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Drug Metabolism Part III

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10:00 AM

1. Describe the factors that can affect the metabolism of drugs.
    a. Availability of cofactors
    b. Competitive reactions
    c. Species differences
    d. Sex differences
    e. Age - metabolic activity peaks at puberty
    f. Nutrition - ascorbate (grapefruit juice), cofactors
    g. Pharmacogenetics
        i. Lack of CYP2D6 prevents codeine being converted to morphine (inefficacious)
        ii. Halothane
            1) Inhaled anaesthetic, smells good, rarely used in US
            2) Reductive dehalogenation
                a) Converted to 2-chloro-1,1,1-trifluoroethane or 2-chloro-1,1-difluoroethylene
                b) Lipid peroxidation -->binds to proteins-->hepatotoxicity
            3) Oxidative dehalogenation by P450 --> trifluoroacetylchloride
                a) Trifluoroacetylchloride binds to proteins that are recognized by immune system
                b) Results in immune hepatitis that results from antibodies attacking liver
            4) Enflurane, isoflurane not nearly as toxic or reactive w/ antibodies
    h. Other xenobiotics: Seldane (terfernadine)
        i. Seldane is an new generation H1 blocker
        ii. It is metabolized by CYP3A and further oxidation to the active form (which is Allegra)
        iii. However, when taking certain antibiotics (ketoconazole, clairthromycin, erythromicin, etc.) it has been known to cause QT prolongation and in rare cases serious CV events
        iv. CYP3A is inhibited by the antibiotics leaving terfenadine in the system, which is cardiotoxic
2. Describe the factors that regulate cytochrome P450 metabolism.
3. What are the inducers and inhibitors of CYP2E1?
    a. Dietary inhibitors: ethanol, diallyl sulfide --> immediate effect while present
    b. Dietary supressors: diallyl sulfide, phenethyl, isothiocyanate
    c. Dietary inducers: lipid/carbs, fasting, ethanol --> take time b/c they induce transcription
    d. Tylenol (acetaminophen) + Alcohol = bad
        i. @ low dose - sulfation
        ii. @ high dose - glucuronidation
        iii. If you take alcohol night b4, CYP2E1 levels elevate due to increased transcription
        iv. CYP2E1 creates reactive intermediates that can be conjugated w/ glutathione, but this becomes easily overwhelmed
        v. The reactive intermediate then binds to protein in the liver --> hepatotoxicity
        vi. Can administer N-acetyl-L-cysteine (glutathione mimic) to try to save from liver toxicity
4. Describe how metabolism can alter the excretion of compounds.
5. Describe how metabolism can alter the toxicity of compounds.
    a. HIV Protease Inhibitors
        i. One drug requires much lower dose (100 mg/once a day), has a longer half life, given once a day but it irreversibly inhibits P450 --> never brought to market b/c of problems it caused
        ii. Indinavir requires much higher doses (800 mg/dose, three/day)
            1) Higher cost of production
            2) Harder to administer accurately
            3) But because not as toxic, ended up being brought to market