Toxicology Take-home Mid-term

By
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1. Valproic Acid pharmacokinetics and pharmacodynamics

Valproic Acid is available in tablets, rectal suppositories, syrup and injectable forms. in the pharmacy it can be found in tablet form under names like Depakote, Stavzor, Convulex, and Myproic acid. When tablets are digested and the Valproic acid (VPA) is in the blood stream this chemical is acted on by carnitine to get VPA into the mitochondria of the liver. In the mitochondria the Valproic acid is oxidized by being catalyzed by Medium-chain acyl-CoA synthase to make valproyl-CoA. This is dehydrogenated to 2-propyl-valproyl-CoA by 2-methyl-branched chain acyl-CoA dehydrogenase or isovaleryl-CoA dehydrogenase. The product from this reaction is catalyzed by enoyl-CoA hydratase to make 3-hydroxyl-valproyl-VPA. Then 2-methyl-3-hydroxybutyryl-CoA dehydrogenase catalyzes that product to make 3-hydroxyl-valproyl-VPA. Then unknown thioestraces metabolize 3-oxo-VPA in slow hydrolysis creating 3-oxo-VPA and Co-ASH. These products start a new pathway where 3-oxo-VPA is cleaved by 3-keto-valproyl-CoA thiolase producing propionyl-CoA and 4-ene-VPA-CoA ester which is then beta oxidized to 2,4-diene-VPA-CoA ester via ACADSB. Finally the body excretes (E)-2,4-diene-VPA in the urine.

If 4-ene-VPA is reacted in a fluoridated environment 2,4,diene-VPA-S-CoA is produced which then grouped with glutathione to create cytotoxic thiols that tend to take from the glutathione stores eventually stopping the beta-oxidation pathway. VPA also increases GABA levels by stopping the inhibition of it's generation. It does this by preventing iGABA's degeneration by blocking ABAT and ALDH5A1 and OGDH reactions. on this. VPA blocks the voltage gated ion channels in neurons. Finally, VPA inhibits and activates HDAC and it's derivatives which can inhibit apoptosis meaning that VPA is associated with antitumor activity. VPA activates HDAC 9 and 11 in cancer cell lines. This means that it might be promoted as a neural cancer fighting drug as well as an antiepileptic.

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2. CYP2C9

i. Provide a description of the type of substrates it metabolizes and give an example of one substrate it is known to metabolize.
ii. Explain the mechanism of catalysis (you can even draw the steps)
iii. Provide the names of any substances known to inhibit the cytochrome, if any

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

Cytochrome P450 2C9 is known to metabolize a large number of drugs in the system. drugs it affects are things like blood pressure medications (losartan) , NSAIDs (ibuprofen) , drugs indicated for diabetic use (glipizide) , and antiepileptics (VPA). Medications like amiodarone, fluconazole, and sulfaphenazole inhibit CYP2C9's activity. CYP2C9 oxidizes and hydroxylizes drugs like Diclofenac and flurbiprofen.CYP2C9 has a crystalline structure and creates a pocket for the chemicals it catalyzes and it may have the ability to perform more than one catalization at a time. With the 4'- OH (S) - flurbiprofen, CYP2C9 consumes 2.8 nmol drug/ min/ nmol CYP2C9 and 13 nmol/ min/ nmol CYP2C9 for diclofenac.

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Yan, Z., Li, J., Huebert, N., Caldwell, G., Du, Y., & Zhong, H. (2005, March 11). DETECTION OF A NOVEL REACTIVE METABOLITE OF DICLOFENAC: EVIDENCE FOR CYP2C9-MEDIATED BIOACTIVATION VIA ARENE OXIDES. Retrieved May 3, 2015, from http://dmd.aspetjournals.org/content/33/6/706.full

3) 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.

It has been noted that females follow medical protocol more when their MD is also a female, and their prognosis is better over all. This may be a cultural preference because women aren't publicly known to be at as high or higher risk of heart disease. Also women don't tend to show effects of heart disease before they have problems like cardio vascular accidents. The article also suggests that the reason may be due to the fact that more seniors are female than male.

The digestion rates of the medication are different between men and women. Female's stomachs are more basic and their digestive systems take longer to process their food than men. The differences may depend on the sex hormones of each gender. Also some

generic medications are metabolized differently than the original. Franconi and Campesi give an example of polyethylene glycol that increases the availability or ranitidine in men but decreases it in women. The fillers in the medications may also have different effects between genders. Females and males present with different genetic markers and morphologies which may be a factor in how women metabolize the medications differently.

Angiotensin converting enzyme inhibitors (ACEIs) tend to have more side effects of coughs and heart swelling than in men. Eplerenone selective aldosterone antagonists showed a greater benefit in women, who tend to have more constant ratio of aldosterone to cardiac wall thickness than males after 30 days of treatment. When compared 16 months later men had done better by avoiding the hospital or mortality. only about 30% of the people in the study were female so they aren't sure if this reflects the population's truly predictable effects. Spironolactone when studied in rats only benefitted the males with high salt diets.

Part of the reason women may have a higher chance of heart rate is the fact that women tend to hold more of their sympathetic stress around their heart. Females also don't react as easily to sympathetic vasoconstriction, this may be due to the beta-adrenoreceptor density in their lymph system.

Females' heart problems when under a prescription regimen increase when estrogen is high and decrease when progesterone levels are high. problems that lead to adverse drug effects(ADEs) like multiple therapies, depression or aging affect women more than men. I wouldn't be surprised if a women's menstrual cycle including nutrient and blood loss may play a part in the increased rates of ADE occurance. it is also suggested several times that the mass difference between males and females alter the way women react to medications.

Franconi, F., & Campesi, I. (2013, August 16). Pharmacogenomics, pharmacokinetics and pharmacodynamics:interaction with biological differences between men and women. Retrieved May 6, 2015, from http://onlinelibrary.wiley.com/doi/10.1111/bph.12362/epdf