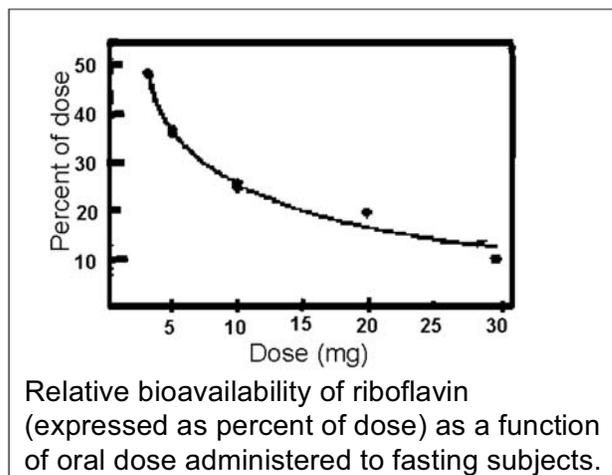## 20.201 Problem Set for Fundamentals
9 Oct 2013

Please prepare your answers in electronic format and submit the answers ˙VYZcfY or on October 11. While this is not a graded problem set, you will get crYX]hZcf˙ completing the problem set and submitting it. An answer key will be posted on OWˉcVYf 12, so no credit will be given for late submissions!

(1) In increase in which of the following parameters will result in faster passive diffusion of a drug? Why or why not?

~ surface area of the absorption site – Yes: the rate of diffusion depends directly on the surface area across which diffusion occurs

~ membrane thickness – No: the rate of diffusion is inversely proportional to the "depth" of the medium through which the molecule diffuses (the membrane here)

~ partition coefficient of the drug between lipid and water – Yes: a larger partition coefficient means that the drug is more lipid soluble, which, to a point, will increase the date of diffusion across a lipid membrane.

~ gradient between drug concentrations on both sides of the membrane – Yes: the rate of diffusion is directly proportion to the size of the drug gradient

~ ATP-concentration in the membrane – No: ATP has nothing to do with diffusion

(2) As shown in the figure shown on the right, riboflavin (vitamin B_2) absorption is dose-dependent. Which of the following absorption mechanisms could be responsible for the absorption from the intestines? Why?

~ Active transport – Yes: the curve indicates that a saturable process is occurring; any protein-mediated process will show this behavior

~ Facilitated transport – Yes, for the reason noted above

~ Passive diffusion – No: the extent of drug uptake from the gut should be independent of dose if passive diffusion is involved.

Relative bioavailability of riboflavin (expressed as percent of dose) as a function of oral dose administered to fasting subjects.

(3) Which of the following drug formulations would lead to absorption of the drug into the general (systemic) circulation, thus bypassing the portal circulation? How?

~ peptide nasal spray – Assuming that the possibly charged and hydrophilic (but nonetheless highly polar) peptide can cross the membranes of the epithelial lining of the nasal cavity, then a nasally administered peptide would enter the general circulation. Blood flow from the lungs enters the venous return to the heart for distribution to the rest of the body.

~ nitroglycerin transdermal system – Yes, transdermally administered drug would enter the venous return from the skin, which enters the general venous blood flow to the heart.

~ intramuscular injection of penicillin G – Yes, injection into well vascularized muscle

tissue leads to venous uptake and entry into the general venous return to the heart.

  ~ injection into the cephalic vein of the forearm – Yes, an intravenous injection in the forearm bypasses the portal circulation

  ~ antipyretic suppository – Yes, venous blood flow from the rectum leads to the general circulation and not the portal circulation.

(4) Explain why these statements are true or false

  ~ drugs that are very lipophilic tend to distribute well into body tissues. True – lipophilic drugs will enter cells and tissues by passive diffusion and will distribute into lipid membranes and adipocytes.

  ~ drugs that are predominantly ionized at physiologic pH do not readily distribute into tissues when compared to drugs that are primarily unionized. (Assuming tight membrane junctions) Generally true, unless there is a specific drug transport protein for the charged form. Uncharged molecules move more readily across lipid membranes than charged forms.

  ~ drugs are generally less well distributed to highly perfused tissues. False – high rates of blood flow means a larger exposure of the cells in a tissue to the drug, which increases the rate of diffusion (maintains the gradient) or maintains a high local concentration for transport proteins.

  ~ the volume of distribution depends only on the degree of tissue binding. False – Vd depends on the ability of a drug to leave the circulation (protein binding, for example) and to cross cell membranes (diffusion or transport protein), in addition to binding to lipids or proteins in tissues.

(5) The volume of distribution in a 70 kg man is observed to be 10 liters. Indicate which one (or more) of the following statements is (are) consistent with the observation when you consider that albumin has a volume of distribution of about 7 liters.

  ~ highly bound to plasma proteins – Very consistent: albumin is the major plasma protein!

  ~ does not pass any membranes – Not necessarily true if there is a high level of plasma protein binding

  ~ not bound to plasma proteins – This is inconsistent with the observations

  ~ high first-pass metabolism in the liver – A high rate of metabolism in the liver would not necessarily lead to a larger V_d if plasma protein binding is high.

(6) Select the correct answer(s). Due to the nature of biological membranes, drugs with the following properties are more likely to diffuse cross most membrane barriers:

  ~ ionized and lipophilic – This is an oxymoron.

  ~ ionized and hydrophilic – Highly unlikely to diffuse across a lipid membrane without a transport protein

  ~ non-ionized and lipophilic – This is the state most likely to move by diffusion

  ~ non-ionized and hydrophilic – Less likely to move by diffusion, but it is possible

(7) The larger the volume of distribution:

  ~ the more sequestration may have occurred – True: binding in a tissue (e.g., adipose) could lead to a large V_d

 ~ the larger the plasma albumin binding – The two are not correlated. High or low plasma

~ the higher the plasma clearance – True: the rate of removal of the drug from the blood will be higher if the drug has a large Vd, since, by definition, the drug is leaving the blood to move into tissues.

~ more drug is outside of the plasma – True: I hope that this is obvious!

(8) The molecule shown below is acetylsalicylic acid (a.k.a., aspirin).

   a)   Please <u>derive</u> the Henderson-Hasselbalch equation using the following acid dissociation equilibrium:
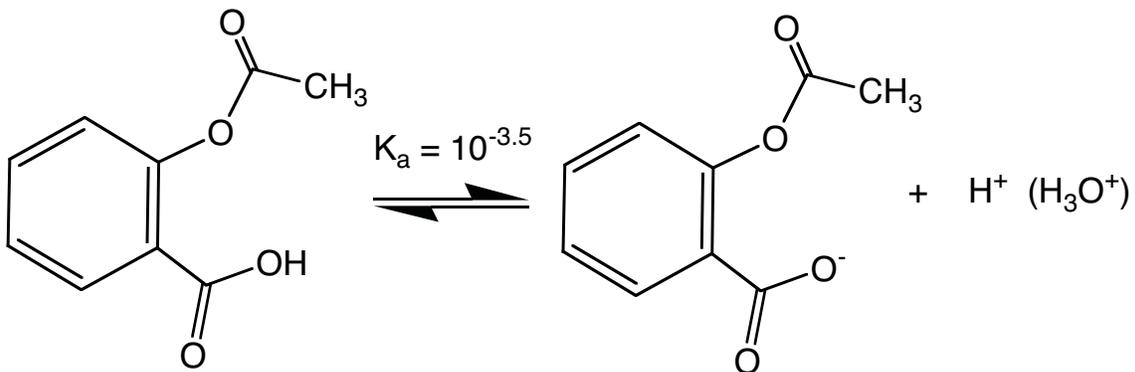
$$K_a = \frac{[ASA^-] \bullet [H^+]}{[ASA-H]} \quad (1)$$

$Remember: \quad pK_a = -\log(K_a), pH = -\log(H^+)$

Take –log both sides of equation 1:

$$-\log(K_a) = -\log\left[\frac{[ASA^-]}{[ASA-H]}\right] - \log[H^+]$$

Rearrange:

$$pK_a = -\log\left[\frac{[ASA^-]}{[ASA-H]}\right] + pH$$

$$pH = pK_a + \log\left[\frac{[ASA^-]}{[ASA-H]}\right]$$

   b)   Calculate the ratio of charged (base) to uncharged (acid) forms of aspirin at pH 2 and pH 7.

$$2 = 3.5 + \log\left[\frac{[\text{ASA}^-]}{[\text{ASA} - \text{H}]}\right] \textbf{ and } \left[\frac{[\text{ASA}^-]}{[\text{ASA} - \text{H}]}\right] = 0.031$$

$$7 = 3.5 + \log\left[\frac{[\text{ASA}^-]}{[\text{ASA} - \text{H}]}\right] \text{ and } \left[\frac{[\text{ASA}^-]}{[\text{ASA} - \text{H}]}\right] = 3162$$

    c)   Where in the body would you expect to find significant diffusion of aspirin into cells if you assume that the charged form does not diffuse across cell membranes?

Stomach: pH <<7 (near 1-2) so that uncharged form predominates and diffusive absorption occurs to a significant extent. Possibly also to a limited extent in the slightly acidic bladder.

(9)   Answer questions a, b and c for nicotine.

    a)   Please <u>derive</u> the Henderson-Hasselbalch equation using the following acid association equilibrium:

$$K_a = \frac{[\text{N}] \bullet [\text{H}^+]}{[\text{NH}^+]}$$

Nicotine

$pK_a \sim 8$

H^+

Uncharged, base form

Charged, acid form
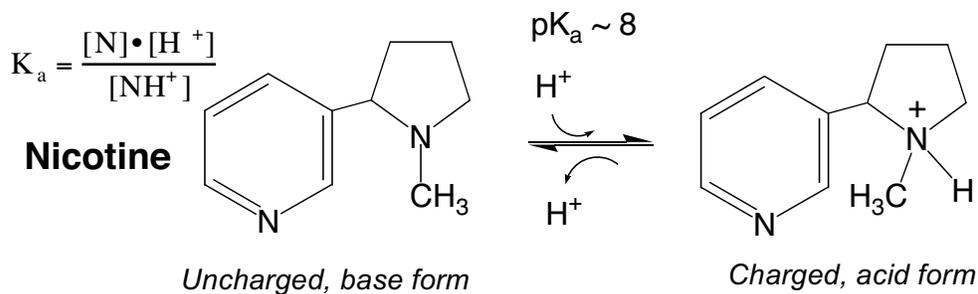
Watch out! The above equation is an acid association not dissociation. Rewrite the equation as a dissociation (reverse the equation) and proceed to derive the adjacent equilibrium expression (K_a is the acid dissociation constant)

$$\text{Re member}: \quad pK_a = -\log(K_a), pH = -\log(\text{H}^+)$$

Take –log both sides of equation 1:

$$-\log(K_a) = -\log\left[\frac{[\text{N}]}{[\text{NH}^+]}\right] - \log[\text{H}^+]$$

Rearrange:

$$pK_a = -\log\left[\frac{[\text{N}]}{[\text{NH}^+]}\right] + pH$$

$$pH = pK_a + \log\left[\frac{[\text{N}]}{[\text{NH}^+]}\right]$$

b)   Calculate the ratio of charged (base) to uncharged (acid) forms of nicotine at pH 2 and pH 7.

$$2 = 8 + \log\left[\frac{[N]}{[NH^+]}\right] \textbf{ and } \left[\frac{[N]}{[NH^+]}\right] = 1x10^{-6}$$

$$7 = 8 + \log\left[\frac{[N]}{[NH^+]}\right] \text{ and } \left[\frac{[N]}{[NH^+]}\right] = 0.1$$

c)   Where in the body would you expect to find significant diffusion of nicotine into cells if you assume that the charged form does not diffuse across cell membranes?

Since 10% of nicotine is uncharged at pH 7, diffusion should occur readily across membranes. So everywhere except stomach!

20.201 Mechanisms of Drug Actions
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