BSc Degree Examinations 2019-20

Department: BIOLOGY

Title of Exam: Pharmacology

Time Allowed: 24 Hours (PLEASE NOTE: Late papers will not be marked)

Time Recommended: 1 hour and 30 minutes

Word limit: Please answer the questions within the line/word limit stated. Content beyond the line/word limit will not be marked.

Allocation of Marks:
Total marks available for this paper: 60
Section A contains interpretation and data handling questions (40 marks).
Section B contains an essay question (one from 2 choices) 20 marks
The marks available for each question are indicated on the paper.

Instructions for Candidates:
All questions should be answered on this question paper using minimum font size Arial 11.
Each question should be answered within the stated line/word limit. Do not adjust the margin width.

Section A: Answer all questions
Section B: Answer either question A or B.
1. Below is the change in plasma concentration ($C_p$) of a newly developed amide local anaesthetic drug immediately following a bolus dose.

![Graph showing plasma concentration over time](image)

a) By what route was this drug most likely administered? Explain your answer.  
(2 marks, 4 lines)

The intravenous route (1 mark). The maximum plasma concentration ($C_{max}$) is reached immediately and there is no time taken for drug to transfer to the central plasma compartment (1 mark).

b) Which compartment model best describes the pharmacokinetic profile of this drug?  
(1 mark, 1 line)

The single compartment model.

c) What is the value of $C_0$?  
(1 mark, 1 line)

$C_0 = 600 \, \mu\text{mol/L}$

d) What is the elimination $t_{1/2}$? Show how you arrived at your answer.  
(2 marks, 3 lines)

Elimination $t_{1/2} = \text{time taken for } C_p \text{ to fall by } 50\%$. 50% $C_p = 300 \, \mu\text{mol/L}$ (1 mark). 
Elimination $t_{1/2}$ therefore is 20 minutes (1 mark).
e) Would you recommend a loading dose for this drug? Explain your answer.

(2 marks, 3 lines)

No (1 mark). This drug has a relatively short $t_{1/2}$ and so it should accumulate to steady state therapeutic level rapidly (1 mark).

Module learning outcomes 1, 2, 4, 6.

2. Below is a Lineweaver Burk plot showing the kinetics of TLR4-MD dimer formation after binding of its ligand LPS. The effect of binding is determined by measuring the % of dimer formation. The black line shows the interaction with LPS alone while the blue line shows LPS with drug Y.

\[ \frac{1}{[\text{LPS}]} \text{ (µM)} \]

\[ \frac{1}{\% \text{ Dimer formation}} \]

a) What is the binding affinity (Kd) and maximum % dimer formation of LPS alone

(2 marks, 5 lines)

Marks for correct answers

$K_d = 10 \text{ µM}$ (must have units) and Maximum % dimer formation = 5 % (or 5)

Students can work this out from the graph; for a lineweaver burk plot the x-intercept = $-1/K_d$

And the y-intercept = $1/V_{\text{max}}$ (in this case the maximum % dimer formation)
b) Drug Y affects the LPS binding and thus dimer formation. What type of agonist or antagonist describes Drug Y? Explain your answer.

(2 marks, 3 lines)

Drug Y is a non-competitive agonist because the maximum % dimer formation decreases in the presence of drug Y (from 5 % to 2.5%)

Module learning outcomes 2, 4, 6.

3. You are investigating two potential receptors (R1 and R2) for Ligand A. To find and characterize the receptor for Ligand A you have generated the following data of cyclic AMP (cAMP) production wherein you measure cAMP production at basal level, after addition of Ligand A, after addition of cAg (a stimulator of cAMP production) and lastly after addition of both cAg and Ligand A to each receptor. Significant changes in cAMP production compared to basal levels are indicated with an asterisk (*).

![cAMP Production Graph](image)

a) Which of the two receptors are responding to Ligand A? Explain your answer.

(2 marks, 5 lines)

Receptor R2 is responding to Ligand A (1 mark). There is no difference in cAMP production following addition of Ligand A to R1 in the absence or presence of cAg. cAMP levels change (decrease) in response to Ligand A on R2 in the presence of cAg. (1 mark)
b) Describe what type of receptor Ligand A is binding to? Explain your answer.

(3 marks, 5 lines)

Ligand A is binding to a G-coupled protein receptor (GCPR) (1 mark) subtype Gαi (1 mark) because it decreases cAMP levels (1 mark; ½ mark for only saying that cAMP levels are affected by GCPRs without mentioning increase or decrease to establish if it is a Gαi or Gαs).

Module learning outcomes 2, 4, 6.

4. It is observed that a novel antibiotic is being rapidly cleared in the urine. Devise a strategy to determine the roles of the OATs and / or OCTs in this process, and explain the logic of your strategy.

(4 marks, 8 lines)

OATs and OCTs are both 12 membrane transporters in the SLC22 family, but OATs transport anions, OCTs transport cations. The first part of the strategy would be to determine if the antibiotic is present as a + or - ion. OATs require energy for their transport, derived from ATP; OCTs facilitate the ions to diffuse down the concentration gradient. Second strategy would be to poison the kidney (inhibit ATP synthesis) and see if transport is reduced.

b) Outline an approach to slow excretion, justifying your answer with evidence from a current drug.

(3 marks, 3 lines)

Use a competitive inhibitor, as with probenecid / penicillin interaction

Module learning outcomes 1, 2

4. a) Explain the sliding filament theory of muscle contraction

(8 marks, 10 lines)

Muscle proteins are assembled into thick (myosin) and thin (actin, tropomyoson, troponin) filaments. Calcium enters and binds to troponin, causing the tropomyosin to move and reveal the attachment site for the myosin heads. This allows myosin to bind ATP and attach to the thin filament. On release of the ADP and P the myosin head changes position and the thick and thin filaments slide sideways.
b) Give an example of a drug that affects muscle contraction, and explain how it interacts with the contractile protein(s)  

eg Omecamtiv mecarbil - interacts with myosin to increase the rate of P release (the rate limiting step of the cycle)  

Module learning outcomes 2

5. Patients with an autoimmune disease are treated with a prodrug ("Inhibinib") that reduces immune activation. Inhibinib is converted to a toxic active metabolite (Inhibinib*) by a cytochrome P450 enzyme CYP2JH. The circulating prodrug : drug ratio in a patient cohort is shown below:

![Graph showing inhibinib : inhibinib* ratio for groups A and B]

a) Explain what the graph shows for groups A and B, and give genetic explanations for this distribution  

Group A patients rapidly convert pro-drug into active drug i.e. are ultra-metabolisers (1 mark), suggesting duplication or activating mutations in the CYP2JH gene (1 mark).

Group B patients cannot convert pro-drug into active drug (1 mark), suggesting that they have a mutated or deleted CYP2JH gene (1 mark).

b) What are the limitations of treating patients in group A and B with this drug?  

Group A drug toxicity / excessive immunosuppression (1 mark)

Group B drug does not work (1 mark)
SECTION B: Essay question

Answer either question B1 or B2 from this section.

Mark total for this section: 20

B1. Epinephrine was used early in the twentieth century to treat asthma but has since been replaced by other drugs such as Salbutamol, which is commonly used in inhalers to treat asthma. Explain key improvements of salbutamol as compared to epinephrine for treating asthma by describing its receptor and signalling, discussing specificity and explaining the relevance of these for drug access, kinetics and side effects (including examples of side effects).

(20 marks, 500 words)

Epinephrine and salbutamol are both agonists of andrenoreceptors. While epinephrine acts nonselectively on all andrenoreceptors, salbutamol acts specifically on β2-andrenoreceptors. The β2 receptor is a G protein-coupled receptor of the Gαs type that stimulates adenylate cyclase to convert ATP into cAMP resulting in smooth muscle cell relaxation. GPCR’s are transmembrane receptors that bind ligands extracellularly or in the membrane – this allows ligands to more easily gain access to the receptor for signalling. GPCR’s also signal rapidly to allow quick relief from asthma. (10 marks)

Epinephrine causes more side effects due to its action on all the other adrenoreceptors which are found in multiple tissues in the body. For example, in addition to airway smooth muscle relaxation it may also increase lipolysis, increase blood glucose, reduce glycogenesis and increase cardiac output. Salbutamol is more specific than epinephrine because it targets β2-andrenoreceptors, which are found primarily in airway smooth muscle (ASM) with less of this receptor subtype present in other muscle cells such as the heart and GI tract. This receptor specificity reduces side effects in the case of Salbutamol but some side effects may still occur due to binding of the drug to B2 andrenoreceptors in other tissues such as intestine, the heart and skeletal muscle. For example overdosing may cause side effects such as increase in heart rate and increase in glucose. Salbutamol side effects are also reduced by limiting the dose and by administering the drug through inhalation to allow drug delivery directly to ASM with less exposure systemically. (10 marks)

Module learning outcomes 1, 2, 3, 4.
B2. Explain the problems posed by ‘first-pass metabolism’ and outline ways in which these can be avoided, illustrating the principles with specific drugs.

(20 marks, 500 words)

‘first-pass metabolism’ is caused by the blood supply from the digestive system passing to the liver before going to any other tissue; the liver is a major site of oxidation and conjugation reactions (e.g., aspirin to salicylate, then to gluconoride). These reactions may inactivate a drug (e.g., serotonin or make it more effective, e.g., morphine-6-glucuronide is an active metabolite of morphine).

[5 ideas, 5 marks for examples]

‘first-pass metabolism’ can be avoided by sub-lingual (e.g., nitroglycerine in people with suspected heart attacks), rectal (e.g., morphine for late-stage cancer patients who cannot swallow) because the blood flow from these areas does not go immediately to the liver. Dermal patches (e.g., nicotine replacement therapy) or intravenous/sub-cutaneous (e.g., antibodies, the antibiotic thienamycin) [or other] injection sites.

[5 ideas, 5 marks for examples]

Module learning outcomes: mainly 2