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Pathology 438
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Midterm Examination

1. Describe toxico/pharmacokinetics and toxico/pharmacodynamics of **Clonidine**

Clonidine is a drug most commonly used to treat high blood pressure and is also alone or in conjunction with other drugs used to treat ADHD. Common brand names for this anti hypertensive drug include Catapres, Kapvay, and Nexiclon XR. It has been used clinically for over 40 years and unfortunately, in the case of treating high blood pressure, is commonly communicated as needed "for the rest of your life."

It's classified as a centrally acting alpha adrenergic agonist. It stimulates alpha2 receptors in the brain which decreases peripheral vascular resistance therefore lowering blood pressure. It specifically targets presynaptic alpha2 receptors in the brainstem, binding decreases presynaptic Calcium levels leading to a net effect of a decrease in sympathetic tone. Clonidine is most often prescribed orally but because of the adverse side effects is being both studied and prescribed transdermally.

When taken orally the drug is absorbed rapidly after an initial lag time of 19-22 minutes and peak levels of plasma concentration (Cmax) is reached between 2.4 and 2.9 hours. Sampling over 48 hours is necessary for accurate pharmacokinetic action. The half life of the elimination phase ranged from 9.0 to 15.1 hours. Cmax increased proportionally with increased doses. Clonidine causes a marked reduction in pulse rate and a dose dependent decrease in blood pressure.

Pharmacodynamics of the drug vary greatly. The most common adverse affects, >10% frequency, include dizziness, drowsiness, dry mouth, headache, and skin lesions if taken transdermally. Other affects with 1-10% frequency include anxiety, constipation, sedation, nausea, and erectile dysfunction.

S.N Anakevar, B. Jarnott, et al. *Pharmacokinetic and Pharmacodynamic studies of oral Clonidine in normotensive subjects.* European Journal of Clinical Pharmacology. 1982. Volume 23, Issue 1. Pp 1-5. link.springer.com/article/10.1007%2FBF01061368

en.m.wikipedia.org/wiki/Clonidine

2. Cytochrome P450 enzyme: CYP3A4

i. Cytochrome P450 is a family of oxidizing enzymes and CYP3A4 is specifically involved in oxidation of small foreign organic molecules or xenobiotics. Acetaminophen and erythromycin are examples of drugs metabolized by CYP3A4.

ii. CYP3A4 is mainly found in the liver and the gut, namely the intestines. It's involved not only with drug metabolism but also with the synthesis of cholesterol, steroids, and other lipids. Cytochrome P450 enzymes have a large active site and can bind more than one substrate at a time to perform complex metabolism including hydroxylation, epoxidation, oxidation, and dehydrogenation reactions.
iii. Fruit ingestion is known to inhibit the action of CYP3A4. Primarily grapefruit and grapefruit juice however, Noni fruit and pomegranates can exhibit the same effects. Ingestion of these can increase the bioavailability of some drugs and in other cases, the reaction can be fatal, astemizole and terfenadine are examples.
iv. All members of the cytochrome P450 family, including CYP3A4, are hemoproteins, a protein containing a heme group with an iron atom. In humans the CYP3A4 protein is encoded by CYP3A4 gene which is on chromosome 7g21.1. Although the CYP3A4 gene has 28 single nucleotide polymorphisms (SNPs), none have been found to contribute to inter individual variability in vivo.
v. In the particular study that I reviewed kinetic parameters of Km, Vmax , and Vmax/Km of 215 CYP3A4 mediated reactions of 113 drugs in human liver microsomes and lipophilicity values of the 113 drugs were calculated. Overall, Km decreases but Vmax/Km increases with increasing substrate lipophilicity, and Vmax appears to be independent of substrate lipophilicity. Another way of putting it would be that a low Km generally produces a highVmax/Km ratio for a substrate.

A literature review of enzymatic parameters for CYP3A4 mediated metabolic reactions of 113 drugs in human liver microsomes. www.ncbi.nlm.nih.gov/pubmed/16611019

en.wikipedia.org/wiki/CYP3A4

3. *Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol in men and women*

This study compared the effects of delta-9-tetrahydrocannabinol (delta9-THC) both intravenously and orally in men and women. (1) No differences in dynamic activity, metabolism, excretion, and kinetics were observed. Delta9-THC is converted by microsomes hydroxylation into an intermediate which is a potent psychoactive metabolite. (2) Major differences in ratio of concentration of this psychoactive metabolite to delta9-THC were found after intravenous dosing compared with oral administration. However, no differences across male and female. (3) For delta9-THC the terminal phase or half life for both sexes irrespective of the route, ranged from 25 to 36 hours.

ME Wall, BM Sadler, et al. *Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol in men and women.* Clinical Pharmacology and Therapuetics. September, 1983. Volume 34, Issue 3. P 179. *onlinelibrary.wiley.com*