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Drug-Nutrient Considerations in Patients Receiving Parenteral and Enteral Nutrition

by Gordon S. Sacks

The complex nature of PN and EN increases the risk for serious drug-nutrient interactions. The existence of various drug dosage forms, metabolites, and inactive ingredients contribute to unpredictable side effects and incompatibilities. Fundamental knowledge of drug absorption, distribution, metabolism, and elimination is imperative to resolving drug-nutrient interactions. A classification system for drug-nutrient interactions will be discussed, giving practical examples and recommendations. Physical incompatibilities between drugs and enteral formulas will be covered, as well as pharmacokinetic alterations caused by nutrients. Alternative delivery systems, routes of administration, or adjustment of the medication/nutrient will be provided as options to avoiding interactions. Recognizing the potential for these interactions can assist in the early treatment and prevention of possible metabolic complications, ultimately improving patient outcomes.

Interactions between drugs and nutrients often occur and can have a detrimental impact on patient outcome (1). The risk of pharmacologic-nutritional interactions continues to grow as specialized nutrition support (i.e., enteral and parenteral nutrition) is initiated earlier and the use of multiple medications increases. Recognition of clinically significant interactions can assist with prevention or early treatment of adverse consequences arising from drug-nutrient interactions. This article will focus on basic knowledge needed for identification and appropriate management of drug-nutrient interactions in patients requiring enteral nutrition (EN) and parenteral nutrition (PN). Drug-nutrient interactions will be divided into four categories based upon their mechanisms: 1) ex vivo biopharmaceutical inactivations; 2) interactions affecting absorption; 3) interactions affecting systemic/physiologic dispositions; and 4) interactions affecting elimination/clearance (2). Each category will be discussed separately and examples will be given to illustrate the use of alternative methods to assure safe drug administration.

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EX VIVO BIOPHARMACEUTICAL INACTIVATIONS

Interactions between drug molecules and nutritional elements that render either agent inactive through biochemical or physical reactions are referred to as ex vivo pharmaceutical inactivations. These interactions usually occur outside of the body in the delivery system (i.e., infusion bag) or during the compounding process. Practitioners caring for nutrition support

Table 1
Compatibility of PN with Selected Medications via Y-site Administration

	Admixture Type	
Medication	*2-in-1*	*3-in-1*
Acyclovir 7 mg/mL D5W	I	I
Amikacin 5 mg/mL D5W	C	C
Amphotericin B 0.6 mg/mL D5W	I	I
Ampicillin 20 mg/mL 0.9% NaCL	C	C
Butorphanol 0.04 mg/mL D5W	C	C
Cefazolin 20 mg/mL D5W	I	C
Ceftazidime 40 mg/mL D5W	C	C
Cimetidine 12 mg/mL D5W	C	C
Ciprofloxacin 1 mg/mL D5W	I	C
Cyclosporine 5 mg/mL D5W	I	I
Dopamine 3200 mcg/mL D5W	C	I
Dobutamine 4 mg/mL D5W	C	C
Famotidine 2 mg/mL D5W	C	C
Fentanyl 12.5 mcg/mL D5W	C	C
Fentanyl 50 mcg/mL undiluted	C	C
Ganciclovir 20 mg/mL D5W	I	I
Gentamicin 5 mg/mL D5W	C	C
Haloperidol 0.2 mg/mL D5W	C	I
Heparin 100 units/mL undiluted	C	I
Hydromorphone 0.5 mg/mL D5W	C	I
Insulin 1 unit/mL D5W	C	C
Lorazepam 0.1 mg/mL D5W	C	I
Midazolam 2 mg/mL D5W	I	I
Morphine 1 mg/mL D5W	C	C
Morphine 15 mg/mL undiluted	NA	I
Ofloxacin 4 mg/mL D5W	C	C
Ondansetron 1 mg/mL D5W	C	I
Potassium Phosphates 3 mmol/mL undiluted	I	I
Ranitidine 2 mg/mL D5W	C	C
Sodium Bicarbonate 1 mEq/mL undiluted	I	C
Tacrolimus 1 mg/mL D5W	C	C
Ticarcillin/Clavulanate 30/0.1 mg/mL D5W	C	C
Tobramycin 5 mg/mL D5W	C	C
Trimethoprim/Sulfamethoxazole 0.8/4 mg/mL D5W	C	C
Vancomycin 10 mg/mL D5W	C	C
Zidovudine 4 mg/mL D5W	C	C

C = compatible, I = incompatible, NA = no data available
Adapted from Trissel LA, et al. *Am J Health-Syst Pharm,* 1997;54:1295-1300; Trissel LA, et al. *JPEN,* 1999;23:67-74.

patients are most familiar with this type of drug-nutrient interaction in regards to the compatibility of an intravenously administered medication with PN.

When discussing medication incompatibilities, a distinction must be made between the different types of PN formulations currently available: 2-in-1 and 3-in-1 formulations. A 2-in-1 formulation does not include the intravenous lipid emulsion (IVLE) in the same container with amino acids, dextrose, electrolytes, vitamins, and trace elements. A 3-in-1 formulation includes the IVLE, so it has a milky-white appearance. Presence of the IVLE in the same container and its chemical properties explain why some drugs are compatible in a 2-in-1 but not in a 3-in-1 formulation. The IVLE consists of an interior oil phase dispersed in an external water phase. An egg yolk phosphatide mixture is added to the IVLE as an emulsifying agent to provide stability for the emulsion. Polar and nonpolar regions on the same lipid droplet are responsible for maintaining stability of the IVLE. The polar regions create a negative charge on the surface of the lipid droplet, promoting repulsion between neighboring lipid particles of the same charge(3). When the surface charge becomes less negative, lipid droplets begin to aggregate into larger fat globules (> 1 micron in diameter) and the emulsion becomes unstable. Clinically, the IVLE becomes unsafe for administration at this point and fat globules may lodge in the pulmonary vasculature compromising respiratory function.

Factors that may alter the electrical charge on the lipid droplet surface include reductions in pH and addition of electrolyte salts. A pH in the range of 6 to 9 favors IVLE stability, whereas additives lowering or increasing the pH outside this range may irreversibly destabilize or "crack" the emulsion. In this case, the oil phase separates from the water phase and appears as an amber oil layer at the top of the admixture bag or as streaks of yellow oil throughout the bag. Certain brands of crystalline amino acids used for pediatric patients may render the final admixture pH < 5 promoting lipid destabilization. Excess amounts of cations such as calcium (Ca^{++}) or magnesium (Mg^{++}), can reduce or neutralize the negative surface charge exerted by the emulsifier, thereby removing the repulsive force and allowing fat particles to combine. Thus, concentrated dextrose solutions cannot

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Table 2
Compatibility of Selected Medications with Enteral Feeding Formulas

	Enteral Feeding Formulations			
Medication	*Ensure*	*Ensure Plus*	*Osmolite*	*Vivonex*
Acetominophen elixir	C	C	C	C
Amphogel	NA	NA	I	C
Bentyl Liquid	NA	NA	I	C
Benadryl elixir	C	C	C	C
Cibalith-S syrup	I	I	I	C
Dimetapp elixir	I	I	I	I
Feosol elixir	I	I	I	C
Guafenesin Liquid	I	I	I	C
Immodium	NA	NA	C	C
KCL liquid	I	I	I	I
Lanoxin elixir	C	C	C	C
Morphine liquid	C	C	C	C
Phenytoin suspension	I	I	I	NA
Phenytoin injection	C	C	C	NA
Sudafed syrup	I	I	I	C
Thorazine concentrate	I	I	I	C

C = compatible, I = incompatible, NA = no data available
Adapted from Cutie AJ, et al. *JPEN,* 1983;7:186-191; Burns PE, et al. *J Am Diet Assoc,* 1988;9:1094-1096; Holtz L, et al. *JPEN,* 1987;11:183-186.

be directly added to IVLE because of its acidic pH and should be combined with the amino acid solution first during the compounding process.

The development of microprecipitates within PN admixtures as a result of drug incompatibility represents ex vivo biopharmaceutical inactivations. In 1994, the FDA released a safety alert in response to reports of two deaths and at least two cases of respiratory distress associated with the administration of PN admixtures thought to contain an undissolvable or unstable intermediate (i.e., calcium phosphate crystals) (4). Diffuse microvascular pulmonary emboli containing calcium phosphate were confirmed upon patient autopsies. Precipitates from drug incompatibilies or emulsion disruption from drug additives has also been reported. Studies of medications with 2-in-1 and 3-in-1 PN formulations during simulated Y-site administration have been performed, and incompatibilities ranged from formation of precipitates, to haziness, discoloration, and emulsion disruption with frank separation of oil and water phases. Table 1 summarizes the Y-site compatibility of selected medications with 2-in-1 and 3-in-1 PN formulations.

Physical incompatibilities may occur with medications and nutrients administered via the gastrointestinal tract. Most problems are related to changes in pH after mixing EN and pharmaceutical agents together. Acidic preparations (such as syrups) cause the greatest problems, with increased clumping of the EN formula or enteral tube obstruction from precipitate formation. Medications such as ferrous sulfate liquid frequently clog the feeding tube when mixed directly into the EN formulation. Sevelamer, a phosphate binder used to manage hyperphosphatemia in renal failure patients, should not be administered through a feeding tube because its contents expand in water and result in tube occlusion. As an alternative, calcium acetate can be administered safely through the tube and have the same therapeutic effect. Components of the EN formula itself can influence the risk for an interaction. Protein in the form of hydrolyzed or free amino acids appears to have a higher compatibility with drugs than intact protein products. Enteral products with fiber generally are not compatible with medications. Table 2 summarizes incompatibilities of selected drugs with different types of EN formulations.

Medication administration devices (i.e., tubing) can interact with drugs through complexation, altering final drug potency and causing a therapeutic failure from suboptimal medication delivery. Adherence of phenytoin (5) and carbamazepine suspensions(6) to the walls of polyvinyl chloride nasogastric tubes has resulted in inadequate drug delivery to patients. Diluting and irrigating the tubes prior to administration of these oral suspensions significantly improved drug recovery and the final amount received by the patient.

Complexation of medications with components of EN formulations can occur, reducing the efficacy of the agent. Fluoroquinolone antibiotics, including ciprofloxacin, levofloxacin, and ofloxacin, have exhibited altered pharmacokinetics when administered in con-

Table 3
Solid Oral Dosage Forms that Should Not Be Altered

Generic	*Examples of Brand Names*	*Dosage Form*	*Comments*
acetaminophen	Tylenol Arthritis Extended-Release	Tablet	Time release
bisacodyl	Dulcolax	Tablet	Enteric coated
bupropion	Wellbutrin SR	Tablet	Sustained release
carbamazepine	Tegretol XR	Tablet	Sustained release
carbidopa/levidopa	Sinemet CR*	Tablet	Sustained release
ciprofloxacin	Cipro	Tablet	Bad taste
clarithromycin	Biaxin-XL	Tablet	Sustained release
diclofenac	Voltaren	Tablet	Delayed release
diltiazem	Cardizem CD†, Cardizem SR†, Tiazac	Capsule	Sustained release
felodipine	Plendil	Tablet	Extended release
fluoxetine	Prozac Weekly	Capsule	Sustained release
lansoprazole	Prevacid†	Capsule	Delayed release
mesalamine	Asacol, Pentasa	Tablet, Capsule	Sustained release
mycophenolate	Cellcept	Tablet, Capsule	Teratogenic
naproxen	Naprelan	Tablet	Sustained release
omeprazole	Prilosec	Capsule	Delayed release
pancreatic enzymes	Creon 10, Creon 20, Pancrease, Ultrase, Zymase	Capsule	Enteric coated spheres
pantoprazole	Protonix	Tablet	Sustained release
rabeprazole	Aciphex	Tablet	Sustained release
sulfasalazine	Azulfidine EN-tabs	Tablet	Enteric coated
verapamil	Verelan†, Calan SR*	Capsule, tablet	Sustained release

*Tablet can be broken at score line without affecting release characteristics.
†Capsule may be opened and contents administered by tube with appropriate fluid.
Adapted from Mitchell JF. *Hosp Pharm,* 2000;35:553-567.

junction with enteral feedings. Decreased bioavailability from proposed binding with divalent cations in the EN formulations has resulted in increased time to peak concentrations and decreased peak concentrations of these fluoroquinolones (7–9). To ensure proper drug delivery, recommendations include parenteral administration of fluoroquinolones in enterally-fed patients with intravenous access. If administration through an enteral feeding tube can not be avoided, the solid dosage form (i.e., tablet) should be crushed into a fine powder and mixed in 30 mL of water. The feeding tube should be flushed with 30 mL of water following administration to clear any residual medication.

The manufacturing processes for certain medications are specialized, and by crushing a tablet or opening the contents of a capsule, the intended dosage form is altered and the medication may not act as intended. Enteric-coated tablets, sustained-release or extended-release coated capsules or tablets, sublingual and buccal tablets, and microencapsulated products should never be opened or crushed in order to be administered through a feeding tube. Altering these dosage forms may increase rates of side effects or reduce efficacy. Table 3 lists some solid oral dosage forms that should not be altered prior to administration. Table 4 provides a list of general recommendations for medication administration via feeding tubes.

One of the best known examples of complexation between EN and a medication is exemplified by the interaction with phenytoin suspension. The exact etiology for impaired absorption of phenytoin is unclear, but possible explanations include binding of phenytoin to the protein source (calcium caseinates), binding to divalent cations (calcium, magnesium), and binding to the feeding tube. The classic study by Bauer documenting this drug-enteral feeding interaction in neurosurgical patients recommends to hold EN two hours before and two hours after phenytoin administration

Table 4
Guidelines for Medication Administration via Feeding Tubes

1. Use the oral route whenever possible. Consider alternative routes (i.e., buccal, nebulized, rectal, intravenous, transdermal).
2. If a feeding tube must be used for medication administration, oral liquid dosage forms are preferred.
   - Elixirs and suspensions are preferable to syrups
   - Dilute hyperosmolar solutions in at least 30 mL of H_2O
3. Crush immediate-release tablets into a fine powder and mix with 30 mL of H_2O to form a slurry.
4. Mix contents of immediate-release capsule with 30 mL of H_2O to form a slurry.
5. Aspirate contents of soft gelatin immediate-release capsules using a needle and syringe, and mix with 30 mL of H_2O.
6. Do not mix medications directly into EN formulations. Give each medication separately and flush feeding tube with 30 mL H_2O between medications.
7. Special Considerations:
   - Proton pump inhibitors, delayed release capsules:
   - Administration via a gastric feeding tube: open capsule and mix intact granules with acidic fruit juices (apple, cranberry, grape, orange, pineapple, prune, tomato, V-8 juice). Pour mixture down the tube, flush with additional acidic fruit juice, and hold feedings for at least 1 hour.
   - Administration via small-bowel feeding tube: open capsule and dissolve intact granules in sodium bicarbonate 8.4% solution. Pour suspension down feeding tube, flush with H_2O, and hold feedings for at least 1 hour.

Adapted from Dickerson RL. *Hosp Pharm,* 2004;39:84-89, 96; Beckwith MC, et al. *Hosp Pharm,* 2004;39:225-237.

(10). From a practical standpoint, this would require the EN be held for 12 hours when immediate-released phenytoin suspension is administered three times daily. Although only one uncontrolled study has evaluated holding EN for one hour before and after phenytoin administration, many institutions (including the author's) have found this practice to be adequate.

The rate of EN must still be adjusted to account for the loss of calories and protein during the six hours of "off time," but nurses find this approach much more accommodating. Other strategies used to deal with this interaction include: using the capsule formulation (versus the suspension) as the powder from the capsules appears less likely to bind; change to a bolus feeding regimen (e.g., 240 mL given four times per day) and administer phenytoin between boluses; and administer intravenous phenytoin via the feeding tube, as the bioavailability is unchanged, but the maximum concentration of phenytoin is significantly greater and the time to maximum concentration is significantly shorter when compared with the suspension formulation (11). Some institutions prefer to not hold EN at all, administer higher doses of phenytoin suspension, and closely monitor serum phenytoin concentrations. Practitioners using this strategy must remember that phenytoin dosages will require adjustment if the feeding regimen is discontinued or temporarily held to prevent toxic serum concentrations.

Proton pump inhibitors present a unique problem for drug administration. Lansoprazole, omeprazole, and esomeprazole are formulated as delayed-release capsules containing enteric-coated granules. When ingested by mouth, the delayed-release capsule protects the base-labile granules until they reach the alkaline pH of the duodenum, at which time the granules dissolve and the drug is absorbed. If these medications must be administered via a nasogastric tube, crushing the enteric-coated granules can result in tube clogging and dissolving the granules in water can destroy the medication before it reaches the absorption site (i.e., small intestine). Thus, intact granules should be mixed with an acidic medium (e.g., apple or orange juice) and flushed with the acidic medium after administered down a gastric feeding tube (12). If the feeding tube terminates in the small bowel (i.e., jejunum), alkaline liquids should be used to dissolve the drug granules prior to administration (13). Pantoprazole and rabeprazole are formulated as enteric-coated, delayed-release tablets, therefore, these agents cannot be crushed and should not be administered down gastric or jejunal feeding tubes. Lansoprazole is also available as a packet of granules that is reconstituted with water to form a suspension, however, this formulation has been reported to clog feeding tubes as it contains xanthan gum (14).

ABSORPTION PHASE INTERACTIONS

Interactions which increase or decrease the percent of active drug that reaches the system circulation are classified as absorption phase interactions. Absorption interactions can be further divided into three subtypes:

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1) presystemic metabolism, 2) presystemic transport, and 3) presystemic binding/complexation.

Presystemic metabolism usually involves inhibition or induction of enzymes in the gastrointestinal tract. For example, grapefruit juice appears to down-regulate cytochrome P450 3A4 (CYP3A4) in the intestinal wall. Thus, the absorption of medications which are substrates of CYP3A4 enzyme (i.e., carbamazepine, cyclosporine, midazolam, saquinavir) is markedly increased when consumed with grapefruit juice (15). A presystemic transport interaction results in an alteration in transit time, dissolution, or drug transport. Vitamin E appears to increase the absorption of cyclosporine via P-glycoprotein inhibition and contribute to variation in cyclosporine oral pharmacokinetics (16). A reduction in oral bioavailability due to complexation represents presystemic binding/complexation. This interaction differs from ex vivo biopharmaceutical inactivation because the binding occurs in vivo within the gastrointestinal tract or systemic circulation versus outside the body in a delivery system (e.g., tubing or infusion bag). Tetracycline binding to divalent cations in the gastrointestinal tract and serum calcium:phophorus product [serum calcium (mg/dL) multiplied by serum phosphorus (mg/dL)] exceeding 55 and increasing the risk for soft tissue calcification are examples of this interaction.

INTERACTIONS AFFECTING SYSTEMIC/PHYSIOLOGIC DISPOSITIONS

Numerous drug-nutrient interactions involve alterations in tissue distribution, systemic metabolism, or penetration into specific tissues. This type of interaction generally occurs after the drug or nutrient has entered the systemic circulation and it may be mediated by hormones or clotting factors. For example, the vitamin K content of EN formulas may be the cause of warfarin resistance. Despite reformulations of all EN products over 20 years ago to decrease the vitamin K content, reports of interference with warfarin activity by enteral feeding continue to appear in the literature (17,18). Although some practitioners empirically hold EN formulas for 1 hour before and after the administration of warfarin, this strategy has never been shown to consistently enhance warfarin absorption or achieve anticoagulation goals more rapidly. General guidelines include more frequent monitoring of prothrombin time and use of alternative anticoagulant regimens (i.e., heparin or low-molecular weight heparin) when possible. Reduction in warfarin dosages may be required when transitioned from EN to an oral diet. Intravenous lipid emulsions are an additional source of vitamin K and have been associated with warfarin resistance when used with parenteral nutrition or as a delivery system for propofol (19).

INTERACTIONS AFFECTING DRUG ELIMINATION OR CLEARANCE

Nutrients and medications occasionally share metabolic pathways, thus changes in dietary composition can influence hepatic metabolism or renal clearance. High protein diets have been noted to accelerate the clearance of certain hepatically-cleared agents, like propranolol (20). A protein-restricted diet may decrease the renal tubular clearance and renal blood flow, thus the metabolite of allopurinol has been shown to accumulate during a low-protein diet (21). These findings imply that patients with poor nutritional intake (i.e., low protein consumption) may be more likely to experience adverse effects of renally-eliminated drugs. Altered nutritional states can also have profound effects on factors that influence drug disposition. Decreased renal clearance of penicillins, aminoglycosides, and methotrexate have occurred in the presence of protein-calorie malnutrition, increasing the risk for drug toxicity (22). Failure to respond to therapy may also occur as a result of altered body composition. Patients who are undernourished and weigh less than 80% of their ideal body weight are at risk for receiving subtherapeutic doses of aminoglycosides (e.g., gentamicin, tobramycin) (23). Edema, low fat mass, or excessive sweating may interfere with transdermal medication delivery (i.e., fentanyl patch) and require an alternative route of medication administration. Malnourished patients have decreased lean tissue mass, resulting in an increased extracellular fluid compartment and expanded volume of distribution for aminoglycoside antibiotics. Clinicians must consider basing their dose calculations on an expanded weight-adjusted volume of distribution in order to obtain therapeutic serum drug concentrations.

ADVERSE EFFECTS OF DRUGS/DRUG VEHICLES

In the intensive care unit, critically-ill patients often require sedation for anxiety or agitation. Propofol is formulated in a 10% lipid emulsion, providing 1.1 kcal/mL. The caloric contribution from this medication must be taken into account in order to avoid excessive calorie intake and hypertriglyceridemia. As much as 500 lipid kcal/day could be provided to a 70-kg patient receiving propofol at a rate of 50 mcg/kg/min. If a patient is receiving a PN formulation, IVLE can be discontinued as essential fatty acid requirements can be provided by propofol. In contrast, lipid combinations of amphotericin B, such as liposomal products or lipid complexes, do not contain linoleic or alpha-linolenic acid. Liposomal amphotericin B contains distearoyl phosphatidylglycerol and amphotericin lipid complex contains dimyristoyl phosphatidylcholine and dimyristoyl phosphatidylglycerol. These preparations have a very small caloric contribution (<150 kcal/day) and do not provide essential fatty acids (24).

Many intravenous products used in the compounding of PN formulations are contaminated with trace elements due to the raw materials or the manufacturing process. Many of the electrolyte solutions have been shown to be contaminated with chromium and aluminum. Increased serum chromium concentrations have been associated with decreased glomerular filtration rate in pediatric patients, thus children receiving long-term PN should have chromium eliminated as a trace element additive to the PN formulation. The FDA recently mandated that manufacturers of products used in the compounding of PN disclose the amount of aluminum contamination on the label of the product. The intent of the FDA is to facilitate competition among manufacturers to lower the amount of aluminum contamination in commercially-available products. An intake of no more than 5 mcg/kg/day via the intravenous route has been identified as the upper limit of safety for aluminum intake since tissue accumulation can occur above this level, resulting in neurologic and bone toxicity in pediatric patients (25).

Adverse gastrointestinal effects, such as bloating, discomfort, or diarrhea, can occur as the result of inactive ingredients contained in liquid medications. Sorbitol is often added as a sweetner or solubilizer for drugs in liquid oral dosage forms. Single sorbitol doses of 10 g or cumulative daily doses of 50 g are capable of producing diarrhea (26–28). The most common sorbitol-containing liquid medications are summarized in Table 5. The hyperosmolality of certain liquid medications may also be a source of gastrointestinal intolerance (29). The osmolality of stomach secretions is approximately 300 mOsm/kg, thus liquid medications exceeding this limit should be diluted to avoid osmotic-induced diarrhea. The small intestine is generally less tolerant than the stomach to undiluted hyperosmolar medication administration. References are available for the osmolality of various drug solu-

Table 5
Medication Formulations with >10 g Sorbitol/Day at Normal Dosages

- Acetaminophen liquid
- Amantadine liquid
- Charcoal, activated
- Cimetidine liquid
- Lithium citrate syrup
- Metoclopramide syrup
- Phenylephrine HCl/brompheniramine maleate elixir
- Pseudoephedrine/triprolidine liquid
- Sodium polystyrene sulfonate liquid
- Theophylline liquid

Adapted from references 26-28.

Table 6
Osmolality (mOsm/kg) of Selected Liquid Medications

Medication	*Average Osmolality*
Acetaminophen elixir	5400
Aminophylline liquid	450
Amoxicillin suspension 50 mg/mL	2250
Ampicillin suspension, 500 mg/5 mL	1850
Cimetidine	5550
Docusate	3900
Furosemide solution, 10 mg/mL	2050
Metoclopramide syrup	8350
Phenytoin suspension, 25 mg/mL	1500
Potassium chloride 40 mEq/5 mL	3550
Phospho-Soda	7250
Theophylline elixir, 5.33 mg/mL	2050
Thioridazine	2050

Adapted from reference 29.

tions and suspensions (29,30). The osmolalities for some of the most common medications are listed in Table 6.

CONCLUSIONS

Numerous issues must be considered to ensure safe and effective drug delivery in patients receiving EN and PN. Interactions between nutrients and medications may be significant, resulting in treatment failure or adverse effects. Patients should be closely monitored to optimize therapeutic responses to pharmacotherapy and specialized nutrition support, while minimizing the side effects and complications of these interventions. ■

References

1. Gauthier I, Malone M. Drug-food interactions in hospitalized patients: methods of prevention. *Drug Safety,* 1998;18:383-393.
2. Chan L-N. Redefining drug-nutrient interactions. *Nutr Clin Pract,* 2000;15:249-252.
3. Washington C. The stability of intravenous fat emulsions in total parenteral nutrition mixtures. *Int J Pharm,* 1990;66:1-21.
4. Food and Drug Administration Safety Alert. Hazards of precipitation associated with parenteral nutrition. *Am J Hosp Pharm,* 1994;51:1427-1428.
5. Cacek AT, Devito JM, Koonce JR. In vitro evaluation of nasogastric administration methods for phenytoin. *Am J Hosp Pharm,* 1986;43:689-692.
6. Clark-Schmidt AL, Garnett WR, Lowe DR, et al. Loss of carbamazepine suspension through nasogastric feeding tubes. *Am J Hosp Pharm,* 1990;47:2034-2037.
7. Healy DP, Brodbeck MC, Clendening CE. Ciprofloxacin absorption is impaired in patients given enteral feedings orally and via gastrostomy and jejunostomy tubes. *Antimicrob Agents Chemother,* 1996;40:6-10.
8. Mueller BA, Brierton DG, Abel SR, et al. Effect of enteral feeding with Ensure on oral bioavailabilities of ofloxacin and ciprofloxacin. *Antimicrob Agents Chemother,* 1994; 38:2101-2105.
9. Mimoz O, Binter V, Jacolot A, et al. Pharmacokinetics and absolute bioavailability of ciprofloxacin administered through a nasogastric tube with continuous enteral feeding to critically ill patients. *Intensive Care Med,* 1998;24:1047-1051.
10. Bauer LA. Interference of oral phenytoin absorption by continuous nasogastric feedings. *Neurology,* 1982;32:570-572.
11. Doak KK, Haas CE, Dunnigan KJ, et al. Bioavailability of phenytoin acid and phenytoin sodium with enteral feedings. *Pharmacotherapy,* 1998;18:637-645.
12. Chun AH, Shi HH, Achari R, et al. Lansoprazole: administration of the contents of a capsule dosage formulation through a nasogastric tube. *Clin Ther,* 1996;18:833-842.
13. Phillips JO, Olsen KM, Rebuck JA, et al. A randomized, pharmacokinetic and pharmacodynamic, cross-over study of duodenal or jejunal adminstration compared to nasogastric administration of omeprazole suspension in patients at risk for stress ulcers. *Am J Gastroenterol,* 2001;96:367-372.
14. Safety briefs. *ISMP Medication Safety Alert!,* 2002;7(12):1-2.
15. Bailey DG, Malcolm J, Arnold O, et al. Grapefruit juice-drug interactions. *Br J Clin Pharmacol,* 1998;46:101-110.
16. Chang T, Benet LZ, Hebert MF. The effect of water-soluble vitamin E on cyclosporine pharmacokinetics in healthy volunteers. *Clin Pharmacol Ther,* 1996;59:297-303.
17. Penrod LE, Allen JB, Cabacungan LR. Warfarin resistance and enteral feedings: two case reports and a supporting in vitro study. *Arch Phys Med Rehabil,* 2001;82:1270-1273.
18. Petretich DA. Reversal of Osmolite-warfarin interaction by changing warfarin administration time. *Clin Pharm,* 1990;9:93.
19. Maclaren R, Wachsman BA, Swift DK, et al. Warfarin resistance associated with intravenous lipid administration: discussion of propofol and review of the literature. *Pharmacotherapy,* 1997;17:1331-1337.
20. Fagan TC, Walle T, Oexmann JM, et al.: Increased clearance of propranolol and theophylline by high-protein compared with high-carbohydrate diet. *Clin Pharmacol Ther,* 1987;41:402-406.
21. Berlinger WG, Park GD, Spector R. The effect of dietary protein on the clearance of allopurinol and oxypurinol. *N Engl J Med,* 1985;313:771-776.
22. Mayhew SL, Christensen ML. Pharmacokinetic alterations in malnutrition and obesity. *Hosp Pharm,* 1993;28:836-837, 840-842, 850.
23. Zarowitz BJ, Pilla LM, Popovich J. Expanded gentamicin volume of distribution in patients with indicators of malnutrition. *Clin Pharm,* 1990;9:40-44.
24. Sacks GS, Cleary JD. Nutritional impact of lipid-associated amphotericin B formulations. *Ann Pharmacother,* 1997;31:121-122.
25. *Federal Register,* 2000;65(17):4103-4111.
26. Miller SJ, Oliver AD. Sorbitol content of selected sugar-free liquid medications. *Hosp Pharm,* 1993;28:741-744, 755.
27. Lutomski DM, Gora ML, Wright SM, et al. Sorbitol content of selected oral liquids. *Ann Pharmacother,* 1993;27:269-274.
28. Johnston KR, Govel LA, Andritz MH, et al. Gastrointestinal effects of sorbitol as an additive in liquid medications. *Am J Med,* 1994;97:185-191.
29. Dickerson RN, Melnik G. Osmolalities of oral drug solutions and suspensions. *Am J Hosp Pharm,* 1988;45:832-834.
30. Niemiec PW, Vanderveen TW, Morrison JI, et al. Gastrointestinal disorders caused by medications and electrolyte solution osmolality during enteral nutrition. *JPEN,* 1983; 7:387-389.