SCSHP 2014 Annual Meeting

Drug Interactions

Aida “Rebecca” Bickley, PharmD, BCPS
Assistant Professor of Pharmacy Practice
Presbyterian College School of Pharmacy

Background

- Drug Interaction (DI) term is used when administration of, or exposure to, a substance modifies a patient’s response to a drug
- DI are possible whenever a person takes two or more medications concurrently
- About 5% of adverse drug reactions (ADRs) are attributed to drug interactions in the hospital
- Cytochrome P450 drug metabolizing enzymes have revolutionized the study of drug interactions

Disclosure

- I do not have a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation

Objectives

- Describe relevant background information including the differentiation between pharmacokinetics and pharmacodynamics of drug interactions (DIs)
- Recognize the most common drug interactions (DIs) observed in practice
- Analyze a specific patient’s medication list to identify potential drug interactions (DIs)

Terminology

- Object drug
  - Drug affected by the interaction
- Precipitant drug
  - Drug causing the interaction
  - Grouped by mechanism – i.e. enzyme inhibitors/inducers
- Pharmacokinetic (PK)
  - One drug affects absorption, distribution, metabolism, or excretion to another
- Pharmacodynamic (PD)
  - Two drugs have additive or antagonistic pharmacologic effects
  - Either type of DI can result in adverse effects

Pharmacokinetic DIs

Inhibition of Absorption

- Drugs acting as binding agents (i.e. cholestyramine & colestipol) can impair the bioavailability of other drugs
- Result in ↓ in therapeutic effect
  - Profound effect with some combinations (i.e. cholestyramine & furosemide)
  - Fluoroquinolone antibiotics are susceptible to chelation with cations such as aluminum, magnesium, & iron
  - Itraconazole, ketoconazole, glipizide, glyburide, cefpodoxime, & cefuroxime have pH dependent absorption
  - Amount of these drugs that is absorbed from the gut may be ↑ or ↓ by drugs that ↑ stomach pH
**Pharmacokinetic DIs**

- **Enzyme Inhibition Increasing Risk of Toxicity**
  - Most drugs are metabolized to inactive or less active metabolites by enzymes in the liver & intestine
  - Inhibition of the metabolism can ↑ the effect
    - If ↑ in the effect is large enough, drug toxicity may result
  - One of the most common mechanisms by which clinically important DIs occur
  - Only a few different cytochrome P450 isozymes are involved in drug metabolism & competition between 2 drugs for these isozymes will occasionally occur
  - This competition may result in 1 drug interfering with the metabolism of another drug

**Examples**

- Analgesic & toxic effects of codeine appear to result from its conversion to morphine by CYP2D6
- CYP2D6 inhibitors can impair the therapeutic effect of codeine
- CYP2D6 inhibitors may similarly affect the analgesic effect of hydrocodone

**Pharmacokinetic DIs**

- **Enzyme Induction Resulting in Reduced Drug Effect**
  - Some drugs are called “enzyme inducers”
    - Capable of increasing the activity of drug metabolizing enzymes, resulting in a ↓ of the effect of certain other drugs
  - Examples
    - Aminogluthethimide, barbiturates, carbamazepine, glutethimide, griseofulvin, phenytoin, primidone, rifabutin, rifampin, & troglitazone
    - Ritonavir may act as either an enzyme inhibitor or inducer
    - Drugs metabolized by CYP3A4 or CYP2C9 are particularly susceptible to enzyme induction
    - Especially for drugs that undergo extensive first-pass metabolism by CYP3A4 in the gut wall & liver, the reduction in serum concentrations of the object drug can be profound

**Pharmacokinetic DIs**

- **Enzyme Inhibitors Resulting in Reduced Drug Effect**
  - Small number of drugs are not active in the form administered to patients
  - These drugs are known as “prodrugs”
    - Require activation by enzymes in the body before they can produce their effect
  - Inhibition of the metabolism of prodrugs may ↓ the amount of active drug formed & ↓ or eliminate the therapeutic effect

**Pharmacokinetic DIs**

- **Enzyme Induction Resulting in Toxic Metabolites**
  - Some drugs are converted to toxic metabolites by drug metabolizing enzymes
  - Example:
    - APAP is converted primarily to non-toxic metabolites, but small amount is converted to a cytotoxic metabolite
    - Enzyme inducers can ↑ the formation of the toxic metabolite and ↑ risk of hepatotoxicity & damage other organs as well
Pharmacokinetic DIs
- Altered Renal Elimination
- Some drugs active secretion into the renal tubules is an important route of elimination
- Example:
  - Digoxin is eliminated primarily via renal excretion
  - Amiodarone, clarithromycin, itraconazole, propafenone, quinidine can inhibit the process
  - Digoxin toxicity may result

Pharmacodynamic DIs
- Additive Pharmacodynamic Effects
  - 2 or more drugs with similar pharmacodynamic effects given → excessive response & toxicity
- Examples:
  - Combining drugs that prolong QTc interval resulting in ventricular arrhythmias
  - Combining drugs with hyperkalemic effects → hyperkalemia

Pharmacodynamic DIs
- Antagonistic Pharmacodynamic Effects
  - Drugs with opposing pharmacodynamic effects may ↓ the response to 1 or both drugs
- Examples:
  - Drugs that tend to ↑ blood pressure (i.e. NSAIDs) may inhibit the antihypertensive effect of drugs such as ACE inhibitors
  - May inhibit the response to benzodiazepines by the concurrent use of theophylline

Operational Classification (ORCA) of Drug Interactions
- Developed by the Drug Interaction Foundation in an effort to improve the clinical utility of classification systems for drug interactions
- System assigns drug interactions to categories based on the management of the interaction
- Practitioners will find it easier to use & of great benefit as clinical decision support tool

ORCA

<table>
<thead>
<tr>
<th>Class</th>
<th>Avoid Combination (Risk of combination outweighs benefit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 1</td>
<td>Usually Avoid Combination (Use only under special circumstances)</td>
</tr>
<tr>
<td>Class 2</td>
<td>Interactions to avoid by using an alternative drug or other therapy unless the benefit is judged to outweigh the increased risk</td>
</tr>
<tr>
<td>Class 3</td>
<td>Consider alternatives: Alternatives are available that are less likely to interact</td>
</tr>
<tr>
<td>Class 4</td>
<td>Monitor: Early detection can minimize the risk of an adverse outcome</td>
</tr>
<tr>
<td>Class 5</td>
<td>Ignore (Evidence suggests that the drugs do not interact)</td>
</tr>
</tbody>
</table>

Drug Interaction Probability Scale
Designed to assess the probability of a causal relationship between a drug interaction and an event
1. Are there credible reports of this interaction in humans?
2. Is the observed interaction consistent with the known interactive properties of the precipitant drug?
3. Is the observed interaction consistent with the known interactive properties of the object drug?
4. Is the event consistent with the known or reasonable time course of the interaction or other effect?
5. Did the interaction remit upon dechallenge of the precipitant drug with no change in object drug?
6. Did the interaction reappear when the precipitant drug was readministered with continued use of the object drug?
7. Are there reasonable alternative causes for the event?
8. Was the object drug detected in the blood or other fluids in concentration consistent with the proposed interaction?
9. Was the object drug detected in the blood or other fluids in concentration consistent with the proposed interaction?
10. Was the reaction greater than the precipitant drug dose was increased or less when the precipitant drug was decreased?

For each question with either: Yes +1, No -1, Unknown or NA 0
Calculate total score → 8 Highly probable, 5-8 Probable, 2-4 Possible, 1-2 Doubtful
Acetaminophen (Tylenol) [APAP]
- Enzyme Inducers ↑ formation of toxic metabolite, thus ↑ risk of hepatotoxicity, especially in overdoses
- Analgesic effect may be ↓ by enzyme inducers
- ORCA Class 3: Assess Risk & Take Action If Necessary
  - Circumvent/Minimize: Avoid prolonged use of large therapeutic doses APAP & should limit to 2 g/day or less
  - Alternative: other analgesics – salicylates or NSAIDS

<table>
<thead>
<tr>
<th>Enzyme Inducers</th>
<th>Nevirapine</th>
<th>Rifabutin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbiturates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Oxcarbazepine</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Phenytoin</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Primidone</td>
<td>St. John's wort</td>
</tr>
</tbody>
</table>

Carbamazepine (Tegretol)
- Inhibition of CYP3A4 by antimicrobials result in carbamazepine toxicity
- ORCA Class 3: Assess Risk & Take Action If Necessary
  - Alternative: Fluconazole & Azithromycin
  - Monitor: Altered carbamazepine effect

<table>
<thead>
<tr>
<th>Antimicrobials</th>
<th>Fluconazole</th>
<th>Posaconazole</th>
<th>Troleandomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Itraconazole</td>
<td>Quinupristin</td>
<td>Voriconazole</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Ketoconazole</td>
<td>Telithromycin</td>
<td></td>
</tr>
</tbody>
</table>

Warfarin (Coumadin)
- ASA ↑ risk of bleeding due to inhibition of platelet function & gastric erosions
- ASA & APAP can ↑ hypoprothrombinemia
- ORCA Class 2: Use Only If Benefit Felt To Outweigh Risk
  - Alternative: Use APAP, but avoid large or prolong doses & opiates is an option
  - Circumvent/Minimize: Avoid taking ASA, APAP, or other salicylates
  - Monitor: INR if large doses of salicylates/APAP or used more than a few days & monitor for GI bleeding

<table>
<thead>
<tr>
<th>Antagonizing</th>
<th>Acetaminophen (APAP)</th>
<th>Aspirin (ASA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbiturates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Oxcarbazepine</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Phenytoin</td>
<td>Rifampin</td>
</tr>
</tbody>
</table>

Lamotrigine (Lamictal)
- Enzyme inducers ↓ lamotrigine serum concentrations
- ORCA Class 3: Assess Risk & Take Action If Necessary
  - Monitor: Altered lamotrigine effect & doses can be adjusted

<table>
<thead>
<tr>
<th>Enzyme Inducers</th>
<th>Nevirapine</th>
<th>Rifabutin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbiturates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Oxcarbazepine</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Dabrafenib</td>
<td>Phenytoin</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Primidone</td>
<td>St. John's wort</td>
</tr>
</tbody>
</table>

Warfarin (Coumadin)
- Enzyme inducers ↓ anticoagulate effect

- ORCA Class 2: Use Only If Benefit Felt To Outweigh Risk
  - Alternative: suitable alternatives are not available
  - St. John's wort should be avoided
  - Monitor: If necessary use enzyme inducers, monitor for altered response

<table>
<thead>
<tr>
<th>Enzyme Inducers</th>
<th>Cloxacillin</th>
<th>Nafcillin</th>
<th>Rifabutin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Dabrafenib</td>
<td>Oxcarbazepine</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Bosantan</td>
<td>Dicloxacillin</td>
<td>Phenytoin</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Griseofulvin</td>
<td>Primidone</td>
<td>St. John's wort</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Precipitant Drug</th>
<th>Valproic Acid (VPA)</th>
</tr>
</thead>
</table>

Lamotrigine (Lamictal)
- VPA ↑ lamotrigine serum concentrations by inhibiting metabolism
- Combination ↑ risk of Stevens-Johnson Syndrome or toxic epidermal necrolysis
- Cases of hyperammonemic encephalopathy
- ORCA Class 3: Assess Risk & Take Action if Necessary
  - Monitor: Altered lamotrigine effect & evidence of encephalopathy
**Linezolid (Zyvox)**
- Weak MAOI, but when combined with serotonergic agents, serotonin syndrome has been reported
- ORCA Class 2: Use Only If Benefit Felt To Outweigh Risk
  - Alternative: Vancomycin or telavancin

<table>
<thead>
<tr>
<th>Serotonergic Drugs</th>
<th>Bupropion</th>
<th>Duloxetine</th>
<th>Meperidine</th>
<th>Propafenone</th>
<th>Triazodone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonazepam</td>
<td>Escitalopram</td>
<td>Methadone</td>
<td>Sertraline</td>
<td>Venlafaxine</td>
<td></td>
</tr>
<tr>
<td>Cyclobenzaprine</td>
<td>Fentanyl</td>
<td>Milnacipran</td>
<td>Tapentadol</td>
<td>Viltadrazine</td>
<td></td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>Fluoxetine</td>
<td>Mirtazapine</td>
<td>Tetrabenazine</td>
<td>Venloutine</td>
<td></td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>Fluvoxamine</td>
<td>Paroxetine</td>
<td>Tramadol</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Phenytoin (Dilantin)**
- Inhibitors of CYP2C9 may ↑ phenytoin levels → toxicity
- ORCA Class 3: Assess Risk & Take Action If Necessary
- Consider alternative:
  - Azoles Antifungals: ketoconazole, posaconazole, & itraconazole
  - Cimetidine: famotidine, nizatidine, & ranitidine
  - Fluvasstatin: other statins do not appear to inhibit CYP2C9
- SSRIs: paroxetine or venlafaxine do not inhibit CYP2C9
- Monitor: For altered phenytoin effect

<table>
<thead>
<tr>
<th>Enzyme Inhibitors</th>
<th>Amiodarone</th>
<th>Deltarem</th>
<th>Imatinib</th>
<th>Voriconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andegens</td>
<td>Disulfiram</td>
<td>Isoniazid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capitabine</td>
<td>Estronix</td>
<td>Lefumonide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Fluconazole</td>
<td>Metronidazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Fluoroabcil</td>
<td>Sulpfopyrazone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co-trimoxazole</td>
<td>Fluoxetine</td>
<td>Tamosifen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Danazor</td>
<td>Fluoxamine</td>
<td>Ticlopidine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Metoclopramide (Reglan)**
- Inhibitors of CYP2D6 prevent metabolism
- Accumulation may ↑ the risk of tardive dyskinesia & other movement disorders
- ORCA Class 3: Assess Risk & Take Action If Necessary
  - Monitor: For movement disorders

<table>
<thead>
<tr>
<th>Binding Agents</th>
<th>Abiraterone</th>
<th>Cinacalcet</th>
<th>Haloperidol</th>
<th>Propoxyphene</th>
<th>Terbutaline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>Clonazepam</td>
<td>Mirabegron</td>
<td>Quinidine</td>
<td>Thoridazine</td>
<td></td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Diphenhydramine</td>
<td>Propafenone</td>
<td>Ritonavir</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Levothyroxine (Synthroid)**
- Binding agents may inhibit thyroid hormone absorption
- ORCA Class 3: Assess Risk & Take Action If Necessary
  - Circumvent/Minimize: give levothyroxine 2 hours before or 6 hours after the binding agent
  - Monitor: Thyroid hormones for reduced effect

<table>
<thead>
<tr>
<th>Binding Agents</th>
<th>Antacids</th>
<th>Iron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiraterone</td>
<td>Cinacalcet</td>
<td>Haloperidol</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Clonazepam</td>
<td>Mirabegron</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Diphenhydramine</td>
<td>Propafenone</td>
</tr>
<tr>
<td>Cholesteryamine</td>
<td>Lanthanum Carbonate</td>
<td></td>
</tr>
<tr>
<td>Colesevelam</td>
<td>Sevelamer</td>
<td></td>
</tr>
<tr>
<td>Colespolosol</td>
<td>Sucrallate</td>
<td></td>
</tr>
</tbody>
</table>

**Levoquinolone -(Cipro,Levo, & Moxi)**
- Absorption ↓ by agents containing cations
  - i.e. aluminum, magnesium, iron, & calcium
- ORCA Class 3: Assess Risk & Take Action If Necessary
  - Consider Alternative: Calcium carbonate does not impair FQ absorption vs. aluminum-magnesium antacids & need to separate doses
  - Circumvent/Minimize: Give FQ 2 hours before or 6 hours after the cation
  - Monitor: Reduced FQ abx efficacy when taking di- or trivalent cations

<table>
<thead>
<tr>
<th>Binding Agents</th>
<th>Antacids</th>
<th>Iron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium Polycarbophil</td>
<td>Sucrallate</td>
<td></td>
</tr>
<tr>
<td>Didanosine</td>
<td>Zinc</td>
<td></td>
</tr>
</tbody>
</table>

**Trimethoprim (Bactrim, Septra)**
- Alone produces modest ↑ in serum K+
- Hyperkalemia can occur when combined with other drugs that ↑ K+
- ORCA Class 2: Use Only If Benefit Felt To Outweigh Risk
  - Use Alternative: If possible use a different abx
  - Monitor: Serum K+ especially if pt has predisposing factors

<table>
<thead>
<tr>
<th>Binding Agents</th>
<th>Benazaapril</th>
<th>Metoprolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>Perindopril</td>
<td></td>
</tr>
<tr>
<td>Enalapril</td>
<td>Quinapril</td>
<td></td>
</tr>
<tr>
<td>Fosinopril</td>
<td>Ramipril</td>
<td></td>
</tr>
<tr>
<td>Lisinopril</td>
<td>Trandolapril</td>
<td></td>
</tr>
</tbody>
</table>
Vignette

GM is a 65 y/o male who was recently admitted for seizures secondary to alcohol withdrawal. PMH: atrial fibrillation, arthritis, & anemia. During his course, he was found to have hypertension, hypothyroidism, & duodenal ulcer.

Inpatient Medication Profile

- Amiodarone 200 mg PO daily for atrial fibrillation
- Phenytoin 100 mg PO Q8H for seizures
- Sulfamethoxazole-Trimethoprim 800 mg-160 mg PO for UTI
- Lisinopril 20 mg PO daily for hypertension
- Levothyroxine 100 mcg PO daily for hypothyroidism
- Sucralfate 1000 mg PO Q6H for duodenal ulcer
- Ferrous Sulfate 300 mg PO three times a day for iron deficiency anemia
- Lamotrigine 150 mg PO twice daily for seizures
- APAP 500 mg PO every 6 hours for arthritis
- Warfarin 5 mg PO daily for atrial fibrillation

Discussion

1. Review patient medication list for DIs
2. Are there any DIs?
3. If so, list all the DIs including what type of interaction and how should one manage each

Conclusion

- Drug interactions occur by one drug affecting the pharmacokinetics or pharmacodynamics of another drug
- Reviewed some of the most common drug interactions recognized in practice
- Evaluated a patient’s medication list for potential drug interactions