Bioavailability Project

For a drug to create its desired therapeutic effect, the compound must not only react properly with the target site, such as a membrane receptor in the brain, but it must also reach the target site. With orally dosed drugs, this requires a balancing act in terms of the physical properties of the drug as well as dosing. In this project, you will examine the path barbiturates (specifically pentobarbital) takes from oral administration to excretion.

We will start with a broad overview of how barbiturates travel through the body. The path begins with oral consumption of the barbiturate. In the stomach the barbiturate pill dissolves; however, the barbiturate itself is unchanged by the highly acidic environment. After it passes through the stomach, the barbiturate enters the intestinal track, where it must be absorbed through the intestinal wall into the blood stream which heads straight to the liver. After passing through the liver, barbiturate enters the circulatory blood stream for delivery to the brain.

The first step we will examine in depth is the passage of barbiturates from the intestinal track to the blood stream. A simple model of this process is that the barbiturate will pass from one aqueous phase through a lipophilic membrane into another aqueous phase. Lipophilic is a term that is not in your book. Lipophilic means lipid loving; in other words, lipophilic compounds would want to dissolve in lipids.

1) (9 points) Explain what structural characteristics make a compound lipophilic and what ones make a compound hydrophilic. Explain why these characteristics are lipophilic or hydrophilic.

2) (9 points) Which structural features of pentobarbital (shown below) are lipophilic? Which are hydrophilic?
Drugs pass from the intestinal track through the lipophilic membrane to the blood stream by passive diffusion.

3.) (9 points) Explain how the concentration of pentobarbital changes as it diffuses from the intestines to the blood stream.

For drugs to passively diffuse from the intestinal track into the blood stream, they must be able to partition themselves between the aqueous phase and the lipophilic membrane. This is an equilibrium process. The more lipophilic barbiturates have a higher percentage absorbed through the intestinal wall.

4) (9 points) Provide an explanation as to why the more lipophilic barbiturates are better absorbed.

It has been written that “[D]rugs must exhibit a balance between hydrophilicity and lipophilicity.”

5) (9 points) Why would a drug that is too lipophilic be a problem? Make sure your explanation clearly states the physical properties that are affected.

Once the barbiturates have been absorbed from the intestines, they pass through the liver before entering the general circulatory system. In the liver, drugs are metabolized. For some drugs, this converts them to active metabolites; however, in the case of barbiturates, they are converted to inactive metabolites which can then be cleared by the renal system, which eliminates waste as part of the aqueous solution known as urine. Not all of the barbiturates are metabolized on the first pass through the liver. Those that are unmetabolized then travel throughout the body, with some passing through the lipophilic blood-brain barrier, to reach target sites within the brain that produce the barbiturates’ CNS depressing effect.

6) (9 points) How would the amount of pentobarbital administered orally compare with the amount that was administered intravenously, which enters the blood stream without passing through the liver first, if both were to achieve the same therapeutic effect? More, less, or the same amount? Explain your answer.

One of the primary metabolites of pentobarbital is the compound shown below.
7) (9 points) What was the functional group that was altered? Does this alteration make the compound more lipophilic or hydrophilic? Explain your answer.

8) (9 points) Why does this change make the metabolite inactive by affecting its ability to cross the blood-brain barrier?

9) (9 points) Why does this change make it better for renal clearance?

10) (9 points) Propose a valid chemical reaction for the enzymatic conversion of pentobarbital to pentobarbital alcohol. All reasonable proposals will be accepted for full credit (consult your organic chapters for ideas). You should justify your proposal.

11) (5 points) Please give constructive feedback regarding this Capstone Project. Was it worthwhile? Did it illustrate CHE 106 concepts? What did you gain/learn from doing the project that you did not learn from the modules individually? What would you keep/recommend in future semesters? What would you change? What other information would you like to convey to your instructor with respect to this project?

References:
