Pediatric Pharmacotherapy

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Drug-Nutrient Interactions

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Pharmacology Literature Review

IDENTIFYING DRUG-NUTRIENT INTERACTIONS

Drug interactions with food and nutritional supplements are a concern to all health care professionals. Questions regarding their clinical significance, however, make this a topic of considerable controversy. The incidence of drug-nutrient interactions appears to be wide-spread (1,2). It has been estimated that up to three potential interactions occur per patient each month in residents of long-term care facilities (2). As the complexity of a patient's medication regimen increases, so does the likelihood of interactions. Although the incidence of significant drug-nutrient interactions in children has not been evaluated, children

with chronic illnesses requiring complex medication regimens are likely to be at greatest risk.

In hospitalized patients, a program for routine monitoring of drug-nutrient interactions is a requirement for JCAHO accreditation (3). For patients being discharged from a hospital or receiving treatment on an out-patient basis, however, counseling regarding drug-nutrient interactions is not always assured. Only 12 of 99 health care professionals polled in a recent survey provided routine patient counseling regarding potential drug-nutrient interactions and the need for dietary modifications (4). All health care professionals interacting should be aware of the need to provide patients and their families with appropriate information on diet. At UVa, this responsibility is shared among nutritionists, pharmacists, nurses, and physicians.

Several different mechanisms may be involved in drug-nutrient interactions. For example, physical interactions may result in changes in bioavailability which can reduce (chelation) or increase (solubilize) the amount of drug reaching the systemic circulation. Other pharmacokinetic interactions may result in changes in drug metabolism or elimination. Pharmacodynamic interactions are often the most serious, where administration of a nutrient results in an unanticipated change in drug effect. Clinically significant interactions are listed in Table 1 (1,5-12). These interactions have been well documented in the medical literature and may lead to either a reduction in the efficacy of treatment or an increase in the potential for development of adverse effects. In most cases, the interacting food does not have to be eliminated from the child's diet, but should be eaten in moderation. Patients should also be instructed to take their medications at the same time in relation to meals each day to reduce fluctuations in drug absorption.

TABLE 1: DRUG-NUTRIENT INTERACTIONS

DRUG	NUTRIENT	INTERACTION
Antihypertensives, Digoxin	licorice	glycyrrhizic acid (large amounts) induces hypokalemia and sodium retention
Digoxin	bran	reduced absorption
Felodipine	grapefruit juice	increased absorption
Iron Supplements, Sucalfate	dairy products	complexation resulting in reduced efficacy
Levodopa/Carbidopa	high protein meals	reduced absorption
Lithium	dietary sodium	large amounts of dietary

	sodium can reduce efficacy	
MAO Inhibitors -Furazolidone -Isoniazid -Pargyline -Phenelzine -Procarbazine -Selegiline -Tranylcypromine	tyramine-containing foods (aged cheese[a], salted/pickled fish, beef or chicken, liver, alcoholic beverages[b])	flushing, hypertension, cerebrovascular accidents
Quinidine	citrus juices	alkalinization of the urine may impair elimination
Quinolones -Ciprofloxacin -Norfloxacin -Ofloxacin	minerals (magnesium, calcium, iron)	reduction of antibiotic efficacy
Theophylline, Neuroleptic Drugs	dietary caffeine	excessive CNS stimulation
Theophylline	charcoal-broiled meats	decrease in elimination halflife
Warfarin	green vegetables, avocado	reduction of anticoagulant effect
Warfarin	fried or boiled onions	increase in anticoagulant effect

[a] Avoid cheddar, camembert, roquefort cheese. Processed cheese, cottage cheese, mozzarella and gouda may be eaten in moderation.

[b] Other interactions involving alcoholic beverages are not included in this brief review. Readers who are interested in this area are encouraged to refer to references 5 and 7.

One of the most common questions regarding drug-nutrient interactions is whether a medication must be taken on an empty stomach. In most cases, the rate of drug absorption may be slowed, but the extent of absorption is unaffected by the presence of food in the GI tract. When treating children, medications should be given with meals whenever possible to minimize the taste and potential GI upset. For some medications such as griseofulvin, itraconazole, atovaquone, and nitrofurantoin, administration with food actually increases bioavailability. Food does reduce the absorption of erythromycin stearate and non-coated erythromycin base dosage forms; however, few patients are able to tolerate the abdominal cramping that these drugs cause unless they are taken with food. Table 2 contains a list of drugs that should **not** be administered with food (7).

Table 2. Medications That Should be Taken on an Empty Stomach

- Ampicillin
- Atenolol[a]
- Bisacodyl[b]
- Busulfan
- Captoprila
- Ciprofloxacin[b]
- Cloxacillin
- Dicloxacillin
- Didanosine (DDI)
- Isoniazid
- Lincomycin
- Lomustine
- Melphalan
- Mercaptopurine
- Methotrexate[b]
- Nafcillin
- Norfloxacin[b]
- Ofloxacin[b]
- Oxacillin
- Penicillin G
- Rifabutin
- Rifampin
- Sulfonamides
- Tetracyclineb
- Zidovudine (AZT)

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[a] Bioavailability is reduced; impact on efficacy is variable. Patients should be instructed to take their medication at the same time each day in relation to meals. Monitor clinical response and adjust dosing if necessary.
[b] Administer at least 2 hours before or after dairy products.

Children who are receiving enteral feedings, whether hospitalized or in their homes, are also at risk for drug-nutrient interactions. Enteral feeding products have been found to interfere with the absorption of several medications. The mechanism for these reactions remains unclear, but likely involves adsorption of the drug onto proteins in the nutritional product. Infant formulas have not been well studied as a vehicle for drug administration, but may react similarly to enteral feeding products.
Medications known to be affected by concomitant use of enteral feedings are listed in Table 3 (13-15). In most cases, stopping the feeding one to two hours prior to a dose and flushing the feeding tube with two to three times its volume (30-60 ml) of water or saline prior to and following administration of the medication will eliminate any problems. Feedings should be resumed

approximately one to two hours after drug administration. In addition to the medications listed below, syrups with an acidic pH and elixirs which contain alcohol may cause clumping of enteral feedings and should be separated from feeding times whenever possible.

Table 3. Medications Incompatible with Enteral Feedings

- Calcium supplements
- Digoxin
- Iron supplements
- Methyldopa
- Penicillin G
- Phenytoin
- Potassium supplements (not all products)
- Propantheline
- Rifampin
- Sulfonamides
- Tetracyclines
- Theophylline
- Warfarin

While the focus of this review has been on the ability of drug-nutrient interactions to reduce or alter the efficacy of medical treatment, medications can have an adverse effect on nutrition as well. For example, nutritional status can be adversely affected by the chronic use of medications which impair appetite. Table 4. lists medications that are known to have a detrimental effect on either taste and appetite (8). In addition many medications alter serum electrolyte and mineral concentrations, making nutritional supplementation necessary (5,8). The relationships between medications and nutrition are complex and all health care professionals are encouraged to take an active part in educating patients and their families about this aspect of their medical care.

Table 4. Examples of Medications that Affect Taste or Appetite

- Amphetamines
- Antineoplastics
- Captopril
- Clofibrate
- Colchicine
- Digoxin
- Furosemide
- Griseofulvin
- Hydralazine
- Isoniazid

- Lidocaine
- Lincomycin
- Lithium carbonate
- Methicillin
- Methotrexate
- Metronidazole
- Penicillamine
- Phenytoin
- Potassium Supplements
- Pyrimethamine
- Spironolactone
- Sulfasalazine
- Thiazide Diuretics

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Pharmacology Literature Review

Atenolol in Marfan Syndrome

Although most research in this patient population has been conducted with propranolol, atenolol offers the advantages of greater cardioselectivity and a longer elimination half-life allowing once or twice daily dosing. The pharmacokinetic parameters of atenolol were evaluated in 13 patients with Marfan syndrome. The patients ranged in age from 15 to 26 years and received an average dosage of 1.78± 0.58 mg/kg/day. A peak serum concentration of 343±120 mcg/L occurred at 1.87±0.16 hours. Mean half-life was 4.2 hours with a range of 2.5 to 6.3 hours, shorter than the reported population average of 6 to 7 hours. As a result, the authors have suggested that some patients with Marfan syndrome may require three doses per day. Phelps SJ, Alpert BS, Ward JL et al. Absorption pharmacokinetics of atenolol in patients with the Marfan syndrome. **J Clin Pharmacol 1995;35:268-74.**

Cyclic Antidepressant Toxicity

A retrospective evaluation of children with cyclic antidepressant ingestions is presented. The authors studied the cases of 45 children (average age 11.8±5.6 years) who were admitted to their institution over a 6.5 year period. Of interest, 10 of the patients were less than six years of age. Agents ingested included imipramine, desipramine, amitriptyline, amoxapine, doxepin, nortriptyline, and trazodone. Initial serum drug concentrations averaged 461.5±477.4 ng/ml. Arrhythmias occurred in 17 patients (38%), primarily with prolongation of the QT interval. Seizures were noted in seven patients (16%). As anticipated, the severity of illness was positively correlated with the serum drug concentration. The authors caution against relying on serum concentrations to predict clinical course; however, since several children experienced arrhythmias with serum concentrations lower than the toxic range (> 1000 ng/ml). James LP, Kearns GL. Cyclic antidepressant toxicity in children and adolescents. **J Clin Pharmacol 1995;35:343-50.**

EMLA for Subcutaneous Infusions

The efficacy of EMLA in preventing pain associated with needle placement for nightly subcutaneous infusion of deferoxamine in children with beta-thalassemia was evaluated in this study. The authors conducted both an open-label "pilot" and a randomized, double-blind, placebo-controlled trial. Sample sizes were small in both trials (12 and 10 children, respectively), but reflect the rarity of this therapy. In both trials, pain was significantly less when EMLA was used, as measured by a visual analogue scale. No adverse effects were noted. Berkovitch M, Davis S, Matsui D et al. Use of a eutectic mixture of local anesthetics for prolonged subcutaneous drug administration. **J Clin Pharmacol 1995;35:295-7.**

IV IgG in Pediatric AIDS

This brief review article focuses on the use of intravenous immune globulin in children diagnosed with AIDS. The results of nine studies evaluating the prophylactic use of IV IgG in children are compared. Although these studies have failed to demonstrate an ability of IV IgG to alter the progression of AIDS, the use of immune globulin has been linked with a reduction in the morbidity associated with serious bacterial infections. Crow ME. Intravenous immune globulin for prevention of bacterial infections in pediatric AIDS patients. **Am J Health-Syst Pharm 1995;52:803-11.**

Non-Prescription Medications

Although targeted at retail pharmacists, this article provides some useful information for all health care professionals. Most non-prescription medications do not carry indications for use in patients less than 12 years of age, but parents frequently administer these products to their children. A thorough table of commonly used products is presented which includes information on dosing and common trade names. Nykamp D. Nonprescription medications in the pediatric population. **Amer Pharm 1995;NS35:10-27.**

Terfenadine in Breastmilk

Good news for moms with allergies! The pharmacokinetics of terfenadine (Seldane®) were evaluated in 4 healthy, lactating women. Blood and breastmilk samples were taken after the subjects received 60 mg every 12 hours for a period of 48 hours. Terfenadine was not detected in either blood or breastmilk. The primary active metabolite reached a peak serum concentration of 309.0±120.5 ng/ml, while the peak breastmilk concentration was 41.0±16.4 ng/ml. Mean ratio of metabolite in milk to plasma was 0.21. Based on a normal dosage, mothers may take terfenadine without significant transfer of drug to their infants. Lucas BD, Purdy CY, Scarim SK et al. Terfenadine pharmacokinetics in breast milk in lactating women. **Clin Pharmacol Ther 1995;57(4):398-402.**

Theophylline Interactions

This thorough summary of theophylline metabolism may be of interest to those practitioners who routinely prescribe or monitor this therapy. Interactions are divided into two categories: endogenous, such as age, gender, and concomitant diseases; and exogenous, such as drug interactions and smoking. The authors cite nearly 300 reference articles. Troger U, Meyer FP. Influence of endogenous and exogenous effectors on the pharmacokinetics of theophylline: Focus on biotransformation. **Clin Pharmacokinet 1995;28(4):287-314.**

Formulary Update

The Pharmacy and Therapeutics Committee did not meet in April. The new vaccines for varicella and hepatitis A were discussed at an Antibiotic Subcommittee meeting on 4/24/95. The recommendations of the subcommittee will be presented to the full P&T membership within the next two to three months for a decision regarding addition to the formulary.

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