Pharmaceutical Issues in Patients Receiving Enteral Nutrition

JOSEPH I. BOULLATA, PHARMD, RPH, BCNSP
Associate Professor, Pharmacology & Therapeutics
University of Pennsylvania, School of Nursing
Pharmacy Specialist, Clinical Nutrition Support Services
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania

A
n important area of clinical practice that traditionally has received less attention among many pharmacists is nutritional pharmacotherapy, including the use of enteral nutrition (EN).

Over the past few years, drug administration with EN has been a focus of a number of pharmacy publications and was included in a national patient safety campaign highlighting pharmacists. This increased emphasis in this area coincided with the publication of the first national practice recommendations for EN. These comprehensive guidelines prepared by the American Society for Parenteral and Enteral Nutrition (ASPEN) are intended for an interdisciplinary audience and include sections on ordering, labeling, formula safety, enteral access, administration, monitoring, and medication administration. This document has a number of implications for pharmacists that serve as the focus of this review.

The EN System

The EN process can be considered parallel to the drug use process, starting from a decision to use the specialized therapeutic intervention and the ordering process to preparation, labeling/dispensing, administration, and monitoring. That is, EN is not just a food substitute but an important therapeutic intervention for all health care providers to take into account. The overlapping route for drug administration in patients requiring EN is particularly significant to pharmacists, who can bring expertise in pharmaceutics, physiology, and pharmacotherapy.

ENTERAL NUTRITION

EN products are specially formulated nutrient products intended for administration into the gastrointestinal (GI) tract through an enteral access device, also commonly referred to as an enteral feeding tube (EFT). The majority of the EN products used in adults are sterile liquids, packaged either in individual cans or, more commonly, in ready-to-hang containers. More specifically, these are pharmaceutically dispersed systems (colloidal dispersions). In rare cases, a patient may need a specialized powdered EN formula that requires reconstitution with sterile water in the pharmacy using aseptic technique and applying a short beyond-use date. The dozens of EN products available vary in their ingredients, nutrient content, nutrient source, and osmolality. These products are regulated by the FDA as medical foods, ie, they are formulated to be administered enterally under the supervision of a physician based on a medical evaluation. Medical foods are exempt from food labeling, dietary supplement labeling, and drug labeling requirements. Many patients in hospitals and other health care institutions, as well as patients at home, receive EN for a variety of indications to meet some or all of their metabolic needs for energy, protein, and micronutrients. The therapy may be administered continuously or intermittently. Continuous infusion into the stomach or small bowel requires a feeding pump, whereas pump-assisted feedings are not always necessary for intermittent administration into the stomach.

ENTERAL ACCESS

Patients unable to take food or medication by mouth will have an EFT in place. The tubes can vary in material, diameter, length, and size of opening(s) at the distal end. The type of tube placed will depend on the patient and the expected duration of forced feeding. Tubes placed through the nose (naso-), or less frequently the mouth (oro-), are used for short-term feeding, whereas percutaneous (-ostomy) tubes are for long-term needs. The
confirmed location of the distal tip in the stomach (gastric) or small bowel (duodenum, jejunum) provides a more valuable description for the pharmacist than the tube’s brand name or manufacturer. After the position of the EFT within the GI tract is confirmed, it may be used for feeding and/or medication administration.

Intragastric administration (via nasogastric or gastrostomy tube) more closely resembles oral administration, for which the drug product was approved by the FDA. The GI milieu at the distal end of the feeding tube needs to accommodate drug-dissolution, permeability, and absorption. It is important to use the ideal site to maximize bioavailability. It is also critical to dilute high-osmolality liquid drug products prior to administration to prevent GI complaints and malabsorption, especially if the drug is introduced directly into the small bowel.

Aside from the position of the tube’s distal end within the GI tract, the size of the EFT is also important for drug administration. An EFT with a diameter of 10 French or less (1 Fr = 0.33 mm) is more likely to become obstructed and is best avoided for drug administration. Even at adequate sizes, if these devices are not routinely flushed with water, they are significantly more likely to become clogged with EN formula and/or drug residue. Inappropriate techniques of drug preparation and administration also contribute to EFT obstruction. Prevention remains the key because, short of replacing the tube, effective methods of resolving clogs have not been well studied.

**Drug Preparation and Administration**

Preparation and administration of a drug via EFT most often are carried out by nurses or caregivers, although in some institutions a pharmacist may take the responsibility for preparing a dosage form for EFT administration, within norms of compatibility and stability. Although most caregivers are confident that they prepare and administer drugs appropriately, surveys suggest that errors such as not flushing tubes before and between administering medications, administering multiple medications mixed together, crushing of modified-release tablets, not diluting medications before administering, and not adhering to institutional guidelines occur fairly commonly. A prospective observational study suggests that such medication errors may occur with about 60% of doses, highlighting the need for pharmacists to be vigilant.

Consequences of inappropriate drug preparation and administration include reduced efficacy, toxicity, and clogged tubes. Best practices for drug administration through an EFT are listed in Table 1. In the absence of drug-specific data, the rationale for some recommendations is based on pharmaceutical principles. Responsibility should be shared by prescribers, pharmacists, and nurses; inappropriate prescriber orders put the nurse in a difficult position if the pharmacist does not clarify them.

**Preparation**

Very few data support the admixture of a drug to an EN formula or to other drugs prior to administration. Modified-release dosage forms (eg, delayed-, sustained-release) also should be avoided for this route of administration. A listing of the many oral dosage forms that should not be crushed or opened is readily available through the Institute for Safe Medication Practices. These dosage forms are implicated not only in interactions and excessive bolus drug doses but also in exposing caregivers (including via inhalation) to cytotoxic and teratogenic products.

Appropriate tablets can be pulverized to a fine powder (triturated) and diluted in water, as can the solid contents of immediate-release capsules. Medication that is in a powdered form—either from pulverized tablets, capsule contents, or dry powder products intended for reconstitution—needs to be diluted to ensure delivery through the EFT. Dilution may be necessary for liquid medication (ie, solutions, suspensions) to reduce viscosity or osmolality. Reducing viscosity, the resistance to flow, allows the full drug dose to reach the distal end of the EFT. Not diluting a suspension that is being administered through an EFT could result in a significant decrease in drug delivery and bioavailability.

Consistent delivery through an EFT requires adequate drug dilution and flushing. The simplest fluid for diluting powdered or liquid medication is water. The U.S. Pharmacopeia requires that purified water be used for preparation of drug dosage forms. Chemical contaminants in drinking water (tap, bottle, well) raise the risk for drug interactions when it is used to dilute medication prepared for administration by tube; this may, in turn, alter drug bioavailability. Although the real potential for acute drug-drug and drug–chemical interactions when contaminated waters are combined with medication has not been evaluated, the practice recommendations attempted to err on the side of safety and recommend purified water (eg, sterile water for irrigation, USP). Such use of the precautionary principle (ie, action based on scientifically plausible risk) serves patients well until more data are generated. More data are needed regarding appropriateness of medication dilution and the potential for drug interactions.

Dilution with 30 to 60 mL of water appears adequate for powdered medication. The volume required to dilute liquid medication depends on the degree of viscosity and/or osmolality. Diluting viscous suspensions in a volume of at least 11 seems adequate for some drugs. High-osmolality medication can result in localized adverse effects at the mucosa or create an osmotic effect throughout portions of the bowel. The higher the osmolality, the greater the volume of diluent required to lower the osmolality. For example, a 500-mg dose of acetaminophen using a liquid product with an osmolality of 6,000 mOsm/kg would require about 100 mL of water dilution to reduce the osmolality toward physiologic values. The case could be made that crushing an acetaminophen tablet to a fine powder and dispersing in a smaller volume of water would be more practical than using a liquid formulation.

**Administration**

Administration of medications through EFTs remains a time-consuming and complex issue in practice that can benefit from a pharmacist’s input (Table 1). Drugs should
be administered after first stopping EN (if administered continuously) and flushing the tube. If more than one drug is due at the same time, each medication should be administered separately with the tube flushed between each to ensure removal of any residual drug or excipient. A volume of at least 15 mL is suggested, but the patient’s volume status and any restrictions should be considered. The tube should be flushed again after drug administration is complete, and the EN should be restarted. The time lapse between stopping the feeding, administering the drug, and restarting the feeding will depend on any potential for drug-nutrient interaction in the GI lumen.\textsuperscript{2,6}

Although a number of surveys have focused on nurses’ inappropriate technique in preparing and administering medication through EFTs, prescribers’ and pharmacists’ responsibilities also need to be considered. According to one study, patients with “NPO” (nothing by mouth) orders who are unable to take medication by mouth are still prescribed drugs orally more than 80% of the time; this is often not corrected by the pharmacist reviewing the orders and, therefore, places the nurse in the precarious position of committing a wrong route medication error.\textsuperscript{29} In this same study of drug administration in enterally fed hospitalized patients, less than 20% of drugs administered directly into the small bowel were considered appropriate.\textsuperscript{29} Therapeutic alternatives or a different route of administration may need to be considered.

Order Review

**ENTERAL NUTRITION**

Even if EN is not dispensed by the pharmacy, putting EN orders (and the EFT description) on the patient’s drug profile is vital and analogous to including parenteral nutrition (PN) orders (and IV access). A quick review of the EN order should note that it is complete. This entails all the essential elements—patient identifiers (eg, name, medical record number), EN product/formula type (eg, either generic or brand name), route of administration (eg, gastric) and access device (eg, gastrostomy), administration method (eg, continuous), and volume or rate (eg, 30 mL/h x 20 h).\textsuperscript{6,30} These minimum data should be reflected on the generated labels affixed to the product.\textsuperscript{6,30}

Although the pharmacy department is less often responsible for procuring and dispensing these products, the complete patient-specific label should be provided by the responsible department. A quick check of product dosing should note that the patient will be receiving 20 to 30 kcal/kg, 1 to 1.5 g/kg protein, and 30 to 40 mL water daily, varying with his or her clinical status; this also may vary if the patient is being transitioned from PN or to an oral diet.\textsuperscript{30} The volume of water delivered is less than the final EN volume, considering that the water content varies with the formula from approximately 70% to 85%. Any additional volume requirement will need to be met by enteral water flushes or IV fluids. A review of the EN orders with enteral drug orders is analogous to the pharmacist’s responsibility to review PN orders for both clinical and pharmaceutical appropriateness.\textsuperscript{21}

<table>
<thead>
<tr>
<th>Table 1. Strategies for Medication Preparation and Administration</th>
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<tbody>
<tr>
<td>• Do not add medication to the EN formula</td>
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<td>• Do not mix medications together</td>
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<tr>
<td>• Use only immediate-release drug dosage forms (solid or liquid)</td>
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<tr>
<td>• Dilute each medication with purified water before administration</td>
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<tr>
<td>• Administer each medication separately through an appropriate access site</td>
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<tr>
<td>• Use clean oral/enteral syringes to measure, prepare, and administer medication</td>
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<tr>
<td>• Flush the feeding tube with purified water before and after each medication</td>
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<tr>
<td>• Flush the tube with purified water (at least 15 mL) and restart the feeding in a timely manner</td>
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<tr>
<td>• Consult with a more educated pharmacist as needed</td>
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**MEDICATION**

Pharmacists play a critical role in supporting prescribers and nurses in addressing issues with drug administration in the patient with an EFT.\textsuperscript{32} Pharmacists evaluating enteral drug orders in a patient receiving EN should go through a systematic evaluation of the drug orders (Table 2). They need to be aware of the patient’s GI status, the EN regimen, and the location of the EFT to identify inappropriate administration routes, potential interactions, and other administration route issues. A drug ordered by the prescriber to be administered “PO” (orally) in the patient with NPO orders is a conflict that needs to be resolved by the pharmacist. If the drug is intended for administration through the EFT, the order should be changed so as not to constitute a medication error when the nurse administers it by the “wrong route.”

An important consideration for pharmacists reviewing such orders is deciding whether the drug and its formulation are appropriate for EFT administration. Given the risks for physicochemical incompatibility and instability, drugs should not be admixed together. Potential drug-nutrient interactions that result from a physical, chemical, physiologic, or pathophysiologic relationship between a drug and EN also need to be considered.\textsuperscript{6} An interaction is considered to be clinically significant if it influences therapeutic response (or compromises nutrition status) with clinical consequences related to altered drug (or nutrient) disposition. For example, the bioavailability of some drugs may benefit from administration in close proximity to EN, whereas that of other drugs may be significantly reduced. In the latter case, administration of drug should be temporally separated from administration of EN. These factors should be considered with other factors for drug administration via EFT (eg, flushing protocol, appropriate drug dilution, location of EFT distal tip).
Table 2. Drug Order Evaluation In Enterally Fed Patients

<table>
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<tr>
<th>Identify the patient’s current enteral status</th>
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<tr>
<td>• “PO” or “NPO except medications” or “NPO”?</td>
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<tr>
<td>• What is the patient’s current EFT site?</td>
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<tr>
<td>• What is the patient’s current EN order?</td>
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<table>
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<tr>
<th>Review oral/enteral drug orders</th>
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<tbody>
<tr>
<td>• Ordered PO or via an EFT?</td>
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<tr>
<td>• Does it match the patient’s current PO status?</td>
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<tr>
<td>• Is the drug dosage form appropriate for EFT administration?</td>
</tr>
<tr>
<td>• Are the drug and the formulation appropriate based on the distal end of the EFT?</td>
</tr>
<tr>
<td>• Is EN administered continuously or intermittently?</td>
</tr>
<tr>
<td>• Should the EN be held for a period of time around any of the ordered drugs? So ordered?</td>
</tr>
<tr>
<td>• Resolve any inappropriate orders with prescriber and nurse</td>
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EFT, enteral feeding tube; NPO, nothing by mouth; PO, by mouth

Conclusion
The pharmacist is in an important position to ensure optimal use of drugs, including those administered to patients receiving EN. The ASPEN practice recommendations can guide drug preparation and administration through EFTs and the development and implementation of institution-specific EN protocols. Clinical observations and research findings related to inappropriate drug preparation and administration, especially if they refute or substantiate current recommendations, should be documented and shared to educate others. Nutritional pharmacotherapy is another area in which pharmacists can advance patient care and clinical practice.

References