Name KEY

MEDCHEM 562

First Midterm

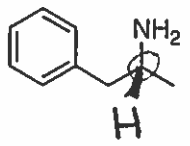
October 24, 2016

Instructions:

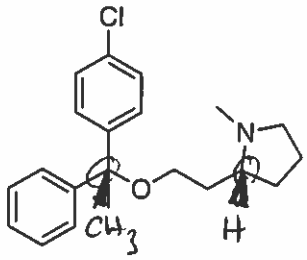
- Exam packet totals 8 pages. Kunze pp 2-4: Xu pp 5-8
- If you need additional space go to the back of that page and tell us you did so.
- Write legibly and in complete sentences when indicated.
- Read the questions carefully and answer the questions you know first.

1. (10 points) Sterochemistry Circle the chiral center(s) in each compound below and indicate the stereochemistry of the R (or all R) isomer.

Amphetamine



Clemastine



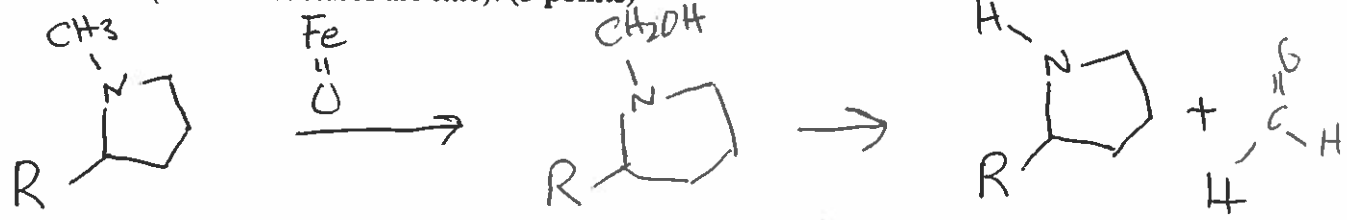
2. (20 points) The single stereoisomer of Clemastine (above right) that you have drawn is a sedating antihistamine and anticholinergic given orally at doses of 1-2 mg/day (OTC). Peak plasma levels occur rather late (3-5 hours). GI absorption is 100% and bioavailability is 30%. Log P is 6. Very little drug is excreted unchanged in urine or feces.

a. Using this information and the physicochemical properties of the drug explain why the absorption of Clemastine is delayed and 100%. **(Sentences: 5 points)**

Clemastine is an aliphatic amine with a pKa of 9-10. The percent non-ionized drug will be highest in the lower upper intestine where the pH is the highest. Thus absorption will be delayed until drug reaches this region The free base of clemastine is very lipophilic (high log P) so one would expect a high absorption (unless efflux transporters were in play). Note but not asked for: Thus it has high absorption (no drug in the feces) and would be expected to be highly reabsorbed in the kidney and thence highly metabolized).

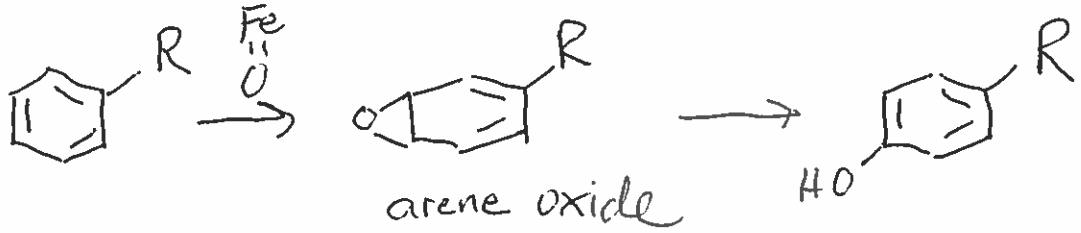
b. Define bioavailability and provide a likely reason why it is so low in this case given the above information. **(Sentences: 5 points)**
Bioavailability is the percent of an oral dose of parent drug the reaches the systemic circulation. The most likely reason it is low (30%) is high first pass metabolism in the liver.

c. One metabolite of Clemastine is made by P450 catalyzed N-dealkylation to form the metabolite and formaldehyde. Show and name the transient intermediate and final product of this reaction (Partial structures are fine). **(5 points)**



carbinolamine
Chemiaminal

d. Another circulating P450 metabolite of Clemastine is the *para* phenol. Show and name the relevant intermediate and product of this reaction. (Partial structures are fine) **(5 points)**



3. **(20 points)** Adderall is used to treat attention deficit hyperactivity disorder (ADHD) and narcolepsy (a sleep disorder). Interestingly Adderall is a combination drug containing a mixture of 3 different kinds of salts of unequal amounts of the two enantiomers of amphetamine (total is 70% S (dextroamphetamine base). The structure of amphetamine is shown in Question 1). This mixture of salts and isomers is superior for the above indications relative to the individual isomers or the racemic mixture. Actual composition [dextroamphetamine sulfate (25%); racemic amphetamine sulfate (25%); dextroamphetamine saccharate (25%); racemic amphetamine aspartate monohydrate] (25%) if interested.

a. There were some major issues with the pharmacological effect profiles of the different generic Adderall products including withdrawals and shortages when they first came on the market in the late 2000's. Based on our discussions of ADME, the typical pharmacologic profiles of neuroactive amine drug isomers, and your knowledge of formulation provide two likely causes of these differences among the products. **(Sentences: 8 points)**

Note that the generic and the brand name drug are supposed to be identical and "bioequivalent". You should know this, I checked. There is some wiggle room on bioequivalent.

The most reasonable explanation starts with the fact that the two isomers of amphetamine will have different pharmacological effects. Thus the desired effect and the side effect profiles will be different for the two enantiomers. The most likely explanation for a difference is that the blood pharmacokinetics (peak levels, AUC etc) of one or both of the isomers are different for the brand name and generic, at least for this patient. Two likely causes are differences in formulation (excipients, tableting) and/or salt composition that leads to reduced or increased dissolution of the salts in the GI and differences in absorption. Another likely explanation is that the isomer content was not correct. **There are other possibilities however many of you seem to think that the salt forms of the drugs (ie sulphate salt) present in the GI are absorbed as the intact salt and circulate as the salt in the blood. THIS IS WRONG. Salts are ions and only non-ionized compounds cross membranes. Thus formulation only affects dissolution and absorption...not distribution metabolism, excretion.**

b. Pretend that you were a pharmacist when this problem arose. A patient asked you the following questions. "Why do I feel so different when I take this new generic form? After all isn't Adderall just amphetamine?" What would you tell the patient? What action would you take? **(Sentences: 5 points)**

I would explain to the patient that there can be subtle differences between the different generics and the named drug that occasionally can cause differences in perceived effects. I would proceed to ask the patient about the changes noted and make a decision about how to proceed based on my clinical judgement.

Actions I would take include:
1. Verify that the correct drug had been dispensed in the first place. Ask the patient to bring in the bottle. THIS IS YOUR FIRST PRIORITY.
2. Contact the physician if the problem is severe in your judgement....otherwise monitor the patient.
3. Determine whether this problem has been reported using the data bases available to you.

c. The plasma half-lives of the amphetamine isomers are extended as much as two fold when the urinary pH is maintained at 7.5 by diet (5.5 is average). Referring to the physiology of the kidney and the physicochemical properties of amphetamine, explain why this urinary pH effect on amphetamine half-life makes sense. **(Sentences: 7 points)**

Amphetamine is a strong base with a pKa of 9-10. The higher the pH of the urine the greater the percent of drug present as the un-ionized free base. Thus reabsorption of amphetamine filtered by the kidney glomulerus will be increased by the 100 fold increase in un-ionized drug concentration at pH 7.5 vs 5.5. Renal clearance of parent drug will fall and the half-life will increase.

Water-soluble vitamins (Xu). 2 pts each for multiple choices. Please circle the correct answer.

1. The Recommended Dietary Allowance (RDA) is the:
+2 (a.) dose of a vitamin that yields no toxicity or insufficiency in 97-98% of the population.
   b. dose of a vitamin at which 50% of the population shows no symptoms of insufficiency.
   c. the highest dose of a vitamin below which no symptoms of insufficiency are observed.
   d. none of the above.

2. The tolerable Upper Limit dose is the:
   a. the lowest does of a vitamin at which benefits are observed with supplementation.
+2 (b.) highest dose of a vitamin at which no toxicity or insufficiency is observed.
   c. 1.2 times the RDA.
   d. none of the above.

3. If the EAR for a vitamin is 1.0 mg/day then the RDA is:
   a. 0.6 mg/day
   b. 1.5 mg/day
+2 (c.) 1.2 mg/day
   d. 1.0 mg/day
   e. none of the above

4. If the RDA for a vitamin is 0.8 mg/day, then the Daily Value (DV) is:
   a. 0.96 mg/day
+2 (b.) the DV can not be determined from the RDA.
   c. 0.8 mg/day
   d. none of the above.

5 – 8. Match each vitamin with the appropriate disease or condition associated with its deficiency

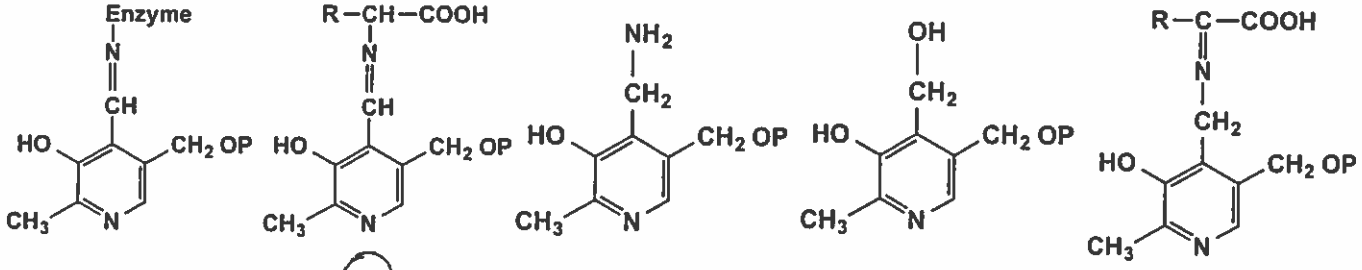
+2	5. C Pernicious anemia	A. Thiamine
+2	6. D Pellagra	B. Folic acid
+2	7. B Neural tube defects in embryos	C. B_{12}
+2	8. A Wernicke-Korsakoff syndrome	D. Niacin

9-11. Match the test for deficiency of a vitamin, with the vitamin:

+2 (9) B Vitamin B_1
+2 (10) C Vitamin B_2
+2 (11) A Vitamin B_{12}

A. urine methylmalonic acid level
B. transketolase assay in red blood cells
C. erythrocyte glutathione reductase activity
D. erythrocyte transaminase activity

12. Which imine form of pyridoxal below yields an amino acid upon hydrolysis [P= HPO_3^-]:



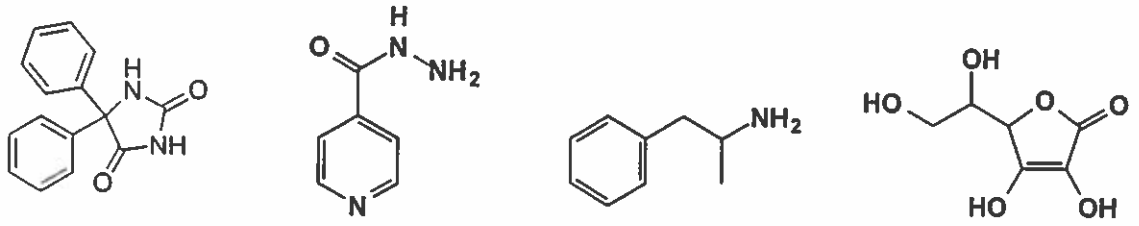
a. +2 (b.) c. d. e.

★13. In principle, which drugs or vitamins below could possibly result in iatragenic Vitamin B_6 deficiency if used chronically, based on the structures shown:

(+1) b. only isoniazid

+2 (d.) isoniazid and amphetamine

a. Phenytoin
c. ascorbic acid
e. none of the above

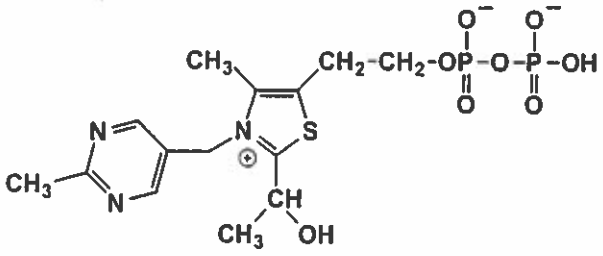


Phenytoin isoniazid amphetamine ascorbic acid

14. Which of the following are possible fates for the hydroxyethyl TPP form of thiamine:

+2 (b.) deprotonation to a carbanion followed by attack at an aldehydic carbon to transfer two carbons to a sugar

a. decarboxylation to yield CO_2 and pyruvate
c. attack by ethanol to reduce systemic ethanol levels and benefit alcoholics
d. reduce dehydroascorbate back to vitamin C



HETPP

6

15. Preparations containing > 0.8 mg of folic acid require Rx because high dose of folate supplements have what risk?
    a. could lead to less resistance to bacteria because bacteria needs THFA
    b. could inhibit DNA methylation and lead to megaloblastic anemia
+2 (c) could mask the magloblastic anemia symptoms of B_{12} deficiency and leave the neurological damages unchecked
    d. could lead to high level of homocysteine

16. Biotin
    a. provides no clear benefit for strengthening brittle nails, based on available evidence
+2 (b) is useful in biotechnology and chemistry because it has an extremely high affinity for the protein avidin (or streptavidin)
    c. is highly abundant in egg whites
    d. all of the above

17. An elderly patient with pernicious anemia and low gastric HCl would most likely benefit from:
    a. oral supplements containing vitamin B_{12}.
    b. oral supplements containing vitamin B_9.
+2 (c) IM injections of vitamin B_{12}.
    d. transdermal patches of containing vitamin B_6.

18. Choose the correct description about Leucovorin:
    a. is contraindicated in levo-DOPA therapy
    b. can cause vitamin B_6 deficiency
+2 (c.) can allow ordinarily lethal dose of methotrexate to be used against tumor
    d. act as an antibiotic by inhibiting bacterial DHFA reductase

19. To lower the plasma level of homocysteine, the best way is to supplement with:
    a. thiamine
    b. thiamine, riboflavin and B_6
+2 (c.) vitamin B_6, folic acid and cobalamin
    d. thiamine, riboflavin and niacin

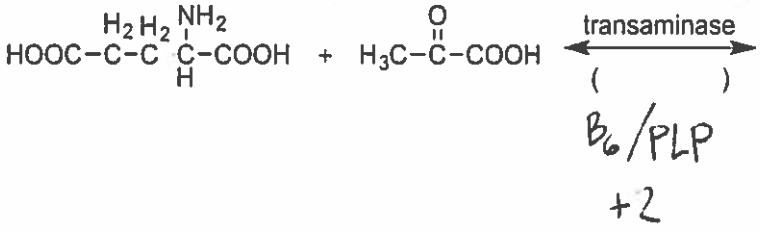
20. In levo-DOPA therapy against Parkinson's disease, carbidopa is commonly used with levo-DOPA in the drug Sinemet®. The reason for this combination is:
    a. vitamin B_6 enhances decarboxylation of levo-DOPA, which prevents it from entering brain. Carbidopa is used because it does not contain vitamin B6.
+2 (b) vitamin B_6 enhances decarboxylation of levo-DOPA, which prevents it from entering brain. Carbidopa is used because it inhibits DOPA decarboxylase.
    c. vitamin B_1 enhances decarboxylation of levo-DOPA, which prevents it from entering brain. Carbidopa suppress the level of vitamin B_1.
    d. Biotin enhances carboxylation of levo-DOPA and carbidopa is a cofactor for this reaction.

12

21. What is the main reason that over-consumption of alcohol can lead to folate deficiency?

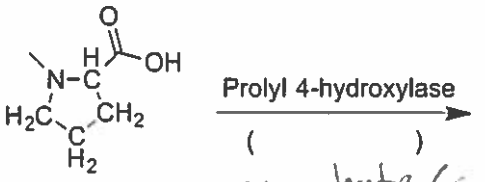
a. Block conversion of folate to its active form THFA
b. Large amount of folates are needed to metabolize alcohol
+2 (c) Alcohol decreases enteroheptatic circulation of folates
d. Increased fluid intake and uring flow causes washout of folate

22. Please write the products for the following transformations and specify which vitamins participated as a cofactor. (4 pts each; 8 pts total)



(α-ketoglutarate) +1

(alanine) +1



+2

(4-hydroxy proline)

10