Drug-Nutrition Interactions in Nutrition Support

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Objectives

Upon completion of this session, the participant will be able to:

• Define the term and describe classes of drug-nutrition interactions

• Provide specific examples that could be seen and managed in nutrition support practice

• Explain the clinician’s role in identifying and managing drug-nutrition interactions
Outline

• Defining DNIs
• EN-Related Features
• PN-Related Features
• Clinician Roles
• Summary
Outline

• **Defining DNIs**

• EN-Related Features

• PN-Related Features

• Clinician Roles

• Summary
Defining Drug-Nutrition Interactions

• The *bioavailability* and *clinical effects* of medications are influenced by a wide array of factors, including interactions
  • Drug-drug interactions
  • Drug-nutrition interactions (DNIs)

• Consider interactions related to enteral nutrition (EN) and parenteral nutrition (PN)
Defining Drug-Nutrition Interactions

• An interaction resulting from:
  • The physical, chemical, physiologic, or pathophysiologic relationship

• Between:
  • A drug

• And:
  • A nutrient, multiple nutrients, food in general, specific foods or components, or nutrition status
Defining Drug-Nutrition Interactions

- Clinically significant when the interaction:
  - Compromises nutrition status
  - Alters therapeutic drug response

- Interactions occur because of similarities in:
  - Inherent physicochemical properties
  - Physiologic disposition
# Defining Drug-Nutrition Interactions

<table>
<thead>
<tr>
<th>Precipitating Factor</th>
<th>Object</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘Perpetrator’</td>
<td>‘Victim’</td>
<td></td>
</tr>
<tr>
<td><strong>Drug</strong></td>
<td><strong>Nutrient</strong></td>
<td>Isoniazid → vitamin B&lt;sub&gt;6&lt;/sub&gt;</td>
</tr>
<tr>
<td><strong>Drug</strong></td>
<td><strong>Nutrition Status</strong></td>
<td>Quetiapine → weight gain</td>
</tr>
<tr>
<td><strong>Drug</strong></td>
<td><strong>Metabolic Status</strong></td>
<td>Olanzapine → hyperglycemia</td>
</tr>
<tr>
<td><strong>Nutrition Status</strong></td>
<td><strong>Drug</strong></td>
<td>Obesity → ertapenem</td>
</tr>
<tr>
<td><strong>Specific Nutrient</strong></td>
<td><strong>Drug</strong></td>
<td>Iron supplement → doxycycline</td>
</tr>
<tr>
<td><strong>Food Component</strong></td>
<td><strong>Drug</strong></td>
<td>Grapefruit juice → simvastatin</td>
</tr>
<tr>
<td><strong>Food</strong></td>
<td><strong>Drug</strong></td>
<td>Meal → alendronate</td>
</tr>
</tbody>
</table>

*J Acad Nutr Diet 2012;112:506 / J Clin Pharm Ther 2013;38:269*
Defining Drug-Nutrition Interactions

• The meal effect
  • Food changes conditions in the gut
    • Gastric emptying, proximal intestinal pH, bile flow, splanchnic blood flow, enterocyte function (permeability, transport, metabolism)
  • May influence the *rate* of drug absorption
  • May influence the drug’s *bioavailability*
    • Area under the concentration-time curve (AUC)
Defining Drug-Nutrition Interactions

• The meal effect
  • U.S. Food & Drug Administration recommends a noteworthy “test meal”
    • 800-1000 kcal, energy from fat ~50%
  • Clinical significance
    • $\text{AUC}_{\text{fed}}:\text{AUC}_{\text{fasted}}$ outside 80-125%
Relative Bioavailability and the Effect of Meal Type and Timing on the Pharmacokinetics of Migalastat in Healthy Volunteers

Franklin K. Johnson
BIOPHARMACEUTICALS CLASSIFICATION SYSTEMS

Class 1
- High Solubility
- High Permeability
- Extensive Metabolism
- Minimal Transporter Effects

Class 2
- Low Solubility
- High Permeability
- Extensive Metabolism
- Efflux Transporter Effects

Class 3
- High Solubility
- Low Permeability
- Poor Metabolism
- Absorptive Transporter Effects

Class 4
- Low Solubility
- Low Permeability
- Poor Metabolism
- Absorptive & Efflux Transporter Effects
Outline

✓ Defining DNIs

• **EN-Related Features**

• PN-Related Features

• Clinician Roles

• Summary
EN-Related Features

• **Drug Admixed with EN**
  • Survey and study findings
  • Concerns
  • Recommendations

• **Drug Co-administered with EN**
  • Preparation and administration
  • Survey findings
  • Concerns
  • Recommendations by drug
Drug Admixed with EN

• **Survey findings**
  • Frequently/occasionally add drug to EN formula → 21%
  • Medication includes:
    • Gastrointestinal agents → 59%
    • Electrolytes → 35%
    • Antimicrobials → 31%
    • Others → 43%

*Nursing* 2013;43(12):26
Drug Admixed with EN

• **Study findings**
  - Barely 2 dozen drugs and a dozen EN products have been evaluated as admixtures
    - Most examined physical compatibility based on visual inspection
    - A few additionally included chemical compatibility
    - Drug (or nutrient) stability rarely evaluated
  - Provided insight into factors that may predict incompatibility
    - Drug-related
    - Formula-related
Drug Admixed with EN

**Concerns**

- Although seemingly convenient, several concerns exist
  - Very few data exist supporting the compatibility and stability of the admixture
  - The physical and chemical interactions between drug and EN may:
    - Alter properties of the drug and of the EN
    - Increase the risk for tube occlusion
    - Alter drug bioavailability
    - Disturb gut function

Drug Admixed with EN

**Recommendations**

- Do not add medication to an EN formula in the absence of data confirming compatibility, stability, and bioavailability.
- Instead:
  - Administer each medication separately (avoid mixing different medication together).
  - Use liquid dosage forms only if appropriate.
  - Otherwise use appropriate immediate-release solid dosage forms.
  - Flush enteral feeding tube before/after med administration.
Enteral Medcations

- Enteral Drug Ordered
- Order Reviewed
- Drug Prepared
- Drug Administered

Any alteration of a dosage form after its retrieval.

Involves timing of drug delivery into the GI tract with respect to the EN regimen, other meds, and flushing protocol.
Drug Co-Administered with EN

• Preparation and Administration
  • Most are confident with their technique (surveys)
  • But error rates approach 60% (observational studies)

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mix meds together</td>
<td>Administer meds together 49-68%</td>
</tr>
<tr>
<td>Crush tabs together</td>
<td>No flush (≥15 mL) pre med 57-99%</td>
</tr>
<tr>
<td>Crush mod-release meds</td>
<td>No flush (≥15 mL) post med 34%</td>
</tr>
<tr>
<td>Don’t dilute liquid meds</td>
<td>No flush between meds 62-99%</td>
</tr>
<tr>
<td>Not shaking suspension</td>
<td>Diluent other than water 18%</td>
</tr>
<tr>
<td>No protective equipment</td>
<td></td>
</tr>
</tbody>
</table>

70% 84% 15-87% 36-46% 51% 100%

References:
- Pediatrics 1988;81:549
- Heart Lung 1996;25:318
- Gastroenterol Nurs 1997;20:118
- Am J Crit Care 1977;6:382
- Am J Health-Syst Pharm 2002;59:378
- Pharm World Sci 2008;30:907
- JC J Qual Patient Safety 2008;34:285
- JPEN 2009;33:122
- Nursing 2013;43(12):26
- Pharm Pract News 2014;Apr:1
Drug Co-Administered with EN

**Survey findings**

- Hold feeds while administering drug → 95%
- Flush tube before/after drug administration → 89-98%
- Avoid crushing modified-release → 87-90%
- Administer each drug separately → 38%
- Dilute medication (solid/liquid) with sterile water → 22% / 13%
- Hold EN for at least 1 hour around dosing of:
  - Levofloxacin → 26%
  - Phenytoin → 50%
  - Warfarin → 22%
- Consult with pharmacist when unsure → 46%

*Nursing 2013;43(12):26*
Drug Co-Administered with EN

• **Concerns**
  
  • Several practices that may alter drug bioavailability and/or drug response
  
  • Interaction between EN formula (or specific components) and medication in the feeding tube or gut lumen
Drug Co-Administered with EN

**Recommendations** (continuous feeds)

- Hold EN only for the time it takes to flush tube, deliver medication, and flush again
  - Several medications may benefit from this close administration to EN

- A few medications may benefit from administration separated by at least 30-60 minutes from EN
  - Which ones are supported by data?

Handbook of Drug Administration via Enteral Feeding Tubes
Third edition
Rebecca White and Vicky Bradnam

Why are these guidelines necessary?
The use of enteral feeding tubes as a route of drug administration is becoming increasingly common. This guidance has been produced in response to the increasing demand for information on the practical aspects of drug administration via this route.

General Considerations
Patient’s medication should be reviewed regularly and any unnecessary medication stopped. Using the feeding tube as a drug should be a last resort, and whenever an alternative route is available.

Types of Feeding Tubes
Most patients on home enteral feeding in the community have a gastrostomy tube (PEG) tube. Although naso-gastric (NG) and jejunal tubes are also used.

Drug Interactions
Interactions between enteral feeds and drugs can be clinically significant. As a general rule if the absorption of a drug is affected by food or antiacids, it is also likely to be affected by enteral feeds.

Preferable
Liquid or semi-solid preferred for via feeding. However, if liquid preparation not possible, suspend food therefore.

Sources of Information
Data Sheet
The summary of product characteristics (SPC) should contain some information about the formulation.

Manufacturer
Administration of a drug via a feeding tube usually falls outside the terms of its product licence and therefore some manufacturers may be unwilling to provide information. However, most manufacturers do have some information on it and may be able to offer assistance.

Ask your Local Pharmacist
Most pharmacists will be familiar with the formulations available, and communication between GP and community pharmacist should be encouraged to ensure that the patient’s treatment is not delayed.

Medicines Information Department
Most acute hospitals and some community hospitals have a medicines information department within the pharmacy department that will be able to assist you.

Who produced the guidelines?
These guidelines were produced by a multi-disciplinary team, with the support of BAPEN and the BPNG.

BAPEN
The British Association for Parenteral and Enteral Nutrition was founded in 1992 from the association of several professional groups representing clinicians, nurses, dietitians, pharmacy, industry and patients. The aim of this group is to promote good practice in all areas of nutrition support.

BPNG
The British Pharmaceutical Nutrition Group, founded in 1988, is an organization with a professional interest in pharmaceutical nutrition support. The members of this group are pharmacists, technicians and scientists from the health service, academia and industry.

BAPEN
Putting patients at the centre of good nutritional care
Drug Administration Via Enteral Feeding Tubes
A Guide for General Practitioners and Community Pharmacists

Produced by the British Association for Parenteral and Enteral Nutrition
www.bapen.org.uk Registered Charity 1053937
The British Pharmaceutical Nutrition Group
www.bpng.co.uk
Drug Co-Administered with EN

- **Antiepileptic Drugs**
  - Carbamazepine
  - Phenytoin

- **Fluoroquinolone Antimicrobials**
  - Ciprofloxacin
  - Levofloxacin
  - Moxifloxacin

- **Other Medication**
  - Levodopa
  - Warfarin
Antiepileptic Drugs

- Carbamazepine
  - Lower bioavailability when administered via NGT than orally (fasted)
  - Drug delivery improves when suspension diluted and tube flushed

- Phenytoin
  - Subtherapeutic levels noted when administered with EN
  - Holding EN has not always improved phenytoin absorption
  - Drug delivery improves when suspension diluted and tube flushed
  - Confirmed in pharmacokinetic study

### Recommendations: Carbamazepine

<table>
<thead>
<tr>
<th>Location</th>
<th>Instructions</th>
</tr>
</thead>
</table>
| Gastric    | • Dilute the suspension with water (at least 1:1) just prior to administration.  
             • No need to hold EN beyond the time required to flush-administer-flush. |
| Postpyloric| • As above.  
             • Jejunal administration may be less effective.  
             • Monitor for any unexpected change in effect. |

### Recommendations: Phenytoin

<table>
<thead>
<tr>
<th>Location</th>
<th>Instructions</th>
</tr>
</thead>
</table>
| Gastric    | • Dilute suspension with water (at least 1:1) just prior to administration.  
             • Alternative: Disperse capsule contents in water just prior to administration.  
             • Holding EN is not necessary, but could hold EN for 1 hour before and 1 hour after drug administration.  
             • Maintain consistent method of administration, with dose adjustments as needed based on appropriate therapeutic drug monitoring. |
| Postpyloric| • Avoid.  
             • Monitor for any unexpected change in effect. |
Fluoroquinolone Antimicrobials

• Ciprofloxacin, Levofloxacin, Moxifloxacin
  • Serum concentrations must remain above a defined AUC:MIC for the organism
  • Multivalent cations (e.g., aluminum, calcium, iron, magnesium, zinc) chelate fluoroquinolones and reduce bioavailability
  • Interact rapidly with EN depending on cation content
  • Temporal spacing (at least 2 hours) may alleviate the interaction
### Recommendations

<table>
<thead>
<tr>
<th>Type</th>
<th>Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric</td>
<td>- Crush and/or disperse tablet in water (25–50 mL) just prior to administration.</td>
</tr>
<tr>
<td></td>
<td>- Consider holding continuous EN by 1–2 hours before and after drug administration; separate drug administration by 2 hours from intermittent EN and any other products containing 500 mg or more calcium.</td>
</tr>
<tr>
<td>Post pyloric</td>
<td>- As above.</td>
</tr>
<tr>
<td></td>
<td>- Significant risks for lower absorption.</td>
</tr>
<tr>
<td></td>
<td>- Monitor for any unexpected change in effect.</td>
</tr>
<tr>
<td>Other</td>
<td>- As with all antimicrobials, consider parenteral alternative for acutely ill patients to ensure therapeutic concentrations.</td>
</tr>
</tbody>
</table>
### Recommendations **Levofloxacin**

| Gastric       | • Dilute oral solution with water (at least 1:1) prior to administration.  
|               | • Consider holding EN for 1 hour before and 2 hours after each drug dose.  |
| Postpyloric   | • As above.  
|               | • Monitor for any unexpected change in effect.  |

### Recommendations **Moxifloxacin**

| Gastric       | • If there is no therapeutic alternative, crush and disperse tablet in water prior to administration.  
|               | • Consider holding EN for at least 2 hours before and after drug administration.  |
| Postpyloric   | • As above.  
|               | • Monitor for any unexpected change in effect.  |
Other

• **Levodopa**
  - Protein/peptides compete with levodopa impairing drug absorption
  - Includes patients receiving EN (gastric or postpyloric)
  - Less interaction potential at low protein dosing or when separated
  - Separate drug administration from intermittent EN administration (or protein supplementation) by at least 2 hours
  - Consider drug administration in daytime, with continuous EN at night
### Other

- **Warfarin**
  - Vitamin K content of EN initially considered problematic
  - Physico-chemical interaction with macromolecular fraction of EN

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Warfarin</th>
</tr>
</thead>
</table>
| **Gastric**     | • If there is no therapeutic alternative, disperse tablet in water just prior to administration.  
                  • Consider holding EN for 1 hour before and at least 1 hour after drug administration. |
| **Postpyloric** | • As above.  
                  • Monitor for any unexpected change in effect. |
| **Other**       | • Monitor patient INR as needed. |
Outline

✓ Defining DNIs
✓ EN-Related Features

• **PN-Related Features**

• Clinician Roles

• Summary
PN-Related Features

• Drug Admixed with PN
  • Survey and study findings
  • Concerns
  • Recommendations

• Co-infusion with PN
  • 2-in-1 studies and 3-in-1 studies
  • Concerns
  • Recommendations
Drug Admixed with PN

**Survey findings**

- Three-quarters of respondents allow non-nutrient medication to be included in the PN admixture
- Most common:
  - Insulin, histamine-receptor antagonists, heparin
- Others included:
  - Albumin, digoxin, dopamine, erythropoietin, furosemide, hydrocortisone, methylprednisolone, metoclopramide, octreotide, ondansetron

*JPEN J Parent Enteral Nutr 2013;37:212*
Drug Admixed with PN

Study findings

- Approximately 3 dozen drugs studied, some in multiple studies (e.g., insulin, H₂-antagonists)
  - In vivo, clinical studies – 3 drugs
  - Drug stability evaluated – 10 drugs
  - Visual compatibility only – 32 drugs

Drug Admixed with PN

• **Concerns**

  • Although convenient, several concerns exist
    • Limited number of drugs evaluated for compatibility *and* stability in PN admixtures
    • Complete description of PN seldom included
    • Stability of the 3-in-1 emulsion is rarely evaluated
    • Limited data on therapeutic bioavailability
Drug Admixed with PN

**Recommendations**

- Include drug in PN admixtures *only* when supported by:
  - **Pharmaceutical data** describing physicochemical compatibility and stability of the additive medication and of the final preparation under conditions of typical use
  - **Clinical data** confirming the expected therapeutic actions of the medication
  - Extrapolation beyond the parameter limits (eg, products, concentrations) of the given data is discouraged
Drug Co-infusion with PN

• **Study findings**
  - Over 100 drugs have been studied
    - Compounded 2-in-1 and 3-in-1; commercial 3CBs

• **Concerns**
  - Majority of co-infusions evaluated physical compatibility, without chemical compatibility, drug stability, or emulsion stability
Drug Co-infusion with PN

• **Recommendations**
  
  • Co-infusion of medications through PN lines shall require a review of compatibility and stability data by a pharmacist; to include evaluation of:
  
  • Drug concentration used
  • PN admixture components and concentration
  • Exposure times
  • Criteria applied

*JPEN 2014;38:296 / JPEN 2014;38:334*
Outline

✓ Defining DNIs
✓ EN-Related Features
✓ PN-Related Features

• Clinician Roles

• Summary
Clinician Role

• **DNIs in General**
  - Use framework model
  - Consider risk factors – age, disease state, genetic variants, medication, nutrition status
  - Clinical observation, analysis, and documentation
  - If unexpected change in nutrition status or in drug effect … “is it related to an interaction?”
Clinician Role

• **DNIs with EN or PN**
  
  • Generally avoid including any medication in an EN formula or a PN admixture
  
  • Become familiar with incompatible drugs co-administered with EN formula or PN admixtures
  
  • Clinical observation and close monitoring
  
  • Documentation of DNI and intervention made
Clinician Role

• An inter-disciplinary, team-based approach is considered ideal

• Decision support systems integrated into ordering systems and electronic health records can be valuable
Clinician Role

• **Policies, Procedures, and Practices**
  • Require performing an evaluation of potential DNIs in all patients receiving EN or PN
    • Identify patients
    • Assign responsibility
    • Document intervention
  • Periodically review accumulated interventions
Outline

- Defining DNIs
- EN-Related Features
- PN-Related Features
- Clinician Roles

• Summary
1. The term drug-nutrition interaction is broad and reflects a physical, chemical, physiologic, or pathophysiologic relationship between a medication and a nutrient, a meal, specific foods or food components, metabolic status, or nutrition status. Some of these interactions may be of concern in patients receiving nutrition support.

2. The stability, compatibility, and bioavailability of medication with PN admixtures or with EN formulas is important to appreciate whether combined or administered concurrently.

3. The clinician’s role in identifying and managing drug-nutrition interactions can include participation to improve policies & procedures, encourage integrated decision support systems, and maintain thorough evidence-based practices to assess the patient and their nutrition support regimen.
Outline

✓ Defining DNIs
✓ EN-Related Features
✓ PN-Related Features
✓ Clinician Roles
✓ Summary