Class mean(S.D.) = 95(14.4)

Answer Key

HST - 151

Principles of Pharmacology
Mid-Term Exam
February 24, 2005

This is a closed book exam. All questions are multiple choice or short answer. Numerical computations should not require a calculator (although you may use one). Please keep your answers brief and legible! Write your name on all pages.

Good Luck!
1. The following graph shows the effect of Drugs A and B on contraction of vascular smooth muscle in a tissue bath.

What is the relative potency of the two drugs? [3]

\[
\text{Potency} = \frac{EC_{50} B}{EC_{50} A} = \frac{10^{-7}}{10^{-9}} = 100
\]

Which is more efficacious? [3]

A (full agonist). B is a partial agonist with 33.3% efficacy.

Redraw the curve for B in the presence of \(10^{-6}\) M drug A (can be approximate). [3]

See graph

2. Why does the antidysrhythmic effect of lidocaine occur at so much lower concentrations than the local anesthetic effect? (Give 2 reasons). [6]

Na channels in a cardiac arrhythmic focus are largely open or inactivated because the tissue is being depolarized. Channels in unstimulated nerve are largely resting. Lidocaine has much higher affinity for open or inactivated channels. Block of peripheral nerve requires diffusion through epineurium and perineurium. Intravenous lidocaine bathes myocardial cells directly.
3. The graph below shows the decline in plasma concentrations following a 50 mg bolus dose of an anticonvulsant medication. The therapeutic window is 100-800 ng/ml.

![Graph showing drug concentration over time]

What are the volume of distribution and clearance of the drug? [6]

From graph: \( C_0 = 200 \text{ ng/ml}, T_{1/2} = 5 \text{ hr} \)

\[
V_d = \frac{\text{Dose}}{C_0} = \frac{50 \text{ mg}}{200 \text{ ng/ml}} = 250L; \quad Cl = \frac{V_d \cdot \ln 2}{T_{1/2}} = \frac{250L \cdot 0.7}{5 \text{ hr}} = 35L/\text{hr} = 583\text{ml/min}
\]

What would be the maximum bolus dose that could be administered? [4]

\[
V_d \cdot C_{\text{Toxic}} = 250L \cdot 800 \text{ ng/ml} = 20 \text{ mg}
\]

How long would the effect of this bolus dose last? [4]

800 ng/ml drops to 100 ng/ml in 3 half-lives = 15 hr

What would be the minimum infusion rate that would still be effective? [4]

\[
Cl \cdot C_{\text{Minimum}} = 583.33 \text{ ml/min} \cdot 100 \text{ ng/ml} = 58.3 \text{ µg/min} = 3.5 \text{ mg/hr}
\]
4. Natives of the Amazon traditionally used curare-tipped darts to hunt animals for food. Why were they able to eat these animals without suffering ill effects from the drug? [5]

Curare (like all neuromuscular blockers) is a quaternary amine. A permanently charged, lipid insoluble molecule works well when injected, but is not absorbed from the GI tract.

5. Which of the following effects is/are expected from hexamethonium in a healthy subject? (Check all that apply) [5]

   a. Diarrhea
   b. Pupil Constriction
   c. Hypotension******
   d. Bradycardia
   e. Urinary retention******

6. You are asked to consult for a new start-up company that has developed a technology for the rapid bedside measurement of drugs and other small molecules in blood. What would you advise them about the following possible applications?

A propofol assay for managing anesthesia  [3]
Highly lipid soluble drug, so plasma and brain equilibrate rapidly. Assay would probably be useful in pseudo steady-state conditions like infusion. Less valuable after bolus because of rapid redistribution.

A warfarin assay for managing anticoagulation.  [3]
No! Anticoagulant effect depends upon concentrations of clotting factors, not drug. A functional assay like PT (INR) is required.

A catecholamine assay for diagnosing pheochromocytoma.  [3]
Bad idea because the increases in catecholamines are so brief you would probably miss the diagnosis. Better to look at cumulative output of urinary catechol metabolites.
7. Assuming that you do not have access to gene-chip technology, how can you determine that a patient has a polymorphism of CYP2D6? [5]

Give a probe drug like dextromethorphan that is metabolized by CYP2D6, and measure the metabolic ratio (concentration of parent drug in plasma / concentration of metabolite in urine).

8. Compared to non-selective NSAIDs, COX-2 inhibitors cause fewer undesirable effects on which of the following? (Check all that apply) [5]

   a. Platelets *******
   b. uterine tone
   c. GI mucosa *******
   d. renal blood flow
   e. bronchomotor tone

9. Which of the following drugs has been shown to decrease mortality in patients with congestive heart failure? (Check all that apply) [5]

   a. Milrinone
   b. Metoprolol *******
   c. Enalapril *******
   d. Spironolactone *******
   e. Digoxin

10. A new, sustained-release preparation of losartan is being tested. The oral bioavailability is 90%, but the new formulation doesn’t lower blood pressure. How can you explain this? [5]

    Releasing too slowly relative to clearance. 90% is absorbed, but the plasma concentration never gets above threshold.
11. After 3 years and $10 million, the FDA is finally letting you test your new intravenous sedative in man. Forty healthy volunteers are each given 5 mg, and sedation is monitored with psychometric scales. Some of the results are depicted in the graph below.

![Graph showing bimodal distribution](image)

What do these results suggest about the drug? Give two likely explanations for the findings. [4]

Bimodal distribution suggests two populations of “long” and “short” responders. This could be due to 1.) Pharmacokinetics (fast and slow metabolizers or 2.) Pharmacodynamics (high and low sensitivity).

Assuming you wish to make the best use of your limited venture capital, what would be the FIRST experiment you would design to investigate this? [4]

The FIRST thing to do is confirm the difference and figure out PK vs PD. Take subjects from long and short group and measure plasma concentrations after another test dose. Different Cmax or Cl implies a PK explanation. You certainly wouldn’t start by paying for genetic studies if you didn’t know that the difference was real, and you had no idea what the phenotypic target might be.

Is this drug a good bet for further development? Explain. [4]

No way –too variable! You would have to screen each patient for phenotype before using it.
12. Describe a way in which a patient’s ethnic background may influence the response to each of the following drugs.

Isoniazid [3]
Fast acetylators like Asians may get too little anti-TB effect

Lisinopril [3]
Hypertensive African Americans may not respond as well.

Nitrofurantoin [3]
Those of African and Mediterranean extraction may have glucose-6-phosphate dehydrogenase deficiency. This drug produces an oxidative load and may cause hemolysis.

13. What is the primary problem in cases of ethylene glycol (antifreeze) toxicity? How may the toxic effects be minimized? [5]

It gets metabolized by alcohol dehydrogenase to nasty metabolites like glycolic acid and oxalate. These can cause acidosis and renal failure. Toxic effects may be minimized by inhibiting alcohol dehydrogenase with a competitive substrate (ethanol) or a direct antagonist (fomepizole).

14. Which of the following has the greatest affinity for muscarinic cholinergic receptors? (Check one) [5]

a. Methacholine
b. Succinylcholine
c. Acetylcholine
d. Atropine ******* (the competitive antagonist)
e. Neostigmine

No, because reduction of plasma LDL with statins depends upon an intact feedback mechanism in the hepatocyte: Inhibition of cholesterol synthesis decreases intracellular cholesterol; this upregulates LDL-receptor synthesis, which takes up LDL from plasma and establishes a lower steady-state. This cannot happen in patients with no LDL receptors.

15. Pilocarpine and timolol are used for treatment of open-angle glaucoma. How do their effects on the eye differ? [5]

Pilocarpine – muscarinic agonist that causes pupil constriction, opens trabecular meshwork and increases aqueous humor drainage through the Canal of Schlemm
Timolol – β blocker that decreases production of aqueous humor

16. Which of the following is a pro-drug? (Check all that apply) [5]

a. Codeine (morphine)
b. Terfenadine (fexofenadine – Allegra)
c. Thiopental (pentobarbital)
d. Procainamide (N-acetylprocainamide)
e. Sulfasalazine (5-ASA)

17. Give an example of a drug that works by blocking the organic anion transporter in the renal tubule. How is this used therapeutically? [5]

Probenecid blocks the active secretion of acids like penicillin and the reabsorption of uric acid.
It has been used to prolong penicillin effects in treating gonorrhea and to increase uric acid excretion in gout.
***Random Factoid Section***

18. The graph below (NEJM 2/15/01) shows a therapeutic trial of botulinum toxin injected intradermally in the armpits of patients with excessive sweat production (I am not making this up).

What can you conclude from this graph? What is the mechanism? How do you suppose they got a grant to do this? [8]

1. There is a small placebo effect
2. Botox causes a profound decrease in sweat production that lasts for at least 6 months. Incidentally, these patients have pathologic hyperhidrosis, not just stinky armpits. Look at the volumes! (1 g sweat = 1 ml)
3. No dose response is evident. 100 units = 200 units
4. The mechanism is inhibition of a cholinergically mediated sympathetic effect. Botox cleaves SNARE proteins and prevents vesicles from docking and releasing Ach.
5. This is industry funded. No NIH money for a proprietary Botox preparation! Massively sweaty armpits constitute a small market (thankfully), but I'm sure this study was a good investment.