THE COLLEGES OF MEDICINE OF SOUTH AFRICA

Incorporated Association not for gain
Reg No 1955/000003/08

Final Examination for the Fellowship of the College of Clinical Pharmacologists of South Africa

26 July 2018

Paper 1 (3 hours)

All questions are to be answered. Each question to be answered in a separate book (or books if more than one is required for the one answer)

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1 A-70-year-old man presents with a 3-week history of a productive cough, fever, night sweats, loss of appetite and loss of weight. On examination, he has temporal wasting, his weight is 59kg, he has tachypnoea, and bronchial breathing in the right upper lobe (RUL). Chest x-ray shows a cavity in the right apex. A diagnosis of drug-sensitive pulmonary tuberculosis is confirmed on the GeneXpert® MTB/RIF assay. Blood tests reveal the following: Urea 29 mmol/L and creatinine of 1100µmol/L

a) Discuss the limitations of only relying on creatinine as an estimate of renal function. (3)

b) Discuss the principles of medicine dose adjustment in renal impairment. (3)

The modified formula of Cockroft and Gault calculates the creatinine clearance of Mr AB as 5ml/min

c) Dose adjust the tuberculosis medicines for his degree of renal impairment. (4)

[10]

2 You are contacted by a medical officer for expert advice as the clinical pharmacologist on call: A 39-year-old woman was admitted with a right femur fracture to the orthopaedic ward in preparation for surgery. She presented with new onset tonic-clonic seizures which resolved after intravenous lorazepam administration. The family reported that she has porphyria and her regular clinical notes document a history of variegate porphyria

a) Briefly discuss the clinical presentation of an acute porphyria attack. (5)

b) Discuss the principles in the management of an acute attack. (3)

The medical officer needs advice on the further management of seizures in this patient

c) Discuss your approach to the selection of medicines in patients with variegate porphyria. (2)

[10]

3 A 17-year-old young woman is known with perinatally acquired HIV infection. She has recently failed zidovudine/lamivudine/efavirenz which she had been taking since she was 6-years-old. She has multiple social issues and has recently been left to live alone, without family support. You commence once-a-day second-line therapy including tenofovir, emtricitabine and atazanavir/ritonavir in order to improve her adherence issues. Six months into second-line treatment her adherence remains poor and her viral load is 63 000 copies/ml. Her CD4 count is 470 cells/µL. She has been feeling unwell, coughing for two weeks and you diagnose pulmonary tuberculosis.

a) Discuss your approach to treating her tuberculosis and HIV treatment. Include discussion on improving her adherence. [10]

4 A 22-year-old woman known with asthma, which is not well-controlled on daily inhaled beclomethasone 400µg twice daily. She has allergies to house dust mites, cats, grasses and ragweed. She presents to the emergency department in winter, with worsening shortness of breath and audible inspiratory and expiratory wheezing after a cold. She is not cyanotic, has no fever, her pulse is 120 beats/min and respiration rate is 32 breaths/min. She finds it difficult to perform her daily duties and has used her salbutamol inhaler several times a day for the past 3 days. You make the diagnosis of chronic persistent asthma with an acute exacerbation.

a) Briefly discuss the acute management of this patient. (3)

You decide to step-up her treatment after she recovers from the acute exacerbation

b) Briefly discuss four options to step-up her treatment. (8)

She reads on the internet about the use of omalizumab to treat moderate to severe asthma.

c) Discuss the mechanism of action of omalizumab and considerations for initiating therapy (4)

[15]

5 A 45-year-old man was involved in a motor vehicle accident 2 days ago. He sustained a fracture of the left femur and had surgery same day. Two days after admission to the hospital, he became aggressive, combative, abusing nurses and also has visual hallucinations. His wife mentioned that he has no past medical history of note, does not use illicit drugs, and has 4-6 alcoholic drinks per day and more during weekends. On examination, he is diaphoretic, disoriented in time, person and place, temperature is 37.9°C, heart rate of 118 beats per minute, blood pressure of 164/102mmHg, respiratory rate of 26 breaths per minute, and oxygen saturation on room air of 99%. Imaging of the brain was normal.

a) What is the most likely diagnosis? (1)
b) What is the underlying mechanism of the condition diagnosed? (4)
c) What is your approach to managing this patient? (5)

[10]

6 Answer both questions below about the cardiac safety of new drugs

a) What is the QT interval on the ECG and what does it represent? (2)
b) Write short notes on when and how the QT/QTc prolongation potential is evaluated in the clinical development of a new drug. (8)

[10]

7 Answer both questions below about pharmacovigilance

a) List the minimum information required for an adverse event report to be valid. (2)
b) You are responsible for the pharmacovigilance activities relating to a flu vaccine. Three fatal seizures have been reported within three weeks of launch of the vaccine. What do you need to know in order to evaluate these cases fully? (8)

[10]

8 Discuss the following potential drug interactions involving traditional medicines. Refer to the mechanism and potential outcome of the interaction

a) Saint John's wort (*Hypericum perforatum*) and paroxetine.
b) Saint John's wort (*Hypericum perforatum*) and theophylline.
c) *Ginkgo biloba* and warfarin. [6]

9 Name four clinical situations where generic substitution may not be done. [4]

10 Your neonatology colleagues contact you. Intravenous phenobarbital is out of stock due to raw material shortage and the shortage is anticipated for the next few months. The neonatologists are therefore required to revise their neonatal convulsion protocol and they want to include tablet formulation levetiracetam administered via nasagastric tube. Only the tablet formulation is registered for marketing in South Africa. They provide supportive data from a case series of adult patients presenting with refractory status epilepticus where the tablet formulation was given via nasogastric tube

a) Discuss pharmacokinetic differences between neonates and adults to take into consideration when making inferences from the adult case series. (10)
b) Discuss principles of administering tablets via nasogastric tube. (5)

[15]

FC Clin Pharm(SA) Part II

THE COLLEGES OF MEDICINE OF SOUTH AFRICA

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Final Examination for the Fellowship of the College of Clinical Pharmacologists of South Africa

27 July 2018

Paper 2 (3 hours)

All questions are to be answered. Each question to be answered in a separate book (or books if more than one is required for the one answer)

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1 A 36-year-old man with bipolar I disorder was admitted for a manic episode in the psychiatric ward. His disease management is challenging and his last outpatient treatment was lithium 500mg 12-hourly, valproate 1g 12-hourly, clozapine 100mg 12-hourly and sulpiride 50mg 8-hourly. He was started on haloperidol 2.5mg orally on admission, and his chronic medications were continued. A week into his admission, he is found in the hospital bed with a decreased level of consciousness and tachypnoea (saturation 77% on room air) requiring intubation. Findings on examination are a temperature of 38.1°, blood pressure increase from 123/79mmHg during admission to 165/102mmHg and muscle rigidity. On laboratory investigations he has a creatinine kinase level of 10 710U/L (range 20-200), but his renal function, urine examination, and ECG findings are normal

a) Provide your diagnosis as well as a differential diagnosis for this patient and reasons why each has been ruled out. (6)

b) Discuss the pathophysiology and treatment of the condition. Comment on the patient's future management once discharged. (14)

[20]

2 A 23-year-old patient is brought into the emergency department by paramedics with new onset generalised tonic-clonic seizures. The paramedic on the scene administered lorazepam 4mg intravenously, but failed to stop the seizures. He is in recovery position and has a saturation of 97% on room air. The patient does not have a history of epilepsy. He is HIV positive and co-infected with drug sensitive tuberculosis. He was found at the scene with empty antiretroviral fixed dose combination bottles (efavirenz/tenofovir/emtricitabine), tuberculosis treatment packets (rifampicin/isoniazid/pyrazinamide/ethambutol) and paracetamol packets. The time of ingestion is approximately 1 hour ago. The exact quantity of his ingestion is unknown. You are on call for toxicology and consulted first to assist with the unresponsive seizures.

a) Discuss your differential diagnosis and the management of this patient in detail. [15]

3 Your psychiatry colleague is treating a 33-year-old female patient with bipolar mood disorder with psychotic mood symptoms with amisulpiride and lithium. On routine monitoring, it is noted that the patient developed an increase in prolactin concentrations with a baseline of 5.3 to 429 microgram/L (normal 4.8 – 23.3), but is asymptomatic. You are contacted for advice on further management.

a) Discuss the pathophysiology of the raised prolactin in this patient, clinical effects of raised prolactin and further management of this patient. [10]

4 The World Health Organization recommends intravenous quinine as an alternative treatment for severe malaria if intravenous artesunate is not available. You are working in a secondary hospital that only occasionally treats severe malaria patients, and where intravenous quinine is the only effective treatment available. Total plasma quinine concentrations are included in the therapeutic drug monitoring (TDM) services offered by your local pharmacology laboratory

a) Provide a list of 5 Top Tips for reminding healthcare workers of what they need to do to get the most useful information from the TDM service. (5)

b) List 5 properties of medicines that would justify their inclusion in a therapeutic drug monitoring service. (5)

c) List 5 pharmacokinetic properties of quinine, and discuss how each of these factors could affect whether or not therapeutic drug monitoring of total quinine concentrations would be appropriate either routinely, or in specific circumstances. (5)

[15]

5 A 60-year-old man complains of pain in both of his feet over the past week. He describes the pain as burning, sharp, and continuous, interfering with sleep and walking. He has never used alcohol. He has multiple comorbid conditions, including hypertension, coronary artery disease, symptomatic benign prostatic hypertrophy, and type 2 diabetes mellitus. On examination he has hyperesthesia in both feet. His blood pressure is 154/95mmHg measured on 3 occasions, pulse 87bpm, body mass index is 30kg/m^2, HbA1c = 6.5% (normal range 3.9 – 6.1), eGFR = 50mL/min1.73m^2; urine albumin/creatinine ratio 50mg/mmol (normal range 2.5-25); serum potassium 5.6mmol/L (normal range 3.5-5.5); LDL-cholesterol = 3.4mmol/L (< 3.0mmol/l); HDL-cholesterol = 0.9mmol/L (>1.2mmol/l females and >1.0 males); total cholesterol = 5.6mmol/L (<5.0mmol/l). His current medications include amlodipine 10mg daily, rosuvastatin 10mg, enalapril 10mg, metformin 850mg three times daily, levofloxacin 500mg and diclofenac 50mg daily for past 4 weeks

a) Discuss the pharmacological approach to the treatment of coronary artery disease and hypertension in this patient. (10)

b) Discuss the pharmacological approach to the treatment of peripheral neuropathy in this patient. (10)

[20]

6 a) Define the terms “biomarker” and “surrogate endpoint” in clinical research, and discuss their practical applications, with 2 specific examples for each of them. (8)

b) You have been asked to prepare the Preclinical Development Plan addressing the regulatory non-clinical safety studies (toxicology and safety pharmacology) to be performed for a new drug candidate selected for clinical development in the indication “rheumatoid arthritis”. Apart from preliminary screening studies, no non-clinical safety studies have been performed yet. List the key studies (with brief explanation) to be planned

i) Before clinical development. (4)

ii) As support of clinical development. (4)

iii) For submission of the marketing authorisation. (4)

[20]