دانشگاه علوم پزشکی کرمانشاه

انجمن متخصصین داروسازی بالینی ایران
Iranian Society of Clinical Pharmacists

Nutrition-drug interactions

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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

Physical interactions

- If multiple enteral accesses are available, administer drugs via the largest tube.
- In adults, flush the feeding tube with 15 mL of water before and after each drug while taking volume status into account.
- In pediatric patients, flush with at least 5 mL when fluid is not restricted.
- Administer each drug separately.
- Do not mix drugs directly with enteral formulas to reduce the risk of microbial contamination and to avoid drug-nutrient incompatibilities

- Flush feeding tube every 4 hours with 15 to 30 mL of water to maintain tube patency.
- Syringes intended for oral or enteral use should be used to prevent inadvertent parenteral administration.
- Choose large catheter tip syringes that cannot fit into luer ports or IV systems, and have a minimal dead-space volume.
- Avoid administering a hypertonic medication directly into the small bowel (eg, via a jejunostomy tube) as adverse effects including bloating, nausea, cramping, and diarrhea may occur


10
20
30
40
50
ml
60

Dosage Form Considerations

- Liquid dosage forms are usually preferred, with elixirs and suspensions preferable to syrups.
- If solid dosage forms are required, determine that the tablet can be crushed or the capsule opened (refer to the Drug Consult entitled "Do Not Crush List").
- Dosage adjustments may be needed, especially if converting from an extended-release to an immediate-release formulation (ie, many liquid products are immediate-release)

Capsules

- The contents of most immediate-release capsules may be mixed to a slurry in 10 to 30 mL water and administered through a large-bore feeding tube
- It is important to mix with water just prior to administration to avoid a loss of drug activity.
- Do not crush specialty formulations including enteric-coated, extended-release, controlled release, sustained-release, and microencapsulated drug formulations.
- EC, CD, CR, ER, LA, SA, SR, TD, TR, XL, XR

- Some microencapsulated products may be opened and the beads or pellets poured down the large-bore enteral feeding tube, provided they are not crushed and the pellets are small enough to pass through the tube.

- To reduce the risk of the pellets sticking to the tube, acidic juice may be used as a vehicle for the pellets.

- Water should be used to clear the tube before and after administration

- Capsules, Liquid Gel Do not pierce or squeeze liquid gel capsules as this may result in an insufficient or inconsistent amount of delivered drug.

- Consider cutting the capsule in half and submersing it to allow the liquid to dissolve or aspirate all the contents of the capsule and mix with 10 to 30 mL water

Tablets

- Standard tablets may be crushed or pulverized to form a fine powder to dissolve or suspend in water.
- To avoid clogging the feeding tube, the powder should be mixed in at least 30 to 60 mL of water to avoid forming thick pastes.
- Other recommendations include mixing pulverized tablets in 15 to 30 mL of water.
- It is important to mix with water just prior to administration to avoid a loss of drug activity .
- Never crush teratogenic, carcinogenic, or cytotoxic drugs such as antineoplastics, hormones, and prostaglandin analogs, which may expose the healthcare provider to aerosolized particles

Intravenous Solutions

- IV solutions are not suited to withstand gastric acidity and enzyme activity within the gastrointestinal tract and may result in substantial loss of drug.
- Intravenous electrolytes preparations are an exception and may be administered via enteral feeding tubes if the osmolality is not too high.
- Diluting hyperosmolar solutions with water may be required

Liquids

- Liquids are the preferred formulation for administration of drugs via enteral tubes.
- Liquid medications should be drawn up in syringes intended for oral or enteral use to prevent inadvertent parenteral administration.
- Choose large catheter tip syringes that cannot fit into luer ports or IV systems, and have a minimal dead-space volume

- Thick syrups and suspensions or other viscous liquids require dilution to avoid clogging the feeding tube.
- Liquids which are too viscous (eg, mineral oil) may not be appropriate for enteral administration
- syrups should generally be avoided, particularly mixed with enteral formulas due to acidic pH (ie, less than 4) resulting in potential to occlude the feeding tube.
- Further dilution of the syrup with water does not prevent the physical incompatibilities.
- Consider alternative liquid formulations when possible, but if use of a syrup is required, flush the tube with 30 mL water or more both before and after administration of the syrup

- Sugar-free liquid formulations may contain large amounts of sorbitol, which may cause diarrhea, gas, cramping, and bloating.

- The effects of sorbitol are cumulative, based on the total daily dose, so patients who receive multiple liquid sorbitol-containing formulations are more likely to experience adverse effects.

- The laxative dose for sorbitol is approximately 20 g; however, some patients may be sensitive to lower doses.

- Additionally mannitol, lactose, saccharin, and sucrose included in liquid formulations may cause diarrhea

- Hyperosmolar liquids may result in diarrhea, cramping, abdominal distension, and vomiting.

- The osmolalities of commercial liquids are well over 1000 mOsm/kg compared with the osmolality of gastrointestinal (GI) secretions which range from 100 to 400 mOsm/kg.

- To reduce the likelihood of GI adverse events, dilute hyperosmolar liquids. This is especially important in patients with enteral tubes into the small bowel

Compatibility of Liquid Oral Medications

- Liquid medications are frequently used in patients requiring enteral feeding, but may cause adverse effects and are not always compatible with the enteral nutrition (EN) formulas.
- Immediate release formulations should be used and the dosage form should be evaluated to determine if there are properties present that might obstruct the tube.
- Medications with osmolality greater than about 700 mOsm for gastric administration or greater than 300 mOsm for jejunal administration may cause cramping, diarrhea and other gastrointestinal adverse events (the osmolar range of the gastrointestinal tract is normally 127 to 357 mOsm/kg).
- To minimize adverse effects from high osmolality, medications should be diluted per the formula below

- To adjust the osmolarity of a liquid medication, dilute with purified water just prior to administration using the following formula to calculate the volume of water to be added:

(mOsm of medication / desired mOsm) x volume of dose = final diluted volume

- Acidic liquids are likely to react with enteral formulas containing intact proteins, often but not always resulting in feeding tube occlusion

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Table 2: Osmolality and Tube Clogging Potential of Selected Liquid Medications				
Medication	Strength	Osmolality (mOsm/kg)	Potential to Clog Large-bore Feeding Tubes (approximately 20 French)	Potential to Clog Fine-bore Feeding Tubes (approximately 8 French)
Acetaminophen solution	325 mg/10.15 mL	4035*	+	+
Acetaminophen suspension	160 mg/5 mL	6425*	+	+
Acyclovir oral suspension	200 mg/5 mL	4205*	-	+
Aluminum hydroxide gel	320 mg/5 mL	1501	+	+
Al(OH)3, Mg(OH)2, simethicone	200 mg, 200 mg, 20 mg/5 mL	990	-	+

Diphenhydramine hydrochloride	12.5 mg/5 mL	3975*	-	-
Guaifenesin solution	200 mg/10 mL	278	+	+
Lactulose solution	10 g/15 mL	4180*	-	-

Levofloxacin (Levaquin) solution	25 mg/mL	2115*	+	+
Loperamide	0.2 mg/mL	6775*	+	+
Magnesium hydroxide suspension	2400 mg/30 mL	1258	-	+
Megestrol acetate	40 mg/mL	3665*	-	+
Metoclopramide solution (PAI)	5 mg/5 mL	5180*	-	+
Mineral oil	n/a	^	-	+

Phenytoin suspension	125 mg/5 mL	3095*	-	+
Posaconazole (Noxafil) suspension	200 mg/5 mL	2050*	-	-
Potassium chloride solution	10% SF (sugar free)	4225*	-	-
Potassium iodide (SSKI) solution	1 g/mL	11,380**	+	+

Ranitidine solution	15 mg/mL	637	-	-
Senna concentrate	8.8 mg/5 mL	3390*	-	-
Senna syrup	8.8 mg/5 mL	3920*	-	-

Sulfamethoxazole-trimethoprim	200 mg/40 mg per 5 mL	5560**	-	+
Valproic Acid (Depakene) solution	250 mg/5 mL	5010**	-	-

* Medications that exceeded the osmometer capacity of 2000 mOsm/kg were diluted 1:5 with sterile water.
** If a medication diluted 1:5 with sterile water still exceeded the osmometer capacity, a dilution of 1:10 with sterile water was made.
^ Capacity of osmometer exceeded (greater than 2000 mOsm/kg) and product immiscible with water, preventing further dilution.

- Large amounts of sorbitol (ie, 20 g/day or more) can lead to an osmotic laxative effect, but even doses in the range of 10 g/day can contribute to gastrointestinal disturbances.

- Consider all sources of sorbitol in the patient's daily intake to assess possible cumulative effects

Selected Medications with Large Quantities of Sorbitol

- Acetaminophen liquid
- Guaifenesin/dextromethorphan syrup
- Pseudoephedrine solution
- Theophylline oral solution

- Liquid formulations of acetaminophen may supply as much as 8 to 24 g of sorbitol when used to reduce fever and may cause osmotic diarrhea.

- Crushing oral tablets and mixing with water prior to enteral feeding tube administration may be a suitable alternative

Alendronate

- Alendronate has low bioavailability and the addition of food decreases absorption and causes subtherapeutic concentrations

- It is recommended that enteral feedings be interrupted or discontinued for an hour before and 2 hours after administration

Esomeprazole

- **Capsules**
  For patients with a nasogastric tube in place, the capsule may be opened and pellets mixed with 50 mL water in a 60-mL syringe.
- After shaking vigorously for 15 seconds, check for granules in the tip and attach to the nasogastric tube and administer contents.
- The nasogastric tube should be flushed with additional water after administration.
- Do not administer pellets if they have dissolved or disintegrated.
- The suspension should be used immediately after preparation

- **Suspension**
  For patients with a nasogastric tube in place, add 15 mL of water, then the packet of esomeprazole into a catheter tipped syringe. Shake the syringe, then leave 2 to 3 minutes to thicken. Shake again and administer through tube, French size 6 or larger, within 30 min. Refill syringe with 15 mL of water then shake and flush tube

Lansoprazole

- Delayed-release Capsule The delayed-release capsule should be opened and the intact granules mixed with 40 mL of apple juice ONLY, and injected through nasogastric tube.
- Flush with additional apple juice to clear the tube.
- For nasogastric administration of delayed-release capsules in adults, a size 16 French or larger nasogastric tube should be used

- Granules from lansoprazole capsules suspended in water and administered through a size 8 French nasogastric tube had very poor through-tube transit with poor quantity of active ingredient delivered to the stomach, and led to results too variable to achieve therapeutic efficacy in a study in pediatric patients.

- Additionally, all size 6 French tubes became blocked during the trial.

Omeprazole

- Duodenal tube:

The suspension was prepared by dissolving the contents of two 20-mg capsules in 20 mL of 8.4% sodium bicarbonate.

- Gastric tube:

Add 5 mL of water ONLY to a catheter tipped syringe and add the contents of a 2.5 milligram (mg) packet, or 15 mL of water for a 10 mg packet.

Immediately shake the syringe and leave for 2 to 3 minutes to thicken. Shake the syringe and inject through the gastric tube, French size 6 or larger, into the stomach within 30 minutes. Refill the syringe with an equal amount of water. Shake and flush any remaining contents from the tube

- Jejunostomy Tube

- Omeprazole pellets administered through a jejunostomy tube has been successful in one institution. Omeprazole pellets were crushed then added to a sodium bicarbonate 8 millimoles/50 mL solution. Upon mixing, the solution was shaken to form a stable suspension. The resultant suspension is then flushed through a jejunostomy tube

Pantoprazole

- Nasogastric Tube

Empty granules into the barrel of syringe
Add 10 mL of apple juice and gently tap and/or shake the barrel of the syringe
Rinse and tap and/or shake again with apple juice; repeat with at least 2 additional 10 mL aliquots of apple juice
No granules should remain in the syringe

Loratadine

- Loratadine has decreased absorption in the presence of food, therefore it is recommended that enteral feedings be interrupted or discontinued for an hour before and 2 hours after administration.

- Others recommend stopping enteral feeding for 30 minutes before and after dosing if the tube is placed in the stomach

- Antacids are intended to neutralize gastric acid secretions and would provide no benefit if delivered to the intestinal portion of the gastrointestinal tract

- **Bismuth**

  Bismuth is intended to provide a protective coating on the stomach and would only provide minimal benefit if administered directly to the small bowel

Calcium

- Calcium binds to dietary phosphorus and in nonrenal failure patients, this may cause significant hypophosphatemia

Carbamazepine

- Carbamazepine may have decreased absorption when administered via an enteral feeding tube.
- Although the exact mechanism is unknown, it may be due to the binding of carbamazepine to the actual feeding tube.
- Dilute with an equal volume of sterile water or NS solution prior to administering, then irrigate the feeding tube following drug administration to reduce drug loss

Ciprofloxacin

- The fluoroquinolone class of drugs are chelated by divalent cations found in enteral feeding formulations, which may decrease bioavailability of the antimicrobial below what is needed for mean inhibitory concentrations.
- To reduce the decrease in bioavailability, it is recommended to hold enteral feeding for at least 1 hour before and 2 hours after fluoroquinolone administration while another guideline recommends at least 2 hours before or 4 hours after enteral formulas.
- Alternatively, the dose of ciprofloxacin could be increased.
- Avoid jejunal administration due to increased risk of poor absorption

- **Tablets**
  If parenteral administration (preferred route) is not possible, and the fluoroquinolone must be administered via an feeding tube, crush tablets and mix in 20 to 60 mL of sterile water

- **Suspension**
  Ciprofloxacin oral suspension has a thick consistency and the oil-based characteristics do not mix with aqueous solutions and cannot be easily flushed with water, therefore it should never be administered via a feeding tube or nasogastric tube

Mycophenolate mofetil

- Mycophenolate mofetil oral suspension can be administered via a nasogastric (NG) tube with a minimum size of 8 French NG tube (1.7 mm interior diameter)

- Iron
  Iron requires the acidic medium of the stomach for dissolution and is absorbed predominantly in the duodenum.

- Administration through a enteral tube with the distal opening in the jejunum risks poor bioavailability

- Cholestyramine
  Cholestyramine (Questran) is prone to clog small-bore feeding tubes

Phenytoin

- Phenytoin concentrations are decreased in the presence of continuous enteral nutrition.
- It is recommended that enteral nutrition be withheld for 2 hours before and after the phenytoin dose, or to change phenytoin dosage to a twice daily regimen and hold the enteral nutrition 1 hour before and after the dose, therefore allowing only 4 hours of interrupted nutrition daily.
- Phenytoin may have decreased absorption when administered via an enteral feeding tube.
- Although the exact mechanism is unknown, it may be due to the binding of phenytoin to the actual feeding tube. Diluting the suspension before administration and irrigating the feeding tube following drug administration reduces drug loss

Pancreatic enzymes

- Microencapsulated formulations of pancreatic enzymes (Creon, Pancreaze) may be opened and the pellets poured down the large-bore enteral feeding tube, provided they are not crushed

- The efficiency of dissolution in 20 mL of 8.4% sodium bicarbonate at 30 minutes among 4 selected enteric coated pancrelipase products is shown in the table below. Zenpep(R) 40,000 and 50,000 lipase units both showed the greatest change in osmolality (1665 and 1667 mOsm/kg after 30 minutes), but among the other admixtures the maximal osmolality varied only by a mean of 11 mOsm/kg from baseline (range of osmolality at 30 minutes, 1611 to 1667 mOsm/kg).
- Larger single doses may require additional sodium bicarbonate for thorough dissolution

Nimodipine

- The liquid contents of the capsule can be extracted into a syringe after making a hole in both ends of the capsule with an 18-gauge needle. To help avoid administration errors, the manufacturer recommends labeling the syringe "Not for IV use". The contents can then be emptied into the patient's in situ nasogastric tube and followed with 30 mL of normal saline

Oxycodone

- Oxycodone immediate-release tablets, specifically marketed as Oxaydo(TM), should not be crushed or dissolved for administration via nasogastric, gastric or other feeding tubes as it may cause obstruction of feeding tubes.

Rivaroxaban

- Adequate absorption of rivaroxaban is dependent on drug passage through the stomach instead of the small intestine.

- Verify gastric placement of the feeding tube prior to administration of the crushed tablet

Sucralfate

- Sucralfate is intended to provide a protective coating on the stomach and would only provide minimal benefit in the small bowel.

- In patients with impaired gastric emptying, sucralfate liquid may be associated with bezoar formation, which are undigestible concretions.

- For administration down a nasogastric tube, a sucralfate tablet was placed in the 60 mL syringe followed by 20 mL of water. The syringe was then allowed to stand with tip up and catheter cap removed for approximately 5 minutes to allow disintegration of the tablet, after which the suspension was directly administered into the NG tube from the syringe

Theophylline

- It is recommended that enteral feeding be stopped for 1 hour before and 2 hours after theophylline dosing.

- Monitoring theophylline levels is recommended

Warfarin

- The vitamin K content of enteral formulations varies between 0 and 125 mcg per 1000 kcal of enteral feeding.

- When switching enteral formulations, changes in vitamin K may require adjustment of the warfarin dose to maintain therapeutic anticoagulation.
- In patients who are receiving large volumes of tube feeds, vitamin K doses of 140 to 500 mcg/day may be reached, which directly blocks the effect of warfarin.
- Protein binding interactions may also occur.
- If alternative anticoagulants are not an option, consider holding enteral feeding for at least 1 hour before and after warfarin administration.
- Careful INR monitoring is recommended when warfarin is used concomitantly with enteral nutrition.

Vancomycin

- Vancomycin hydrochloride injection solution may diluted in 1 ounce of water and administered via a nasogastric tube

Prevention of Occlusion

- Feeding tubes should be flushed with sterile water before and after medication administration in adults and neonatal/pediatric patients.

- To prevent enteral feeding tube occlusion, routinely flush the tube with 30 mL of tap water every 4 hours, before and after intermittent feedings and administration of medications, and after gastric aspiration procedures.

Clearing Clogged Feeding Tubes

- Withdraw any enteral solution remaining in the tube.
- Attempt to remove obstruction with:
  Warm water - inject 5 mL warm water in tube and clamp for 5 minutes. Unclamp tube, apply gentle pressure, and attempt suction. If tube is unclogged, flush with water until clear.
- Carbonated water - inject carbonated water into tube and clamp for 1 hour. Unclamp tube, apply gentle pressure, and attempt suction. If tube is unclogged, flush with water until clear.
- Alkalinized enzyme solution - crush 1 sodium bicarbonate 324 mg tablet. Mix powder with contents of 1 pancrelipase capsule and 5 mL sterile water. Inject mixture into tube and clamp for 5 minutes. Flush with water until clear.
- Replace feeding tube only if methods above are ineffective.