UNIVERSITI SAINS MALAYSIA

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PROGRAM SARJANA FARMASI
1993-94

JUN 1994

FCP 556 BIOSTATISTICS AND CLINICAL PHARMACOKINETICS
(2 HOURS)

This examination consists of **two sections** and 48 printed pages.

Section A consists of 50 multiple choice questions.

Section B consists of **two (2)** long questions.

Answer **ALL** questions.

Answers to Section A must be entered into the scripts provided.

...2/-

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Section A

Mark (/) all answers on the opposite space corresponding to a correct or most appropriate answer for each question. Each question has only one correct or most appropriate answer or statement.

1. Which of the following statements regarding results of scientific research is true?

..... (a) They must comform to public expectations.
..... (b) They should not be used to support existing theories.
..... (c) They should be made available for critique and replication.
..... (d) They must be obtained in controlled laboratory situations.

2. If the internal validity of a study is adequate then.....

..... (a) the results will be statistically significant.
..... (b) the study can demonstrate causal effect.
..... (c) the results will be clinically useful.
..... (d) the results can be generalized to other situations.

3. If a well designed study demonstrates a convincing disadvantage of one drug therapy over another but is based on a sample of eight (8) people in the two groups, then the study is likely to have.....

..... (a) high internal and high external validity.
..... (b) high internal and low external validity.
..... (c) low internal and high external validity.
..... (d) low internal and low external validity.

3/-

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4. If a pilot study indicates that the effect is likely to be small in relation to the sampling error then the investigator should.....

..... (a) use a relatively large sample.
..... (b) use a relatively small sample.
..... (c) abandon the research project.
..... (d) use incidental method of sampling.

5. If a study is externally valid then.....

..... (a) it must have been an experiment.
..... (b) quota sampling must have been used.
..... (c) all the subjects in the sample must have been equivalent.
..... (d) its results can be generalised to other equivalent settings.

6. The threats to all the internal validity could be controlled by employing the .....

..... (a) one-shot case study.
..... (b) static group comparison design.
..... (c) one-group , pre-test, post-test design.
..... (d) pre-test, post-test control group design.

7. Which of the following statements regarding representative sample is <u>true</u>?

..... (a) It reflects precisely the crucial dimension of a population.
..... (b) It must be a random sample.
..... (c) It consists of at least 500 cases.
..... (d) It is defined as the inverse of the square root of the sample size.

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8. Which of the following is/are an aim(s) of research planning?

(i) To select an appropriate research strategy.
(ii) To select relevant variables for study.
(iii) To formulate appropriate aims.
(iv) To ignore previous research evidence.

..... (a) (i) and (iii) only.
..... (b) (ii) and (iv) only.
..... (c) (i), (ii) and (iii) only.
..... (d) (iv) only.

9. Which of the following is unique to experimental design?

..... (a) Assignment.
..... (b) Selection of cases to be studied.
..... (c) Definition of population.
..... (d) Participant observation.

10. A 'literature review' .....

..... (a) should include only findings which directly support the hypothesis being investigated.
..... (b) should be a critical review of findings relevant to an investigation.
..... (c) should discredit research findings which are inconsistent with the hypothesis.
..... (d) is a list of research publications relevant to an investigation.

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11. Which of the following statements is true?

..... (a) If a research produces statistically significant results, then its design must have been adequate.
..... (b) The outcome of an investigation can be useful even with a small sample size.
..... (c) Random assignment of subjects to treatment groups ensures that the investigation uncovers causal effects.
..... (d) If an investigation is published in a reputable journal by established investigators then the validity of the investigation can be taken for granted.

12. Which of the following statements is <u>not true</u>?

..... (a) The application of scientific method ensures the validity of a researcher's conclusions.
..... (b) To understand a clinical phenomenon we should review the range of relevant research findings.
..... (c) Disagreements among researchers in an area are useful in generating new hypotheses.
..... (d) Without adequate controls the size of an effect may be difficult to estimate.

13. Which of the following is not the aim of critical analysis of a publication?

..... (a) To identify the internal and external validity of the investigation.
..... (b) To evaluate the planning of the investigation.
..... (c) To identify and attack incompetent researchers in one area of interest.
..... (d) To evaluate the relevance of the results for clinical practice.

14. An incidental sample is.....

..... (a) generally difficult to study.
..... (b) used only in non-experimental investigations.
..... (c) not necessarily biased.
..... (d) the most expensive sampling method.

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15. The improvement observed in a group of patients on a long term treatment study with no control could be attributed to .....

..... (a) the treatment.
..... (b) maturation.
..... (c) history.
..... (d) all of the above.

16. Control group patients who receive inert treatment, yet respond as if they have received real treatment are demonstrating .....

..... (a) external validity.
..... (b) internal validity.
..... (c) placebo effect.
..... (d) regression to the mean.

17. The expectancy effects, where the expectations of the experimenter are conveyed to the experimental subjects is termed a .....

..... (a) placebo effect.
..... (b) Murphey's effect.
..... (c) Rosenthal's effect.
..... (d) Hawthorne's effect.

18. Which of the following statements is <u>true</u>?

..... (a) The dependent variable is the variable measured by the investigator.
..... (b) If in a clinical trial more people die in the control group than in the experimental group, then the investigation lacks internal validity.
..... (c) Ideally, the control group and the experimental group should receive exactly the same treatment.
..... (d) The Hawthorne's effect could be eliminated by blind folding.

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19. Which of the following statements is true?

..... (a) If the researcher can attribute the outcome in a study to the treatment programme employed and not to other factors, then the study is internally valid.
..... (b) In a test of skill that is easily learnt, testing effects are unlikely to be a problem.
..... (c) If a study is internally valid then it must be externally valid.
..... (d) Control groups will eliminate assignment errors.

20. Random assignment of subjects in an experiment is typically employed to.....

..... (a) maximize generality of the results.
..... (b) ensure that the experimental and control group are similar at the outset.
..... (c) minimize Hawthorne's effect.
..... (d) minimize Rosenthal's effect.

21. The placebo effect .....

..... (a) occurs only when studies are not double-blind
..... (b) is another name for relaxed subjects.
..... (c) happens only in drug studies.
..... (d) occurs in experimental as well as control groups.

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22. Which of the following statements regarding study designs is false?

..... (a) Time series designs involve the repeated observation of subjects before and after treatment.
..... (b) An important difference between quasi-experimental and experimental designs is that in the former the subjects are not assigned into treatment groups by the investigators.
..... (c) A quasi-experimental design affords greater control over extraneous variables than an experiment.
..... (d) Quasi experimental designs can involve the production of 'time-series'.

23. In which of the following ways is survey research similar to an experimental research design?

..... (a) The selection of a representative sample from the population.
..... (b) The assignment of subjects into treatment groups.
..... (c) The manipulation of the stimulus by the investigators.
..... (d) All of the above.

24. Which of the following statements is <u>true</u>?

..... (a) The use of correct research methods do not constitute an ethical necessity.
..... (b) A hypothesis is a proposition about the relationship existing between variables or prediction of differences between groups.
..... (c) A research protocol is a summary of the data obtained in an investigation.
..... (d) The population being studied is defined after the sample has been selected.

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25. Which of the following statements regarding quinidine is/are true?

(i) Intramuscular administration may cause pain and muscle damage due to tissue necrosis.
(ii) Quinidine serum concentrations are approximately doubled in hemodialysis patients compared to non-azotemic patients.
(iii) Increased free quinidine concentrations can be seen immediately following an acute myocardial infarction.
(iv) Patients with CHF have increased clearance and a smaller volume distribution.

..... (a) (i), (ii) and (iii) only
..... (b) (i) and (iii) only
..... (c) (ii) and (iv) only
..... (d) (v) only

26. Which of the following statements regarding quinidine is/are true?

(i) Trough serum concentration measurements are generally adequate to provide data for evaluating quinidine kinetics.
(ii) Quinidine can increase the degree of AV block and depress escape rhythms.
(iii) Propanolol causes reduction of hepatic blood flow therefore reducing quinidine clearance.
(iv) Concomitant therapy with digoxin usually produces decreased digoxin concentration due to decreased distribution.

..... (a) (i), (ii) and (iii) only
..... (b) (i) and (iii) only
..... (c) (ii) and (iv) only
..... (d) (iv) only

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27.. Which of the following statements regarding quinidine therapy is/are true?

(i) Concomitant therapy with cimetidine may prolong quinidine half-life by approximately 55% due to decrease in quinidine clearance.
(ii) Quinidine-induced hepatotoxicity is the result of hypersensitivity to the drug.
(iii) Liver function test should be monitored at baseline, then according to patient condition.
(iv) Serum potassium concentration monitoring is not necessary for quinidine therapy.

..... (a) (i), (ii) and (iii) only
..... (b) (i) and (iii) only
..... (c) (ii) and (iv) only
..... (d) (iv) only

28. Which of the following factors causes increased α_1-acid glucoprotein concentration?

..... (a) Pregnancy
..... (b) Cirrhosis
..... (c) Nephritis
..... (d) Pulmonary tuberculosis

29. Which of the following side effects is/are common with lithium therapy?

(i) Slurred speech
(ii) Nausea
(iii) Polyuria
(iv) Weight gain

..... (a) (i), (ii), and (iii) only
..... (b) (i) and (iii) only
..... (c) (ii) and (iv) only
..... (d) (iv) only

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30. Which of the following statements regarding the clinical pharmacokinetic of lithium is/are true?

(i) Lithium is not metabolized but is excreted exclusively by renal route.
(ii) Gastrointestinal absorption of conventional lithium carbonate tablets is virtually complete (95% - 100%).
(iii) In patients with normal sodium balance, lithium clearance is approximately 25% of creatinine clearance.
(iv) Lithium distribution follows a one compartment model and it is imperative that sample for lithium be obtained at least 12 hours after the last dose.

..... (a) (i) and (ii) only
..... (b) (i), (ii) and (iii) only
..... (c) (i), (ii), (iii) and (iv)
..... (d) (iv) only

31. Which of the following range of lithium serum levels is minimally effective for mania?

..... (a) 0.6 - 1.2 mEq/L
..... (b) 0.2 - 0.4 mEq/L
..... (c) 1.0 - 1.5 mEq/L
..... (d) more than 2.0 mEq/L

32. A.L. is a 35 years old, 65 kg, Indian male being treated for acute mania. He is receiving 300 mg of lithium carbonate at 9.00 a.m., 2.00 p.m. and 9.00 p.m. His serum creatinine concentration is 0.9 mg/dl, AL's lithium clearance is

..... (a) 1.6 L/hr
..... (b) 1.0 L/hr
..... (c) 3.0 L/hr
..... (d) 2.2 L/hr

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33. Which of the following factors decrease(s) lithium serum concentration?

(i) Increased cardiac output.
(ii) Decreased sodium intake.
(iii) Acute phase therapy.
(iv) Increased sodium intake.

..... (a) (i), (ii) and (iii) only
..... (b) (i) and (iii) only
..... (c) (ii) and (iv) only
..... (d) (iv) only

34. Which of the following statements regarding quinidine serum assay is/are <u>true</u>?

(i) Spectroscopic method of analysis is highly specific for quinidine.
(ii) Liquid chromatographic method of analysis is able to separate and distinguish quinidine from dihydroquinidine.
(iii) Commercial quinidine immunoassays, Emit and TDX, will be able to differentiate between quinidine and dihydroquinidine.
(iv) O-desmethylquinidine cross-react with quinidine in serum quinidine analysis.

..... (a) (i), (ii) and (iii) only
..... (b) (i) and (iii) only
..... (c) (ii) and (iv) only
..... (d) (iv) only

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35. Which of the following statements regarding quinidine therapeutic drug monitoring is/are true?

(i) Therapeutic range for quinidine is highly dependent on the specificity of the assay used.
(ii) Trough level is more reliable than peak level in quinidine dosage adjustment.
(iii) Steady state concentration of quinidine should be obtained at least one day after the initial therapy.
(iv) Serum quinidine concentration decreases with concurrent administration of cimetidine.

..... (a) (i) and (ii) only
..... (b) (i), (ii) and (iii) only
..... (c) (i), (ii), (iii) and (iv)
..... (d) (iv) only

36. Which of the following statements is/are true regarding excretion characteristic of quinidine?

(i) The excretion of quinidine by the kidneys accounts for 40% to 50% of the dose.
(ii) Quinidine exhibits dose-dependent pharmacokinetic as a result of nonlinear excretion.
(iii) Quinidine is significantly dialyzable by both peritoneal dialysis and hemodialysis.
(iv) Renal excretion occurs by glomerular filtration and is dependent upon the pH of the urine.

..... (a) (i), (ii) and (iii) only
..... (b) (i) and (iii) only
..... (c) (ii) and (iv) only
..... (d) (iv) only

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37. Which of the following sets of quinidine salt - percent of base content is true?

..... (a) Quinidine sulfate - 75%
..... (b) Quinidine gluconate - 62%
..... (c) Quinidine polygalacturonate - 40%
..... (d) Quinidine sulfate - 60%

38. Which of the following sets of drug-monitoring parameters is/are appropriate?

(i) Quinidine - renal function test.
(ii) Quinidine - liver function test.
(iii) Quinidine - ECG.
(iv) Lithium - EEG.

..... (a) (i), (ii) and (iii) only
..... (b) (i) and (iii) only
..... (c) (ii) and (iv) only
..... (d) (iv) only

39. Which of the following causes an increase of more than 50% of lithium elimination?

..... (a) Osmotic diuretics
..... (b) Theophylline
..... (c) Steroid
..... (d) Peritoneal dialysis

40. Which of the following is the bioavailability of slow release lithium preparation?

..... (a) More than 85%
..... (b) Less than 80%
..... (c) 50 - 60%
..... (d) Less than 50%

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41. A pharmacist conducted a study to examine whether the frequency of a prescribing error decreased following the implementation of prescription screening procedures. Data were collected on the number of errors before and after the introduction of the screening procedures. Which of the followings is the most appropriate statistical test for the above study?

..... (a) ANOVA
..... (b) Student's t
..... (c) Chi square
..... (d) Kendall's tau

42. The most common measure of data variation reported in the scientific literature is the .....

..... (a) range
..... (b) standard deviation
..... (c) standard error
..... (d) F statistic

43. Which of the following is a parametric statistic?

..... (a) Pearson r
..... (b) Spearman rho
..... (c) Kendall's tau
..... (d) Mann-Whitney U

44. Which of the following represents a nonparametric alternative to the student's t-test?

..... (a) Kendall's tau
..... (b) Spearman's rho
..... (c) Mann-Whitney's U
..... (d) Point Biseral

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45. Which of the following represents an assumption associated with parametric statistics?

..... (a) There is homogeniety of variance.
..... (b) The measures are continous and of equal intervals.
..... (c) There is normality of data.
..... (d) All of the above assumptions.

46. Which of the following is not a statistic that indicates a relationship between variables?

..... (a) Kendall's tau.
..... (b) Spearman's rho.
..... (c) Chi square.
..... (d) Pearson's r

47. The calculation of the arithmatic mean for a group of data is appropriate for data measured on ..... scales.

..... (a) nominal.
..... (b) ordinal.
..... (c) ratio.
..... (d) interval.

48. The most common statistic that is reported with data measured on the nominal scale is the

..... (a) median.
..... (b) mean.
..... (c) frequency.
..... (d) quartrille.

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49. Which of the following statements regarding the use of folinic acid rescue is true?

..... (a) Rescue should be started 1 hour prior to the dose of methotrexate.
..... (b) A dose of 15 mg/m^2 is recommended in all cases.
..... (c) Rescue could be terminated once the methotrexate levels fall below 0.2×10^{-7} Molar.
..... (d) Rescue should be terminated after 48 hours of methotrexate infusion.

50. Which of the following statements regarding the pharmacokinetic of methotrexate is true?

..... (a) The half life of methotrexate is dependent on the liver function of the patient.
..... (b) The absorption of methotrexate from gastrointestinal tract is relatively poor and erratic.
..... (c) Leucoverine rescue is used to accelerate methotrexate elimination.
..... (d) Approximately 50% of the methotrexate in the blood is bound to albumin.

(50 marks)

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Section B

Question 1

A 52 year old female was admitted to HUSM for the complaints of fever, polyurea and dysuria of three days duration. On physical examinations, the following findings were noted:

General condition: four

Vital sign: pulse 102/minute, regular
BP 130/100 mmHg
Temperature - 38.5°C

Chest: coarse crepitation especially on LLL

CVS: DRNM

KUT: Positive for renal punch.

Other systems: no abnormalities were detected.

Initial laboratory tests reveeled the following results:
Blood hrca-8.9 mmol/L; Sodium-140 mmol/L; Potassium-3-9 mmol/L.

Numerous pus cells was noted on U/FEME but there was no RBC or cast.
A provisional dignosis of fever with pylonephritis was made and it was decided that the patient be started with ampicillin IV 500 mg OLD, and gentamicin IV 80 mg tDs.

(A) What do you predict the maximum and minimum concentrations to be for gentamicin for the above patient. (Assume V_d = 0.25 L/kg, k_e = 0.333 hr^{-1}).

(5 marks)

Three days after gentamicin therapy was initiated, blood was obtained for serum concentration determination. Results obtained were as in the attached TDM form.

...19/-

(B) Calculate the following pharmacokinetic parameters for the above patient.

(i) Rate constant of elimination, k_e
(ii) Plasma half-life, $t^{1/2}$
(iii) Maximum plasma concentration, C_{max}
(iv) Minimum plasma concentration, C_{min}
(v) Apparent volume of distribution, V_d
(vi) Apparent plasma clearance, Cl

(6 marks)

(C) Discuss factors which have been described to alter the pharmacokinetics of gentamicin.

(10 marks)

(D) What is your recommended dose of gentamicin for the above patient to achieve a C_{max} of 5-8 mg/l and a C_{min} of 1-2 mg/l?

(4 marks)

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Question 2

Drug XYZ is a new non-steroidal anti-inflammatory drug recently introduced into the malaysian market. A few reports of acute renal failure has been reported in patients taking the drug. The DCA is interested in carrying out a study to determine the relationship between drug XYZ and acute renal failure. You have been called to provide assistance in designing the study.

(A) DCA wants to know if they should conduct a randomised clinical trial, a case-control study or cohort study. Explain what these studies are and highlight the advantages and disadvantages of each.

(15 marks)

(B) Recommend an appropriate study. Explain the steps involved in carrying out the study.

(7 marks)

(C) Show how you would be able to determine the relative risk for the development of ARF associated with the drug based on the method that you recommend.

(3 marks)

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B

REQUEST FOR TDM/DRUG CONCENTRATION MEASUREMENT

PLEASE FILL FULLY

Name: RBJ R/N: 000000 Ward: 7U
Weight (Kg): 44 kg Height (cm/inches): 156 cm Sex: M/F F Age: 52
Clinical Diagnosis: Pyelonephritis with fever
Concurrent illness (Please circle appropriately): CCF/COPD/Renal Impairement/Liver Disease/Edema/Smoker
Laboratory indices and Concurrent Drug(s)

	Date	Result
Blood urea	1/1/93	8.9
Potassium		3.9
Creatinine		not done

Concurrent Drug (s):
1. Ampicillin 500 mg QID
2. _____
3. _____
4. _____

Drug Requested	Date Started	Dose/Frequency/Route
Gentamisin	30/12/93	80 mg Q 8H IV

Blood sampling:

Date	Time Last dose	Time Sample (PRE)	Time Last dose	Time Sample (POST)
1/1/94	2400 (31/12/93)	0745	0800 (1/1/94)	0900

Reason For Request (Please circle)
(1) TDM 2. Suspected Toxicity 3. ? Compliance 4. Other: _____
Impression of Clinical Response to Drug Requested (Please tick):
1. No/Inadequate (2) Good 3. Unknown 4. Other: _____
Name of Requesting Doctor and Bleeper Number: Noraini D.D

PERKHIDMATAN FARMAKOKINETIK & TOKSIKOLOGI

Name: RBJ R/N: 000000 Ward/Unit: 7U Drug: Gentamicin
Date: 1/1/94

Time Sample	Result	Desired Concentration
0745	14.2 mg/l	
0900	18.4 mg/l	

Calculations:

	Calculated	Expected
K_e		
V_d		
Clearance		

Assessment

Recommendation:

337

Nama Pegawai & Tandatangan