Handling Drug / Tube Feeding Interactions

September 29, 2011

Jeffrey Fish, PharmD, BCPS
University of Wisconsin Hospital and Clinics
email: jfish@uwhealth.org

Disclosures

Nothing to Disclose

Objectives

- Gain the skills necessary for developing a guideline for drug / tube feeding interactions at your institution
- Describe various techniques for avoiding potential drug / tube feeding interactions
- Develop a method for avoiding potential drug / tube feeding interactions when specific recommendations are not available

Outline

- Issues with feeding tubes
  - Placement
  - Size
- Issues with medications
  - Osmolality
  - Medication form
- ASPEN guidelines
- Recommendations on how to handle specific interactions
- Specific medication examples
- How to handle admistration if no specific recommendations exist
- Helpful hints

Issues with Feeding Tubes

- Placement
  - Gastric
  - Duodenal
  - Jejunum
    - **Difficult to determine where medications are absorbed**
- Size of tube
  - Clogging tubes
    - Per ASPEN guidelines: “is both time- and resource-intensive to address, and therefore is best prevented.”

Issues With Medications

- Hypertonic medications
  - Elecrolyte supplements
  - Osmolality of stomach secretions is ~ 300 mOsm/kg
    - > 600 mOsm/kg is considered high

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

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

Prac Gastroent 2004;July:39-48

Appendix A—Partial list of liquid medications that have an osmolality of ≥3000 mOsm/kg[17]

- Acetaminophen elixir, 65 mg/mL
- Acetaminophen with codeine elixir
- Amantadine hydrochloride solution, 10 mg/mL
- Chloral hydrate syrup, 50 mg/mL
- Cimetidine solution, 60 mg/mL
- Dexamethasone solution, 1 mg/mL
- Dextromethorphan hydrobromide syrup, 2 mg/mL
- Diphenoxylate hydrochloride–atropine sulfate suspension
- Docusate sodium syrup, 3.3 mg/mL
- Ferrous sulfate liquid, 60 mg/mL
- Hydroxyzine hydrochloride syrup, 2 mg/mL
- Lactulose syrup, 0.67 g/mL
- Lithium citrate syrup, 1.6 mEq/mL
- Metoclopramide hydrochloride syrup, 1 mg/mL
- Multivitamin liquid
- Potassium chloride liquid, 10%
- Potassium iodide saturated solution, 1 g/mL
- Promethazine hydrochloride syrup, 1.25 mg/mL
- Sodium phosphate liquid, 0.5 g/mL

AJHP 2008;65:2347-57

Issues With Medications

- Sorbitol in preparations
  - Issues if ≥ 10 G/dose or 50 G/day

Appendix B—Partial list of liquid medications that contain considerable amounts of sorbitol with typical daily dosing[20,21]

- Acetaminophen liquid
- Amantadine hydrochloride solution
- Aminocaproic acid syrup
- Charcoal liquid, with sorbitol
- Cimetidine solution
- Guaifenesin/dextromethorphan syrup
- Isoniazid syrup
- Lithium citrate syrup
- Metoclopramide hydrochloride syrup
- Phenylephrine hydrochloride/brompheniramine maleate elixir
- Phenylephrine hydrochloride/chlorpheniramine maleate elixir
- Pseudoephedrine syrup
- Pseudoephedrine/triprolidine syrup
- Sodium polystyrene sulfonate suspension
- Tetracycline hydrochloride suspension
- Theophylline oral solution

AJHP 2008;65:2347-57

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

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

Prac Gastroent 2004;July:39-48

Issues With Medications

- Other issues with liquid medications
  - Viscosity
  - Syrups
- Other medication issues
  - Extended release / enteric coated preparations
  - Liquid filled capsules
  - Toxic medications
  - Micromedex: type “crush” into search box
- Good resources
  - Williams NT. Medication administration through enteral feeding tubes. AJHP 2008;65:2347-57
  - Sacks GS. Drug-nutrient considerations in patients receiving parenteral and enteral nutrition. Prac Gastroent 2004;July:39-48.

ASPEN Guidelines

- Do not add medication directly to an enteral feeding formula
- Administer each medication separately through an appropriate access site
- Dilute the solid or liquid medication as appropriate and administer using a clean oral syringe
  - Use 10-30 ml to dilute
  - Usually don't give IV formulations enterally
    - Acid in GI tract may break down medication
    - Most have increased osmolality
  - Try to avoid syrups since they usually have acidic pH
- Avoid mixing medications intended for administration through an enteral feeding tube
- Stop the feeding and flush the tube with at least 15ml sterile water before and after administering each medication
  - Flush the tube one final time with at least 15ml sterile water
- Restart the feeding in a timely manner to avoid compromising nutritional status

AJN 20009;109:34-42

Recommendations for How to Handle Potential Interactions

- Adjust the dose of the oral medication
  - Increase ciprofloxacin dose
- No medication administration changes are needed
- Give the medication with enteral nutrition
  - Atovaquone
- Hold enteral nutrition around the administration of the medication
  - Phenytoin
- Hold the oral medication while the patient is on enteral nutrition
- Use an alternative administration route for the medication
  - Fosphenytoin

AJHP 2009;66;1458-67

How to Handle No Specific Recommendations

- Contact the manufacturer or consult the package insert for the medication
- Look for any documented food interactions
- Try to get a multidisciplinary consensus on how to handle potential drug / enteral nutrition interactions
  - Develop an institutional guideline

AJHP 2009;66;1458-67

UWHC Guidelines

Medication	Documented interaction with continuous enteral feedings	Documented Food Interaction	Recommendation: Adjustments with regards to continuous enteral feedings[89]	Reference
Acyclovir	No data available.	No interactions.	No dose adjustment required. Grade of evidence: 2C	1
Aminophylline	Short-term administration of the enteral feeding (Ensure) does not influence the absorption of theophylline when administered as the sustained-release product.	Food does not affect absorption. Avoid extremes of dietary protein and carbohydrate intake. Changes in diet may affect the elimination of theophylline (aminophylline); charcoal-broiled foods may increase elimination, reducing half-life by 50%.	No dose adjustment required. Grade of evidence: 1A	2,3
Amiodarone	No data available.	Food may enhance rate and extent of absorption. After consuming a high-fat meal, the AUC of amiodarone increased 2.3 times the fasting and the C_{max} increased 3.8 times the fasting value.	No dose adjustment required. Administer consistently with regard to feeding. Grade of evidence: 2C	4
Amoxicillin/ Clavulanate	No data available.	Optimally administered at the start of a standardized meal. Absorption of amoxicillin is decreased in the fasting state. High fat meals decrease the absorption of the clavulanate component.	No dose adjustment required. Grade of evidence: 2C	5
Atovaquone	The mean AUC of atovaquone suspension in serum after enteral administration with concomitant Sustacal Plus enteral feeds was significantly greater when compared with fasting.	Food significantly increases bioavailability. Therapeutic plasma concentrations may not be achieved if administered during fasting.	No dose adjustment required. Need to administer with tube feedings for maximal absorption. Grade of evidence: 1A	6
Azithromycin	No data available.	Food produces no clinically significant change in bioavailability. Tablets: Food was shown to increase C_{max} by 23% but had no effect on AUC. Suspension: Food increased C_{max} by	No dose adjustment required. Grade of evidence: 2C	7

Specific Medications

- Phenytoin

Phenytoin Suspension	Feeding tubes and/or food may decrease absorption up to 80% via protein binding, poor solubility, or binding to feeding tubes.	Food has no effect on the absorption of brand-name Dilantin® or generic phenytoin made by Teva. Food decreases the absorption of the generic phenytoin made by Mylan.	Recommend keep as IV fosphenytoin; alternatively holding tube feeds at least 1 hour before and 1 hour after dose. Also could, consider increasing the dose to overcome enteral feeding interactions. Total daily dose should be divided into twice daily dosing. Monitor phenytoin levels. Grade of evidence: 2B

- Ciprofloxacin

Ciprofloxacin	Increased T_{max}, while decreasing Cmax and bioavailability. Enteral feeds have sufficient concentrations of Ca^{2+}, Al^{2+}, Mg^{2+}, and Zn^{2+}, to chelate drug and decrease absorption. Absorption decreased if given	Food decreases bioavailability (31-82% of fasting state).	Severe Infection: Change to IV formulation. For mild-to-moderate (non-urinary tract) infections: Recommend administering higher doses. Increase dose to 750mg bid. No dose adjustment needed for UTI. If

Specific Medications

- Levofloxacin

Levofloxaxin	Decreased bioavailability, increased time to peak concentration, and decreased peak concentrations.	Oral administration of 500 mg levofloxacin tablets with food prolongs the T_{max} by 1 hour and decreases the C_{max} by 14% following tablet and approximately 25% following oral solution administration.	Severe Infection: Change to IV formulation. If given with enteral nutrition, recommend holding tube feedings 1 hour before and 2 hours after administration. Due to poor absorption of ciprofloxacin if given thru jejunostomy tube, would recommend giving IV or other enteral route. Grade of evidence: 2C

- Moxifloxacin

Moxifloxacin	A single dose of moxifloxacin 400mg was given to healthy volunteers in a crossover fashion. Moxifloxacin AUC was slightly decreased when given with enteral nutrition through an NGT compared to oral dosing. The difference was not deemed clinically significant.	Moxifloxacin 400 mg has demonstrated bioequivalance with respect to C_{max} and AUC when given in fasting and fed states. T_{max} is also similar between fed and fasted conditions. High fat food may delay rate of absorption; however, the extent of absorption is unaffected.	No dose adjustment required. Due to poor absorption of ciprofloxacin if given thru jejunostomy tube, would recommend giving IV or other enteral route. Grade of evidence: 1C

Specific Medications

- Cyclosporine

Cyclosporine	No data available.	High-fat meals (45 g fat) within 0.5 hour of a dose decreased AUC 13% and decreased C_{max} 33%; effects of low-fat meals (15 g fat) were similar.	No dose adjustment required. Monitor levels. Grade of evidence: 2C

- Tacrolimus

Tacrolimus	Enteral feedings through a nasojejunal feeding tube did not interfere with tacrolimus capsule absorption.	Good bioavailability with food. High fat may decrease AUC and C_{max} by 37% and 72%, respectively; T_{max} was lengthened 5-fold.	No dose adjustment required. Monitor levels. Grade of evidence: 1B
		High carbohydrate foods decreased mean AUC and mean C_{max} by 28% and 65%, respectively.	

- Levothyroxine

Levothyroxine Sodium	Decreased levels as levothyroxine may bind to enteral feeding tubes and/or may be lost during crushing and transfer.	Food may decrease absorption and may increase fecal elimination.	For use < 7 days: No dose adjustment required. For use > 7 days: Hold tube feedings 1 hour pre and post dose. Monitor thyroid function weekly. Grade of evidence: 2B

Specific Medications

- Pantoprazole

Pantoprazole	Crushing the delayed-release tablet can result in tube clogging. Dissolving the enteric-coated granules in water prior to administration can destroy the medication before it reaches its absorption site in the small intestine. This is avoided by the suspension compounded at UWHC, which uses sodium bicarbonate powder and sterile water for irrigation.	Food has no effect on pantoprazole pharmacokinetics. Neither food nor antacids altered the bioavailability of pantoprazole. T_{max} is highly variable and may increase when pantoprazole is given with meals.	No dose adjustment required when using UWHC's compounded pantoprazole suspension. Pantoprazole delayed-release; enteric-coated tablets should not be crushed for administration down gastric or jejunal feeding tubes. Grade of evidence: 2B

- Omeprazole

Omeprazole	Crushing capsule granules destroys the enteric coating, allowing gastric acid to inactivate the medication.	Omeprazole should be taken before meals. The immediate release capsules and powder for oral suspension Zegrid® should be taken one hour before meals. Absorption is delayed by food. When given one hour after meals the C_{max} and AUC were reduced by 63% and 24%, respectively.	Hold feeding at least 1 hour before and 1 hour after dose. Grade of evidence: 2B

Specific Medications

- Lansoprazole

Lansoprazole	Crushing the delayed-release capsule can result in tube clogging. Dissolving the enteric-coated granules in water prior to administration into the NGT can destroy the medication before it reaches its site of absorption in the small intestine. Lansoprazole is available as a granule packet that is reconstituted with water to form a suspension; however, this formulation has been reported to clog feeding tube as it contains xanthan gum.	The administration of lansoprazole 30 minutes after ingestion of food will reduce both C_{max} and AUC by approximately 50%. T_{max} can be delayed up to 3.7 hours. However, serum pharmacokinetics are not altered if lansoprazole is administered prior to the ingestion of food.	Delayed-release capsule: Intact granules of the delayed-release capsule can be mixed with 40 mL of an acidic medium (e.g. apple or orange juice) and flushed with the acidic medium after administrated down gastric feeding tubes. Orally disintegrating tablet: Place 15 mg tablet in syringe & draw up 4 mL of water, or if using 30 mg tablet use 10 mL of water. Shake gently; inject into gastric feeding tube within 15 minutes. Refill syringe with 5 mL of water, shake gently, & flush tube. If the feeding tube terminated in the small bowel, alkaline liquids should be used to dissolve the delayed-release granules prior to administration. The granule packet may also be tried. Grade of evidence: 2B

- Esomeprazole

Esomeprazole	No data available.	Take at least one hour before meals. AUC decreased by 43-53% when a single 40 mg dose was administered in a non-fasting state.	Hold feeding at least 1 hour before and 1 hour after dose. The delayed release capsules may be opened and the intact granules emptied into a syringe for administration into an NG tube. Grade of evidence: 2C

Specific Medications

- Itraconazole

Itraconazole	No data available.	Capsule formulation is maximally absorbed when administered with a "full meal." Oral liquid is maximally absorbed when administered in a fasting state.	No dose adjustment required. Recommend administration of the liquid formulation in patients who are concomitantly prescribed PPI or H_2RA. Patients not concomitantly prescribed PPI or H_2RA should receive the capsule content and
			NOT the liquid formulation. Grade of evidence: 2C

- Voriconazole

Voriconazole	Crushed voriconazole tablets delivered via a NGT (enteral feeding interrupted only for duration of dose administration) was associated with adequate plasma levels in 88% of study patients.	Bioavailability of twice-daily 200mg voriconazole is reduced by ~22% as measured by AUC after multiple dosing when taken with food as compared to fasting.	Recommend holding tube feeds 1 hour before and 1 hour after administration. Monitor voriconazole levels with use > 7 days. Grade of evidence: 2C

Specific Medications

- Posaconazole

Posaconazole	Giving posaconazole with a nutritional supplement increased C_{max} 3.4-fold and AUC 2.6-fold in healthy volunteers.	A 4-fold and 2.6-fold increase in C_{max} and AUC was observed in subjects given high-fat (~50g) and nonfat meals, respectively. A 400mg dose of posaconazole oral suspension had increased bioavailabilities (AUC) and C_{max} with increasing amounts of Boost Plus. After 8 oz of Boost Plus, the AUC increased 2.9 fold and the C_{max} increased 3.5 fold as compared to fasting. A low-fat meal (14g) resulted in a ~3-fold increase in C_{max} and a 2.1-fold increase in AUC as compared to fasting.	Must give with enteral nutrition for adequate absorption. Recommend giving posaconazole with at least 14g of fat. Grade of evidence: 1B

- Fluconazole

Fluconazole	The mean AUC of fluconazole in serum after enteral administration with concomitant enteral feeds did not significantly differ from IV. The concentrations of fluconazole reached via enteral administration were lower than those in serum for IV, but adequate to treat most cases of deep mycoses.	Minimal food effect on bioavailability.	No dose adjustment required. Grade of evidence: 1A

Specific Medications

- Lanthanum

Lanthanum	No data available. Not water soluble, making tube feed administration difficult.	Therapeutic effect of drug requires that it be taken with food.	Use not recommended with tube feeds. May clog tube. Alternative: calcium carbonate suspension Grade of evidence: 2C

- Sevelamer

Sevelamer	Manufacturer does not recommend administering through feeding tubes as contents expand in water and result in tube occlusion.	Therapeutic (phosphate binding) effect of drug requires that it be taken with food.	Use not recommended with tube feeds as sevelamer can clog feeding tube. Alternative: calcium carbonate suspension or may try to compound suspension. Grade of evidence: 2C

Specific Medications

- Sucralfate

Sucralfate	Binds to protein in tube feedings. Insoluble complexes form with tube feeding. No activation due to alkaline pH of tube feeding.	Sucralfate may bind to the protein in food and reduce efficacy; therefore, it is recommended to give sucralfate 1 hour before or 2 hours after meals.	Use not recommended with enteral feedings. Alternative: use PPI or H_2RA.. Grade of evidence: 2C

- Warfarin
  - May be primarily absorbed in proximal small bowel

Warfarin	Possible sequestering of warfarin in the macromolecular fraction of the formulas. Current enteral formulations have minimal amounts of Vitamin K to interact with warfarin. Proteins in formula may bind to warfarin.	No interactions.	Recommend no dose adjustment. Alternatively, consider holding feeds 1 hour before and 1 hour after administration. Either method requires close INR monitoring. Avoid formulas containing soy protein. Grade of evidence: 2B

Helpful Hints

- HIV/AIDS website
  - From the National HIV/AIDS Clinicians' Consultative Center
    - University of California, San Francisco
  - "Dosage form modifications and renal/hepatic dosing of antiretrovirals"
    - Includes information of whether you can open capsule, crush tablet or if liquid dosing form is available
  - http://www.nccc.ucsf.edu/hiv_clinical_resources/pharmacy_central/

Generic Name (Brand Name)	Dosage Forms & Color	Adult Dose in Renal Insufficiency**	Adult Dose in Hepatic Impairment**	Open Capsule			Crush Tablet			Liquid Form	
NUCLOESIDE/TIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs)				Yes	No	NOT	Yes	No	NOT	Yes	No
Abacavir (Ziagen)	300mg (yellow tablet) 300mg scored tablets for pediatric dosing 20mg/ml oral solution (yellow)	No dosage adjustment required	Child-Pugh: Dose 5-6: 200mg BID >6: Contraindicated						√	√	
Didanosine (Videx EC)	All Videx EC are white opaque capsules: 125mg (tan imprint), 200mg (green imprint), 250mg (blue imprint), 400mg (red imprint) Generic capsules: 200mg (green/white), 250mg (red/white), 400mg (blue/white) 2, 4 gram bottles (pediatric powder)	CrCl: >60 Kg / <60 Kg 30-59: 200mg QD / 125mg QD 10-29: 125mg QD / 125mg QD <10 or HD: 125mg / 75 mg oral solution	No dosage recommendation		√					√[2]	
Emtricitabine (Emtriva)	200mg (blue/white capsule) 10mg/mL oral solution (orange)	CrCl: Capsule / Solution 30-49: 200mg q48h / 120mg q24h 15-29: 200mg q72h / 80mg q24h <15 or HD: 200mg q96h / 60mg q24h	No dosage recommendation			√[2]				√	
Lamivudine (Epivir)	Tablets: 100mg (butterscotch-colored, capsule-shaped), 150mg (white, diamond), 300mg (gray, diamond) 10mg/ml oral solution (pale yellow)	CrCl: Dose 30-49: 150mg QD 15-29: 150mgx1, then 100mg QD 5-14: 150mgx1, then 50mg QD <5 or HD: 50mgx1, then 25mg QD	No dosage recommendation						√	√	
Stavudine (Zerit)	Capsules: 15mg (yellow/dark red), 20mg (light brown), 30mg (light & dark orange), 40mg (dark orange) 1mg/ml (powder for oral solution) Generic capsules: 30mg, 40mg	CrCl: >60 Kg / <60 Kg 26-50: 20mg q12h / 15mg q12h 10-25 or HD: 20mg q24h / 15mg q24h	No dosage recommendation			√				√[2]	
Tenofovir (Viread)	300 mg (light blue, almond shaped tablet)	CrCl[3]: Dose 30-49: 300mg q48h 10-29: 300mg twice weekly ESRD on HD: 300mg q7d	No dosage recommendation						√[1]		√

Helpful Hints

- Lexi-comp pediatric dosing
  - Part of Up-to-Date
  - Contains recipes for suspensions
    - Especially in pediatric dosing section at bottom
    - Copied from “Up-to-date” for valacyclovir
      - **Extemporaneous Preparations** A 50 mg/mL oral suspension may be made with caplets and either Ora-Sweet® or Ora-Sweet SF®. Crush eighteen 500 mg caplets in a mortar and reduce to a fine powder. Add 5 mL portions of chosen vehicle (40 mL total) and mix to a uniform paste; transfer to a 180 mL calibrated amber glass bottle, rinse mortar with 10 mL of vehicle 5 times, and add quantity of vehicle sufficient to make 180 mL. Label "shake well" and "refrigerate". Stable for 21 days refrigerated.
      - Fish DN, Vidaurri VA, and Deeter RG, "Stability of Valacyclovir Hydrochloride in Extemporaneously Prepared Oral Liquids," *Am J Health Syst Pharm*, 1999, 56(19):1957-60.10554914
- Try to follow levels if available

Conclusions

- Both feeding tube and medication issues make potential interactions challenging
- ASPEN recommendations are difficult to follow due to time and knowledge constraints
- Little published data on specific medication / enteral nutrition interactions
  - Practice is based mainly on expert opinion (or guess)

Questions ?