



THE COLLEGES OF MEDICINE OF SOUTH AFRICA

Incorporated Association not for gain
Reg No 1955/000003/08Final Examination for the Fellowship of the
College of Clinical Pharmacologists of South Africa

4 March 2021



Paper 1

(45 mins)

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

Section B

- 1 A 47-year-old man is brought to the Emergency Department. He is ataxic when walking and complains of dizziness and vomiting. He is hyperventilating. On physical examination, the patient appears well nourished, agitated, and disoriented. His breath has no odour. His vital signs are: blood pressure 145/90 mmHg; temperature 37.2°C; pulse rate 118 beats/minute; and respirations 32 breaths/minute. Neurologic examination, apart from mild peripheral nystagmus, is normal. Abdominal and cardiorespiratory examinations are also normal. Upon interviewing the patient's relative, he reports that the patient was found with a bottle of radiator antifreeze.

The following point of care investigations are done immediately

Arterial blood gas:

pH	7.10	(normal range 7.35 – 7.45)
P _a O ₂	95 mmHg	(normal range 80 – 100) /
	12.7 kPa	(normal range 10 – 13) [SI units]
P _a CO ₂	20 mmHg	(normal range 35 – 45) /
	2.7 kPa	(normal range 4.7 – 6.0) [SI units]
HCO ₃	8.0 mmol/L	(normal range 22 – 26)
Base excess	-21.2 mmol/L	(normal range ± 2)
Anion gap	32	(normal range 8 -12)

Random glucose: 4.4 mmol/L (normal 3.3 – 7.8)

- What is your provisional diagnosis? (1)
 - Provide 2 differential diagnoses. (2)
 - Which additional investigations are indicated and should be requested? (1)
 - Discuss appropriate therapeutic management of this patient. (4)
- [8]

- 2 A 62-year-old man presents to the emergency unit with a week history of feeling unwell with severe diarrhea and vomiting. On examination he has a blood pressure of 109 / 72 mmHg and a pulse rate of 103 beats per minute. He is known with atrial fibrillation for the last 10 years for which he receives digoxin and warfarin. His digoxin concentration is 3.49 mmol/L (therapeutic range 0.65 – 1.1 nmol/L) 16 hours after the last dose.
- a) Interpret the digoxin concentration by referring to the time of sampling and the therapeutic window of digoxin. (3)
 - b) Discuss the mechanism of action of digoxin and relate it to electrolytes that should be measured in this patient. (4)
- [7]
- 3 A 28-year-old man is admitted to the medical ward with nephrotic syndrome and a serum albumin concentration of 16 g/L. Twelve days after admission, a tonic-clonic seizure occurred in association with hypocalcemia (0.4 mmol/L) and hypomagnesemia (0.49 mmol/L). He was treated with phenytoin, 300 mg daily. In the following days he had recurrent seizures, which were treated with repeated administration of an intravenous bolus of phenytoin. Seizures were controlled. On neurologic examination, he was drowsy and demonstrated marked ataxia, dysmetria, and nystagmus. His total phenytoin concentration is 18.2 µg/mL (normal range 10 – 20 µg/ml).
- a) What is the likely diagnosis? (1)
 - b) What are the contributing factors of his presentation? (2)
 - c) How should the patient be managed further? (2)
- [5]



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Paper 2

(3 hours)

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

- 1 A 42-year-old female with a history of renal transplant 2 years ago was admitted with signs of worsening graft rejection and epistaxis on slight blowing of her nose. She was on treatment with sirolimus and low dose aspirin once daily. On further evaluation, she revealed that for the past 4 weeks she was advised to take two herbal preparations: St. John's Wort (*Hypericum perforatum*) for depression and Garlic (*Allium sativum*) for high cholesterol.
 - a) What is the proposed mechanism of action of St. John's Wort (*Hypericum perforatum*) in depression? (2)
 - b) Describe two mechanisms by which St. John's Wort (*Hypericum perforatum*) can lead to reduced concentration of sirolimus, leading to graft rejection. (2)
 - c) What is the proposed mechanism of action of Garlic (*Allium sativum*) for hypercholesterolaemia? (2)
 - d) Describe two mechanisms by which Garlic (*Allium sativum*) can lead to increased bleeding tendency. (2)

[8]
- 2 A 56-year-old man was diagnosed with recurrent focal seizures and treatment with carbamazepine was begun. One month later he presents with fatigue and confusion. Laboratory findings are serum sodium 122 mmol/L (136 – 144 mmol/L), normal potassium, urea and creatinine; urine sodium 42 mmol/L and urine osmolality was increased.
 - a) What is the most likely diagnosis? (2)
 - b) How would you manage the low serum sodium? (3)

[5]
- 3 A 68-year-old male is diagnosed with early-stage idiopathic Parkinson's disease and initiated on carbidopa/levodopa.
 - a) Why is carbidopa co-administered with levodopa? (2)
 - b) What is dopamine dysregulation syndrome? (2)
 - c) Provide two management principles of levodopa-induced dyskinesia. (2)

[6]
- 4
 - a) Provide 2 examples where it is appropriate to use patients as volunteers for the first in man studies. (2)
 - b) Provide 3 advantages of using patients in first in man studies. (3)

- 5 You are a principal investigator for a sponsored first-in-man study investigating the pharmacokinetics and safety of a new chemical entity (NCE) antiretroviral, named NOHIV-007 to treat HIV.
- a) Describe your planned study population and justify your answer. (3)

In vitro assessment suggests that NOHIV-007 is likely to be a substrate and an inhibitor of CYP3A4.

- b) List an example of a probe drug that can be used for the evaluation of potential inhibition of CYP3A4 metabolism *in vivo* by NOHIV-007. (1)
- c) You are tasked to design drug-drug interaction studies of NOHIV-007. List two relevant drug-drug interactions to be evaluated before NOHIV-007 can be marketed and justify your answer. (4)
- [8]

- 6 A 26-year-old woman with a known history of acute intermittent porphyria is brought to the emergency department with severe abdominal pain, nausea and vomiting. Her heart rate is 120 beats per minute and blood pressure 174/114 mmHg. The diagnosis of an acute porphyria attack is confirmed biochemically.

- a) Outline the pharmacotherapeutic management principles for this patient. (5)
- b) The evening of her admission the nursing staff report tonic-clonic seizure. Outline the pharmacotherapeutic management of her seizures. (2)
- c) Provide three principles when prescribing medicines to this patient. (3)
- [10]

- 7 Briefly discuss the influence of obesity on the pharmacokinetics on both lipophilic and polar drugs. Provide an example of a lipophilic and polar drug. [5]

- 8 The first full peer-reviewed results of phase 3 vaccine trials against SARS-CoV-2 were published early December 2020. The vaccine investigated was the ChAdOx1 nCoV19.

- a) What are the characteristics of a Phase 3 clinical trial design? (5)
- b) Provide three regulatory considerations that will be reviewed before ChAdOx1 nCoV19 can be approved for marketing in South Africa. (6)
- c) Discuss the importance of post-marketing surveillance of ChAdOx1 nCoV19 after regulatory approval. (5)
- d) List 4 methods of how post-marketing surveillance of ChAdOx1 nCoV19 can be performed. (4)
- [20]

- 9 A patient is found to have a 1 mg/L concentration of a drug with a half-life of 7 hours and a volume of distribution of 100 L.

- a) What is the clearance rate of this drug for this patient? Provide the value and units. Assume that the $\ln(2) = 0.7$. (2)
- b) What is the fractional elimination rate of this drug at this moment? Provide the value and units. (2)
- [4]

- 10 An 85-year-old woman who is receiving donepezil for dementia is brought to hospital with increasing confusion of 5 days' duration. Her other medications are hydrochlorothiazide, enalapril, alendronate, diphenhydramine, simvastatin and omeprazole.

- a) Name the medication on this list that is most likely to cause confusion in geriatric patients. (1)

- b) Her creatine kinase (CK) level on admission is five times the upper limit of normal. Name the medication that is most likely responsible for this abnormal laboratory test result. (1)
- c) History reveals that her family administers her medications with grapefruit juice. Name the specific drug-metabolizing enzyme that is inhibited by components of grapefruit juice. (1)
- d) Her potassium is 5.8 mmol/L. Name the medication that is most likely responsible for this abnormal laboratory test result. (1)
- [4]

- 11 A 65-year-old woman is treated in the emergency unit with worsening chronic cardiac failure complicated by renal failure (last eGFR 6 weeks ago was 33 mL/min). Her cardiac failure is caused by longstanding uncontrolled atrial fibrillation. Her chronic treatment is furosemide, enalapril, digoxin, spironolactone and carvedilol. She is diuresed with intravenous furosemide while awaiting his blood results. She has auditory hallucinations which makes her a very difficult patient to nurse. The treating physician requests that a benzodiazepine be avoided and prescribes haloperidol 5 mg intramuscularly. The staff nurse gave the haloperidol intravenously in error. Thirty minutes later she is unresponsive, and resuscitation is started. The following rhythm strip is recorded



- a) What is the diagnosis? (1)
- b) What is the immediate management? (2)
- c) What are the contributing factors to her adverse event? (5)
- d) What was the treating physician's rationale for avoiding a benzodiazepine? (2)
- [10]
- 12 The National Department of Health is reviewing the inclusion of a long-acting muscarinic antagonist (LAMA) for the treatment of Chronic Obstructive Pulmonary Disease on the National Essential Medicines List. A Cochrane review is studied which concluded that the LAMA was associated with a significant improvement in patients' quality of life and it reduced the risk of exacerbations, with a number needed to treat (NNT) to benefit of 16 to prevent one exacerbation after 52 weeks of treatment. The cost of the LAMA is R412.69 per month.
- a) Calculate the estimated cost to the National Department of Health to prevent one exacerbation. (2)
- b) Will you recommend the inclusion of the LAMA on the formulary? Provide reasons. (3)
- [5]
- 13 A 35-year-old HIV positive woman presents with a 2-day history of maculopapular rash, fever, gastrointestinal symptoms (abdominal pain, nausea and vomiting), shortness of breath and fatigue. She commenced antiretroviral therapy 2 weeks prior: abacavir, lamivudine and dolutegravir. Her baseline CD count was 280 cells/mm³.
- a) Which of the medicines that she is taking could be implicated in this presentation? Which is the most likely? Provide a justification. (3)
- b) What other possible diagnoses require exclusion before concluding that this is an adverse drug reaction?

- c) What are the risk factors for this condition? (2)
 - d) What test could have been performed to identify patients at risk of this presentation?
Should this test be used routinely in the South African public sector? Justify your answer. (3)
 - e) How would you manage the patient further? (2)
- [12]