NATIONAL UNIVERSITY OF LESOTHO

FACULTY OF HEALTH SCIENCES

DEPARTMENT OF PHARMACY

COURSE: PHA 2403 – GENERAL PHARMACOLOGY I

FINAL EXAMINATION

JANUARY 2024 MARKS: 100 TIME: 3 HOURS

INSTRUCTIONS:

The paper has THREE (3) sections, section A to C.

- **Answer ALL questions**

SECTION A – MULTIPLE CHOICE QUESTIONS (MCQs) **[10 MARKS]**

Write the letter that corresponds to the correct answer on the answer sheet provided.

1. A new drug is developed that blocks the transporter for H^+ secretion in gastric parietal cells. Which of the following absorption mechanisms is being inhibited?
   A. Primary active transport
   B. Facilitated diffusion
   C. Simple diffusion
   D. Co-transport

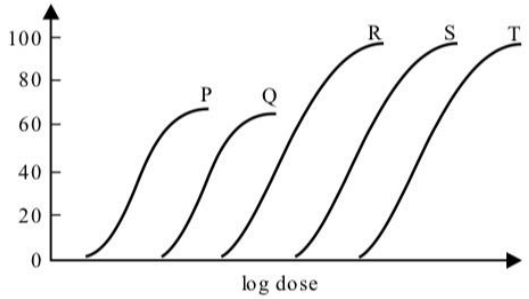
2. Sodium bicarbonate is usually given as an antidote for patients who have ingested large amounts of aspirin to increase its elimination. Which of the following best explains the mechanism of this increased elimination?
   A. Increased glomerular filtration of aspirin
   B. Urinary ion trapping of aspirin
   C. Decreased renal biotransformation of aspirin
   D. Decreased bioavailability of aspirin

3. In one study, Aspirin also known as Acetylsalicylic acid, was given to patient at an oral dose of 200 mg. Aspirin was found to follow first-order, one-compartment model kinetics and had a volume of distribution of 100 L. After the oral administration of the drug, the theoretical plasma concentration at time 0 turned out to be 1 mg/L. which of the following was most likely the oral bioavailability of aspirin in this study?
   A. 0.1
   B. 0.5
   C. 1.0
   D. 2.3

4. Paracetamol is a drug indicated for pyrexia or mild to moderate pain. Given that the half-life ($t_{1/2}$) of paracetamol is 4 hours, calculate the elimination rate constant (k). NB: *Paracetamol elimination follows first order kinetics*.
   A. k = 0.173
   B. k = 2.772
   C. k = 0.693
   D. k = 5.772

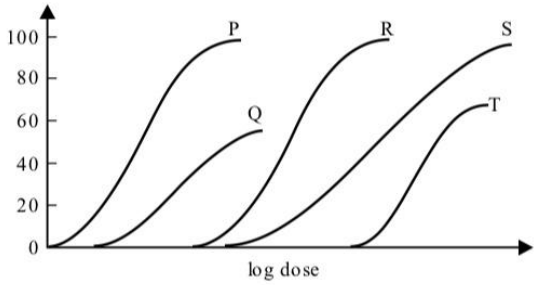
5. In one clinical study, paracetamol was given at intravenous dose of 2 mg. In this study it followed a first-order, one-compartment model kinetics and had a volume of distribution of 10 L. after 6 hours paracetamol plasma concentration was 50 µg/L. Which of the following was most likely the half-life of paracetamol in this study (in hours)?
   A. 1
   B. 2
   C. 3
   D. 4

6. The figure below depicts the in vitro log dose-response curves of different drugs acting on the same receptors.



   Which of the drugs has the highest affinity for the receptor?
   A. Drug P
   B. Drug R
   C. Drug S
   D. Drug T

7. The figure below depicts the in vitro log dose-response curves of five different drugs,



   (P,Q,R,S and T).
   Which of the following pairs of drugs can fully activate the same receptors?
   A. Drugs P and Q
   B. Drugs P and R
   C. Drugs P and S
   D. Drugs Q and T

8. A man suffering from continuous pain and started treatment with morphine. After a few days of treatment, the initial dose was no longer effective, and the physician gradually increased the dose knowing that pharmacodynamic tolerance most likely had occurred. Which of the following best explains the mechanism of tolerance in this patient?
    A. Accelerated morphine metabolism
    B. Increased affinity of receptors to morphine
    C. Decreased morphine receptor density
    D. Decreased binding of morphine to plasma proteins

9. Two new drugs were tested in laboratory animals. Which of the following drug parameters was most likely recorded to estimate the relative potency of both drugs?
    A. The therapeutic index of both drugs
    B. The maximal responses produced by each drug
    C. The graded log dose-response curve of both drugs
    D. The volume of distribution of both drugs

10. A patient had been taking a drug to treat a condition for 6 months. The drug had no intrinsic activity and bound reversibly to β_1 receptors. Which of the following terms best defines this drug?
    A. Partial agonist
    B. Non-competitive antagonist
    C. Competitive antagonist
    D. Functional antagonist

SECTION B – TRUE OR FALSE **[20 MARKS]**

State whether the following statements are TRUE or FALSE

1. Intrinsic activity refers to the fact that the number of receptors can vary with time.
2. Affinity refers to the maximal effect that can be produced by a drug.
3. Potency refers to the dose of a drug required to produce a given effect.
4. Efficacy refers to the effect that can be produced by a drug.
5. The liver, kidney and brain are among the human organs known to be well-perfused organs.
6. The muscle, skin and fat are among the tissues known to be well-perfused and receive the drug at the initial phase of distribution.
7. Binding to albumin of acidic drugs is usually reversible.
8. Cancer may lead to increased levels of α_1-acid glycoprotein (a protein in plasma that binds basic drugs) and this may lead to increased distribution of such basic drugs.
9. The bioavailability is by definition equal to 1 for drugs given by intravascular (IV) route.
10. The bioavailability of drugs given by subcutaneous (SC) or intramuscular (IM) route is relatively better than that given by the oral route.
11. Drugs given by sublingual route bypass the first pass effect.
12. Approximately 50% of the drug that is absorbed from the rectum will bypass the liver, thereby reducing hepatic first-pass metabolism.
13. Phase I reactions are those in which enzymes catalyze the conjugation of the substrate with a second molecule.
14. Phase II reactions are those that include oxidation, reduction or hydrolytic reactions.
15. The phase I enzymes lead to the introduction of functional groups such as -OH, -COOH.
16. Phase II enzymes produce a metabolite with improved water solubility.
17. If the drug is extensively bio-transformed by the liver before it gets into the systemic circulation, oral bioavailability will be increased.
18. If the drug is extensively bio-transformed by the liver before it gets into the systemic circulation, oral bioavailability will be reduced.
19. Sublingual and intramuscular administrations avoid first-pass effect.
20. Bioavailability of the drug is independent of first-pass effect.

SECTION C – LONG/SHORT ANSWER QUESTIONS **[70 MARKS]**

1. Discuss drug action at the following sites, giving an example of one (1) drug, the specific target and cellular effects. **[20]**
    a. Organelles and structural proteins (4)
    b. Cell membrane ion pump (4)
    c. G_s protein coupled receptor (4)
    d. Enzymes (4)
    e. G_q protein coupled receptor (4)

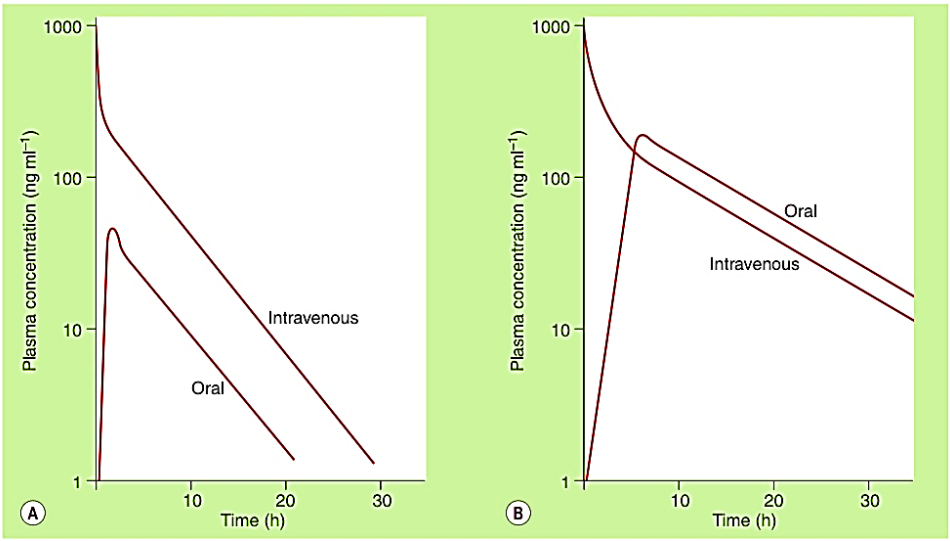
2. A man with osteoarthritis had been taking naproxen, 500 mg daily for 1 month. The drug was effective, but the patient suffered from nausea and heartburn due to the drug. The pharmacist decided to try another non-steroidal anti-inflammatory drug (NSAID); celecoxib, a drug 5 times more potent than naproxen with negligible gastrointestinal side effects. **[10]**
    a. What would be the most recommended daily dose of celecoxib (in mg) to the patient? (2)
    b. What drug parameters were most likely recorded to estimate the relative potency of both drugs? (4)
    c. Compare and contrast potency and efficacy. (4)

3. The effect of a new autonomic drug was tested on a healthy volunteer during a clinical trial. The subject was treated with saline or with the drug, and cardiac rate was recorded at rest or after exercise. The results are reported below. **[10]**

Treatment	**Heart rate (beat per minute)**	
	At rest	**After exercise**
Saline	70	150
Drug	85	100

    a. Describe the effect of the tested drug on the heart rate relative to the effect of saline. (4)
    b. Is the tested drug a competitive antagonist or a partial agonist? (2)
    c. Justify your answer in b. above. (4)

4. The figure below shows the changes in plasma levels of two drugs, A and B, each given as 10 mg doses by both the oral and intravenous routes to an adult man. From the plasma concentration-time curves, describe how the drugs compare for the following properties. **[10]**



a. Absorption from the gastrointestinal tract [2]
b. Oral bioavailability [2]
c. Distribution to tissues [2]
d. Elimination half-life [2]
e. Extend of accumulation with once-daily administration of each drug [2]

5. A man weighing 70 kg was admitted to hospital with a serious infection and was treated with two antibacterial drugs. Gentamicin is given by intravenous administration, and cefalexin is given orally with bioavailability of 90% (F = 0.9). **[20]**

	Gentamicin	**Cefalexin**
Volume of distribution (Vd) **(L)**	18	18
Clearance (CL) **(L/hr)**	5.4	18
Half-life **(hr)**	2-3	0.9

Gentamicin is very toxic and its therapeutic plasma concentrations **should not exceed 5 mg/L,** since higher concentrations can lead to ototoxicity and nephrotoxicity.

a. You have calculated that you will give 900 mg of gentamicin by injection as a bolus (single) dose. Is this a safe dose? [4]
b. Because of the short half-life of gentamicin, you then decide that it will be best to give him a continuous intravenous infusion to maintain a steady-state plasma concentration of 2.5 mg/L. What rate of infusion should be given? [6]
c. What maximum plasma concentration would be obtained if a single oral loading dose of 500 mg cefalexin was given? [5]
d. What is a loading dose and why is it often given? [5]

END