Clinically Significant Drug Interactions: A Case Series Presentation

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Objectives

1. Differentiate between a pharmacokinetic and a pharmacodynamic drug-drug interaction.

2. Stratify the severity and potential outcomes of a drug-drug interaction based on a patient scenario.

3. Develop a plan to manage a drug-drug interaction, including safe therapeutic alternatives and monitoring.
The Drug Interaction Pair

- **Object Drug:** activity of this drug is altered
  - The SUBSTRATE of a CYP450 enzyme
  - Amiodarone inhibits the metabolism of warfarin via CYP2C9 inhibition

- **Precipitant Drug:** drug causing the change
  - The INHIBITOR or INDUCER of a CYP450 enzyme
  - Amiodarone inhibits the metabolism of warfarin via CYP2C9 inhibition
Pharmacokinetic (PK) Interactions

- “The body’s effect on the drug”
- Precipitant drug alters the rate or extent of the object drug’s ADME
  - Absorption
  - Distribution
  - Metabolism
  - Excretion
Pharmacodynamic (PD) Interactions

▪ “The drug’s effect on the body”

▪ The effect of one drug is changed by presence of another drug at its site of action
  ▪ Beta-agonists + beta-blockers = wheezing

▪ Result in *additive or antagonistic effects* based on pharmacology of the drugs
  ▪ Lisinopril + Furosemide + Naproxen = ↑BUN/SrCr
How Do We Remember Them All?

- Over 2,000 drug interactions listed in the most updated references

- Must be alert for those situations when the patient is truly at risk

- Knowledge of the general principles of drug interactions can help you anticipate some adverse effects before they occur
Who is at Risk?

- Pts with impaired pathways of drug elimination
  - Renal or hepatic impairment

- Pharmacogenetic polymorphism
  - CYP450 enzymes

- Pts receiving narrow therapeutic index (NTI) drugs
  - Digoxin, phenytoin, theophylline, warfarin

- Pts receiving “common culprit” drugs
  - Amiodarone, azoles, HIV protease inhibitors
Who is at Risk?

- Very young and very old
- Females
- Multiple chronic conditions
- Number of medications
- Multiple prescribers or pharmacies
- Infrequent monitoring or non-compliance
Double Trouble: PK & PD Interaction

- Pt is an 82 yo F with a hx of Vfib/Vtach admitted with HF

- **Home Meds:**
  - Quinidine gluconate 324 mg po q8hrs (Vfib/Vtach)
  - Carvedilol 6.25 mg po BID (HF)
  - Spironolactone 25 mg po BID (HF)
  - Levothyroxine 100 mcg po daily (hypothyroidism)

- **New Meds in Hospital:**
  - Furosemide 40 mg IV BID for HF
  - Ceftriaxone 1 g IV daily for pneumonia
  - Fluconazole 100 mg po daily for oral thrush

- Can you identify any clinically significant drug interactions?
**Time Course of Interaction**

- **Quinidine level** ↑ after fluconazole initiated
  - NL = 2-5 mg/L
- **Thrombocytopenia, N/V/D** same time course
- ↓ K⁺, ↓ Mg++
- **QT prolongation** (QTc 450 → 680)
- **Quinidine held**
Mechanism of Interaction

“DOUBLE TROUBLE”:

- **Pharmacodynamic Interaction**
  - Quinidine + fluconazole = ↑ risk of QT prolongation

- **Pharmacokinetic Interaction:**
  - Fluconazole is a moderate inhibitor of CYP 3A4
  - Quinidine is a CYP 3A4 substrate
  - ∴ ↑ Quinidine levels

- Additive effects that increase risk of cardiotoxicity
Double Trouble: Pharmacokinetic & Pharmacodynamic Interaction

What Would You Do?

A. Choose an alternative antifungal agent to treat the thrush
B. If using fluconazole, monitor the EKG and quinidine levels
C. Monitor electrolytes, such as potassium and magnesium, and replete if necessary
D. Any of the above would be appropriate
Management of QT prolongation

- Identify drugs that can prolong QT interval
  - Focus on NEW drugs

- Choose safer alternatives
  - \( \Delta \) Fluconazole → nystatin or clotrimazole troches

- Assess patient risk factors
  - Elderly, female sex, Afib, diuresis, diarrhea

- Monitor K+ and Mg++ closely
  - Replete K+ ≥ 4 and Mg++ ≥ 2

- Monitor the EKG, quinidine levels
QT Prolongation & Torsade de Points (TdP)

Torsades de pointes = “twisting of the points”
## Risk Factors for TdP

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Use of QT prolonging drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female Sex</td>
<td>Use of QT prolonging drugs</td>
</tr>
<tr>
<td>Advanced Age</td>
<td>Rapid rate of IV infusion with a QT-prolonging drug</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>Diuretics, diarrhea</td>
</tr>
<tr>
<td>Baseline QT prolongation (QTc &gt; 500 ms)</td>
<td>Hypokalemia, hypomagnesemia</td>
</tr>
<tr>
<td>Congenital long-QT syndrome</td>
<td>Impaired renal function</td>
</tr>
<tr>
<td>Cardiac disease (MI, Afib, HF)</td>
<td>Impaired hepatic function</td>
</tr>
</tbody>
</table>
# Drugs that May Cause TdP

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Individual Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azole Antifungals</td>
<td>Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole</td>
</tr>
<tr>
<td>Class Ia Antiarrhythmics</td>
<td>Disopyramide, procainamide, quinidine</td>
</tr>
<tr>
<td>Class III Antiarrhythmics</td>
<td>Amiodarone, sotalol, dofetilide</td>
</tr>
<tr>
<td>Macrolide Antibiotics</td>
<td>Clarithromycin &gt; erythromycin &gt; azithromycin</td>
</tr>
<tr>
<td>Quinolone Antibiotics</td>
<td>Moxifloxacin &gt; levofloxacin &gt; ciprofloxacin</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td><em>Typical</em>: chlorpromazine, haloperidol, thioridazine</td>
</tr>
<tr>
<td></td>
<td><em>Atypical</em>: ziprasidone, olanzapine</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Methadone, citalopram, escitalopram, tamoxifen, ondansetron</td>
</tr>
</tbody>
</table>
1. “Known Risk of TdP”
   - Flecainide, methadone, thioridazine

2. “Possible Risk of TdP”
   - Mirtazapine, olanzapine, tamoxifen

3. “Conditional Risk of TdP”
   - Fluoxetine, ketoconazole, metoclopramide
No Monitoring for DOACs… A Good or a Bad Thing?

- Pt is a 67 yo M with hx of HTN, Afib and dyslipidemia admitted for new-onset seizures.

- **Home Meds:**
  - Hydrochlorothiazide 25 mg po daily (HTN)
  - Metoprolol tartrate 75 mg po BID (HTN)
  - Lisinopril 20 mg po daily (HTN)
  - Pravastatin 20 mg po daily (hyperlipidemia)
  - Rivaroxaban 20 mg po daily for Afib
  - Digoxin 0.125 mg po daily for Afib

- **New Meds:**
  - Phenytoin 100 mg po q8h (seizures)

- Can you identify any clinically significant interactions?
Mechanism of Interaction

- Dual PK Mechanism:
  - **Phenytoin** is a strong inducer of CYP 3A4 & p-glycoprotein (PGP)
  - **Rivaroxaban** is a substrate of PGP & CYP 3A4

- PGP and CYP 3A4: coordinated regulation in the intestine to eliminate drugs

- PGP and CYP3A4 have common substrates
### Rivaroxaban (Xarelto®) Drug Labeling

<table>
<thead>
<tr>
<th>Precipitant Drug</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dual PGP &amp; STRONG CYP 3A4 Inhibitors</td>
<td>Avoid Use</td>
</tr>
<tr>
<td>• Ketoconazole</td>
<td></td>
</tr>
<tr>
<td>• Itraconazole</td>
<td></td>
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<tr>
<td>• Lopinavir/ritonavir (Kaletra®)</td>
<td></td>
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<tr>
<td>• Ritonavir</td>
<td></td>
</tr>
<tr>
<td>• Indinavir</td>
<td></td>
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<tr>
<td>• Conivaptan</td>
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</table>

<table>
<thead>
<tr>
<th>Dual PGP &amp; STRONG CYP 3A4 Inducers</th>
<th>Avoid Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Carbamazepine</td>
<td></td>
</tr>
<tr>
<td>• <strong>Phenytoin</strong></td>
<td></td>
</tr>
<tr>
<td>• Rifampin</td>
<td></td>
</tr>
<tr>
<td>• St. John’s Wort</td>
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</tbody>
</table>
### Rivaroxaban (Xarelto®) Drug Labeling

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<tr>
<th>Precipitant Drug</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td><strong>Dual PGP &amp; MODERATE CYP 3A4 Inhibitors</strong></td>
<td>Xarelto® should NOT be used in pts with CrCl 15-80 ml/min unless the BENEFIT &gt; RISK</td>
</tr>
<tr>
<td>• Amiodarone</td>
<td></td>
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<tr>
<td>• Dronedarone</td>
<td></td>
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<tr>
<td>• Diltiazem</td>
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<td>• Verapamil</td>
<td></td>
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<tr>
<td>• Cimetidine</td>
<td></td>
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<tr>
<td>• Erythromycin</td>
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</table>
No Monitoring for DOACs: A Good or a Bad Thing?

What Would You Do?

A. Change phenytoin to an alternative anticonvulsant, such as levetiracetam 500 mg po q12h

B. Change rivaroxaban to warfarin, with close INR monitoring

C. Change rivaroxaban to an alternative NOAC, such as dabigatran or apixaban

D. A or B

E. All of the above would be appropriate
Management of Interaction

- Be aware of potential interactions with rivaroxaban
  - Focus on NEW drugs (phenytoin)
  - Consider STRONG & MODERATE CYP 3A4 inhibitors
  - ↑ Risk in renal insufficiency

- Choose safer alternatives
  - Δ Phenytoin → levetiracetam (Keppra®) 500 mg po BID
  - OR
  - Δ Rivaroxaban → warfarin
    - Warfarin CAN be monitored and dose adjusted
The $181,000 Drug Interaction

- A 52 yo M, 14 months s/p heart transplant, was admitted to the hospital with neutropenic fever.

**Home Meds:**
- Cyclosporine 100 mg po q12hrs *(Heart transplant)*
- Azathioprine 150 mg po q12hrs *(Heart transplant)*
- Prednisone 10 mg po daily *(Heart transplant)*
- Rosuvastatin 10 mg po QHS *(Hyperlipidemia)*
- Amlodipine 10 mg po daily *(HTN)*
- Allopurinol 300 mg po daily *(Hyperuricemia)*

**Are there any clinically significant drug interactions?**

The $181,000 Drug Interaction

<table>
<thead>
<tr>
<th>Patient’s Admission Laboratory Values</th>
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<tbody>
<tr>
<td>WBC</td>
</tr>
<tr>
<td>ANC (absolute neutrophil count)</td>
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<tr>
<td>Hemoglobin</td>
</tr>
<tr>
<td>Platelets</td>
</tr>
<tr>
<td>BUN</td>
</tr>
<tr>
<td>SrCr</td>
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</table>

• Pt hospitalized x 31 days, with slow bone marrow recovery

• **Cost of hospital stay: $181,000**

• PCP had prescribed allopurinol 2 months prior for cyclosporine-induced hyperuricemia

• Transplant physicians were unaware of allopurinol

Azathioprine/6-MP + Xanthine Oxidase Inhibition

- Xanthine oxidase metabolizes azathioprine & 6-MP to an INACTIVE metabolite.
- Xanthine oxidase inhibition by allopurinol or febuxostat shunts the metabolic pathway to ↑↑ ACTIVE metabolites.
- ↑ Risk of myelosuppression.
Theophylline + Xanthine Oxidase Inhibition

- Allopurinol & febuxostat inhibit xanthine oxidase
- This leads to ↓ metabolism & accumulation of theophylline (xanthine)
- ↑ Risk of seizures, arrhythmias
The $181,000 Drug Interaction

What Would You Do?

A. If allopurinol continued, monitor the CBC closely, and for s/sx of infection

B. Decrease the dose of azathioprine to 100 mg po q12h

C. Change allopurinol to febuxostat (Uloric®)

D. A or B

E. All of the above would be appropriate
# Management of Interaction

<table>
<thead>
<tr>
<th></th>
<th>Theophylline</th>
<th>Azathioprine (Imuran®)</th>
<th>6-MP</th>
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</thead>
<tbody>
<tr>
<td><strong>Allopurinol</strong></td>
<td>↓ <em>Theophylline dose by 25-33%</em> with allopurinol doses ≥ 600 mg/day</td>
<td>↓ <em>Azathioprine dose by 25-33%</em> with concomitant allopurinol</td>
<td>↓ <em>6-MP dose by 25-33%</em> with concomitant allopurinol</td>
</tr>
<tr>
<td></td>
<td>Monitor theophylline levels (5 -15 mcg/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Febuxostat (Uloric®)</strong></td>
<td>Use with caution</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
</tr>
<tr>
<td></td>
<td>Monitor theophylline levels (5 – 15 mcg/mL)</td>
<td></td>
<td></td>
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</table>
Hyperkalemia & Cardiac Risk

- An 82 yo M with a history of DM was admitted to the hospital for urosepsis.

Hospital Discharge Meds:
  - Bactrim DS 1 tab po BID
  - Simvastatin 10 mg po daily
  - Aspirin EC 81 mg po daily
  - Losartan 100 mg po daily
  - Metformin 500 mg po BID
  - Dyazide 25/37.5 mg po daily

- Which drugs can increase the risk of hyperkalemia?
Hyperkalemia & Cardiac Risk

- Patient discharged with a new Rx for Bactrim DS (Sulfamethoxazole/Trimethoprim) 1 po BID & instructions to continue home medications, including:
  - Losartan 100 mg po daily
  - HCTZ 25mg/ triamterene 37.5 mg po daily

- 5 days later, patient re-admitted with:
  - BUN = 45, SrCr = 2.8, K = 6.7
  - ECG changes
Trimethoprim (TMP)-Induced Hyperkalemia

ECG Changes:
- Peaked or “Tented” T-waves
- Prolonged PR interval
- Disappearing P wave
- Widening of the QRS
- Amplified R wave

Treatment:
- IV Ca^{++} gluconate to ↓ cardiac toxicity
- K^+ correction
Trimethoprim-Induced Hyperkalemia

- Losartan, HCTZ/ triamterene & Bactrim held

- For hyperkalemia:
  - Regular insulin 10 units IV + 1 amp D50%
  - Ca gluconate 1 gm IV infused over 3 minutes
  - IV fluids

- $K^+ = 5.2$ the next AM
- BUN/Cr baseline in 3 days (BUN 20, SrCr 1.1)
- Patient discharged
Trimethoprim-Induced Hyperkalemia

TMP functions like amiloride in distal renal tubule

Risk Factors

- Concurrent Drugs that ↑ K⁺:
  - **K-sparing diuretics**: spironolactone, eplerenone, amiloride, triamterene
  - **ACE-Is**: enalapril, lisinopril, benazepril, fosinopril
  - **ARBs**: candesartan, losartan, valsartan
  - **NSAIDS**
  - **K+ supplements/ K+ salt substitutes**

- Advanced age
- Renal dysfunction
- DM
TMP- Induced Hyperkalemia: Prevention

- **Consider alternatives** to SMX/TMP in pts receiving multiple drugs that can ↑ K⁺
  - *I.e.*, Quinolones or cephalosporins for UTI

- **Dose reduce SMX/TMP in renal impairment**

<table>
<thead>
<tr>
<th>CrCl 15 – 30 ml/min</th>
<th>Administer 50% of dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl &lt; 15 ml/min</td>
<td>NOT recommended</td>
</tr>
</tbody>
</table>

- **Monitor BUN, SrCr, K⁺ (within 5-7 days)**
- **Monitor early s/sx of hyperkalemia:**
  - Muscle weakness, bradycardia
Conclusions

Stepwise Approach to Preventing Drug Interactions

1. Take a thorough medication history
2. Focus on high-risk patients
3. Focus on high-risk drugs
   - Object drugs: NTI
   - Precipitant drugs: common culprits
4. Keep a short list of top DDIs
5. Use multiple resources
Focus on High Risk Patients
Drug-Drug Interaction References


4. www.hanstenandhorn.com

5. www.drug-interactions.com
References