel et al. are similar (47,48). Doses as low as 300 mg have caused moderate toxicity (hallucinations), while doses of 1000 mg or more have been documented to cause severe toxicity (delirium/psychosis, seizures, coma) or death. Rhabdomyolysis has occurred in the absence of severe toxicity. Although the accuracy of the ingested doses in these reports can be questioned because all cases involved intentional ingestions (for self-harm or abuse purposes), the data from these case series are consistent. It is also noted that all reported cases involved patients 14 years of age and older. Because of the lack of information for children between 6 and 13 years of age, the panel concluded that patients 6 years of age and older who ingest at least 7.5 mg/kg (the referral dose for younger children) or at least 300 mg, whichever is less, should be referred for emergency department evaluation.

All reported cases of chronic toxicity in patients 6 years of age and older involved doses close to those causing severe toxicity or subtherapeutic doses. Therefore, the dose at which chronic toxicity requiring emergency department evaluation would be expected cannot be determined from the literature. In the absence of an established toxic dose (oral or dermal), the panel concluded that any patient already 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 many include (but are not limited to) agitation, staring spells, inconsolable crying, hallucinations, abnormal muscle movements, loss of consciousness, seizures, or respiratory depression.

Dystonias have been documented with therapeutic doses. Patients experiencing dystonias should be referred to an emergency department.

Time to Symptom Onset – Diphenhydramine

In the majority of cases, the time to symptom onset was not reported, or the patient was found with severe symptoms so it could not be determined when the first symptoms appeared. In the cases involving children less than 6 years of age, where time to symptom onset could be determined, symptoms occurred as early as less than 30 minutes to less than 4 hours after ingestion. In the cases involving those 6 years of age and

older, symptoms reportedly were first observed in less than 30 minutes to less than 3 hours after ingestion. Therefore, the panel concluded that observation for up to 4 hours would be appropriate. In children less than 6 years of age with chronic diphenhydramine exposures, symptoms cleared within 8–48 hours following cessation of oral therapy and removal of the diphenhydramine. Therefore, the panel concluded that patients who remain asymptomatic 8 hours after the last application of diphenhydramine are unlikely to develop toxicity.

Dimenhydrinate

There is little information on the metabolic fate of dimenhydrinate, and the contribution of 8-chlorotheophylline to the drug's toxicity profile is unknown. Whether the effects of 8-chlorotheophylline would be similar to those of theophylline, either pharmacokinetically or pharmacodynamically, has not been studied. Therefore, it cannot be assumed that the toxicity of dimenhydrinate is solely due to its diphenhydramine component. Although 62.5% of a dimenhydrinate dose contains the same amount of diphenhydramine base as an equivalent dose of diphenhydramine hydrochloride (diphenhydramine hydrochloride contains 87.5% diphenhydramine; dimenhydrinate contains between 53 and 55.5% diphenhydramine), there is no literature to support a triage guideline that would be based on multiplying a dimenhydrinate dose by 0.625 prior to utilizing the same toxic dose established for diphenhydramine hydrochloride.

Minimum Toxic Dose of Dimenhydrinate in Children Less Than 6 Years of Age

The published literature is inadequate to determine an acute toxic dose for children less than 6 years of age. Four of the five cases of nonfatal acute exposures in children less than 6 years of age occurred in infants 4 months of age or younger, and in three of these cases dimenhydrinate was administered rectally and not orally. The dose ingested by the sole non-infant, a 4-year-old, was not reported (101). This case, combined with the one reported case of a 700-mg dose causing death in a 22-month-old (33), was not enough to determine a minimum toxic dose. Therefore, the panel had no information on which to make a recommendation for a toxic dose of dimenhydrinate in children. The use of the same toxic dose identified for diphenhydramine (at least 7.5 mg/kg) was considered to be a conservative, but reasonable, approach to dimenhydrinate ingestions in this age group.

The cases of chronic toxicity in children less than 6 years of age were not well documented and all involved infants 2 months of age or younger (103). In two of the three cases, toxicity occurred following rectal and not oral administration. In the case published by Wolf et al. (103), the reported oral dose administered was subtherapeutic. Therefore, a chronic dose expected to cause toxicity cannot be determined from the literature. In the absence of an established toxic dose, the panel

concluded that any patient already 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.

Minimum Toxic Dose of Dimenhydrinate in Patients 6 Years of Age and Older

There was only one case of acute toxicity that was unintentional. In this case, the dose was not reported (107). Hallucinations were reported following intentional ingestions of 250–350 mg in one patient (105) and in five adolescents following doses of 500–750 mg (108). Based on this information, the panel selected a dose of 300 mg or more as the criterion for emergency department evaluation. Of note, all reported cases involved patients 14 years of age or older. Because of the lack of information for children between 6 and 13 years of age, the panel concluded that patients 6 years of age and older who ingest at least 7.5 mg/kg (the referral dose for younger children) or at least 300 mg, whichever is less, should be referred for emergency department evaluation.

There were no cases of chronic dimenhydrinate toxicity resulting from supratherapeutic doses given over 8 hours or more in patients 6 years of age or older reported in the literature. Therefore, a chronic dose that can be expected to cause toxicity cannot be determined from the literature. In the absence of an established toxic dose, the panel concluded that any patient already 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 many include (but are not limited to) agitation, staring spells, inconsolable crying, hallucinations, abnormal muscle movements, loss of consciousness, seizures, or respiratory depression.

Time to Symptom Onset – Dimenhydrinate

Only three cases were published that provided information on time to symptom onset following an oral ingestion of dimenhydrinate (33,102,109). The time to symptom onset ranged from less than 30 minutes to less than 6 hours after the ingestion. Based on these cases, and being conservative because the information was limited, the panel concluded that a minimum 6-hour observation time would be a reasonable approach in this age group.

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 the 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 pre-hospital 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).

These recommendations are summarized in Appendix 4.

IMPLICATIONS FOR RESEARCH

The expert consensus panel identified the following topics where additional research is needed or analysis of existing databases might be useful.

1. The acute toxic doses of diphenhydramine and dimenhydrinate in children less than 6 years of age need to be determined.

2. The acute toxic doses of diphenhydramine and dimenhydrinate in children 6 years of age and older need to be determined.
3. The contribution of 8-chlorotheophylline to dimenhydrinate's toxicity requires study.
4. The toxic dose of diphenhydramine tannate in children and adults needs to be determined.
5. The efficacy of sodium bicarbonate for the management of diphenhydramine and dimenhydrinate induced cardiac toxicity requires further validation.
6. The safety and efficacy of physostigmine in the prehospital management of diphenhydramine and dimenhydrinate toxicity requires further study.

DISCLOSURES

There are no potential conflicts of interest reported by the expert consensus panel or project staff regarding this guideline.

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APPENDIX 1**Expert Consensus Panel Members**

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APPENDIX 2**Grades of Recommendation and Levels of Evidence**

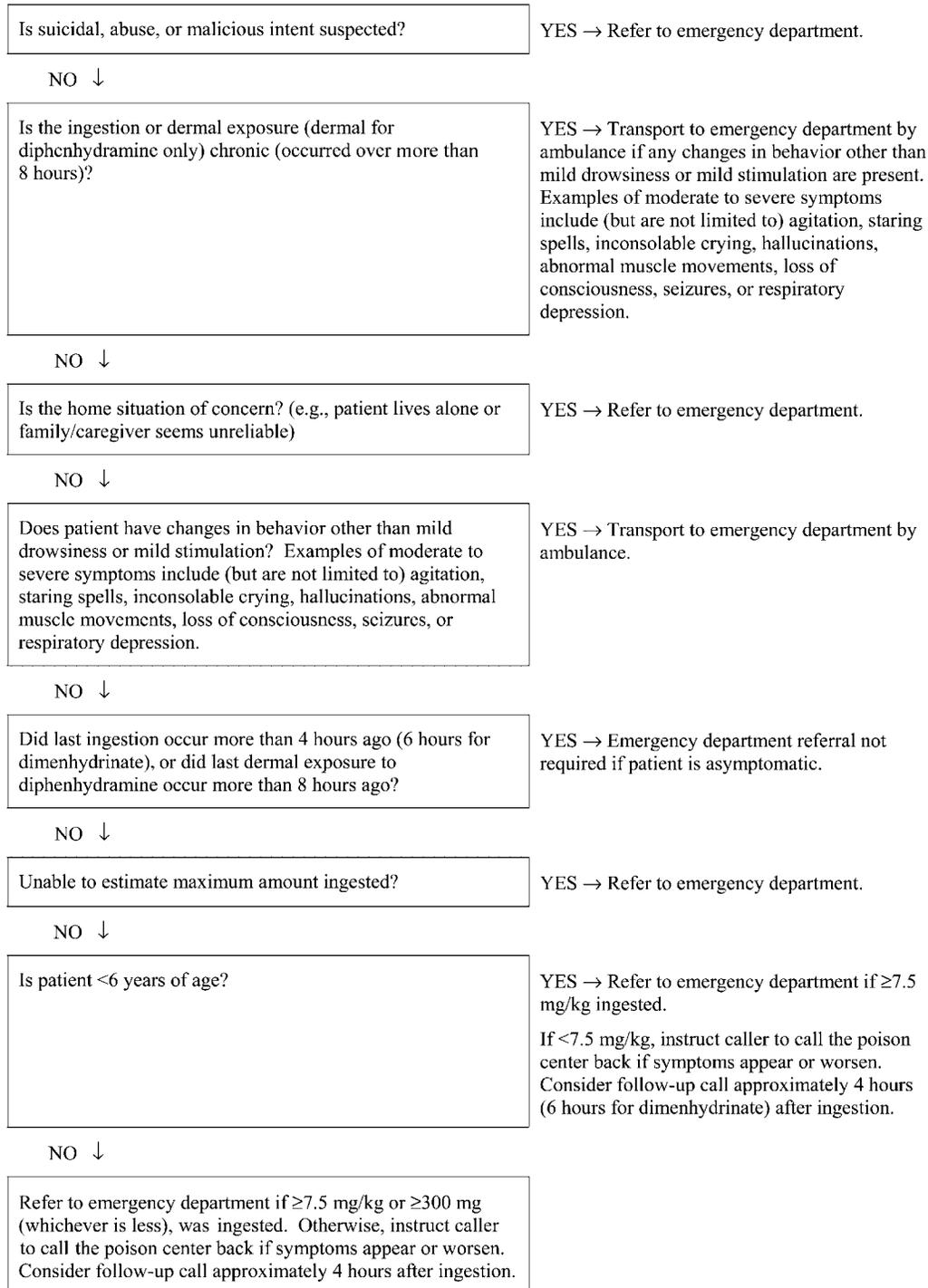
Grade of Recommendation	Level of Evidence	Description of Study Design
A	1a	Systematic review (with homogeneity) of randomized clinical trials
	1b	Individual randomized clinical trials (with narrow confidence interval)
	1c	All or none (all patients died before the drug became available, but some now survive 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
Z	6	Abstracts

APPENDIX 3**Secondary Review Panel Organizations**

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

APPENDIX 4

Algorithm for Triage of Diphenhydramine* or Dimenhydrinate Poisoning



* All diphenhydramine doses refer to diphenhydramine hydrochloride. If the product contains diphenhydramine citrate, multiply the dose by 0.658 to obtain the equivalent dose of diphenhydramine hydrochloride. If the product contains diphenhydramine tannate, assume that the dose is equivalent to diphenhydramine hydrochloride.

For skin exposures, the affected area(s) should be washed thoroughly with soap and water. If the patient is symptomatic, referral should occur based on the severity of symptoms.

