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.

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1. A/D = 3 +

b) clonidine: Is usually administered orally as treatment for patients with high blood pressure medication to decrease the risk of stroke and heart attack. It is also an anti-hypersensitive drug class used for ADHD (attention deficit hyperactive disorder). Also categorized in the class of Central Alpha-2 Adrenergic Agonist drugs. Can be used to help with withdrawal symptoms from tobacco, opiates and benzodiazepines.
-An article from the European Journal of Clinical Pharmocology reported the action of this drug is mediated by alpha adrenoceptor agonist for both the central and peripheral nervous system. It has a high lipid solubility that makes the side effects correlated directly with how much serum clonidine is in the plasma. The absorption half life of a dose of 300 µg was about .6 hours and only able to be studied now because of specific and sensitive mass-fragmentographic studies. The two most commonly experienced side-effects are severe sedation and dry mouth. [Pharmacokinetics and side-effects of clonidine]
-Another study done showed that most studies stated that the elimination half-life was 20 hours but that this was actually not long enough, it is closer to over 25 hours. When it is prescribed for antihypertensive therapy it is given in very small doses that are difficult to study effects in the plasma. They used a radioimmunoassay analysis with normotensive subjects. They found that 62% of a single doses is excreted in the urine, independently of quantity of dose given.

[New Aspects of Pharmacokinetics and Pharmacodynamics of Clonidine in Man]

-Clonidine changes the amount of noradrenaline that is released by stimulating presynaptic receptors in the medulla that decrease the sympathetic output to the peripheral blood vessels by means of vasoconstriction. This leads to a decrease in blood pressure. Should not be used with BPH or Urinary Incontinence and adverse side-effects include drowsiness, depression and postural hypertension.

Thorp, Christine M., Pharmacology for the Health Care Professions. Wiley-Blackwell, Oxford, UK; 2008.

2. Select one 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

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

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

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

1.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

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

CYP2C9

1.

1. There are several substrates metabolized by this enzyme including NSAIDs (diclofenac, ibuprofen, naproxen and piroxicam), Oral Hypoglycemic (tolbutamide, glipizide and glyburide), Angiotensin II Blocker (Iosartan, irbesartan) and other drugs for essential hypertension (celecoxib, fluvastatin, phenytoin, rosiglitazone, torsemide, valproic acid, warfarin, zafirlukast). [P450 Drug Interactions]
2. In the Journal of Biological Chemistry, they studied the structure of this enzyme with Fluriprofen. This study showed the catalytic efficiency of this enzyme when it regioselectively oxidizes NSAIDs. This enzyme aids in hepatic metabolism and can decrease the metabolic capacity of other substrates with low therapeutic margins and lead to toxicity at normal therapeutic doses. Other structural bindings are shown on this article but too confusing to try to draw. [CYP2C9]

"CYP2C9 is the enzyme responsible for the metabolism of the S-isomer of warfarin that is principally responsible for the anticoagulant effect of the drug. The crystal structure of human CYP2C9 was described by Williams et al. [46], for both CYP2C9 in complex with warfarin and unliganded CYP2C9 (Protein Data Bank ID: 1OG2 and 1OG5, respectively). The structure showed unanticipated interactions between CYP2C9 and warfarin, revealing a new binding pocket, suggesting that CYP2C9 may simultaneously accommodate multiple ligands during its biological function [46]. Structural analysis suggested that CYP2C9 may undergo an allosteric change when binding warfarin [46]." [CYP2C9]

3. Moderate inhibitors include amiodarone and efavirenz. Strong inhibitors include: fluxaonazole, isoniazid, metronidazole, paroxetine, sulfamethoxazole and voriconazole. This means that you would need to increase the dosage if you are taking one of these at the same time.[P450 Drug Interaction]
4. Inducers associated with this include: carbamazepine, nevirapine, phenobarbital, rifampin and St. John's Wort. [P450 Drug Interaction]

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

1.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.

The article I found studied the differences between men and women hepatocyte function with 5 drugs: Diclofenac, Chlorpromazine, Acetaminophen, Verapamil and omeprazole. Caffeine was used as a negative control. Women were found to be more sensitive to drugs invitro. Findings showed differences in plasma permeability, nuclear condensation, endoplasmic reticulum function and mitochondria. There was also evidence that there might be a difference with post-menopausal women's cells and women who have menses. There is little understood on this topic still because the studies are primarily on animals and not also directly correlated to human genome. Also the number of women that are participating in the study was smaller sample size and takes away from the findings.[men vs women]