Clinical Pearls: Significant Drug Interactions

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Learning Objectives

- Describe the classifications of drug interactions
- Explain clinical outcomes resulting from drug interactions
- Identify examples and management strategies of drug interactions in the oncology population

Patient Case

JW is a 43 yo male admitted for newly diagnosed Ph+ B-cell ALL

- Past Medical History
  - Hyperlipidemia
  - Depression
- Allergies
  - Penicillin

- Labs
  - Ca: 8.4  Mg: 2.3  Uric acid: 6.9  LDH: 764
  - 138  102  18  106
  - 4.1  24  0.96  15.3
  - 15.3  7.1  20.2  16
  - ANC: 0.3

Other Medications

- Allopurinol
- Levofoxacin (prophylaxis)
- Pantoprazole
- Posaconazole (prophylaxis)
- Sertraline
- Simvastatin
- Valacyclovir (prophylaxis)
- Ondansetron premed + prn
- Prochlorperazine prn

Prevalence

- At least one potential drug-drug interaction found in 27-58% of ambulatory cancer patients
- At least one potential severe drug interaction involving chemotherapy found in 14% of patients ≥70 years old
- At least one potential drug-drug interaction in 46% of patients receiving oral anticancer drugs
- Drug-drug interactions estimated to be cause of approximately 4% of deaths

Disclosures

- Nothing to disclose
Current Trends

- FDA estimates that >25% of antineoplastic agents in pipeline now are planned as oral drugs
- Chronic daily dosing of oral chemotherapies
- Chronic disease state = Long-term cancer treatment
- Longer survival time = Increased medications for treatment of comorbidities

Cost of Drug Interactions

- Morbidity and mortality due to drugs costs $136 billion per year
- Drug interactions represents 3-5% of in-hospital medication errors
- Drug interactions may contribute to 20-30% of adverse drug reactions
- Drug-drug interactions associated with longer length and increased cost of hospitalization (OR 4.38 and 1.79, respectively)

Medications Involved

- Chemotherapy (13-29%)
  - Traditional
  - Oral chemotherapy
  - Hormonal agents
- Supportive care medications
  - Anti-emetics
  - Pain medications
  - Anti-infectives
- Non-cancer-related medications
- Complementary alternative medications

Risk Factors for Drug Interactions

- Number of drugs
  - Each additional medication (OR 1.4; P<0.0001)
  - Use of ≥8 drugs associated with potential drug interaction (P=0.0004)
- Use of over the counter drugs (OR 0.56; P=0.045)
- Type of medication (vs. supportive care meds only)
  - Drugs for comorbid conditions only (OR 8.6; P<0.0001)
- Cancer type – Brain (OR 6.7; P=0.0025)

Effects from Drug Interactions

- Efficacy
  - Increase or decrease in anti-neoplastic or other drug effect
- Safety
  - QT-interval prolongation
  - Central nervous system depression
  - Increased bleeding risk

Audience Response Question #1

- Which one of these factors increases JW’s risk for drug interactions?
  A. Age
  B. Number of medications
  C. Type of cancer diagnosis
  D. Sex

Classification of Drug Interactions

- Pharmaceutical
- Pharmacokinetic
- Pharmacodynamic

Pharmaceutical Interactions

- Two or more drugs are altered due to physical or chemical incompatibility when combined
- Mitomycin mixed in Dextrose 5% (D5W) versus NaCl 0.9% (NS)
  - At 12 hours: concentrations decreased 10% in NS vs. 33% in D5W
  - At 24 hours: concentrations decreased 23% in NS vs. 42% in D5W

Pharmacokinetic Interactions

- One drug alters absorption, distribution, metabolism, or excretion of another drug

Effects of Gastric pH Modifier

DASATINIB (and other TKIs)

- pH-dependent solubility
- Randomized, 3-treatment, crossover study in healthy patients
- Compared to dasatinib alone
  - No difference in exposure when antacid given 2 hours before dasatinib
  - Dasatinib exposure reduced by ~60% when famotidine given 10 hours before dasatinib
- Recommendations
  - H2 receptor antagonists and proton pump inhibitors (PPIs) should not be given with dasatinib
  - Antacids may be given if doses are separated from dasatinib by 2 hours

Methotrexate + PPIs: Significant Interaction?

- Theoretical mechanisms
  - PPI inhibition of renal H+/K+-ATPase decreases active tubular secretion of methotrexate
  - Inhibition of breast cancer resistance protein (BCRP) involved in methotrexate transport
- Adverse effects
  - Increased mucositis
  - Enhanced myelosuppression
  - Nephrotoxicity

Methotrexate + PPIs: Significant Interaction?

- Survey of FDA Adverse Event Reporting System (AERS) found evidence of PPI interference of methotrexate elimination
- Retrospective analysis identified risk factors for delayed methotrexate clearance
  - Abnormally high serum creatinine and AST
  - Co-administration of PPIs
  - Within group of patients with delayed elimination of methotrexate: significantly more PPI given vs. no PPI given (41.9% vs. 20%, P<0.05)
Methotrexate + PPIs: Significant Interaction?

INSIGNIFICANT

- Retrospective analysis of methotrexate elimination in patients receiving high dose methotrexate (N=56 patients; 201 cycles)

<table>
<thead>
<tr>
<th></th>
<th>PPI</th>
<th>No PPI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate level (micromole/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 24 hr</td>
<td>8.0</td>
<td>3.9</td>
<td>0.013</td>
</tr>
<tr>
<td>At 48 hr</td>
<td>0.28</td>
<td>0.215</td>
<td>NS</td>
</tr>
<tr>
<td>At 72 hr</td>
<td>0.075</td>
<td>0.05</td>
<td>0.037</td>
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</tbody>
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Delayed elimination (%)

<table>
<thead>
<tr>
<th></th>
<th>PPI</th>
<th>No PPI</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>At 24 hr</td>
<td>19.2</td>
<td>20.2</td>
<td>NS</td>
</tr>
<tr>
<td>At 48 hr</td>
<td>20.0</td>
<td>11.3</td>
<td>NS</td>
</tr>
<tr>
<td>At 72 hr</td>
<td>36.2</td>
<td>33.7</td>
<td>NS</td>
</tr>
</tbody>
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- After controlling for confounders and possible clustering, PPI not significant predictor of methotrexate level, delayed elimination, or time to level <0.1 micromole/L

- Conclusions
  - Lack of association between use of PPI and methotrexate elimination
  - Clinical significance of potential interaction is likely small
  - Future prospective trial would allow for control of multiple cycles

Cytochrome P450 (CYP)

- CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 responsible for estimated >90% of drug oxidation
- CYP3A4
  - Metabolizes ~50% of drugs
  - Primarily in liver, but presence in small intestines plays important role in first-pass metabolism
- Genetic polymorphisms identified for CYP2A6, CYP2D6, CYP2C9, and CYP2C19
- Induction typically seen several days to weeks after drug administration
- Inhibition seen immediately after drug administration

Vincristine + Azole Antifungals

- Vincristine metabolism mediated by CYP3A subfamily and substrate of P-glycoprotein (P-gp)
- Triazole antifungals inhibit CYP3A4
- Itraconazole and posaconazole also inhibit P-gp
- Increased adverse effects
  - Severe neurotoxicity (peripheral neuropathy)
  - Severe GI symptoms: constipation, ileus, abdominal pain/distension
  - Electrolyte abnormalities (hyponatremia and SIADH)
  - Seizures

- Literature review and analysis of vincristine and azole antifungal case reports
- No case reports found for fluconazole
- Median time to adverse drug interaction with vincristine
  - Itraconazole: 9.5 days
  - Posaconazole: 13.5 days
  - Voriconazole: 30 days
- Recommendations
  - Use alternative non-azole antifungal agent (i.e. echinocandins or liposomal amphotericin B)
  - Discontinue azole antifungal prior to vincristine administration

Audience Response Question #2

- How would you manage JW’s vincristine-posaconazole interaction?
  A. Continue with concomitant use of both
  B. Hold vincristine
  C. Empirically dose reduce vincristine
  D. Switch posaconazole to alternate anti-fungal
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**Pharmacodynamic Interactions**

- Mechanism of action of multiple drugs influence the same physiological process
- Can be additive, synergistic, or antagonistic

<table>
<thead>
<tr>
<th>Pharmacodynamic Interaction</th>
<th>Incidence (%)</th>
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<tbody>
<tr>
<td>CNS Interactions</td>
<td>73%</td>
</tr>
<tr>
<td>GI Interactions</td>
<td>8%</td>
</tr>
<tr>
<td>QT Prolongation</td>
<td>4%</td>
</tr>
<tr>
<td>Other</td>
<td>15%</td>
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**QT Prolongation**

- Torsade de pointes (TdP) more likely to occur with:
  - QTc > 500 msec
  - Long intervals of prolongation
- Incidence of TdP: range from <1 in 10,000 to 1 in 100,000 cases
- Considerations in oncology patients:
  - Prolonged QTc interval at baseline
  - General risk factors: older age, underlying coronary disease, previous myocardial infarction
  - Cancer-related risk factors: altered drug clearance, low electrolyte levels, multiple offending medications

**Common QT Prolonging Agents**

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Tyrosine kinase inhibitors (TKIs)</td>
<td>Crizotinib, lapatinib, nilotinib, pazopanib, sorafenib, sunitinib, vandetanib, vemurafenib</td>
</tr>
<tr>
<td>Azole antifungal agents</td>
<td>Fluconazole, voriconazole, posaconazole</td>
</tr>
<tr>
<td>SHT antagonist antiemetic</td>
<td>Ondansetron, granisetron, palonosetron, dolasetron</td>
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<tr>
<td>Arsenic trioxide</td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Levofloxacin, moxifloxacin, ciprofloxacin</td>
</tr>
<tr>
<td>Macrolide antibiotics</td>
<td>Clarithromycin, azithromycin, erythromycin</td>
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**Recommendations**

- Check EKG 24-48 hours prior to and 1 week after concomitant therapies of multiple QT prolonging medications
- Clinical concern when QTc prolongation of ~>500 msec or change from baseline of >60 msec
- Baseline EKG and thorough cardiac and medication history should be obtained
- Monitor and aggressively replace electrolytes (i.e. K⁺, Mg²⁺, and Ca²⁺)
- Preclinical identification of QT effects should have expanded QT assessment in subsequent trials

**Current Strategies**

- Drug interaction alerts at point of Computerized Physician Order Entry (CPOE)
- Drug interaction alerts upon pharmacist verification
- Admission medication reconciliation
- Discharge medication reconciliation
- Adverse event reporting (i.e. FDA MedWatch)
Alert Fatigue

- Frequent “false” alarms or warnings that may not be clinically significant
- Institute for Safe Medication Practices (ISMP) recommendations
  - Reduce sensitivity of alert system
  - Identify conditions that lead to the most serious adverse events
  - Report invalid or clinical insignificant warnings
  - Generate report of bypassed alerts

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Therapeutic Drug Monitoring

**Rationale**

- Marked inter-individual pharmacokinetic variability
- Relationship identified between plasma concentrations and pharmacodynamic end points
- Oral targeted chemotherapy
  - Significant drug-drug interactions
  - Chronic usage
  - Availability of bio-analytical methods
  - Limited intra-individual PK
  - Expensive treatments

**Examples**

- **Imatinib**
  - Cmin associated with hematological, cytogenetic, and molecular responses and progression-free survival
  - Free AUC relationship with number of toxicities
- **High dose methotrexate**
  - Monitoring of drug elimination and prevention of toxicity
  - Does not provide guidance for dose adjustment
- **Busulfan**
  - Target AUC range minimizes non-relapse mortality and toxicities, while maximizing efficacy

**Challenges**

- Time and cost of lab draws, processing, and interpretation
- Shipment to laboratory if not done at location
- Prospective validation of TDM challenging to perform
- Relationships between PK and PD are more difficult to ascertain for drug combinations
- Accounting for other specific factors

Role for Pharmacists

- Link between oncologists and general practitioners
- Reporting adverse drug events
- Therapeutic drug monitoring
- Complementary alternative medicine and food interactions
- Tempering alert fatigue

Audience Response Question #3

Which of the following do you think is the most effective way to prevent adverse events caused by drug interactions?

A. Increase adverse event reporting
B. Therapeutic drug monitoring
C. Refining clinically significant drug interaction alerts
D. Increase accuracy of medication reconciliation
Conclusion

• Drug-drug interactions can be categorized into pharmaceutical, pharmacokinetic, and pharmacokinetic interactions
• Despite significant advancements in technologies and clinical knowledge, drug-drug interactions continue to account for costly adverse drug events
• The role for pharmacists is expanding and evolving as new strategies for identifying clinical outcomes of interactions are explored and developed

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