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Drug-Nutrient Interactions

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Objectives

Describe 3 different types of drug-nutrient interactions (DNIs) related to parenteral nutrition (PN) or enteral nutrition (EN), and give an example of each.

List 2 drug- or formula-related factors that may contribute to DNIs with PN formulations and EN formulations.

Determine when intermittently stopping enteral feeding or changing the EN formulation is more likely to result in successful management or prevention of a DNI.

List the usual steps for administering a drug via the feeding tube or when PN is also being administered, and explain why these steps are more appropriate than other methods including admixture of a drug with parenteral or enteral feeding formulations.

Test Your Knowledge Questions

1. An alert and oriented adult patient is receiving a continuous infusion of a standard, fiber-containing EN formulation through an 8-Fr nasogastric (NG) tube. Drugs administered by bolus administration through the side port of the tube are phenytoin suspension 400 mg daily and nizatidine 150 mg every 12 hours. The feeding tube becomes occluded and must be removed. A

new tube is placed because a long-term tube will not be considered until after a swallow study is completed 2½ weeks from now. Which of the following measures is most appropriate for preventing occlusion of the new tube?

A. Replace the 8-Fr tube with an 18-Fr NG tube.
B. Flush the feeding tube with 15 mL of water before and after administering each medication.
C. Discontinue the fiber-containing enteral feeding formulation, and initiate feeding with a fiber-free formulation.
D. Hold the feeding infusion for 2 hours before and after administering phenytoin.

2. The EN formulation for a home patient receiving EN through a percutaneous gastrostomy was recently changed from a high-protein, fiber-containing, 1 kcal/mL formulation to the only 1.5 kcal/mL formulation available in the local store. The new product is marketed for use in patients with compromised pulmonary function and contains low amounts of carbohydrate, 55% of energy from fat, about 15% less protein per day than the 1 kcal/mL formulation, and no fiber. What component of the new formulation is most likely to contribute to interactions resulting from slow gastric emptying?

A. Lower fiber content
B. Lower protein content
C. Higher fat content
D. Higher energy density

3. Which of the following is the preferred method of administering a hospitalized patient's antihypertensive medication when tube feeding is started due to poor oral intake?

A. By the oral route
B. As an oral liquid via the feeding tube
C. As a crushed tablet via the feeding tube
D. By the intravenous (IV) route

4. A medication that is ordered as a liquid to be administered via the feeding tube is available in the pharmacy in the IV form, as a capsule (powdered drug in a hard gelatin capsule), and as a film-coated tablet. What is the most appropriate and cost-effective choice for administration of this medication?

A. Administer the IV form via the IV route.
B. Administer the IV form via the feeding tube.
C. Make a slurry of the capsule's powder and administer via the feeding tube.
D. Crush the tablet to a fine powder and administer via the feeding tube.

Test Your Knowledge Answers

1. The correct answer is B. The most likely cause of the feeding tube occlusion is improper flushing technique (see Chapters 12 and 13). The tube should be flushed with a minimum of 15 mL of water before and after each medication, but 30 mL is commonly recommended and may be required to properly flush longer or larger tubes.1,2 Although the risk of occlusion is potentially greater with an 8-Fr small-bore tube than with an 18-Fr tube, the discomfort associated with such a large-bore tube would make it a poor choice for nasoenteral access in an alert patient, especially when needed for more than 2 weeks. Switching from a fiber-containing to a fiber-free EN formulation would have little influence on risk of tube occlusion. The fiber used in EN formulations has been processed to a degree that makes its viscosity similar to that of polymeric, fiber-free formulations.3 Holding the feeding infusion for 2 hours before and after phenytoin administration has been recommended as a method to enhance drug absorption; it would not be expected to influence tube occlusion.
2. The correct answer is C. High fat intake slows gastric emptying. High protein intake and high energy density can also slow gastric emptying but have less effect than high fat. In addition, protein intake will be lower with the new formulation. Low fiber intake has been associated with slow colonic transit and constipation rather than altered gastric emptying.
3. The correct answer is A. The oral route is preferred whenever possible because it is the route by which oral medications are designed to be administered. If the patient is allowed to take adequate water to swallow the medication, the oral route should be considered. For medications to be taken with food, the patient should have either food from oral ingestion or enteral formulation in the stomach before medication administration by mouth. Medications that are not administered via the feeding tube will not cause tube occlusion, making oral administration a very effective method of preventing tube occlusion caused by medications.
4. The correct answer is C. IV administration is generally the most expensive method and requires IV access. Use of IV dosage forms via the gastrointestinal (GI) tract is not usually recommended because these dosage forms are not designed to withstand the environment of the GI tract (gastric acid), and adequate amounts may not reach the bloodstream after presystemic metabolism in the GI tract mucosa (eg, cytochrome P450 [CYP450] metabolism) and first-pass metabolism in the liver. Crushing a film-coated tablet can be difficult because the film coating tends to remain intact and can become sticky when wetted with water. That makes administration via a feeding tube challenging. Most hard gelatin capsules can be opened and the powder inside combined with water to make a slurry for administration via a feeding tube.

Background

Interactions between medications (ie, drugs) and PN or EN have the potential to adversely affect patient outcomes because of loss of feeding access, loss of access for drug administration, or inappropriate response to drugs and/or altered absorption of nutrients. Numerous factors must be considered to prevent or mitigate DNIs, including the route and method of drug administration, the dosage form, and the medication's pharmacokinetic properties (primarily absorption and metabolism), as well as its

stability and compatibility characteristics. Factors related to nutrition support that may influence DNIs include the type and site of access, method of administration, and content of the PN or EN formulation.

Unfortunately, the US Food and Drug Administration does not require manufacturers to evaluate drugs for altered pharmacokinetic parameters or potential DNIs when administered via tube into the stomach, duodenum, or jejunum. Few DNIs are well studied in patients receiving PN or EN therapy, and studies that do exist often focus on in vitro physical interactions or use small numbers of healthy volunteers with simulated feeding access (eg, ingesting an EN formulation by mouth rather than by feeding tube). Studies in patients are typically not blinded, lack placebo control, and are retrospective in nature. Observational studies and case reports from very small numbers of patients are often the only data available. Thus, understanding of the mechanism of interaction is often poor, and the strength of evidence supporting methods to prevent or mitigate DNIs in patients receiving PN or EN therapy is seldom strong. Even the limited data available in the literature are sometimes conflicting, leading to multiple approaches to manage a DNI. Despite these limited and conflicting data, it is often possible to identify general principles that apply to management of DNIs. This chapter presents general principles to consider with DNIs and discusses specific issues related to the concurrent administration of drugs with PN or EN therapy. The chapter is not intended to be inclusive of all potential DNIs that the clinician may encounter; rather, it is intended to illustrate certain common clinical dilemmas.

Types of Interactions

The American Society for Parenteral and Enteral Nutrition has defined a DNI as “an event that occurs when nutrient availability is altered by a medication, or when a drug effect is altered or an adverse reaction is caused by the intake of nutrients.”4 This is a broad definition that encompasses many types and potential mechanisms of interaction between drugs and nutrients. Table 18-1 illustrates one system for classifying DNIs; other systems using somewhat different categories and terminology are also in use.5 The focus of this chapter is primarily on the physical, pharmaceutical, and pharmacokinetic interactions because these are the types most likely to present problems specific to PN or EN therapy, although they can occur in patients receiving an oral diet as well. Other types of interactions, such as electrolyte alterations related to specific medications, also occur in patients receiving nutrition support, but they tend to be independent of the route of nutrition and will occur whether the patient receives PN, EN, or an oral diet.

TABLE 18-1 Classification of Drug-Nutrient Interactions

Type of Interaction	Effects of Interaction	Associated Factors
Physical	• Precipitation in PN or EN formulations • Disruption of emulsion for ILEs or EN formulation • Altered viscosity, change in consistency, clumping, or curdling of EN formulation	• Drug and formulation pH • Reactive chemical moieties • Protein complexity • Time • Temperature • Duration of exposure
Pharmaceutical	• Loss of drug activity • Toxicity	• Alteration of a specialized dosage form or administration by a different route than that for which it was designed
Pharmacokinetic	• Loss of drug activity • Toxicity	• Occurs before the drug or nutrient reaches the site of action • Altered absorption, presystemic metabolism, hepatic metabolism
Pharmacodynamic	• Loss of drug activity • Toxicity	• Occurs at the site of action • Binding sites or receptors usually involved
Pharmacological	• Inability to provide PN or EN therapy because of adverse effects	• Extension of a drug’s normal pharmacological actions

EN, enteral nutrition; ILE, lipid injectable emulsion; PN, parenteral nutrition.

Physical Interactions

Interactions that result in altered physical characteristics of the nutrition formulation or the drug occur with both PN and EN therapy. Occlusion of the feeding access device is frequently the outcome of physical interactions. Other outcomes can include reduced bioavailability of the drug or nutrients, although studies seldom address effects of DNIs on nutrients. Physical interactions typically occur in the delivery device before the drug or nutrients reach the patient; therefore, this type of interaction can be referred to as an ex vivo interaction.5 Variables to consider when assessing the risk of physical interactions include the pH at which the drug and the PN or EN formulation is most stable; presence of cations and anions known to react chemically; concentration and chemical complexity of nutrients; and time, temperature, and duration of exposure to one another. This latter factor is one reason that admixture of drugs with a PN or EN formulation is very different than y-site administration or coadministration.

Parenteral Nutrition

Many studies evaluating compatibility between drugs and PN rely on visual inspection, measured turbidity, or increased particle count. Visually evident physical changes, such as turbidity, haziness, cloudiness, color changes, or precipitate formation in PN formulations, indicate incompatibility, as does emulsion disruption in lipid-containing PN. Drugs that show no evidence of physical interaction with PN are generally classified as compatible. However, some interactions result in a loss of drug or nutrient activity that requires chemical or molecular analysis for detection; no visible changes occur in the product(s). Admixture of octreotide acetate to PN formulations results in no visible changes (visibly compatible); nevertheless, incompatibility occurs due to development of a glycosyl octreotide conjugate and loss of drug activity (chemically incompatible).6,7 In addition, injectable multivitamin preparations are compatible with PN formulations, although some vitamins, such as thiamin, have limited stability and begin to very quickly lose their activity once added to the PN formulation because of hydrolysis, photodegradation, or other forms of chemical degradation (see Chapter 15) that may not be visible. Visual compatibility does not ensure chemical stability and drug or nutrient activity.

Safety guidelines that address the stability and compatibility of PN formulations have been developed.8–10 When drugs are administered with PN, either by admixture or co-infusion, the method of administration should ensure that both the drug and the PN formulation are stable and free from incompatibility. General principles for evaluating compatibility of drugs with a PN formulation include obtaining data for both physical compatibility and chemical stability of the drug and PN components whenever possible.

Both physical compatibility and chemical stability are influenced by pH. Because most PN formulations have a slightly acidic pH (5 to 6.5), drugs requiring a high pH or low pH for best solubility are typically incompatible with PN (see Practice Scenario 18-1 for a discussion of drug compatibility with PN). Increasing time of exposure between the PN and drug increases the risk of interactions; therefore, admixture of a drug into a PN formulation poses greater risk of interaction than co-infusion. Factors to

consider include (1) details related to the specific drug formulation (eg, with or without preservative, salt form) and drug concentrations evaluated, (2) specific components in the PN formulation, and (3) environmental conditions during evaluation (temperature[s] in particular). Dextrose and amino acid concentration, specific brand of amino acids used for compounding, inclusion of lipid injectable emulsion (ILE), the specific type of ILE, electrolyte concentrations and specific electrolytes added, and addition of trace elements, heparin, insulin, and other components can all influence compatibility and stability of PN formulations. When admixing a drug with PN, efficacy and toxicity profiles must be acceptable with administration by continuous infusion rather than intermittent infusion. Clinical application of principles of drug compatibility and PN formulations is discussed in Chapter 15.

Practice Scenario 18-1

Question: What factor(s) is most likely to result in occlusion of the vascular access device (VAD) when a patient is receiving several drugs and parenteral nutrition (PN) through the VAD?

Scenario: A 44-year-old man who underwent hematopoietic cell transplant 6 weeks ago is currently receiving PN with separate lipid injectable emulsion and patient-controlled analgesia with morphine sulfate (1 mg/mL concentration) through his tunneled VAD. Ceftazidime, fluconazole, and foscarnet are also administered through the VAD. Calcium chloride, 1 g every 8 hours, is ordered for adding to PN to address the patient's increased calcium requirements. This form of calcium is chosen because of a shortage of calcium gluconate and because the patient requires high phosphate content in the PN, which would limit addition of calcium gluconate. Medications are ordered for "minimum fluid" to limit fluid administration because he receives platelet and red blood cell transfusions 3 or 4 times weekly. The VAD is double lumen; however, the patient's nurse states that 1 lumen is occluded. Two attempts to clear the catheter with a thrombolytic agent failed. The morphine has continued through the patent line. Foscarnet, ceftazidime, fluconazole, and PN are on hold until access can be obtained.

Intervention: A 0.1-N hydrochloric acid solution is ordered. After confirming acceptability of hydrochloric acid use with the patient's silicone catheter, the nurse instilled the ordered dose in the occluded lumen and allowed it to dwell for 30 minutes before attempting to withdraw the solution. The procedure is repeated once because the catheter was still "sluggish" after the first attempt.

Answer: Several factors, including pH, time, administration method, and PN composition can contribute to physical interactions that occlude the VAD. When the pH of PN and the pH at which a drug is most soluble differ significantly, there is a high risk of the drug precipitating when co-infused with PN. The administration regimen should be reviewed. In addition, the composition of the PN and the co-infused drug should be reviewed. A high concentration of a potentially incompatible component of PN (eg, phosphate) and/or a high concentration of a potentially incompatible product to be co-infused (eg, calcium chloride) will increase precipitation risk. Electrolyte concentrations are typically several times higher in a supplemental dose than in PN; thus, the rationale that an electrolyte such as calcium is usually in PN and therefore can be co-infused is erroneous. Precipitation of calcium phosphate is the most likely cause of VAD occlusion if calcium is co-infused with PN, particularly when the co-infusion occurs below the PN filter.

Rationale: Evidence supports most antibiotics in the cephalosporin class, including ceftazidime, as compatible with PN; therefore, ceftazidime is unlikely to have caused the occlusion.7 Data also support fluconazole compatibility with PN. Limited evidence suggests foscarnet is compatible for co-infusion with PN; however, other data indicate its incompatibility with calcium-containing solutions. Given this mixed picture of compatibility, foscarnet may cause problems if co-infused with PN containing calcium. In this case, the patient is receiving calcium chloride outside the PN. Calcium is known to precipitate with phosphate when the solubility product of calcium phosphate is exceeded, which is likely to occur if calcium chloride is co-infused with PN containing phosphate. Thrombolytic agents are not effective in clearing drug precipitate. Altering the pH within the VAD lumen to make the drug more soluble can often clear the occlusion. However, the risk vs benefit of attempting line salvage should be considered. Generally, salvage is more likely to be attempted with a long-term tunneled or implanted VAD. However, the compatibility between catheter materials and the recommended clearance solution should be confirmed prior to attempting salvage. Many peripherally inserted central catheters are made from polyurethane whereas tunneled catheters are often composed of silicone. With calcium phosphate precipitate, decreasing the pH by instilling 0.1 N hydrochloric acid will increase calcium phosphate solubility and may be effective in clearing the occlusion. Discussion with the nurse reveals the infusion arrangement changed last evening. The patient was receiving a blood transfusion when his calcium dose was due, and he was to receive platelets once the red cell transfusion was completed. Therefore, the nurse co-infused calcium chloride with the PN, which contained above-standard amounts of potassium phosphate due to effects of foscarnet. A 0.22-micron filter was on the PN lumen of a bifurcation device connected to the catheter lumen; however, there was no filter after the calcium mixed with the PN solution.

Enteral Nutrition

Use of enteral feeding tubes as a drug delivery device increases the risk of various interactions between the drug, the EN formulation, and the feeding tube. Physical interactions can be a significant problem when drugs are allowed to mix with EN formulations. Several studies have evaluated physical compatibility between various drugs in liquid form (elixirs, solutions, suspensions) and EN formulations. Almost all of these studies were performed more than 25 years ago and tested relatively few drugs and even fewer EN formulations.11–16 Direct application of these results to current clinical practice is difficult because drug and EN formulations may have been altered by the manufacturer while maintaining the same product name. Nevertheless, principles of compatibility can be gleaned from these studies.

Both the drug and the EN formulation affect the risk of physical interactions. The presence of complex protein (ie, intact or whole protein, not hydrolyzed protein or free amino acids) seems to be a critical property for determining risk of developing a physical interaction. Protein source (caseinates, soy, whey) may have some effect on interactions; however, fiber content, nitrogen content, and dilution of the EN formulation have not been shown to affect the risk of physical interactions with drugs in studies reported in the literature.11–15,17 Theoretically, dilution of the EN formula is expected to improve drug

dissolution and reduce interactions; however, formula dilution is not recommended because it increases risk of microbial contamination.2 Two factors are of particular importance with drugs in liquid form: (1) acidic pH, and (2) base components, especially sugar-water syrups, alcohol-containing elixirs, or oil-based products.11–13,17,18 These factors are probably more important than the drug per se in most cases; however, it is important to recognize that pH and base components are selected to optimize solubility of a particular drug.

Overall, approximately one-third of drugs in liquid dosage forms evaluated for physical interactions with EN formulations have demonstrated undesirable effects (precipitation, curdling, clumping) with at least 1 EN formulation.11–14,17,18 Of 25 drugs reported to be incompatible with intact protein formulations in these studies, only 3 (1 potassium chloride liquid and 2 oil-based products—medium chain triglyceride oil and methenamine suspension) were incompatible with a hydrolyzed EN formulation. Of the 12 drugs tested with both fiber-free and fiber-containing EN formulations, 1 drug (Reglan syrup, Baxter Healthcare Corporation, Deerfield, IL) was reported as incompatible with fiber and compatible without fiber. The formulation tested contained soy polysaccharide as the fiber source. There are no data for EN formulations containing soluble fiber (guar gum, acacia, gum arabic, pectin) or fructooligosaccharides. Soluble fibers have a propensity to form gels. Therefore, the risk of undesirable interactions between drugs and EN formulations containing these fiber sources may be greater than with soy polysaccharide, although the relatively low amounts of soluble fiber in current EN formulations may mitigate the risk. An acidic pH was reported for all but 2 of the incompatible drugs, the exceptions being antacids (Mylanta II, McNeil Consumer Pharmaceuticals Co., Fort Washington, PA; Riopan, Takeda Pharmaceuticals International, Inc., Deerfield, IL), both with pH 7.5. Characteristics of the antacids other than pH, such as their composition of divalent and trivalent cations and formulation as suspensions, likely contributed to the incompatibility.

The protein source for all of the intact protein EN formulations in these studies included caseinates.11–14 There is limited evidence that soy protein results in finer precipitate than caseinates, and whey-based formulations are unlikely to curdle and clump when mixed with acidic drug products because of the acid-stable characteristics of whey protein.17 However, these are primarily observations that should be confirmed in scientifically rigorous studies with current EN and drug formulations. The data suggest protein denaturation, especially for caseinates, may be responsible for much of the physical incompatibility when drugs in liquid dosage form and EN formulations interact.

Preventing or Mitigating Physical Interactions

Physical interactions are best avoided by not allowing drugs to mix with either PN or EN formulations. Ideally, drugs should be administered via a route other than the feeding administration device (vascular access device [VAD] or feeding tube), although that is not always possible. There are a few exceptions where products are added directly to the PN or EN formulation, including drugs such as insulin and histamine-2 receptor antagonists in PN. For patients who are allowed oral intake, the best route for administration of oral drugs is by mouth (see Practice Scenario 18-2 for a discussion of oral vs tube administration of medications). Routes such as rectal, transdermal, sublingual, intramuscular, and subcutaneous can be considered when drugs are available in these forms.

Practice Scenario 18-2

Question: What is the most effective method for preventing feeding tube occlusion related to medication administration in a patient receiving jejunal feedings to supplement inadequate oral intake associated with gastroparesis?

Scenario: A 63-year-old woman is admitted to the hospital because of nausea and weight loss. The gastrointestinal workup, including small bowel follow-through, indicates gastroparesis, likely secondary to type 2 diabetes mellitus. Thin liquids empty from the stomach with only slight delay; however, progression of thick liquids and solids into the duodenum is severely delayed. A percutaneous gastrojejunostomy tube is placed by interventional radiology, and the patient is started on tube feeding in addition to a modified consistency (thin liquid) diet. Although the patient's chart from another hospital indicates poor response to prokinetic agents, metoclopramide is ordered and home medications are restarted, including levothyroxine, lovastatin, amlodipine, calcium citrate, and fluoxetine.

Intervention: Medications are ordered for administration through the feeding tube. After reviewing the chart, the nutrition support clinician recommends changing the order to oral administration of medications.

Answer and Rationale: Medication administration through a feeding tube is a contributing factor to tube occlusion. Medications administered by mouth do not cause tube occlusion. In this case, the patient is allowed an oral diet with thin liquids to reduce gastric stasis. Medications taken with water should have minimal effect on gastric emptying compared with water alone, and thin liquids empty with only slight delay per the gastrointestinal evaluation.

When a drug must be administered through the same device as the PN or EN formulation, feeding should be stopped, and the access device should be flushed with fluid that is compatible with the PN or EN formulation as well as the drug. The access device should be flushed before and after drug administration and between drugs if multiple drugs are administered. The "flush" volume must be adequate to clear the administration device of the feeding formulation or the drug. Sodium chloride 0.9% is the usual fluid of choice for flushing VADs, but 5% dextrose solution is sometimes required. Minimum flush volume for VADs is typically specified by the manufacturer based on catheter size and type. Water is the fluid of choice for flushing enteral feeding tubes.19 Other fluids should generally be avoided to reduce the risk of interactions with the EN formulation. Acidic products, such as carbonated beverages and cranberry juice, may be particularly problematic.20,21 The minimum recommended volume used to flush enteral feeding tubes in adults is 15 mL, although larger volumes are often used.2

Other potential methods of preventing physical interactions with PN and EN formulations include altering the infusion time, the nutrition formulation, or the drug. For PN, a cyclic regimen might allow an incompatible drug to infuse during the off time, although this approach is rarely effective for drugs administered more than once daily. Ideally, a therapeutically equivalent drug with evidence of

compatibility for coadministration with the PN formulation could be used if changing the administration schedules is not possible. Altering the PN formulation to omit the interacting component may be possible in limited circumstances and for a limited duration. For example, it may be possible to omit the ILE for a few days while other vascular access is obtained when the emulsion is known to be the incompatible component and the patient's clinical condition is acceptable for this approach.

Changing to a hydrolyzed or free amino acid EN formulation rather than an intact protein source could be considered, although these formulas tend to be considerably more expensive and this approach is not typically a preferred way to prevent interactions. Viable options in some cases include alternative dosage forms (eg, powder from a capsule can be made into a slurry rather than using an elixir) or drugs that are therapeutic equivalents (different drug with the same therapeutic effect) but with different potential to interact.

Pharmaceutical Interactions

Dosage Forms

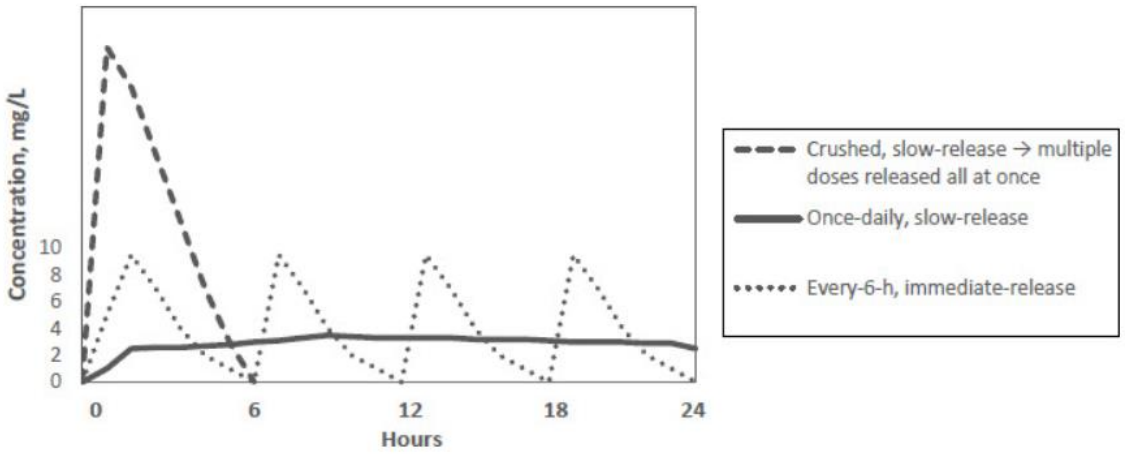
Interactions that occur because a drug dosage form is altered are more likely to occur with EN therapy and are seldom necessary for consideration with PN therapy. Drug dosage forms include the drug itself and other nonmedicinal components (excipients) necessary to make a stable and efficacious product that has suitable administration characteristics (eg, palatable for oral administration, nonirritating for dermal administration). Some dosage forms are designed for specific applications, such as enteric-coated tablets to protect drugs from gastric acid or the stomach from an irritating drug, long-acting products to reduce the number of daily doses, and sublingual or rectal products that avoid first-pass metabolism in the liver. Altering certain dosage forms can dramatically increase or decrease drug bioavailability and trigger adverse effects or, conversely, destroy the active ingredient. Thus, pharmaceutical interactions can also be classified as pharmacokinetic interactions.

The most common method of altering a dosage form is to crush or dissolve solid dosage forms to create a liquid for administration via the feeding tube. When a solid dosage form is to be administered via a feeding tube, it must first be determined that crushing or dissolving will not disrupt the drug's pharmaceutical activity. Solid dosage forms that are appropriate to crush should be prepared as a very fine powder and mixed with warm water before administering through the tube. In addition, many capsules may be opened and the contents administered after forming a slurry with water from the powder or finely crushed solids. Consult manufacturers' product information and the medical literature for information regarding crushing tablets or capsules. A frequently updated list of dosage forms that should not be crushed is available.22

As a general rule, special dosage forms such as long-acting, sustained-release, slow-release, or delayed-release forms containing several doses in 1 tablet or capsule should not be crushed or dissolved. These dosage forms are designed to slowly release the drug in the GI tract, often over 12 to 24 hours. Crushing may cause immediate release of the total drug dose, increasing the risk of toxicity and reducing efficacy. A 200-mg, extended-release morphine capsule is designed to gradually release drug over 24 hours; when crushed or dissolved before administration, the full 200-mg dose is immediately released,

resulting in increased risk of respiratory depression and, potentially, respiratory arrest. However, conventional (non-extended-release) morphine is usually dosed every 4 to 6 hours so the patient is likely to experience pain, and potentially withdrawal symptoms if the conventional dosage form is given according to the schedule intended for the extended-release formulation. Figure 18-1 provides a graphic representation of expected effects on serum concentrations of a drug from crushing a once-daily, slow-release formulation compared with an every-6-hour, immediate-release formulation or oral administration of the once-daily formulation without crushing. The risk of toxicity from crushing an extended-release formulation is exacerbated when bioavailability is increased disproportionately as the drug dose increases, as it does with diltiazem.23 The metabolic effects of the immediate release of large drug doses intended for extended delivery, such as nifedipine from crushing an extended-release tablet, can be life-threatening.24 Drugs whose names are followed by initials such as CD, CR, ER, LA, SA, SR, TR, XL, or XR generally need to be taken intact and should not be crushed or dissolved for administration.

FIGURE 18-1 Expected Blood Concentration Effects of Crushing a Once-Daily, Slow-Release Product



The graph depicts expected blood concentration effects of crushing a once-daily, slow-release product (high peak followed by near zero concentration by 6 hours) compared with an immediate-release product dosed every 6 hours (4 moderate size peaks between 9 and 10 mg/L evenly spaced across 24 hours) or the normal oral administration of the once-daily, slow-release product (concentration consistently between 2 and 4 mg/L over 24 hours).

Source: Reprinted by permission of Carol J. Rollins.

Enteric-coated products, often denoted by EC after the name, are another special dosage form that generally should not be altered for administration. The coating is intended to protect a drug from destruction by gastric acid or to protect the stomach from irritation caused by the drug. When the coating is disrupted by crushing or dissolving the tablet, adverse effects are likely to occur if the medication is administered into the stomach. In one case, the drug is destroyed by exposure to gastric acid, and the patient receives less than the desired dose, thereby placing the patient at risk for treatment failure. Gastric irritation from removal of a protective tablet coating may also result in

treatment failure if the patient experiences emesis from the drug. Administration into the jejunum negates the need for an enteric coating since the jejunum is where the coating is designed to dissolve. Therefore, dissolving the coating in bicarbonate solution, then crushing the tablet is acceptable for jejunal administration, although the process can be slow (30 to 45 minutes) and caution is still required to avoid tube occlusion.25,26

Enteric coatings should be distinguished from film coatings on tablets. Film coatings are used to make tablets easier to swallow or to mask unpleasant taste, but they do not impart special characteristics such as those associated with enteric coatings. Crushed film-coated tablets should not result in altered drug activity or increased risk of adverse effects. However, as with enteric coatings, film coatings can be problematic because they often remain as undissolved pieces that become sticky in water and can occlude the feeding tube. Sublingual dosage forms are designed to dissolve under the tongue for absorption via oral mucosa. Enteric mucosal and endoplasmic reticulum enzymes (eg, CYP450) and transporters (eg, P-glycoprotein and anion-transporting polypeptides) are bypassed with this route, thereby eliminating presystemic metabolism. In addition, blood flow is not routed to the liver, so first-pass effects from hepatic enzymes, including hepatic CYP450 enzymes, are eliminated. Sublingual doses are typically small compared with oral doses, and sublingual doses administered via a feeding tube are unlikely to provide an appropriate treatment dose of the drug. Buccal doses are similar to sublingual doses in this respect.

Dosage forms designed to disintegrate rapidly in the mouth before swallowing (solutabs) avoid the need for crushing and administering through the feeding tube when the patient is able to take such products by mouth. Pellets contained inside microencapsulated dosage forms should generally not be crushed because they are either enteric coated and/or time-released. Intact pellets may be administered through the feeding tube, provided the pellets are small enough to completely pass through the tube. Usually, a larger tube (minimum 16-Fr gastrostomy tube) is necessary for successful administration of these dosage forms. Suggestions for administering the microencapsulated beads or pellets include pouring them down the tube or suspending them in an acidic juice before administering through the tube.27 Using an acidic juice as the vehicle for microencapsulated pieces should reduce the risk of the beads or pellets sticking to the tube. However, water should be used to clear the tube of the EN formulation before and after administration of the acidic juice–drug mixture to avoid physical DNIs between the EN formulation and an acidic product (see Practice Scenario 18-3 for an example of such a drug administration situation).25,28–30 If the feeding tube diameter is too small to administer intact beads or pellets, a therapeutic option with better characteristics for tube administration is highly recommended. For a few drugs with no viable options, such as pancreatic enzymes, it may be necessary to dissolve an enteric coating on the beads or pellets in a sodium bicarbonate solution, then crush and administer the drug with a small volume of sodium bicarbonate solution.

Practice Scenario 18-3

Question: Which of the available dosage forms of lansoprazole should be ordered, and how should it be administered through a nasal-jejunal feeding tube?

Scenario: A 49-year-old man is receiving lansoprazole due to a gastrointestinal bleed. He is being fed via a small-bore nasal-jejunal tube because of poor nutrition status, inability to take an oral diet, and aspiration risk while on mechanical ventilation. He was taken off mechanical ventilation yesterday and is transferring from the intensive care unit (ICU) to a medicine unit today. His continuous intravenous infusion of lansoprazole was stopped today and administration via the feeding tube is ordered.

Intervention: The ICU pharmacist discusses the options for acid suppression with the physician and obtains an order to change lansoprazole to famotidine.

Answer: Lansoprazole is problematic for administration through a small-bore feeding tube using commercially available dosage forms. Either an extemporaneously prepared oral suspension or therapeutic alternatives should be considered to avoid occlusion of the feeding tube. In addition, the continued need for acid suppression once the patient is off mechanical ventilation, especially after he leaves the ICU, should be addressed. If acid suppression is to continue, the histamine-2 receptor antagonist on the hospital's formulary may be adequate. Otherwise, extemporaneous preparation of a suspension will be required or specific manufacturer's directions for an orally disintegrating tablet (ODT) followed.

Rationale: Lansoprazole is available as a delayed-release capsule and as a delayed-release ODT. These dosage forms should not be crushed because of the delayed-release characteristics. The capsule can be opened and intact granules administered with apple juice (40 mL recommended) via feeding tube.28 However, the tube must be of adequate size (equal to or greater than 16 Fr) to allow intact granules to pass through the tube without causing occlusion. Because of the risk of tube occlusion, caution must be used with any ODT administered through a small-bore feeding tube.28 Specific directions for administration of the lansoprazole ODT are provided by the manufacturer and should be followed to minimize the risk of occlusion.29 A histamine-2 receptor antagonist available in a liquid dosage form or crushable tablet, such as famotidine, can be considered if acid suppression is still necessary once the patient leaves the ICU. Recipes are available for preparation of an oral lansoprazole liquid dosage form; however, this approach requires preparation from the available delayed-release capsule.25,30

Administration of IV dosage forms via the GI tract is similar to altering a dosage form. In general, IV dosage forms are poorly suited to withstand gastric acidity and enzyme activity within the GI tract. Substantial drug loss can occur, resulting in poor drug absorption and delivery to the site of activity. IV electrolyte preparations are an exception and seem to be effective when administered via the GI tract. However, the osmolality of such preparations can be very high and potentially result in GI intolerance, including osmotic diarrhea. Oral liquid dosage forms can also have a high osmolality and result in diarrhea or cramping. The osmolality of oral liquids and IV drugs often exceeds 1000 mOsm/kg and may

be several thousand mOsm/kg.18,31,32 The effect of high osmolality is most pronounced when a large volume is needed for each dose of drug. Diluting hyperosmolar products with water before administration reduces the osmolality and may reduce the risk of GI intolerance.

Sweetening agents such as mannitol, sucrose, and sorbitol are used in many oral liquid dosage forms and contribute to increased osmolality. Sorbitol is particularly troublesome because the cumulative daily dose from oral liquid drugs can reach 20 to 50 g, an amount commonly used as an osmotic laxative.33,34 With only 5 to 10 g of sorbitol daily, a considerable portion of people experience bloating and flatulence.35 An important factor in promoting EN tolerance is identification, prevention, and management of diarrhea due to the sorbitol content or hypertonicity of concurrent liquid medications. See Chapter 13 for additional discussion of diarrhea as a complication of EN.

Preventing or Mitigating Pharmaceutical Interactions

Methods of preventing or mitigating pharmaceutical interactions include using immediate-release dosage forms rather than long-acting forms and avoiding special dosage forms, such as enteric-coated or sublingual, when they must be crushed or dissolved for administration through the feeding tube. Proper tube flushing cannot prevent pharmaceutical interactions. However, flushing with adequate quantities of water remains an important technique to prevent concomitant physical interactions. Pharmaceutical interactions may also be minimized by using alternate routes of administration or by using a therapeutic alternative that is available in a form conducive to administration via the feeding tube. Exposure to sorbitol may be controlled by use of alternate administration routes or by use of therapeutic alternatives. Unfortunately, current information on the sorbitol content of a drug is often unavailable, so selecting a therapeutic alternative with less sorbitol may not be easy. The drug manufacturer is generally the best source of information for current sorbitol content. Published information may not reflect current content, and a wide variation in sorbitol content can be found in versions of a given product from different manufacturers. Many pediatric drugs in liquid form, such as antibiotics, are now formulated without sorbitol.25,29

Pharmacokinetic Interactions

Definition

The term pharmacokinetics refers to studies of the time course for drug absorption, distribution, metabolism, and excretion.36 However, the term can also be applied to nutrients because these same processes occur with nutrients. Pharmacokinetic DNIs are characterized by alterations in one or more pharmacokinetic parameters of a drug or nutrient due to an interaction between them. Changes in drug absorption and metabolism are most often reported. The effects of drugs on nutrient pharmacokinetics are rarely evaluated. Pharmacokinetic DNIs occur as the result of multiple factors, including those related to administration of EN or PN, the drug, and the PN or EN formulation. The disease process resulting in a requirement for EN or PN can also contribute to pharmacokinetic DNIs, especially as it affects protein status, organ perfusion, and GI motility.

Apparent Absorption and Metabolism

Bioavailability describes the amount of drug that reaches systemic circulation after administration. Drug or nutrient loss during administration, adverse pH effects, complex formation between nutrient(s) and drug, presystemic metabolism in the gut mucosa (eg, CYP450 metabolism), and hepatic first-pass metabolism can cause product losses that decrease bioavailability. Product loss during administration may reflect a chemical interaction that results in deterioration of the drug or nutrient without causing a change in the physical appearance of the PN or EN formulation or the drug product. A change in product color without precipitate formation or changes in viscosity may also indicate an interaction. Photodegradation, oxidation, and hydrolysis are typical chemical reactions resulting in stability problems. These chemical reactions tend to be exacerbated by pH changes, increased time of exposure (eg, admixture in a PN formulation rather than co-infusion), and increased temperature. Photodegradation requires light exposure and tends to be limited by opaque formulations, including ILEs and most EN formulations.

Amino acids are frequently associated with chemical reactions in PN and EN formulations. The Maillard reaction occurs between the amine group of amino acids, including those in proteins, and the carbonyl moiety of certain carbohydrates, resulting in a browning reaction that alters taste, appearance, and, potentially, nutritional value. The carbohydrates involved are reducing sugars (eg, glucose, lactose). Sucrose and complex carbohydrates commonly found in EN formulations do not react unless hydrolyzed to monosaccharides. Heat (eg, heat sterilization) and water accelerate the reaction.

The potential for chemical reactions and stability issues exists whenever a solid dosage form of drug is made into a liquid form. Water tends to accelerate chemical reactions that result in loss of drug activity. Solid dosage forms (tablets, capsules) may not contain protective additives or stabilizers needed for liquid dosage forms of the same drug. Aspirin illustrates the effect of water on stability; an aspirin tablet dissolved in water quickly loses most of its pharmacological activity. Therefore, solid drug dosage forms should be prepared as a slurry with water just before administration through the feeding tube. Occasionally, extended stability data for extemporaneous liquid preparations are available, and the pharmacist can make the liquid product a few days in advance.7,25,30

Administration-Related Factors

Tubing and Bag Characteristics

Adsorption of a drug or nutrient into a container or administration tubing results in product loss without changes in the physical appearance of the products and is difficult to separate from chemical instability without sophisticated analysis. Specific chemical characteristics of the container or administration set must be considered before extrapolating data from a study to the practice site. Results of studies conducted in foreign markets relative to the clinician’s practice may be especially problematic for extrapolation because differences in container and tubing characteristics, as well as medication formulation, may influence results.

Products with high fat solubility are more likely to undergo adsorption with plastics, but other drugs (eg, insulin) can also be adsorbed. The classic example of nutrient loss to the container is vitamin A loss into diethylhexylphthalate (DEHP)-containing plastics.37 ILEs actually leach DEHP from the bags into the emulsion, as does the castor oil emulsion used in formulating certain fat-soluble drugs, such as cyclosporine A. Although not DNIs in the usual sense, these interactions are concerning because the solubilized DEHP may pose a health risk.38

Loss of certain drugs into feeding tubes has been suggested.39–41 A small in vitro study to determine the extent of warfarin binding to polyurethane feeding tube material evaluated warfarin recovery from a mixture of simulated gastric fluid and a crushed warfarin tablet, and the investigators found significantly less recovery when pieces of feeding tube were added to the container vs no feeding tube.39 In contrast, it is likely that most, if not all, of the drug losses during in vitro studies with phenytoin and carbamazepine suspensions were caused by adherence to the intraluminal surface of the tube; diluting the suspensions before administration reduced drug losses.40,41 Irrigating the feeding tubes after drug administration also reduced drug loss. Thus, suspensions, especially viscous suspensions, are best diluted to a relatively thin consistency before administration through a feeding tube. Slurries made from a powdered or crushed drug should also be a thin consistency to avoid drug loss in the feeding tube. In addition, the tube must be adequately flushed to remove any residual drug. Failure to properly flush the tube may result in physical DNIs between the drug retained in the feeding tube and the EN formulation, resulting in a high likelihood of feeding tube occlusion.

Site of Delivery

The site of drug delivery has minimal effect on PN-associated DNIs but can be a major administration-related factor for EN therapy. For PN therapy, the delivery sites are peripheral vein or central venous circulation, and the primary difference in PN formulations is the lower osmolarity of peripheral PN. On the other hand, efficacy and bioavailability of EN therapy may be greatly altered by site of delivery. Drugs with a “local” effect must be delivered to that locale. Antacids and sucralfate are examples of drugs with a local effect; they have no therapeutic effect with postpyloric delivery because they act locally in the stomach. Drug or nutrient absorption from the GI tract requires that the product be in a ready state for absorption. Nutrients must be released from the food matrix and specific complexes (eg, vitamin B12 and intrinsic factor) or valences (eg, ferric vs ferrous iron) may be needed. Drugs generally must be dissolved and have some portion in the nonionized (noncharged) state. The site of feeding and drug delivery determines the environment to which a product is exposed, thereby affecting readiness for absorption. The location of the tube’s distal tip determines the delivery environment for products administered through a feeding tube.

Delivery Environment

Feeding tubes can deliver drugs and nutrients to the stomach, duodenum, or jejunum (see Chapter 12). The environment changes from highly acidic to moderate acidity to near neutrality as the tip of the feeding tube moves deeper into the GI tract. These environmental changes in pH influence the degree of absorption. Feeding and drug delivery into the stomach allow most of the normal physiological functions

associated with digestion to be utilized. The stomach serves as a mixing chamber, helping release nutrients from the food matrix and mixing foods and drugs with gastric acid. Drugs soluble in acid generally complete the dissolution process in the stomach. Drugs that are not soluble in acid dissolve once they reach the small bowel.

Little absorption actually occurs in the stomach; rather, the vast majority of absorption occurs in the small bowel because of the enormous surface area. Thus, gastric emptying is a rate-controlling step for absorption, and any nutrient or drug that alters the gastric emptying rate will affect pharmacokinetic parameters. Table 18-2 lists several EN formulation characteristics and drug examples that may be associated with altered gastric emptying.42–44 The rate of nutrient and drug absorption typically follows the direction of change in gastric emptying. Slow gastric emptying slows absorption, and rapid gastric emptying increases the absorption rate.

TABLE 18-2 Factors Associated with Delayed Gastric Emptying

Factors	Amount/Characteristics	Concomitant Effect on Gastrointestinal Motility
Formulation-related:	• High concentration	• Decrease (gastric)
• Long-chain fats[a]	• High concentration	• Decrease (gastric)
• Protein	• Low	• Decrease (gastric)
• pH		• Increase (small bowel)
Osmolarity, mOsm/L	• <250 and >800	• Decrease (gastric) • Increase (small bowel)
Viscosity	• High	• Decrease (gastric)
Volume	• Large	• Decrease (gastric) • Increase (small bowel)
Drug particle size	• Large or tablets	• Decrease (gastric)
Drugs:[b]		
• Anticholinergic agents		• Decrease (gastric and small bowel)
• Narcotic agents		• Decrease (gastric and small bowel)
• Octreotide		• Decrease (gastric and small bowel)

[a]Greatest effect of formulation-related factors.

[b]This list of drugs is not all-inclusive.

Sources: Data are from references 42, 43, and 44.

Effects of altered gastric emptying on bioavailability, or extent of absorption, can be difficult to predict and are dependent on the chemical characteristics and mechanisms of absorption for a particular drug or nutrient. Rapid gastric emptying accompanied by rapid GI transit can result in poor absorption because there is insufficient contact time between the drug or nutrient and the absorptive surface of the small bowel. Rapid gastric emptying in the presence of normal small bowel motility is expected to reduce the extent of absorption for nutrients and drugs that require an acidic environment to create readiness for absorption. Slow gastric emptying allows increased release of nutrients from the food matrix, increased exposure to acid, and slower presentation of chyme to the small bowel. Thus, slow gastric emptying increases the extent of absorption for nutrients such as iron, calcium, and magnesium

that benefit from acid exposure and for nutrients such as riboflavin that undergo active absorption by a saturable mechanism in the upper small bowel. Dissolution of acid-soluble (eg, tetracycline) and poorly soluble (eg, carbamazepine, digoxin) drugs is improved with slow gastric emptying; however, bioavailability depends on stability in an acid environment. For example, bioavailability increases for carbamazepine, an acid-stable drug, but decreases for digoxin, which is hydrolyzed in the presence of acid.

Delivery of the EN formulation and drugs into the small bowel bypasses problems with gastric emptying. Experience with use of short- and long-term jejunal feeding using both hydrolyzed and intact protein formulations suggests that delivery beyond the duodenum has negligible effects on overall nutrient absorption. The effect of delivery into the small bowel on drugs largely depends on their solubility and need for acid exposure for absorption. Poorly soluble drugs that benefit from an increased time for dissolution and drugs that require exposure to acid are expected to exhibit reduced bioavailability with administration into the small bowel. Thus, drugs such as carbamazepine, itraconazole, and tetracycline are likely to have reduced bioavailability with postpyloric administration. Limited data support poor itraconazole absorption with jejunal administration.45

The balance between reduced dissolution and less acid destruction with postpyloric administration of poorly soluble but acid-labile drugs, such as digoxin, is difficult to predict. Reduced hydrolytic products (0.6% vs 2.9%) and greater nonmetabolized digoxin recovery (96.3% vs 90.8%) were reported with jejunal administration compared with oral intake in a small study, suggesting that the balance may be in favor of reduced destruction.46 Because serum digoxin levels were not reported in this study, it is unclear if more nonmetabolized digoxin in the jejunum results in greater drug absorption. Published data, including the manufacturers' package inserts, rarely provide information on the proportion of a drug absorbed in specific segments of the small bowel. Fortunately, most drugs have a wide therapeutic range and seem to be efficacious and nontoxic, despite potential changes in bioavailability related to the delivery site and environment. For drugs with a narrow therapeutic index, it is advisable to monitor for changes in the serum drug level whenever administration occurs through a feeding tube.

Administration Regimen

Food is known to interact with many drugs and alter pharmacokinetic profiles, particularly absorption and metabolism.44 Recommendations for oral administration of many drugs commonly include directions for taking the drug with or without food. Logic suggests that an EN formulation is equivalent to oral food ingestion; however, limited data indicate that the method of EN administration influences GI tract response. Particular patterns of GI motility and secretions are associated with the "fed" state, including slowed gastric emptying and increased release of digestive enzymes and GI tract secretions. The "nonfed" state is associated with more rapid gastric emptying and fewer digestive enzymes and secretions.

A study of hydralazine pharmacokinetics in 8 healthy volunteers receiving an EN formulation via NG tube reported similar results with fasting and continuous infusion of the EN formulation.47 Hydralazine parameters with bolus administration of the EN formulation were similar to those with a standard

breakfast (controlled for effects of nutrient content, such as fat) and differed from fasted parameters. These results suggest that holding continuous EN administration for drugs to be taken on an empty stomach (1 hour before or 2 hours after a meal) is not necessary. However, extrapolating results from a single investigation of a particular drug in healthy subjects to other patient populations and other medications is difficult. There is little evidence of therapeutic failure in most cases when continuous EN administration is stopped only during the short time needed to properly flush the tube and administer the drug (a few notable exceptions are discussed later in the chapter). Clinical experience does, however, suggest that holding EN administration for approximately 1 to 2 hours every 6 to 8 hours for drug administration is likely to result in inadequate nutrition support and deterioration in nutrition status unless a volume-based feeding protocol is used.

Drug-Related Factors

Factors associated with the drug itself can result in pharmacokinetic DNIs. These factors include the dosage form, chemical characteristics, and susceptibility to presystemic enzymatic degradation, cellular transport, and hepatic metabolism. For PN formulations, drug-related factors are largely associated with stability of the IV dosage form and the potential for loss of drug activity due to chemical reactions (photodegradation, oxidation, hydrolysis). As discussed previously in this chapter, alteration of dosage forms and chemical characteristics relative to the delivery environment are important drug-related factors pertinent to EN therapy. Susceptibility of drugs to presystemic enzymatic degradation, cellular transport, and hepatic metabolism can play a major role in apparent absorption for drugs administered into the GI tract; however, these processes are not specific to EN therapy and are reviewed only briefly here.

Presystemic Metabolism

Metabolism that occurs before reaching systemic circulation is known as presystemic metabolism and occurs in both the gut mucosa and liver. The CYP450 enzyme system includes many isoenzymes involved in drug metabolism and is a major component of presystemic metabolism. It is estimated that about 60% of drugs currently available are metabolized by CYP450 isoenzymes, specifically CYP3A4.48 Drug interactions with grapefruit juice are the classic example of CYP450-mediated DNIs. Grapefruit juice inhibits the isoenzyme CYP3A4, thereby increasing serum levels of drugs normally metabolized by this isoenzyme.49 Considerable research has been devoted to understanding effects of the CYP450 system on drug metabolism and DNIs because these enzymes can dramatically alter bioavailability, and, in some cases, this can result in life-threatening DNIs. In addition, drug transporters have increasingly been recognized for their importance in drug metabolism and disposition.

The best-known transporter is P-glycoprotein, which serves as an efflux mechanism to pump xenobiotics (drugs and other chemicals or substances not normally present in the body), out of cells and prevent entry to the compartment that the cells protect. P-glycoprotein is located on the luminal surface of cells lining the small bowel and prevents systemic absorption of certain drugs. The bile canalicular membrane in the liver and cells in the renal proximal tubule also contain P-glycoprotein. Organic anion-transporting polypeptides serve as uptake transporters in the intestine, opposing the efflux effect of P-

glycoprotein.50 The net effect of inhibition, induction, and interaction between CYP450 enzymes, uptake transporters, and efflux transporters can be complex and requires continued research to understand. To date, there are no data to suggest that any component of EN formulations significantly inhibits or induces these enzymes and transporters.

Therapeutic Index

Drugs with a narrow therapeutic index require serum drug concentrations within a small range to avoid therapeutic failure or toxicity. Any alteration in absorption of these drugs can be problematic; thus, routine monitoring of serum drug levels or surrogate markers (eg, prothrombin time [PT]/international normalized ratio [INR] for warfarin) is generally conducted. Monitoring of narrow therapeutic index drugs is also advised with initiation and changes in an EN regimen.

Formula-Related Factors

Macronutrients

The association of complex proteins and fiber with physical DNIs was discussed previously in this chapter. Protein may also influence drug metabolism through effects on enzymes of the mixed-function oxidase system in the liver.44,51 Activity of the mixed-function oxidase system seems to be stimulated with high protein intake and with riboflavin, niacin, and large ascorbic acid doses, thereby increasing clearance of drugs metabolized by these enzymes. Protein intake may also influence blood flow, with low intake reducing flow to the kidney and lowering renal elimination of some drugs. However, most data on protein effects come from animal studies, and more research is required before any definitive statement or recommendations can be made regarding the effect of protein on DNIs in the clinical setting. Nutrients that alter gastric emptying and GI motility can alter the rate and extent of drug absorption, thereby contributing to DNIs. The effects of macronutrients on gastric emptying and GI motility are included in Table 18-2.

Micronutrients

Micronutrients in EN formulations have the potential to cause DNIs. Divalent and trivalent minerals (calcium, magnesium, and iron) are known to form complexes with certain drugs, such as tetracycline and ciprofloxacin, which results in poor absorption of the drugs. Degradation products from micronutrients have also been reported to cause physical interactions. For example, oxalate from ascorbic acid degradation has been reported to interact with calcium in PN formulations, forming an insoluble precipitate.52

The vitamin K content of EN formulations is a concern because of potential DNIs with warfarin. Formation of vitamin K–dependent blood clotting factors in the liver (Factors II, VII, IX, X) is inhibited by warfarin, resulting in an anticoagulation effect. Significant vitamin K intake from an EN formulation can antagonize this anticoagulant effect and result in treatment failure. Most EN formulations marketed today contain modest amounts of vitamin K and provide daily vitamin K intake similar to average dietary intake from foods (90 to 120 mcg/d in adults).53 Consistent intake of an EN formulation containing less

than 100 mcg vitamin K per 1000 kcal is not expected to cause warfarin resistance. Nonetheless, warfarin resistance has been reported in EN patients with relatively low vitamin K intake and seems to respond to changes in the warfarin administration schedule.54,55 This evidence suggests a mechanism other than vitamin K antagonism of warfarin activity, because the duration of warfarin antagonism is several days, not hours. This interaction is discussed further in the "Specific Drug–Enteral Nutrition Interactions" section later in this chapter.

Disease-Related Factors

The alterations in body composition associated with malnutrition may affect the risk of pharmacokinetic DNIs. Pharmacokinetic parameters can be affected by decreased serum concentrations of visceral proteins, especially albumin, which binds many drugs (eg, phenytoin, valproic acid, warfarin). Edema, increased body water, and decreased lean muscle mass may also affect pharmacokinetic parameters. Other disease-related factors include alterations in organ function and perfusion, as well as effects on GI motility. A full discussion of disease-related factors is beyond the scope of this chapter.

Specific Drug–Enteral Nutrition Interactions

There are many potential DNIs involving EN therapy; however, a few drugs are particularly troublesome and have generated more discussion than most. Four of these drugs are discussed in this section.

Phenytoin

Phenytoin is a notorious drug for interaction with EN therapy. Many studies and case reports have been published, but few are prospective, randomized, controlled trials. There are multiple theories regarding the interaction and many proposed solutions. Four prospective, randomized, controlled trials of phenytoin and EN in healthy volunteers have been reviewed.56,57 Only 1 study investigated the effect of the EN formulation delivered through a feeding tube while the others investigated the effect of oral EN on serum phenytoin concentrations. None of these studies found an interaction between phenytoin and EN formulations. Countering these results were 25 reports and studies with less rigorous designs (no randomization or placebo control) that supported an interaction in patients.56 Theories regarding the mechanism of interaction focus on issues related to pH58–61 and phenytoin binding, either to tubing40 or to an EN component.62 Dosage form issues (eg, suspension, chewable tablets, capsule, IV formulation), chemical form (phenytoin acid vs phenytoin sodium), and solubility are encompassed in the discussion of pH.

Of the various methods proposed to manage the phenytoin-EN interaction, none is completely reliable, and monitoring of serum phenytoin concentrations is highly recommended. Holding administration of the EN formulation for at least 1 hour, and possibly 2 hours, before and after phenytoin administration seems to produce the most consistent results.62,63 However, some practitioners choose to continue adjusting the phenytoin dose to achieve therapeutic serum concentrations because adjustment of the EN infusion schedule can create problems related to inadequate EN delivery. Relatively high phenytoin doses are typically required to achieve therapeutic levels with this approach, and close monitoring of serum concentrations is required when the EN is discontinued. Dilution of phenytoin suspension is also

recommended when the suspension is administered through a feeding tube.40 Regardless of the method used, consistency of administration is important to control one of the variables influencing the phenytoin concentration.

Carbamazepine

Carbamazepine is a relatively insoluble drug and is acid stable; thus, slow gastric emptying improves bioavailability. Limited data suggest that EN therapy reduces bioavailability, possibly by altering solubility. Relative bioavailability of 90% was reported in a randomized, crossover study comparing administration of carbamazepine suspension via NG tube with continuous EN and oral intake after an overnight fast in 7 healthy males.64 Serum carbamazepine concentrations with tube feeding were significantly lower at 8 hours, and the lower maximum concentration approached statistical significance, although the small study size limited the ability to show significance. In vitro recovery of carbamazepine also seemed to be reduced after it was mixed with an intact protein EN formulation (58% recovery) compared with recovery after mixture with a simulated gastric juice (79% recovery).65 Recovery was similar for the EN formulation and simulated intestinal juice (59% recovery). These data suggest that postpyloric administration of carbamazepine may result in poor bioavailability.

Binding of carbamazepine to a component of EN formulations has not been demonstrated; thus, it is unclear if holding administration of the EN formulation for 2 hours before and after the drug dose, as has been recommended, is the best method of mitigating this potential interaction.66,67 Adequate dilution of the suspension (or slurry from a crushed tablet) prior to administration and adequate flushing after the dose should be the first choice of methods to mitigate the EN-carbamazepine interaction because this approach does not affect delivery of adequate nutrition. When adequate dilution and flushing fail in patients with postpyloric administration, it would be reasonable to hold feedings before and after drug administration in this population. Gastric administration may be cautiously monitored without routinely holding the EN formulation, unless there is evidence of an interaction. Carbamazepine suspension should be diluted at least 1:1, preferably 3:1, with water if administered via a feeding tube because drug loss in the feeding tube seems to be reduced with dilution.41

Fluoroquinolones

Bioavailability of some fluoroquinolone antibiotics seems to be reduced by EN formulations. Studies in healthy volunteers have reported a 25% to 28% decrease in ciprofloxacin bioavailability when it is administered with an EN formulation, and decreases of 27% to 67% have been reported in hospitalized patients.68–70 Reduced bioavailability is also reported with repeated doses of ciprofloxacin via NG tube in critically ill patients receiving continuous infusion of an EN formulation.71,72 Jejunal feeding has the greatest potential of reducing ciprofloxacin bioavailability because significant absorption normally occurs in the duodenum; however, the limited data available do not provide clear evidence of clinically significant differences in absorption based on the site of administration.47,68,73–75 It is unclear whether reduced bioavailability with gastric or jejunal feeding is clinically significant because serum drug concentrations above the minimum inhibitory concentration have been reported for many pathogenic microorganisms with either administration route.73,76

Complex formation of ciprofloxacin with divalent cations in the EN formulation was initially thought to be responsible for reduced bioavailability of ciprofloxacin with EN therapy. Fluoroquinolones are known to bind with divalent cations, and manufacturers' instructions advise separating drug administration from intake of foods, dietary supplements, or other drugs containing calcium, magnesium (eg, antacids), or iron. However, an in vitro study failed to find a correlation between cation content of the EN formulation and loss of different fluoroquinolones mixed directly into the formulation.77 Ciprofloxacin loss was greatest (82.5%), followed by levofloxacin (61%) and ofloxacin (46%). The amount of loss seemed to increase with the degree of hydrophilicity of the individual drug. Limited in vivo data support this finding. Better bioavailability of ofloxacin (90%) compared with ciprofloxacin (72%) has been reported in healthy volunteers receiving the antibiotics with an EN formulation.76 Currently, many facilities follow a policy of holding administration of the EN formulation for at least 1 hour before a fluoroquinolone dose and 2 hours after the dose, as recommended previously.67 This approach seems to minimize effects of the DNI on ciprofloxacin and norfloxacin; however, data supporting the holding of EN are very limited, especially in patients actually receiving tube feedings. Evidence from studies of 16 critically ill patients and 12 healthy volunteers does not support holding gatifloxacin or moxifloxacin, respectively.78,79 The studies were small; however, when the drug was crushed and administered via a feeding tube with or without an EN formula, there were no clinically relevant effects on serum concentrations.

For each of the fluoroquinolones, well-designed studies of adequate size comparing proper drug dilution and adequate flush volumes with holding of EN therapy are necessary to confirm the validity of holding or not holding feedings. Nonetheless, in the absence of such a study, holding feedings remains a potential method of mitigating EN interactions with ciprofloxacin or norfloxacin; however, holding feedings with other fluoroquinolones should not be done routinely.

Warfarin

One proposed mechanism for warfarin resistance with low vitamin K intake is binding of warfarin to a component of the EN formulation, most likely protein.80 Warfarin resistance due to protein binding has not been adequately studied to confirm whether protein binding is an in vivo mechanism of DNI. The study used to promote protein binding as a mechanism of interaction was conducted in vitro at a pH outside the physiological range.80 Use of a free amino acid (elemental) EN formulation is expected to prevent the interaction if protein binding actually causes the DNI; however, this premise has not been tested. Given the higher cost of elemental formulations, the potential for the high osmolality to cause GI intolerance, and the greater difficulty in justifying use of these formulas, practitioners may elect to manage the interaction by other methods (ie, increase the warfarin dose or change to an alternative anticoagulant therapy). Many questions remain relative to the theory of warfarin-EN protein binding, including the reversibility of such binding during or after absorption, and potential for release of warfarin from protein during protein metabolism. Binding of warfarin to the protein component of EN remains a theory with limited data to support this mechanism of interaction.

A recent in vitro study presents data supporting another potential mechanism for the warfarin-EN interaction.39 Loss of warfarin was demonstrated when drug was infused through a polyurethane

feeding tube under defined laboratory conditions and when weighed amounts of sliced feeding tube were added to beakers containing 3 different concentrations of warfarin. Binding of warfarin to the polyurethane feeding tube material did not seem to be a saturable process in this study. The authors concluded that holding EN around administration of warfarin through a feeding tube should not affect bioavailability of warfarin, and they did not recommend holding feedings to mitigate the warfarin-EN interaction. This study only evaluated warfarin binding to polyurethane feeding tube material under simulated gastric conditions. Further studies are needed to determine whether other feeding tube materials or small bowel conditions would produce the same effects.

The mechanism of interaction between warfarin and EN has not been clearly delineated, and no definitive recommendation can be provided for mitigating warfarin resistance associated with relatively low vitamin K intake. Nonetheless, interactions involving warfarin can be life-threatening. Response to warfarin therapy must be closely monitored when EN therapy is started, stopped, or altered (see Practice Scenario 18-4).80,81

Practice Scenario 18-4

Question: Should tube feeding be held when a therapeutic international normalized ratio (INR) is not achieved with the home dose of warfarin after tube feeding starts?

Scenario: A 68-year-old man was admitted to the hospital with suspected sepsis and required mechanical ventilation. His past medical history included hypertension, recurrent deep vein thrombosis, and osteoarthritis with left knee replacement 2 months ago. Medications before admission included lisinopril, 20 mg tablet daily; acetaminophen/hydrocodone, 500/5 mg, 1 tablet every 6 hours and up to 2 additional tablets daily as needed for pain; paroxetine, 20 mg tablet daily; and warfarin, 5 mg tablet daily.

Broad-spectrum antibiotic coverage was initiated immediately after admission. Antibiotics were changed to high-dose intravenous (IV) nafcillin on hospital Day 3, based on blood culture results. Tube feeding was started on hospital Day 5 through a small-bore nasogastric (NG) tube and reached goal rate within 48 hours. Mechanical ventilation was stopped on Day 10, and the patient was transferred to a medical floor. Tube feeding was continued due to possible esophageal damage, as was IV nafcillin and a heparin infusion. Lisinopril and warfarin were initiated through the feeding tube at home dosages. Morphine liquid was ordered via NG tube, with 1 mg IV morphine allowed every 4 hours, as needed for pain. After 2 weeks of gradually increasing the daily warfarin dose from 5 mg (home dose) to 12 mg, the INR remained subtherapeutic at 1.4.

Answer: The pharmacist recommends restarting paroxetine and changing to acetaminophen/hydrocodone (home medication) for pain management, rather than holding tube feedings around warfarin administration.

Rationale: Assessing drug interactions with warfarin before altering the tube feeding regimen is important. Paroxetine increases INR. The patient received paroxetine at home and will likely be discharged on this medication. Acetaminophen interrupts the vitamin K cycle through effects of the N-acetyl (p)-benzoquinone imine metabolite on vitamin K–dependent carboxylase, an enzyme in the vitamin K cycle.81 Standard doses of acetaminophen increase INR significantly in some patients. Nafcillin decreases INR and could contribute to warfarin resistance. Keeping the warfarin concentration relatively high in the slurry prepared for administration through the feeding tube and administering it rapidly would be an appropriate administration technique. Holding tube feedings for 1 to 2 hours on each side of the warfarin dose, and adjusting the feeding rate to provide full daily volume, may be reasonable if the INR does not increase within a few days of restarting acetaminophen/hydrocodone and paroxetine at the home doses; however, data supporting this action are limited. Binding of warfarin with a component of the EN formulation has been proposed to explain warfarin resistance with modest vitamin K intake.80 Use of a free amino acid (elemental) EN formulation should prevent the interaction if protein binding actually causes the drug-nutrient interaction; however, no studies support this approach. A low-molecular-weight heparin or one of the new oral anticoagulants could also be used for anticoagulation, but the risks and benefits must be carefully considered for each patient.

Potential methods of mitigating the warfarin-EN interaction include rapidly administering a concentrated form of the drug to minimize contact with the feeding tube, separating warfarin administration from EN administration, increasing the warfarin dose until a therapeutic PT/INR is achieved, or changing to an alternative anticoagulation therapy that does not interact with EN therapy. Minimizing contact with the feeding tube has a low potential to cause unintended consequences and is a reasonable first approach. If this option fails to resolve warfarin resistance, separating the warfarin dose from EN by holding EN for at least 1 hour before and after the warfarin dose can be tried; however, if the interaction is actually with the feeding tube material, avoiding contact between the drug and EN formulation is unlikely to improve warfarin response. If the warfarin resistance does improve, any increases in PT/INR should be evident within a few days. Increasing the warfarin dose periodically until a therapeutic INR is achieved can result in high drug doses that may place the patient at risk for bleeding should EN administration be reduced for any reason. In addition to routine monitoring, the PT/INR should be re-evaluated with any change in the EN regimen.

Summary

DNIs are an important consideration with both PN and EN therapy. The consequences of such interactions range from relatively benign to life-threatening. Pharmacists typically have the most specific training regarding drug interactions and should be involved in decisions related to DNIs; however, all nutrition support clinicians should be involved in establishing safe practices that minimize the risk of various types of DNIs occurring and limit adverse effects associated with such interactions. Few DNIs that occur with nutrition support, especially EN, are well studied or well understood and further research is needed to better mitigate such interactions.