Pathology 438 Midterm Examination due: by 1:00 PM, 6 May 2015
Spring 2015
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The electronic responses to this examination are due at 1:00 PM on Wednesday, 6 May 2015. Submit them to shalloran@lifewest.edu.

You are not allowed to consult with classmates or any individuals *other than* the instructor as you research, prepare and compose your responses to the questions posed in this examination. You may use the information available from lecture content (slides) in MOODLE, the LCCW library, reference books and course text books, and on-line resources. Please proofread and organize your work and assemble the exam before submitting it.

Some answers require you to include a citation of the sources you consult to formulate your response. Format your citation according to MLA or APA standards. (If you wish, you can use the built-in Word feature that formats your references: under the References tab, use Insert Citation and fill in the fields as much as possible. Later you will use Bibliography->Insert Bibliography at the point of the cursor. You might learn how to use Section Break too in order to insert bibliographies under separate answers. I have put in section breaks in this document between questions.)

By working the examination and submitting it for grading you are agreeing to work independently of all other individuals and you are certifying that all the responses and answers to the examination questions are your own work.

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1. Select one of the substances below: (a) OR (b) OR (c). Provide as a complete a description of the toxico/pharmacokinetics and toxico/pharmacodynamics as possible. Support your description with at least two references, one of which must be from a published book or a journal article.

   a) Doxorubicin: Is thought to inhibit DNA synthesis causing cell death.

Distribution:
Doxorubicin is measured to be 90% liposomally encapsulated, after being steadily administered over an extended period of time. The small steady state volume of distribution suggests that Doxorubicin is confined to the vascular fluid. Doxorubicin gets into the vascular system after it becomes activated, this happens when the liposomes become extravasated.

3.5

Metabolism:
It is estimated that 50% of the Doxorubin exits the body unchanged. There are 3 ways Doxorubicin is metabolized; one-electron reduction, two-electron reduction and deglycosidation Doxorubicin enters the cell with a carnitine transporter. It then is metabolized further through dehydrogase enzymes and reduction enzymes. After these enzymes react with Doxorubicin, it is broken down into Doxorubicin semiquinone, Doxorubicin Deoxyaglycone, Doxorubicin hydroxyaglycone, Doxorubicinol. The remaining Doxorubicin molecule is than bound to an

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active transporter protein molecule and proceeds to inhibit the DNA synthesis in the nucleus of the cell.

Elimination

3.5

40% of the Doxorubicin appears in bile after 5 days, and only 5-12% of Doxorubicin appears in urine. Elimination of Doxorubicin is decreased in obese patients and decreased to a greater degree in obese women. This decreased elimination in obese patients suggests that some Doxorubicin stays in the liposomes and is not extravasated as well in obese patients.

Pharmacodynamics:

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Doxorubicin is know have a cardiotoxic effect after administration. Studies have been done on rats, Ca2+ATPase was used a a biological marker to measure cardiotoxicity. By using the drug with multiple doses studies have found that plasma concentration of Doxorubicin is higher and will hopefully help eliminate cancer.

https://www.doxil.com/shared/product/doxil/prescribing-information.pdfhttps://www.pharmgkb.org/pathway/PA165292177#
http://www.drugs.com/pro/doxorubicin.html
Cheng, Rong C. "Total Flavonoids from Clinopodium Chinense (Benth.) O. Ktze Protect against Doxorubicin-Induced Cardiotoxicity In Vitro and In Vivo." Evidence-Based Complementary and Alternative Medicine (2015): n. pag. PubMed. Web. 3 May 2015.

2. Select <u>one</u> of the cytochrome P450 enzymes below in the (a) through (d) list, and describe it as thoroughly as possible in points (i) through (v) below. You should cite at least one reference to a peer-reviewed publication or to a monograph for the course. For any information you put in your response, ensure that it is sourced/referenced. Your response will be compared to the information in the reference

CYP3A4

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

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The purpose of Cytochrome P450 3A4 is to oxidize small foreign organic molecules such as xenobiotics to be removed from the body. CYP 3A4 belongs to a class of heme containing mono-oxygenase enzymes. Cytochrome P450 3A4 is responsible for metabolizing nearly 50% of clinical drugs. CYP3A4 is significantly involved in metabolizing cyclic peptide cyclosporine A and macrolide antibiotics. CYP3A4 does not fit the Machelis Menton type kinetics and has been shown to bind more then one substrate during in-vivo and in-vitro studies. CYP3A4 modifies the substrate through hydroxylation, aromatic oxidation, heteroatom oxidation, and dealkylation reaction processes.

Fa, Batao. "Pi-pi Stacking Mediated Cooperative Mechanism for Human Cytochrome P450 3A4." Molecules (2015): 7558-573. Web. 4 May 2015.

ii. Explain the mechanism of catalysis (you can even draw the steps)

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First CYP3A4 forms a strong hydrogen bond with an amino acid in its structure. The hydrogen bond along with hydrophobic interactions of the molecules allows the CYP3A4 enzyme to position itself in an optimal position for binding the substrate molecule and facilitating the reaction.

Fa, Batao. "Pi-pi Stacking Mediated Cooperative Mechanism for Human Cytochrome P450 3A4." Molecules (2015): 7558-573. Web. 4 May 2015.

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

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Studies have shown that grapefruit juice is an inhibitor of the CYP3A4 enzyme. Grapefruit juice is known to inhibit first pass enzymes, CYP3A4 is an enzyme that breaks down most substrates on the first pass.

Bressler R (November 2006). "Grapefruit juice and drug interactions. Exploring mechanisms of this interaction and potential toxicity for certain drugs". *Geriatrics* **61** (11): 12–8. PMID 17112309.

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

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The CYP3A4 molecule is divided up into 13 exons and 12 introns. GT and AG were found at the boundaries of all introns. Arg372 formed a strong hydrogen bond and hydrophobic forces were present in order to put the substrate in an optimal binding site for further metabolism.

Fa, Batao. "Pi-pi Stacking Mediated Cooperative Mechanism for Human Cytochrome P450 3A4." Molecules (2015): 7558-573. Web. 4 May 2015.
Hashimoto, Hasashi. "Gene Structure of CYP3A4, an Adult-specific Form of Cytochrome P450 in Human Livers, and Its Transcriptional Control." Eauropean Journal of Biochemistry 218.2 (1993): 585-95. Web.

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

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CYP3A4 has the highest rate of catalysis among all cytochrome p450 enzymes. CYP3A4 has shown in studies that it requires a phenolic group for ortho hydroxylation of estradiol and mono-O-demethylated methoxychlo. I don't quite understand this chemistry but it was the best that I could find.

Stresser, David M., and David Kupfer. "Catalytic Characteristics of CYP3A4: Requirement for a Phenolic Function in Ortho Hydroxylation of Estradiol and Mono-O-demethylated Methoxychlor." Biochemistry (1997): 2203-210. ACS Publications. Web.

3. Select (a) or (b) or (c) to answer:

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 broad survey. In any article you obtain, be sure to indicate at least three significant points, but list all of them if there are more.

This was a study done on men and women and compared brain activity after using alcohol, cocaine, and both alcohol and cocaine. PET scans of the brain were done on patients that participated in the study.

The results showed that men and women responded similarly to alcohol consumption. The participants scored similarly. It was noted that women had a greater increase in heart rate than men did.

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The second part of the study recorded how women responded to both alcohol and cocaine at the same time. The doses were delivered at 30 minute intervals for an 8 hour period. Both men and women responded similarly to the combination of alcohol and cocaine.

When testing Cocaine consumption alone, the study showed that women had a greater response to the cocaine by itself than the men did. They were observed to have a greater feel good rating 36-54, and the men in the study had a feel good rating of 20-34. This shows that women metabolize cocaine different than men do. It also provides evidence to the high amount of female deaths that reveal traces of cocaine in the autopsy report.

This study suggests that drugs should be studied on both men and women and data collected cannot be generalized for both men and women. Discovering different metabolic pathways for men and women will improve effectiveness of treatments for pathologies and will benefit human kind as a whole.

http://archives.drugabuse.gov/NIDA_Notes/NNVol20N6/Drugs.html