# THE COLLEGES OF MEDICINE OF SOUTH AFRICA

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

### Part I Examination for the Fellowship of the
### College of Clinical Pharmacologists of South Africa

8 March 2021

Paper 1                                                                                          (45 minutes)

*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)*

1    Define the following pharmacodynamic concepts:
   a)    Partial agonist and provide an example.                                                    (2)
   b)    Inverse agonist and provide an example.                                                    (2)
   c)    Non-competitive antagonist and provide an example.                                         (2)
   d)    Therapeutic index.                                                                          (2)
   e)    Quantal dose-effect curve                                                                   (2)
                                                                                                    [10]

2    Use the following pharmacokinetic data of propranolol to answer the subsequent questions.

| Bioavailability | 0.25 |
|---|---|
| Clearance | 700 mL/min or 42 L/hour |
| Volume of distribution | 300 L / 70kg |

   a)    What is the half-life of propranolol? Show your calculations.                              (3)
   b)    What daily dose of propranolol is needed to reach steady-state plasma concentration of
         25 µg/L?                                                                                    (6)
   c)    List three factors that could be responsible for the oral bioavailability of 0.25.          (3)
                                                                                                    [12]

3    Discuss the influence of pH on ionizable drugs by using the example of sodium bicarbonate
     to treat salicylate toxicity.                                                                   [8]

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### Part I Examination for the Fellowship of the College of Clinical Pharmacologists of South Africa

## 9 March 2021

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)*

1    Gemfibrozil was compared with placebo in a 5-year randomised double-blind cardiovascular study. The study included 4080 asymptomatic men aged 40 – 55 years with dyslipidaemia and the primary outcome was a composite endpoint of cardiac death, non-fatal myocardial infarction or death due to other causes. The table below summarises the treatment allocation and events.

| Treatment allocation | Primary outcome: reached | Primary outcome: not reached | Total |
|---|---|---|---|
| Gemfibrozil | 56 | 1995 | 2051 |
| Placebo | 84 | 1946 | 2030 |
| **Total** | **140** | **3941** | **4081** |

a)    Calculate the relative risk.                                                              (2)
b)    Calculate the relative risk reduction.                                              (1)
c)    Calculate the absolute risk reduction.                                            (1)
d)    Calculate the number to treat and provide an interpretation.            (2)
                                                                                                              [6]

2    A 55-year-old male with type II diabetes mellitus is treated with glimepiride 2 mg per day and omeprazole 20 mg per day for gastro-oesophageal reflux disease. He is admitted with an acute coronary syndrome and has a drug-eluting stent inserted into his right coronary artery. He is commenced on aspirin 100 mg per day and clopidogrel 300mg immediately, followed by 75 mg per day.

Identify the potential drug-drug interactions, provide a mechanism if known and briefly outline the potential management.                                                                          [6]

3   A 62-year-old man is brought to the emergency unit with severe diarrhea and vomiting. He is known with bipolar mood disorder for more than 20-years for which he takes lithium. He was diagnosed with hypertension 3-months ago and was started on 25 mg per day hydrochlorothiazide and 10mg per day enalapril. His estimated glomerular filtration rate is 23 ml/min and his lithium concentration is 3.49 mmol/L (therapeutic range 0.6 to 1.2 mmol/L for bipolar mood disorder). His serum potassium concentration is 3.2 mmol/L.

Identify the potential drug interactions between lithium and the antihypertensive drugs and discuss the mechanism of the interaction.                                                                                         [4]

4   A chemotherapy drug (called drug A) is evaluated as additional treatment to standard of care. The table below provides survival and quality of life data for both drug A added to standard of care, and standard of care alone.

| Variable | Standard of care + drug A | Standard of care |
|---|---|---|
| Estimated survival | 10 years | 5 years |
| Estimated quality of life | 0.8 | 0.5 |

Calculate the cost per quality-adjusted life year (QALY) gained when using drug A in addition to standard of care, if the cost of treatment is R120 000. Show all your calculation steps.   [5]

5   You're tasked to calculate the incremental cost-effectiveness ratio (ICER) for rituximab or an alternative tumor necrosis factor (TNF)-alpha-inhibiting drug as second line biological treatment in patients with active rheumatoid arthritis who have had an inadequate response to conventional disease modifying drugs.

a)   Define the incremental cost effectiveness ratio (ICER). Use an equation in your answer.
                                                                                                                                                         (2)

Provide examples for the following types of costs:
b)   Direct costs.                                                                                                                     (2)
c)   Resource utilisation costs.                                                                                          (2)
d)   Indirect costs.                                                                                                                  (1)
                                                                                                                                                        [7]

6   You plan to initiate a 32-year-old HIV-positive male patient on efavirenz, tenofovir and emtricitabine antiretroviral therapy and isoniazid prophylaxis. Rapid genotyping testing is done using a cheek swab for DNA prior to treatment initiation. The results show that the patient is a poor *CYP2B6* metaboliser, poor *CYP2A6* metaboliser, and slow *NAT2* acetylator.

Briefly explain the potential clinical consequence should this patient be initiated on treatment.
                                                                                                                                                        [5]

7  a)  Define respect for patient autonomy in clinical research.  (2)
   b)  Provide three obligations of investigators to protect autonomy.  (3)
   [5]

8  Provide two examples of vulnerable research participants and with reasons for your selection.  [4]

9  Evaluating risks and benefits are challenging for Research Ethics Committee (REC) members to review. List 3 principles that will need to be considered when a risk-benefit assessment is being deliberated upon by a REC.  [3]

10  List 5 characteristics that a research protocol would need to comply with to meet the ethical principle of scientific validity.  [5]

11  On 20th of September 2020, Dr. Kolter received a call from a pharmacist regarding a patient known with epilepsy, he had prescribed phenytoin for on the script below.

| **Dr. Kolter, MBChB** |
| HPCSA registration number MP987654 |

32 Core Road
Morningside
Johannesburg

Tel: 012 123 4567

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20 July 2020

Ms Sally Sickly (F)          ID number: 987 654 321
Age 32 years

2 Wild Street
Morningside
Johannesburg

Rx
        Phenytoin 200 mg capsules 12 hourly orally

Diagnosis: Epilepsy

Dr AG Kolter

The pharmacist informed Dr. Kolter that by law she is not allowed dispense the phenytoin and that a new prescription needs to be written. The pharmacist also informed the Dr. Kolter that she has four different products (brands) containing phenytoin and that the patient is insisting on a specific brand. She also pointed out that the script is not meeting all the legal requirements.

   a)  Why did the pharmacist request a new prescription?  (1)
   b)  Indicate how Dr. Kolter should address the pharmacist's requests in the new prescription.  (3)
   [4]

12 A patient is prescribed benzoyl peroxide 5% gel to apply in the morning (Schedule 0) and doxycycline capsules 100 mg daily (Schedule 4) for 3-months for acne vulgaris.
    a) Contrast the differences between Schedule 0 and 4 medicines including the prescribing requirements. (4)

The patient is reviewed after 3-months and referred to a dermatologist who prescribes isotretinoin capsules (Schedule 5).
    b) What is the legal difference between Schedule 4 and Schedule 5 medicines? (2)
                              [6]

13 Briefly describe the aetiology and mechanism of Type 1 allergic drug hypersensitivity reaction and name a typical example of a drug associated with this type of allergic reaction. [3]

14 Briefly describe the mechanism by which paracetamol can cause acute liver cell injury during overdose. [3]

15 What are important aspects of the history that should be elicited to assess a drug hypersensitivity reaction? [3]

16 What is your understanding of a dechallenge-rechallenge testing in the evaluation of a suspected drug hypersensitity reaction and what needs to be considered before initiating dechallenge and rechallenge? [5]

17 List 5 criteria you would use for assessment of causality when assessing a report of a suspected adverse drug reaction. [5]

18 List 5 limitations of randomised controlled trials in characterising the safety profile of chronic medicines. [4]

19 A pregnancy registry is being established to identify adverse outcomes of an antidepressant used during pregnancy. Of interest to the investigators are rates of spontaneous abortion, congenital malformations, and effect on early childhood development. List key elements to include in design in the registry, with reasons. [5]

20    Read the following abstract and the selected results table to answer the questions.

**Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report**

## ABSTRACT
## BACKGROUND
Coronavirus disease 2019 (Covid-19) is associated with diffuse lung damage. Glucocorticoids may modulate inflammation-mediated lung injury and thereby reduce progression to respiratory failure and death.
## METHODS
In this controlled, open-label trial comparing a range of possible treatments in patients who were hospitalized with Covid-19, we randomly assigned patients to receive oral or intravenous dexamethasone (at a dose of 6 mg once daily) for up to 10-days or to receive usual care alone. The primary outcome was 28-day mortality. Here, we report the preliminary results of this comparison.
## RESULTS
A total of 2104 patients were assigned to receive dexamethasone and 4321 to receive usual care. Overall, 482 patients (22.9%) in the dexamethasone group and 1110 patients (25.7%) in the usual care group died within 28 days after randomization (age-adjusted rate ratio, 0.83; 95% confidence interval [CI], 0.75 to 0.93; $P<0.001$). The proportional and absolute between-group differences in mortality varied considerably according to the level of respiratory support that the patients were receiving at the time of randomization. In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81) and among those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94) but not among those who were receiving no respiratory support at randomization (17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.91 to 1.55).
## CONCLUSIONS
In patients hospitalized with Covid-19, the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support.

DEXAMETHASONE IN HOSPITALIZED PATIENTS WITH COVID-19

| Characteristic | Treatment Assignment | | Respiratory Support Received at Randomization | | |
|---|---|---|---|---|---|
| | Dexamethasone (N=2104) | Usual Care (N=4321) | No Receipt of Oxygen (N=1535) | Oxygen Only (N=3883) | Invasive Mechanical Ventilation (N=1007) |
| Age† | | | | | |
| Mean — yr | 66.9±15.4 | 65.8±15.8 | 69.4±17.5 | 66.7±15.3 | 59.1±11.4 |
| Distribution — no. (%) | | | | | |
| <70 yr | 1141 (54) | 2504 (58) | 659 (43) | 2148 (55) | 838 (83) |
| 70 to 79 yr | 469 (22) | 859 (20) | 338 (22) | 837 (22) | 153 (15) |
| ≥80 yr | 494 (23) | 958 (22) | 538 (35) | 898 (23) | 16 (2) |
| Sex — no. (%) | | | | | |
| Male | 1338 (64) | 2749 (64) | 891 (58) | 2462 (63) | 734 (73) |
| Female‡ | 766 (36) | 1572 (36) | 644 (42) | 1421 (37) | 273 (27) |
| Median no. of days since symptom onset (IQR)§ | 8 (5–13) | 9 (5–13) | 6 (3–10) | 9 (5–12) | 13 (8–18) |
| Median no. of days since hospitalization (IQR) | 2 (1–5) | 2 (1–5) | 2 (1–6) | 2 (1–4) | 5 (3–9) |
| Respiratory support received — no. (%) | | | | | |
| No oxygen | 501 (24) | 1034 (24) | 1535 (100) | NA | NA |
| Oxygen only | 1279 (61) | 2604 (60) | NA | 3883 (100) | NA |
| Invasive mechanical ventilation | 324 (15) | 683 (16) | NA | NA | 1007 (100) |
| Previous coexisting disease | | | | | |
| Any | 1174 (56) | 2417 (56) | 911 (59) | 2175 (56) | 505 (50) |
| Diabetes | 521 (25) | 1025 (24) | 342 (22) | 950 (24) | 254 (25) |
| Heart disease | 586 (28) | 1171 (27) | 519 (34) | 1074 (28) | 164 (16) |
| Chronic lung disease | 415 (20) | 931 (22) | 351 (23) | 883 (23) | 112 (11) |
| Tuberculosis | 6 (<1) | 19 (<1) | 8 (1) | 11 (<1) | 6 (1) |
| HIV infection | 12 (1) | 20 (<1) | 5 (<1) | 21 (1) | 6 (1) |
| Severe liver disease¶ | 37 (2) | 82 (2) | 32 (2) | 72 (2) | 15 (1) |
| Severe kidney impairment‖ | 166 (8) | 358 (8) | 119 (8) | 253 (7) | 152 (15) |
| SARS-CoV-2 test result | | | | | |
| Positive | 1850 (88) | 3848 (89) | 1333 (87) | 3416 (88) | 949 (94) |
| Negative | 247 (12) | 453 (10) | 193 (13) | 452 (12) | 55 (5) |
| Test result not yet known | 7 (<1) | 20 (<1) | 9 (1) | 15 (<1) | 3 (<1) |

Table 1. Characteristics of the Patients at Baseline, According to Treatment Assignment and Level of Respiratory Support.*

* Plus–minus values are means ±SD. HIV denotes human immunodeficiency virus, IQR interquartile range, NA not applicable, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.
† There was a significant (P=0.01) difference in the mean age between patients in the dexamethasone group and those in the usual care group, but there were no significant differences between the groups in any other baseline characteristic.
‡ Included in this category were 6 pregnant women.
§ Data regarding the number of days since symptom onset were missing for 4 patients in the dexamethasone group and 13 patients in the usual care group; these patients were excluded from estimates of the median number of days since onset.
¶ Severe liver disease was defined as requiring ongoing specialist care.
‖ Severe kidney impairment was defined as an estimated glomerular filtration rate of less than 30 ml per minute per 1.73 m$^2$.

a) What does "open label" mean? (2)
b) Discuss problems with an open label design. (3)

The "age-adjusted rate ratio" for death in this study overall was 0.83; 95% confidence interval [CI], 0.75 to 0.93; P<0.001).

c) What is a rate ratio? (1)
d) What does "age adjusted" mean? (1)
e) What is a 95% confidence interval? (1)
f) What is your interpretation of the age-adjusted rate ratio for death and 95% confidence interval? (2)
g) With reference to table 1, suggest a reason that the investigators adjusted for age in their analysis. (1)
h) How could the study design have been modified to remove the need for age adjustment? (1)

[12]