Killer Drug Interactions

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Disclosure

• I have no financial interests or relationships to disclose
Primum Non Nocere

• “first do no harm”
• 3 – 5% of preventable in-hospital adverse drug reactions are due to drug interactions
• 4th leading cause of death in hospitalized patients

Categories

• Drugs with food/beverage
  – Alcohol
  – Grapefruit
  – Licorice
  – Chocolate

• Drugs with dietary supplements
  – St John’s Wort
  – Vitamin E
  – Gingko biloba

• Drugs with other drugs (see common culprits)
Common Culprits

- Warfarin
- Digoxin
- Anticonvulsants
- Antibiotics
- Theophylline
- Serotonergic agents
- Azole antifungals
- Antiretrovirals
Mechanisms

- Competition at drug transporters
- Drug binding in GI tract
- Induction/inhibition of metabolism
- Additive effect

Case 1
• 64 y/o female presents to ER after two syncopal events; complains of weakness, palpitations, dizziness & light-headedness

• PMHx: Afib, CHF, CVA 2012, Hypothyroidism, diagnosed with pneumonia 2 days prior

• Home Medications:
  – Amiodarone 200mg BID
  – Rivaroxaban 20mg daily
  – Lisinopril 20mg daily
  – Metoprolol succinate 50mg daily
  – Levothyroxine 88mcg daily
  – Levofloxacin 750mg daily x5 days *new med*
QT Prolonging Medications

- **Cardiovascular**
  - Amiodarone
  - Dofetilide
  - Dronedarone
  - Flecaïnine
  - Procainamide
  - Quinidine
  - Sotolol

- **Antiemetic**
  - Droperidol
  - Ondansetron

- **Antimicrobial**
  - Macrolides
  - Fluoroquinolones
  - Fluconazole

- **Neurologic/Psyciatric**
  - Chlorpromazine
  - Citalopram/escitalopram
  - Paroxetine
  - Methadone
  - Haloperidol
  - Donepezil
Case 2
• 64 y/o female presents to ER after two syncopal events; complains of muscle weakness & palpitations,
• PMHx: Afib, CHF, CVA 2012, Hypothyroidism, diagnosed with UTI 2 days prior
• Home Medications:
  – Amiodarone 200mg BID
  – Rivaroxaban 20mg daily
  – Lisinopril 20mg daily
  – Metoprolol succinate 50mg daily
  – Levothyroxine 88mcg daily
  – Sulfamethoxazole/TMP 800-160mg BID x5 days *new med*
Potassium Raising Medications

- ↓ aldosterone production
  - Cyclosporine
  - Tacrolimus
  - NSAIDs

- Aldosterone antagonists
  - Spironolactone
  - Elperenone

- K⁺ sparing diuretics
  - Amiloride
  - Triamterene

- Beta-blockers
  - Propranolol
  - Labetalol

- Angiotensin inhibitors
  - Angiotensin-converting enzyme (ACE) inhibitors
  - Angiotensin II receptor blockers (ARBs)
  - Direct renin inhibitors

- Trimethoprim

Reid JL, Am J Cardiol 1986;57(12):23F
Case 3
• 64 y/o female presents to ER after two syncopal events; complains of weakness, palpitations, dizziness, light-headedness & black stools
• PMHx: Afib, CHF, CVA 2012, Hypothyroidism, diagnosed with UTI 2 days prior
• Home Medications:
  – Amiodarone 200mg BID
  – Warfarin 4mg daily
  – Lisinopril 20mg daily
  – Metoprolol succinate 50mg daily
  – Levothyroxine 88mcg daily
  – Sulfamethoxazole/TMP 800/160mg BID x5 days *new med*
  – Fluconazole 150mg PO x1 PRN vaginal yeast
Meds that Potentiate Warfarin

• Antibiotics
  – Fluoroquinolones
  – Azole antifungals
  – Isoniazid
  – Metronidazole
  – Sulfamethoxazole/TMP

• Cardiovascular
  – Amiodarone
  – Diltiazem
  – Fenofibrate
  – Propafenone

• CNS Drugs
  – Alcohol
  – Citalopram
  – Sertraline
  – Phenytoin

• Food/Herbals
  – Fish oil
  – Mango
  – Grapefruit
  – Boldo-fungreek
  – Don quai

Meds that Inhibit Warfarin

• Antibiotics
  – Griseofulvin
  – Nafcillin
  – Ribavirin
  – Rifampin
  – Ritonavir

• Cardiovascular
  – Cholestyramine
  – Bosentan

• CNS Drugs
  – Barbiturates
  – Carbamazepine

• Food/Herbals
  – Vitamin K
    • Kale, Collards, Spinach, Turnip greens, Mustard greens
  – Avocado
  – Soy milk
  – Ginseng

Case 4
• 42 y/o male brought to ER by EMS for unresponsiveness. Per patient’s spouse, he was acting confused & off balance the day prior. Patient has been self-treating acid reflux with an OTC H2-blocker & OTC proton pump inhibitor since last week

• PMHx: Seizure disorder, HTN, GERD, obesity

• Home medications
  – Phenytoin 200mg PO BID
  – Amlodipine 10mg daily
  – Cimetidine 200mg PO BID *new med*
  – Omeprazole 20mg PO BID *new med*
Phenytoin Pharmacokinetics

• Absorption
  – IR: 1.5 – 3 hours
  – ER: 4 – 12 hours
  – Acute ingestion: up to 2 weeks

• Protein binding: 90 – 95%
  – Free phenytoin is only pharmacologically active form

• Metabolism: CYP2C9 & 2C19

• Elimination: First-order and ZERO-ORDER kinetics
# Phenytoin Levels & Clinical Effects

<table>
<thead>
<tr>
<th>Free concentration</th>
<th>Clinical Effects</th>
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<tbody>
<tr>
<td>&lt;10 mg/L</td>
<td>No effects, subtherapeutic</td>
</tr>
<tr>
<td>10 – 20 mg/L</td>
<td>Therapeutic range, rare occassional horizontal nystagmus</td>
</tr>
<tr>
<td>20 – 30 mg/L</td>
<td>Nystagmus</td>
</tr>
<tr>
<td>30 – 40 mg/L</td>
<td>Vertical nystagmus, diplopia, ataxia, slurred speech, tremor, hyperreflexia, nausea &amp; vomiting</td>
</tr>
<tr>
<td>40 – 50 mg/L</td>
<td>Lethargy, confusion, disorientation, hyperactivity, clonus, asterixis, choreoathetosis</td>
</tr>
<tr>
<td>&gt; 50 mg/L</td>
<td>Coma, seizures</td>
</tr>
</tbody>
</table>

\[
\text{Phenytoin}_{\text{normal}} = \frac{\text{Phenytoin}_{\text{measured}} \times 4.4}{\text{albumin concentration}}
\]

Craig S, Neurocrit Care 2005; 3:161 – 170
Meds that Decrease Phenytoin Effects

- Folic acid
- Dexamethasone
- Phenobarbital
- Diazepam
- Rifampin
- Methadone
- Nitrofurantoin
- Estrogens

Craig S, Neurocrit Care 2005; 3:161 – 170
Meds that Increase Phenytoin Effects

- Valproic acid
- Carbamazepine
- Warfarin
- Isoniazid
- Cimetidine
- Ranitidine
- Omeprazole
- Ibuprofen
- Metronidazole
- Chloramphenicol
- Fluconazole
- Fluoxetine
- Risperidone
- Amiodarone
- Allopurinol

Craig S, Neurocrit Care 2005; 3:161 – 170
Case 5
• 42 y/o male presents to ER for agitation, confusion, hallucinations, hyperthermia, hyperreflexia, and tremor. Patient was seen by PCP and initiated on paroxetine 2 days ago for new diagnosis of depression

• PMHx: Migraines, h/o heroin abuse (follows with methadone clinic x3 years), obesity

• Home medications
  – Methadone 80mg daily
  – Rizatriptan 10mg PRN headache
  – Paroxetine 30mg daily*new med*
Methadone Safety Concerns

- Long & variable half-life (up to 120 hours)
- Respiratory depressant effect starts later and lasts longer than analgesic effect
- Multicompartmental pharmacokinetics
- QT prolongation & ventricular arrhythmias
- CYP450 drug interactions
- NMDA & SNRI activity
- Morphine ↔ Methadone conversion
Serotonergic Medications

• ↑ serotonin release
  – Amphetamines
  – Levodopa
  – Methadone

• Direct serotonin agonist
  – Buspirone
  – Triptans
  – Ergot derivatives

• ↑ serotonin sensitivity
  – Lithium

• Inhibits serotonin metabolism
  – MAOIs

• Impairs serotonin reuptake
  – SSRIs & SNRIs
  – TCAs
  – 5-HT3 antagonists
  – Metoclopramide
  – Carbamazepine
  – Dextromethorphan
  – Tramadol

Boyer EW, NEJM 2005; 352:1112
Methadone & CYP450

• R-methadone: analgesic effects
  – CYP3A4 (primarily)
  – CYP2B6
  – CYP2C19 (minor)

• S-methadone: QT interval
  – CYP2B6 (primarily)
  – CYP3A4
  – CYP2D6 (if patient ultrarapid CYP2D6 metabolizer)
Summary

• Commonly prescribed medications can cause fatal drug interactions
• Causes of interactions are often due to either additive effects or to metabolism/elimination
• Certain medications should always be prescribed with caution (see Karen’s red alarm medications)
• Encourage patients to fill all medications at same pharmacy to help catch interactions
Karen’s Red Alarm Medications

- Amiodarone
- Warfarin
- Phenytoin
- Azole antifungals
- Fluoroquinolones
- Sulfamethoxazole/trimethoprim
- Methadone