

AMERICAN ACADEMY OF PEDIATRICS

Committee on Drugs

“Inactive” Ingredients in Pharmaceutical Products: Update (Subject Review)

ABSTRACT. Because of an increasing number of reports of adverse reactions associated with pharmaceutical excipients, in 1985 the Committee on Drugs issued a position statement¹ recommending that the Food and Drug Administration mandate labeling of over-the-counter and prescription formulations to include a qualitative list of inactive ingredients. However, labeling of inactive ingredients remains voluntary. Adverse reactions continue to be reported, although some are no longer considered clinically significant, and other new reactions have emerged. The original statement, therefore, has been updated and its information expanded.

ABBREVIATIONS. FDA, Food and Drug Administration; MDIs, metered-dose inhalers

Pharmaceutical products often contain agents that have a variety of purposes, including improvement of the appearance, bioavailability, stability, and palatability of the product. Excipients (substances added to confer a suitable consistency or form to a drug, such as the vehicle, preservatives, or stabilizers) frequently make up the majority of the mass or volume of oral and parenteral drug products. These pharmaceutical adjuvants are usually considered to be inert and do not add to or affect the intended action of the therapeutically active ingredients.

Some 773 chemical agents have been approved by the Food and Drug Administration (FDA) for use as inactive ingredients in drug products.² Inasmuch as these compounds are classified as “inactive,” no regulatory statutes require listing on product labeling. Pharmacopeial guidelines, enforceable under the Food, Drug, and Cosmetic Act, do require labeling of inactive ingredients for topical, ophthalmic, and parenteral preparations; orally administered products are currently exempt. Because of pressure from professional and consumer organizations asking the FDA to require complete disclosure of all ingredients, voluntary labeling was adopted by the two major pharmaceutical industry trade associations. These voluntary guidelines contain an exemption for “trade secret” components and do not require complete disclosure of all fragrance and flavoring ingredients.

Current problems encountered with “inactive” ingredients include benzalkonium chloride-induced

bronchospasm from antiasthmatic drugs, aspartame-induced headache and seizures, saccharin-induced cross-sensitivity reactions in children with sulfonamide allergy, benzyl alcohol toxicity in neonates receiving high-dose continuous infusion with preserved medications, dye-related cross-reactions in children with aspirin intolerance, lactose-induced diarrhea, and propylene glycol-induced hyperosmolality and lactic acidosis. Although many other excipients have been implicated in causing adverse reactions, these are the most significant in the pediatric population.

ANTIASTHMATIC MEDICATIONS

It is readily appreciated that some percentage of asthmatic children will develop a “paradoxical” bronchospasm after they inhale their medication. Because many of these reactions were attributed to sulfite, which had been highly publicized as a causative agent, it was often first suspected. During the past 10 years, however, the active ingredient in sulfite-containing preparations, the nonselective β_2 -agonists isoproterenol, isoetharine, and metaproterenol, have been replaced as drugs of choice by more selective agents, primarily albuterol, that do not contain sulfites. Paradoxical reactions continue to be reported, in some cases resulting in product reformulation because of excessive adverse reactions. Inactive ingredients that have been implicated in causing these reactions include benzalkonium chloride, oleic acid, chlorofluorocarbons, soya lecithin, and sorbitan trioleate.

Sulfites

Sulfiting agents are widely used as antioxidants. Six sulfite compounds (sulfur dioxide, sodium sulfite, sodium bisulfite, potassium bisulfite, sodium metabisulfite, and potassium metabisulfite) have been categorized as “Generally Recognized as Safe” for use in foods and drugs. This status was revoked for raw fruits and vegetables (excluding potatoes) in 1986 after the FDA received reports of more than 250 cases of adverse reactions, including six deaths associated with the ingestion of sulfites in foods.^{3,4} Although primary exposure in children is through foods, serious reactions have also occurred after oral, inhalational, parenteral, and ophthalmic administration of sulfite-containing drugs.

Signs and symptoms most frequently reported include wheezing, dyspnea, and chest tightness in patients with known reactive airway disease.⁵⁻⁹ Nonimmunologic anaphylactoid reactions have also

The recommendations in this statement do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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occurred.^{7,8,10,11} Reactions to sulfites rarely occur in patients without reactive airway disease.¹² Metabisulfite hypersensitivity was demonstrated in 19 (66%) of 29 children with a history of chronic moderately severe asthma.¹³ The incidence of sulfite sensitivity increases with age in severely asthmatic children (31% of children up to 10 years of age and 71% of older children).¹⁴

The presence of sulfites in antiasthmatic medications has been a concern, but many of these medications have been reformulated or replaced in clinical practice by more β -selective agents, which do not contain sulfites. Metered-dose aerosol bronchodilators do not contain sulfites. Nonsulfite-containing products used to treat asthma are presented in Table 1. Parenteral drugs, such as corticosteroids, aminoglycosides, and epinephrine, may contain sulfites (Table 2) but rarely produce reactions because of the small amounts present. Patients who react to oral challenges with small amounts (5 to 10 mg) are at risk for similar reactions from these parenteral agents.¹⁵ Local dermal reactions accompanied by eo-

TABLE 1. Some Medications Used by Asthmatics That Do Not Contain Sulfites

Brand Name*	Manufacturer
Aerobid inhaler	Forest
Airet solution	Adams
Alupent aerosol	Boehringer Ingelheim
Alupent solution 5%*	Boehringer Ingelheim
Alupent solution Unit-dose 0.4, 0.6%	Boehringer Ingelheim
Alupent syrup	Boehringer Ingelheim
Alupent tablets	Boehringer Ingelheim
Atrovent aerosol	Boehringer Ingelheim
Azmacort	Rhone-Poulenc Rorer
Beclivent inhaler	Glaxo
Brethine injection	Ciba-Geigy
Brethine tablets	Ciba-Geigy
Bricanyl injection	Marion Merrell Dow
Bronkaid Mist aerosol	Sterling-Winthrop
Bronkometer aerosol	Sterling-Winthrop
Celestone injection*	Schering
Decadron respihaler	Merck
Duo-Medihaler aerosol	3M
Elixophyllin elixir	Forest
Intal capsules, solution, inhaler	Fisons
Isoetharine solution	Astra
Isoetharine solution	Dey
Isuprel Mistometer	Winthrop-Breon
Maxair autohaler	3M
Medihaler-Epi aerosol	3M
Medihaler-Iso aerosol	3M
Metaprel aerosol	Sandoz
Metaprel solution 5%*	Sandoz
Primatene Mist suspension aerosol	Whitehall
Primatene Mist solution aerosol	Whitehall
Proventil aerosol	Schering
Proventil solution 0.5%*	Schering
Quibron tablet, capsule	Bristol-Myers Squibb
Sus-Phrine injection	Forest
Theo-Dur sprinkle, tablets	Key
Tilade inhaler	Fisons
Tornalate inhaler	Sterling Winthrop
Tornalate solution	Sterling Winthrop
Vanceril inhaler	Schering
Ventolin aerosol	Glaxo
Ventolin nebulas solution 0.083%	Glaxo
Ventolin solution 0.5%*	Glaxo
Ventolin rotacaps, syrup, tablets	Glaxo

* Contains benzalkonium chloride.

TABLE 2. Some Sulfite-containing Medications Used by Asthmatics

Brand Name	Manufacturer
Adrenalin Chloride 1:100	Parke-Davis
Adrenalin injection 1:1000	Parke-Davis
Amikin injection	Apothecon
Arm-a-Med isoetharine solution	Armour
AsthmaNefrin	Menley & James
Beta 2 isoetharine solution	Nephron
Bronkosol solution	Sanofi-Winthrop
Dey-dose epinephrine	Dey
Dey-dose isoetharine solution	Dey
Dispos-a-Med isoetharine	Parke-Davis
Epipen/Epipen Jr	Center
Garamycin injection (all but intravenous piggyback and intrathecal)	Schering
Isoetharine hydrochloride	Roxane
Isuprel injection	Sanofi-Winthrop
Isuprel solution	Sanofi-Winthrop
MicroNefrin	Bird
Minocin syrup	Lederle
Nebcin injection	Lilly
Netromycin injection	Schering

sinophilia have been reported after continuous infusion with dobutamine.¹⁶ Sulfite-preserved amino acids contained in most mixtures of total parenteral nutrition are a less commonly appreciated source. Nevertheless, life-threatening situations requiring the administration of epinephrine should be treated with sulfite-preserved epinephrine if no preservative-free product is available, even in very sensitive patients. The diagnosis of sulfite sensitivity is made by history and through challenge testing.⁷ Avoidance of foods containing sulfites through careful reading of packaged food labels and inquiry at restaurants as to the use of agents that contain sulfites may prevent reactions. A commercial sulfite-detection strip was found to be unreliable, especially when used on acidic foods or foods removed from their original containers.¹⁷ Drug manufacturers must disclose the presence of sulfites in product labeling.

Benzalkonium Chloride

Benzalkonium chloride is a commonly used bactericidal preservative in albuterol and metaproterenol nebulizer solutions in the United States and in beclomethasone and ipratropium bromide nebulizer solutions in other countries. Inhalation of pure benzalkonium chloride causes reproducible, dose-related, cumulative bronchoconstriction, with a rapid onset and prolonged duration compared with sulfites. It is frequently accompanied by a cough and burning sensation and, occasionally, by facial flushing and pruritus. Bronchoconstriction is inhibited by concurrent treatment or pretreatment with β_2 -agonists and cromolyn sodium and partially by histamine₁ antagonists.¹⁸⁻²⁰ The mechanism appears to be non-IgE-mediated release of mast cell mediators, with atopic patients being more susceptible.²¹

Because the reaction is dose-related and cumulative and may be masked by the active agent in many patients, few clear-cut cases of paradoxical bronchoconstriction have been attributed to benzalkonium, primarily in patients using more than one agent containing this excipient or in those receiving frequent

dosing.²²⁻²⁶ Unit-dose vials deliver five times as much benzalkonium as the same dose given from a multiple-dose vial, which resulted in one case of bronchoconstriction.²⁶ Other potential sources of benzalkonium in children with asthma and concurrent sinusitis include nasal saline, nasal corticosteroid, and nasal decongestant solutions.

In several studies of adult asthmatics, the lowest dose of pure benzalkonium chloride that produced a 20% decrease in forced expiratory volume in 1 second ranged from 124 to 159 μg . Albuterol (from a multidose vial) contains 50 μg per 0.5 mL of solution^{18,19}; thus, a single dose is unlikely to cause a reaction. Even in patients without overt deterioration after the use of benzalkonium-preserved antiasthmatic agents, some evidence exists that benzalkonium-free solutions may have improved efficacy.^{21,27} Thus, although the presence of benzalkonium probably has a minimal effect in most patients using single, infrequent doses of a preserved bronchodilator, development of a unit-dose, nonpreserved preparation may significantly benefit the severely ill, hospitalized patient in whom disease-related deterioration in pulmonary function may be difficult to distinguish from preservative toxicity.

Metered-dose Inhalers (MDIs)

Paradoxical bronchoconstriction has been reported in up to 6.9% of asthmatic patients after inhalation of pure MDI vehicle.²⁸ When combined with an active ingredient, this incidence decreases to approximately 1.5% to 4%.²⁹ Most studies of MDI-related bronchoconstriction have been confounded by the lack of testing of individual vehicle components, inherent irritability of some active ingredients (corticosteroids), or concurrent use of potent active ingredients (bronchodilators). Inactive ingredients that have been implicated in the deterioration of pulmonary function attributable to hypersensitivity or irritant effects include chlorofluorocarbons,³⁰⁻³³ sorbitan trioleate,^{30,34} oleic acid,^{28,35} and soya lecithin (H. G. Wilms, written communication, October 27, 1989).^{28,36} One metaproterenol product, reformulated to contain soya lecithin, was withdrawn from the market after 1 month because of escalating reports of coughing, gagging, and asthma exacerbation (H. G. Wilms, written communication, October 27, 1989).

ARTIFICIAL SWEETENERS

Aspartame

Aspartame, a dipeptide of aspartic acid and a methyl ester of phenylalanine, is approved for use in pharmaceutical products and is being used increasingly in chewable tablet and sugar-free formulations. Labels for both prescription and nonprescription products must include the phenylalanine content. The major consideration in the use of aspartame in children is in patients with autosomal recessive phenylketonuria. Although heterozygotes do not appear to have clinically significant increases in phenylalanine after ingestion of even large amounts (equivalent to 24 12-oz cans of diet beverages), homozygotes with strict dietary restrictions should avoid aspar-

tame. Children without dietary restrictions could safely ingest 10 mg/kg/d.³⁷⁻⁴⁰ Dietary consumption of aspartame is typically less than 5 mg/kg/d⁴¹; young children, however, could ingest considerably more. For example, a 2-year-old child weighing 12 kg consumes 17 mg/kg from drinking one 12-oz can of diet soda and one serving of a sweetened product (eg, cereal, pudding, gelatin, or frozen dessert).⁴²

Headache is the most common adverse effect attributed to aspartame but is seldom confirmed by single-dose double-blind challenge. Up to 11% of patients with chronic migraine headaches reported headaches triggered by aspartame⁴³; however, a double-blind challenge with three doses of 10 mg/kg given every 2 hours triggered no more headaches than did placebos in patients with vascular headaches believed to be exacerbated by aspartame.⁴⁴ A small, double-blind 4-week trial showed an increase in frequency of headaches after ingestion of 1200 mg/d, indicating that a longer challenge period may be necessary.⁴⁵

In anecdotal reports, aspartame has been linked to various neuropsychiatric disorders, including panic attacks, mood changes, visual hallucinations, manic episodes, and isolated dizziness.⁴⁶⁻⁴⁹ A small, double-blind crossover study of patients with major depression revealed a higher incidence of reactions in these patients compared with nondepressed volunteers after administration of 30 mg/kg for 7 days; symptoms included headache, nervousness, dizziness, memory impairment, nausea, temper outbursts, and depression.⁵⁰ None of these conditions has been rigorously proven to be caused by aspartame, but carefully conducted double-blind challenges may be indicated in patients with histories that suggest aspartame as a cause. Patients with underlying mitral valve prolapse or affective disorders may be at increased risk for neuropsychiatric effects⁵¹; several studies have shown that individuals without psychiatric or seizure disorders do not demonstrate these effects.^{50,52}

Seizures have been reported via passive surveillance data collected by the FDA and in a few case reports.^{47,48,53} A recent analysis of FDA reports showed 41 cases of rechallenge with a temporal relationship to aspartame consumption. Most seizures occurred in patients who had an acceptable dietary intake, except for a 16-year-old who ingested up to 57 mg/kg of aspartame.⁵⁴ Aspartame is generally considered safe for children with epilepsy. One study found increased spike-wave discharges in children with untreated absence seizures after a high dose of aspartame and suggested that children with poorly controlled absence seizures avoid aspartame.⁵⁵

Several studies have shown no relationship between aspartame and aggressive or hyperactive behaviors or cognitive function in children; thus, children with attention deficit disorder, with or without hyperactivity,^{56,57} do not need to avoid this sweetener.

Isolated confirmed hypersensitivity reactions resulting from ingestion of aspartame have been reported, including two patients who developed sub-

TABLE 3. Parenteral Medications That Contain Benzyl Alcohol

Drug	Benzyl Alcohol Content, %	Estimated Average Daily Intake of Benzyl Alcohol in Infants
Aminophylline	2.0	2–4 mg/kg
Aquamephyton neonatal injection	0.9	4.5 mg
Ativan injection	2.0	0.4–1 mg/kg
Bacteriostatic saline	1.5	99–234 mg/kg
Bacteriostatic water	1.5	99–234 mg/kg
Dexamethasone injection	1.0	2.5 mg
Dopram	0.9	21.6–32.4 mg/kg
Folate sodium	1.5	0.6–0.9 mg
Heparin injection (1000 U/mL)	1.0	1.2 mg
Multivitamin infusion	0.9	45 mg
Netromycin injection*	1.0	0.4–0.65 mg/kg
Norcuron with supplied diluent	0.9	0.4 mg/kg
Pavulon injection	1.0	2–3 mg/kg
Tracrium multidose vial	0.9	3.6 mg/kg
Vasotec injection	0.9	0.1–0.5 mg/kg

* Netromycin neonatal injection does not contain benzyl alcohol.

cutaneous nodules or granulomas resembling erythema nodosum.^{58,59} Other reported reactions include orofacial granulomatosis, erythema, pruritus, urticaria, and angioedema.^{60–62} A meticulous workup with double-blind challenge usually fails to confirm the purported reaction; hypersensitivity reactions appear to be rare.^{63,64} These reactions may be related to breakdown products formed during the storage of liquid products, such as diketopiperazine derivatives, especially after exposures to higher temperatures.⁶² If so, rechallenge with fresh encapsulated powder could produce a false-negative reaction.

Saccharin

Many oral drugs, including both solid and liquid dosage forms, contain saccharin as a sweetening agent. Saccharin is not included in drug labeling. The most frequent use of saccharin is in foods and beverages, accounting for 70% of the total consumption. A British survey found that conventional soft drinks were the predominant source of saccharin in children aged 2 to 9 years, replaced by diet soft drinks in adolescents. The median intake of saccharin was 0.2 to 0.9 mg/kg/d in the general population and 0.6 to 2.3 mg/kg/d in diabetics.⁶⁵ Foods containing saccharin must carry a label stating that the “use of this product may be hazardous to your health . . . contains saccharin which has been determined to cause cancer in laboratory animals.”

Saccharin may be present in drugs in substantial amounts. Ingestion of the recommended daily dosage of chewable aspirin or acetaminophen tablets in a school-age child would provide approximately the same amount of saccharin contained in one can of a diet soft drink. This amount, relative to the body weight of a child younger than 9 or 10 years, ingested for prolonged periods would be considered as “heavy use,” as defined in a major large-scale FDA/National Cancer Institute epidemiologic study.⁶⁶ In this study, heavy use of artificial sweeteners was associated with a significantly increased risk for the development of bladder cancer. An independent review of this study concluded that there was no association.⁶⁷ An investigation of saccharin performed by the American Medical Association in 1985 con-

cluded that bladder changes were species-specific, were confined to the second generation of male rats, and occurred in association with large doses (equivalent to several hundred cans of diet soft drink per day). The no-effect level was equivalent to 500 mg/kg/d.^{68,69} Saccharin is not genotoxic; the presumed mechanism of toxicity is the binding of saccharin to urinary proteins (not normally found in humans), creating a nidus for the formation of silicate crystals, which are cytotoxic to bladder epithelium.⁷⁰

Saccharin is an o-toluene sulfonamide derivative and causes similar dermatologic reactions. Cross-sensitivity with sulfonamides has been demonstrated; therefore, children with “sulfa” allergy should also avoid saccharin. Hypersensitivity can usually be confirmed by a radioallergosorbent test for saccharin.⁷¹ In a series of 42 patients with adverse effects resulting from consumption of saccharin in pharmaceutical agents, pruritus and urticaria were the most common reactions, followed by eczema, photosensitivity, and prurigo.⁷² Other reactions include wheezing, nausea, diarrhea, tongue blisters, tachycardia, fixed eruptions, headache, diuresis, and sensory neuropathy.^{73–77}

Ingestion of saccharin-adulterated milk formula by infants was associated with irritability, hypertonia, insomnia, opisthotonos, and strabismus, which resolved within 36 hours after ingestion. Two anecdotal reports of an accidental overdose in an adult and a child discussed reactions of generalized edema, oliguria, and persistent albuminuria.⁷⁵ Because of the paucity of data on the toxicity of saccharin in children, the American Medical Association has recommended limiting the intake of saccharin in young children and pregnant women.⁶⁸

BENZYL ALCOHOL

Benzyl alcohol is commonly used as a preservative in many injectable drugs and solutions. A number of neonatal deaths and severe respiratory and metabolic complications in low-birth-weight premature infants have been associated with use of this agent in bacteriostatic saline intravascular flush and endotracheal tube lavage solutions.^{78–80} In a controlled study, intraventricular hemorrhage, metabolic acidosis, and

TABLE 4. Examples of Dye-free Orally Administered Liquid Medications

Classification and Product (Manufacturer)	Active Ingredients (per 5 mL Unless Otherwise Indicated)
Analgesics	
Demerol (Sanofi Winthrop)	Meperidine 50 mg
Indomethacin (Roxane)	Indomethacin 25 mg
Meperidine* (Roxane)	Meperidine 50 mg
Methadone Intensol* (Roxane)	Methadone 50 mg
Opium tincture (Lilly)	Morphine 50 mg
Rescudose* (Roxane)	Morphine sulfate 20 mg
Roxanol* (Roxane)	Morphine sulfate 100 mg
Roxanol* (Roxane)	Morphine sulfate 20 mg
Roxicodone Intensol* (Roxane)	Oxycodone 100 mg
Antibiotics/anti-infective	
Furoxone (Roberts)	Furazolidone 50 mg
Gantrisin syrup (Roche)	Sulfisoxazole 500 mg
Gantrisin pediatric suspension (Roche)	Sulfisoxazole 500 mg
Mandelamine 250 (Parke-Davis)	Methenamine mandelate 250 mg
Minocin (Lederle)	Minocycline 50 mg
Mintezol (Merck Sharp & Dohme)	Thiazabendazole 500 mg
Nystatin (Roxane)	Nystatin 500,000 units
Pediazole (Ross)	Erythromycin 200 mg, sulfisoxazole 600 mg
Suprax (Lederle)	Cefixime 100 mg
Vancocin** (Lilly)	Vancomycin 250 or 417 mg
Vantin (Upjohn)	Cefpodoxime axetil 50 mg
Antihistamine/decongestant/antitussive	
Atarax syrup (Roerig)	Hydroxyzine 10 mg
Chlorafed (Hauck)	Chlorpheniramine 2 mg, pseudoephedrine 30 mg
Codclear DH (Central)	Hydrocodone 5 mg, guaifenesin 100 mg
Deconamine syrup (Berlex)	Chlorpheniramine 2 mg, pseudoephedrine 30 mg
Entuss-D (Hauck)	Hydrocodone 5 mg, pseudoephedrine 30 mg, guaifenesin 300 mg
Iodinated glycerol (Roxane)	Iodinated glycerol 60 mg
Iodinated glycerol/Dextromethorphan (Roxane)	Iodinated glycerol 30 mg, dextromethorphan 10 mg
Isoclor (Fisons)	Chlorpheniramine 2 mg, pseudoephedrine 30 mg
Tuss-Ornade (SmithKline Beecham)	Phenylpropanolamine 12.5 mg, caramiphen 6.7 mg
Cardiovascular agents	
Aldomet (Merck Sharp & Dohme)	Methyldopa 250 mg
Colestid** (Upjohn)	Colestipol 5 g per packet
Digoxin elixir (Roxane)	Digoxin 0.25 mg
Hydrochlorothiazide (Roxane)	Hydrochlorothiazide 50 mg
Propranolol oral solution (Roxane)	Propranolol 20 or 40 mg
Propranolol Intensol (Roxane)	Propranolol 400 mg
Gastrointestinal	
AlternaGEL (Johnson & Johnson-Merck)	Aluminum hydroxide 600 mg
Aluminum hydroxide gel (Roxane)	Aluminum hydroxide 450 mg
Aluminum hydroxide concentrated (Roxane)	Aluminum hydroxide 675 mg
Aromatic cascara fluid extract (Roxane)	Cascara sagrada extract equivalent to 1 g/mL
Castor oil** (Roxane)	Castor oil
Citrocarbonate+ (Upjohn)	Sodium citrate 1.82 g, sodium bicarbonate 0.78 g
Doxinate (Hoechst-Roussel)	Docusate 50 mg
Effersyllium+ (Johnson & Johnson-Merck)	Psyllium hydrocolloid 3 g
Gaviscon ESRF (Marion Merrell Dow)	Aluminum hydroxide 254 mg, magnesium carbonate 237.5 mg
Ipecac syrup (Roxane)	Ipecac alkaloids 20 mg/15 mL
Kaolin pectin (Roxane)	Kaolin, pectin
Kaopectate regular flavor (Upjohn)	Attapulgit 200 mg
Loperamide (Roxane)	Loperamide 1 mg
Maalox plus, extra strength (Rhone-Poulenc Rorer)	Aluminum hydroxide 500 mg, magnesium hydroxide 450 mg, simethicone 40 mg
Milk of Magnesia* (Roxane)	Magnesium hydroxide 400 mg
Milk of Magnesia concentrated (Roxane)	Magnesium hydroxide 1200 mg
Mylanta double strength (Johnson & Johnson-Merck)	Aluminum hydroxide 400 mg, magnesium hydroxide 400 mg, simethicone 40 mg
Parapectolin (Rhone-Poulenc Rorer)	Attapulgit 200 mg
Perdiem+ (Rhone-Poulenc Rorer)	Psyllium (82% w/v), senna (18% w/v)
Hormonal agents	
Dexamethasone solution (Roxane)	Dexamethasone 0.5 mg
Dexamethasone Intensol* (Roxane)	Dexamethasone 5 mg
Prednisone solution (Roxane)	Prednisone 5 mg
Prednisone Intensol* (Roxane)	Prednisone 25 mg
Proglycem (Baker Cummins)	Diazoxide 250 mg

TABLE 4. Continued

Classification and Product (Manufacturer)	Active Ingredients (per 5 mL Unless Otherwise Indicated)
Psychotropics	
Chlorpromazine Intensol (Roxane)	Chlorpromazine 150, 500 mg
Cibalith-S (Ciba-Geigy)	Lithium 8 mEq
Haldol* (McNeil)	Haloperidol 10 mg
Haloperidol Intensol* (Roxane)	Haloperidol 10 mg
Lithium citrate (Roxane)	Lithium 8 mEq
Navane (Roerig)	Thiothixene 25 mg
Prozac (Lilly)	Fluoxetine 20 mg
Sinequan (Roerig)	Doxepin 50 mg
Thioridazine solution (Roxane)	Thioridazine 80 mg/15 mL
Thioridazine Intensol (Roxane)	Thioridazine 150, 500 mg
Thiothixene Intensol* (Roxane)	Thiothixene 25 mg
Thorazine (SmithKline Beecham)	Chlorpromazine 10 mg
Trilafon (Schering)	Perphenazine 16 mg
Sedatives/hypnotics	
Chloral hydrate syrup (Roxane)	Chloral hydrate 250, 500 mg
Lorazepam Intensol* ⁺ (Roxane)	Lorazepam 10 mg
Spasmolytics/bronchodilators	
Aquaphylline (Ferndale)	Theophylline 5.33 mg
Elixophyllin GG (Forest)	Theophylline 100 mg, guaifenesin 100 mg,
Marax DF (Roerig)	Ephedrine 6.25 mg, theophylline 32.5 mg, hydroxyzine 2.5 mg
Slo-Phyllin GG (Rhône-Poulenc Rorer)	Theophylline 50 mg, guaifenesin 30 mg
Somophyllin DF (Fisons)	Theophylline 90 mg
Theoclear-80 (Central)	Theophylline 26.66 mg
Theolair liquid (3M Riker)	Theophylline 26.66 mg
Theophylline solution (Roxane)	Theophylline 26.66 mg
Theostat 80 syrup (Laser)	Theophylline 26.66 mg
Vitamins	
DHT intensol (Roxane)	Dihydrotachysterol 1 mg
Drisdol (Sanofi Winthrop)	Ergocalciferol 8000 U/mL
Theragran liquid (Apothecon)	Multivitamins
Miscellaneous	
Antiminth (Roerig)	Pyrantel pamoate 250 mg
Glyoxide (Marion Merrell Dow)	Carbamide peroxide 100 mg/mL, anhydrous glycerol
Klorvess (Sandoz)	Potassium chloride 10%

* Flavoring free.

⁺ Preservative free.

increased mortality were positively correlated with substantial benzoic acid and benzyl alcohol levels in neonates.⁸¹ The incidence of premature infant mortality, kernicterus, and intraventricular hemorrhage decreased markedly after discontinuation of preserved flush solutions.⁸²⁻⁸⁴ In surviving infants, exposure to benzyl alcohol was also found to be associated with morbidity, including cerebral palsy and developmental delay.⁸³

Most therapeutic agents, other than large-volume fluids, contain amounts of benzyl alcohol smaller than those associated with neonatal death. The effects of lower amounts, however, have not been adequately studied (Table 3). Toxicity has been described in one infant weighing 3350 g who received 32 to 105 mg/kg/d.⁸⁰ Continuous infusions of high doses of some medications containing benzyl alcohol, such as doxapram, may reach the range of benzyl alcohol dosage associated with toxicity in this case report. Premature infants receiving low doses in medications were found to have peak benzoic acid levels 10 times higher than those in term infants but without evidence of toxicity.⁸⁵ Two studies noting the striking decrease in kernicterus after removal of benzyl alcohol did not reveal a dose-response relationship and could not exclude the possibility that other advances in therapy were responsible.^{84,86}

The US Pharmacopeia requires labeling of bacteriostatic water and saline for injection with the phrase, "Not for use in newborns." The FDA declined similar labeling for multidose parenteral medications, because serious toxic effects from benzyl alcohol had virtually disappeared.⁸⁷ The toxic effects in newborns relate primarily to the use of preservative-containing flush solutions, which clearly are to be avoided in newborns. At low doses, such as those present when medications preserved with benzyl alcohol are administered, benzyl alcohol is safe for newborns.

Bacteriostatic saline solution containing benzyl alcohol was associated with severe bronchitis and hemoptysis when used to dilute albuterol for nebulization in an adult man.⁸⁸ Nonpreserved saline solution should be used in children to dilute nebulized bronchodilators.

Benzyl alcohol may also rarely cause hypersensitivity reactions. Contact dermatitis,⁸⁹ as well as more generalized allergic symptoms including nausea, fatigue, fever, maculopapular rash, or angioedema, may occur after parenteral administration of products containing benzyl alcohol as a preservative.⁹⁰⁻⁹²

COLORING AGENTS

Numerous dyes are used in pharmaceutical manufacturing. These dyes give products a distinctive,

identifiable appearance, and they impart a uniform and attractive color to products that might otherwise be drab and unappealing or exhibit color variation among batches.

Several groups of dyes have been associated with serious adverse effects. The azo dye tartrazine (FD&C Yellow No. 5) is known to be potentially dangerous in aspirin-intolerant individuals. Approximately 2% to 20% of asthmatics are sensitive to aspirin. The incidence of cross-reaction to tartrazine was previously believed to be as high as 10%,^{93,94} but more recent carefully blinded studies have shown the incidence to be less than 2.4%.⁹⁵⁻⁹⁸ Unlike aspirin, tartrazine does not alter prostaglandin synthesis and does not, therefore, exert anti-inflammatory actions. Nonetheless, reactions to tartrazine are similar to those produced by aspirin, occur in patients both with and without a history of aspirin intolerance, and include acute bronchospasm, nonimmunologic urticaria, eosinophilia, and angioedema.^{94,99-107} Rarely, nonimmunologic anaphylactoid reactions occur.^{108,109} The most likely mechanism for these reactions is dose-related histamine release from mast cells.^{110,111} Patients with recurrent allergic vascular purpura may experience exacerbations after exposure to azo dyes, such as tartrazine, sunset yellow, and new cocine.¹¹²⁻¹¹⁴ Because of both the seriousness of these reactions and the widespread use of tartrazine in foods and over-the-counter and prescription drugs, since 1980 the FDA has required that all products containing tartrazine be labeled so that these substances can be avoided.¹¹⁵

Patients with the classic aspirin triad reaction (asthma, urticaria, and rhinitis) or anaphylactoid reactions may also develop similar reactions from dyes other than tartrazine, including amaranth,¹¹⁶⁻¹¹⁸ erythrosine,^{118,119} indigo carmine (FD&C Blue No. 2),¹⁰³ ponceau,^{106,116,118} new cocine,^{113,117} sunset yellow,^{103,106,108,113,117,118} Brilliant Blue (FD&C Blue No. 1),^{106,118} methyl blue,¹²⁰ quinolone yellow,¹²¹ and FD&C Red No. 40.¹²²

Gastrointestinal intolerance, with abdominal pain, vomiting, and indigestion, has been associated with sunset yellow; in one case, eosinophilia and hives were also present.^{123,124} Other dermatologic reactions, including photosensitivity, erythroderma, and desquamation,¹²⁵ have been attributed to erythrosine, an iodine-containing dye. By mandate, erythrosine has been removed from topical products and is being voluntarily removed from many oral drug products because of concerns about carcinogenicity.

Contact dermatitis has been associated with neutral red,^{126,127} D&C Yellow No. 11,^{128,129} indigo carmine (FD&C Blue No. 2),¹³⁰ quinoline yellow,¹²⁹ and gentian violet (CI Basic Violet No. 3).^{131,132}

Dyes and other food additives have also been suggested as a cause or aggravating factor in some cases of hyperactivity in children¹¹⁶; carefully controlled trials¹³³⁻¹³⁶ and current opinion¹³⁷⁻¹³⁹ generally refute a possible association.

Because carefully controlled double-blind challenges often fail to confirm suspected reactions in children with atopic eczema,¹⁴⁰ a controlled challenge is recommended before dyes are eliminated

from the diet. Hypersensitive individuals should avoid dyes; liquid medications and nutritional supplements that do not contain dyes are listed in Table 4. These listings were originally compiled from voluntary responses to personal communications received from 56 US drug manufacturers and updated with a repeat mailing in December 1992. Until complete ingredient labeling is mandated, these lists will provide a tool to prevent reactions through avoidance in sensitive children using liquid dosage forms. Because inactive ingredients may change without changes in labeling, information in these tables should be verified.

LACTOSE

Lactose (milk sugar) is widely used as a filler or diluent in tablets and capsules and to give bulk to powders. Lactase deficiency, occurring either as a rare congenital disorder or more commonly as an acquired lack of intestinal brush border disaccharidase, may lead to diarrhea, abdominal cramping, bloating, and flatulence after ingestion of milk products or lactose. These effects are produced either by lactic acid formed in the intestine by bacteria from undigested lactose or by a high intestinal osmotic load caused by unabsorbed carbohydrate with production of carbon dioxide and hydrogen gas by bacterial fermentation.¹⁴¹ Lactose intolerance in infants and young children may be associated with severe, prolonged diarrhea complicated by bacterial proliferation in the small bowel, dehydration, and metabolic acidosis.¹⁴² Lactose may be detrimental to the galactose-intolerant infant.

Late-onset lactase deficiency (adult hypolactasia) is a common disorder. Approximately 90% of adult American blacks and 60% to 80% of Mexican-Americans, Native Americans, Asians, and most Middle Eastern and Mediterranean populations have abnormal findings on lactose tolerance tests.¹⁴³⁻¹⁴⁸ Approximately 10% of the white population with Scandinavian or European ancestry is affected.¹⁴⁸ Lactase deficiency may develop sporadically in otherwise tolerant individuals while they are suffering from an intestinal disease, such as tropical sprue or acute gastroenteritis.¹⁴⁹

Sensitivity to lactose varies widely in severity, although some individuals (adults and children) may experience diarrhea, gaseousness, or cramping after ingestion of as little as 3 g or less of lactose.^{150,151} Such symptoms can occur in sensitive individuals after ingestion of drugs containing lactose.¹⁵²⁻¹⁵⁴ Two adult asthmatics who developed bronchospasm from lactose-containing medications had positive double-blind challenges with 300 and 500 mg of lactose.^{155,156}

PROPYLENE GLYCOL

Propylene glycol is commonly used as a drug solubilizer in topical, oral, and injectable medications.

Absorption of the agent from creams applied to burns^{157,158} and injection of multivitamin products or enoximone (a phosphodiesterase inhibitor) in infants has resulted in serum hyperosmolality,^{159,160} which was associated with cardiorespiratory arrest in one case.¹⁶⁰ Neonates have a longer propylene glycol

half-life (16.9 hours) compared with adults (5 hours).^{158,159} Although the use of a multivitamin containing propylene glycol correlated strongly with serum osmolality in very low-birth-weight premature infants,¹⁶¹ propylene glycol from phenobarbital injection contributed an insignificant amount to the osmolar gap in another study.¹⁶² The higher amount of propylene glycol contained in an intravenous multivitamin product delivering 3 g/d was associated with a higher incidence of seizures in these infants compared with those receiving lower doses from an alternative product delivering 300 mg/d.¹⁶³ Hyperosmolality related to topical propylene glycol occurred in 9 of 262 hospitalized burn patients.¹⁶⁴

Because propylene glycol is metabolized to lactic acid, lactic acidosis may occur.¹⁶⁵ Hemolysis, central nervous system depression, hyperosmolality, and lactic acidosis have been reported after intravenous administration.¹⁶⁵⁻¹⁶⁸ Hyperlactemia is associated with high propylene glycol levels, usually in patients with renal insufficiency, and is generally of minor clinical importance.¹⁶⁹ Rapid infusion of concentrated propylene glycol-containing drugs has also been associated with respiratory depression, arrhythmias, hypotension, and seizures.¹⁷⁰ Inadvertent administration of a highly concentrated solution can occur during manual push infusions; a piggyback infusion is preferred.¹⁷¹ Seizures and respiratory depression have also occurred in children who have ingested oral liquid medications containing propylene glycol.^{172,173}

Several cases of localized contact dermatitis from the application of propylene glycol as a vehicle to skin or mucous membranes have been reported.¹⁷⁴⁻¹⁸⁰ In a series of 487 patients with eczematous contact dermatitis, 4.5% were found to be sensitive to propylene glycol.¹⁸¹ Oral or parenteral administration may exacerbate dermatitis in sensitized patients.^{182,183} The high concentration of propylene glycol contained in certain drug products, such as phenytoin, diazepam, digoxin, and etomidate, may induce thrombophlebitis when administered intravenously.^{184,185} In one study, 22% of patients experienced venous reactions to etomidate in propylene glycol, with no reactions to etomidate lipid emulsion.¹⁸⁶

RECOMMENDATIONS

In a previous review of inactive ingredients, the American Academy of Pediatrics recommended mandatory labeling of inactive ingredients for all prescription and over-the-counter products. Since voluntary labeling was adopted, the legislative push for mandatory labeling has been abandoned, other than for nutritional supplements. A recently published survey of labeling on 102 chewable and liquid pediatric preparations found that only 90% labeled sweeteners, 80% labeled dyes and coloring agents, and 65% labeled preservatives. Although 90% of the preparations labeled flavorings, few provided the specific ingredient, in accordance with the voluntary guidelines.¹⁸⁷ Therefore, the voluntary system is clearly inadequate. Again, the American Academy of Pediatrics recommends mandatory labeling for all prescription and over-the-counter drugs.

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