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Good Luck.
QUESTION 1 *(Required)*

Drug X is an antiarrhythmic drug (structure is shown). The drug is prescribed to a 75-year old 165 lb (75 kg) patient with a history of congestive heart failure and cardiac arrythmias. Use the following drug information to answer the questions below:

<table>
<thead>
<tr>
<th>Drug</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fractional Oral Bioavailability</td>
<td>0.50</td>
</tr>
<tr>
<td>Fractional urinary excretion (unchanged drug)</td>
<td>1</td>
</tr>
<tr>
<td>Clearance (mL/min/kg) (first order)</td>
<td>8.7</td>
</tr>
<tr>
<td>MTC (mg/L)</td>
<td>1</td>
</tr>
<tr>
<td>MEC (mg/L)</td>
<td>0.33</td>
</tr>
<tr>
<td>Volume of Distribution (L/kg)</td>
<td>30</td>
</tr>
<tr>
<td>pKa</td>
<td>5.5</td>
</tr>
</tbody>
</table>

1. Use the H-H equation to predict where the drug is absorbed: stomach (pH 2.5) or intestine (7.5). Would you be concerned that use of antacids (Pepto Bismol) would affect the absorption of the drug? Defend your position.

2. Calculate the half life of the drug.

3. Propose the space/location/body water compartment that the drug appears to distribute into in the body.

4. What is an appropriate steady state plasma drug concentration (Css) to target?

5. Based on your estimate of half life of the drug, would the administration of a loading dose be useful? Explain why or why not. Calculate the loading dose. Show your work.

6. What oral dose of Drug X given at 6 hr intervals would maintain the appropriate plasma drug Css?

7. If 500 mg of drug X is administered every 6 hrs, how long would it take to reach 94% of the Css?

8. What effect would you predict the following drugs/diseases would have on the pharmacokinetics of drug X. Briefly explain.

   a. cimetidine
   b. phenobarbital
   c. probenecid
   d. heart disease.
QUESTION 2. Choose between this question and QUESTION 3

There is currently great interest in the development of “targeted” antitumor drugs, which are directed at specific molecular perturbations in the tumor cell. While these approaches hold promise, traditional screening efforts are still likely to provide a source of new compounds for the treatment of malignant disease.

You have been hired by a large pharmaceutical company (at an obscene salary) to manage their antitumor drug development efforts (based, in large part, on the extraordinary education you received in the Department of Pharmacology and Toxicology at Virginia Commonwealth University relating to cancer chemotherapy).

Your first task is to develop guidelines for your staff that will determine whether any compounds developed by the chemistry section should eventually move into the clinic for testing in patients.

Outline the types of studies that would be critical for moving any potential drug forward based on basic principles of cancer chemotherapy and what you know about the limitations and problems of conventional antitumor drugs.

Note: Although the mechanism of drug action will ultimately be of importance, this question does NOT require an exploration of mechanism of drug action.

Hints:

1. You will need to consider what kinds of cell lines would be used for drug testing and provide a rationale for your choices.

2. The proposed guidelines would need to consider (but would not be limited to) cellular as well as animal studies.

3. You need to indicate the types of problems this drug would overcome or circumvent in order for it to be potentially useful in the clinic.
QUESTION 3

Some antimicrobial agents are toxic to the patient because of a lack of specificity; that is, the agent inhibits some microbial enzyme or process, but to some extent inhibits an analogous enzyme or process of human cells. For other agents, the mechanism of clinical toxicity is completely unrelated to the mechanism of antimicrobial action. Cite one antiviral agent and one antibacterial agent that fall into each of these categories (total of four drugs). For each of these drugs, describe the mechanism of antimicrobial action, including if possible the molecular target and mechanism of microbial resistance to the drug. For the antiviral agents, identify the type of virus against which it is effective. Likewise, describe the clinical toxicity of each drug, and its mechanism and molecular target, if known.
QUESTION 4 – (Choose between this question and QUESTION 5)

Intracellular free calcium concentration is widely appreciated to be an important signal in cells, and communicates signals from receptor occupation to a variety of cellular and molecular effectors.

Please discuss the key elements of intracellular Ca signaling in cells, including pathways leading to an increase in Ca, and mechanisms which have evolved to deal with terminating the Ca signal. In your answer, please speculate as to why intracellular free calcium concentration is an ideal second messenger in terms of cell signaling. You should feel free to include examples if this helps clarify your points.

QUESTION 5

Two of the major signaling pathways that regulate gene expression result from the activity of two effector systems: phospholipase Cβ (PLCβ) and adenylyl cyclase (AC). Please compare and contrast these pathways, noting characteristics that they have in common and those which differ, starting from upstream activation down to regulation of the transcription factor CREB.
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Good Luck.
QUESTION 6 - (Choose between this question and QUESTION 7)

Drugs that act on beta-adrenoceptors (agonists and antagonists) represent major tools in the arsenal of a physician available for the treatment of various medical disorders. List two drugs from each division (agonists and antagonists) and discuss the following points:

i) Two diseases/conditions appropriate for their use for both beta-agonists and antagonists

ii) Mechanism of action (if known)

iii) Possible side effects
QUESTION 7

Schematic representation of the cardiovascular effects (blood pressure, BP; total peripheral resistance, TPR; heart rate, HR) of intravenous infusions of norepinephrine (NE) and epinephrine (EPI) in a human are depicted below.

![Diagram showing BP, HR, and TPR responses to NE and EPI]

a. Describe the receptors and mechanisms involved (direct & indirect) in these responses.

b. Describe the cardiovascular changes (BP, HR, TPR) that would result from an intravenous infusion of the β-adrenoceptor antagonist, propranolol alone.

Discuss how the responses to norepinephrine and epinephrine would be modified by the presence of the propranolol.
QUESTION 8 - (Choose between this question and QUESTION 9)

Methamphetamine ("ice") has been available since the 1960's, however, it's abuse grew considerably in the 1990's. While levels of use have fallen slightly since then, synthesis and abuse of this psychostimulant remains a significant problem in this country.

A) What is the mechanism of action of methamphetamine? (20 points)

B) What are the acute behavioral and physiological effects of methamphetamine administration? (20 points)

C) What are the results of chronic administration? How do they differ from chronic heroin administration? (30 points)

D) Describe 2 pharmacological approaches which could be used to treat a methamphetamine addiction. (30 points)

Hint: There currently is no accepted treatment for meth addiction. I want you to speculate, consider the goal of addiction treatment (maintaining abstinence), think about other abused substances which have treatments available, think about your answer to question C

QUESTION 9

There are 25 million of tobacco consumers in the US. Estimated annual tobacco-related mortalities are 350,000 in the US. An average cigarette contains more than 2,000 substances. Nicotine is the main psychoactive substance in cigarettes.

A. Is smoking an addictive behavior or simply a habit? What is the role of environmental cues in smoking behavior? Provide evidence for your answer from animal and human studies.

B. Discuss the impact of pharmacokinetic factors on the pharmacotherapy of smoking cessation.

C. Describe the different approaches that you can use to discover and characterize neuronal nicotinic receptors.
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Good Luck.
QUESTION 10 - (Choose between this question and QUESTION 11)

Discuss the roles of and sites of action of PTH and calcitonin in the maintenance of serum calcium homeostasis. Discuss two disease states for which calcitonin and/or PTH or their stable analogs are used and the therapeutic mechanism of action of each drug.

QUESTION 11

Diabetes mellitus is diagnosed as fasting plasma hyperglycemia, and this disorder is reaching epidemic proportions in the United States currently. It is known that diabetes results from problems with insulin, the anabolic hormone produced by the pancreas.

Please contrast type 1 and type 2 diabetes, and then discuss the key pharmacologic approaches for treating type 1 vs. type 2, and why they are effective given the likely causes of these two types of diabetes.
QUESTION 12 - (Choose between this question and QUESTIONS 13 and 14)

The media have increasingly become a mediator of knowledge about pharmacology and drug action for the general public (e.g., advertisements for specific brand-name drugs; articles on problems with currently available drugs such as Vioxx; medicinal marijuana; increase in suicidality in adolescents taking SSRIs). As a pharmacologist, you will be (or have been) approached by friends or family for your opinion about drug issues raised by the popular press. Recently, anti-inflammatory drugs such as Vioxx (rofecoxib) and Celebrex (celecoxib) have come under media (and FDA) scrutiny due to observation of an increased risk for heart attack in some patients. As with many anti-inflammatories, these drugs act by disrupting metabolism of arachidonic acid. Based upon your knowledge of inflammation and the actions of anti-inflammatory drugs, answer each of the following questions.

a. Draw a diagram of the arachidonic acid (AA) cascade. Include the names of the three major enzymes that degrade arachidonic acid as well as the end products of each metabolic step.

b. List and describe the mechanism of action for drugs that act at three different “locations” in the pathway. Do NOT include mechanism of action for Vioxx as one of the three locations.

c. In relation to the AA cascade, specifically describe the mechanism of action for Vioxx and other drug in the same class. How are these drugs distinguished from acetaminophen and other non-steroidal anti-inflammatories, such as ibuprofen? (Answer the latter question both in terms of mechanism of action as well as in terms of therapeutic and/or side effects.)

d. Briefly describe the physiological effects of the end products of the branch of the AA cascade at which Vioxx and other drugs in its class work. How might these substances contribute to observed cardiovascular problems (e.g., increased risk of heart attack) that are associated with this class of drugs?
QUESTION 13

Discuss in detail at least 3 mechanisms underlying the use of corticosteroids as anti-inflammatory drugs and the effects associated with the long-term use of the drugs. Include diagrams of the major pathways at which corticosteroids act to decrease inflammation.

QUESTION 14

Among the newer immunosuppressive “drugs” are biotechnology products such as monoclonal antibodies (mab) and the fusion proteins (fp). Select two (2) of these immunosuppressive drugs (they can be mabs or fps), each with a different mechanism of action. The drugs you select can be used for organ transplantation or treatment of autoimmune disease.

A. For each, discuss what you know of the drug. Include in your answer for each drug, mechanism of action, the therapy for which it is used, and why it is effective in the particular disease state for which it is prescribed.

B. Describe side effects which have been associated with the biotechnology products and contrast these side effects with polyclonal antibodies produce in animals or polyclonal antibodies therapies resulting from pooled human immunoglobulins. List two examples (describe them if you do not recall specific names) of polyclonal antibodies which have been used therapeutically.
QUESTION 15- (Choose between this question and QUESTION 16)

A. Using a diagram, discuss and illustrate how the Benchmark Dose is determined. Continue, from the Benchmark Dose and discuss how the Reference Dose (RfD) is derived. Is the Reference Dose (RfD) used in evaluating carcinogenic or non-carcinogenic compounds?

B. In conducting a mathematically based risk assessment of a known carcinogen in drinking water, which would give the lowest estimate of the Virtually Safe Dose (VSD) a Multi-stage or Probit Model? What does q1* represent in mathematically based models and how does it impact on VSD?

QUESTION 16

On May 3, 1991 one of Mexico’s worst environmental pesticide disasters occurred. A pesticide formulation plant exploded some eleven blocks from the center of Cordoba, Veracruz, sending thick toxic clouds of methyl parathion, paraquat and “2,4-D” into the air. Fire fighters attempted to douse the fire with thousands of gallons of water. The result was toxic, green streams of runoff coursing through the streets and drainage system. The local river as well as many local drinking water wells were contaminated.

a. Suggest a ranking for these pesticides in terms of their toxicological hazard assuming oral exposure to equivalent doses. (20%)

b. For each pesticide, name their respective chemical class, their pesticide class, and the types of toxicological effects that would occur with each pesticide, if known. Include a description of the time course of development of toxicity. Which of the pesticides would elicit immediate effects? Which would cause delayed effects? (20%)

c. List the mechanisms of toxicity of each pesticide and offer a prediction, based on the stated mechanisms, whether you might expect interactions to occur between the three agents. (20%)

d. Polymorphisms in the PON1 gene are considered to influence susceptibility to which of the three pesticides? Describe what PON1 does and how it is thought to influence toxicity from this pesticide (20%).

e. Discuss likely clinical strategies for management of toxicities associated with exposure to these three pesticides. (20%)
DEPARTMENT OF PHARMACOLOGY & TOXICOLOGY
Virginia Commonwealth University
Medical College of Virginia

Written Comprehensive Examination - Part I

TUESDAY - June 21, 2005

2:00 P.M. - 4:00 P.M.

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QUESTION 17 – (Choose between this question and QUESTION 18)

Benzodiazepines are thought to produce both their therapeutic effects and side effects through actions at the benzodiazepine modulatory site on the GABAA receptor complex. To help describe what is known about the actions of drugs that bind at this benzodiazepine "receptor," please address the following questions:

(30 points) Describe the role of the GABA receptor complex in CNS function. Discuss some of the regulatory sites on this receptor.

(30 points) Describe the modulatory role of diazepam as a representative therapeutic benzodiazepine. Include a discussion of how these actions are involved in both the therapeutic and side effects of diazepam. Describe these therapeutic effects and side effects.

(40 points) Finally, discuss how the intrinsic efficacy of drugs which bind to the benzodiazepine receptor alters their pharmacological properties. Be sure to include in this discussion agonists, antagonists and inverse agonists.

QUESTION 18

Discuss the effects of drugs used to treat the symptoms of (1) schizophrenia and (2) Parkinson's disease on dopaminergic neurotransmission. Include in your discussion the dopaminergic neuronal pathways involved and the mechanism behind the therapeutic and/or adverse actions of drugs used to treat these conditions. Include in your discussion the names of specific drugs for treating schizophrenia and for treating Parkinson’s disease. (90%)

Finally, based on your knowledge of dopamine metabolism and extrapyramidal pathways, speculate on the mechanism by which long-term use of “classical” antipsychotic drugs can lead to the development of tardive dyskinesias. (10%)
QUESTION 19 – (Choose between this question and QUESTION 20)

Glucocorticoids are frequently utilized for the treatment of a variety of immuno-dysregulation diseases/symptoms. Use your knowledge of the use of these agents in respiratory pharmacology to answer the following questions:

1) Describe the brain/endocrine system that regulates the release of glucocorticoids. How/where does feedback regulation occur? (20 points)

2) Describe the general metabolic pathway producing glucocorticoids and list two other types of circulating hormones derived from this pathway, including some information regarding the physiological roles of glucocorticoids and these other agents. (20 points)

3) Give an overview of what steps in respiratory inflammation are sensitive to glucocorticoids. Why are these agents so effective? (10 points)

4) Give a detailed description of the mechanism(s) of action of glucocorticoids in producing anti-inflammatory responses. Give details on the intracellular mechanisms of action. *Hint: include details at least two different responses to glucocorticoids that, together, are important for their effectiveness.* (30 points)

5) Describe some of the toxicity of acute versus chronic glucocorticoid action. (20 points)
Warfarin (COUMADIN), the oral anticoagulant, is near the top of the list of common drugs that are difficult to administer in the clinic. Reducing coagulation in patients who are at risk of a heart attack or stroke with Warfarin is often a problem in the clinic due to Warfarin’s numerous drug interactions (14 common drugs decrease the anticoagulant effect of Warfarin whereas 33 common drugs increased its effect) as well as its low therapeutic index. Because of the clear need for a better oral anticoagulant to treat human disease, you are asked by your new large Pharmaceutical employer to supervise the research and development of a new oral anticoagulant drugs. Based on your knowledge of coagulation and anticoagulation drugs from PHTX 536, how would you begin to approach your new assignment? To answer this question, write a short essay to briefly summarize the highlights of the current understanding of the control of coagulation and mechanism of action of either injectable or oral drugs that inhibit coagulation. Then give me your ideas (yes, speculate) on the mechanism of action of new orally administered drugs that could replace Warfarin in clinical medicine. **BIG HINT!** What step or steps in coagulation would you attempt to target with your new drug? Would it or they be the same or different than Warfarin? Why does Warfarin have a low therapeutic index and what could be done to increase the therapeutic index with a new drug? (Minor **HINT**: why are low molecular weight heparins more useful than high molecular weight heparin in certain clinical situations?)