

20.201 Take-Home Exam

Distributed: October 19, 2012, at 2:30 p.m.

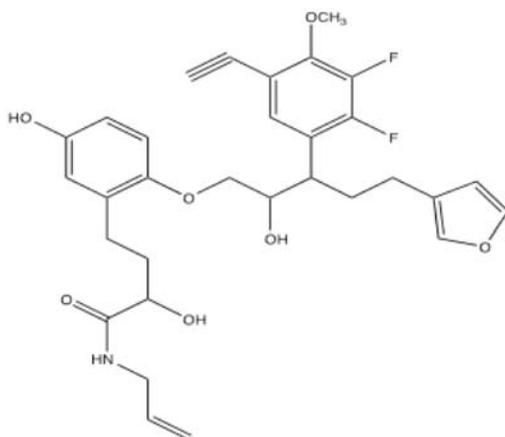
Due: October 24, 2012, at 1:30 p.m.

Directions: This take-home exam is to be completed without help from any other individual except Drs. Dedon, Tannenbaum, Hoffmaster or Lim. This includes help from other students (whether or not they are taking 20.201), faculty, people via the Internet, and so on. You are permitted to use your books, class notes, library resources, internet information resources, and other inanimate materials.

Please prepare your answers to all questions as a single PDF document - labeled with your name. Please prepare your answers using word processing software and insert either digitized hand-drawn graphics or computer-generated graphics. The answers should not exceed the stipulated length per question. Please submit your answers by email to all of the following email addresses before class starts at 1:30p on November 7. Late exams, without prior approval, will not be accepted.

Question 1 - 45 points total

- A. Hypoamericillin 2 has just been developed (structure below). It is more potent than Hypoamericillin (structure in your lecture notes) in terms of the concentration in vitro that gives



a 50% inhibition of its target, but you have been given the job of predicting solely on the basis of its structure whether it would be a safer drug. Since the original Hypoamericillin was isolated from soil in the Brazilian rain forest, you are not certain of its pharmacophore, but both molecules have obvious toxicophores. Speculate on what you think is the pharmacophore and the toxicophores in this potential drug and back up your analysis with specific ideas.

- B. For the drug you have been assigned you have already been asked to work out the metabolic pathways. Now you are to describe the following:

1. What are the safety considerations for your drug?
2. Examine the metabolic pathways to determine whether there are one or more reactive intermediates that could lead to toxicity. Are there other potential mechanisms for consideration of safety?

Question 2 – 35 points total

A. You have been hired as the Chief of ADME at ACME Pharmaceuticals. Your predecessor characterized the pharmacokinetics of a new antibiotic, Hypoamericillin (Ha), in mice and rats and obtained a plasma elimination half-life of 14 hr and a volume of distribution (V_d) of 0.08 L/kg with a dose of 0.1 mg/kg in both rodent models. Your job is to define the pharmacokinetics in humans in the first phase I clinical trial for this drug candidate. In your first human studies, you administered 25 mg doses and obtained a V_d of 0.08 L/kg, which is similar to the rat and mouse studies. In addition, you performed comparative bioavailability studies with Ha alone and in combination with ibuprofen (Ib; Ha causes headaches in 90% of patients) and another experimental compound (X) that was designed to prevent Ha metabolism (Table shown above). Use these data to answer the following questions. **1.5 PAGE MAX FOR ALL ANSWERS.**

Ha Dose, mg	Plasma elimination $t_{1/2}$, hr	Route	AUC, $\mu\text{g/l}\cdot\text{h}$
25	10	IV	750
	10.2	Oral	700
	9.9	IM	100
25 + 250 mg Ibuprofen	14.2	IV	1070
	14.5	Oral	1000
25 + 250 mg Compound X	10	IV	740
	10	Oral	220

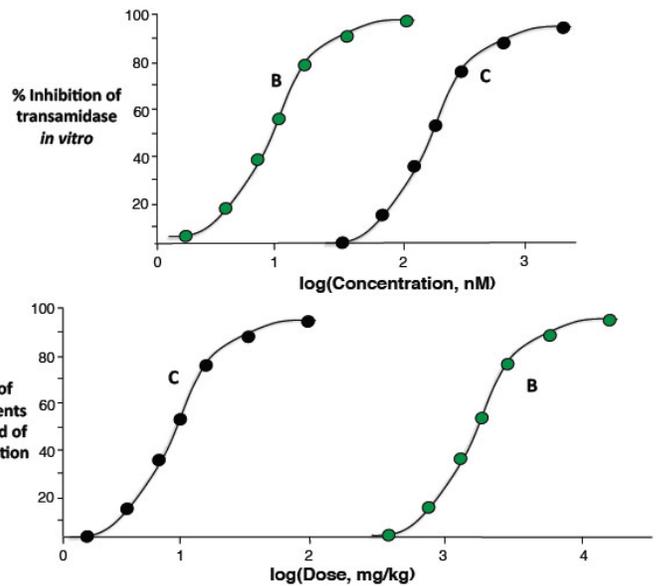
- A.1)** Calculate the bioavailability of Ha for the Oral and IM routes of administration. Describe possible mechanisms that could explain the different AUC values for Ha administered alone. What additional information would you need to establish the mechanisms?
- A.2)** Calculate the plasma elimination rate constants for the IV and Oral routes in the presence of ibuprofen. Describe possible mechanisms that would account for the changes in both plasma elimination rates and the AUC values caused by co-administration of ibuprofen. What additional information would you need to establish the mechanisms?

A.3) Describe possible mechanisms that would account for the changes in the AUC values caused by co-administration of compound X in light of the lack of change in the plasma elimination kinetics. What additional information would you need to establish the mechanisms?

B. You compared dose-response behavior for Ha analogs B and C, as shown in the figure below. The upper panel shows the concentration-dependence of inhibition of the activity of the drug target: a transamidase responsible for cell wall cross-linking in the bacteria. The lower panel shows the in vivo dose-response behavior for oral administration of the drug, with complete cure of the infection as the response end-point.

B.1) What class(es) of antibiotics has the same mechanism of action as Ha and its analogs B and C?

B.2) Explain the basis for the observed differences between the enzyme inhibition dose-response curve and the patient cure rate dose-response curve.

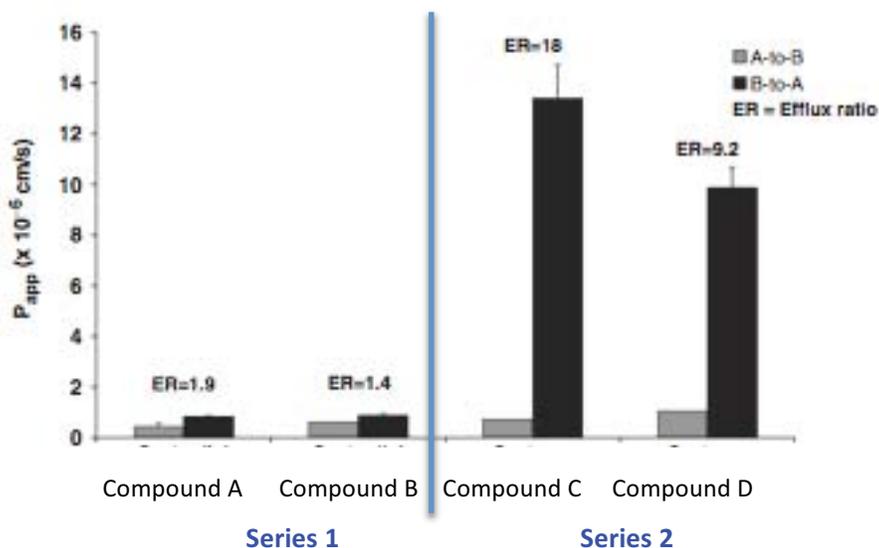


B.3) Which drug is more potent in terms of curing patients of infection? Which drug is more efficacious? Why?

Question 3 - 20 points total

A recent startup, MIT pharmaceuticals, is developing therapies to treat renal dysfunction and renal failure in patients with diabetes. The mechanism of action involves a protein target selectively localized to the kidney tissue (e.g., not expressed elsewhere in the body), although two other closely related protein homologs are expressed in the liver and the brain. They have just hired you as the head of the ADME laboratory and are looking to your expertise to help them address several concerns around drug transporters. Several lead compounds are in early development and two candidates have been into Phase I clinical trials in healthy volunteers.

- A.** Data from the current lead molecule suggests that renal clearance is 0.9 L/min in early clinical trials. Do you suspect active transport to be involved in the clearance? Why or why not?
- B.** The lead clinician on the team is proposing to go into phase II trials with patients that will take metformin concomitantly throughout the trial. An alternate clinical design would be to select a patient population that would be on rosuvastatin (Crestor), injectable insulin, and sitagliptin (Januvia). Which patient population would you recommend the team pursue and why?
- C.** One patient from the phase I trial had clinical signs of acute renal toxicity. Further investigation of this patient's medical history showed that the patient should have been excluded from the trial since they were also taking cimetidine. Provide a hypothesis as to what may have contributed to this patient's nephrotoxicity – be specific and support with 1-2 relevant publications (citations only please).
- D.** The lead chemist on the discovery team is worried that the two lead backup series of compounds are very potent against one of the closely related targets (expressed in the brain). She favors Series 1 because these compounds are 10x more potent against the desired target. Below are representative data from two compounds in each series in Caco-2 cells. Interpret these data and provide guidance to the chemist.



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20.201 Mechanisms of Drug Actions
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