**1) Valproic Acid (VPA) - Used to treat seizures and epilepsy**.

Pharmacokinetics:

Absorption:

Valproic acid is absorbed in the GI tract quick, with time depending on the type of tablet consumed. In the GI tract, valproic acid breaks into valproate ion. The time after consumption when the absorption rate is equivalent to the elimination rate, also known as the time when maximum concentration in the blood is reached (Tmax), is 4-17 hours depending on the type and dose of the tablet (Wolters Kluwer Health, 2009).

Distribution:

The volume of distribution (Vd) is known as the volume of fluid that is needed to keep a drug in the body with an equal concentration to the plasma. The lower the Vd means that the substance can be found mainly in the vascular system, whereas a higher Vd means it is absorbed more by the tissues. Vd of valproic acid is 11L/1.73m2 for total amount, and 92L/1.73m2 for the free amount. These values match Leppik & Birnbaum's (2010) statement that VPA is "highly protein bound (87-95%)", as we see the low total VPA Vd showing primary isolation in the vascular system as bound to plasma proteins, and the total free amount as moving to the tissues because it is not bound to proteins.

Metabolism:

Valproic acid (VPA) is branched short-chain fatty acid that is metabolized in the mitochondria of the liver. The 3 well-known pathways of VPA metabolism are glucuronidation (50%), beta oxidation in the mitochondria (40%) and oxidation by cytochrome P450 (CYP) (10%). Prior to entrance into the mitochondria, VPA is activated into several compounds, including 4-ene-VPA. This 4-ene-VPA enters the mitochondria and is converted to 2,4-diene-VPA-CoA via B-oxidation. 2,4-diene-VPA-CoA is hepatotoxic and is therefore conjugated with glutathione to form thiol conjugates, which are excreted from the liver mitochondria (Ghodke-Puranik et al., 2013).

Elimination:

The excretion of thiol conjugates serves as detoxification for the liver. Since VPA is protein bound, the clearance rate is slow, approximately 6-20 mL/hr/kg. Valproate-glucuronide is approximately 30-50% of VPA urinary metabolites (Argikar et al., 2008).

Pharmacodynamics:

According to Ghodke-Puranik et al. (2013), VPA acts on gamma amino butyric acid (GABA) in the brain, it blocks voltage-gated ion channels and also inhibits histone deacetylase. With epilepsy, GABA receptors are impaired and can not be inhibited, which leads to the convulsive symptoms. VPA has been found to inhibit key enzymes that function in the pathway of GABA degradation. By having more circulating GABA, and by decreasing firing of neurons through the blocking calcium, potassium and sodium voltage-gated channels, this decreases epileptic instances (Johannessen et al., 2003).

## 2. CYP3A4

i) CYP3A4 is a cytochrome P450 enzyme that metabolizes xenobiotics, seen as clinical drugs such as antibiotics and endogenous compound bile acids. CYP3A4 is the most abundant hepatic and phase I intestinal enzyme, known to metabolize approximately 50% marketed drugs and detoxify bile acids, as high levels of bile acids can injure tissues, especially the liver (Zhou, 2008). Erythromycin is an example of an antibiotic that is metabolized by CYP3A4.

ii) CYP3A4 catalysis reactions are an integral part in the metabolism of drugs, and the synthesis of cholesterol, steroids, and various lipids. CYP3A4 is induced by glucocorticoid presence and catalysis of the substrates is localized at the endoplasmic reticulum. Catalysis begins with $sp^3$ C-H bond hydroxylation, which in turn affects the ligand. Further mechanism includes substrate dehydrogenation, which creates further complex metabolites.

iii) Some examples of strong CYP3A4 inhibitors, meaning they decrease clearance of substrates by at least 80%, are: protease inhibitors, and some macrolide antibiotics and azole antifungals (Flockhart, 2007).

iv) CYP3A4 is a cytochrome P450 oxidizing enzyme, which contains a hemoprotein, meaning that it is a protein with a heme group containing an iron atom. This CYP3A4 protein is encoded by the CYP3A4 gene (Hashimoto et al., 1993), has a large active site, and has the ability to bind more than one substrate at a time. The ability to bind multiple substrates allows CYP3A4 to work on several endogenous and exogenous substrates through various reactions including hydroxylation, aromatic oxidation, and dehydrogenation to name a few (Shahrokh et al., 2012).

v) Turnover rate estimates of the CYP3A4 enzyme have extreme varying values. With hepatic in vivo methods, the half-life has been estimated as 70-140 hours. Hepatic in vitro methods have estimated 26-79 hours. CYP3A4 in the GI tract also has its own estimates, however likely has additional role-playing factors to consider, such as the enterocyte renewal. One study did get results of the GI tract half-life estimates, seen as 12-33 hours (Yang et al., 2008).

3. Nephrotoxic substances I am interested in are non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen. NSAIDs can cause inflammatory changes in the glomerulus, renal tubules, and interstitium, leading to further problems including fibrosis and scarring of the kidney. In healthy young adults, the glomerular filtration rate (GFR) is usually close to 120 mL/min. The kidney regulates intraglomerular pressure by constriction and dilation of the afferent and efferent arterials, to optimize urine output and GFR, through the action of angiotensin-II. There are two known effects that NSAIDs have on the kidney; acute kidney injury and acute interstitial nephritis. Acute kidney injury (AKI) from NSAIDs is seen as decreased prostaglandin production, which resultantly reduces renal plasma flow because these prostaglandins regulate glomerular vasodilation. By decreasing the substance doing vasodilation, vasoconstrictor hormones have a greater effect on the vessels (Whelton, 2009). Inhibition of prostaglandins begins acute renal function deterioration. AKI is also acute interstitial nephritis (AIN), but it is characterized by inflammatory cells in the kidney interstitium. AIN is caused by an immunological reaction after approximately a week of NSAID usage, and it causes 15% of ANI (Dixit et al., 2007).

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