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PRACTICE GUIDELINE

Salicylate poisoning: An evidence-based consensus guideline for out-of-hospital management*

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A review of U.S. poison center data for 2004 showed over 40,000 exposures to salicylate-containing products. A guideline that determines the conditions for emergency department referral and pre-hospital care could potentially optimize patient outcome, avoid unnecessary emergency department visits, reduce health care costs, and reduce life disruption for patients and caregivers. An evidence-based expert consensus process was used to create the guideline. Relevant articles were abstracted by a trained physician researcher. The first draft of the guideline was created by the lead 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 out-of-hospital management of patients with a suspected exposure to salicylates by 1) describing the process by which a specialist in poison information should evaluate an exposure to salicylates, 2) identifying the key decision elements in managing cases of salicylate exposure, 3) providing clear and practical recommendations that reflect the current state of knowledge, and 4) identifying needs for research. 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. Recommendations are in chronological order of likely clinical use. The grade of recommendation is in parentheses: 1) Patients with stated or suspected self-harm or who are the victims of a potentially malicious administration of a salicylate, should be referred to an emergency department immediately. This referral should be guided by local poison center procedures. In general, this should occur regardless of the dose reported (Grade D). 2) The presence of typical symptoms of salicylate toxicity such as hematemesis, tachypnea, hyperpnea, dyspnea, tinnitus, deafness, lethargy, seizures, unexplained lethargy, or confusion warrants referral to an emergency department for evaluation (Grade C). 3) Patients who exhibit typical symptoms of salicylate toxicity or nonspecific symptoms such as unexplained lethargy, confusion, or dyspnea, which could indicate the development of chronic salicylate toxicity, should be referred to an emergency department (Grade C). 4) Patients without evidence of self-harm should have further evaluation, including determination of the dose, time of ingestion, presence of symptoms, history of other medical conditions, and the presence of co-ingestants. The acute ingestion of more than 150 mg/kg or 6.5 g of aspirin equivalent, whichever is less, warrants referral to an emergency department. Ingestion of greater than a lick or taste of oil of wintergreen (98% methyl salicylate) by children under 6 years of age and more than 4 mL of oil of wintergreen by patients 6 years of age and older could cause systemic salicylate toxicity and warrants referral to an emergency department (Grade C). 5) Do not induce emesis for ingestions of salicylates (Grade D). 6) Consider the out-of-hospital administration of activated charcoal for acute ingestions of a toxic dose if it is immediately available, no contraindications are present, the patient is not vomiting, and local guidelines for its out-of-hospital use are observed. However, do not delay transportation in order to administer activated charcoal (Grade D). 7) Women in the last trimester of pregnancy who ingest below the dose for emergency department referral and do not have other referral conditions should be directed to their primary care physician, obstetrician, or a non-emergent health care facility for evaluation of maternal and fetal risk. Routine referral to an emergency department for immediate care is not required (Grade C). 8) For asymptomatic patients with dermal exposures to methyl salicylate or salicylic acid, the skin should be thoroughly washed with soap and water and the patient can be observed at home for development of symptoms (Grade C). 9) For patients with an ocular exposure of methyl salicylate or salicylic acid, the eye(s) should be irrigated with room-temperature tap water for 15 minutes. If after irrigation the patient is having pain, decreased visual acuity, or persistent irritation, referral for an ophthalmological

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examination is indicated (Grade D). 10) Poison centers should monitor the onset of symptoms whenever possible by conducting follow-up calls at periodic intervals for approximately 12 hours after ingestion of non-enteric-coated salicylate products, and for approximately 24 hours after the ingestion of enteric-coated aspirin (Grade C).

Keywords Aspirin/poisoning; Salicylic acid/poisoning; Poison control centers/standards; Practice guidelines

Introduction

Scope of the problem and importance of the guideline

In 2004, poison control centers in the U.S. reported 40,405 human exposures to salicylates. Of these, 25,239 (63%) were unintentional exposures and 17,659 (44%) involved children under the age of 6 years. Aspirin as a single agent was involved in 18,181 cases (45%), aspirin in combination with other drugs contributed 9,267 cases (23%), methyl salicylate was involved in 12,005 cases (30%), and other non-aspirin salicylates accounted for 952 cases (2%). Exposures to salicylates resulted in 3,804 cases (9%) with moderate toxicity and 524 (1%) with severe toxicity. There were 64 (0.2%) deaths. Aspirin alone was involved in 54 of the deaths; none were young children (1).

During the 1950s through 1970s the drug category most frequently responsible for poisoning deaths in children in the U.S. was salicylates. A combination of factors such as child-resistant packaging, mandatory restrictions on the number of children's aspirin tablets per bottle, the association of aspirin use and Reye's syndrome, decline in market share, and improved critical care have all contributed to nearly eradicating aspirin-related deaths in children after the 1990s. Despite this decline in childhood deaths, poison exposures and toxicity from salicylates still persist as a common problem in all ages. Poisoning can follow the unintentional ingestion of a single large dose or it can follow repeated supratherapeutic doses, particularly in the elderly. Salicylates are also used as a means to commit or attempt suicide. Some salicylates, such as methyl salicylate (oil of wintergreen), are not intended to be ingested but are ingested intentionally or swallowed mistakenly for another product. Chronic dermal application of some salicylate-containing products can produce systemic salicylate toxicity. Due to the number of salicylate exposures, their potential life-threatening severity, and the variety of exposure situations, a guideline on the out-of-hospital management of salicylate poisoning is indicated for consistency in case management by poison control centers.

Background on Salicylates

Salicylate products

Salicylates represent a group of compounds that are derivatives of salicylic acid in which an ester or salt is added to modify its properties in order to make the substance suitable for therapeutic use. Salicylic acid is irritating to mucous membranes and it is only used topically. Although aspirin (acetylsalicylic acid) is the most commonly used salicylate, the salicylates discussed in this guideline are all metabolized to salicylate, which is primarily responsible for the toxicity observed. Since salicylates are used for many everyday maladies such as fever, inflammation, and pain and for cardiovascular prophylaxis, they are found in most homes (Table 1). Dermal products are used for local relief of pain and soreness in muscles and joints.

Several forms of salicylate are available for use as tablets, powders, and suppositories. In addition to regular aspirin, it is also formulated as an enteric-coated tablet intended for dissolution in the small intestine. Dermal preparations of salicylates may be absorbed and cause systemic toxicity. In order to compare the relative toxicity of the salicylates in this guideline, the dose of the salicylates has been standardized to be equivalent to aspirin (Table 2) (2). Not all forms of non-aspirin salicylate, such as salsalate (3), fully dissociate to salicylate and the extent of this dissociation is variable. Salicylamide does not convert to salicylate, does not cause symptoms of salicylate poisoning (4), and is not considered in this guideline.

Pharmacokinetics and pathophysiology of salicylate toxicity

Aspirin is readily absorbed from the gastrointestinal tract as both aspirin and salicylate, with peak serum concentrations of therapeutic doses typically achieved in 1 hour. Enteric-coated tablets exhibit variable rates of absorption with peak serum concentrations achieved in 4–6 hours after therapeutic doses (5), but the onset of systemic effects can be delayed by 8–12 hours (6). The rate of absorption may be greatly delayed when a large number of tablets are ingested and form tablet bezoars or concretions (7). Dermal formulations of some salicylates, such as 15% methyl salicylate cream (8), can exhibit less bioavailability when applied to the buccal cavity compared to oral ingestion.

Since aspirin is readily hydrolyzed to salicylate in the gastrointestinal tract and bloodstream (aspirin's serum half-life is 15 minutes), salicylate is principally responsible for the systemic toxic effects. The rate of decline of salicylate concentrations will slow as the amount of salicylate in the body increases. Two major metabolic pathways of biotransformation are capacity-limited (Michealis-Menten kinetics) and lead to accumulation and slower elimination as salicylate in the body increases. Healthy adults begin to exhibit saturation kinetics with acute aspirin doses of 1–2 g (9). This dose-dependent, prolonged excretion increases a person's risk of serious toxicity. Salicylate kinetics are also a factor in chronic and acute-on-chronic poisonings. A small increase in dose or slowed excretion due to evolving renal dysfunction can cause a greatly prolonged elimination time, and a disproportionate increase in serum salicylate concentration with

Table 1. Aspirin dosage by indication and age (211)

Indication	Usual oral dosage
Analgesic and antipyretic	Adults and adolescents: 325–500 mg every 3 hr, 325–650 mg every 4 hr, or 650–1,000 mg every 4 hr, as needed Maximum recommended daily dose: 4 g
Analgesic	Children: 1.5 g/m^2 body surface area in 4–6 divided doses 2–4 years old: 160 mg every 4 hr 4–6 years old: 240 mg every 4 hr 6–9 years old: 320–325 mg every 4 hr 9–11 years old: 320–400 mg every 4 hr 11–12 years old: 320–480 mg every 4 hr
Antirheumatic (anti-inflammatory)	Adults and adolescents: 3.6–5.4 g/day in divided doses Children: 80–100 mg/kg per day in divided doses
Cardiac prophylaxis and platelet aggregation inhibition in adults	81–325 mg/day, uncomplicated cases 325–1,000 mg/day after ischemic episodes
Thrombosis inhibition in adults	325 mg preoperatively, then 325 mg three times/day

Table 2. Relationship of salicylates to aspirin equivalent doses (2,212)

Salicylate	Conversion factor	Type of use
Aspirin	1.00	Oral, suppositories
Bismuth subsalicylate*	0.50	Oral
Choline magnesium trisalicylate	1.30	Oral
Choline salicylate	0.75	Oral
Magnesium salicylate	1.21	Oral
Methyl salicylate	1.18	Dermal, flavoring agent
Oil of wintergreen†	1.40	Dermal, flavoring agent
Salicylic acid‡	1.30	Dermal
Salsalate	1.40	Oral
Sodium salicylate	1.13	Oral
Trolamine salicylate	0.63	Dermal

Multiply the dose of the non-aspirin salicylate by the conversion factor to get the equivalent dose of aspirin. The conversion factor is calculated by dividing the molecular weight of aspirin by that of the non-aspirin salicylate except for those that dissociate into more than 1 molecule of salicylate. Magnesium salicylate and salsalate yield two molecules of salicylate; choline magnesium trisalicylate yields three molecules of salicylate. Salsalate may not fully convert to salicylate.

*Pepto-Bismol, Maalox Total Stomach Relief, and Kaopectate (manufactured in 2004 and thereafter) contain 262 (regular strength) or 525 mg (extra strength) of bismuth subsalicylate per 15 mL, which yield 8.7 or 17.5 mg of an aspirin equivalent dose per mL, respectively.

†Oil of wintergreen is a liquid that contains methyl salicylate 98% w/w; 1 mL is equivalent to aspirin 1.4 g. The conversion factor allows for the specific gravity of 1.18 for w/w % expressions.

‡Salicylic acid in concentrations greater than 6% may be destructive to tissues upon contact; ingestion can produce chemical burns.

attendant severe toxicity. The serum half-life of salicylate is typically 2–4 hours at low doses, approximately 12 hours with anti-inflammatory doses, and can be prolonged to 15–30 hours or more following overdosage. Approximately 2–30% of salicylate is excreted unchanged in the urine, with less renal excretion occurring in acidic urine or in patients with renal dysfunction (5,10).

The signs and symptoms of salicylate intoxication are related to local irritation of the gastrointestinal tract, direct stimulation of the central nervous system respiratory center, stimulation of the metabolic rate, disturbance of carbohydrate and lipid metabolism, and interference with hemostasis (11–14). Typical gastrointestinal symptoms of acute ingestion include vomiting, abdominal pain, and occasional hematemesis. Symptoms of acute systemic toxicity include hyperpnea, tachypnea, tinnitus, deafness, hyperpyrexia, diaphoresis, lethargy, confusion, coma, and seizures. Complications of salicylate poisoning include dehydration, electrolyte disturbances,

mixed and complex acid-base disturbances, gastrointestinal ulcers, hepatitis, cerebral edema, CSF glucopenia, and non-cardiogenic pulmonary edema. Although salicylates rarely produce spontaneous hemorrhage, they can decrease prothrombin formation, platelet adhesiveness, and platelet numbers. Contact to the eye or mucous membranes with dermal preparations of salicylate can be irritating and can cause temporary discomfort (15).

Symptoms of chronic salicylate poisoning are similar to those of acute exposures except that gastrointestinal symptoms may be less pronounced, patients appear more severely ill, and CNS symptoms may be more prominent (14). Neurological findings such as agitation, confusion, slurred speech, hallucinations, seizures, and coma can be the presenting symptoms and can potentially mislead initial assessment (16–19). Often pulmonary edema is present in adults upon admission to a healthcare facility (16). Salicylate poisoning should be considered in adults with acid-base disorders of unknown origin, particularly when neurological symptoms are present (20).

Salicylic acid presents additional and unique toxicities. Salicylic acid is found in creams and liquids (in varying concentrations) for the topical treatment of acne (0.5–10%), psoriasis (3–6%), and warts (5–60%). Concentrations of 3–6% are keratolytic, and concentrations greater than 6% are destructive to tissues (21). Salicylic acid is well absorbed into the bloodstream through healthy skin, and the extent of absorption varies with the concentration and formulation (22). When a salicylic acid-containing product with a concentration greater than 6% is swallowed, tissue may be subject to chemical burns upon contact, particularly from wart removal products (17% salicylic acid and greater) (23). Lower concentrations produce local irritation and erythema. Risks for systemic and local toxicity should be recognized for products that contain salicylic acid.

Definition of terms

This guideline is intended to address exposure to the salicylates found in Table 2. Other salicylates may share some of the toxicity of these agents, but they can exhibit different properties and are not included in this document. Since aspirin is the best known salicylate, aspirin equivalent doses (AED) have been calculated for non-aspirin salicylates in this guideline. The AED represents the salicylate content of a substance expressed as a comparable dose of aspirin. The term "out-of-hospital" is defined as the period before a patient reaches a healthcare facility. For the purpose of this guideline, two age groups are defined as either children less than 6 years of age and older children and adults. The older age group is more likely to attempt self-harm and to conceal an exposure. To be consistent with TESS definitions, acute exposures are defined as those occurring over a period of up to 8 hours, and chronic exposures are those that occur over a period of more than 8 hours (1). Acute-on-chronic exposure is an acute exposure in a patient who has already been exposed to salicylate for more than 8 hours, typically as drug therapy of a disease.

Intended users of this guideline

The intended users of this guideline are personnel in U.S. poison control centers. This guideline has been developed for the conditions prevalent in the U.S. While the toxicity of salicylates is 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 also provides information for poison center staff members and researchers who wish to further develop the information base available for the development of guidelines for the out-of-hospital management of poisoning.

Objective of this guideline

The objective of this guideline is to assist poison center personnel in the appropriate out-of-hospital triage and initial out-of-hospital management of patients with a suspected exposure to salicylates by 1) describing the process by which a specialist in poison information should evaluate an exposure to salicylates, 2) identifying the key decision elements in managing cases of salicylate exposure, 3) providing clear and practical recommendations that reflect the current state of knowledge, and 4) identifying needs for research.

This guideline applies to exposure to the specified salicylates alone. Exposure to additional substances could require different referral and management recommendations depending on the combined toxicities of the substances. This review focuses on the ingestion of more than a single therapeutic dose and the effects of an overdose. Although therapeutic doses of salicylate can sometimes cause adverse effects in adults and children—some idiosyncratic and some dose-dependent—these cases are not considered. The management of Reye's syndrome associated with aspirin use in children is beyond the scope of this guideline (24). It does not address bismuth toxicity resulting from bismuth subsalicylate ingestion.

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 (25,26). An expert consensus panel was established

to develop the guideline (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 in clinical care and scientific research in toxicology, board certification as a clinical or medical toxicologist, significant U.S. poison control 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.

Search strategy

Literature searches for relevant articles were performed by a single investigator. The National Library of Medicine's MEDLINE database was searched (1966–March 2004) using aspirin or salicylic acid (exploded as MeSH terms) with the subheadings poisoning (po) or toxicity (to), limited to humans. The MEDLINE database was further searched using aspirin or bismuth subsalicylate or choline salicylate or ethyl salicylate or glycol salicylate or homomenthyl salicylate or magnesium salicylate or methyl salicylate or methylsalicylate or octyl salicylate or phenyl aminosalicylate or phenyl salicylate or potassium aminosalicylate or potassium salicylate or salicylamide or salicylic acid or salsalate or sodium aminosalicylate or sodium salicylate or sodium thiosalicylate or triethanolamine salicylate or trolamine salicylate as textwords (title, abstract, MeSH term, CAS registry), plus either poison* or overdos* or intox*, limited to humans. This 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 Cochrane Central Register of Controlled Trials (accessed March 2004). Reactions (1980–March 2004), the salicylate poisoning management in Poisindex, and the bibliographies of recovered articles were reviewed to identify previously undiscovered articles. Furthermore, NACCT abstracts published in the Journal of Toxicology Clinical Toxicology (1995–2004) and Clinical Toxicology (2005) were reviewed for original human data.

Four major toxicology textbooks were reviewed for recommendations on the management of salicylate poisonings and for citations of additional articles with original human data in the chapter bibliographies. The Toxic Exposure Surveillance System (TESS) maintained by the American Association of Poison Control Centers was searched for deaths resulting from unintentional salicylate poisoning. These cases were abstracted for review by panel members. All U.S. poison control centers were surveyed in 2004 to ascertain their out-of-hospital management and triage practices for salicylate poisonings.

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, searching specifically for those that dealt with estimations of doses with or without subsequent signs or symptoms of toxicity, and management techniques that might be suitable for out-of-hospital use (e.g., gastrointestinal decontamination). Articles that did not meet either of the preceding criteria, did not add new data (e.g., reviews, editorials), or that exclusively described inpatient-only procedures (e.g., dialysis) were excluded.

Data extraction process

All articles that were retrieved from the original search were reviewed by a single trained physician abstractor. The complete article was reviewed for original human data regarding the toxic effects of salicylates or original human data directly relevant to the out-of-hospital management of patients with salicylate toxicity or overdose. Relevant data (e.g., dose, effects, time of onset of effects, therapeutic interventions or decontamination measures provided, efficacy or results of any interventions, and overall patient outcome) were compiled into a table and a brief description of each article was written. This evidence table is available at http://www.aapcc. org/DiscGuidelines/Guidelines%20Tables/Salicylate%20Evidence%20Table.pdf. The table of all abstracted articles was then forwarded to the panel members for review and consideration in developing the guideline. Every attempt was made to locate foreign language articles and have their crucial information extracted, translated, and tabulated. A written summary of the data was created and distributed by the abstractor. Copies of all of the abstracted articles were made available for reading by the panel members on a secure 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 and case series were classified as level 4.

Guideline writing and review

A draft guideline was prepared by the lead author (listed first). 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 lead author for response. The lead 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 lead author, the draft was prepared for the external review process. External review of the second draft was conducted by distributing it electronically to AAPCC, AACT, and ACMT members and the secondary review panel. The secondary review panel consisted of representatives from the federal government, public health, emergency services, pediatrics, pharmacy practice, and consumer organizations (Appendix 3). Comments were submitted via a discussion thread on the AAPCC website or privately through email communication to AAPCC staff. All submitted comments were rendered anonymous, copied into a table of comments, and reviewed by the expert consensus panel and the lead author. The lead author responded to each comment in the table and his responses and subsequent changes in the guideline were reviewed and accepted by the panel. Following a meeting of the expert consensus panel, the final revision of the guideline was prepared.

Estimation of weight-based dose

When the mg/kg dose was not provided and the child's weight was not stated in articles describing patients under 6 years of age, the mg/kg dose was estimated by the use of pediatric growth charts (27). 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 wherever they are presented.

Evaluation of Evidence

Current poison control center practices

The triage and management of salicylate ingestions by U.S. poison control centers appears to vary based on the responses of 16 centers (Table 3); two other centers reported that they did not have guidelines for salicylates. The average dose that the responding centers utilize to refer patients to an emergency department is 225 mg/kg, but there is a two-fold difference in the range of doses (150–300 mg/kg) with equal numbers on both sides of the average. Ten of 16 poison centers' guidelines did not specify whether the dose referred to salicylate or aspirin. This difference could result in a 23% variance in interpreting the dose. The duration for follow-up monitoring was stated by five poison centers as 2, 4, 6, 6, and 24 hours after initial contact. Three centers indicated that ipecac syrup was indicated for ingestions of 150–300 mg/kg, and one center used a dose of 130–300 mg/kg. Three centers recommended activated charcoal at home when 150–300 mg/kg (two centers) or 100–200 mg/kg (one center) was ingested, and two utilized an unspecified gastric decontamination method when the dose exceeded 150 mg/kg. Some centers

Table 3. Acute salicylate ingestion action threshold (mg/kg) guidelines of 16 poison centers, 2004

Poison center	Observe at home	Ipecac at home	Charcoal at home	Decontamination at home NOS	Send to ED	Dose expression*
1	<150		150–300		>300	ASA
2	<200				>200	ASA
3	<150	150–300			>300	Sal
4	<150			150–250	>250	Sal
5	<150	150–300			>300	Sal
6	≤300				>300	Sal
7	≤130	>130–300			>200	Sal
8	<100		100–200		>200	Sal
9	<150				≥150	Sal
10	<150				≥150	ASA
11	≤250				>250	Sal
12	<150	150–250†			>250	Sal
13	<150		150–300		>300	ASA
14	≤150				>150	ASA
15	≤150				>150	Sal
16	≤150			>150	>150‡	ASA

*The doses refer to the heading of the guideline or the specific salicylate stated in the guideline. A salicylate dose (Sal) is 23% less by weight than aspirin (ASA), but it is presumed that the doses refer to aspirin.
†If the ingestion was more than 4 hours earlier, refer to ED.
‡If no emesis.
ED = emergency department.
NOS = not otherwise specified.

cited one of two reviews as a reference for their guideline (19,28). In a review of his experiences with pediatric salicylate poisoning, Done indicated that 240 mg/kg of aspirin would be required for moderate severity poisoning and approximately 480 mg/kg for lethality (28). In a general review of salicylate toxicity, Temple stated that doses of 150–300 mg/kg would be expected to produce mild to moderate toxic reactions, 300–500 mg/kg would produce serious reactions, and doses in excess of 500 mg/kg would be potentially lethal (19). Neither of these reviews cited original research as the basis for the recommendations.

Review of textbooks

The review of salicylate poisoning chapters in toxicology textbooks revealed variation in their recommendations (11–14). Three books provided no dose guidelines for emergency department referral for acute exposures and one recommended referral when doses exceed 150 mg/kg (11). The acute toxic dose was stated as 150 mg/kg or more by all four texts. Severe toxicity was expected at doses of 300–500 mg/kg (11) or in excess of 500 mg/kg (13). Three books indicated that chronic poisoning was possible with doses exceeding 100 mg/kg per day (11,13,14). The threshold doses were not referenced to reports of original research. It was unclear whether the doses referred to doses of aspirin or salicylate.

Poisindex, a computerized toxicology reference used by poison control centers, indicates that unintentional ingestions under 150 mg/kg can usually be managed at home. Induction of emesis should be considered for doses between 150–300 mg/kg if ingested within the preceding hour. Patients who ingest more than 300 mg/kg should be referred to a health care facility (29). A review article is cited as the reference for these recommendations (19). Poisindex also indicates that chronic ingestion of more than 100 mg/kg/day over 2 days can produce toxicity.

Review of TESS mortality data

An analysis of the American Association of Poison Control Centers' Toxic Exposure Surveillance System (TESS) database for deaths from unintentional exposures to salicylates during 1985 to 2003 identified 23 deaths (Table 4). Aspirin (15 cases) and methyl salicylate (eight cases) were the only salicylates associated with the deaths and the only substances implicated in the exposures. Six cases of acute methyl salicylate poisoning involved ingestions (expressed as mL of oil of wintergreen) of 5–15 mL (AED 7–21 g), 10 mL (AED 14 g,

Table 4. Deaths from salicylates with an unintentional reason from TESS, 1985–2003

Chronicity	Age (yr)	Substance*	Estimated dose
Acute	0.3	Aspirin	Unknown
Acute	1	Aspirin	Unknown
Acute	1.2	Aspirin	Unknown
Acute	1.3	Aspirin	Unknown
Acute	2	Aspirin	Unknown
Acute	3	Aspirin	558 mg/kg
Acute	55	Aspirin	Unknown
Acute	88	Aspirin[†]	Unknown
Acute	Adult	Aspirin	Unknown
Acute	2	Methylsalicylate	10 mL (AED 14 g, 959 mg/kg)
Acute	2	Methylsalicylate	15 mL (AED 21 g, 1,438 mg/kg)
Acute	45	Methylsalicylate	60 mL (AED 84 g)
Acute	70	Methylsalicylate	Unknown
Acute	80	Methylsalicylate	10 mL (AED 14 g)
Acute	80	Methylsalicylate	Unknown
Acute	88	Methylsalicylate	5–15 mL (AED 7–21 g)
Acute	91	Methylsalicylate	120 mL (AED 168 g)
Acute-on-chronic	72	Aspirin	Unknown
Chronic	2	Aspirin[‡]	Unknown
Chronic	14	Aspirin[§]	Unknown
Chronic	71	Aspirin	Unknown
Chronic	87	Aspirin	Unknown
Chronic	92	Aspirin	Unknown

*Other substances were not suspected as causes of death, but other drugs were available in two cases as noted in the footnotes.
[†]Patient was taking a ß-blocker as therapy.
[‡]Reye's syndrome suspected as contributing to the cause of death.
[§]Dimenhydrinate was available to the patient, but there was no confirmation that it was involved in toxicity.
AED = aspirin equivalent dose.

959 mg/kg), 10 mL (AED 14 g), 15 mL (AED 21 g, *1,438 mg/kg*), 60 mL (AED 84 g), and 120 mL (AED 168 g). One case of acute aspirin ingestion involved 558 mg/kg of aspirin. Serum salicylate concentrations were reported in all but two cases. Ten of the cases were elderly adults and nine were young children.

Review of the literature

There were no articles specifically addressing out-of-hospital management of salicylate exposures, but several articles contained information relevant to out-of-hospital care. Evidence regarding dose, toxicity, and time of onset is primarily limited to case reports and case series (level 4). The literature search did not identify any level 1 articles specifically investigating a toxic threshold dose or onset of effects of any salicylate.

The severity of salicylate toxicity was categorized into one of three categories when sufficient information was available. These categories are used throughout this guideline: mild = not life-threatening local effects (e.g., vomiting, erythema); moderate = not life-threatening systemic effects (e.g., mild acidosis, lethargy, coagulopathy); severe = serious or potentially life-threatening local effects (e.g., hematemesis), systemic effects (e.g., coma, severe acidosis, seizures, pulmonary dema, shock), or clinical effects requiring dialysis. These categories were developed specifically for this guideline but generally are comparable to those utilized by TESS (1).

The evidence is organized into sections dealing with acute ingestions by age group, chronic ingestions by age group, acute-on-chronic ingestions, and dermal exposures. In cases where it was difficult to determine whether the exposure was acute or chronic, the cases were not included. For non-aspirin drugs, the AED was estimated when possible (Table 2).

Acute ingestions in patients less than 6 years of age

Aspirin

Several case reports or series (levels 4 and 6) of aspirin poisoning in children less than 6 years of age were found, but many articles did not describe total dose, exact age of the child, or the severity of toxicity. There were two large case series (30,31) and 17 case reports with sufficient dose and effect information (32–39). The lowest dose of aspirin reported to cause toxicity was *99 mg/kg* (1,875 mg) in a $3^1/_2$-year-old boy who developed vomiting, restlessness, and hyperpnea. He was treated with intravenous fluids and had an uneventful recovery (37). A retrospective review (level 4) stated that doses as low as 46 mg/kg produced toxicity, but the authors only described the child as being toxic from aspirin (30). The lowest dose of aspirin associated with severe toxicity was 143 mg/kg (1,944 mg) in a 14-month-old boy who developed vomiting, restlessness, hyperpnea, tachypnea (56 breaths per minute), a temperature of 39°C, cyanosis, and dehydration. He was treated with intravenous fluids and sent home after 10 days of hospitalization (39). The lowest fatal dose from salicylate poisoning was 800 mg/kg in a 20-month-old boy who ingested 10.8 g 19.5 hours prior to admission to a hospital. Within 2 hours of ingestion he was lethargic and irritable. Marked hyperpnea later prompted his transportation to a hospital. Upon hospital admission he was comatose, hyperpneic, tachypneic, and tachycardic with a temperature of 38.3°C. Peritoneal dialysis was begun 21.5 hours after ingestion, but his condition continued to deteriorate and he died 54 hours after ingestion. Salicylate was measured in the urine and dialysate; the serum salicylate concentration was approximately 100 mg/dL at the start of dialysis (36). The only fatality reported to TESS with a known dose of aspirin was a 3-year-old child who ingested 558 mg/kg (Table 4).

Bismuth subsalicylate

In the only case report (level 4) identified for acute bismuth subsalicylate exposure, the ingestion of Pepto-Bismol 90 mL (AED 787 mg, *30 mg/kg*) resulted in the death of a 4-year-old girl, but an aspirin 325 mg suppository was given at the hospital, which likely contributed to the toxicity. A serum salicylate concentration of 111.2 mg/dL (8.05 mmol/L) was measured approximately 24 hours after ingestion and suggests that a much larger dose was ingested than was reported (40). This case was not included in subsequent considerations of toxic doses.

Methyl salicylate

Fifteen cases of methyl salicylate ingestion were found with sufficient information described in 11 case series or reports (level 4) (41–51). The smallest amount of methyl salicylate reported to cause toxicity was approximately 346 mg/kg (AED 408 mg/kg) in a 5-year-old girl who became "acutely ill" (47). The ingestion of approximately 4 mL of oil of wintergreen (AED 5,600 mg, *378 mg/kg*) by a 21-month-old boy resulted in moderate toxicity (45). Ingestion of less than 5 mL of oil of wintergreen (AED 7000 mg, *486 mg/kg*) by a 20-month-old boy resulted in severe toxicity (41). The lowest dose of methyl salicylate associated with death was approximately 5 mL of oil of wintergreen ingested by a $2^1/_2$-year-old boy (AED 7,000 mg, *432 mg/kg*) (42). In two other cases of small-volume ingestions of oil of wintergreen, ingestion of a mouthful by a 22-month-old girl led to moderate toxicity and the administration of 5 mL (AED 7000 mg, *1,400 mg/kg*) in a 1-month-old girl resulted in death (50). Two fatal doses of oil of wintergreen reported in TESS were 10 mL (AED 14,000 mg, *959 mg/kg*) and 15 mL (AED 21,000 mg, *1,438 mg/kg*), both in 2-year-old girls (Table 4).

Sodium salicylate

One case report (level 4) was found with dose and effect information for sodium salicylate (52). The ingestion of up to 56,000 mg of sodium salicylate (AED 63,280 mg, *4,219 mg/kg*)

in an alcoholic solution by a 23-month-old boy led to moderate systemic toxicity.

Unspecified salicylate

A single cohort study (level 2b) was found with dose and effect information on unspecified salicylate ingestions in patients less than 6 years of age. In this prospective study of 38 children with acute salicylate poisoning, specific clinical effects were not listed, but doses as low as approximately 90 mg/kg were noted in two children with mild severity of toxicity (53).

Summary

When the doses for all salicylates within the categories of severity of toxicity (Fig. 1) are compared, there is wide variability for all categories. Ranges of 99–5,526 mg/kg for non-fatal cases and 432–2,763 mg/kg for fatalities were evident (see details in Tables 5 and 6). The lowest AEDs categorized as moderate, severe, and fatal toxicity were 99, 144, and 432 mg/kg, respectively. The median doses for these categories were 378, 493, and 1,130 mg/kg, respectively. For oil of wintergreen, doses of approximately 5 mL were associated with moderate, severe, and fatal toxicity.

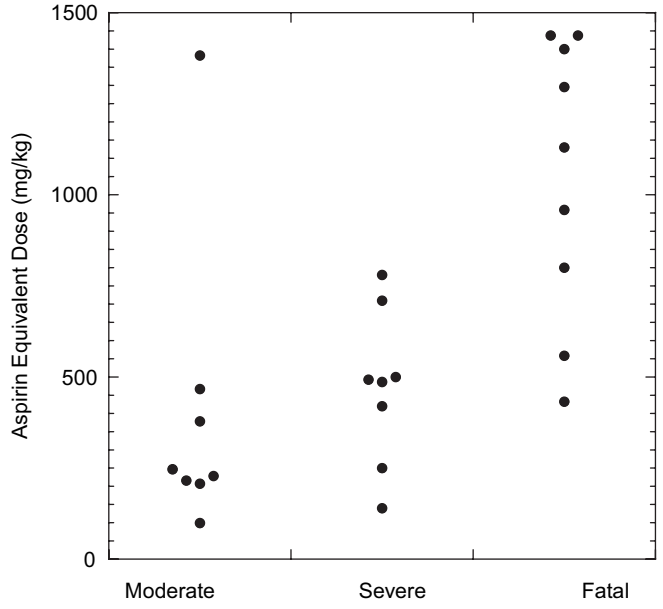

Fig. 1. Acute ingestion of salicylate with aspirin equivalent doses under 1,500 mg/kg and severity of salicylate toxicity in patients less than 6 years of age. See text for definitions. Data from Tables 4 and 6.

Acute ingestions in patients 6 years of age and older

Aspirin

There were two studies (level 2b) that reported dose and effect information for aspirin exposures in patients older than 6 years of age (54,55). Multiple case reports or series (levels 4 and 6) were found in which 66 cases with sufficient detail were reported in 42 articles (31,38,39,56–94). The lowest fatal aspirin dose reported in a patient older than 6 years of age was 13,000 mg in a 24-year-old man who died in 1918. He took the aspirin to relieve flu-like symptoms and died within 2 days after "a large quantity of blood was passed by the bowel." There was no laboratory confirmation of the presence of salicylate in his body (78). The next lowest fatal dose was 32,500 mg in a 30-year-old patient (58). In a 1949 report, a 54-year-old man presented to a hospital in an anuric and stuporous state approximately 12 hours after ingesting 5,000–6,100 mg of aspirin. He died within 30 hours of ingestion, but it is unclear whether the cause of death was aspirin or treatment with "artificial antipyresis and rapidly acting stimulants" (79). The lowest dose associated with severe toxicity was 12,600 mg in a 6-year-old child who developed agitation, hyperventilation, and acute renal failure that required peritoneal dialysis (38). The next lowest dose causing severe toxicity was 19,500 mg in 21-year-old patient who received peritoneal dialysis (63). The lowest aspirin dose reported as moderate toxicity involved a 14-year-old boy who ingested 9,750 mg (195 mg/kg) at home and exhibited vomiting, headache, tinnitus, orthostatic hypotension, and tachypnea within 6 hours of ingestion. At the hospital he had a respiratory rate of 28 breaths per minute and a serum salicylate concentration of 60 mg/dL (4.3 mmol/L). After 9 hours of hospitalization

Table 5. Guide to information found in Tables 6–11

Key to severity: Mild = non-life-threatening local effects (e.g., vomiting, erythema); Moderate = non-life-threatening systemic effects (e.g., acidosis or symptoms of mild acidosis, lethargy, coagulopathy); Severe = serious or potentially life-threatening local effects (e.g., hematemesis), systemic effects (e.g., coma, severe acidosis, seizures, pulmonary edema, shock), or clinical effects requiring dialysis.

Note for onset of symptoms: the value represents maximal time of onset from the time of exposure. When a value is preceded by a "<" symptoms were present on arrival at a healthcare facility but might have begun earlier.

Abbreviations: AED = aspirin equivalent dose; EC = enteric coated; LOE = level of evidence; m.o. = months old; NR = not reported; Pos. = positive by qualitative analysis; SSC = serum salicylate concentration; URI = upper respiratory illness; y.o. = years old; ? = unknown or unclear.

Doses for children in italics represent calculated mg/kg doses based on pediatric growth charts at the 95th percentile weight (27).

Table 6. Cases with dose information on acute ingestions in patients less than 6 years of age, sorted by drug and dose

Dose	Age (yr)	Other factors	Severity	Onset	Confirmed by SSC	Reference (LOE)
Aspirin						
Retrospective review of children with salicylate poisoning treated at 1 hospital over 10 years found that acute ingestion of as little as 3,185 mg (46 mg/kg) in a 2 y.o. resulted in toxicity. Confirmed by serum salicylate concentrations.						30 (4)
Series of 19 children with acute salicylate toxicity. Doses as low as 88 mg/kg resulted in toxicity, but severity could not be assessed for individual cases.						31 (4)
99 mg/kg, 1,875 mg	3.5		Moderate	13 hr	Yes	37 (4)
143 mg/kg, 1,944 mg	1.17		Severe	30 min	NR	39 (4)
207 mg/kg, 2,400 mg	1.08	Acetaminophen	Moderate	12 hr	Yes	38 (4)
216 mg/kg	2		Moderate	1.5 hr	Yes	32 (6)
228 mg/kg, 3,969 mg	3		Moderate	?	Yes	34 (4)
247 mg/kg, 3,900 mg	2.5		Moderate	<24 hr	NR	39 (4)
250–380 mg/kg	3		Severe	<20 hr	Yes	33 (4)
>420 mg/kg	1.33		Severe	<5 hr	Yes	33 (4)
500–670 mg/kg	1.5		Severe	<7 hr	Yes	33 (4)
>710 mg/kg	2.33		Severe	<3 hr	Yes	33 (4)
1,130 mg/kg	1.83		Death	<24 hr	Yes	33 (4)
780 mg/kg	1.08		Severe	<17 hr	Yes	35 (4)
800 mg/kg, 10,800 mg	2		Death	<2 hr	Yes	36 (4)
7,000–8,000 mg, *467 mg/kg*	2.17		Moderate	?	Yes	34 (4)
~10 tablets (? strength)	2.75		Moderate	?	Yes	34 (4)
15 tablets (? strength)	2.42		Moderate	?	Yes	34 (4)
Bismuth subsalicylate						
90 mL 1.8%; (AED 783 mg)	4	Aspirin 325 mg given 13 hr after hospitalization	Death	3 hr	Yes	40 (4)
Methyl salicylate						
~4 mL oil of wintergreen; AED 6,000 mg, *378 mg/kg*	1.75		Moderate	Over 5 hr	Yes	45 (4)
~346 mg/kg; AED 408 mg/kg	?		"Acutely ill"	NR	Yes	47 (4)
5 mL; AED 7,000 mg, *432 mg/kg*	2.5		Death	NR	NR	42 (4)
~5 mL oil of wintergreen; AED 7,000 mg, *486 mg/kg*	1.67		Severe	?	Yes	41 (4)
<5 mL oil of wintergreen; AED 7,000 mg, *493 mg/kg*	1.83		Severe	?	Yes	46 (4)
15 mL; AED 21,000 mg, *1,296 mg/kg*	2.5		Death	<12 hr	NR	42 (4)
15 mL oil of wintergreen; AED 21,000 mg, *1,382 mg/kg*	2		Moderate	6	NR	50 (4)

5 mL oil of wintergreen; AED 7,000 mg, *1,400 mg/kg*	0.08		Death	2	NR	50 (4)
15 mL; AED 21,000 mg, *1,438 mg/kg*	2		Death	?	NR	42 (4)
20 mL oil of wintergreen; AED 28,000 mg, *1,842 mg/kg*	2		Moderate	<25 min	Yes	44 (4)
30 mL oil of wintergreen; AED 42,000 mg, 2,763 mg/kg	2		Death	Immediate (local); 4 hr (systemic)	Yes	51 (4)
60 mL; AED 84,000 mg, *4,828 mg/kg*	3		Moderate	15 min	Yes	49 (4)
60 mL oil of wintergreen; AED 84,000 mg, *5,526 mg/kg*	2		Severe	?	Yes	43 (4)
20 mL (? strength)	0.8	Other ingredients in product	Severe	30 min	Yes	48 (4)
1 mouthful oil of wintergreen	1.83		Moderate	6	NR	50 (4)
Sodium salicylate						
Up to 56,000 mg; AED = 63,280 mg, *4,219 mg/kg*	1.92	Alcohol	Moderate	15 min	Yes	52 (4)
Unspecified salicylate						
Prospective study of 38 children with acute salicylate poisoning. Individual effects not specified, but the lowest dose resulting in clinical effects was 900 mg (approximately 90 mg/kg).						53 (2b)

See Table 5 for key to abbreviations.

he developed clinical and laboratory signs of hypocalcemia and alkalemia during treatment with a sodium bicarbonate infusion. He eventually recovered following restoration of his electrolyte and acid-base balance (65).

Choline magnesium trisalicylate

There were no reports of acute self-poisoning or unintentional toxicity identified for acute choline magnesium trisalicylate ingestions. One randomized clinical trial (level 1b) involved 24 adult volunteers who received choline magnesium trisalicylate (AED 1,300 mg) as tablets or as an aqueous solution. One subject in each group complained of nausea (95).

Methyl salicylate

There was one retrospective case series (96) and four case reports (levels 4 or 6) with sufficient detail identified (97–100). An 86-year-old woman experienced moderate local and systemic symptoms after the ingestion of 5 mL of Red Flower Oil, estimated to contain 30–67% methyl salicylate (AED 1,770–3,950 mg) (96). The ingestion of 30 mL of oil of wintergreen (AED 42,000 mg) resulted in the death of a 44-year-old man (98). The lowest fatal dose reported in TESS was 5–15 mL of oil of wintergreen (AED 7,000–21,000 mg) in an 88-year-old patient (Table 4).

Salicylic acid

One case report (level 4) of the ingestion of a dermal preparation of salicylic acid was identified. A 13-year-old boy intentionally ingested 9 mL of Compound W wart remover (17% salicylic acid) and experienced burning pain in his mouth and throat. He attempted to induce vomiting and drank some milk. He was evaluated at an emergency department within 4 hours of ingestion and multiple grayish lesions were observed on his tongue and posterior pharynx. His hard and soft palate had multiple erythematous lesions. Endoscopy revealed circumferential burns of the hypopharynx. He eventually had a full recovery. A serum salicylate concentration was not obtained (23).

Sodium salicylate

No reports of acute self-poisoning or unintentional toxicity for acute sodium salicylate exposures were identified. One cohort study (level 2b), in which adult volunteers received 2,000 mg of sodium salicylate (AED 2,260 mg) intravenously, reported moderate systemic effects in several subjects (101).

Unspecified salicylate

One retrospective case series (102) and a single case report (103) (level 4) were found for ingestions of unspecified salicylate products. In a review of coroner's data, the smallest dose of salicylate reported to cause fatal toxicity was 32,000 mg of an unspecified salicylate product in a patient with unspecified age (102).

Summary

A summary of doses for all salicylates associated with the categories of severity of toxicity (Fig. 2) indicates wide variability for all categories of 9.75–210 g for nonfatal cases and 13–168 g for fatalities (see details in Table 7). The lowest AEDs categorized as moderate, severe, and fatal toxicity were 9.75, 12.6, and 13 g, respectively. The median doses for these categories were 32, 50, and 56 g, respectively.

Chronic ingestions in patients less than 6 years of age

Aspirin

There was a single, retrospective cohort study (level 2b) identified with dose and effect information for chronic aspirin toxicity in patients under 6 years of age (104). Several case reports or series with dose and effect information were identified with three of these reports being large retrospective case series (level 4) (30,105,106), and 25 being case reports or series (level 4) which described 45 other cases with sufficient detail (33,36,51,63,79,87,107–125). Due to differences in duration of therapy, regimen for administration, aspirin formulation, presence of underlying medical problems, and the inability to clearly define the time of onset for clinical effects, the comparison of these cases was difficult. In one case series, a total dose as low as 580 mg given over 5 days was reported to cause toxicity in a 2-month-old child (30). Another article reported moderate toxicity in a 7-month-old

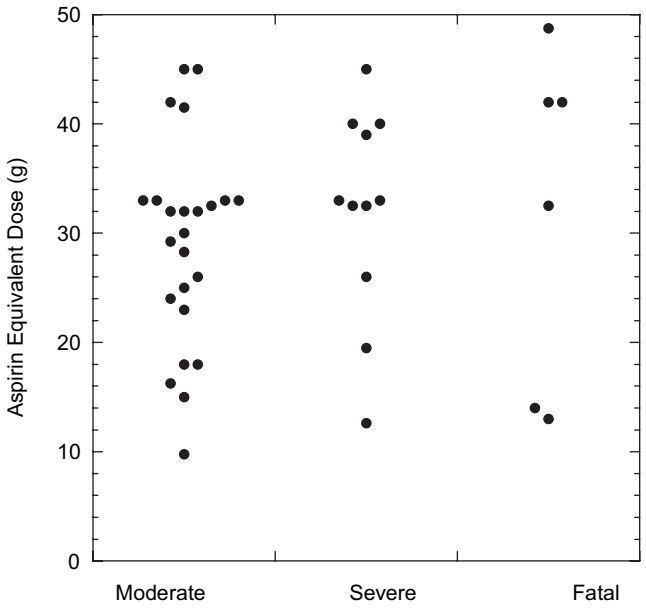

Fig. 2. Acute ingestion of salicylate with aspirin equivalent doses under 50 g and severity of salicylate toxicity in patients 6 years of age and older. See text for definitions. Data from Tables 4 and 7.

Table 7. Cases of acute ingestions in patients 6 years of age and older with dose information, sorted by drug and dose

Dose	Age (yr)	Other factors	Severity	Onset	Confirmed by SSC	Reference (LOE)
Aspirin						
Series of 208 adults with acute salicylate poisoning collected over 3 years. Only 28 patients presented in article, but doses of 20–100 g resulted in toxicity; doses of 23–100 g resulted in severe toxicity and 2 deaths.						54 (2b)
Retrospective review of 11 adults with acute aspirin poisoning; ingestion doses ranged from 26–96 g and all 11 patients had clinical effects.						55 (2b)
560 mg/kg	NR		Moderate	NR	NR	31 (4)
5,000–6,100 mg	54		Death (? from adverse drug effects)	?	Pos. blood and gastric contents	79 (4)
6,480 mg	21		Mild	<2 hr	Yes	59 (4)
9,750 mg	14		Moderate	<6 hr	Yes	65 (4)
12,600 mg	6	Acetaminophen	Severe	?	Yes	38 (4)
13,000 mg	24		Death (? from GI bleeding)	?	NR	78 (4)
15,000 mg	57	Alcohol, kaolin, morphine	Moderate	<4 hr	Yes	70 (4)
18,000 mg	19	Calcium carbonate	Moderate	<4 hr	Yes	84 (4)
18,000–24,000 mg	39	Calcium carbonate	Moderate	<6 hr	Yes	84 (4)
19,500 mg	21		Severe	<10 hr	Yes	63 (4)
23,000 mg	33		Moderate	NR	Yes	54 (4)
24,000 mg	17		Moderate	NR	Yes	81 (4)
25,000 mg	52		Moderate	?	Yes	87 (4)
26,000 mg	23		Moderate	NR	Yes	81 (4)
26,000 mg	42	Phenacetin 26 g, codeine 800 mg	Severe		Yes	54 (4)
28,275 mg	26		Moderate	?	Pos. urine	61 (4)
30,000 mg	19		Moderate	<4 hr	Yes	36 (4)
32,000 mg	18		Moderate	6 hr	Yes	66 (4)
32,000 mg	47		Moderate	6 hr	Yes	66 (4)
32,000 mg	19		Moderate	NR	Yes	81 (4)
32,500 mg	52		Severe	<3.5 hr	Pos. urine	82 (4)
32,500 mg	30		Severe	<4 hr	Yes	87 (4)
32,500 mg	30		Death	2–3 hr	Pos. gastric contents and at necropsy	58 (4)
33,000 mg	18		Moderate	NR	Yes	54 (4)
33,000 mg	39		Moderate	NR	Yes	81 (4)
33,000 mg	19		Moderate	<12 hr	Yes	87 (4)
33,000 mg	57		Severe	NR	Yes	54 (4)
33,000 mg	21		Severe	NR	Yes	81 (4)
33,300 mg	21		Moderate	<7 hr	NR	79 (4)

(Continued)

Table 7. (Continued)

Dose	Age (yr)	Other factors	Severity	Onset	Confirmed by SSC	Reference (LOE)
39,000 mg (780 mg/kg)	15		Severe	<12 hr	Yes	80 (4)
40,000 mg	14	Codeine	Severe	12 hr	Yes	56 (4)
40,000 mg	42		Severe	?	Yes	77 (4)
41,500 mg	19		Moderate	<18 hr	Yes	90 (4)
42,000 mg	34		Moderate	NR	Yes	54 (4)
42,000 mg	46	Self-inflicted laceration	Death	?	Yes	66 (4)
45,000 mg	35		Moderate	NR	Yes	81 (4)
45,000 mg	26		Moderate	NR	Yes	81 (4)
45,000 mg	41		Severe	NR	Yes	81 (4)
48,750 mg	72		Death	<12 hr	NR	82 (4)
50,000 mg	38		Severe	<8 hr	Yes	72 (4)
50,000 mg	18		Severe	<8 hr	Yes	87 (4)
53,000 mg	17		Severe	NR	Yes	54 (4)
60,000 mg	57		Severe	NR	Yes	54 (4)
60,000 mg	54		Severe	<6 hr	Yes	72 (4)
65,000 mg (2097 mg/kg)	19	Anorexia nervosa	Severe	<12 hr	Yes	67 (4)
65,000 mg (761 mg/kg)	41		Death	<4 hr	Yes	68 (6)
65,000 mg (784 mg/kg)	41		Death	<6 hr	Yes	68 (6)
65,000 mg	50		Death	<12 hr	NR	82 (4)
81,250 mg	31		Severe	<3 hr	Pos. urine	71 (4)
81,250 mg	22	Alcohol	Severe	?	Yes	74 (4)
90,000 mg	36		Severe	<1.5 hr	Yes	89 (4)
100,000 mg	48		Moderate	NR	Yes	54 (4)
100,000 mg	34		Severe	NR	Yes	54 (4)
100,000 mg	20		Death	?	Yes	57 (4)
105,000 mg	43	Attempted electrocution	Severe	<5 hr	Yes	70 (4)
125,000 mg	21		Moderate	<3 hr	Yes	88 (4)
135,000 mg	43	Alcohol	Severe	<5 hr	Yes	70 (4)
195,000 mg	18		Severe	<2 hr	Yes	60 (4)
210,000 mg	44	Unknown acuity	Severe	?	Yes	90 (4)
9,720 mg (EC)	14	Ciprofloxacin	Mild	35 hr	Yes	86 (4)
9,750 mg (189 mg/kg) (EC)	14	None	Mild	<4 hr	Yes	83 (4)
19,500 mg (EC)	NR		"Toxic effects"	10–12 hr	Yes	69 (4)
29,250–32,500 mg (EC)	25	Chronic tranylcypromine use	Moderate	<4 hr	Yes	76 (4)
44,200 mg (EC)	NR		"Toxic effects"	10–12 hr	Yes	69 (4)
97,500 mg (EC)	NR		"Toxic effects"	10–12 hr	Yes	69 (4)

15,000–18,000 mg	NR	Pregnant (taken 27 hr prior to delivery)	NR (maternal) Severe (fetus)	3 hr after delivery	Yes	62 (4)
16,250 mg	19	Pregnant	Moderate (maternal) Severe (fetus)	?	Yes	92 (6)
32,500 mg	22	Pregnant	Moderate (maternal) Death (fetus)	NR	Yes	85 (4)
65,000 mg	19	Pregnant	Severe (maternal) Death (fetus)	?	Yes	64 (4)
200,000 mg	NR	Pregnant	Moderate (maternal) Death (fetus)	<9 hr	Yes	73 (4)
15 tablets (? strength)	23		"Moderate to severe"	NR	Yes	213 (4)
250 tablets (? strength)	23		Severe	<2 hr	Yes	75 (4)
500 tablets (? strength)	19		Death	<1–2 hr	Yes	91 (4)
500 tablets (? strength)	16	Automobile accident	Death	6 hr	Yes	94 (6)
700 tablets (? strength)	48	Taken as an enema	Severe	~1 hr	Yes	93 (4)
Methyl salicylate						
9-yr retrospective review of patients admitted to 1 hospital after ingesting medicated oils. As little as 5 mL of a 30–67% solution resulted in nausea, vomiting, diarrhea, dizziness.						96 (4)
30 mL (oil of wintergreen); AED 42,000 mg	44	Theophylline and prednisone	Death	<6 hr	Yes	98 (4)
60 mL of 70% solution; AED 58,800	72	Other essential oils	Moderate	<5 hr	Yes	97 (4)
60 mL of a 67% solution; AED 56,280 mg	70	Other ingredients in product	Death (late complication)	1 hr	Yes	100 (4)
~100 mL (Red Flower Oil, 30–67%)	44	Acetaminophen	Severe	<12 hr	Yes	99 (4)
Salicylic acid						
9 mL of 17% solution	13	No systemic salicylate toxicity	Moderate (chemical burns to hypopharynx	<4 hr	No	23 (4)
Unspecified salicylate						
Retrospective 1-yr review of adult salicylate deaths reported to a coroner's office. Ages not specified. Of 27 cases, 7 had enough dose information for analysis. Of these, the dose ranged from 32–123 g, but the product was not specified (6 were acute ingestions and the chronicity of the other case was unknown).						102 (4)
70,000 mg	21	Acetaminophen 25 g, phenazone 12 g, caffeine 7 g, codeine 1.5 g, chlordiazepoxide 1 g, promethazine 500 mg	Severe	<16–68 hr	Yes	103 (4)

See Table 5 for key to abbreviations.

child after daily doses of 162 mg administered for 7 days (111). The ingestion of 650 mg over 1 day (46 mg/kg/day) by a 19-month-old child resulted in acidosis and a serum salicylate concentration of 36 mg/dL (2.61 mmol/L) (106). There was one clinical trial found (level 2b) in which aspirin was chronically administered to acutely ill patients under 6 years of age. Unspecified toxicity developed in some patients after daily doses as low as 150 mg/kg were given for 3–14 days (126).

Bismuth subsalicylate

One abstract (level 6) described moderate toxicity from the ingestion of bismuth subsalicylate by a 3-month-old boy who developed CNS depression, respiratory distress, tachypnea (66 breaths per minute), metabolic acidosis, increased prothrombin time, increased INR, and a serum salicylate concentration of 74.7 mg/dL (5.41 mmol/L). He had been given a liquid bismuth subsalicylate formulation (1,050 mg/10 mL) in AEDs of 57–84 mg/kg/day for 3 weeks. He recovered uneventfully following general supportive care for 6 days (127).

Choline salicylate

There was a single case report (level 4) identified in which a 21-month-old boy developed symptoms of moderate toxicity after a dose of 2,610 mg (AED 1,958 mg) was applied to his gums over 48 hours (128).

Sodium salicylate

Two cases reported in one article (level 4) were found with dose and effect information for chronic sodium salicylate toxicity, but both patients had also received aspirin. The lowest dosage resulting in toxicity involved an 8-month-old child with an upper respiratory illness who was given 70 mg/kg/day (AED 79 mg/kg/day) of sodium salicylate and 60 mg/kg/day of aspirin for 3 days which led to moderate toxicity (108). Two prospective, cohort studies (level 2b) described the effects of chronic administration of sodium salicylate to children under 6 years of age (114,126). Dosages as low as 150 mg/kg/day (AED 170 mg/kg/day) given to acutely ill children for 3–14 days resulted in moderate toxicity (126). A 5-year-old child developed unspecified toxicity after 300 mg/kg/day (AED 339 mg/kg/day) for 4 days (114).

Unspecified salicylate

A cohort study (level 2b) was found that described 112 children, 1 month to 18 years of age, who were hospitalized for salicylate toxicity; 47 cases of chronic toxicity were identified after dosages as low as 32 mg/kg/day (18). Patients' ages and types of salicylate products were not specified. Two level 4 articles were reviewed with dose and effect information on chronic salicylate toxicity (114,129). The lowest dosage resulting in toxicity was reported in a case series of children who had developed toxicity after being given 65 mg of an unspecified salicylate per year of age per day for variable durations (129).

In a prospective cohort study (level 2b), the chronic administration of salicylates was described in patients (ages unstated) with acute rheumatic fever. Oral or intravenous salicylate doses of 10,000–16,000 mg daily resulted in moderate toxicity in some patients (130).

Summary

The wide variation in dosage regimens that led to salicylate toxicity makes it difficult to generalize any dose associated with chronic toxicity (see details in Table 8). Doses above the upper end of the therapeutic daily dose range (100 mg/kg) for aspirin taken for several days led to toxicity in some patients (126).

Chronic ingestions in patients 6 years of age and older

Aspirin

Several case reports or series were found with dose and effect information for chronic aspirin toxicity in patients older than 6 years of age. There were 31 cases with sufficient detail reported in 21 level 4 or 6 articles (17,37,82,131–149). In general, there was similar difficulty in comparing doses and effect as described above for chronic exposures in patients under 6 years of age. Several articles reported that the daily ingestion of doses as low as 4–8 "typical tablets" (strength unspecified) led to moderate or even severe toxicity (144,148,149).

Four prospective cohort studies (level 2b) described toxic effects of aspirin when it was chronically administered to adult volunteers or patients older than 6 years of age (101,126, 151,152). Daily doses as low as 2,400–3,600 mg caused prolonged bleeding time (151). Daily doses of 3,000 mg of enteric-coated aspirin tablets were found to result in moderate toxicity in some individuals (101). No severe effects were described in these articles.

Bismuth subsalicylate

A daily dose of greater than 360 mL of a bismuth subsalicylate-containing product (product not specified) taken for months produced moderate toxicity in a diabetic patient (level 4) (153). In one clinical trial (level 1b), bismuth subsalicylate was chronically administered to adults. Tinnitus developed in 16% of the subjects at daily doses of 2,000–3,000 mg (AED 1,000–1,500 mg) (154).

Choline magnesium trisalicylate

No reports of chronic self-poisoning or unintentional toxicity from choline magnesium trisalicylate exposures were identified. A clinical trial (level 2b) was located in which adult volunteers developed nausea, drowsiness, and lightheadedness after receiving daily doses of 2,000–3,000 mg (AED 2,600–3,900 mg) for 5 days (155).

Table 8. Cases of chronic ingestions in patients less than 6 years of age with dose information, sorted by drug and toxicity severity

Dose	Age (yr)	Other factors	Severity	Onset	Confirmed by SSC	Reference (LOE)
Aspirin						
10-yr retrospective review of 42 children (<6 y.o.) with salicylate toxicity seen at 1 hospital. There were 29 cases of chronic toxicity, 8 are presented in this article. Among these, the lowest dose was 580 mg over 5 days given to a 2 m.o. child.						30 (4)
Retrospective 7-yr review of 12 children (age 3 wk–11 mo) presenting to 1 institution with chronic toxicity; doses ranging from 163–813 mg per day × 0.5–6 days caused toxicity.						105 (4)
Prospective trial of sodium bicarbonate administration in 20 children (age 4 m.o.–4 yr) hospitalized with salicylate toxicity. Three had chronic toxicity with aspirin doses as low as ~65 mg/kg given over 36 hr resulted in toxicity. Confirmed by serum salicylate concentrations.						104 (2b)
Retrospective 2-yr review of 79 cases of childhood aspirin poisoning admitted to 2 institutions; 11 of these appear to have been children aged <6 y.o. with chronic toxicity; total doses 650–29,250 mg over 1.5–30 d.						106 (4)
650 mg/d × 1 d, *46 mg/kg/d*	1.58		Moderate	1 d	Yes	106 (4)
60 mg/kg/d × 3 d of ASA+75 mg/kg/d × 3 d of sodium salicylate; AED 85 mg/kg	0.67	URI	Moderate	?	NR	108 (4)
70 mg/kg/d × 4.4 d of ASA+100 mg/kg/d × 4.4 d of sodium salicylate; AED 113 mg/kg	2	URI	Moderate	?	NR	108 (4)
220 mg/kg/d × 1 d	5	Previously taking 90 mg/kg/d × 5 d; post-tonsillectomy	Moderate	After 6 d	NR	108 (4)
162 mg (20 mg/kg) daily × 7 d	0.58	Caused toxicity again when re-administered at same dose × 5 d; ? underlying illness	Moderate	After 7 d	NR	111 (4)
1,560 mg over 2 d	3.5	URI	Moderate	?	Yes	114 (4)
975 mg over 2 d	2.33	URI	Moderate	?	Yes	114 (4)
1,950–3,900 mg over 3 d	2	URI	Moderate	?	Yes	114 (4)
2,925 mg over 2 d	1.67	URI	Moderate	?	Yes	114 (4)
1,463 mg over 2 d	0.08	URI	Moderate	?	Yes	114 (4)
8,190 mg over 3 d	2	URI	Moderate	?	Yes	114 (4)
1,755 mg over 1 d	0.5	URI	Moderate	?	Yes	114 (4)
187 mg/kg rectally over 20–25 hr	0.5	Febrile illness; on antibiotics and triprolidine	Moderate	?	Yes	118 (4)
1,400 mg/kg over 3 d	0.08		Moderate	After 3 d	Yes	33 (4)
771 mg/kg over 5 d	0.5	URI	Moderate	After 2 d	NR	79 (4)

(Continued)

Table 8. (Countinued)

Dose	Age (yr)	Other factors	Severity	Onset	Confirmed by SSC	Reference (LOE)
1,200 mg over 24 hr	0.92	None	Moderate	?	Yes	121 (4)
680 mg over 16 hr	0.33	Given aspirin 340 mg in hospital; mild cold; also on protein silver/castor oil nose drops	Severe	After 4 doses	NR	107 (4)
70 mg/kg/d × 1 d	1	URI	Severe	After 1 d	NR	108 (4)
324 mg every 4–8 hr × 7 d	5.5	Continued receiving aspirin 300 mg every 4 hr × 12 hr; acetaminophen, viral illness	Severe	After 7 d	Yes	109 (4)
900 mg daily × 3 d	3	Febrile illness	Severe	After 2 d	Yes	110 (4)
125 mg/kg/d × 17 d	0.5	Kawasaki's; CSF with elevated WBC; elevated LFTs	Severe	After 16–17 d	Yes	113 (4)
1,920 mg over 12 hr	5	Febrile illness	Severe	?	Yes	113 (4)
325 mg every 4 hr × 3 d	2.5	Measles	Severe	After 3 d	Yes	63 (4)
146 mg every 3 hr × 3 d	0.42	Chickenpox	Severe	After 3 d	Yes	63 (4)
650–975 mg/d	2.5	URI	Severe	?	Yes	114 (4)
3,900 mg over 3.5 d	0.25	URI	Severe	?	Yes	114 (4)
26 mg/kg every 4 hr × 10 d	1.58	Viral illness	Severe	?	Yes	117 (4)
325 mg daily × 3 d	0.17	Pneumonia, underlying illness	Severe	After 3 d	Yes	119 (4)
267 mg/kg over 12 hr	0.42	URI	Severe	?	NR	79 (4)
3,000 mg daily × ? duration	5	Rheumatoid arthritis	Severe	?	Yes	87 (4)
1,600 mg over 16 hr	1.25		Severe	Within 1 hr of first dose	Yes	36 (4)
2,700 mg over 12 hr	3	? acute rheumatic fever with carditis	Severe	After 3rd dose	Yes	36 (4)
90–360 mg every 4 hr × 4 d	1.33	URI	Severe	?	Yes	123 (4)
150 mg every 3 hr × 3 d	5.5	Fever and vomiting	Severe	?	Yes	123 (4)
30 mg/kg every 4 hr × 2.5 d	1.75	Given another 15 mg/kg in hospital; febrile illness; on erythromycin	Severe	?	Yes	124 (4)
40 mg/kg every 4 hr × 1 wk	0.33	URI; on antibiotics	Severe	After 4 d	Yes	124 (4)
37.5 mg × 13 over 36 hr	0.25		Severe	20 hr	NR	31 (4)
150 mg/kg/d × 2 wk	5.5	Juvenile rheumatoid arthritis, ? upper respiratory illness	Severe (hepatotoxicity)	After 3 d	Yes	115 (4)
225 mg/kg over 3 d	0.83	URI	Severe (hypoglycemia)	After 2 d	Yes	112 (4)

81 mg every 2 hr × 3 d	1.5	Additional salicylate given before admission	Death	?	Yes	116 (4)
2,000 mg over 10 hr	0.42		Death	NR	NR	120 (4)
341 mg/kg over 14 hr	0.42	URI	Death	?	Yes and postmortem tissue	79 (4)
1,105 mg in 24 hr	0.75		Death	NR	Yes	30 (4)
325 mg every 2 hr × 3–4 d	4		Death	NR	Yes	30 (4)
1,950 mg in 24 hr	0.42		Death	NR	Yes	30 (4)
1,625–1950 mg in 35 hr	0.25		Death	NR	Yes	30 (4)
975 mg in 30 hr	2.5		Death	NR	Yes	30 (4)
900 mg daily × 4 d	3.5	? measles; paregoric, Emetrol	Death	After 2–3 d	Yes	122 (4)
81 mg every 4–6 hr × 2 d	1.5	URI	Death	?	Yes	123 (4)
1,920 mg daily × 7 d	2.5	Previously on 960 mg daily × 3 d; URI; cathartics	Death	After 9 d	NR	51 (4)
6 tablets (? strength) over 2 d	0.42	Febrile illness	Death	?	Yes	125 (4)
37.5 mg every 3 hr × 2 d; 75 mg every 3 hr × 1 d	0.75		Death	1 d	NR	31 (4)
Bismuth Subsalicylate						
57–84 mg/kg/d × 3 wk	0.25	Colic	Moderate	?	Yes	127 (6)
Choline salicylate						
2,610 mg (AED 1,958 mg) applied to gums over 48 hr	1.75		Moderate	?	Yes	128 (4)
Sodium salicylate						
60 mg/kg/d × 3 d of aspirin + 75 mg/kg/d × 3 d of sodium salicylate; AED 85 mg/kg	0.67	URI	Moderate	?	NR	108 (4)
70 mg/kg/d × 4.4 d of aspirin + 100 mg/kg/d × 4.4 d of sodium salicylate; AED 113 mg/kg	2	URI	Moderate	?	NR	108 (4)
Unspecified salicylate						
Case series of 8 children <6 y.o. with salicylate toxicity after being treated with a regimen of salicylates at 65 mg per year of age/d for an unstated duration.						129 (4)
Review of 112 children (ages 1 m.o.–18 y.o.) admitted to hospital with salicylate poisoning included 47 cases of chronic toxicity after doses ranging from 32 to 230 mg/kg/d (ages and clinical effects not specified); confirmed by SSC >20 mg/dL.						18 (2b)
40 mL (? strength)/d × 2.5 d	0.42	URI	Moderate	?	Yes	114 (4)
8 tablets (? strength)/d × 4 d	0.67	URI	Severe	?	Yes	114 (4)

See Table 5 for key to abbreviations.

Methyl salicylate

There were no reports identified of chronic self-poisoning or unintentional toxicity from methyl salicylate ingestions. One study (level 2b) described adult patients who were convalescing from acute rheumatic fever and who received incrementally increasing doses of methyl salicylate orally. Doses as low as 6,640 mg (AED 7,835 mg) over 10 hours resulted in unspecified toxicity (156).

Salsalate

Three cases (level 4) with sufficient detail were reported in which a daily dose of 3,000 mg (AED 4,200 mg) for an unstated duration resulted in severe toxicity (157).

Sodium salicylate

Four cases with sufficient detail were found in four articles (level 4) (51,107,158,159). The lowest dose of sodium salicylate (based on an estimation of average daily exposure) leading to death was a total of 26,000 mg (AED 29,380 mg) given over 7 days to a 16-year-old girl with rheumatic fever (159). There were three clinical trials (level 2b) in which sodium salicylate was chronically administered to individuals over 6 years of age (114,126,160). Dosages as low as 75 mg/kg/day (AED 85 mg/kg/day) were given to acutely ill children older than 6 years of age, which resulted in toxicity such as hyperpnea, lethargy, tinnitus, seizures, hyperpyrexia, and dehydration in some cases (126). Coagulopathy developed in some patients with acute rheumatic fever who were being treated with daily sodium salicylate doses of 10,000–20,000 mg (AED 11,300–22,600 mg), intravenously or orally (160). Healthy children older than 6 years of age were given sodium salicylate 170–190 mg/kg/day (AED 192–215 mg/kg/day), and some developed symptoms of toxicity such as hyperpnea, coma, dehydration, and seizures (114).

Unspecified salicylate

A cohort study (level 2b) was found with dose and effect information from chronic salicylate toxicity, but the salicylate was not specified. In this retrospective review of 112 children aged 1 month to 18 years who were hospitalized with salicylate toxicity, 47 cases of chronic toxicity were identified after dosages as low as 32 mg/kg/day. The ages of individual patients were not specified (18). Another study (level 2b) reported the effects of chronic administration of salicylates to patients of unspecified age with acute rheumatic fever. In this report, daily salicylate (unspecified type) doses of 10,000–16,000 mg resulted in moderate toxicity in some cases (130).

Summary

The wide variation in dosage regimens that led to salicylate toxicity makes it difficult to generalize any dose associated with chronic toxicity (see details in Table 9). Daily AEDs of 2–3 g, which are near the maximum therapeutic daily dose (4 g), taken for several days led to toxicity in some patients (101,154,155,157).

Acute-on-chronic exposures

Little information on cases of acute-on-chronic salicylate toxicity was found, and aspirin was the only salicylate identified (see details in Table 10). Four case reports (level 4) were found with dose and effect information for acute-on-chronic aspirin toxicity in patients over 6 years of age (80,120,161,162). The lowest dose leading to toxicity involved a 54-year-old man who died after acutely ingesting 5,000–6,000 mg aspirin after taking 1,300–2,000 mg aspirin daily for weeks (120).

A single case report (level 4) was found with dose and effect information for acute-on-chronic aspirin toxicity in patients less than 6 years of age. In this case, a 2-year-old boy developed severe toxicity after acutely ingesting 15,000 mg (*986 mg/kg*) after he had received 105 mg aspirin (*7 mg/kg*) for 6–8 dosage intervals (49).

Dermal exposures

Cases of systemic toxicity after dermal salicylate exposure were difficult to characterize because the doses could not be reliably estimated. These cases were described on the basis of the percentage of the active ingredient reported in the dermal preparation. One case of chemical burns of the tongue, pharynx, and larynx following the ingestion of a dermal preparation of 17% salicylic acid was identified in the literature search and is described in the section dealing with ingestions by adults (23).

Methyl salicylate

Two case reports (level 4) were identified in which patients developed toxicity after dermal methyl salicylate use. A 62-year-old man developed local necrosis 1 day after he applied Bengay (18.3% methyl salicylate, 16% menthol) to his forearms and legs and used a heating pad periodically on the area (163). Another 62-year-old man presented to an emergency department with a 3-day history of tinnitus, diplopia, and shortness of breath with a serum salicylate concentration of 51.5 mg/dL (3.73 mmol/L) and a mixed metabolic acidosis and respiratory alkalosis. He had used a methyl salicylate ointment (concentration unstated) for several weeks on his thigh, twice daily (164).

Salicylic acid

Eighteen case reports were found in 14 articles (levels 4 or 6) with dose and effect information for dermal salicylic acid exposures in patients older than 6 years of age (165–178). The lowest concentration resulting in toxicity occurred in a 10-year-old girl with ichthyosis who developed moderate toxicity 2 days after beginning dermal applications of a 3% salicylic acid preparation every 4 hours (178). The lowest concentration

Table 9. Cases of chronic ingestions in patients less than 6 years of age with dose information, sorted by drug and toxicity severity

Dose	Age (yr)	Other factors	Severity	Onset	Confirmed by SSC	Reference (LOE)
Aspirin						
Up to 650 mg every 4–6 hr × 3 d	26	Poured into mouth; product also contained salicylamide and caffeine	Local ulceration	?	NR	133 (4)
7,200 mg/d × 9 d	54	Prior aspirin use at lower doses; alcohol and tobacco use; also on theophylline, ephedrine, phenobarbital, griseofulvin	Moderate	After 2 d	Yes	135 (4)
1,040 mg/d × ? duration	67	Rheumatoid arthritis	Moderate	?	Yes	134 (4)
3,000 mg/d × 2 wk	50	Pericarditis, renal insufficiency; acetazolamide	Moderate	?	Yes	139 (4)
3,250 mg or more/d × 7 d	48	Alcohol abuse history	Moderate	?	Yes	140 (6)
>6–8 tablets (? strength)/d × ? duration	58	Recently increased dose; breast cancer, renal insufficiency	Moderate	?	Yes	122 (4)
13,000–15,000 mg/d × ? duration	52	Combination product with salicylamide; also on chlordiazepoxide, clidinium bromide, caffeine	Moderate	?	Yes	147 (4)
~2 tablets (? strength) every 4 hr × ~6 d	14	URI	Moderate	?	Yes	91 (4)
2,600–3,900 mg/d	13		Moderate	After 3 d	Yes	148 (4)
1,950 mg (EC/d × ? duration	58	Gastric outlet obstruction, rheumatoid arthritis	Moderate	?	Yes	149 (4)
3,000–4,000 mg/d × ? duration	90	Osteoarthritis, dementia, alcoholism, angina, glaucoma, cellulitis; pilocarpine, diltiazem	Severe	?	Yes	17 (4)
2,400 mg/d × ? duration	78	Rheumatoid arthritis, congestive heart failure	Severe	?	Yes	131 (4)

(Continued)

Table 9. (Continued)

Dose	Age (yr)	Other factors	Severity	Onset	Confirmed by SSC	Reference (LOE)
6,500–13,000 mg/d × 10 d	32	Previously 650–975 mg daily × 10 d; sinus infections	Severe	4 d after dose increase	Yes	136 (4)
150,000 mg over 2 wk	51	Abdominal pain, neuritis	Severe	?	Yes	137 (4)
16,250 mg every 7–10 d × over 1 mo	51	Cancer	Severe	?	Yes	135 (4)
227,000 mg over 15 d	59	Dose escalated toward end of 2 wk; neuralgia	Severe	?	Yes	135 (4)
16,250 mg/d × several wk	31	Taking 20–25 tablets daily × months prior	Severe	?	Yes	135 (4)
2,600–3,900 mg (EC)/d × yr	29	Taking additional 1,288 mg aspirin × 3 wk; gastric outlet obstruction	Severe	3 mo	Yes	138 (4)
1,950 mg/d × 7 d	77	Gout, depression; ? additional salicylate use	Severe	?	Yes	144 (4)
40,000–45,000 mg over 2 d	62		Severe	?	Yes	145 (4)
1,300 mg 4 times/d	13	Rheumatic heart disease	Severe	After 6 d	NR	148 (4)
1,300 mg 4 times/d	13	Previously given sodium salicylate then aspirin for several d; rheumatic heart disease	Severe	?	NR	148 (4)
30,000 mg over 48 hr	65	Alcoholism	Severe	?	Yes	150 (4)
150,000 mg over 7 d	23	Wrist lacerations	Severe	?	Yes	150 (4)
400 tablets over 7 d	29	Pregnant	Severe (maternal) Severe (fetal)	After 2 d	NR	142 (6)
50 tablets/d × 1 mo	17	Pregnant	Severe (maternal) Death (fetal)	?	Yes	143 (4)
Up to 20 tablets (? strength)/d × ? duration	40		Death	?	Yes	132 (4)
600 mg (24 mg/kg) every 4 hr × 3 d	9	Rash, ? viral illness	Death	?	Yes	117 (4)
3,900 mg/d × ? duration	65	Rheumatoid arthritis, pulmonary fibrosis; also on prednisone, gold	Death	?	Yes	141 (4)
13,000 mg over 36 hr	38		Death	?	NR	82 (4)
7,100 mg (EC)/d × 10 d	64	Previously 3,900 mg daily chronically; rheumatoid arthritis	Death	After 10 d	Yes	146 (4)

Bismuth subsalicylate						
360 mL (AED 3,132 mg) daily × mo	68	Diabetes; insulin and meclizine	Moderate	Over 1 wk	Yes	153 (4)
Salsalate						
3,000 mg/d × ? duration	44		Severe	?	Yes	157 (4)
4,500 mg/d × ? duration	88	Osteoarthritis, hypothyroidism; doxepin, sucralfate and thyroid	Severe	?	Yes	17 (4)
6,000 mg/d × ? duration	59	Angina, congestive heart failure	Severe	?	Yes	157 (4)
Sodium salicylate						
59,600 mg (AED 67,348 mg) over 12 d	7	Given orally and rectally; also applied methyl salicylate topically for ankle swelling	Moderate	After 12 d	NR	51 (4)
26,000 mg (700 mg/kg) (AED 29,380 mg, 791 mg/kg) over 7 d	16	Rheumatic fever	Death	After 15 doses	NR	159 (4)
10,000 mg (AED 11,300 mg) daily × 6 d	41	IV for 4 d then oral for 2 d; also given bicarbonate × 2 d; rheumatoid arthritis	Death	?	Yes	158 (4)
10,000 mg (AED 11,300 mg) daily × 7 d	20	IV for 2 doses; ? acute rheumatic fever	Death	?	NR	107 (4)
Unspecified salicylate						
Review of 112 children (ages 1 m.o.–18 y.o.) admitted to hospital with salicylate poisoning included 47 cases of chronic toxicity after doses ranging from 32–230 mg/kg/d (ages and clinical effects not specified); confirmed by SSC >20 mg/dL.						18 (2b)

See Table 5 for key to abbreviations.

Table 10. Cases of acute-on-chronic ingestions of aspirin with dose information, sorted by toxicity severity

Dose	Age (yr)	Other factors	Severity	Onset	Confirmed by SSC	Reference (LOE)
Acute: 10,500 mg Chronic: 10,500 mg/d × many yr	53	Chest pain	Moderate	?	Yes	161 (4)
Acute: 15,000 mg (1,370 mg/kg) Chronic: 105 mg (9.6 mg/kg) × 6–8 doses	2	Gastrointestinal illness; paregoric use	Severe	<0.5–2 hr	Yes	49 (4)
Acute: 50,000 mg Chronic: 8,000–10,000 mg/d	55		Severe	Over 1 wk	Yes	162 (4)
Acute: 81,000 mg Chronic: ? amount	16	Headaches	Severe	<12 hr	Yes	80 (4)
Acute: 5,000–6,600 mg Chronic: 1,300–2,000 mg/d × wk	54	Headaches	Death	?	Yes; postmortem tissues	120 (4)

See Table 5 for key to abbreviations.

resulting in severe toxicity occurred in a 31-year-old man with HIV and psoriasis, in whom applications of a 30% salicylic acid preparation continuously for 2 days resulted in severe effects. No drug interactions with HIV medications and salicylates were identified to account for this effect (174).

Three case reports (level 4) were found with specific dose and effect information for dermal application of salicylic acid in patients less than 6 years of age (179–181). The lowest concentration resulting in systemic toxicity occurred in a 3-month-old child with ichthyosis who was treated with a 4% salicylic acid preparation with sulfur (duration and frequency of applications unknown), and later developed vomiting, hyperpnea, metabolic acidosis, convulsions, and coma with a serum salicylate concentration of 67 mg/dL (4.85 mmol/L) (179).

Unspecified salicylate

There was a single case report (level 4) of a patient who developed toxicity after dermal salicylate use, but the product was not specified. In this report, the entire body of a 40-year-old man with psoriasis was sprayed with a Chinese herbal preparation containing salicylate and sulfur and an occlusive dressing was applied. Within 6 hours he developed tinnitus, vomiting, tachypnea, metabolic acidosis superimposed on respiratory alkalosis, and a serum salicylate concentration of 48.5 mg/dL (3.51 mmol/L) (182).

Summary

Dose ranges associated with different categories of toxicity are difficult to estimate (see details in Table 11). Systemic toxicity from these dermal preparations is associated with their application to skin that is typically not intact due to skin lesions or with the use of an occlusive dressing.

Onset of effects after acute exposures

The expert consensus panel members considered the time of onset for toxicity to develop after salicylate exposure to assist decision-making about out-of-hospital management. All articles with toxicity information were searched for estimates of a time of onset. The available data are summarized herein for acute oral and chronic dermal exposures by the type of salicylate.

Aspirin

The longest reported time to onset of symptoms in a patient less than 6 years of age was 13 hours in a $3^1/_2$-year-old who had ingested 25 aspirin tablets and was observed at home (37). Three children developed symptoms within 24 hours of ingestion, but the exact time is unknown (33,39). Two reports (level 4) described cases in which effects began 7–8 hours after ingestion (112,183). In a case series (level 4), some children who arrived at a hospital as late as 54 hours after ingestion with symptoms were noted, but their clinical effects had developed at an unknown time prior to arrival (184).

The longest time to onset of symptoms in a patient over 6 years of age after acute aspirin exposure was within 18 hours in a 19-year-old woman, but the exact time was not known (90). The next greatest interval to effect was 12 hours, which was noted in two cases (56,185).

For enteric-coated aspirin tablets, the longest reported time to develop effects was 35 hours in a 14-year-old girl who ingested 120 enteric-coated aspirin 81-mg tablets. She was observed in a hospital and began to developed mild toxicity at that time (86). The published report stated that extended-release aspirin tablets were involved, but a review of hospital records determined that enteric-coated aspirin was ingested (G. Shepherd, personal communication, November 2, 2005). Other reports included intervals of 10–12 hours in a patient over 6 years of age (69) and 12 hours in a 13-month-old child who was observed in a hospital and exhibited an apparent peak serum salicylate concentration at 20 hours (38).

Table 11. Cases of dermal exposures with dose information, sorted by toxicity severity

Dose	Age (yr)	Other factors	Severity	Onset	Confirmed by SSC	Reference (LOE)
Methyl salicylate						
15% applied to forearms and legs × ? duration	62	Heating pad used; 10% menthol in product	Severe local effects	"Next day"	NR	163 (4)
Unknown concentration applied to thigh twice/d × weeks	62		Moderate	After "several weeks"	Yes	164 (4)
Salicylic acid						
10% applied to 75% of skin twice/d × 18 mo	62	Psoriasis	NR	NR	Yes	172 (4)
10% applied to torso for 4 wk	0.17	Seborrhea	Moderate	?	No	180 (4)
3% applied to body 3 times/d	45	Psoriasis; UV radiation treatments	Moderate	After 5 d	Yes	175 (4)
3% applied every 4 hr	10	Ichthyosis; daily baths	Moderate	After 2 d	Yes	178 (4)
3% applied × 7 d	10	Previously used 5% for 1 d; boric acid dermal treatments; ichthyosis; daily baths	Moderate	After 48 hr	Yes	166 (4)
3% applied to trunk and scalp 6 times/d × 7 d	47	Psoriasis; daily baths; UV treatments; sulfur in product	Moderate	After 4 d	Yes	177 (4)
5% to body 4 times daily × 6 d, 10% to hands and feet 4 times/d × 6 d, 2% to scalp nightly × 6 d	80	Erythroderma	Moderate	After 6 d	Yes	165 (4)
6% applied to scalp, trunk, arms, thighs 6 times/d × 11 d	39	Psoriasis; daily baths; UV treatments; sulfur in product	Moderate	After 2 d	Yes	177 (4)
6% applied to entire body × 3 d	NR	Psoriasis	Moderate	After 3 d	Yes	171 (4)
6% applied to 2/3 surface area 6 times daily × 3 d	55	Psoriasis; occlusive dressings; topical steroids; daily baths	Moderate	After 3 d	Yes	177 (4)
10% (18 g) applied to skin 3 times over 24 hr	6	Ichthyosis	Moderate	5 hr after last application	Yes	166 (4)
10% (50 g) applied daily to trunk and limbs × 10 d	44	Psoriasis	Moderate	After 8 d	Yes	169 (4)
10% (400 g) applied daily to large area × 4 wk	7	Ichthyosis	Moderate	?	Yes	170 (4)
12% to limbs and trunk twice daily × 12 d	30	Previously used 12% for 20 d, then 6% for 6 d; ichthyosis	Moderate	12 d after starting most recent dose	Yes	168 (4)

(Continued)

Table 11. (Continued)

Dose	Age (yr)	Other factors	Severity	Onset	Confirmed by SSC	Reference (LOE)
20% applied to 56% surface area once	27	Intact skin, pre-application shower, liberal application	Moderate	10 hr	Yes	167 (6)
50% applied to trunk × 3 hr	NR	Previously used 12%; psoriasis	Moderate	3 hr	Yes	171 (4)
4% applied to skin × ? duration	0.25	Ichthyosis; sulfur in ointment	Severe	?	Yes	179 (4)
20% applied to entire body twice daily × 8 d	Newborn	Ichthyosis; retinoid therapy	Severe	?	Yes	181 (4)
20% applied × 6 d	48	Psoriasis	Severe	?	Yes	176 (4)
30% applied to back and limbs continuously × 2 d	31	Psoriasis; HIV	Severe	After 2 d	Yes	174 (4)
40% applied to 41% surface area × 2 hr	27	Psoriasis; topical steroid use	Severe	<2 hr	Yes	173 (4)
Unspecified salicylate						
Chinese herbal preparation applied to body × 1 hr	40	Psoriasis; occlusive dressing; sulfur in compound	Moderate	<6 hr	Yes	182 (4)

See Table 5 for key to abbreviations.

Bismuth subsalicylate

The longest reported time to onset of effects after bismuth subsalicylate ingestion in a patient less than 6 years of age was 3 hours (40).

Methyl salicylate

For patients under 6 years of age, the longest reported time to onset of effects was described as a "few hours" (45,186). In numerous cases, initially mild symptoms of gastrointestinal irritation (e.g., burning sensation or vomiting) were followed by the development of systemic effects up to 15 hours later (41,49,51). In other cases, exact times were not available, but the onset of significant systemic effects appeared to be delayed by several hours after ingestion (42,43).

The longest reported time to onset of effects after methyl salicylate ingestion in patients 6 years of age and older was less than 12 hours in a 44-year-old woman (99).

Salsalate

The longest interval to reported effects after salsalate ingestion was under 45 minutes in an 18-year-old woman (187).

Sodium salicylate

In patients less than 6 years of age, the only reported time to onset of effect was 15 minutes in a 23-month-old boy, but the sodium salicylate had been mixed with alcohol (52).

Summary

The onset of symptoms following the acute ingestion of nonenteric-coated aspirin tablets ranged from 15 minutes to 24 hours (see details in Tables 6 and 7). The most frequent time of onset for systemic symptoms was 4–8 hours (41% of 49 cases) after ingestion, followed by 9–12 hours (20%), and 2–3 hours (18%). Liquid forms of salicylate, such as methyl salicylate, exhibited earlier onsets of local and systemic symptoms. Ninety percent of patients (Fig. 3) who had ingested a non-enteric-coated formulation had their onset of symptoms within 12 hours of ingestion. Cases that involved enteric-coated aspirin tablets had onsets of symptoms at 9–12 hours (three cases), 4–8 hours (two cases), and 35 hours (one case). One case of an aspirin tablet bezoar was confirmed by endoscopy, but the time for onset or duration of symptoms was not stated (7). In a series of 29 children and nine adults, the frequency of serious or fatal salicylate toxicity generally increased as the interval between ingestion and treatment extended beyond 12 hours (184).

Onset of effects with chronic and acute-on-chronic exposures

Time of onset for toxicity from chronic exposures could not reliably be determined, in part due to the insidious onset of symptoms and the late recognition of salicylate as the cause of hospitalization. The shortest interval for the recognition of chronic salicylate poisoning was 1 day for aspirin ingestion reported in four cases (31,36,108). The most frequent times of onset were after 2 and 3 days of drug administration with each day representing 23% of 26 cases (see details in Tables 8–10). Some patients were exposed to salicylate for more than a week before symptoms of toxicity were evident. There were too few cases of acute-on-chronic exposure to make any reliable generalizations.

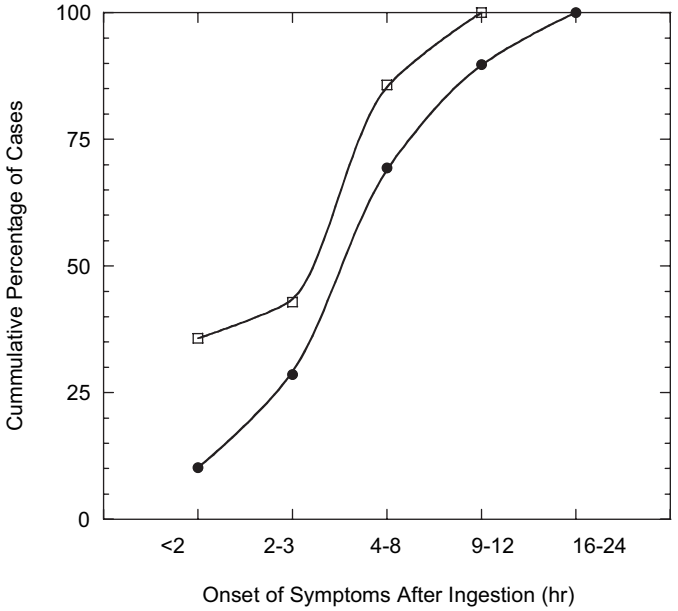

Fig. 3. Onset of symptoms following the acute ingestion of non-enteric-coated aspirin tablets in 49 cases (closed circle) and liquid methyl salicylate formulations in 14 cases (open square).

Onset of effects with dermal exposures

Time to onset of symptoms after dermal exposures was difficult to assess because most patients were subject to chronic, repeated applications over variable periods of time. There were cases in which effects manifested or worsened several hours after the last application of chronic use, or after a single, high concentration exposure (166,171,182). The most frequent times of onset were within 1 day, after 2 days, and after 3 days of drug administration, with each interval representing 29%, 24%, and 12%, respectively, of 17 cases. Some patients were exposed to salicylate for more than a week before symptoms of toxicity were evident. Salicylic acid produced tissue irritation and discomfort shortly after ingestion (23).

Risks during pregnancy

Salicylate crosses the placenta and can result in a concentration in the fetal serum that is higher than that of the mother (188). Acute salicylate overdose during the last trimester of pregnancy can result in fetal death or severe maternal and fetal toxicity (62,64,73,85,92). Salicylates are in FDA pregnancy

category C except for the last trimester of pregnancy. Since chronic use during the last trimester can be associated with antepartum and postpartum bleeding and prolonged pregnancy and labor, salicylates during the last trimester are placed in FDA pregnancy category D with positive evidence of human fetal risk (21).

Treatment measures

There are a number of different treatment measures for salicylate poisoning reported in the literature including parenteral sodium bicarbonate, intravenous fluids, intravenous dextrose, acetazolamide, diuretics, lactate, various electrolytes, aminophylline, insulin, vitamin K, vitamin C, antacids, extracorporeal drug removal methods, and supportive measures such as endotracheal intubation, oxygenation, vasopressors, and anticonvulsants. Since most of these measures had little evidence available to evaluate their efficacy and many are unlikely to be available or appropriate in an out-of-hospital setting, only some of these therapies will be reviewed here.

Endotracheal intubation and assisted ventilation should be cautiously implemented and carefully monitored. Abrupt decreases of salicylate-induced hyperventilation and hyperpnea by the effects of CNS depressant drugs (20) or underventilation (189) can lead to life-threatening effects such as severe acidosis.

Several approaches to gastrointestinal decontamination have been reported in the literature. Single-dose activated charcoal and ipecac syrup are decontamination measures that could reasonably be expected to be performed in some out-of-hospital settings and for which evidence was greater than case series or reports. The utility of these measures for a variety of toxins and the shortcomings of the evidence to assess their effectiveness has recently been reviewed (190–192).

Activated charcoal, single-dose

There were 13 clinical trials (level 1b) that examined the effect of activated charcoal on aspirin absorption (193–205). None of these studies was performed as out-of-hospital care. In a randomized controlled trial in 339 overdose patients (10 of whom involved aspirin), the efficacy of gastric lavage plus activated charcoal was compared to lavage alone. There was no benefit to the addition of activated charcoal to lavage based on the proportion of patients whose serum salicylate concentrations continued to rise after the intervention. The number of aspirin patients was small and the serum concentrations were low, indicating non-serious poisoning (194). The other 11 clinical studies involved adult volunteers who received non-toxic doses of aspirin prospectively. Although these 11 studies varied in aspirin dose, aspirin product (enteric-coated versus regular), time to activated charcoal administration, sample size, and methodology, all studies showed a reduction in aspirin absorption with activated charcoal given 0–4 hours after aspirin ingestion. One study showed it to be more efficacious than ipecac syrup (195), but another study found that both treatments were equally efficacious (196). The addition of magnesium citrate to activated charcoal had little effect on the efficacy of charcoal in two studies (198, 205). The addition of sorbitol improved the efficacy of activated charcoal in one study (200), but reduced it in another (202). Use of whole bowel irrigation after activated charcoal administration reduced the efficacy of activated charcoal (204). Food had a variable effect (203). These studies were performed with non-toxic aspirin doses making their applicability to the overdose patient unknown. There was one controlled trial in volunteers (level 2b) that found that activated charcoal reduced the absorption of three forms of aspirin (regular, enteric-coated, and aspirin in solution) when given up to 3 hours after ingestion (206).

There were no level 1–3 articles identified on the effects of activated charcoal single-dose on salicylates other than aspirin. Numerous case series and reports (levels 4 and 6) were reviewed in which single-dose activated charcoal was used for various salicylates, but the efficacy or effectiveness of activated charcoal could not be determined without a control for comparison.

Ipecac syrup

There were two clinical trials (level 1b) that investigated the efficacy of ipecac syrup in reducing aspirin absorption in which ipecac was given 1 hour after the administration of non-toxic doses of aspirin to adult volunteers. The studies demonstrated a reduction in aspirin absorption equal to that achieved by activated charcoal (196), or less than that of activated charcoal (195).

A study (level 1b) compared the efficacy of ipecac syrup and gastric lavage at recovering ingested salicylate. Twenty patients with acute aspirin overdoses were randomized to receive gastric lavage followed by ipecac syrup or ipecac syrup followed by lavage. The authors concluded that the use of ipecac syrup led to more salicylate recovery than gastric lavage based on the ratio of salicylate recovered by each method (207). Another study (level 1b) was identified, but it was not designed to investigate the efficacy of ipecac syrup. The authors estimated 0–81% recovery of ingested salicylate in 22 patients with acute aspirin overdose (208).

Numerous case series and reports (levels 4 and 6) were reviewed in which ipecac syrup was administered after the ingestion of a salicylate, but its effectiveness could not be measured in these case reports. Ipecac syrup was used in one level 2b study and a level 3b study, but its efficacy was not evaluated in either study (209, 210).

Limitations of the literature

Literature based on case reports can be inherently difficult to evaluate because patient histories can be unreliable and are often obtained during a period of extreme emotional stress for

patients and caregivers. The exact product, salicylate content, patient weight, patient age, or specific effects were often not known or not documented. There were infrequent mentions whether the accuracy of the history was confirmed by outside sources (e.g., caregivers or witnesses) or objective evidence (e.g., empty product containers or serum concentrations); however, most cases had serum salicylate concentrations reported or salicylate detected in the urine, indicating exposure to salicylate. A statement of whether confirmation of the exposure was obtained is included in the data summaries (Tables 6–11).

Wide dosage ranges were observed for all groupings of toxic severity. Besides interpatient variability, the dose ranges could also be attributed to spontaneous emesis in some cases, time of onset for treatment, and inaccuracies in the history of the exposure. Advances in critical care in the past five decades have likely had an influence on the assessment, treatment, and outcome of salicylate poisoning. This influence could not be gauged but should be considered in the interpretation of the literature.

Some proprietary products were not sufficiently described and the contents could not be verified in domestic or foreign references. In some reports, only tablet counts were provided without any statement of tablet strength. Some reports did not specify the salicylate and only stated that the dose or product referred to "salicylate." Some reports of case series indicated a percentage of patients with salicylate toxicity and the range or mean of doses, so that specific doses resulting in toxicity could not be determined. When clinical effects were listed as percentages of exposed individuals, it was impossible to determine which effects were associated with a particular dose.

There were inherent difficulties in quantifying exposures to salicylate-containing dermal products. The amount of salicylate in the product, the condition of the skin, surface area of the skin affected, whether occlusive dressings were used, whether the skin was intact, and the frequency and duration of application affected the dose estimation of salicylate.

For the interval to the onset of symptoms, in most cases it was only possible to establish an upper limit of time to onset because often only the time of presentation to a hospital was noted, and effects were often present by that time. Few reports documented an exact time of onset after exposure. The times recorded in the summary tables are estimates of the maximum possible delay to onset of symptoms. The data in Tables 6–11 refer only to the time of first effect and do not give information on the time to achieve maximum effects or the total duration of effects. The practice of documenting essential data (e.g., dose, patient weight, and time since ingestion) for all salicylate exposures should be reinforced at poison control centers, emergency departments, and in published reports.

Conclusions

Key decision points for triage

The expert consensus panel chose to emphasize the importance of information that would be needed in order to make a sound triage decision for a patient with a known salicylate poisoning. These variables include the patient's intent, dose and formulation of the product, the presence of symptoms, time of ingestion, and pregnancy status. The expert consensus panel agreed that in each case, the judgment of the specialist in poison information, the poison center medical director, or other poison center-affiliated clinicians might override any specific recommendation from this guideline.

Patient intent

The panel concluded that all patients with suicidal intent or in whom a malicious intent was suspected (e.g., child abuse or neglect) should be expeditiously transported to an emergency department regardless of the dose ingested. Patients without these characteristics (e.g., adults with definite unintentional ingestion or children below the age of 6 years in whom abuse is not suspected) are candidates for more selective referral to healthcare facilities.

Dose and formulation of the salicylate

The estimation of dose is based largely on the patient's history and the type of product and its packaging (when available for evaluation). If precise data for the ingestion are unknown or unclear (e.g., package size, unit size, or number of units ingested), poison centers often utilize a method in which the maximum potential dose is calculated. For example, if the actual dose ingested cannot be ascertained, the amount of the drug product that is missing from the container is multiplied by the concentration of the formulation.

For asymptomatic patients with acute, unintentional ingestions of salicylates, the expert consensus panel concluded that home observation might be suitable for some low-dose exposures. However, the panel recognized that a definite threshold dose for toxicity, based on a large-scale, prospective study, has not been established. After a thorough review of published case reports, recommended therapeutic dosage regimens, current poison control center practices, and expert experience, the panel concluded that the acute ingestion of an amount that exceeds 150 mg/kg or 6.5 g, whichever is less, of aspirin or aspirin equivalent doses warrants referral to an emergency department. Ingestion of greater than a lick or taste of oil of wintergreen (98% methyl salicylate) by children under 6 years of age and more than 4 mL of oil of wintergreen by patients 6 years of age and older could cause systemic salicylate toxicity and warrants referral to an emergency department. The 6.5 g aspirin equivalent dose represents the ingestion of 20 aspirin 325 mg tablets or 4.6 mL of oil of wintergreen. For oil of wintergreen, 4 mL is below the 5 mL amount reported to produce moderate, severe, or fatal toxicity. The panel considered these threshold values to be internally consistent among the salicylate products and to provide some measure of safety. The thresholds chosen for this guideline are more conservative than some current

poison center practices. Prospective study might provide more definitive data and could result in adjustments of the recommended threshold doses.

Presence of symptoms

In a patient with a demonstrated unintentional salicylate ingestion, medical evaluation in an emergency department is warranted if the patient is significantly symptomatic. Symptoms such as hematemesis, tachypnea, hyperpnea, dyspnea, tinnitus, deafness, lethargy, confusion, and seizures might individually or together suggest evidence of significant acute or chronic salicylate toxicity. All patients with these symptoms, whether or not attributed to salicylate exposure, should be referred to an emergency department regardless of the dose ingested. The importance of each of these variables can be difficult to judge in a telephone conversation, but a low threshold for emergency department evaluation is considered prudent at this time, particularly for very young and elderly patients.

Time of onset of toxicity after overdose

The onset of symptoms following the acute ingestion of non-enteric-coated aspirin ranged from 1 to 24 hours. Gastric discomfort and emesis may occur shortly after ingestion, but symptoms of systemic toxicity typically begin between 4 and 12 hours after acute ingestion. The expert consensus panel concluded that asymptomatic patients who unintentionally ingest more than the referral dose of a salicylate within 12 hours (24 hours for enteric-coated tablets) of contacting the poison center, warrant consideration for medical evaluation in a healthcare facility. However, if the ingestion occurred more than 12 hours (24 hours for enteric-coated tablets) before contacting the poison center and the patient had never been symptomatic, the patient could remain at home because the risk of toxicity beyond this time is small.

Pregnancy

The panel concluded that a woman in the last trimester of pregnancy who does not have other conditions for referral and ingests less than the dose for emergency department referral, should be directed to her primary care physician, obstetrician, or a non-emergency healthcare facility for evaluation of maternal and fetal risk.

Potential out-of-hospital management

The expert consensus panel concluded that skin and eye decontamination should be instituted as soon as possible to reduce the risk of local effects, if so exposed. Out-of-hospital gastrointestinal decontamination offers potential benefit, but the potential risks and overall benefit were difficult to determine. Induced emesis with ipecac syrup carries the potential risk of pulmonary aspiration of gastric contents if the patient becomes lethargic, has a seizure, or develops tachypnea; moreover, ipecac-associated drowsiness could confound evaluation of a patient's symptoms of salicylate poisoning. Use of ipecac syrup would likely delay or prevent the use of alternative, potentially more effective treatments such as activated charcoal. Members of the panel concluded that ipecac syrup does not provide sufficient benefit to warrant its use for the treatment of salicylate ingestions. Activated charcoal was determined to be a potentially useful treatment in some cases for which it could be administered in out-of-hospital settings, but its administration is not without risk. Since salicylates are irritants of the gastrointestinal tract that can produce vomiting, the benefits of activated charcoal administration should be weighed against the risk of aspiration of gastric contents secondary to vomiting. The panel agreed that transportation to a healthcare facility should not be delayed in order to attempt administration of activated charcoal, and that local guidelines for its use should be established.

Recommendations

1. Patients with stated or suspected self-harm or who are the victims of a potentially malicious administration of a salicylate, should be referred to an emergency department immediately. This referral should be guided by local poison center procedures. In general, this should occur regardless of the dose reported (Grade D).
2. The presence of typical symptoms of salicylate toxicity such as hematemesis, tachypnea, hyperpnea, dyspnea, tinnitus, deafness, lethargy, seizures, unexplained lethargy, or confusion warrants referral to an emergency department for evaluation (Grade C).
3. Patients who exhibit typical symptoms of salicylate toxicity or non-specific symptoms such as unexplained lethargy, confusion, or dyspnea, which could indicate the development of chronic salicylate toxicity, should be referred to an emergency department (Grade C).
4. Patients without evidence of self-harm should have further evaluation, including determination of the dose, time of ingestion, presence of symptoms, history of other medical conditions, and the presence of co-ingestants. The acute ingestion of more than 150 mg/kg or 6.5 g of aspirin equivalent, whichever is less, warrants referral to an emergency department. Ingestion of greater than a lick or taste of oil of wintergreen (98% methyl salicylate) by children under 6 years of age and more than 4 mL of oil of wintergreen by patients 6 years of age and older could cause systemic salicylate toxicity and warrants referral to an emergency department (Grade C).
5. Do not induce emesis for ingestions of salicylates (Grade D).
6. Consider the out-of-hospital administration of activated charcoal for acute ingestions of a toxic dose if it is immediately available, no contraindications are present, the

patient is not vomiting, and local guidelines for its out-of-hospital use are observed. However, do not delay transportation in order to administer activated charcoal (Grade D).
7. Women in the last trimester of pregnancy who ingest below the dose for emergency department referral and do not have other referral conditions should be directed to their primary care physician, obstetrician, or a non-emergency healthcare facility for evaluation of maternal and fetal risk. Routine referral to an emergency department for immediate care is not required (Grade C).
8. For asymptomatic patients with dermal exposures to methyl salicylate or salicylic acid, the skin should be thoroughly washed with soap and water and the patient can be observed at home for development of symptoms (Grade C).
9. For patients with an ocular exposure of methyl salicylate or salicylic acid, the eye(s) should be irrigated with room-temperature tap water for 15 minutes. If after irrigation the patient is having pain, decreased visual acuity, or persistent irritation, referral for an ophthalmological examination is indicated (Grade D).
10. Poison centers should monitor the onset of symptoms whenever possible by conducting follow-up calls at periodic intervals for approximately 12 hours after ingestion of non-enteric-coated salicylate products and for approximately 24 hours after the ingestion of enteric-coated aspirin (Grade C).

These recommendations are summarized in Appendix 4.

Implications for Research

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

1. A careful analysis of existing poison control center records to further clarify the effect of different salicylate products, onset of systemic toxicity, ingested dose, and outcome is needed.
2. Large-scale, prospective studies of unintentional acute and chronic salicylate poisoning should be conducted to better characterize the nature and care of patients in the out-of-hospital setting.
3. The effectiveness and safety of using activated charcoal for the out-of-hospital gastric decontamination, specifically for salicylate ingestions, are unknown and need further study.
4. A large case series of patients who ingested salicylic acid dermal preparations might better characterize the risks from this type of exposure.

Disclosure

There are no potential conflicts of interest reported by the panel regarding this guideline.

References

1. Watson WA, Litovitz TL, Rodgers Jr GC, Klein-Schwartz W, Reid N, Youniss J, Flanagan A, Wruk KM. 2004 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am J Emerg Med 2005; 23:589–666.
2. Vandenberg SA, Smolinske SC, Spoerke DG, Rumack BH. Non-aspirin salicylates: conversion factors for estimating aspirin equivalency. Vet Hum Toxicol 1989; 31:49–50.
3. Dromgoole SH, Cassell S, Furst DE, Paulus HE. Availability of salicylate from salsalate and aspirin. Clin Pharmacol Ther 1983; 34:539–545.
4. Chan TY. Salicylamide toxicity in overdose. Int J Clin Pharmacol Ther 1996; 34:366.
5. Needs CJ, Brooks PM. Clinical pharmacokinetics of the salicylates. Clin Pharmacokinet 1985; 10:164–177.
6. Elko C, Von Derau K. Salicylate undetected for 8 hours after enteric-coated aspirin overdose [abstract]. J Toxicol Clin Toxicol 2001; 39: 482–483.
7. Salhanick S, Levy D, Burns M. Aspirin bezoar proven by upper endoscopy [abstract]. J Toxicol Clin Toxicol 2002; 40:688.
8. Wolowich WR, Hadley CM, Kelley MT, Walson PD, Casavant MJ. Plasma salicylate from methyl salicylate cream compared to oil of wintergreen. J Toxicol Clin Toxicol 2003; 41:355–358.
9. Levy G. Pharmacokinetics of salicylate elimination in man. J Pharmaceut Sci 1965; 54:959–967.
10. Roberts II LJ, Morrow JD. Analgesic-antipyretic and antiinflammatory agents and drugs employed in the treatment of gout. In: Hardman JG, Limbird LE, Gilman AG, eds. Goodman & Gilman's the Pharmacological Basis of Therapeutics. 10th ed. New York: McGraw-Hill, 2001. p. 696–703.
11. Donovan JW, Akhtar J. Salicylates. In: Ford MD, Delaney KA. Ling J, Erickson T. Clinical Toxicology. Philadelphia: WB Saunders, 2001. p. 275–280.
12. Flomenbaum NE. Salicylates. In: Goldfrank LR, Flomenbaum NE, Lewin NA, Howland MA, Hoffman RS, Nelson LS, eds. Goldfrank's Toxicologic Emergencies. 7th ed. New York: McGraw-Hill, 2002. p. 507–527.
13. Krenzelok EP, Kerr F, Proudfoot AT. Salicylate toxicity. In: Haddad LM, Shannon MW, Winchester JF, eds. Clinical Management of Poisoning and Drug Overdose. 3rd ed. Philadelphia: WB Saunders, 1998. p. 675–687.
14. Yip L. Salicylates. In: Dart RC, ed. Medical Toxicology. 3rd ed. Philadelphia: Lippincott, Williams & Wilkins, 2004. p. 739–749.
15. Grant WM, Shuman JS. Toxicology of the Eye. 4th ed. Springfield: Charles C Thomas, 1993. p. 1250–1251.
16. Anderson RJ, Potts DE, Gabow PA, Rumack BH, Schrier RW. Unrecognized adult salicylate poisoning. Ann Intern Med 1976; 85:745–748.
17. Bailey RB, Jones SR. Chronic salicylate intoxication. A common cause of morbidity in the elderly. J Am Geriatr Soc 1989; 37:556–561.
18. Gaudreault P, Temple AR, Lovejoy FH, Jr. The relative severity of acute versus chronic salicylate poisoning in children: a clinical comparison. Pediatrics 1982; 70:566–569.
19. Temple AR. Acute and chronic effects of aspirin toxicity and their treatment. Arch Intern Med 1981; 141:364–369.
20. Gabow PA, Anderson RJ, Potts DE, Schrier RW. Acid-base disturbances in the salicylate-intoxicated adult. Arch Intern Med 1978; 138:1481–1484.
21. Salicylic acid Drugdex evaluation:. In: Klasco RK, ed. Drugdex System. Thomson Micromedex, Greenwood Village (CO), edition expires March 2006.
22. Schwarb FP, Gabard B, Rufli T, Surber C. Percutaneous absorption of salicylic acid in man after topical administration of three different formulations. Dermatol 1999; 198:44–51.
23. Sacchetti A, Ramoska E. Ingestion of compound W, an unusual caustic. Am J Emerg Med 1986; 4:554–555.
24. Waldman RJ, Hall WN, McGee H, Van Amburg G. Aspirin as a risk factor in Reye's syndrome. JAMA 1982; 247:3089–3094.

25. Shaneyfelt TM, Mayo-Smith MF, Rothwangl J. Are guidelines following guidelines? The methodological quality of clinical practice guidelines in the peer-reviewed medical literature. JAMA 1999; 281:1900–1905.
26. Shiffman RN, Shekelle P, Overhage JM, Slutsky J, Grimshaw J, Deshpande AM. Standardized reporting of clinical practice guidelines: a proposal from the Conference on Guideline Standardization. Ann Intern Med 2003; 139:493–498.
27. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, Wei R, Mei Z, Curtin LR, Roche AF, Johnson CL. CDC growth charts: United States. Advance data from vital and health statistics; no. 314. Hyattsville (MD): National Center for Health Statistics. 2000. Available at http://www.cdc.gov/nchs/data/ad/ad314.pdf (accessed 28 March, 2005).
28. Done AK. Aspirin overdosage: incidence, diagnosis, and management. Pediatrics 1978; 62:890–897.
29. Salicylates management. In: Klasco RK, ed. Poisindex System. Greenwood Village (CO): Thomson Micromedex, edition expires March 2004.
30. Riley Jr HD, Worley L. Salicylate intoxication. Pediatrics 1956; 18:578–594.
31. Winters RW, White JS, Hughes MC, Ordway NK. Disturbances of acid-base equilibrium in salicylate intoxication. Pediatrics 1959; 23:260–285.
32. Cantrell FL, Nordt SP, Farson-Collier M. Low-dose aspirin poisoning in a child—how accurate are existing triage guidelines? [abstract]. Clin Toxicol (Phila) 2005; 43:647–648.
33. Leikin SL, Emmanouilides GC. The use of exchange transfusion in salicylate intoxication; report of 7 cases. J Pediatr 1960; 57:715–720.
34. Quak SH. Acid-base disturbance in salicylate intoxication—a local experience. J Singapore Paediatr Soc 1980; 22:50–55.
35. Ralston ME, Pearigen PD, Ponaman ML, Erickson LC. Transient myocardial dysfunction in a child with salicylate toxicity. J Emerg Med 1995; 13:657–659.
36. Schlegel RJ, Altstatt LB, Canales L, Goiser JL, Alexander JL, Gardner LI. Peritoneal dialysis for severe salicylism: an evaluation of indications and results. J Pediatr 1966; 69:553–562.
37. Schwartz R, Fellers FX, Knapp J, Yaffe S. The renal response to administration of acetazolamide (Diamox) during salicylate intoxication. Pediatrics 1959; 23:1103–1114.
38. Todd PJ, Sills JA, Harris F, Cowen JM. Problems with overdoses of sustained release aspirin. Lancet 1981; 1:777.
39. Williams SW. Treatment of aspirin poisoning by intravenous sodium lactate solution. Br Med J 1937; 1:550–552.
40. Fisher Jr CJ, Albertson TE, Foulke GE. Salicylate-induced pulmonary edema: clinical characteristics in children. Am J Emerg Med 1985; 3:33–37.
41. Adams JT, Bigler JA, Green OC. A case of methylsalicylate intoxication treated by exchange transfusion. J Am Med Asoc 1957; 165:1563–1565.
42. Cann HM, Verhulst HL. The salicylate problem with special reference to methyl salicylate. J Pediatr 1958; 53:271–276.
43. Diamond EF, DeYoung VR. Acute poisoning with oil of wintergreen treated by exchange transfusion. AMA J Dis Child 1958; 95:309–310.
44. Done AK. Exchange transfusion in the treatment of oil of wintergreen (methyl salicylate) poisoning. Pediatrics 1956; 18:80–85.
45. Howrie DL, Moriarty R, Breit R. Candy flavoring as a source of salicylate poisoning. Pediatrics 1985; 75:869–871.
46. Lester H, Davis K. Oil of wintergreen. Vet Hum Toxicol 1984; 26:308.
47. Levy G, Yaffe SJ. Relationship between dose and apparent volume of distribution in children. Pediatrics 1974; 54:713–717.
48. Malik AS, Zabidi MH, Noor AR. Acute salicylism due to accidental ingestion of a traditional medicine. Singapore Med J 1994; 35:215–216.
49. Rentsch JB, Bradley A, Marsh SB. Two cases of salicylate intoxication successfully treated by exchange transfusion. Am J Dis Child 1959; 98:778–785.
50. Stevenson CS. Oil of wintergreen (methyl salicylate) poisoning. Report of three cases, one with autopsy, and a review of the literature. Am J Med Sci 1937; 193:772–788.
51. Troll MM, Menten ML. Salicylate poisoning. Report of four cases. Am J Dis Child 1945; 69:37–43.
52. Vertrees JE, McWilliams BC, Kelly HW. Repeated oral administration of activated charcoal for treating aspirin overdose in young children. Pediatrics 1990; 85:594–598.
53. Oliver Jr TK, Dyer ME. The prompt treatment of salicylism with sodium bicarbonate. Am J Dis Child 1960; 99:553–565.
54. Beveridge GW, Forshall W, Munro JF, Weston IAG. Acute salicylate poisoning in adults. Lancet 1964; 41:1406–1408.
55. Dukes DC, Blainey JD, Cumming G, Widdowson G. The treatment of severe aspirin poisoning. Lancet 1963; 13:329–331.
56. Alvan G, Bergman U, Gustafsson LL. High unbound fraction of salicylate in plasma during intoxication. Br J Clin Pharmacol 1981; 11:625–626.
57. Berg KJ. Acute acetylsalicylic acid poisoning: treatment with forced alkaline diuresis and diuretics. Eur J Clin Pharmacol 1977; 12:111–116.
58. Biddle E. Aspirin poisoning. Br Med J 1938; 1:1365.
59. Black RA, Bensinger RE. Bilateral subconjunctival hemorrhage after acetylsalicylic acid overdose. Ann Ophthalmol 1982; 14:1024–1025.
60. Chase P, Walter F, James S. Whole bowel irrigation, hemodialysis, and continuous venovenous hemodiafiltration in the successful treatment of severe salicylate poisoning: Case report. Dial Transplant 2002; 31:387–391.
61. Dyke SC. A case of acetylsalicylic acid (aspirin) poisoning. Lancet 1935; 2:613–614.
62. Earle RJ. Congenital salicylate intoxication—report of a case. N Engl J Med 1961; 265:1003–1004.
63. Elliott GB, Crichton JU. Peritoneal dialysis in salicylate intoxication. Lancet 1960; 2:840–842.
64. Etchart LW. Peritoneal dialysis in salicylate intoxication. Rocky Mt Med J 1965; 62:55–56.
65. Fox GN. Hypocalcemia complicating bicarbonate therapy for salicylate poisoning. West J Med 1984; 141:108–109.
66. Ghose RR, Joekes AM. Treatment of severe aspirin poisoning without dialysis. Lancet 1964; 41:1409–1412.
67. Gren J, Woolf A. Hypermagnesemia associated with catharsis in a salicylate-intoxicated patient with anorexia nervosa. Ann Emerg Med 1989; 18:200–203.
68. Hantsch C, Seger D, Meredith T, McKinzie J, Santen S. Intra-alveolar hemorrhage in fatal salicylate toxicity [abstract]. J Toxicol Clin Toxicol 1998; 36:445–446.
69. Henry AF. Overdoses of Entrophen. Can Med Assoc J 1983; 128:1142.
70. Higgins RM, Connolly JO, Hendry BM. Alkalinization and hemodialysis in severe salicylate poisoning: comparison of elimination techniques in the same patient. Clin Nephrol 1998; 50:178–183.
71. Hopkins P. Aspirin poisoning, report of a case. Lancet. 1945; 1:145.
72. Hormaechea E, Carlson RW, Rogove H, Uphold J, Henning RJ, Weil MH. Hypovolemia, pulmonary edema and protein changes in severe salicylate poisoning. Am J Med 1979; 66:1046–1050.
73. Jackson AV. Toxic effects of salicylate on the fœtus and mother. J Path Bact 1948; 60:587–592.
74. James SH, Martinak JF. Recovery following massive self-poisoning with aspirin. NY State J Med 1975; 75:1512–1514.
75. Krause DS, Wolf BA, Shaw LM. Acute aspirin overdose: mechanisms of toxicity. Ther Drug Monit 1992; 14:441–451.
76. Kwong TC, Laczin J, Baum J. Self-poisoning with enteric-coated aspirin. Am J Clin Pathol 1983; 80:888–890.
77. Leventhal LJ, Kuritsky L, Ginsburg R, Bomalaski JS. Salicylate-induced rhabdomyolysis. Am J Emerg Med 1989; 7:409–410.
78. Lewis FW. A case of aspirin poisoning. Lancet 1919.
79. Lipman BL, Krasnoff SO, Schless RA. Acute acetylsalicylic acid intoxication. Report of five cases with two deaths. Am J Dis Child 1949; 77:477–481.
80. Mofenson HC, Caraccio TR, Greensher J, D'Agostino R, Rossi A. Gastrointestinal dialysis with activated charcoal and cathartic in the treatment of adolescent intoxications. Clin Pediatr (Phila) 1985; 24:678–684.

81. Morgan AG, Polak A. Acetazolamide and sodium bicarbonate in treatment of salicylate poisoning in adults. Br Med J 1969; 1:16–19.
82. Neale AV. Aspirin poisining. Br Med J 1936; 1:109–110.
83. Pierce RP, Gazewood J, Blake Jr RL, Salicylate poisoning from enteric-coated aspirin. Delayed absorption may complicate management. Postgrad Med 1991; 89:61–62, 64.
84. Reid IR. Transient hypercalcemia following overdoses of soluble aspirin tablets. Aust N Z J Med 1985; 15:364.
85. Rejent TA, Baik S. Fatal in utero salicylism. J Forensic Sci 1985; 30:942–944.
86. Rivera W, Kleinschmidt KC, Velez LI, Shepherd G, Keyes DC. Delayed salicylate toxicity at 35 hours without early manifestations following a single salicylate ingestion. Ann Pharmacother 2004; 38:1186–1188.
87. Robin ED, Davis RP, Rees SB. Salicylate intoxication with special reference to the development of hypokalemia. Am J Med 1959; 26:869–882.
88. Rupp DJ, Seaton RD, Wiegmann TB. Acute polyuric renal failure after aspirin intoxication. Arch Intern Med 1983; 143:1237–1238.
89. Savege TM, Ward JD, Simpson BR, Cohen RD. Treatment of severe salicylate poisoning by forced alkaline diuresis. Br Med J 1969; 1:35–36.
90. Schreiner GE, Berman LB, Griffin J, Feys J. Specific therapy for salicylism. N Engl J Med 1955; 253:213–217.
91. Surapathana LO, Futrakul P, Campbell RA. Salicylism revisited. Unusual problems in diagnosis and management. Clin Pediatr (Phila) 1970; 9:658–661.
92. Velez LI, Keyes DC, Roth B, Reynolds L, Purcell C. Aspirin overdose in mother and fetus [abstract]. J Toxicol Clin Toxicol 2001; 39:483–484.
93. Watson JE, Tagupa ET. Suicide attempt by means of aspirin enema. Ann Pharmacother 1994; 28:467–469.
94. Yambo CM, McFee RB, Caraccio TR, McGuigan MA. The ethical implications of delayed treatment for intentional aspirin overdose—a case report [abstract]. J Toxicol Clin Toxicol 2002; 40:690–691.
95. Cohen A. Comparison of two oral dosage forms of choline magnesium trisalicylate: bioavailability/bioequivalence study. Curr Ther Res Clin Exp 1980; 27:692–698.
96. Chan TY. Ingestion of medicated oils by adults: the risk of severe salicylate poisoning is related to the packaging of these products. Hum Exp Toxicol 2002; 21:171–174.
97. Baxter AJ, Mrvos R, Krenzelok EP. Salicylism and herbal medicine. Am J Emerg Med 2003; 21:448–449.
98. Cauthen WL, Hester WH. Accidental ingestion of oil of wintergreen. J Fam Pract 1989; 29:680–681.
99. Chan TH, Wong KC, Chan JC. Severe salicylate poisoning associated with the intake of Chinese medicinal oil (Red Flower Oil). Aust N Z J Med 1995; 25:57.
100. Hofman M, Diaz JE, Martella C. Oil of wintergreen overdose. Ann Emerg Med 1998; 31:793–794.
101. Tenney SM, Miller RM. The respiratory and circulatory actions of salicylate. Am J Med 1955; 19:498–508.
102. McGuigan MA. Death due to salicylate poisoning in Ontario. Can Med Assoc J 1986; 135:891–894.
103. Skjoto J, Reikvam A. Hyperthermia and rhabdomyolysis in self-poisoning with paracetamol and salicylates. Report of a case. Acta Med Scand 1979; 205:473–476.
104. Whitten CF, Kesaree NM, Goodwin JF. Managing salicylate poisoning in children. An evaluation of sodium bicarbonate therapy. Am J Dis Child 1961; 101:178–194.
105. Connell JR. Babies, dehydration, and aspirin. Rocky Mt Med J 1969; 66:57–61.
106. Craig JO, Ferguson IC, Syme J. Infants, toddlers, and aspirin. Br Med J 1966; 5490:757–761.
107. Ashworth CT, McKemie JF. Hemorrhagic complications with death from salicylate therapy. report of two cases. J Am Med Assoc 1944; 126:806–809.
108. Barnett HL, Powers JR, Benward JH, Martmann AF. Salicylate intoxication in infants and children. J Pediatr 1942; 20:214–223.
109. Bickers RG, Roberts RJ. Combined aspirin/acetaminophen intoxication. J Pediatr 1979; 94:1001–1003.
110. Brown DC, Savage JM. Therapeutic aspirin overdose in a three-year-old boy. Ulster Med J 1987; 56:63–65.
111. Bulugahapitiya DTD, Hebron B, Beck PR. Salicylate hepatitis with acidosis in an infant. Lancet 1979; 1:1295–1296.
112. Cotton EK, Fahlberg VI. Hypoglycemia with salicylate poisoning. A report of two cases. Am J Dis Child 1964; 108:171–173.
113. Dove DJ, Jones T. Delayed coma associated with salicylate intoxication. J Pediatr 1982; 100:493–496.
114. Erganian JA, Forbes GB, Case DM. Salicylate intoxication in the infant and young child, a report of thirteen cases. J Pediatr 1947; 30:129–145.
115. Everson GW, Krenzelok EP. Chronic salicylism in a patient with juvenile rheumatoid arthritis. Clin Pharm 1986; 5:334–341.
116. Fiscina S. Death associated with aspirin overdose. Mil Med 1986; 151:499.
117. Friedman SB, Stocks JF. Observations on the treatment of salicylism in children. N Engl J Med 1961; 265:1237–1241.
118. Griffith RA, Decker WJ, Wright CM. Iatrogenic salicylate poisoning of an infant by adult rectal aspirin suppositories. J Fam Pract 1981; 12:757–758.
119. Khan MI, Miller MT, Bartlett M. Complete recovery after profound acidosis (pH 6.49). Arch Dis Child 1984; 59:573–574.
120. Krasnoff SO, Bernstein M. Acetylsalicylic acid poisoning: with a report of a fatal case. J Am Med Assoc 1947; 135:712–714.
121. Mitchell I. "Therapeutic" salicylate poisoning in children. Br Med J 1979; 1:1081.
122. Schwartz JE. Chronic aspirin intoxication: a case report and literature review. Ariz Med 1984; 41:799–802.
123. Snodgrass W, Rumack BH, Peterson RG, Holbrook ML. Salicylate toxicity following therapeutic doses in young children. Clin Toxicol 1981; 18:247–259.
124. Temple AR, George DJ, Done AK, Thompson JA. Salicylate poisoning complicated by fluid retention. Clin Toxicol 1976; 9:61–68.
125. Whitehall J. Fatal salicylate poisoning: report on three fatal cases. Cent Afr J Med 1973; 19:25–27.
126. Dubow E, Solomon NH. Salicylate tolerance and toxicity in children. Pediatrics 1948; 1:495–503.
127. Lewis TV, Schaeffer SE, Hagemann TM, Badillo RB, McGoodwin PL. Misleading product packaging contributing to salicylate toxicity in an infant [abstract]. Clin Toxicol (Phila) 2005; 43:651.
128. Paynter AS, Alexander FW. Salicylate intoxication caused by teething ointment. Lancet 1979; 2:1132.
129. Hartmann AF. Acute salicylate poisoning. J Pediatr 1945; 26:214–215.
130. Coombs FS, Warren HA, Higley CS. Toxicity of salicylates. J Lab Clin Med 1945; 30:378–379.
131. Bressler R, Katz M, Conrad K. Woman with salicylate intoxication. Hosp Ther 1986; 11:117–118, 121.
132. Davis PR, Burch RE. Pulmonary edema and salicylate intoxication. Ann Intern Med 1974; 80:553–554.
133. Dellinger TM, Livingston HM. Aspirin burn of the oral cavity. Ann Pharmacother 1998; 32:1107.
134. Greer 3rd HD, Ward HP, Corbin KB. Chronic salicylate intoxication in adults. JAMA 1965; 193:555–558.
135. Good AE, Welch MH. Hospital-acquired salicylate intoxication. report of a case with psychosis, acidosis, and coma. J Rheumatol 1975; 2:52–60.
136. Granville-Grossman KL, Sergeant HG. Pulmonary œdema due to salicylate intoxication. Lancet 1960; 1:575–577.
137. Greenstein SM. Pulmonary edema due to salicylate intoxication: report of a case. Dis Chest 1963; 44:552–553.
138. Halla JT, Fallahi S, Hardin JG. Acute and chronic salicylate intoxication in a patient with gastric outlet obstruction. Arthritis Rheum 1981; 24:1205–1207.

139. Hazouard E, Grimbert M, Jonville-Berra AP, De Toffol MC, Legras A. Salicylisme et glaucome: augmentation réciproque de la toxicité de l'acétazolamine et de l'acid acétyl salicylique. J Fr Ophtalmol 1999; 22:73–75.
140. Kennedy J, Telford J. Altered mental status in salicylate poisoning: reversal with IV glucose [abstract]. J Toxicol Clin Toxicol 1998; 36:445.
141. Leatherman JW, Schmitz PG. Fever, hyperdynamic shock, and multiple-system organ failure. A pseudo-sepsis syndrome associated with chronic salicylate intoxication. Chest 1991; 100:1391–1396.
142. McVittie LAJ, Vicas IMO. A case of neonatal salicylism from maternal salicylate ingestion [abstract]. J Toxicol Clin Toxicol 1996; 34:570–571.
143. Palatnick W, Tenenbein M. Aspirin poisoning during pregnancy: increased fetal sensitivity. Am J Perinatol 1998; 15:39–41.
144. Paul BN. Salicylate poisoning in the elderly: diagnostic pitfalls. J Am Geriatr Soc 1972; 20:387–390.
145. Pei YP, Thompson DA. Severe salicylate intoxication mimicking septic shock. Am J Med 1987; 82:381–382.
146. Shkrum MJ, Gay RM, Hudson P. Fatal iatrogenic salicylate intoxication in a long-term user of enteric-coated aspirin. Arch Pathol Lab Med 1989; 113:89–90.
147. Steele TE, Morton Jr WA. Salicylate-induced delirium. Psychosomatics 1986; 27:455–456.
148. Sutcliffe J. Pulmonary œdema due to salicylates, with report of a case. Br J Radiol. 1955; 28:314–316.
149. Wise CM, Owen Jr DS, Jessee Jr EF. Another case of salicylate intoxication with enteric coated aspirin: association with gastric outlet obstruction. J Rheumatol 1982; 9:482–483.
150. Wrathall G, Sinclair R, Moore A, Pogson D. Three case reports of the use of haemodiafiltration in the treatment of salicylate overdose. Hum Exp Toxicol 2001; 20:491–495.
151. Estes D, Kaplan K. Lack of platelet effect with the aspirin analog, salsalate. Arthritis Rheum 1980; 23:1303.
152. Myers EN, Bernstein JM, Fostiropolous G. Salicylate ototoxicity: a clinical study. N Engl J Med 1965; 273:587–590.
153. Vernace MA, Bellucci AG, Wilkes BM. Chronic salicylate toxicity due to consumption of over-the-counter bismuth subsalicylate. Am J Med 1994; 97:308–309.
154. DuPont HL, Ericsson CD, Johnson PC, Bitsura JA, De la Cabada FJ. Prevention of travelers' diarrhea by the tablet formulation of bismuth subsalicylate. JAMA 1987; 257:1347–1350.
155. Cohen A, Thomas GB, Cohen EB. Serum concentration, safety and tolerance of oral doses of choline magnesium trisalicylate. Curr Ther Res Clin Exp 1978; 23:358–367.
156. Hanzlik PJ, Presho NE. Liberation of salicyl from and excretion of methyl salicylate with a note on the irregular toxicity of the ester in man. J Pharmacol Exp Therap 1925; 26:71–81.
157. Chalasani N, Roman J, Jurado RL. Systemic inflammatory response syndrome caused by chronic salicylate intoxication. South Med J 1996; 89:479–482.
158. Graham JDP, Parker WA. The toxic manifestations of sodium salicylate therapy. Q J Med 1948; 17:153–163.
159. Ryder HW, Shaver M, Ferris EBJ. Salicylism accompanied by respiratory alkalosis and toxic encephalopathy. N Engl J Med 1945; 232:617–621.
160. Owen GC, Bradford HA. The prothrombinopenic effect of massive salicylate therapy in acute rheumatic fever. Ann Intern Med 1946; 25:97–102.
161. Vladutiu AO, Reitz M. Creatine kinase isoenzymes in aspirin intoxication. Lancet 1980; 2:864.
162. Andersen R, Refstad S. Adult respiratory distress syndrome precipitated by massive salicylate poisoning. Intensive Care Med 1978; 4:211–213.
163. Heng MC. Local necrosis and interstitial nephritis due to topical methyl salicylate and menthol. Cutis 1987; 39:442–444.
164. Morra P, Bartle WR, Walker SE, Lee SN, Bowles SK, Reeves RA. Serum concentrations of salicylic acid following topically applied salicylate derivatives. Ann Pharmacother 1996; 30:935–940.
165. Brubacher JR, Hoffman RS. Salicylism from topical salicylates: review of the literature. J Toxicol Clin Toxicol 1996; 34:431–436.
166. Cawley EP, Wheeler CE. Salicylic acid poisoning in dermatological therapy. J Am Med Assoc 1953; 151:372–374.
167. Cull M, Vicas IM-O. Salicylate toxicity with topical exposure on intact skin [abstract]. Clin Toxicol 2005; 43:640.
168. Davies MG, Briffa DV, Greaves MW. Systemic toxicity from topically applied salicylic acid. Br Med J 1979; 1:661.
169. Dwyer CM, McCloskey RH, Kerr RE. Poisoning from topical salicylic acid. Postgrad Med J 1994; 70:146.
170. Germann R, Schindera I, Kuch M, Seitz U, Altmeyer S, Schindera F. Lebensbedrohliche salicylat-intoxikation durch perkutane resorption bei einer schweren ichthyosis vulgaris. Hautarzt 1996; 47:624–627.
171. Leslie-Roberts H. On the absorption of salicylic acid by the human skin. Br J Dermatol Syph 1928; 40:328–344.
172. Luderschmidt C, Plewig G. Die chronisch perkutane salizylsäureintoxikation. Hautarzt 1975; 26:643–646.
173. Pec J, Strmenova M, Palencarova E, Pullmann R, Funiakova S, Visnovsky P, Buchanec J, Lazarova Z. Salicylate intoxication after use of topical salicylic acid ointment by a patient with psoriasis. Cutis 1992; 50:307–309.
174. Peyriere H, Balmes N, Rouanet I, Mauboussin JM, Hillaire-Buys D, Arich C, Blayac JP, Vincent D. Acute salicylate intoxication after percutaneous absorption in an HIV patient treated for psoriasis. AIDS 2002; 16:1843–1844.
175. Shupp DL, Schroeter AL. An unusual case of salicylate toxicity. J Am Acad Dermatol 1986; 15:300–301.
176. Treguer H, Le Bihan G, Coloignier M, Le Roux P, Bernard JP. Intoxication salicylée par application locale de vaseline salicylée à 20% chez un psoriasique. Nouv Presse Med 1980; 9:192–193.
177. Von Weiss JF, Lever WF. Percutaneous salicylic acid intoxication in psoriasis. Arch Dermatol 1964; 90:614–619.
178. Young CJ. Salicylate intoxication from cutaneous absorption of salicylic acid. South Med J 1952; 45:1075–1077.
179. Abdel-Magid EH, el-Awad Ahmed FR. Salicylate intoxication in an infant with ichthyosis transmitted through skin ointment—a case report. Pediatrics 1994; 94:939–940.
180. Weigert SR, Gorisch V, Kluge C. Perkutane salizylsäurevergiftung im säuglingsalter. Z Arztl Fortbild (Jena) 1978; 72:427–432.
181. Yamamura S, Kinoshita Y, Kitamura N, Kawai S, Kobayashi Y. Neonatal salicylate poisoning during the treatment of a collodion baby. Clin Pediatr (Phila) 2002; 41:451–452.
182. Bell AJ, Duggin G. Acute methyl salicylate toxicity complicating herbal skin treatment for psoriasis. Emerg Med (Freemantle) 2002; 14:188–190.
183. Etteldorf JN, Dobbins WT, Summitt RL, Rainwater WT, Fischer RL. Intermittent peritoneal dialysis using 5 percent albumin in the treatment of salicylate intoxication in children. J Pediatr 1961; 58:226–236.
184. Done AK. Salicylate intoxication. Significance of measurements of salicylate in blood in cases of acute ingestion. Pediatrics 1960; 26:800–807.
185. Winter JH. Hemoptysis and aspirin ingestion? Lancet 1983; 1:1441.
186. Botma M, Colquhoun-Flannery W, Leighton S. Laryngeal oedema caused by accidental ingestion of Oil of Wintergreen. Int J Pediatr Otorhinolaryngol 2001; 58:229–232.
187. Spontak SF, Hassan FM, Spadafora MP. Salsalate intoxication and ramifications of utilizing nonspecific analytical methods in estimating quantitative blood concentrations. J Anal Toxicol 1994; 18:229–231.
188. Garrettson LK, Procknal JA, Levy G. Fetal acquisition and neonatal elimination of a large amount of salicylate. Study of a neonate whose mother regularly took therapeutic doses of aspirin during pregnancy. Clin Pharmacol Ther 1975; 17:98–103.
189. Greenberg MI, Hendrickson RG, Hofman M. Deleterious effects of endotracheal intubation in salicylate poisoning (letter). Ann Emerg Med 2003; 41:583–584.
190. Chyka PA, Seger D, Krenzelok EP, Vale JA. American Academy of Clinical Toxicology, European Association of Poisons Centres and

Clinical Toxicologists. Position paper: Single-dose activated charcoal. Clin Toxicol (Phila). 2005; 43:61–87.
191. Krenzelok EP, McGuigan M, Lheur P. Position statement: ipecac syrup. American Academy of Clinical Toxicology, European Association of Poisons Centres and Clinical Toxicologists. J Toxicol Clin Toxicol. 1997; 35:699–709.
192. Manoguerra AS, Cobaugh DJ. Guidelines for the Management of Poisoning Consensus Panel. Guideline on the use of ipecac syrup in the out-of-hospital management of ingested poisons. Clin Toxicol (Phila) 2005; 43:1–10.
193. Barone JA, Raia JJ, Huang YC. Evaluation of the effects of multiple-dose activated charcoal on the absorption of orally administered salicylate in a simulated toxic ingestion model. Ann Emerg Med 1988; 17:34–37.
194. Comstock EG, Boisaubin EV, Comstock BS, Faulkner TP. Assessment of the efficacy of activated charcoal following gastric lavage in acute drug emergencies. J Toxicol Clin Toxicol 1982; 19:149–165.
195. Curtis RA, Barone J, Giacona N. Efficacy of ipecac and activated charcoal/cathartic. Prevention of salicylate absorption in a simulated overdose. Arch Intern Med 1984; 144:48–52.
196. Danel V, Henry JA, Glucksman E. Activated charcoal, emesis, and gastric lavage in aspirin overdose. Br Med J (Clin Res Ed) 1988; 296:1507.
197. Dillon Jr EC. Wilton JH, Barlow JC, Watson WA. Large surface area activated charcoal and the inhibition of aspirin absorption. Ann Emerg Med 1989; 18:547–552.
198. Easom JM, Caraccio TR, Lovejoy Jr FH. Evaluation of activated charcoal and magnesium citrate in the prevention of aspirin absorption in humans. Clin Pharm 1982; 1:154–156.
199. Juhl RP. Comparison of kaolin-pectin and activated charcoal for inhibition of aspirin absorption. Am J Hosp Pharm 1979; 36:1097–1098.
200. Keller RE, Schwab RA, Krenzelok EP. Contribution of sorbitol combined with activated charcoal in prevention of salicylate absorption. Ann Emerg Med 1990; 19:654–656.
201. Kirshenbaum LA, Mathews SC, Sitar DS, Tenenbein M. Whole-bowel irrigation versus activated charcoal in sorbitol for the ingestion of modified-release pharmaceuticals. Clin Pharmacol Ther 1989; 46:264–271.
202. Mayersohn M, Perrier D, Picchioni AL. Evaluation of a charcoal-sorbitol mixture as an antidote for oral aspirin overdose. Clin Toxicol 1977; 11:561–567.
203. Olkkola KT, Neuvonen PJ. Do gastric contents modify antidotal efficacy of oral activated charcoal? Br J Clin Pharmacol 1984; 18:663–669.
204. Rosenberg PJ, Livingstone DJ, McLellan BA. Effect of whole-bowel irrigation on the antidotal efficacy of oral activated charcoal. Ann Emerg Med 1988; 17:681–683.
205. Sketris IS, Mowry JB, Czajka PA, Anderson WH, Stafford DT. Saline catharsis: effect on aspirin bioavailability in combination with activated charcoal. J Clin Pharmacol 1982; 22:59–64.
206. Levy G, Tsuchiya T. Effect of activated charcoal on aspirin absorption in man. Part I. Clin Pharmacol Ther 1972; 13:317–322.
207. Boxer L, Anderson FP, Rowe DS. Comparison of ipecac-induced emesis with gastric lavage in the treatment of acute salicylate ingestion. J Pediatr 1969; 74:800–803.
208. Prowse K, Pain M, Marston AD, Cumming G. The treatment of salicylate poisoning using mannitol and forced alkaline diuresis. Clin Sci 1970; 38:327–337.
209. Chapman BJ, Proudfoot AT. Adult salicylate poisoning: deaths and outcome in patients with high plasma salicylate concentrations. Q J Med 1989; 72:699–707.
210. Godfrey EE. Sodium bicarbonate therapy for salicylate poisoning. J Am Osteopath Assoc 1969; 69:346–355.
211. USP DI. Drug information for the Health Professional. Greenwood Village (CO): Thompson Micromedex, 2004. p. 2523–2524.
212. McEvoy GK, ed. AHFS Drug Information 2004. Bethesda: American Society of Health-System Pharmacists, 2004:1956.
213. Chan TY. The risk of severe salicylate poisoning following the ingestion of topical medicaments or aspirin. Postgrad Med J 1996; 72:109–112.

Appendix 1

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

Appendix 4

Triage Algorithm for Salicylate Poisoning

Is suicidal intent, self-harm, or malicious administration by another person suspected?	YES → Refer to emergency department.
NO ↓	
Is the home situation of concern? (e.g., patient lives alone or family/caregiver seems unreliable)	YES → Refer to emergency department.
NO ↓	
Is the patient symptomatic? (e.g., hematemesis, tachypnea, hyperpnea, dyspnea, lethargy, confusion, seizures, deafness)	YES → Refer to emergency department.
NO ↓	
Have more than 12 hours (24 hours for enteric-coated aspirin) passed since the acute ingestion and the person is asymptomatic?	YES → Toxicity unlikely to occur.
NO ↓	
Unable to estimate maximum amount ingested?	YES → Refer to emergency department.
NO ↓	
Maximum acute dose based on aspirin equivalent dose:* Greater than 150 mg/kg or 6.5 g, whichever is less For oil of wintergreen (98% methylsalicylate): Greater than a lick or taste by children under 6 years of age Greater than 4 mL by patients 6 years of age and older	YES → Refer to emergency department.
NO ↓	
Observe at home, with normal follow-up procedures. Consider follow-up at periodic intervals for approximately 12 hours after acute ingestion of non-enteric-coated salicylate products (24 hours for enteric-coated aspirin).	

*A dose for dermal or chronic exposures could not be established; therefore, determine referral to an emergency department on the presence of symptoms or the suspicion that symptoms might be attributable to salicylate exposure.

For eye exposures, the eye should be irrigated with room-temperature tap water for 15 minutes. If after irrigation, the patient is having pain, decreased visual acuity or persistent irritation, referral for an ophthalmological examination is indicated.

For skin exposures, the affected areas should be washed thoroughly with soap and water. If the patient is asymptomatic, it is unlikely that toxicity will occur. If the patient is symptomatic, referral should occur based on the severity of symptoms. It is unlikely that the toxicity will worsen once the material has been removed from the skin.