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Drug Interactions—A Review

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The incidence and severity of drug interactions are on the rise as more medications are brought to market. Following the absorption, distribution, metabolism, and excretion model of pharmacokinetics, this review will provide an overview of the varied mechanisms of drug-drug, drug-herb, and drug-food interactions with emphasis placed on the interactions most likely to cause harm. This information is intended to assist the pediatric emergency physician in recognizing drug interactions to identify and remove the offending agent when appropriate. Understanding the mechanisms of drug interactions will assist all clinicians in avoiding these serious, often preventable, events.

KEYWORDS cytochrome *P*450, P-glycoprotein, monoamine oxidase inhibitors, drug interactions

As pharmaceutical technology continues to expand at a phenomenal rate, so does the incidence of drug interactions. A regimen of 2 or more drugs, admission to a critical care unit, and increasing age are risk factors for experiencing a drug interaction [1,2]. These interactions can range in severity from theoretical to clinically significant, including prolonged morbidity and even death. The emergency department (ED) is a particularly unique setting where drug interactions may occur because of the lack of information about a patient's current drug regimen and preexisting drug interactions, the addition of short-term treatments to chronic disease states, and the need for follow-up outside the ED. One study examining the risk of drug interactions demonstrated a 25% incidence of a preexisting drug interaction and a 5% interaction rate for those who received a medication while in the ED [3]. Pediatric emergency physicians, like all emergency care providers, must be knowledgeable about drug interactions and the mechanisms involved to avoid these events and recognize them when they occur.

Drug interactions occur not only with other medications, but also with herbal preparations, dietary supplements, and foods. In this review, we will provide an overview of the varied mechanisms of drug-drug, drug-herb, and drug-food interactions with emphasis placed on the interactions most likely to cause harm (Table 1). Following the absorption, distribution, metabolism, and excretion model of pharmacokinetic properties, we will attempt to organize the interactions by process.

Administration/Absorption

Administration of 2 medications at or around the same time can result in clinically significant drug interactions. It has been well documented that some antibiotics such as the fluoroquinolones and tetracyclines will bind to iron, calcium, calcium-fortified foods, and antacids if given simultaneously [4-8]. The resulting compound will be excreted with little or no systemic absorption of the antibiotic. This can result in treatment failures and emergence of resistant organisms. Phenytoin may also bind to iron, calcium, and magnesium in antacids, as well as continuous tube feedings [9-14]. Low phenytoin serum

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levels and subsequent loss of seizure control may result if the interactions are not recognized. To avoid these drug interactions, the iron, calcium, and antacids must be given either 2 hours before or 2 hours after the dose of the interacting drug. It is also recommended that continuous tube feedings be turned off for 2 hours before and after phenytoin administration.

Sucralfate and cholestyramine will also physically bind other medications such as chlorothiazide, ciprofloxacin, cyclosporine, digoxin, ketoconazole, phenytoin, valproic acid, and warfarin. In some cases, administering the drug 2 hours before sucralfate or cholestyramine and monitoring for effects will be adequate. In other cases, the combination may need to be avoided altogether, such as with warfarin and cholestyramine.

Several factors are responsible in determining the amount of drug that is absorbed by the body, including age, hydrochloric acid secretion, gastric emptying time, intestinal motility, and bile acid secretion. The primary mechanism of absorption is passive diffusion of nonionized drug molecules via the lipophilic gastrointestinal (GI) mucosa. Therefore, drugs that change the pH, gastric emptying time, or GI motility will interact with the absorption of other agents.

More recently, induction and inhibition of intestinal P-glycoprotein drug efflux pump have been described in significant drug interactions, particularly involving cyclosporine. P-glycoprotein is genetically encoded and widely distributed among the body cells [15]. The primary role of P-glycoprotein is the expulsion of toxins and drugs from the cells. If the expression of P-glycoprotein is enhanced, especially in the intestine, the substrate drugs have reduced bioavailability. Supratherapeutic levels and toxicity can occur if the P-glycoprotein expression is decreased [15]. Of note, orange juice may inhibit the P-glycoprotein intestinal transport and absorption of levofloxacin [4].

Erythromycin, a macrolide antibiotic, is also known to increase gut motility and, in recent years, has been exploited for this property as an alternative to cisapride. Cisapride was removed from the market secondary to life-threatening arrhythmias and torsades de pointes that occurred when combined with other drugs that inhibited cytochrome *P*3A4 isoenzyme, depleted electrolytes, or prolonged the QT interval [16]. Drugs that delay gastric emptying will usually slow the transition of drug into the small intestine, thus delaying and decreasing absorption.

Warfarin is known to interact with many foods, herbal supplements, and medications [17]. Diets high in vitamin K such as those with a high quantity of green leafy vegetables (Table 2) can decrease or even reverse the anticoagulation effect. In addition, supplements of vitamin A, E, or C may alter the prothrombin time.

Other interactions can be exploited to enhance absorption of the drug. Didanosine liquid is prepared with antacid suspension to ensure adequate pH for optimum stability. Ferrous sulfate is converted to the ferric state in the presence of vitamin C, resulting in enhanced absorption. Many drugs should be taken with food to ensure absorption, whereas other drugs should be given on an empty stomach (Table 3). Often, the presence of food will delay the absorption but not decrease the overall bioavailability of the drug. Consistency, either with or without food, should be stressed for medications with the potential to have fluctuation of serum levels and resultant toxicities such as phenytoin, propranolol, and warfarin.

Drug interactions occurring during the administration phase are not only limited to the oral route. Intravenous aminoglycoside antibiotics can be inactivated if given within 30 minutes of a penicillin derivative. Postexposure prophylaxis that requires both passive (immune globulin) and active (vaccine) immunizations should be given at separate intramuscular injection sites and different extremity to avoid decreasing the immune response to the vaccine.

Much like the enteral drug interactions that are sometimes used to enhance the effect of a drug, injectable drug interactions can also be useful. Small amounts of epinephrine can be added to local anesthetic injections during laceration treatment. Epinephrine is a potent local vasoconstrictor and will decrease blood flow to the area, creating a more visible working environment and enhancing the effect by decreasing the removal of the local anesthetic.

It is well known that alcohol-containing beverages can potentiate the sedative effects of anxiolytics and opioids. However, alcohol can be involved in other types of interactions as well. Metronidazole in combination with alcohol, even a small amount such as that found in mouthwash, can cause severe nausea and

Table 1 Drugs frequently involved in serious drug interactions.

Cyclosporine
Erythromycin
Fluconazole
HMG-CoA reductase inhibitors
Itraconazole
Ketoconazole
Linezolid
MAOIs
Meperidine
Neuroleptics
Phenytoin
Protease inhibitors (especially ritonavir)
Rifampin
SSRIs
Theophylline
Warfarin

HMG-CoA indicates 3-hydroxy-3-methylglutaryl coenzyme A.

Table 2 Foods that interact with warfarin.

Vegetables
Alfalfa
Asparagus
Broccoli
Brussel sprouts
Cabbage
Cauliflower
Kale
Lettuce
Onions
Spinach
Turnip greens
Watercress
Herbal products
Ginseng
Green teas
Melilot
Tonka beans
Woodruff
Miscellaneous
Avocado
Fish oils
Liver
Soybeans
Papain

vomiting—the "disulfiram" effect. Often overlooked is the amount of alcohol in other medications. Ranitidine (Zantac) syrup contains 7.5% ethanol and can be responsible for unexplained nausea and vomiting in a patient who is also receiving metronidazole.

Antidotal therapy is the ultimate use of a drug interaction for positive outcomes. Administration of calcium may treat calcium channel blocker overdose by overcoming the blockade. Naloxone and nalmefene selectively antagonize opioid receptors, reversing respiratory and mental status depression secondary to opioid intoxication. Flumazenil reverses benzodiazepine intoxication via competitive binding to the benzodiazepine receptor. Activated charcoal adsorbs many drugs and toxins and is used successfully for GI decontamination after toxic ingestions.

Distribution

Distribution of medications depends on total body water, extracellular fluid, percentage of adipose tissue, and capacity to bind to plasma proteins. Albumin and α-1 glycoprotein are the primary circulating plasma proteins to which drugs bind. Some drug interactions occur because of competition for the binding sites on these proteins. In effect, one drug "knocks" the other off the binding site or, alternatively, occupies the site, not allowing the other drug to bind. Drugs that are highly protein bound are listed in Table 4 [18]. For an interaction to become clinically significant, the involved drugs must be highly (>95%) protein bound or have a very narrow therapeutic window. For example, phenytoin is not only involved in several cytochrome *P*450 (CYP450) interactions to be discussed later and the physical binding interactions discussed previously, but also is between 89% and 93% protein bound with a very narrow therapeutic window. When phenytoin is given concurrently with valproic acid or salicylates, the free fraction of phenytoin increases because of competition for the same binding sites by the other drugs. The free fraction of phenytoin is usually 10% to 20% of the total serum concentration (10-20 μg/mL). When the free fraction of phenytoin rises above 2 mcg/mL, toxicity is generally seen, consisting of ataxia, nystagmus, increased seizure activity, and, if high enough, coma.

Metabolism

Drug metabolism is divided into 2 categories, phase I and phase II transformation reactions. Phase I reactions include oxidation, hydrolysis, and reduction, resulting in a compound that is generally less toxic and more hydrophilic, allowing for easy excretion. In some cases, metabolism of a parent compound may lead to the formation of active metabolites (eg, acetaminophen, methanol, and ethylene glycol). Phase II reactions primarily result in the termination of biologic activity of the drug. Phase II transformation reactions include glucuronidation, sulfation, acetylation, and methylation. Although there are several routes of drug metabolism as

Table 3 Partial list of drugs that should be taken with food or on an empty stomach.

Take With Food	Take on Empty Stomach
Albendazole	Ampicillin
Atovaquone	Didanosine
Carbamazepine	Efavirenz
Griseofulvin[a]	Erythromycin
Lithium[b]	Furosemide
Nelfinavir	Glipizide[c]
Ritonavir	Indinavir
Trazodone[b]	Iron
	Isoniazid
	Itraconazole
	Loracarbef
	Mercaptopurine
	Metformin[c]
	Minocycline
	Penicillamine
	Rifampin
	Tetracycline

[a] Take with high-fat meals.
[b] Take immediately after eating.
[c] Administer 30 minutes before eating.

described above, this review will focus on the phase I CYP450 enzymes and acetylation.

A rapidly expanding wealth of knowledge has become available since the late 1980s with regard to CYP450 interactions. In fact, most drug interactions occurring during metabolism are the result of CYP450 enzyme inhibition or induction. The CYP450 enzymes are unique isoenzymes found primarily in the liver and are responsible for the metabolism of many drugs and toxins. These enzymes may inactivate a drug by creating a metabolite or, alternatively, activate the drug. The enzymes are so named because of the absorption of light at a wavelength of 450 nm [19]. The CYP450 enzymes are grouped into families 1, 2, and 3 and divided into subfamilies A to E. The individual member enzymes are further designated by a number (eg, 3A4, 2D6).

The CYP450 enzymes are genetically encoded. Interpatient variability in CYP450 enzyme activity makes it difficult to adequately predict who will experience an adverse reaction or an exaggerated drug interaction. Age-related development of CYP450 enzymes matures and even surpasses adult capacity during the first year of life [20]. As pharmacogenomics develops, a source of reliable and rapid information targeted at the individual capability to metabolize medications will be available for more routine use [21].

Induction of CYP450 enzymes occurs when a drug stimulates the synthesis of more enzyme protein, enhancing the enzyme's metabolizing capacity. Ginseng may induce the enzyme that metabolizes warfarin, decreasing warfarin effectiveness. St John's wort is a potent inducer of CYP3A4 and is involved in the most severe drug-herb interactions noted to date (see Table 5 for drugs metabolized by CYP3A4). The protease inhibitors, cyclosporine, warfarin, digoxin, oral contraceptives, and many other medications can be rendered ineffective with concomitant use of St John's wort [22-31]. Patients and families must be asked directly about their herbal and dietary supplement use, as many do not consider these products as drugs or even as over-the-counter drugs because they are touted as "all natural" [32-34]. In fact, a study examining herbal therapy use in a pediatric ED reported that 77% of caregivers did not believe or were not sure that herbal products had any side effects and 66% did not believe or were not sure that herbal products interacted with other medications [33].

Inhibition of CYP450 enzymes may occur secondary to competitive binding between 2 drugs or to permanent inactivation [19]. Generally, inhibition begins after the first dose of the inhibitor and the length of inhibition correlates with the half-life of the drug. Discontinuation of the inhibitor will usually cause the serum concentrations of other drugs metabolized by that enzyme to decrease, whereas discontinuation of an inducer will result in an increased serum concentration and risk of toxicity.

The enzymes responsible for most drug metabolism and interactions are listed in more detail.

Table 4 Drugs that are highly protein bound (>95%).

Drug	Protein Bound (%)
Amitriptyline	96
Chlorpromazine	96
Clofibrate	95
Diazepam	97
Dicloxacillin	96
Diphenhydramine	98
Furosemide	99
Glyburide	95
Ibuprofen	99
Imipramine	96
Indomethacin	97
Ketoconazole	99
Mebendazole	95
Naproxen	99
Nifedipine	98
Nortriptyline	95
Oxazepam	96
Phenytoin*	89-93
Thyroxine	99
Valproic acid*	90
Warfarin	99.5

* Narrow therapeutic window.

Cytochrome *P*1A2

Approximately 15% of medications used today are metabolized by cytochrome *P*1A2 (CYP1A2), including caffeine, theophylline, tricyclic antidepressants (TCAs), and warfarin. Activity of CYP1A2 can be induced by cigarette smoke, charbroiled foods, and cruciferous vegetables (eg, broccoli and cabbage). Several medications also affect CYP1A2 activity. Carbamazepine, phenobarbital, and rifampin induce CYP1A2 as well as several other enzymes, leading to clinically significant drug interactions. Omeprazole and ritonavir simultaneously induce CYP1A2 and inhibit 1 or more other enzymes. Inhibitors of CYP1A2 include erythromycin, ciprofloxacin, fluvoxamine, and grapefruit juice.

Cytochrome *P*2C9

Cytochrome *P*2C9 (CYP2C9) is responsible for the metabolism of several common medications including ibuprofen, phenytoin, and warfarin. Rifampin and rifabutin are powerful inducers of CYP2C9 activity and will therefore decrease serum concentrations of the above substrates. Other inducers include carbamazepine, ethanol, and phenobarbital. Amiodarone, fluoxetine, and fluconazole are among several drugs known to inhibit CYP2C9 activity. Genetic polymorphisms occur in 1% to 3% of whites, contributing to abnormally decreased enzyme activity in these individuals (poor metabolizers).

Cytochrome *P*2C19

Medications metabolized by cytochrome *P*2C19 (CYP2C19) include several benzodiazepines, citalopram, TCAs, omeprazole, and lansoprazole. Rifampin induces CYP2C19 activity, whereas fluvoxamine, fluoxetine, and ticlopidine inhibit this enzyme. Genetic polymorphisms are responsible for interpatient variability in CYP2C19 activity. The enzyme is absent in 13% to 23% of Asians and 3% of whites [35].

Cytochrome *P*2D6

Cytochrome *P*2D6 (CYP2D6) comprises a relatively small percentage (2%-6%) of the total CYP450 in the liver but is involved in the metabolism of many medications (up to 25%). Multiple TCAs, β-blockers, haloperidol, sertraline, and thioridazine are metabolized by CYP2D6. The conversion of codeine to the active form, morphine, is catalyzed by CYP2D6, and patients with low activity demonstrate a poor analgesic response [19]. Unlike other CYP450 enzymes, there are no known inducers of this activity except pregnancy. Several medications inhibit CYP2D6, the most potent include cimetidine, fluoxetine, haloperidol, paroxetine, and codeine. Genetic polymorphisms play a significant role in determining CYP2D6 activity, as with CYP2C19. Approximately 1% to 3% of African American and Asian patients and 5% to 10% of whites lack this enzyme, placing them at risk for increased toxicity from medications that are metabolized by CYP2D6 [35].

Cytochrome *P*2E1

Although cytochrome *P*2E1 (CYP2E1) metabolizes a relatively small fraction of clinically used medications, this enzyme plays a significant role in the activation and inactivation of toxins. Cytochrome *P*2E1 metabolizes primarily small organic molecules (eg, ethanol, carbon tetrachloride) as well as acetaminophen and dapsone. Although only a small percentage of acetaminophen is metabolized by CYP2E1, this hydroxylation produces *N*-acetyl-*p*-benzoquinoneimine, a hepatotoxin. Chronic ethanol use can induce CYP2E1 activity leading to a greater percentage of acetaminophen metabolized to *N*-acetyl-*p*-benzoquinoneimine, increasing the risk of hepatotoxicity from acetaminophen. The use of inhibitors such as disulfiram to prevent toxicity associated with compounds that form toxic metabolites when metabolized via CYP2E1 is currently being investigated [36].

Cytochrome *P*3A3/4

Cytochrome *P*3A (CYP3A) is both the most abundant and clinically significant family of CYP450 enzymes. The CYP3A family is composed of 4 major enzymes: CYP3A3, CYP3A4, CYP3A5, and CYP3A7. Cytochrome *P*3A4 is the most common and is implicated in most drug interactions. However, because these enzymes are so closely related (most are 97% similar), they are often referred to collectively by the subfamily name, CYP3A. Up to 60% of the liver's total CYP450 is CYP3A, and nearly 50% of all clinically relevant medications are metabolized by CYP3A. The presence of CYP3A in the small intestine results in decreased bioavailability of many drugs. Cytochrome *P*3A inducers include the glucocorticoids, rifampin, carbamazepine, phenobarbital, and phenytoin. Among the many significant CYP3A inhibitors are grapefruit juice, erythromycin, ketoconazole, clarithromycin, and verapamil.

N-acetyltransferase

Acetylation is a unique, non-CYP pathway of drug metabolism. Dapsone, hydralazine, isoniazid, procainamide, and sulfonamides are examples of drugs metabolized via acetylation. Acetylation polymorphisms are well described. Variants in the alleles coding for the conjugating *N*-acetyltransferase enzymes occur in 50% of Americans, white and black, resulting in slow acetylators. Slow acetylator phenotypes occur in 60% to 70% of Northern Europeans and 5% to 10% of Asians [35]. These slow acetylators demonstrate enhanced toxicity, but longer drug effectiveness. The fast acetylator phenotypes may not demonstrate the desired therapeutic response to treatment.

Excretion\Elimination

Excretion and elimination of drugs occur primarily via the kidneys. Biliary secretion, plasma esterases, and other minor pathways are important routes, albeit less common than renal elimination. As with absorption in the GI tract, renal elimination is dependent on multiple factors. These include glomerular filtration rate, tubular secretion, and tubular reabsorption.

Urinary alkalinization and acidification by some drugs can cause others to be more (or less) readily excreted (Table 6). Other agents can inhibit renal tubular secretion and assist in maintaining a higher serum concentration than the body would normally allow. A classic example is the use of probenecid and penicillin, secondary to probenecid blocking tubular secretion of β-lactams. More recently, probenecid has become an integral part of the regimen for decreasing the nephrotoxic effects of cidofovir by limiting the exposure of renal proximal tubular cells to the drug. Alternatively, probenecid should not be used with sulfonamides, ketorolac, or methotrexate because of increased serum concentrations and half-life, resulting in increased toxicity [37]. Quinidine may undergo increased renal tubular reabsorption in alkalinized urine. Sodium bicarbonate–containing infusions are used to alkalinize the urine to enhance excretion of aspirin in the overdose setting.

In other instances, this interaction can be potentially detrimental as in the case of methotrexate and the proton

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