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Medications available from over-the-counter (OTC) sources have the capacity to produce adverse reactions, serious side effects, and problematic drug-drug and drug-disease interactions. Examples of OTC formulations of prescription drugs that have the potential to cause such complications include cimetidine, nonsteroidal anti-inflammatory drugs (NSAIDs), and antihistamines.

The first part of this two-part series focused on formulations delivered topically and by mucosal routes of administration. This, the second and final part of the series, focuses on agents that are consumed orally and have the potential to cause serious toxicity, especially if taken inappropriately by the patient.

— The Editor

Over-the-Counter (OTC) Medications: A Quick Consult Guide to the Evaluation and Management of Toxic Effects and Adverse Reactions

Part II: Systemic, Oral, and Miscellaneous Preparations

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Oral Topical Products

Toothpastes. Toothpastes and gels contain fluoride, which is added for dental caries protection. Studies conducted in the 1950s showed that fluoride was beneficial to dental health and the variable availability of fluoridated water prompted its addition to dentifrices.

Fluoride usually is present in dentifrices as a salt, including sodium fluoride, stannous fluoride, and sodium monofluorophosphate. The maximum amount of fluoride allowed in a tube of toothpaste is 260 mg.[1] Generally, estimates of elemental fluoride concentration in toothpastes and gels is a maximum of 1 mg/g.[2] The dose is calculated based on the amount of elemental fluoride present, regardless of the salt form. Symptoms have occurred with ingestion of 3-5 mg/kg. An acute toxic exposure is estimated to be between 5 mg and 10 mg of elemental fluoride/kg—a dose that is certainly possible in the case of toothpaste ingestion by a small child.[3]

Trivial ingestions of mouthful amounts are unlikely to cause symptoms, but calculations of potential fluoride dose should be done for ingestions of larger amounts. If the specific fluoride salt concentration is unknown, then the elemental fluoride concentration (1 mg/g) may be used to determine exposure risks. Acute ingestion commonly causes gastrointestinal (GI) upset, with nausea and vomiting; the response is thought to be caused by the conversion of fluoride to hydrofluoric acid in the acidic environment of the stomach.[4] Diarrhea also is a possible reaction, due to both the fluoride content and the vehicle (which commonly uses sorbitol as a sweetener to improve palata-

bility). The more serious symptoms seen with significant fluoride ingestion are hypocalcemia and hyperkalemia, with resultant tetanic spasms and dysrhythmias.[5,6] In severe poisoning, dysrhythmias and hypotension can develop, progressing to cardiac or respiratory failure.[2] This is unlikely with over-the-counter (OTC) dentifrices.

Management of ingestion of fluoride-containing toothcare products depends on the estimated dose ingested. Asymptomatic patients who have ingested fewer than 8 mg/kg are managed with dilution, preferably with milk (calcium binds the fluoride ion).[7] Observation for development of GI symptoms and disposition after 4-6 hours are usually sufficient for patient treatment.[8] Development of GI symptoms or the potential ingestion of greater than 8 mg/kg requires determination of baseline serum electrolyte and calcium levels and the administration of calcium- and magnesium-containing antacids after initial dilution.

Mouthwashes and Gargles. Mouthwashes and gargles are a routine part of oral hygiene. These formulations are generally composed of water, ethanol, and flavoring agents, which may include sorbitol, saccharin, and essential oils. The germicidal activity of these products is primarily due to the ethanol content, which may be as high as 30%, although other agents with mild antibacterial activity may be present in low concentrations (e.g., cetylpyridinium).

Mouthwashes are made to have an agreeable taste; therefore, ingestion by unassuming children is a special concern because ethanol is particularly toxic in this age group.[9] Acute ingestion can produce coma, respiratory and cardiac depression, hypothermia, hypotension, and hypoglycemia. Mouthful or greater ingestions of the products containing higher concentrations of ethanol have the potential to produce clinically significant serum ethanol levels.[10] Due to rapid absorption, peak levels are reached between 20 minutes and 60 minutes after ingestion; the presence of food delays absorption.[11] Children presenting to the emergency department (ED) may be hypoglycemic, even with serum ethanol levels as low as 20-30 mg/dL; fatal complications have been seen with concentrations as low as 50 mg/dL.[10] Often, the initial clinical presentation is marked sleepiness with ataxia. This can progress to coma, respiratory depression, and seizures. Blood glucose should be determined immediately, with administration of an intravenous dextrose bolus in symptomatic patients. Supportive care is essential.

Antiseptics. The mild antiseptics employed in OTC lozenges, sprays, and gargles are cetylpyridinium, hexylresorcinol, thymol, and eucalyptol. Cetylpyridinium is a cationic detergent/surfactant (one of the quaternary ammonium compounds discussed previously in Part I). Used in low concentrations of 0.05-0.45%, ingestion of even large amounts would be expected to cause only nausea and vomiting. Phenol and the phenolic derivative hexylresorcinol are found in sprays and lozenges. Applied topically, they have local anesthetic effects—hence their use in oral sprays and lozenges. The concentrations in sprays range from 0.3% to 1.4%, levels that are too low to have a caustic effect on tissues. Hypersensitivity is the only toxicity of the phenols and their derivatives at these concentrations.[12] Thymol is another phenolic compound often used in lozenges and mouthwashes. It is used in such low concentrations (usually unspecified), that it is ineffective as a therapeutic agent and is non-toxic. Eucalyptol is derived from oil of eucalyptus, and also is used in very low, non-toxic concentrations.

Anesthetic Agents. Oral anesthetic agents are used for their analgesic and mild antiseptic properties. They are available in gels and liquids and are used for teething, denture/dental pain, and minor ulcers and irritations of the buccal mucosa. Lozenges and troches are used for mild cases of pharyngitis, as are sprays and gargles.

OTC anesthetics include benzocaine (see section on local anesthetics in Part I of this two-part series) and dyclonine. The counterirritants, menthol, camphor, and phenol, also may be found in low concentrations in OTC anesthetics. These agents are commonly used in a population of teething-age children, and misuse or accidental poisoning is a possibility. Dyclonine is a synthetic anesthetic, with an onset and a duration of action similar to that of procaine.[12] It is readily absorbed into mucus membranes, and has a low order of toxicity. Dyclonine is available OTC in lozenge form, with a maximum adult dose of 3 mg/lozenge, and as a 0.1% spray.[13] Higher concentration sprays (0.5% and 1%) are used to provide relief from mouth ulcers secondary to chemotherapy.[14]

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Table 1. Incidence of OTC Exposures in 1998[24]

OVER-THE-COUNTER (OTC) PREPARATION	NUMBER OF EXPOSURES	NUMBER OF MORBIDITIES	NUMBER OF MORTALITIES
Analgesics (acetaminophen, NSAIDs, salycilates)	133,899	5,383	107
Cosmetics and personal care products	210,224	33,769	3
Cough and cold formulations (antihistamines, decongestants)	118,280	23,050	16
Topicals (dermal, nasal, ocular, oral, rectal, vaginal)	83,455	9,702	1
Vitamins and iron supplements	53,657	4,237	1
Gastrointestinal formulations (antacids, antidiarrheals, laxatives)	45,696	4,355	6

These higher concentration products are not available OTC.

The primary toxicity of OTC dyclonine is hypersensitivity, with isolated case reports of contact dermatitis.[15] The more concentrated prescription products have produced adverse effects in the cardiovascular and central nervous systems. These include hypotension, hypertension, bradycardia, and cardiac arrest, as well as variable central nervous system (CNS) effects.[14] This degree of toxicity is unlikely given the concentrations found in these OTC products, but is a possibility that clinicians should anticipate in cases of excessive use.

Vaginal and Rectal Preparations

Vaginal products are available OTC to treat vaginal candidiasis (moniliasis). These are limited to the imidazole antifungals: clotrimazole, miconazole, and butoconazole. The antifungals terconazole, tioconazole nitrate, and nystatin (a polyene antibiotic) are still available by prescription only. These products are formulated as creams, suppositories, and vaginal tablets. The tablets use lactose as an excipient and the suppositories use hydrogenated vegetable oil. All have a very low order of toxicity. The only adverse effect that has been reported is hypersensitivity.[16] There have been no reports of oral toxicity.

Other OTC vaginal products include douches, spermicides, vaginal lubricants, and miscellaneous items. Vaginal douches are used for general cleaning and removal of secretions, deodorizing, and relief of pruritis. They reflect a combination of ingredients, including phenol, methyl salicylate, menthol, eucalyptol, thymol, cetylpyridinium, surfactants, and pH-altering agents. All of these components are present in essentially non-toxic concentrations. The only potentially toxic products are concentrated povidone-iodine douches. These come in concentrations as high as 12% and are designed to be diluted prior to use to a final concentration of 0.3%. Povidone-iodine is absorbed from the vaginal tissue and, therefore, may affect thyroid function with continued or prolonged use.[17] The toxicity of povidone-iodine was discussed in Part I.

Topical spermicides are used to prevent conception. Nonoxynol-9 is the only approved spermicide. It is available in foams, suppositories, gels, jellies, and a vaginal film. Concentrations used are: 8-12% in the foams, 3-5% in the gels and jellies, a 28% concentration in the film , and 100-150 mg strengths in suppositories. The only potential toxicity of nonoxynol-9 is hypersensitivity.

Miscellaneous vaginal products are used as moisturizers, lubricants, and antipruritics. Some products contain benzocaine or counterirritants, such as resorcinol. They are available in creams, gels, and suppositories. The products containing benzocaine (some in concentrations as high as 20%) have some potential for toxicity. All of the moisturizers and lubricants are non-toxic, with essentially water soluble or water-miscible ingredients such as glycerine, hydroxyethylcellulose, or propylene glycol.

Anorectal combination products are used primarily for relief of pruritis and irritation secondary to hemorrhoids. They contain topical anesthetics such as benzocaine and pramoxine, counterirritants such as camphor, or astringents such as zinc oxide and witch hazel. None of these OTC products contain steroids. Other ingredients in these preparations are emollients, mild antiseptics (e.g., benzalkalonium chloride, phenylmercuric nitrate), local vasoconstrictors (e.g., ephedrine, phenylephrine), or wound healing agents (e.g., peru balsam, yeast-cell extract).[18] The local anesthetic products are available in the forms of creams, foams, and ointments. The benzocaine and pramoxine concentrations may be as high as 20% and 1%, respectively. Although toxicity has not been described, the potential exists if the products containing local anesthetics are misused or ingested, since these products are highly concentrated.[18] All other products are more likely to produce symptoms relative to the vehicle rather than the active ingredients.

Oral and Over-the-Counter Preparations

Analgesic Preparations. Analgesic preparations available for self-treatment include acetaminophen, aspirin, and nonsteroidal anti-inflammatory drugs (NSAIDs). Because of their routine use for fever and pain control, these agents are readily accessible to many patients. Wide availability has created a high rate of toxic exposure to these drugs. *(See Table 1.)* This discussion will focus on the NSAIDs because the toxic effects of acetaminophen and salicylate have been reviewed in previous issues of *Emergency Medicine Reports*.[19,20]

The number of NSAIDs available as OTC formulations has increased over recent years and includes: ibuprofen in 100 mg and 200 mg tablets, and 100 mg/5 mL suspension; naproxen in 200 mg tablets; and ketoprofen in 12.5 mg tablets. Among these agents, exposure to ibuprofen has been the most extensively studied. Ibuprofen ingestions of fewer than 100 mg/kg are unlikely to result in clinical symptoms.[21] However, the onset of symptoms in patients with significant ibuprofen exposures occurs within four hours of ingestion. In the majority of these patients, toxicity is mild and consists of GI distress and CNS depression. Significant toxicity is uncommon and is manifested by seizures, metabolic acidemia, and renal insufficiency.[22] Patients with manifestations of mild toxicity can be managed in the

ED with intravenous fluid hydration, antiemetics, and repeat serum electrolytes after four hours. Standard supportive treatment is required for more serious symptoms. Serum ibuprofen concentrations lack clinical correlation and are not necessary to determine toxicity.[23]

Despite their well-documented renal and GI side effects, NSAIDs are among the most widely prescribed medications and OTC agents used for pain relief. GI toxicities represent some of the most serious side effects of this drug class, and common complications include gastric mucosal ulceration, hemorrhage, or perforation. The analgesic and anti-inflammatory mechanism of action of NSAIDs has been attributed to their capacity for inhibiting the enzyme cyclooxygenase (COX). Recently, two isoforms of cyclooxygenase have been identified. COX-1 is believed to have a gastroprotective effect, while COX-2 specific inhibition is responsible for the production of pro-inflammatory mediators.

Pharmacological differences among NSAIDs are playing an increasingly important role in drug selection, and clinicians must be aware of the possible advantages and disadvantages of drugs that belong to this large and potentially problematic therapeutic class. For example, generally speaking, older NSAIDs, such as ibuprofen and ketoprofen, are relatively more potent inhibitors of COX-1 than COX-2, whereas newer NSAIDs, such as nabumatone and etodolac, have more balanced inhibition. A new and recently approved class of selective COX-2 inhibitors (represented by celecoxib [Celebrex] and rofecoxib [Vioxx]) offer new opportunities for high-benefit/low-risk therapy in appropriately selected and risk-stratified patients who would have previously required conventional NSAID therapy.

It is estimated that NSAIDs are taken by approximately 17 million Americans every day.[24] Overall, NSAIDs account for about 4.5% of all prescriptions written in the United States and approximately 22-31% of prescriptions written in the outpatient setting and/or ED.[25] Worldwide, it has been estimated that 100 million prescriptions are written annually, accounting for more than $2 billion in sales (excluding OTC purchases). These usage patterns reflect a large segment of the population suffering from such conditions as osteoarthritis (OA) and rheumatoid arthritis (RA), for whom NSAIDs represent initial therapy for control of inflammation and relief of pain and stiffness. Not surprisingly, more than 50% of NSAID prescriptions are written for individuals older than 60 years of age for the management of OA.

As a therapeutic class, NSAIDs exhibit analgesic, anti-inflammatory, antipyretic, and platelet inhibitory properties.[24] Generally speaking, analgesic effects are obtained at lower doses than those required for anti-inflammatory activity. Although there is some controversy surrounding the issues of relative effectiveness, most experts agree—and clinical experience supports the observation—that when prescribed at equipotent doses, NSAIDs are purported to show similar clinical efficacy. Clinical responses, however, may vary among individuals.

Unfortunately, complications associated with NSAID use in the United States result in approximately 100,000 hospitalizations a year at a cost of $4 billion; moreover, it is estimated that NSAIDs are directly linked to about 10,000-20,000 deaths each year. Among the elderly alone, an estimated 41,000 hospitalizations and 3300 deaths annually are thought to be secondary to NSAID therapy.[26] Studies comparing diclofenac, naproxen, and acetaminophen showed that NSAID use in the elderly increased GI complications three- to five-fold as compared with non-NSAID use.

As the geriatric population has grown, the incidence of OA has increased. As might be expected, elderly patients with OA and RA have been identified as being at high risk for NSAID toxicity. GI intolerance has been reported in up to 50% of patients on long-term NSAIDs. Among long-term users of NSAIDs, endoscopic ulcers have a reported incidence of 15-25% per year, with an estimated complication rate of 1-2%. Overall, the incidence rate of symptomatic ulcers and/or ulcer complications has been reported to be in the range of 2% to 4%, with similar rates observed in patients with RA and OA.

Although GI side effects and complications occur with the greatest frequency, adverse renal and/or cardiovascular effects of NSAIDs and COX-2 inhibitors also have been well-recognized and play an equally important role in drug selection and identifying risk management upgrades for specific patient subgroups. A prudent and rational selection process among NSAIDs and COX-2 specific inhibitors requires a comparative, evidence-based evaluation of drug efficacy as well as a comparative analysis of the full range of safety end points, including GI, cardiovascular, and renal organ systems.

Cough and Cold Preparations

Antihistamines. Antihistamines block one of the two major histamine receptor types (H1 or H2), which in turn determines their clinical use. H1-receptor antagonists are used alone or in combination with other agents for the suppression of motion sickness and vertigo, sedation, and the treatment of hypersensitivity reactions and cold symptoms.[27] In 1998, nearly 90% of exposures to antihistamines were to H1-receptor antagonists.[24] Diphenhydramine (DPH) was involved in 25,000 exposures and 16 deaths. Some of the other H1-receptor antagonists available OTC include brompheniramine, chlorpheniramine, cyproheptadine, doxylamine. *(See Table 2.)*

In addition to relief of allergic symptoms, antihistamines have other important pharmacologic properties that are variably manifested at therapeutic and toxic concentrations. Central H1-receptor antagonism causes both CNS stimulation and depression. Decreased alertness and sedation are common, but restlessness, agitation, insomnia, and seizures occur in some. These excitatory effects are more likely to occur in children and in patients with large exposures.[27] Many H1-receptor antagonists have anticholinergic effects and cardiac membrane stabilizing activity, both of which bear toxicity in overdose. Second-generation, or non-sedating, H1-receptor blockers have less CNS activity, but have been associated with serious cardiac dysrrhythmias, including torsades des pointes.[28] These preparations are available only by prescription.

Acute overdose of DPH is most commonly associated with some degree of impaired consciousness, including coma.[29] Psychomotor agitation, hallucinations, and seizures also can occur.[30] Anticholinergic signs can be prominent and include: impaired vision, dry mouth, tachycardia, hypertension, decreased GI motility, and urinary retention. Increased heart rate, significant QTc prolongation, and wide-

Table 2. Oral OTC Preparations and Their Ingredients

OTC PREPARATION	ACTIVE AGENTS
Antacids	Aluminum salts, calcium carbonate, magnesium hydroxide, sodium bicarbonate
Antidiarrheals	Bismuth subsalicylate, loperamide
Antihistamines	
Histamine (H1) receptor	Brompheniramine, chlorpheniramine, cyproheptidine, diphenhydramine, doxylamine, phenindamine, pheniramine
Histamine (H2) receptor	Cimetidine, famotidine, ranitidine
Antispamodics	Attapulgite (e.g., Donnagel), Kaolin/pectin
Decongestants	Ephedrine, phenylephrine, phenylpropanolamine, pseudoephedrine
Iron salts	Elemental iron
Laxatives (e.g., saline, bulk, stool softener, stimulants)	Lactulose, phenophtalein, magnesium salts, mineral oil
Nonsteroidal anti-inflammatory agents	Ibuprofen, ketoprofen, naproxen
Vitamins	A, B complex, C, D, E, K

complex tachycardia are documented cardiac complications of DPH overdose.[27,31,32] Death has been the result of cardiovascular collapse and respiratory failure.[31,33] In the pregnant patient, DPH poisoning may produce uterine contractions by an oxytocin-like effect.[34]

Laboratory evaluation of antihistamine overdose includes a 12-lead ECG with continuous monitoring as needed. Because aspirin, acetaminophen, and ethanol are frequently combined with antihistamines in OTC preparations, co-ingestions of these compounds should be assessed. Treatment is generally supportive, with initial efforts focused on stabilization of vital signs. Gastric lavage is recommended for the patient presenting within an hour of the ingestion or with significant clinical toxicity and an unknown time of ingestion. Activated charcoal may be useful. Attempts to control seizures begin with benzodiazepines. Wide complex tachycardia is treated with serum alkalinization by intravenous sodium bicarbonate.[32] Physostigmine, an anticholinesterase inhibitor, is considered only in cases of significant central anticholinergic symptoms (e.g., psychomotor agitation and seizures refractory to standard therapies). This treatment should be avoided if co-ingestion of tricyclic antidepressants is suspected or if cardiac conduction abnormalities are observed.

Antitussives. The antitussive dextromethorphan is found in a number of cough and cold preparations, cough drops, and throat lozenges. Dextromethorphan is the opposite stereoisomer of codeine. Unlike codeine, it is an effective cough suppressant and has few analgesic or addictive properties.[35] The dextromethorphan concentrations in OTC products vary, with the usual adult dose being 10-30 mg every 4-6 hours. This agent is generally safe, but children taking large doses may experience toxicity. The most common toxic effect is CNS depression, manifesting as drowsiness, stupor, and coma.[36] Respiratory depression, which can be fatal, also is seen in overdose.[36-38] These symptoms are reversed by the administration of naloxone.[36]

If dextromethorphan is co-administered with monoamine oxidase inhibitors or serotonin-reuptake inhibitors, such as fluoxetine and paroxetine, a serious interaction, known as the serotonin syndrome, can occur. This syndrome is characterized by hypertension, hyperthermia, muscular rigidity, and mental status changes.[39-41] Symptoms can rapidly progress to include seizures, cardiovascular collapse, and death. Treatment is generally supportive and includes controlling hypertension with intravenous nitroprusside or nitroglycerin, intravenous fluids and vasopressors for hypotension, benzodiazepines for myoclonous and seizures, and aggressive cooling to enhance evaporative heat loss.

Decongestants. Decongestants are widely available in nonprescription cough and cold preparations. Their decongestant effect is secondary to sympathomimetic agents that are supplied as either oral or topical (ocular, nasal) formulations. Common oral agents are ephedrine, psuedoephedrine, phenylephrine, and phenylpropanolamine (PPA), which recently was removed from the market. These agents produce arteriolar vasoconstriction by stimulation of the alpha-adrenergic system. Vasoconstriction of engorged nasal mucosa leads to relief of congestion. Combined with antihistamines, analagesics, and antitussives, these drugs help to alleviate the symptoms of the common cold. Topical decongestants in the form of ophthalmic and nasal solutions are used for the treatment of sinusitis, hayfever, colds, and ocular irritations.[42] The imidazoline compounds found in these topical preparations cause local vasoconstriction by their action on alpha-adrenergic receptors. These compounds, which are structurally related to clonidine, include tetrahydrozoline, naphazoline, oxymetazoline, and xylometazoline.

The toxic effects of this group are related to excessive adrenergic stimulation, with hypertension being the most serious result. Co-ingested antihistamines can potentiate hypertension by preventing reflex reduction of heart rate.[43] Three times the single therapeutic dose of PPA (85 mg in an adult) can increase the diastolic blood pressure to greater than 100 mmHg.[44] With larger exposures (e.g., overdose) hypertensive emergencies can ensue.[43] Severe headache, mental status changes, seizures, intracranial hemorrhage, myocardial infarction, and death are all possible complications.[45-47] Evaluation of the hypertensive patient includes measurement of cardiac isoenzymes and an ECG. A computer tomography scan of the brain may be required to evaluate for intracranial hemorrhage. GI decontamination is accomplished with oral activated charcoal. Treatment is directed at controlling elevated blood pressure. Intravenous nitroprusside, phentolamine, or labetalol may be used for this purpose.[46]

The pediatric population is at greatest risk for imidazole decongestant toxicity. A retrospective review of tetrahydrozoline exposures showed that 89% involved children younger than 2 years of age.[48] Most of these cases resulted from unintentional oral ingestions of either ophthalmic or nasal solutions. The ingestion of 2.5 mL of 0.05% tetrahydrozoline eyedrops can produce serious toxicity in toddlers, including miosis, bradycardia,

Table 3. Serum Magnesium Levels and Clinical Manifestations of Toxicity

SERUM MAGNESIUM LEVEL (mEq/L)	CLINICAL MANIFESTATIONS
4	Depression of deep tendon reflexes
4-7	CNS depression, bradycardia, hypotension, nausea, vomiting, diarrhea, skin flushing
8-10	Paralysis, respiratory depression
15	Asystole

hypotension or hypertension, agitation, and coma. An adult who ingested 30 mL of 0.05% tetrahydrozoline developed chest pain, bradycardia, and mental status changes.[49]

The systemic toxicity of imidazole decongestants appears to be related to stimulation of central alpha2 adrenergic-receptors. Stimulation of these receptors results in a decreased output from central vasomotor centers and a reduction in heart rate and blood pressure.[42,49-51] CNS depression is manifested by lethargy and obtundation, but fluctuations of consciousness, such as stupor alternating with psychomotor agitation, have been observed.[50] Respiratory depression also is a common finding. Due to the rapid gut absorption of these liquid preparations upon ingestion, GI decontamination is not recommended. Treatment is otherwise supportive.

Gastrointestinal Agents

Antacids. Antacids are salts (e.g., magnesium hydroxide, aluminum hydroxide, aluminum phosphate, calcium carbonate, and sodium bicarbonate) that react with gastric acid to increase the pH in the stomach and the duodenal bulb. Current uses include the treatment of gastritis, gastroesophageal reflux, peptic ulcer disease, hyperphosphatemia, calcium deficiency states, and hypomagnesemia. Oral doses are 15-30 mL four times a day in adults, and 0.5-5 mL four times a day in children.

Acute ingestion of antacids rarely contributes to toxicity because of their limited gut absorption, although calcium carbonate and sodium bicarbonate require some monitoring.[52] The long-term administration of these agents or excessively large exposures can result in GI disorders and electrolyte abnormalities, which commonly manifest as cardiovascular and CNS disturbances. GI decontamination is not necessary unless co-ingestants are involved. Serum electrolytes, blood pH, serum aluminum, calcium, and magnesium should be monitored in patients with renal insufficiency.

Most reported cases of hypermagnesemia occur in patients with renal insufficiency who use magnesium-containing antacids. Toxicity can occur within one week of standard use, especially in patients with a creatinine clearance of less than 10-30 mL/min.[53] Aside from patients with renal insufficiency, elderly patients also are at risk for increased serum magnesium toxicity. Increased serum magnesium impairs nerve conduction and depresses peripheral neuromuscular function to cause muscle weakness and paralysis.[54] The manifestations of hypermagnesemia correlate with serum concentrations and include neuromuscular paralysis, respiratory failure, bradycardia, and hypotension. *(See Table 3.)* The initial clinical finding in hypermagnesemia is diminished deep tendon reflexes, which occurs at a serum magnesium level of 4 mEq/L.[55] Respiratory depression can be seen at 10 mEq/L in adults and at lower concentrations in infants.[56] Laboratory findings associated with hypermagnesemia include decreased anion gap, hypocalcemia, and prolonged QT interval.[57]

Treatment of hypermagnesemia begins with stabilization of the airway and mechanical ventilation as needed. Cardiac monitoring is needed when the serum magnesium concentration is greater than 5 mEq/L. Patients without life-threatening symptoms and normal renal function can be managed with saline loading and furosemide-induced diuresis to promote renal clearance of magnesium. Calcium infusion (0.2-0.5 mL/kg of 10% calcium gluconate up to 10 mL over 10 minutes) displaces magnesium from cell membranes and antagonizes respiratory depression. Hemodialysis is indicated for symptomatic hypermagnesemia with either diminished renal clearance, pulmonary edema, failure of forced diuresis, or resistant cardiotoxicity.

Aluminum toxicity is observed in patients with decreased renal clearance and chronic use of aluminum salt antacids.[58,59] The manifestations are neurologic and include myoclonus, encephalopathy, and seizures.[60] Additionally, constipation, bowel obstruction, bezoar formation, and electrolyte abnormalities, such as hypocalcemia and hypophosphatemia, can occur with the chronic use of aluminum salts.[61-64] Along with phosphate loss, there is the potential for development of osteomalacia and osteoporosis. This occurs because aluminum binds to phosphate in the gut, which in turn prevents phosphate absorption.[65] Phosphate depletion leads to bone demineralization. Patients who use aluminum hydroxide on a regular basis and complain of weakness or bone pain should be evaluated for calcium and phosphate depletion. In addition, these patients should have directed skeletal radiographs to look for osteomalacia and pathologic fractures.[66] Aluminum toxicity is treated with chelation therapy and hemodialysis.[67]

Metabolic alkalosis can result from the long-term use of antacids containing sodium bicarbonate or calcium carbonate.[68] This state is secondary to nephrocalcinosis, which causes renal insufficiency and diminished bicarbonate ion excretion.[69] Patients may present with hypotension due to dehydration from GI fluid losses, a compensatory hypoventilatory response to the alkalemia, and myalgia and muscle spasms from hypokalemia and hypocalcemia. Neurologic manifestations include seizures, increased deep tendon reflexes, and mental status changes. Severe alkalemia (i.e., pH > 7.60) can cause serious cardiac dysrhythmias.[69] Electrolyte disorders associated with metabolic alkalosis include hypochloremia, hypocalcemia, and hypokalemia. Increased sodium load from sodium bicarbonate can exacerbate congestive heart failure.[70] In addition, hypercalcemia can be seen with calcium carbonate use and initially is treated with saline diuresis.[71]

When the blood pH is greater than 7.50, treatment is advised. Hypovolemic patients should be rehydrated with intravenous normal saline containing potassium chloride. This promotes renal excretion of bicarbonate and the retention of chloride. When the patient is euvolemic, intravenous fluid therapy is reduced and hypokalemia is corrected. Severe alkalemia (i.e., > 7.60) can be corrected by endotracheal intubation with careful

Table 4. Potentiated Drug Effects When Used with Cimetidine[28]

DRUG	CLINICAL MANIFESTATIONS
Benzodiazepine (alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, flurazepam)	Sedation, impaired psychomotor function and cognition
Beta adrenergic antagonists (labetolol, metoprolol, propanolol)	Hypotension, bradycardia (possible)
Calcium channel blockers (diltiazem, nifedipine)	Hypotension, tachycardia, bradycardia
Carbamazepine	Ataxia, nystagmus, diplopia, headache, vomiting, seizures, coma
Phenytoin	Ataxia, nystagmus, tremor
Theophylline	Tachycardia, nausea, vomiting
Tricyclic antidepressants	Anticholinergic syndrome
Warfarin	Hypoprothrombinemia

hypoventilation, provided that adequate oxygenation is maintained. Ammonium chloride may be administered intravenously as an acidifying agent (100-200 mEq of ammonium chloride may be administered in 500-1000 mL normal saline (NS) and infused at a rate below 5 mL/min). In renal failure patients, hemodialysis may be needed to remove bicarbonate ions.

The "milk alkali" syndrome is associated with the chronic use of antacids (e.g., sodium bicarbonate or calcium carbonate) and milk.[72] The manifestations include hypercalcemia, nausea, vomiting, anorexia, reduced parathyroid hormone secretion, precipitation of calcium in the kidneys leading to renal insufficiency, and metabolic alkalosis. Treatment is primarily supportive. Further antacid and calcium use must be discontinued and other causes of hypercalcemia evaluated.

H2-receptor antagonists also are used in the treatment of peptic ulcer disease and gastroesophageal reflux disease. These agents decrease the production of gastric acid by their antagonism of H2-receptors. OTC formulations include cimetidine, famotidine, and ranitidine. H2-receptor antagonists, particularly cimetidine, cause adverse effects by interfering with the metabolism of other potentially dangerous drugs. Cimetidine inhibits hepatic metabolism by its interaction with cytochrome P-450 and may thereby increase certain drug concentrations.[73] *(See Table 4.)* In addition, H2-receptor antagonists have been implicated in producing acute confusional states, especially in the elderly.[74]

Antidiarrheals. Loperamide is a meperidine analogue, and it is available OTC as Imodium. Opioid toxicity is a concern in large exposures and can be observed at a dose of 0.1-0.2 mg/kg. Other manifestations include bradycardia, nausea, and vomiting. Children are more susceptible to the drug's effects, and deaths have been reported.[75] Ingestions of up to 0.4 mg/kg in children older than 6 months of age can be safely monitored at home.[76] Peak serum levels occur within four hours of ingestion, and the administration of activated charcoal can limit GI drug absorption. Naloxone is effective in reversing the manifestations of opioid toxicity from loperamide.[77,78]

Bismuth salts are used medicinally for GI disorders (diarrhea, dyspepsia, ulcerogenic therapy) and as a skin protectant. They work as antidiarrheal agents due to their antimicrobial and anitsecretory properties.[79] They are clinically differentiated by their solubility.[80] The inorganic salts and subsalt forms (e.g., bismuth subsalicylate) are water insoluble and have minor gut absorption.[81] The dermal preparations are generally non-soluble (e.g., bismuth subgallate) and are less concerning from a toxicological point of view.

The salicylate component of bismuth subsalicylate is extensively absorbed; however, systemic salicylate toxicity is not a concern during recommended use of this product since peak plasma levels are below the toxic range even after maximum daily dosing.[82] In contrast, little bismuth is absorbed from intact gut epithelium. Thus, patients at risk for salicylate or bismuth toxicity from bismuth subsalicylate are those who exceed the recommended daily dose or those with enteropathies (e.g., inflammatory bowel disease, HIV enteropathy).[83]

The primary manifestation of bismuth toxicity is neurologic toxicity. Central neurologic findings include cognitive and affective disorders and can progress to clonic jerks, dysarthria, and ataxia.[84,85] The onset of symptoms varies from weeks to years.[84,85] Treatment for bismuth toxicity includes chelation and hemodialysis for patients in renal failure. Consultation with a regional poison center or medical toxicologist is recommended for the management of these patients.

Laxatives. Clinical toxicity from acute exposure to laxatives is uncommon because of their limited gut absorption. However, when ingested in large amounts, fluid and electrolyte disorders can occur. There are several preparations, including irritants, bulk formers, osmotic agents, stimulants (e.g., castor oil, phenolphthalein, bisacodyl, phenisatin, cascara sagrada, and senna), and emollients. Mineral oil, an example of the latter category, has the potential to cause aspiration pneumonitis upon ingestion.[86] Patients at risk for chronic misuse of these agents are those with eating disorders (e.g., anorexia, bulimia) and factitious disorders (e.g., Munchausen's). Nausea, vomiting, abdominal pain, and diarrhea are frequent findings in laxative abuse.

The clinically important agents in this category are those containing lactulose (e.g., Cephulac, Chronulac), magnesium salts (magnesium citrate, magnesium sulfate), and phenophthalein (Ex-Lax). Lactulose causes an osmotic load in the gut that draws water into the intestinal tract. In excessive amounts, lactulose can cause hypovolemia, hypokalemia, and hypernatremia. Lactic acid is a byproduct of gut bacterial metabolism of lactulose and can be absorbed systemically in the presence of bowel ileus.[87] Magnesium causes increased gut motility by inducing the secretion of cholecystokinin. Significant hypermagnesemia can occur from increased use of magnesium salts, or use of these agents by patients with either renal insufficiency or bowel motility disorders. Phenolphthalein directly stimulates the gut to increase motility. Toxicity from this agent is uncommon, but appears to include GI bleeding, pancreatitis, liver failure, and hypotension.[88-90]

Phenolphthalein can cause red colored stools, which are not secondary to bleeding. Children ingesting more than 1 gram of phe-

Table 5. Elemental Iron Equivalents for Iron Salts[+]

COMPOUND	PERCENTAGE OF ELEMENTAL IRON
Ferrous carbonate	48
Ferrous cholinate	12
Ferrous fumarate	33
Ferrous gluconate	12
Ferric phosphate	37
Ferric sulfate (hydrate)	20

[+] To determine risk of toxicity, calculate dose of elemental iron ingested.

Total dose of elemental iron ingested (mg/kg) = [Number of tablets x Amount of iron compound (mg) in one tablet*] x Percentage of elemental iron in compound/Patient weight (kg)

* See product labeling.

nolphthalein should be evaluated at a health care facility and receive activated charcoal for GI decontamination. Symptomatic patients require monitoring of serum electrolytes and are managed supportively.

Miscellaneous Oral Agents

Caffeine. Caffeine is a socially accepted stimulant that is available in numerous beverages and foodstuffs (e.g., soda, coffee, tea, cocoa, chocolate), and as an OTC formulation. Caffeine is a methylxanthine compound, similar to theophylline and theobromine. These agents stimulate the cardiovascular, GI, and central nervous systems by increasing cyclic adenosine monophosphate (cAMP) activity and increasing intracellular calcium concentration. The amount of caffeine varies in different products. The maximum allowable caffeine concentration is 72 mg in a 12-ounce can of soda. Coffees and teas contain between 50 mg and 200 mg of caffeine in 5 ounces. Various OTC preparations contain between 32 mg and 200 mg of caffeine in a single tablet.

Caffeine is generally considered safe. However, serious toxicity, including death, can occur in overdose. Caffeine toxicity is primarily due to sympathomimetic effects, but clinical manifestations can be variable and include nausea, vomiting, psychomotor agitation, seizures, and tachydysrhythmias. Leukocytosis, hypokalemia, hyperglycemia, lactic acidosis, and metabolic acidemia can be found as well. CNS hyperactivity, tachycardia, and tachypnea were reported after ingestion of approximately 3 grams of caffeine by an infant.[91] A fatality in an adult occurred after ingestion of only 6.5 grams,[92] while others have survived much larger ingestions.[93]

Treatment of caffeine toxicity is similar to theophylline exposure and includes GI decontamination with repeat doses of oral activated charcoal, stabilization of the vital signs, and enhanced elimination with hemoperfusion. Adenosine is not effective in treating supraventricular tachycardia because the methylxanthines are adenosine receptor antagonists.[94] Supraventriclur tachydysrhythmias can be rate controlled with either calcium channel blocking or beta adrenergic receptor-blocking agents.[95] Patients with hypotension should be administered an intravenous fluid challenge before receiving these agents. Seizures can be refractory to standard supportive care and may require consultation with either a regional poison center or a medical toxicologist to arrange for hemoperfusion.

Iron. Iron is a popular dietary supplement that is available as individual iron salts and in combination with multivitamins. There are nearly 100 iron-containing preparations, and more than 20 of these are available for purchase without a prescription.[96] Due to the high prevalence of these supplements, iron poisoning is common, particularly in the pediatric population. The annual incidence of iron poisoning in children is estimated to be about 22,000 and usually represents about 80% of all iron exposures. Each year, iron accounts for approximately 2% of all toxic exposures in children younger than 6 years of age.[97]

The dose of ingested elemental iron determines toxicity. *(See Table 5.)* Elemental iron ingestions of less than 20 mg/kg are considered non-toxic, and ingestions of greater than 60 mg/kg are associated with significant systemic toxicity. The toxic effects of iron burden the GI, cardiovascular, and central nervous systems. Excess iron in the GI tract exerts a local corrosive effect on the mucosa that can cause hemorrhage, necrosis, and perforation. The clinical manifestations of this local GI irritation include abdominal pain, nausea, vomiting, hematemesis, bloody diarrhea, and even hypovolemic shock.[96,97] The development of hypotension is multifactorial, including hypovolemia from GI losses, iron-mediated vasodilation, and myocardial depression.[98,99] The CNS effects of iron poisoning are variable and range from minor alterations of consciousness to coma.

Laboratory assessment in toxic patients includes CBC, serum electrolytes, blood urea nitrogen (BUN), creatinine, glucose, liver function tests, coagulation studies, and a serum iron level. An abdominal radiograph can assist in identifying iron pills.

Treatment begins with support of vital functions. Cardiovascular status should be optimized with intravenous fluids, blood and blood products, and vasopressors. Activated charcoal does not absorb iron and is not recommended. GI decontamination with gastric lavage and whole bowel irrigation is indicated in symptomatic patients with large gut iron load.[96,100] Patients with systemic toxicity require deferoxamine, an iron chelator, to remove excess free iron from the body. Indications for its use include significant GI symptoms, altered mental status, metabolic acidosis, and hypotension.[96,97] Also, the finding of an elevated serum iron level (> 500 (g/dL) is an indication for deferoxamine treatment.[97]

Vitamins. An estimated 40% of the U.S. population take vitamins on a regular basis.[101] This practice is generally safe, but vitamin intoxication does occur. Vitamins are available in a wide range of oral formulations designed for dietary supplementation. The fat-soluble vitamins A, D, E, and K have a greater potential for toxicity than the water-soluble vitamins B and C, which are readily eliminated by the kidneys and, therefore, rarely accumulate to dangerous levels. *(See Table 6.)*

Vitamin A is required for normal development of epithelial cells and for maintenance of night vision.[102] Toxicity occurs in the setting of both acute and chronic over exposure. Acute overdose was documented in individuals who had consumed polar bear, seal, dog, and halibut livers. Additionally, doses of 500,000 IU to 4

Table 6. Clinical Manifestations of Hypervitaminosis[114]

VITAMIN	RDA+	TOXIC DOSE	CLINICAL MANIFESTATIONS
A			
	1000 IU/ day	*Acute:* 150,000 IU to 1.5 million IU *Chronic:* 10 times the RDA for a period of weeks	Altered mental status, dermatitis, hepatitis, cerebral edema, hypercalcemia
B_1 (THIAMINE)			
	1.5 mg/day	Undefined	
B_2 (RIBOFLAVIN)			
	1.7 mg/day	Undefined	
B_3 (NIACIN)			
	19 mg/day	*Acute:* 2 gm/kg	Skin flushing, hepatitis
B_6 (PYRIDOXINE)			
	2 mg/day	*Acute:* 2 gm/kg	Peripheral neuropathy
B_{12} (COBALAMIN)			
	2 mcg/day	Undefined	
C (ASCORBATE)			
	60 mg/day	*Acute:* > 4g	Diarrhea, hemolysis
D			
	200 IU/ day	*Acute:* > 1000 IU/kg	Altered mental status, anorexia, nausea, vomiting, hypercalcemia
E			
	10 mg/day	*Acute:* > 200 mg/kg	Increased bleeding tendency
K			
	80 mcg/day	Undefined	Reversal of therapeutic anticoagulation (PT) therapy

+ Recommended daily allowance for 25- to 50-year-old male

million IU of vitamin A have resulted in acute toxic symptoms, including: nausea, vomiting, fatigue, lethargy, headache, increased intracranial pressure, and papilledema.[103] Chronic intoxication is more common and generally requires the intake of more than 100,000 IU/day over a period of weeks to months.[103]

Toxicity involves multiple organ systems: skin changes include dryness, desquamation, and pruritis; musculoskeletal irregularities resemble the clinical spectrum of the seronegative spondylarthropathies; liver involvement is evidenced by elevated transaminase levels, ascites, and jaundice; CNS abnormalities manifest as benign intracranial hypertension, diplopia, and psychosis; and metabolic alterations are observed, especially hypercalcemia.[103-107] Laboratory assessment includes measurement of serum calcium and liver function studies. Therapy generally is supportive and begins with discontinuation of the vitamin supplement. Hypercalcemia may require specific treatment with forced saline diuresis, intravenous furosemide, and corticosteroids as necessary. Increased intracranial pressure may require aggressive management.

Vitamin D is an important regulator of calcium and phosphorous homeostasis. Over-supplementation causes hypercalcemia. Hypercalcemia was observed in 21 patients who had been taking milligram doses (range equivalent to 25,000 IU and 400,000 IU) of vitamin D/day.[108] Prolonged daily intake of 75,000 IU (almost 200 times the RDA) significantly increases serum calcium in most patients. The pathophysiologic mechanisms for this process include increased resorption of calcium from bone, increased gut absorption of dietary calcium, and increased renal calcium reclamation.[109]

The symptoms of hypercalcemia are non-specific: anorexia, nausea, vomiting, generalized weakness, mental status changes, polydipsia, and polyuria. Metastatic calcifications and cardiac dysrythmias also can occur.[108,110] Laboratory evaluation reveals elevated serum calcium and phosphorus. Hypercalciuria can be seen on urine analysis. Activated charcoal is recommended for acute ingestions that are 100 times greater than the RDA. Otherwise, treatment is largely directed at correcting hypercalcemia. Bisphosphonates and calcitonin may be necessary to inhibit bone resorption.

Daily vitamin E ingestions as high as 3200 mg (nearly 10 times the RDA) have produced few adverse effects.[111] In the 1980s, hepatotoxicity, necrotizing enterocolitis, and sepsis were observed in premature neonates given high-dose vitamin E to prevent retinopathy of prematurity.[103] Excess vitamin E can augment anticoagulation in patients who also are taking warfarin. This effect is due to vitamin E-mediated inhibition of vitamin K-dependent carboxylases. Significant coagulopathy is not observed in normal adults who take high doses of vitamin E and probably is not important in warfarin-treated patients if daily intake is less than 100 mg.[103,111] Nevertheless, laboratory evaluation of significant overdose should include coagulation studies. Treatment is supportive and includes vitamin E withdrawl

and cessation. Intramuscular vitamin K reverses coagulopathy.[103]

Vitamin K is necessary for the synthesis of clotting factors 2, 7, 9, and 10. These same factors are inhibited by anticoagulation therapy with warfarin. Vitamin K is available in some multivitamins and as single oral supplements. Additionally, a significant amount of vitamin K is found in several foods, such as green tea, turnip, broccoli, spinach, cabbage, asparagus, and lettuce. Excess vitamin K from these sources can inhibit or reverse the therapeutic effects of warfarin. This supplement has not been shown to have other major toxicities.

The vitamin B complex is made up of the following compounds: thiamine (B_1), riboflavin (B_2), niacin (B_3), pyridoxine (B_6), and cobalamin (B_{12}). These supplements are essential for a range of vital processes, from DNA and amino acid synthesis to important redox reactions that power cellular metabolism. Deficiencies of these vitamins have been characterized in well-known clinical syndromes. Toxicity is extremely rare. Niacin routinely causes skin flushing and pruritus at therapeutic doses. Daily doses of time-release preparations of niacinamide greater than 1 g have resulted in lactic acidosis, myopathy, and extensive liver damage.[112] Excess of pyridoxine has been associated with sensory neuropathy.[113] Treatment for these conditions is supportive and toxic effects generally improve after removal of the vitamin supplement.

Vitamin C is involved in the production of collagen and also has antioxidant properties. Vitamin C is considered safe at doses up to 2 grams/day.[103] Greater daily intake most commonly results in an osmotic diarrhea. Additional adverse effects of high-dose vitamin C are renal calculi and decreased prothrombin time in patients who also are taking warfarin.[103] Treatment is supportive.

Summary

A wide range of products are available for OTC use. These products are designed for administration by a variety of routes. Exposures to OTC agents can produce a significant and wide range of toxicities that must be recognized and managed by emergency health care providers. Although fatalities are rare, more than 500,000 OTC exposures were reported to the American Association of the Poison Control Centers Toxic Exposure Surveillance System (AAPCC TESS) in 1998, a number that certainly underestimates the actual incidence. The pediatric patient, the elderly, and those with co-morbid conditions are at greater risk for serious toxicity from these products. The ED history should include detailed questions regarding OTC products, which should be considered in all cases of intentional overdose. Per protocol, treatment begins with advanced life support of the unstable patient. Consultation with a regional poison control center is necessary to determine the proper method of decontamination and the need for specific therapies, including potential antidotes.

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Physician CME Questions

25. Which vitamin(s) cause(s) hypercalcemia in toxicity?
    - A. A and C
    - B. A and D
    - C. C and D
    - D. D only

26. The ingestion of 20 mg/kg of elemental iron will result in which of the following?
    - A Absent to mild gastrointestinal symptoms
    - B. Chelation therapy with deferoxamine
    - C. Metabolic acidosis
    - D. The amount of elemental iron ingested does not correlate with clinical toxicity

27. The management of iron toxicity includes all of the following *except*:
    - A. intravenous fluid hydration.
    - B. abdominal radiograph.
    - C. serum iron level.
    - D. whole bowel irrigation.
    - E. serum ferritin level.

28. The clinical manifestations of toxicity from histamine (H1) receptor antagonists include all of the following *except:*
    - A. decreased alertness.
    - B. agitation.
    - C. insomnia.
    - D. seizures.
    - E. dry mucous membranes.

29. Which one of these patient groups is at risk for toxicity from bismuth subsalicylate?
    - A. The elderly
    - B. Patients with enteropathies
    - C. Patients with renal insufficiency
    - D. Children

30. Bismuth toxicity primarily presents with which one of these clinical manifestations?
    - A. Gastrointestinal bleeding
    - B. Bradycardia and hypotension
    - C. Cognitive and affective disorders
    - D. Hemolytic anemia

31. The serotonin syndrome is a potentially life-threatening interaction between monoamine oxidase inhibitors or serotonin reuptake inhibitors and which of the following OTC agents?
    - A. Diphenhydramine
    - B. Ephedrine
    - C. Dextromethorphan
    - D. Acetaminophen

32. Seizures and tachydysrhythmias are potential manifestations of acute exposure to which of the following substances?
    - A. Dextromethorphan
    - B. Iron
    - C. Loperamide
    - D. Ethanol
    - E. Caffeine

In Future Issues: Movement Disorders