The Case of Libby Zion and Dangerous Drug Interactions

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I. MAOI and Meperidine

- Libby Zion
- 18 yo female
- Rx c phenelzine (Nardil)
- Meperidine given for shaking chills
- Outcome
  - Death
  - Libby Zion Law in NY

II. MAOIs and Drug Interactions

- Phenelzine (Nardil)
- Tranylcypromine (Parnate)
- Isocarboxazid (Marplan)
- Selegiline (Emsam)

III. Danger at the Drugstore

- 1996 investigative study
- Major metropolitan areas across the US
- 30-50% dispensed potentially life-threatening combinations (fatal arrhythmias)
- No warning issued to patient or prescriber in 1/3rd of the cases—“have a nice day”

IV. Cost of ADEs

- Drug related morbidity and mortality costs more than 136 billion/yr in the US
- Cost is higher than CV or DM care
- 140,000 deaths/yr—over 300/day

V. Types of Drug Interactions

  A. Pharmacodynamic

  - A drug interaction in which the physiologic effect of one drug is altered by another drug
• No change in drug concentration of either drug

• Types
  • Additive
  • Inhibitory

B. Pharmacokinetic

1. Absorption
  • Cimetidine and ketoconazole
  • Erythromycin and digoxin
  • Sulcralfate and ciprofloxacin
  • Iron and tetracycline
  • Troglitazone and food

2. Distribution
  • ASA and warfarin
  • Valproic acid and phenytoin
  • Phenytoin and renal failure
  • Digoxin and quinidine

3. Excretion
  • Probenecid and MTX
  • HCTZ and Lithium
  • Cimetidine and procainamid

4. Metabolism
  • Inhibition and Induction

VI. CYP Review

• Heme containing
• Location- smooth ER of liver and intestinal tract
• Spectral absorbance ≈ 450 nm
• Aka
  ◦ Mixed-function oxidase
  ◦ P-450 mono-oxygenase
  ◦ heme-thiolate protein

• Ancestral gene in existence for > 3.5 billion years
• Metabolism of endogenous substances (ex. steroids)
• Metabolism of exogenous substances (toxins, drugs)

**CYP 3**

• Family name denoted by Arabic numeral
• 14 families identified in mammals
• In humans CYP1, CYP2, and CYP3 mediate most drug metabolism
• ≈ 70% CYP content in the liver

**CYP 3A**

• Sub family name denoted by uppercase letter
• 20 sub-families identified
• CYP3A4- individual enzyme designated by second Arabic numeral

CYP 450 enzymes- important in drug interactions and metabolism (90% of drugs)

• 1A2
• 2C9
• 2C19
• 2D6
• 3A4
• 3A5

**VII. CYP Inhibition**

• Most often responsible for life-threatening interactions
• Some drugs may inhibit many isoenzymes but most are isoenzyme specific
• An inhibitor may or may not be metabolized by the isoenzyme that it inhibits
  ◦ Erythromycin is a substrate for and an inhibitor of CYP3A4
Quinidine inhibits CYP2D6 but is metabolized by CYP3A4

A. Competitive

- Most common type of inhibition
- Begins with first dose
- Max at SS
  Reversed 5 t½ s after discontinuation

B. Permanent

- Drug essentially takes the enzyme out of use via binding to active surface
- Duration depends on t½ of turnover of isoenzyme
- Inhibition may last longer than with competitive inhibition- once inhibited, new isoenzymes must be synthesized
- Example:
  - Erythromycin is metabolized to nitroso-alkane metabolite by 3A4 → the metabolite then complexes with 3A4
  - Theophylline metabolism may be inhibited days after erthyromycin administration

VIII. CYP Induction

- induction of an isoenzyme by any substance causes increased synthesis of that particular isoenzyme
- this induction leads to increased metabolism of **ALL** substrates through that particular pathway
- this process is more complex than and difficult to predict than inhibition
- some compounds (ex. φ-barb, rifampin) are capable of inducing many different isoenzymes
- some compounds(ex. carbamazepine, imipenem) can cause auto-induction of the isoenzyme responsible for their own metabolism
the timing of onset and offset of increased enzyme activity is related to:
- plasma [C] and duration of use of the inducing drug
- \( t \frac{1}{2} \) of the drug
- \( t \frac{1}{2} \) of turnover of the isoenzyme

φ barbital
- \( t \frac{1}{2} \) - 50-120 hrs
- enzyme induction in 1 week
- reversal of induction in 2 to 6 weeks (dependent on dose and duration of treatment)

Rifampin
- \( t \frac{1}{2} \) - 2-3 hours
- enzyme induction in 2-3 days
- reversal of induction in 1-3 weeks

IX. Drug features associated with potential for interactions
- Steep dose response curve
- Narrow therapeutic window
- Dose dependent rate of metabolism

X. Is each particular interaction the same as the next?
- baseline rate of metabolism
- presence of disease state
- patient’s diet
- patient’s age
- genetics
- drug dose
XI. Worth a Second Look?

- BCPs
- ACEIs
- Digoxin
- Warfarin
- any that prolongs QT interval
- MAOIs
- Phenytoin
- Theophylline
- Triazole antifungals

XII. Top Ten Dangerous Drug Interactions in Long-term care

The Multidisciplinary Medication Management Project is a joint collaboration of the American Society of Consultant Pharmacists and the American Medical Directors Association

- 1. Warfarin + NSAIDs
  - Impact
  - MOA
  - Prevention
  - Management

- 2. Warfarin + Sulfa
  - Impact
  - MOA
  - Prevention
  - Management

- 3. Warfarin + Macrolides
4. *Warfarin + Quinolones*
   - Impact
   - MOA
   - Prevention
   - Management

5. *Warfarin + Phenytoin*
   - Impact
   - MOA
   - Prevention
   - Management

6. *ACEIs + K+ supplements*
   - Impact
   - MOA
   - Prevention
   - Management

7. *ACEIs + Spironolactone*
   - Impact
   - MOA
   - Prevention
   - Management

8. *Digoxin + Amiodarone*
• Impact
• MOA
• Prevention
• Management

9. *Digoxin + Verapamil*
• Impact
• MOA
• Prevention
• Management

10. *Theophylline + Quinolones*
• Impact
• MOA
• Prevention
• Management

XIII.

XIV. Juice and Interactions

A. *Types*

• OJ- no
• Seville OJ- yes (3A4 inhibitor)
• Lime, star, pomegranate- maybe (3A4 inhibitor)
• Grapefruit- yes (3A4 inhibitor)

B. Grapefruit Juice

• Interacts only with oral drugs
• Drugs metabolized by 3A4 with F<50% are most likely to interact
• Magnitude of interaction will vary 5-6 fold between patients
• Inhibition may last up to 24 hrs after single dose and up to 72 hours after multiple doses
• Buspirone
  • ↑800%
• Lovastatin
  • ↑1200%
• Simvastatin
  • ↑1500%

*Dr. Carl Sagan - “Absence of evidence is not evidence of absence”*

References (in order of appearance)

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2. NY Times, A Life-Changing Case for Doctors in Training, March 2, 2009
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