AMERICAN COLLEGE OF EMERGENCY PHYSICIANS
SCIENTIFIC ASSEMBLY
1999

Drug Interactions: Which Ones Are Potentially Life Threatening?

How much disease is really iatrogenically induced due to drug interactions? Do you really take the time necessary to sort out each possible interaction and determine whether it really matters? The lecturer will discuss the more common, potentially life-threatening interactions. Sources of drug information that may prevent this dangerous problem will be addressed.

- Describe the mechanisms of drug interaction.
- Recognize the signs and symptoms of drug interactions that may be life-threatening.
- Develop an approach to the initial treatment of patients with life-threatening drug interactions.
- Identify the sources of drug information that can help identify potential interactions.

MO-39
Monday, October 11, 1999
3:00 PM - 3:55 PM
Room # N227
Las Vegas Convention Center

FACULTY

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DRUG INTERACTIONS:
Which Ones Are Potentially Life Threatening

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ACEP Scientific Assembly
October 11, 1999

INTRODUCTION

Drug-drug interactions occur commonly however the majority are clinically insignificant (limited interaction, high therapeutic margin). Only 1% are clinically significant but these can be life threatening. Most are predictable and preventable.
Two types of reactions: pharmacokinetic and pharmacodynamic

1.Pharmacokinetic

One drug altering the absorption, distribution, metabolism or excretion of another

a. Absorption
Many factors including altered intestinal blood flow, motility, pH, metabolism, and flora
ex. oral antibiotics destroy normal gut bacteria that metabolize some drugs resulting in greater absorption (e.g. digoxin)
ex. bacteria aid in the recycling of drugs that are secreted in the biliary tract by metabolizing them from the bile salt and allowing the active metabolites to be reabsorbed (e.g. oral contraceptives)

b. Distribution
protein binding - not clinically relevant

c. Metabolism - majority of drug interactions here!!
enzyme induction and inhibition

d. Elimination
ex. probenicid and PCN
ex. thiazides increase reabsorption of Li^{+2} in proximal tubule

2. Pharmacodynamics

Concomitant use of drugs with similar mechanisms of action or toxicity:
a. Antagonistic

beta blocker and a beta agonist - a pt s/p an MI with reactive airway disease taking metoprolol and albuterol

b. Additive

ototoxicity - furosemide/aminoglycosides
agranulocytosis - carbamazepine/clozapine

c. Synergistic

bradycardia - digoxin/beta adrenergic antagonist/calcium channel antagonist
respiratory depression - ethanol/another sedative-hypnotic

CASE #1

Hx: A 24 year old female presents complaining of palpitations, dizziness, and near syncope. She was recently seen at the cross town emergency department where she presented several days prior with productive cough and runny nose, was diagnosed with bronchitis, and was prescribed erythromycin. When further history was obtained she revealed that she also was taking over-the-counter acetaminophen and terfenadine.

SELECTIVE (H1) ANTIHISTAMINES - terfenadine (Seldane), astemizole (Hismanal)

1. Mechanism of Interaction

Normally terfenadine and astemizole rapidly undergo phase I metabolism by the cytochrome P450 system (CYT3A4)
However, in overdose or if this enzyme is inhibited, the toxic parent compound builds up. In high doses, terfenadine and astemizole block myocardial potassium channels delaying cardiac repolarization. (as potent as quinidine)
This manifests clinically as QT prolongation and ventricular dysrhythmias including torsades de pointes.

Fexofenadine (Allegra) and loratadine (Claritin) are selective antihistamines without any cardiotoxicity so safe with erythromycin, antifungals

2. General overview of drug metabolism

Phase I - oxidation, reduction, hydrolysis
performed in great extent by the cytochrome P450 system (AKA mixed function oxidase system)
the mixed function oxidase system is a group of many different enzymes that are able to metabolize a wide variety of drugs based on general structure.
categorized with specific nomenclature – ex. CY3A4, CY2A1

Phase II - conjugation
attachment of a large water soluble moiety such as sulfate
so it can be freely filtered by the kidney

3. COMMON INHIBITORS OF CYTOCHROME P450 3A4 (CPY3A4)
most common isoenzyme involved in drug/drug interactions
inhibition occurs rapidly - within 24 hours

ketoconazole, itraconazole, fluconazole
erythromycin, clarithromycin
cimetidine
protease inhibitors – rotinavir, indinavir
diltiazem, verapamil, quinidine
cimetidine

azithromycin (Zithromax) is the macrolide antibiotic that does not inhibit CYP3A4 isoenzyme

4. Cisapride (Propulsid)
In 1996, FDA reported 34 cases of torsades and 23 or prolonged QT intervals developed while using cisapride. Majority of cases (56%) involved concomitant use of an antifungal (ketoconazole, fluconazole, intraconzole) or a macrolide antibiotic (erythromycin, clarithromycin)
mechanism - similar to terfenadine w/ parent compound causing the toxicity via K^+ channel blockade

CASE #2
Hx: A 67 year old female with a history of NIDDM, HTN, CAD, glaucoma, TIA's, osteoarthritis and newly diagnosed atrial fibrillation is sent to the emergency department by her neurologist with complains of lightheadedness and a large bruise on her left thigh. Her medications include glyburide, acetaminophen, cimetidine, nifedipine, enalapril, enteric coated aspirin, warfarin, and colace.

PE: Pale, ill appearing elderly female with HR = 105 irreg, BP = 120/75. On her skin there were several large eccymoses and she had a melanic stool in the ED.

Labs: hemoglobin 8 g/dL (her baseline 13 g/dL) and PT > 50 sec

ORAL ANTICOAGULANTS - Warfarin

One of the drugs most frequently involved in drug/drug interactions.

Warfarin prevents the recycling of vitamin K by inhibiting vitamin K 2,3 epoxide reductase. This decreases the amount of reduced vitamin K which is essential for activation of coagulation factors II, VII, IX, X and proteins C and S.

1. Potential Mechanisms of Interactions with Warfarin

a. reduced absorption
binding resins - cholestyramine [interupts the enterohepatic circulation]

b. inhibition of metabolism
metabolized by many p450 isoenzymes (1A2, 2C9,3A4)
inhibitors most commonly involved include cimetidine, miconazole, clotrimoxazole, metronidazole, erythromycin

c. induction of metabolism
rifampin, phenobarbitol, phenytoin

d. drug synergism
heparin, NSAIDS, ticlopidine

e. drug antagonism
eating vit K-rich foods (avocado, brocolli, fiddlehead ferns), enteral nutrition

f. others - ? mechanism
ofloxacin, anabolic steroids, clofibrate

2. HIGH RISK DRUGS

a. characteristics of high risk drugs
prescribed commonly
low therapeutic margin
significant toxicity

b. high risk drugs
warfarin
theophylline
terfenadine, astemizole, cisapride
cyclosporine

monoamine oxidase inhibitors (MAOI's)
lithium
digoxin

CASE # 3

A 66 year old male with a history of HTN, IDDM, and COPD presents to your emergency department complaining of 10 days of progressive dyspnea. Physical examination reveals an irregular HR @ 130 beats/min, diaphoresis, and a significant resting tremor. One week earlier he was at the VA and was diagnosed with "early pneumonia". He was treated with ciprofloxacin and counseled about the value of smoking cessation.

THEOPHYLLINE

Mechanisms of interactions

Theophylline, like most methylxanthines, is metabolized by the cytochrome p450 system (1A2, 3A4). Several agents induce or inhibit its metabolism

1. Inhibitors of p450 metabolism

ciprofloxacin, macrolides, antifungals, cimetadine, diltiazem

2. INDUCERS OF P450 METABOLISM (LOWER SERUM LEVEL)

tend to be lipid soluble, gradual onset of effect - days to weeks
rifampin, INH
phenytoin, phenobarbital, carbamazepine,
cigarette smoke (polyaromatic hydrocarbons)
chronic ethanol

In this case the patient stopped smoking 1 week prior because he was feeling poorly and the metabolism of theophylline slowed. In addition he began taking ciprofloxacin which is a potent inhibitor of theophylline metabolism.
Within 7 days of smoking cessation there is a 35% decrease in theophilline clearance

HIGH RISK PATIENTS

patients with complex medical hx or multiple physicians
elderly - altered metabolism, multiple medications
nursing home residents
transplant recipients
HIV + patient

5-20% incidence of drug interactions which is due to the fact that they often take multiple medications that many physicians are unfamiliar with and that many of these agents have high interaction potential

a. pharmacokinetic

antiretrovirals, protease inhibitors (ritonovir, indinavir)
antifungals, and antituberculous medications

b. pharmacodynamic

bone marrow suppression - ganciclovir, TMP-SMZ, zidovudine
peripheral neuropathy - INH, didanosine (DDI), stavudine
pancreatitis - didanosine (DDI), pentamidine

CASE #4
A 46 year old female with a history of depression presents complaining of a severe headache, and chest pain. Physical examination reveals a BP = 180/115 mmHg.

MONOAMINE OXIDASE INHIBITOR (MAOI's)

Monoamine oxidase is found in the nervous system and alimentary tract.
MAO-A degrades amines in the brain, gut
MAO-B degrades amines, particularly dopamine, in brain, liver
These agents inhibit monoamine oxidase and prevent the degradation of bioactive amines including dopamine, norepinephrine, and serotonin and results in their accumulation in presynaptic vesicles. This increase in neurotransmitters in regions of the brain that have reduced levels (dopamine in the basal ganglia for Parkinson's disease and serotonin and norepinephrine in multiple regions of the brain for depression)

Mechanism of Interaction - sympathetic exaggeration

If any indirect acting catecholamine is ingested, a large quantity of catecholamines may be released precipitating a sympathomimetic discharge.

a. clinical presentation
headache, palpitations, flushing, diaphoresis, hypertension
typically short lived (1 to 3 hours)
may require aggressive intervention for severe hypertension

b. agents involved
indirect sympathetic amines - dopamine, OTC cough and cold preparations containing ephedrine, pseudoephedrine, phenylpropanolamine
direct sympathomimetics - amphetamines (inc MDMA or ecstacy), cocaine
antihypertensives - reserpine, guanethidine, methyldopa
tyramine-rich foods - red wine, smoked or aged cheese and meats, beer, broad beans

c. treatment – particularly for severe HTN
phentolamine 5-10 mg IV
nitroprusside
benzodiazepines IV

CASE #5

Patient is a 35 yr old male with a history of depression presents tachycardic, diaphoretic, and restless. Physical examination is notable for an agitated, restless but cooperative male with T 98.5, RR 18, HR 115, BP 145/80. His skin was cool and diaphoretic and his neurologic examination was notable for hyperreflexic and stiff lower extremities with myoclonus.

SEROTONIN SYNDROME

Serotonin syndrome is a clinical syndrome produced by drugs that increased intrasynaptic serotonin in the CNS specifically at postsynaptic 5-HT1A receptor. It can be produced either by an acute overdose of a serotonergic agent or more commonly by therapeutic dosing of 2 serotonergic drugs.

1. The clinical presentation is varied and nonspecific
    a. alterations in cognitive or behavioral function
        irritability, restlessness, confusion, disorientation
    b. autonomic nervous synstom function
        fever, chills, diaphoresis, diarrhea
    c. neuromuscular activity
        hypertonia, hyperreflexia, myoclonus, ataxia
        lower extremities more commonly involved

2. Agents involved
    selective serotonin reuptake inhibitors (SSRI's)
    monoamine oxidase inhibitors
    tricyclic antidepressants
    meperidine, dextromethorphan
    L-tryptophan, lithium
    venlafaxine
    trazadone, nefazodone
    St Johns Wort (Hypericum perforatum) ?

3. Treatment
    cyproheptadine (Periactin) 4 mg PO, repeat Q30 min
    benzodiazepines - diazepam 5-10 mg or lorazepam 1-2 mg IV
    cooling
    paralysis rarely needed

In this case the patient was unhappy with his primary psychiatric's care or the effectiveness of his sertraline (Zoloft) so he presented to his primary physician with his depressive symptoms but did not inform her of his psychiatrists care and was placed on venlafaxine (Effexor).

In this case the patient added two serotonergic agents and developed symptoms over 2 -3 days of therapy. He was treated with benzodiazepines for 3 days and his symptoms resolved slowly and he was restarted on his sertraline.

SUMMARY

1. How to recognize drug/drug interactions
    a. Identify high risk patients early
        multiple drugs
        elderly
        HIV, transplant

b. Obtain a complete medication history
multiple prescribers/pharmacies
herbals/OTC's

c. Identify high risk drugs - low therapeutic margin
warfarin
theophylline
astemizole, cisapride
cyclosporine
monoamine oxidase inhibitors (MAOI's)
lithium
digoxin

d. Identify common inhibitors of the cytochrome p450 system
erythromycin, clarithromycin
fluconazole, intraconazole, ketoconazole
cimetidine
protease inhibitors (ritonavir, indinavir)
fluoxetine, fluvoxamine
quinidine
diltiazem, verapamil
ciprofloxacin

e. Identify common inducers of the cytochrome p450 system.
rifampin, INH
phenytoin, phenobarbital, carbamazepine,
cigarette smoke (polyaromatic hydrocarbons)
chronic ethanol

f. Identify potentially toxic medications that are metabolized by the cytochrome p450 system
theophylline
warfarin
terfenadine, astemizole, cisapride
cyclosporine
carbamazepine

RESOURCES AVAILABLE
Regional Poison Control Center
The Medical Letter (1-800-211-2769) – highly recommended
a biweekly nonprofit publication that reviews new drugs and if they have any benefits to previously marketed or cheaper agents.
Handbook of Adverse Drug Interactions.

Software

Physician's Desk Reference (800-232-7379)

www.drugfoodinteractions.com

an adverse drug effect and drug interaction database that is perhaps too comprehensive, not practical

Online

www.virtualdrugstore.com

overall not practical for ED use.

www.internetpharmacist.com

"personal consulting pharmacist"

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