Tanner
Spring 2015
Pathology 438
Midterm Exam

1. Doxorubicin

Complete description of the toxico/pharmacokinetics and toxico/pharmacodynamics:

There are 3 metabolic routes for doxorubicin metabolism: "one-electron reduction, two-electon reduction and deglycosidation." About 50% of DOX is eliminated from the body without any performed change.

One electron reduction of DOX: "carried out by several oxidoreductases to form a DOX-semiquinone radical. These enzymes include mitochondrial NADH dehydrogenases present in the sarcoplasmic reticulum and mitochondria as well as cytosolic enzymes NADPH dehydrogenase, xanthine oxidase and nitric oxide synthases."

Two-electron reduction of DOX: "to a secondary alcohol, DOX ol is the major metabolic pathway. There are several enzymes that can carry out this reaction and their respective balance is different in different cell types."

Deglycosidation: (1-2% of DOX metabolism) "This can be reductive to form the deoxyaglycone, or hydrolytic to form the hydroxyaglycone. The enzymes and their candidate genes for this process are less well characterized. In heart, no DOX hydroxyaglycone could be detected. It appears to be rapidly converted to DOX ol aglycone. In heart, NADPH is required for formation of aglycones suggesting that NADPH dependent hydrolase and reductase-type glycosidases are responsible. NADPH-cytochrome P450 reductase was shown in vitro to metabolize DOX to DOX 7-deoxyaglycone."

Doxorubicin. (n.d.). Retrieved May 3, 2015, from https://www.pharmgkb.org/drug/PA449412#tabview=tab4&subtab=32

Baylon, J., Lenov, I., Sligar, S., & Tajkhorshid, E. (n.d.). Characterizing the Membrane-Bound State of Cytochrome P450 3A4: Structure, Depth of Insertion, and Orientation. Retrieved May 3, 2015, from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3682445/

2. CYP3A4
   a. Provide a description of the type of substrates it metabolizes and give an example of one substrate it is known to metabolize:

Cytochrome P450 3A4 is typically found in the liver and intestines. The main purpose is to oxidize same foreign molecules (toxins and drugs) and remove them from the body. P450 3A4 initiates drug metabolism as well as synthesis of cholesterol, steroids, and other lipids. It is located in the endoplasmic

reticulum and metabolizes many of the drugs that are used today. (acetaminophen, codeiene, diazepam)

b. Explain the mechanism of catalysis:

Cytochrome P450 performs many modifications on several ligands. It has a large active site, which allows it to bind substrates more readily, and also more difficult compounds such as endogenous and exogenous compounds. (hydroxylation, epoxidation of olefins, aromatix oxidation) Ex. Tamoxifen: It is hydroxylated to 4-hydroxy-tamoxifen then dehydrated to 4-hydroxy-tamoxifen quinone methide.

c. Provide the names of any substances known to inhibit the cytochrome, if any:

Grapefruit and certain drugs (astemizole and terfenadine)

d. If its gene and/ or protein structure is known, describe the domains (functional parts) of the enzyme, and any molecular detail that are interesting or significant to the enzyme's function

The first structure was determined around 2005 as "an active site of sufficient size and topography to accommodate either large ligands or multiple smaller ligands, as suggested by the heterotropic and homotropic cooperativity of the enzyme.

e. Provide, if any, known enzyme kinetic parameters: turnover/ catalysis rate:

The only information I could find here was the half-life for CYP3A4 which ranges from 26-140h.

Retrieved May 3, 2015, from http://www.cell.com/trends/biochemical-sciences/abstract/S0968-0004(04)00294-4?_returnURL=http://linkinghub.elsevier.com/retrieve/pii/S0968000404002944?showall=true&cc=y=

Retrieved May 3, 2015, from http://www.ncbi.nlm.nih.gov/pubmed/10594474 RCSB Protein Data Bank - RCSB PDB - 2J0D Structure Summary. (n.d.). Retrieved May 3, 2015, from http://www.rcsb.org/pdb/explore.do?structureId=2J0D
RCSB Protein Data Bank - RCSB PDB - 2J0D Structure Summary. (n.d.). Retrieved May 3, 2015, from http://www.rcsb.org/pdb/explore.do?structureId=2J0D

3. a. Find at least one report/ article that discusses the differences in how men and women respond to toxicants or drugs. Your search for an article may focus on one particular toxicant/drug or you may summarize an article that treats these differences in a board survey. In any article you obtain, be sure

to indicate at least three significant points, but list all of them if there are more"

"Physiologic differences between men and women affect drug activity."
"Pharmacokinetics in women is affected by lower body weight, slower gastrointestinal motility, less intestinal enzymatic activity, and slower glomerular filtration rate."
"Pharmacodynamic differences in women include greater sensitivity to and enhanced effectiveness of beta blockers, opioids, selective serotonin reuptake inhibitors, and typical antipsychotics."
"Women are 50 to 75 percent more likely than men to experience an adverse drug reaction."

Sex-Based Differences in Drug Activity. (n.d.). Retrieved May 3, 2015, from http://www.aafp.org/afp/2009/1201/p1254.html

## Work Cited


1. Baylon, J., Lenov, I., Sligar, S., & Tajkhorshid, E. (n.d.). Characterizing the Membrane-Bound State of Cytochrome P450 3A4: Structure, Depth of Insertion, and Orientation. Retrieved May 3, 2015, from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3682445/

2. Doxorubicin. (n.d.). Retrieved May 3, 2015, from https://www.pharmgkb.org/drug/PA449412#tabview=tab4&subtab=32

3. Retrieved May 3, 2015, from http://www.cell.com/trends/biochemical-sciences/abstract/S0968-0004(04)00294-4?_returnURL=http://linkinghub.elsevier.com/retrieve/pii/S0968000404002944?showall=true&cc=y=

4. Retrieved May 3, 2015, from http://www.ncbi.nlm.nih.gov/pubmed/10594474 RCSB Protein Data Bank - RCSB PDB - 2J0D Structure Summary. (n.d.). Retrieved May 3, 2015, from http://www.rcsb.org/pdb/explore.do?structureId=2J0D

5. RCSB Protein Data Bank - RCSB PDB - 2J0D Structure Summary. (n.d.). Retrieved May 3, 2015, from http://www.rcsb.org/pdb/explore.do?structureId=2J0D

6. Sex-Based Differences in Drug Activity. (n.d.). Retrieved May 3, 2015, from http://www.aafp.org/afp/2009/1201/p1254.html