Drug-Nutrition Interactions in Clinical Practice

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

Outline

• Introduction
• Defining DNIs
• Clinical Examples
• Recommendations
• Conclusions

Introduction

The Background

• History of Drug-Nutrient Interactions
  – Isolated reports and reviews
  – Focus on drug-food interactions
  – Memorize lists of interactions
  – Poor clinical relevance
  – Little mechanistic perspective

Drug (Medication) Use

• Prescription medicines
• Non-prescription medicines
• Natural/traditional medicines

Nutrition Variability

• Nutrition status
• Dietary habits
• Food composition
• Dietary supplement use

Defining Drug-Nutrition Interactions

“... reintroducing the topic of drug and nutrition interactions.”

“Drug-Nutrition Interaction”

• An interaction resulting from:
  – A physical, chemical, physiologic, or pathophysiologic relationship
• Between:
  – A drug
• And:
  – A nutrient, multiple nutrients, food in general, specific foods or components, or nutrition status

Why Does This Occur?

Mechanisms of Interaction

• Related to:
  – Physico-chemical attributes
  – Environmental matrix
  – Location
• Viewed as:
  – Pharmaceutical
  – Pharmacokinetic
  – Pharmacodynamic
How Does This Occur?

**Pharmaceutical**
- Solubility
- Stability

**Pharmacokinetic**
- Absorption
- Distribution
- Metabolism
- Excretion

**Pharmacodynamic**
- Effects
- Signal transduction
- Genetic polymorphisms
- Enzymes, transporters, receptors

Physiologic Outcome
- Bioavailability
- Volume of Distribution
- Clearance
- Biomarkers

Dose of drug administered

**Pharmacokinetics**
- Absorption
- Distribution
- Metabolism
- Excretion

Drug in tissues of distribution

Drug metabolized or excreted

Pharmacologic Effect

Clinical Response

TOXICITY  Efficacy

Drug concentration at site of action
Transporters

<table>
<thead>
<tr>
<th>Gene Family</th>
<th>Protein</th>
<th>Substrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCB1</td>
<td>MDR1 (Pgp)</td>
<td>Cyclosporine, digoxin</td>
</tr>
<tr>
<td>ABCB1</td>
<td>MRP1</td>
<td>Folate, glutathione, adefovir, indinavir</td>
</tr>
<tr>
<td>ABCB2</td>
<td>MRP2</td>
<td>Amicilline</td>
</tr>
<tr>
<td>ABCB3</td>
<td>MRP3</td>
<td>Folate, etoposide, methotrexate</td>
</tr>
<tr>
<td>ABCG2</td>
<td>BCRP</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>SLC5</td>
<td>SMVT</td>
<td>Folin, lipolic acid, pantothenic acid</td>
</tr>
<tr>
<td>SLC6</td>
<td>SERT</td>
<td>Sertraline</td>
</tr>
<tr>
<td>SLC15</td>
<td>PEPT</td>
<td>Ampicillin, captopril, cephalaxin, valacyclovir</td>
</tr>
<tr>
<td>SLC16</td>
<td>MCT</td>
<td>Aromatic amino acids, atorvastatin, salicylate</td>
</tr>
<tr>
<td>SLC19</td>
<td>RFC, THTR</td>
<td>Folate, thiamin, methotrexate</td>
</tr>
<tr>
<td>SLC21</td>
<td>OATP</td>
<td>Digoxin, prostaglandins</td>
</tr>
<tr>
<td>SLC22</td>
<td>OAT, OCT</td>
<td>Acyclovir, salicylates, carnitine</td>
</tr>
<tr>
<td>SLC23</td>
<td>SVCT</td>
<td>Ascorbic acid</td>
</tr>
<tr>
<td>SLC27</td>
<td>FATP</td>
<td>Fatty acids</td>
</tr>
<tr>
<td>SLC31</td>
<td>hCtr</td>
<td>Copper, cisplatin</td>
</tr>
</tbody>
</table>

Drug Metabolizing Enzymes

Clinical Consequences

- Altered disposition of drug and/or nutrient
  – Absorption, distribution, elimination

- Altered effect of drug and/or nutrient
  – Physiologic action at the cellular level

The End Result

- Clinically significant
  – Compromises nutrition status
  – Alters therapeutic drug response

Patient Outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No A</th>
<th>Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsened</td>
<td>Nutrition Status</td>
<td>Improved</td>
</tr>
<tr>
<td>Toxic or ineffective</td>
<td>Drug Effect</td>
<td>Optimal</td>
</tr>
</tbody>
</table>

Classification

Precipitating Factor → Object of Interaction

• Nutrition status
• Food or food component
• Specific nutrient
• Drug

Classification System

- Recognize the object of the interaction
- Identify the precipitating factor
- Explain the likely location and mechanism
- Describe potential consequences

Clinical Examples

Nutrition Status → Drug

- Obesity
  - Lower drug concentration (ertapenem)
  - Higher toxicity (acyclovir)

- Micronutrients
  - Vitamin C deficiency prolongs drug action (pentobarb)
  - Zinc deficiency increases drug toxicity (aspirin)
Food Component → Drug

- **Enteral nutrition**
  - Impairs drug absorption (ciprofloxacin)

- **Food**
  - Interferes with drug absorption (alendronate)
  - Improves drug absorption (gabapentin-enacarbil)

Food Component → Drug

- **Grapefruit juice**
  - Increases drug bioavailability (atorvastatin, dasatinib, sildenafil, simvastatin) and risk for drug toxicity
  - Decreases drug bioavailability (etoposide, levothyroxine)
Specific Nutrient → Drug

- Iron
  - Reduces drug concentration (doxycycline)
- Vitamin C
  - May reduce drug activity (fluconazole)
- Vitamin D
  - Reduces drug concentration (atorvastatin)
- Daidzein
  - Increases drug bioavailability (theophylline)

Dietary Supplement → Drug

- ω3 Fatty Acids
  - Improves drug response (irinotecan) or reduces toxicity (paclitaxel)
- St John’s wort
  - Reduces drug concentrations (imatinib, irinotecan)
- Ginseng
  - Increases toxicity (imatinib)

Influence of ‘Polypharmacy’ on Nutrition

Key Points:
- About 82-91% of adults use at least one medication on a regular basis many taking five or more
- Medication use is a significant, seldom recognized, factor for altering nutrition status that is not routinely assessed prior to marketing
- Drug-induced poor nutrition status can be manifest by changes in body mass or composition, in metabolic function, or in nutrient biomarkers
- Mechanistically, drugs can impact food preparation/intake, gastrointestinal structure/function, nutrient absorption, distribution, metabolism or elimination

Drug → Nutrition Status

- Quetiapine
  - Alters body weight (weight gain)
- Sorafenib
  - Associated with altered body comp (sarcopenia)
- Capecitabine
  - May cause metabolic disorder (hypertriglyceridemia)
- Many medications
  - Alter GI tract function (taste change, anorexia, stomatitis, nausea, vomiting, diarrhea)

Drug → Specific Nutrient Status

- Carbamazepine
  - Lowers nutrient (vitamin D, biotin) status
- Ezetimibe
  - Reduces nutrient (vitamin E) absorption
- Isoniazid
  - Impairs nutrient (vitamin B6) status
- Ribavirin + peginterferon-α-2b
  - Impairs nutrient (vitamin B12) status
Recommendations

Clinician’s Role

- Use the framework to optimize patient outcome
- Clinical observation, analysis, and documentation

Is my patient’s change in nutrition status related to an interaction?

Is my patient’s unexpected drug effect related to an interaction?

Risk Factors

- Factors that influence risk for developing a clinically significant drug-nutrient interaction:
  - Age
  - Disease status
  - Genetic variants
  - Medication
  - Nutrition status

Expectation

- LEAST Significant
  - Acute use of one drug in a patient with good nutrition status

- WORST Scenario
  - Elderly patient, with poor nutrition status, requiring multiple chronic medications

Policy & Procedures

- TJC
  - Less prescriptive than in the past
  - Suggests performing evaluation of DN interactions

- P&T subcommittee or work group
  - High-risk meds (AEDs, antimicrobials, warfarin)
  - High-risk patients (elderly, obese, ICU)
  - Identify patients, assign responsibility, document interventions
  - Periodically review P&P and interventions
**Patient Approach**

- **Who**
  - Coordinated, interdisciplinary, team-based approach is considered critical to managing patients with potential drug-nutrition interactions

- **How**
  - Decision support systems integrated into screening tools and ordering systems could be valuable

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**The Drug Interaction Probability Scoring System and Scale**

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>Unknown or N/A</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there previous credible reports of this interaction in humans?</td>
<td>+1</td>
<td>0</td>
<td>-1</td>
</tr>
<tr>
<td>Is the observed interaction consistent with the known interactive properties of the precipitating factor?</td>
<td>+1</td>
<td>0</td>
<td>-1</td>
</tr>
<tr>
<td>Is the observed interaction consistent with the known interactive properties of the object?</td>
<td>+1</td>
<td>0</td>
<td>-1</td>
</tr>
<tr>
<td>Is the event consistent with the known or reasonable time course of the interaction (event mild or severe)?</td>
<td>+1</td>
<td>0</td>
<td>-1</td>
</tr>
<tr>
<td>Did the interaction exist prior to commencement of the precipitating factor with no change in the event?</td>
<td>+1</td>
<td>0</td>
<td>-1</td>
</tr>
<tr>
<td>If yes, did the interaction decrease when the precipitating factor was discontinued?</td>
<td>+2</td>
<td>0</td>
<td>-1</td>
</tr>
<tr>
<td>Are there reasonable alternative causes for the event?</td>
<td>+1</td>
<td>0</td>
<td>-1</td>
</tr>
</tbody>
</table>

*Adapted from: Ann Pharmacother 2007;41:674*

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**Conclusions**

**Drug-Nutrition Interactions**

- Relevant to every day clinical practice
- Requires a systematic patient assessment
- Much more research is still needed (mechanisms, management)
- Better incorporate into the process of drug development, regulation, and review
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