Pediatric Pharmacotherapy

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A Guide to Pharmaceutical Excipients

Excipients, or inert ingredients, are those substances added to pharmacologically active compounds to facilitate dosage form production, enhance drug stability, and improve palatability for the patient.[1,2] While their impact is often overlooked, these chemicals can cause adverse reactions apart from the active compound, including allergic reactions.[1-4] Awareness of the potential for excipients to cause adverse effects has improved in the past decade, with increasing reports in the medical literature. However, the increasing availability of generic compounds and, in the case of oral products, incomplete product labeling make assessment of the risks associated with the inert ingredients difficult.[2] This brief overview will describe the rationale for the addition of these ingredients and discuss some of the adverse reactions reported with their use.

Preservatives

Antimicrobials and antioxidants are added to pharmaceutical products to prolong shelf life and maintain sterility. Common antimicrobial agents include chlorbutol, benzyl alcohol, sodium benzoate, sorbic acid, phenol, thimerosal, parabens, and benzalkonium chloride. Antioxidants used in pharmaceutical products include butylated hydroxytoluene and hydroxyanisole, as well as propyl gallate and sulfites.[3,4] While necessary to ensure the safety of pharmaceutical products, the addition of these agents has been associated with significant adverse effects in certain patient populations.

The link between benzyl alcohol and neonatal cardiovascular collapse, "the gasping baby syndrome," is perhaps the most widely publicized adverse reaction related to the use of inert ingredients. This relationship was discovered in 1982 after a series of neonates died or developed a severe illness associated with gasping respirations, metabolic acidosis, and hematologic abnormalities. These cases were linked to the use of intravenous flush solutions and medications containing benzyl alcohol.[5] As a result, both the FDA and the American Academy of Pediatrics now recommend that benzyl alcohol containing products should be avoided whenever possible in infants.[6,7] In older patients, benzyl alcohol use has been associated with hypersensitivity reactions, including contact dermatitis, nausea, and angioedema.[1]

Benzalkonium chloride has received considerable attention in the past several years, as a result of its use in many nasal sprays and metered dose inhalers. In some asthmatic patients, benzalkonium chloride can produce significant bronchoconstriction. In a study by Zhang and colleagues [8] of 28 asthmatic patients, a significant decrease in pulmonary function tests was observed after benzalkonium chloride administration. The effect was greatest at 1 minute following exposure and lasted up to 60 minutes. The response was blocked by concomitant administration of cromolyn, suggesting an allergic mechanism. In non-asthmatic patients, the use of nasal sprays with benzalkonium chloride has been linked to increasing nasal congestion, and may, in part, explain the rebound congestion associated with prolonged use of these products.[9] Many patients with asthma also experience hypersensitivity reactions when exposed to sulfites, a common antioxidant in inhaled medications.[1]

Sweeteners and Flavorings

In a recent survey of medications for oral use, Kumar and colleagues[2] found that more than 90% of the products they evaluated contained both sweeteners and flavorings. The wide-spread use of these excipients reflects society's desire for medications which look and taste appealing. When prescribing medications for children, clinicians should keep in mind that taste perception changes with age.[10] A preference for sweet taste is innate in humans and is most

pronounced in infants. Individual differences in taste develop throughout life, influenced by early feeding experiences and genetic factors.[11] As a result, products that are appealing to infants and young children will not necessarily be accepted by older children and young adults. This may be of particular importance in teens who are unable to swallow tablets and capsules. Liquids containing large amounts of artificial sweeteners can leave a noticeable bitter aftertaste and result in decreased patient compliance.

Saccharin, sucrose, sorbitol, aspartame, and fructose are the most commonly used sweeteners in the United States.[2,4,12,13] Often, two or more sweeteners are combined in the preparation of oral liquids. Lactose is used in the manufacturing of tablet and capsule dosage forms as a diluent or filler, rather than as a sweetener. Although most patients tolerate these sugars without adverse effects, some may experience hypersensitivity reactions. The use of sorbitol and lactose may be associated with diarrhea and abdominal pain, but rarely is the quantity in pharmaceutical preparations large enough to be responsible for these effects. However, patients who are known to be lactose-intolerant have been reported to develop diarrhea even with the intake of small quantities in tablet dosage forms.

The concentration of sweeteners in oral solutions and suspensions averages 30-50% w/v of the formulation. In some antibiotic and cough/cold preparations, the sweetener content can be as high as 80% w/v.[13] Use of products containing large quantities of sugar should be avoided in children with diabetes, whenever possible. If these products must be used, blood glucose monitoring should be performed regularly to tailor insulin therapy.

Long-term use of oral medications containing large amounts of sweeteners has been linked to excessive development of dental caries in children.[14,15] Sugars, especially sucrose, cause a decrease in dental plaque pH, dissolving tooth enamel and promoting dental cariogenesis. [13,14] As a result, it is recommended that sugar-free products be used whenever long-term therapy is expected. If a product containing a sweetener must be used, parents or care providers should be instructed to have the child rinse his or her mouth out with water following ingestion of each dose.[13]

A wide variety of flavorings, both natural and synthetic, are used in the production of pharmaceutical products. Flavorings contain numerous ingredients. As an example, one brand of synthetic strawberry flavoring on the market contains more than 30 different components.[11] While most manufacturers are moving towards full disclosure on product labeling, flavorings often remain unspecified as a "trade secret." In Kumar's survey[2], 35% of products evaluated did not provide information on flavorings. As a result, it may be difficult to identify adverse reactions or allergies to specific ingredients. Reports of adverse effects associated with flavorings are uncommon, but menthol, lemon oil, and oil of peppermint have been associated with hypersensitivity reactions. [2]

Dyes and Colorants

Dyes and other coloring agents are used both to improve a medication's appearance and to provide a unique product identity. There are currently more than 100 dyes and coloring agents approved by the Food and Drug Administration for use in pharmaceutical preparations.[3] Most oral liquid dosage formulations contain between one and three different dyes. [12]

Exposure to dyes and colorants in medications has been associated with hypersensitivity reactions in susceptible patients, including anaphylaxis, bronchoconstriction, angioedema, urticaria, abdominal pain and vomiting, and contact dermatitis. Although not borne out in controlled clinical trials, some parents and clinicians have suggested a link between dyes and hyperactivity and aggressive behavior in children.[1]

Some of the dyes associated with hypersensitivity reactions include azo dyes such as tartrazine (FD&C Yellow 5), FD&C Yellow 6, FD&C Red 36, FD&C Red 17, and triphenylmethane dyes (FD&C Blue 1 and 2 and Green 3). The first two of these dyes (Yellow 5 and 6) have demonstrated cross-reactivity with aspirin and indomethacin. They should be avoided in patients with known allergies to these medications. Quinoline dyes (Yellow 10 and 11) have been linked with contact sensitization. Some xanthene dyes (FD&C Red 3 and Red 22) are potent photosensitizers.[1,2]

As reactions to dyes become more well described in the medical literature, many manufacturers

have begun producing dye-free preparations. Sensitive patients should be instructed to look for these products when purchasing nonprescription medications. Most prescription products, such as the oral antibiotics, contain dyes. For these cases, health care providers must work with patients and their families to identify those dyes most likely to be related to the adverse reaction and to select products without the potential triggering agents.

Solvents

Medications which are not highly water soluble present a problem for pharmaceutical manufacturers. The product must be made soluble enough for oral, topical, or parenteral use, without significantly altering its stability. Propylene glycol and polyethylene glycol are used as solvents in many dosage formulations.[3] Propylene glycol has been associated with a number of adverse effects, including cardiac arrhythmias, seizures, respiratory depression, severe hyperosmolality, lactic acidosis, and severe thrombophlebitis when administered by rapid intravenous injection.[1] For this reason, medications such as phenobarbital, phenytoin, and diazepam must be administered slowly when given intravenously. Polyethylene glycol has recently been associated with nephrotoxicity in a patient exposed to large doses while receiving sedation with lorazepam.[16]

Ethanol is commonly used as a solvent in the manufacturing of oral liquid dosage formulations.[3,17] Two concerns exist with the use of ethanol in products designed for the pediatric market, acute intoxication with accidental overdose and chronic toxicity associated with routine use for chronic medical conditions.

In 1984, the American Academy of Pediatrics recommended limiting alcohol content to no more than 5% and restricting the volume of products containing alcohol to non-lethal quantities.[17] In 1993, a committee representing the Food and Drug Administration and the Nonprescription Drug Manufacturers Association agreed to develop voluntary limits for the alcohol content of liquid dosage preparations. The committee concluded that all over-the-counter products designed for children less than six years of age should be alcohol-free. Products labeled for children 6-12 years of age should contain no more than 5% alcohol. Products for children over 12 years and adults should be limited to 10% alcohol content. In certain products requiring higher alcohol contents to achieve solubility, warning labels would instruct parents to contact a physician prior to giving these products to children.[18]

In summary, the use of pharmaceutical excipients is necessary to produce the wide variety of medications available to patients. While most patients tolerate these inert ingredients without problems, it should be remembered that these compounds are capable of inducing adverse effects. The trend towards more prudent use of these chemicals by pharmaceutical manufacturers and the increasing availability of labeling information will help clinicians to select appropriate products for their patients.

References

1. Committee on Drugs, American Academy of Pediatrics. “Inactive” ingredients in pharmaceutical products. Pediatrics 1985;76:635-43.
2. Kumar A, Rawlings RD, Beaman DC. The mystery ingredients: sweeteners, flavorings, dyes, and preservatives in analgesic/antipyretic, antihistamine/decongestant, cough and cold, antidiarrheal, and liquid theophylline preparations. Pediatrics 1993;91:927-33.
3. Golightly LK, Smolinske SS, Bennett ML et al. Pharmaceutical excipients: Adverse effects associated with inactive ingredients in drug products. Part I. Med Toxicol 1988;3:128-65.
4. Golightly LK, Smolinske SS, Bennett ML et al. Pharmaceutical excipients: Adverse effects associated with inactive ingredients in drug products. Part II. Med Toxicol 1988;3:209-40.
5. Gershanik J, Boecler B, Ensley H et al. The gasping syndrome and benzyl alcohol poisoning. New Engl J Med 1982;307:1384-88.
6. Centers for Disease Control. Neonatal deaths associated with use of benzyl alcohol- United States. MMWR 1982;31(22):290-1.
7. Committee on Fetus and Newborn, Committee on Drugs, American Academy of Pediatrics. Benzyl alcohol: Toxic agent in neonatal units. Pediatrics 1983;72:356-8.
8. Zhang YG, Wright WJ, Tam WK et al. Effect of inhaled preservatives on asthmatic subjects. II. Benzalkonium chloride. Am Rev Respir Dis 1990;141:1405-8.
9. Hallen H, Graf P. Benzalkonium chloride in nasal decongestive sprays has a long-lasting adverse effect on the nasal mucosa of healthy volunteers. Clin Exp Allergy 1994;25:401-5.
10. Ruff ME, Schotik DA, Bass JW. Antimicrobial drug suspensions: A blind comparison of taste of fourteen common pediatric drugs. Pediatr Infect Dis J 1991;10:30-3.
11. Schiffman SS, Gatlin CA. Sweeteners: State of knowledge review. Neurosci Biobehav Rev 1993;17:313-45.
12. Kumar A, Weatherly RM, Beaman DC. Sweeteners, flavorings, and dyes in antibiotic preparations. Pediatrics 1991;87:352-60.
13. Hill EM, Flaitz CM, Frost GR. Sweetener content of common pediatric oral liquid medications. Am J Hosp Pharm 1988;45:135-42.

14. Feigal RJ, Jensen ME, Mensing CA. Dental caries potential of liquid medications. Pediatrics 1981;68:416-9.
15. Maguire A, Rugg-Gunn AJ. Consumption of prescribed and over-the-counter liquid oral medications in Great Britain and the northern region of England, with special regard to sugar content. Public Health 1994;108:121-30.
16. Laine GA, Hossain SMH, Solis RT et al. Polyethylene glycol nephrotoxicity secondary to prolonged high-dose intravenous lorazepam. Ann Pharmacother 1995;29:1110-4.
17. Committee on Drugs, American Academy of Pediatrics. Ethanol in liquid preparations intended for children. Pediatrics 1984;73405-7.
18. Anon. Panel recommends limits on alcohol content of nonprescription products. Am J Hosp Pharm 1993;50:400.

Pharmacology Literature Review

Famotidine Use in Children

The authors of this brief review present a summary of the eight pharmacokinetic, pharmacodynamic, and safety studies of famotidine, an H_2-antagonist, in children. To date, three kinetics studies have been performed, demonstrating similar results. The average volume of distribution of famotidine in the children studied ranged from 0.3-0.7 L/kg and the average elimination half-life varied from 2.3 to 3.3 hours, similar to adult values. Based on the results of several pharmacodynamic studies, the authors suggest a famotidine starting dose of 0.5 mg/kg given every 8 to 12 hours for children with normal renal function. Doses should be reduced by 25% in children with moderate renal dysfunction and by 50% in patients with severe renal insufficiency. James LP, Kearns GL. Pharmacokinetics and pharmacodynamics of famotidine in p(a)ediatric patients. **Clin Pharmacokinet 1996;31:103-10.**

Predicting Psychotropic Medication Use

A retrospective study of 3,144 children treated at a university medical center clinic was conducted to identify risk factors associated with the need for psychotropic medications. A total of 122 children (3.9%) received psychotropic medications, including CNS stimulants, antianxiety agents, antidepressants, antipsychotics, and sedatives. Children from higher socioeconomic environments and two-parent households were more likely to receive psychotropic medications. The authors theorize that this higher rate of use reflects a greater likelihood for parents in these environments to seek medical attention and the availability of health insurance.

Gender patterns revealed that boys were more likely than girls to receive psychotropic drugs at an early age (usually methylphenidate). This use then declines with advancing age. Usage in girls followed the opposite pattern, with higher rates of prescribing during teen-age years. The authors also found a direct relationship between parental psychotropic use and the use of these medications in their children. Although the retrospective nature of this study limits its application, it does provide useful basic demographic information on these medications in the pediatric population. Hong SH, Shepherd MD. Psychosocial and demographic predictors of pediatric psychotropic medication use**. Am J Health-Syst Pharm 1996;53:1934-9.**

Formulary Update

The Pharmacy and Therapeutics Committee took a summer recess and did not meet during August. Monthly sessions will resume in September.

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