Drug Interactions with Smoke and Smoking Cessation Medications

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Disclosures

• Advisory Boards
  – Amgen, AstraZeneca, BMS, Janssen, Novartis, Pfizer, Sanofi

• Research Funding
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• Professional Affiliations:
  – CACR, CCN, CDA
Objectives

• review pharmacokinetic principles – what is the disposition of a medication once ingested?
• highlight the role of the drug metabolism cytochrome P450 system as a particular site for many important drug interactions
• Case based discussion of common interactions – drug-drug (SCT) and drug-smoke
Cased Based Questions

1. What is a “CYP” and what does it do?
2. How can a sinus infection make you pass out?
3. Why is this workout so painful?
4. How do cigarettes and coffee go together?
5. Why is quitting possibly hazardous to your drug health?
6. What makes someone with heart disease and depression slow down?
First-Pass Metabolism

Gut Lumen

Gut Wall

Portal Circulation

Liver

Fraction Absorbed

Fraction Metabolized

Metabolism

Metabolism
Drug Metabolism in the Liver

PORTAL VEIN

LIVER

SYSTEMIC CIRCULATION

Eliminated unchanged by the kidneys

To the kidneys for elimination
Drug Metabolism in the Liver

- Eliminated unchanged by the kidneys
- P-450 OH
- Phase I metabolism
- Glucuronide
- Phase II metabolism
- Sulfate
- To the kidneys for elimination
Overview of Pharmacology Concepts

Cytochrome P450 System

• Nomenclature: e.g., CYP3A4
  – "CYP" = cytochrome P450 protein abbreviation
  – family; subfamily; isoform

• The most important isoforms are CYP3A4, CYP2D6, CYP1A2
  – anticipate drug interactions if prescribing drugs using these enzymes.
Traffic at the Cytochrome P450 Enzymes

Substrates metabolized by P-450 isoenzymes

Inhibitors or inducers of P-450 isoenzymes

Changes in Substrate Concentration

Potential for Adverse Drug Reactions
Case Study: A Lethal Sinus Infection

- 39 yo woman
- CC: multiple episodes of syncope with palpitations
- no seizures or syncope in past
- recent sinusitis
  - treated with cefaclor and terfenadine
- subsequent vaginal candidiasis
  - treated with ketoconazole

*JAMA 1990*
Case Study

Torsades de pointes

ketocnazole

cefaclor

terfenadine

day

0 5 10 15 20

JAMA 1990
Cytochrome P450 Interaction

- terfenadine

- Inhibitors: ketoconazole

- LIVER CYP Metab:
  - 2C9
  - 3A4
  - 2D6
  - 1A2
  - Others

- Increase in terfenadine

- Potential for ADR: Arrhythmia
CYP3A4

- Most abundant of all P450s in the liver and gut
- Many important substrates (50% of all drugs)
- Inducers: barbiturates, phenytoin, rifampin
- Inhibitors: antifungals (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin), CCBs, SSRIs, cyclosporine, omeprazole, midazolam & grapefruit juice
Case: Painful workout

- 44 yo man
- Post heart transplant
- ASA
- Simvastatin
- Ramipril
- Sirolimus
- Recent fungal infection – Rx: itraconazole
- Muscle aches and pains – interfering with rehab / exercise
Painful workout

inflamed

normal
Interaction Between Itraconazole and Simvastatin (3A4 inhibitor) (3A4 substrate)

Simvastatin Pharmacokinetics

- C max 17 x
- AUC 19 x
- t \frac{1}{2} 25%

Cytochrome P450 Interaction

Substrate: simvastatin

Inhibitors: itraconazole

LIVER CYP Metab
- 2C9
- 3A4
- 2D6
- 1A2
- Others

Increase in simvastatin

Potential for ADR: Myositis
Effects of Grapefruit Juice on Simvastatin* Plasma Concentrations

Also for:
- lovastatin
- atorvastatin

* 200 ml 2x strength grapefruit juice tid for 2 days
** simvastatin administered 24 hours after last dose of grapefruit juice in above regimen

Identification of 6',7'-dihydroxybergamottin, a cytochrome P450 inhibitor, in grapefruit juice.

D J Edwards, F H Bellevue, 3rd and P M Woster
Cytochrome P450 Interaction

Substrate: simvastatin

Inhibitors: grapefruit

LIVER CYP Metab

Increase in simvastatin

Potential for ADR: Myositis
CYP 2D6 Genetics/Anthropology

- genetic diversity in CYP2D6
- drugs using this enzyme pathway (e.g., SSRIs, β-blockers, opiates)
- 3 groups in population
  - Poor metabolizers (PM)
  - Extensive metabolizers (EM) = NORMAL
  - Ultrarapid metabolizers (UM)
- PMs
  - Europeans, White Americans PM = 7.5%
  - Asians, Black Americans PM < 2%
Genetic Polymorphism of metabolizing enzymes

A 2D6 story....

Demethylation

Codeine (inactive) \[\xrightarrow{\text{CYP2D6}}\] Morphine (active)
A 2D6 Story

• New mother given standard dose of Tylenol #3 for post-episiotomy pain
• Complained of significant drowsiness and constipation
• Breast fed Infant – poor feeding
• Infant died
2D6 Story

- Mom’s serum – high morphine
- Breast milk – high morphine
- Baby’s blood – high morphine
- Mom found to have variant 2D6 (ultrarapid) – 2x higher conversion of codeine to morphine – affects 1.4% of population
Smoking, SCTs and Interactions
Smoking and Cytochromes

• Polycyclic aromatic hydrocarbons (PAHs) -- products of incomplete combustion -- are some of the major lung carcinogens found in tobacco smoke.

• PAHs are also potent inducers of the hepatic cytochrome P-450 (CYP) isoenzymes 1A1, 1A2, and, possibly, 2E1.

• Many drugs are substrates for hepatic CYP1A2, and their metabolism can be induced in smokers, resulting in a clinically significant decrease in pharmacologic effects. Thus, smokers may require higher doses of drugs that are CYP1A2 substrates.

Prev Med. 1997; 26:427-34
Drug Interaction after Smoking Cessation

- After a person quits smoking, the induction of CYP1A2 dissipates. This is particularly important when a patient is hospitalized and abruptly quits smoking.
- CYP1A2 activity falls to half by ~40hrs after quitting

Clin Pharmacol Ther 2004;76:178-84
Case: The Smoking Gun

• If smoking is so bad.... why do I feel worse after quitting?
Caffeine is metabolized by CYP1A2
Caffeine and Smoking

- Caffeine is >99% metabolized by CYP1A2
- Clearance is increased by 56% in smokers.
- Median caffeine concentrations are twofold to threefold higher in nonsmokers.
- When a patient quits smoking, the patient's caffeine intake should be reduced by half to avoid excessive caffeine levels.
- Symptoms of caffeine toxicity can mimic those of nicotine withdrawal

Clozapine and Smoking

• clozapine, an atypical antipsychotic drug with a narrow therapeutic range, is metabolized primarily by CYP1A2
• clozapine levels of smokers are much lower than nonsmokers
• when smokers quit, clozapine levels can rise dangerously if not adjusted

Cytochrome P450 Interaction

Substrate: caffeine clozapine

Inhibitor: Stopping chronic smoking

LIVER CYP Metab

2C9
3A4
2D6
1A2
Others

Increase in:
    a) caffeine
    b) clozapine

ADR:
    a) Tachycardia
    b) Tremor
    c) Anxiety
    b) blood/liver
Case: Seizures Due To Smoking Cessation?

- 35 yr old male
- Chronic schizophrenia
- Stable (7 years Clozapine 700-725mg)
- Sudden onset tonic clonic seizures, coma ICU admission
- Full recovery within 2 days
Case: Seizures Due To Smoking Cessation?

- Abrupt cessation of heavy smoking 2 weeks prior
- After recovery, Clozapine stabilized at 425mg (40% reduction)
- Likely cause is loss of CYP 1A2 induction caused by smoking resulting in plasma level rise of clozapine
Case: Slowing Down

- 70 year old woman
- Post MI – Rx ASA, metoprolol, statin, ACE-I
- Smoking still and depressed – started on bupropion
- Feeling really “slow”
- HR 42
SCTs and Interactions

Drug Interactions

Pharmacology

The mechanism by which ZYBAN (bupropion hydrochloride) enhances the ability of patients to abstain from smoking is mediated by noradrenergic and/or dopaminergic mechanisms. ZYBAN is a weak inhibitor of the neuronal uptake of monoamine oxidase. ZYBAN is chemically unrelated to nicotine or other agents currently used in the treatment of nicotine dependence.
Monitor/Modify Tx

1. bupropion HCl <-> metoprolol
monitor BP, HR; consider lower beta blocker dose or non-hepatically metabolized beta blocker. combo may incr. beta blocker levels, risk of hypotension, bradycardia, AV block, other adverse effects (hepatic metab. inhibited)
Cytochrome P450 Interaction

Substrate: metoprolol

Inhibitors: bupropion

LIVER CYP Metab

2C9
3A4
2D6
1A2
Others

Increase in metoprolol

Potential for ADR: Bradycardia Fatigue
SCTs - Varenicline

- Minimal metabolism; cleared via kidney
- “Based on varenicline pharmacokinetic characteristics, and clinical experience to date, it appears unlikely that CHAMPIX would produce or be subject to clinically meaningful drug interactions.”
- If co-administered with NRT: “vomiting, dizziness, dyspepsia and fatigue were greater for the combination of varenicline and NRT than for NRT alone”
Pharmacodynamic Interactions

- Smoking in asthma
  - Less benefit from inhaled steroid
- Nicotine and beta-blockers
  - Greater residual sympathetic activation (higher heart rate and BP)

Prev Med. 1997; 26:412-7
Thorax. 2002; 57:226-30
Pharmacodynamic Interactions: Smoking and Oral Contraceptives

Risk of Death from CVD (per 100,000)

# Drug Interactions with Smoking

Many interactions between tobacco smoke and medications have been identified. Note that in most cases it is the tobacco smoke—not the nicotine—that causes these drug interactions. Tobacco smoke may interact with medications through pharmacokinetic (PK) or pharmacodynamic (PD) mechanisms. PK interactions affect the absorption, distribution, metabolism, or elimination of other drugs, potentially causing an altered pharmacologic response. The majority of PK interactions with smoking are the result of induction of hepatic cytochrome P450 enzymes (primarily CYP1A2). PD interactions alter the expected response or actions of other drugs. The amount of tobacco smoking needed to have an effect has not been established and the assumption is that any smoker is susceptible to the same degree of interaction. The most clinically significant interactions are depicted in the shaded rows.

<table>
<thead>
<tr>
<th>Drug/Class</th>
<th>Mechanism of Interaction and Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmacokinetic Interactions</strong></td>
<td></td>
</tr>
<tr>
<td>Alprazolam (Xanax)</td>
<td>↑ Metabolism (induction of CYP1A2), ↑ clearance (50%), ↓ half-life (35%).</td>
</tr>
<tr>
<td>Caffeine</td>
<td>↑ Metabolism (induction of CYP1A2), ↑ clearance (50%).</td>
</tr>
<tr>
<td>Chlorpromazine (Thorazine)</td>
<td>↑ Area under the curve (AUC) (36%) and serum concentrations (24%).</td>
</tr>
<tr>
<td>Clozapine (Clozaril)</td>
<td>↑ Metabolism (induction of CYP1A2), ↑ plasma concentrations (15%).</td>
</tr>
<tr>
<td>Flucphenicol (Tambocor)</td>
<td>↑ Clearance (81%), ↑ trough serum concentrations (25%).</td>
</tr>
<tr>
<td>Fluvoxamine (Luvox)</td>
<td>↑ Metabolism (induction of CYP1A2), ↑ clearance (24%), ↓ AUC (31%), ↓ plasma concentrations (32%).</td>
</tr>
<tr>
<td>Haloperidol (Haldol)</td>
<td>↑ Clearance (44%), ↓ serum concentrations (70%).</td>
</tr>
<tr>
<td>Heparin</td>
<td>Mechanism unknown but ↓ clearance and ↓ half-life are observed. Smoking has prothrombotic effects.</td>
</tr>
<tr>
<td>Insulin, subcutaneous</td>
<td>Possible ↓ insulin absorption secondary to peripheral vasoconstriction, smoking may cause release of endogenous substances that cause insulin resistance.</td>
</tr>
<tr>
<td>Insulin, inhaled (Exubera)</td>
<td>↑ Systolic exposure is greatly increased in smokers, greater maximal insulin concentrations (3-5 fold) and faster (by 20-30 minutes), ↑ AUC 2-3 fold.</td>
</tr>
<tr>
<td>Mexiletine (Mexitil)</td>
<td>↑ Clearance (25%, via oxidation and glucuronidation), ↓ half-life (36%).</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa)</td>
<td>↑ Metabolism (induction of CYP1A2), ↑ clearance (88%), ↓ serum concentrations (12%).</td>
</tr>
<tr>
<td>Propranolol (Inderal)</td>
<td>↑ Clearance (77%, via side chain oxidation and glucuronidation).</td>
</tr>
<tr>
<td>Tacrine (Cognex)</td>
<td>↑ Metabolism (induction of CYP1A2), ↓ half-life (80%), serum concentrations three-fold lower.</td>
</tr>
<tr>
<td>Theophylline (Theo-Dur, etc.)</td>
<td>↑ Metabolism (induction of CYP1A2), ↑ clearance (58-100%), ↓ half-life (63%).</td>
</tr>
<tr>
<td>Tricyclic antidepressants (e.g., imipramine, nortriptyline)</td>
<td>↑ Possible interaction with tricyclic antidepressants in the direction of ↓ blood levels, but the clinical importance is not established.</td>
</tr>
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<td>Benzodiazepines (diazepam, chlordiazepoxide)</td>
<td>↓ Sedation and drowsiness, possibly caused by nicotine stimulation of central nervous system.</td>
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<tr>
<td>Beta-blockers</td>
<td>Less effective antihypertensive and heart rate control effects; might be caused by nicotine-mediated sympathetic activation.</td>
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<tr>
<td>Corticosteroids, inhaled</td>
<td>Asthmatic smokers may have less of a response to inhaled corticosteroids.</td>
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<tr>
<td>Hormonal contraceptives</td>
<td>↑ Risk of cardiovascular adverse effects (e.g., stroke, myocardial infarction, thromboembolism) in women who smoke and use oral contraceptives.</td>
</tr>
<tr>
<td>Opioids (propoxyphene, pentazocine)</td>
<td>↑ Analgesic effect; smoking may ↑ the metabolism of propoxyphene (15-20%) and pentazocine (40%).</td>
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UH, DAD... YOU MIGHT WANT TO TALK TO YOUR DOCTOR ABOUT DRUG INTERACTION...