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.

Valproic Acid

Valproic acid is used as an anticonvulsant for epilepsy patients primarily. It has a very narrow therapeutic index (TI) of 50-125 µg/mL. Toxicity > 150 µg/mL is due to metabolites mostly from beta oxidation. These metabolites cause death of hepatocytes which can be detected by increased GSH.

Absorption: Valproic acid is administered orally and is rapidly absorbed in the GI tract. It is absorbed at an estimated rate of 100% and fully absorbed within 4 to 8 hours depending on what form it is taken in.

Distribution: It is highly protein bound (87-95%) and can cross the mitochondrial membrane via carnitine. It also appears in the breast milk and can cross the placenta which poses a concern for pregnant and breastfeeding mothers as it would be dangerous for the child.

Metabolism: There are at least 3 routes of absorption in humans: Glucuronidation (50%), beta oxidation in the mitochondria (40%) and cytochrome P450 mediated oxidation (10%)

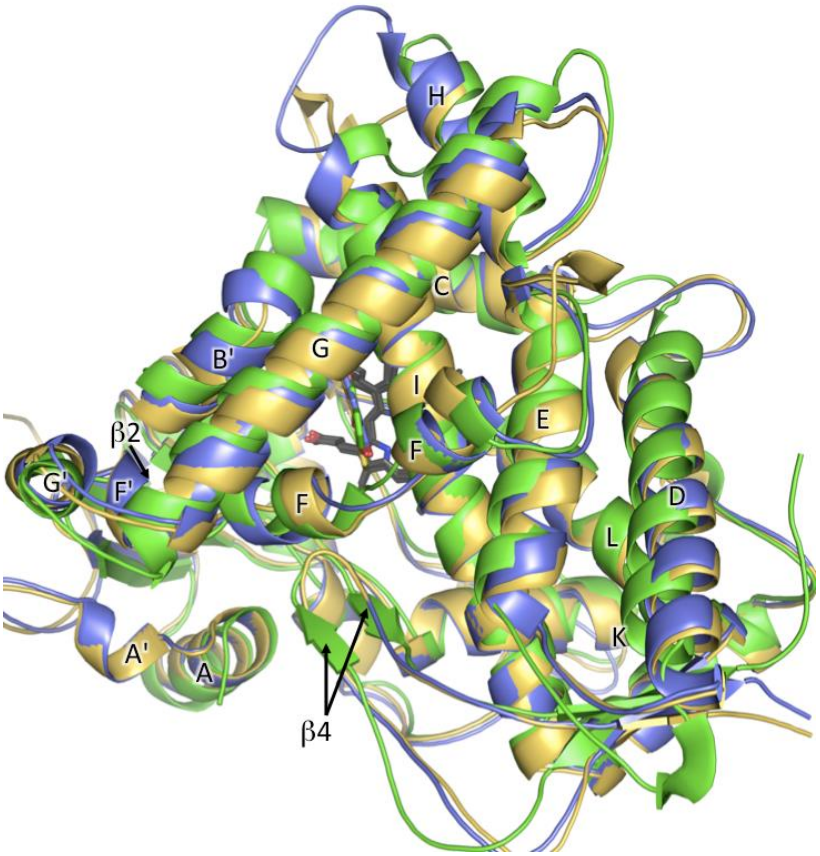
Elimination: Plasma elimination half-life is 10-16 hours but can be as short as 6-8 hours when used with other antiepileptic drugs. This necessitates careful monitoring especially when pairing valproic acid with other medications.

2.CYP1A1

CYP1A1 is a cytochrome P450 that is especially important for the metabolism of xenobiotics in the fetal placenta. It oxygenates polycyclic aromatic hydrocarbons such as benzo(a)pyrene so that they can be made water soluble for elimination. It is activated by AhR and Amt proteins which induce CYP1A1 transcription. It can be inhibited by the flavonoid galangin.

It seems that the unique functions of CYP1A1 are not well known. The only information I could find specific to this Cytochrome P450 is in its induction by AhR.

Below is a proposed drawing of the CYP1A1.



Acetominophen is a nephrotoxic substance that is classified as a non-steroidal anti-inflammatory. It affects the proximal renal tubules and causes a decrease in glomerular filtration rate. Metabolites of Acetominophen are produced in the form of quinones which are highly reactive. These quinones react with glutathione and sulfhydryl groups on proteins and cause cellular dysfunction. This cellular dysfunction leads to renal failure.

Normally Acetominophen is not toxic and is metabolized by cytochrome P450 and excreted. It is toxic when given in doses >2,000mg/kg.

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