Pathology 438 Midterm Examination due: by 1:00 PM, 6 May 2015
Spring 2015
NAME **Kristen Chila**

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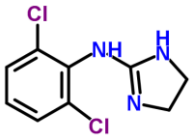
1. Select <u>one</u> of the substances below: (a) OR (b) OR (c). Provide as a complete a description of the toxico/pharmacokinetics and toxico/pharmacodynamics as possible. Support your description with at least two references, one of which must be from a published book or a journal article.

<u>Clonidine</u>



<u>Toxicokinetics:</u>
Absorption: offered orally, transdermally, and intravenously; absorption unaffected by food or race of patient
Distribution: antihypertensive effects noted between 0.2 – 2.0 ng/mL, excreted in human milk
Metabolism: 50% of absorbed dose metabolized in the liver
Elimination: 40-60% of absorbed dose eliminated in urine unchanged

<u>Toxicodynamics:</u>
Protonated clonidine is the active form.
Effects of Clonidine are reduced when taken with tricyclic antidepressants.
Corneal lesions developed in rats after five days with Clonidine was taken in combination with amitriptyline.

Qin J, Wang L, Wu L, Chen J, Shen T, Li Y, Han L, Wang J. "Development of an LC-MS/MS method for determining the pharmacokinetics of clonidine following oral administration of Zhenju antihypertensive compound." *National Center for Biotechnology Information*. U.S. National Library of Medicine, n.d. Web. 03 May 2015.
http://www.ncbi.nlm.nih.gov/pubmed/25776729

"Catapres ® (Clonidine hydrochloride, USP)." Boehringer Ingelheim. October 2011. Web 03 May 2015.
http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/017407s037lbl.pdf

Norberto F, Moreira J, Rosa E, et al. "Kinetics and mechanism of nitrosation of clonidine – a bridge between nitrosation of amines and ureas." *Journal od Chemical Society Perkin*. University of Santiago, Chile. 09, 1993. Web. 04 May 2015.
http://www.researchgate.net/publication/225029255_KINETICS_AND_MECHANISM_OF_NITROSATION_OF_CLONIDINE_-_A_BRIDGE_BETWEEN_NITROSATION_OF_AMINES_AND_UREAS

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

<u>CYP2C9</u>

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

Metabolizes xenobiotics (ex. ibuprofen, warfarin, NSAIDS, oral anti-diabetic agents (hypoglycemics), angiotensin II receptor blockers).

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

Hydroxylation.

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

Phenytoin (substrate, inhibitor, and inducer), fluconazole, miconazole, amentoflavone, sulfaphenazole, valproic acid, apigenin.

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.

Found on chromosome 10q24. N-terminal sequence MALLAVF.

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

Acidity.

"CYP2C9 cytochrome P450, family 2, subfamily C, polypeptide 9." *National Center for Biotechnology Information*. U.S. National Library of Medicine, April 26 2015. Web. 03 May 2015. http://www.ncbi.nlm.nih.gov/gene/1559

Kumar V, Rock D, Warren C, Tracy T, Wahlstrom J. "Enzyme Source Effects on CYP2C9 Kinetics and Inhibition." *National Center for Biotechnology Information*. U.S. National Library of Medicine, April 23 2006. Web. 03 May 2015. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2377028/

Horn J, Hansten P. "Get to Know an Enzyme: CYP2C9" *Pharmacy Times*. March 1 2008. Web. 03 May 2015. http://www.pharmacytimes.com/publications/issue/2008/2008-03/2008-03-8462

Locuson C.W., Wienkers L.C., Jones J.P., Tracy T.S. "CYP2C9 protein interactions with cytochrome b5: Effects on the coupling of catalysis." Drug Metab Dispos. 2007 Jul;35(7): 1174-1181. Web 04 May 2015. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2386961/

3. Search for a nephrotoxic substance (toxicant, poison or drug). Explain what part(s) of the nephron it disrupts (describe the mechanism of toxicity). Describe how normal kidney physiology would be disrupted for the parts of the nephron affected. Describe how the nephrotoxic substance is detoxified (metabolism? elimination? both?) What doses or concentration levels are required to obtain the toxic effect?

Cyclosporine

Vasoconstriction of afferent arterioles through altered release of vasoactive substances (such as angiotensin II, endothelin, prostaglandins, and nitric oxide) causes nephrotoxicity. Also stimulates genes to produce growth-factor beta , osteopontin, and collagen I and IV. Biopsies have shown interstitial fibrosis, tubular atrophy, glomerulosclerosis, vascular damage (smooth muscle).

NSAIDS + cyclosporine may increase risk of renal toxicity, especially in patients with rheumatoid arthritis.

6-10mg/kg/day associated with toxic manifestations in the kidneys.

Detoxified in the liver by CYP450 enzymes.

Busauschina A, Schnuelle P, van der Woude F.J. “Cyclosporine nephrotoxicity.” *Transplant Proceedings.* March 2004. Vol 36, Issue 2, Supplement. P S229-S233. Web. 03 May 2015. http://www.transplantation-proceedings.org/article/S0041-1345(04)00022-3/abstract

Miller L. “Cyclosporine-Associated Neurotoxicity: The Need for a Better Guide for Immunosuppressive Therapy.” *AHA Journals.* 1996. Web. 03 May 2015. http://circ.ahajournals.org/content/94/6/1209.full

“Cyclosporine Side Effects in Detail - Drugs.com." *Cyclosporine Side Effects in Detail - Drugs.com*. N.p., n.d. Web. 04 May 2015. http://www.drugs.com/sfx/cyclosporine-side-effects.html

Ragab, Ahmed Refat. "Cyclosporine Toxicity and Toxicokinetics Profiles in Renal Transplant Recipients." *Journal of Clinical Toxicology* 03.01 (2012): n. pag. Web. http://omicsonline.org/cyclosporine-toxicity-and-toxicokinetics-profiles-in-renal-transplantrecipients-2161-0495.1000154.pdf

The Proceedings From The 13Th International Symposium Of, and The Institute For Functional Medicine. "Managing Biotransformation: The Metabolic, Genomic, and Detoxification Balance Points." *Managing Biotransformation: The Metabolic,* (n.d.): n. pag. Web. http://www.alternative-therapies.com/at/web_pdfs/ifm_proceedings_low.pdf