Bioavailability Project – General Information & Thinking Questions

You will not be able to access the "thinking questions" drop box until you score at least 80% on one take of the “information review questions”.

General Information:
Before taking the Information Review Questions, it is recommended that you review the following topics:

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Project Overview & Thinking Questions:
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 bloodstream for delivery to the brain.

The first step we will examine in depth is the passage of barbiturates from the intestinal track to the bloodstream. A simple model of this process is that the barbiturate will pass from one aqueous phase (the intestinal track) through a lipophilic membrane (the intestinal wall) into another aqueous phase (the bloodstream) by passive diffusion.

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aqueous intestinal track | lipophilic membrane | aqueous bloodstream
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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. So the compound dissolves in the lipophilic membrane and then dissolves in the aqueous bloodstream.

1.) (3 points) Explain what characteristics of functional groups make an organic compound lipophilic and what ones make a compound hydrophilic. Explain why these characteristics are lipophilic or hydrophilic.
2.) (3 points) Which structural features of pentobarbital (shown on next page) are lipophilic? Which are hydrophilic?
As mentioned earlier, drugs pass from the intestinal track through the lipophilic membrane to the bloodstream by passive diffusion.

3.) (3 points) Explain why pentobarbital diffuses from the intestines to the bloodstream from a concentration perspective.

For drugs to passively diffuse from the intestinal track into the bloodstream, they must be able to partition themselves between the aqueous phase and the lipophilic membrane. This is an equilibrium process. Just as reversible reactions move to equilibrium, compounds will partition themselves between two immiscible solvents. Immiscible means the two solvents are not soluble in one another, for example oil and water. When comparing barbiturates, the more lipophilic barbiturates have a higher percentage absorbed through the intestinal wall compared to the more hydrophilic barbiturates.

4.) (3 points) Provide an explanation as to why the more lipophilic barbiturates are better absorbed into the cell membrane.

While it is very important for many drugs to be able to dissolve into cell membranes, the ability of drugs to travel through the body by the bloodstream is equally important. Because of this, it has been written that “[D]rugs must exhibit a balance between hydrophilicity and lipophilicity.”

5.) (3 points) Why would a drug that is too lipophilic have trouble travelling in the bloodstream? 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; in other words, they undergo reactions which convert them into new compounds. For some drugs, this converts them to active metabolites; however, in the case of barbiturates, they
are converted to inactive metabolites. Not all of the barbiturate is converted in the liver, so some barbiturate is able to enter the bloodstream.

6. (3 points) How would the amount of pentobarbital administered orally compare with the amount that was administered intravenously, which enters the bloodstream without passing through the liver first and being metabolized, 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 (metabolite A).

7. (2 points) What was the functional group that was altered in pentobarbital to make metabolite A?

8. (2 points) What functional group was added to pentobarbital to make metabolite A?

9. (3 points) Does this change make the compound more lipophilic or hydrophilic? Explain your answer.

10. (2 points) What is this general type of reaction called?

11. (3 points) Propose a valid balanced chemical equation for the enzymatic conversion of pentobarbital to metabolite A. Your balanced chemical equation must show molecular formulas for all reactants and products involved in the reaction. For the organic molecules, remember the molecular formulas are written as $C_nH_{n+m}N_1O_{n+m}$. Think about what atoms are different between pentobarbital and metabolite A. All reasonable proposals will be accepted for full credit (consult your organic chapters for ideas). For full credit, you must justify your proposal.

The inactive metabolite can be cleared by the renal system, which eliminates waste as part of the aqueous solution known as urine. But not all of the barbiturates are metabolized on the first pass through the liver. Those that are un-metabolized 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.
Since the book does not talk about the blood-brain barrier, here is a short bit of background on it. The blood-brain barrier describes how blood is kept totally apart from brain cells by the endothelial cells that line the capillaries within the brain. The endothelial cells are packed especially close together so that nothing can flow around the outside of the endothelial cells into the brain without passing through the endothelial cells. This means that everything that enters the brain must physically pass through the endothelial cells that make up the blood-brain barrier. The blood-brain barrier plays an important role in keeping the brain healthy and safe. Because of the lipophilic nature of the blood-brain barrier, only small lipophilic compounds pass through the blood-brain barrier easily.

12.) (3 points) Why does the change in structure between pentobarbital and metabolite A make metabolite A inactive by affecting its ability to cross the blood-brain barrier?
13.) (2 points) Why does this change make metabolite A better for renal clearance?
14.) (2 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:
