UNIVERSITI SAINS MALAYSIA

PEPERIKSAAN PERTAMA
PROGRAM SARJANA FARMASI
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FCP 556:BIOSTATISTICS, STUDY DESIGN AND CLINICAL PHARMACOKINETICS

(2 HOURS)

This Examination consists of **two sections**.

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

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SECTION (A)

1. Which of the following is an appropriate statistical test to compare three independent samples, the dependent variable of which is on a ratio scale?

..... (a) Chi-square test

..... (b) Mann-Whitney U

..... (c) t-test

..... (d) ANOVA (analysis of variance)

2. Which of the following is a non-parametric test?

..... (a) ANOVA (analysis of variance)

..... (b) t-test

..... (c) z-test

..... (d) Kruskal-Wallis H.

3. Which of the following is true regarding the selection of an appropriate statistical test?

..... (a) z-test should be used as it is most powerful

..... (b) t-test should be used as it takes the sample size into account

..... (c) the choice depends on the design of the study

..... (d) chi-square test should be avoided for nominal data.

4. Which of the following statements is/are true?

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(i) The selection of descriptive and inferential statistics is independent of the scaling of the data

(ii) Inferential statistics should be used, regardless of the nature and aims of the investigation

(iii) It is impossible to select an appropriate statistical test before the data is collected

(iv) The number of groups being compared in an investigation influences the selection of the appropriate statistical test.

..... (a) (i) and (iii) only

..... (b) (ii) and (iv) only

..... (c) (i), (ii) and (iii) only

..... (d) (iv) only.

5. Which of the following tests is appropriate for analyzing data where 3 or more groups were used?

..... (a) z-test

..... (b) t-test

..... (c) Sign test

..... (d) Chi-square test.

6. In a study there was a 1% difference in improvement of systolic pressure for two groups of patients receiving different treatments. This was statistically significant at

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P=0.05. The results probably demonstrate:

..... (a) clinical and statistical significance for the difference

..... (b) clinical significance only

..... (c) statistical significance only

..... (d) neither clinical nor statistical significance.

7. Which of the following is likely for the results in a study if the effect of size is large?

..... (a) clinically and statistically significant for the difference

..... (b) clinically significant only for the difference

..... (c) statistically significant only for the difference

..... (d) neither clinically nor statistically significant for the difference.

8. Which of the following is/are considerations for the selection of an appropriate statistical test?

(i) The scale of measurement

(ii) Measurements from independent subjects or repeated in the same subject

(iii) The number of groups studied

(iv) Sample size.

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..... (a) (i) and (iii) only

..... (b) (ii) and (iv) only

..... (c) (i), (ii) and (iii) only

..... (d) (iv) only.

9. An investigation generated some interesting findings but the investigators used an inappropriate statistical test. You should .....

(i) regretfully discard the study as useless

(ii) reanalyse the data from the descriptive statistics provided

(iii) accept it as a human error

(iv) write to the investigators for their raw data and reanalyse it yourself.

.....(a) (i) and (iii) only

.....(b) (ii) and (iv) only

.....(c) (i), (ii) and (iii) only

.....(d) (iv) only.

10. Which test is appropriate to analyse a study comparing two independent samples where the dependent variable is on an ordinal scale?

.....(a) chi-square test

.....(b) Mann-Whitney U

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.....(c) t-test

.....(d) Wilcoxon test.

11. Which of the following is not important in the selection of a theophylline product, dose, and dosing interval?

..... (a) The objective: treatment of acute symptoms or maintenance of prophylactic therapy

..... (b) The absorption characteristics of the formulation

..... (c) The individual variations in the volume of distribution of theophylline

..... (d) The rate of elimination of the drug in the individual patient.

12. Which of the following can explain the failure of theophylline therapy when the serum level is therapeutic?

(i) Presence of irreversibility of airways obstruction

(ii) Possibility of theophylline hypersensitivity

(iii) Concurrent infection

(iv) Possibility of overdose.

..... (a) (i) and (iii) only

..... (b) (ii) and (iv) only

..... (c) (i), (ii) and (iii) only

..... (d) (iv) only.

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13. Which of the following combinations is not true?

..... (a) Phenytoin - increased theophylline metabolism

..... (b) Cirrhosis - increased theophylline clearance

..... (c) Severe airway destruction - decreased theophylline clearance.

..... (d) Pneumonia - decreased theophylline clearance.

14. Which of the following is/are disadvantage(s) of the steady-state method of theophylline dosing?

(i) Exposure of patients to sub therapeutic or excessive theophylline concentrations

(ii) It assumes no change in underlying disease states

(iii) It assumes first-order kinetics for theophylline

(iv) It needs multiple serum samples.

..... (a) (i) and (iii) only

..... (b) (ii) and (iv) only

..... (c) (i), (ii) and (iii) only

..... (d) (iv) only.

15. Which of the following does not significantly interact with theophylline?

..... (a) Cimetidine

..... (b) Metoprolol

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..... (c) Influenza A vaccine

..... (d) Phenytoin.

16. Which of the following is true?

..... (a) C_{max} after an IV bolus dose is affected by the half life of the drug

..... (b) Amount of drug in the body after an IV injection is linearly related to plasma concentration

..... (c) The unit for clearance is HOUR

..... (d) The half life of a drug usually changes with dose.

17. Which of the following is a true statement?

..... (a) Absorption of theophylline in a slow release formulation follows a first order process

..... (b) The rate of administration after an IV constant rate infusion can be described by a first order process

..... (c) Metabolism of phenytoin occurs via a zero order process

..... (d) hydrolysis of aspirin is an example of a zero order process.

18. Which of the following statements is/are true?

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..... (a) Pharmacokinetics is the study of the effect of drugs on the body

..... (b) Bioavailability studies are also considered in pharmacokinetics

..... (c) The human body can be described as comprising of one central (plasma) compartment and another peripheral (tissue) compartment

..... (d) The transfer of drug from the blood into the tissues account for the loss of drug from the plasma.

19. Fitting into a curve the plasma ticarcillin concentration versus time after a 5g IV dose yielded the following equation.

$C = (370\ \mu g/ml)\ e^{-(0.614/h)t}$

Which of the following conclusion is true?

..... (a) the ticarcillin decay in the plasma follows a biexponential disposition

..... (b) half life for ticarcillin in this patient = 0.614 h

..... (c) ticarcillin should not be given every 6 hourly because it accumulates rapidly

..... (d) if 2 g IV is given, the C_{max} = 148 mg/L.

20. Fitting into a curve, the plasma theophylline versus

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time after a 200 mg IV dose yielded the following equation

$C = (4.70 \text{ ug/ml})\ e^{-(2.07/h)t} + (8.18 \text{ ug/ml})\ e^{-(0.18/h)t}$

Which of the following conclusion is true?

..... (a) the theophylline decay in the plasma follows a biexponential disposition

..... (b) half life for theophylline in this patient is 0.18 h

..... (c) theophylline should not be given 6 hourly because it accumulates rapidly

..... (d) if 400 mg IV is given, the C_{max} = 16.36 mg/L.

21. Which of the following is/are true regarding a constant rate infusion?

(i) The plasma drug level will increase until it reaches infinity

(ii) When plasma concentration C^{ss}, the rate of administration total body clearance

(iii) At steady state, the rate of administration = rate of elimination

(iv) Plasma concentration is inversely related to the rate of infusion.

..... (a) (i), (ii), (iii) and (iv)

..... (b) (ii) and (iii) only

..... (c) (iii) and (iv) only

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..... (d) (iv) only.

22. Which of the following is/are true regarding the aim(s) of research planning?

(i) To generate appropriate aims or clear-cut research hypothesis
(ii) To select an appropriate research strategy
(iii) To identify possible ethical or economics limitations in conducting the investigations
(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.

23. Which of the following is/are true?

(i) A hypothesis is a proposition about the relationship between variables or prediction of differences between groups
(ii) The use of correct research methods does not constitute an ethical necessity
(iii) Some scientific research projects do not involve the testing of hypothesis
(iv) A population being studied is defined after the sample

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has been selected.

..... (a) (i) and (iii) only

..... (b) (ii) and (iv) only

..... (c) (i), (ii) and (iii) only

..... (d) (iv) only.

24. Which of the following is/are true?

(i) If the sample size is halved, the sampling error is doubled

(ii) If a sample is large (say n 500) the sample is representative

(iii) If a population contain 50% males and 50% females, and our sample is 10% males and 90% females, the sample is said to be biased

(iv) The basic idea underlying sampling is to select a representative sample.

..... (a) (i) and (iii) only

..... (b) (ii) and (iv) only

..... (c) (i), (ii) and (iii) only

..... (d) (iv) only.

25. Which of the following is common to both experimental and non-experimental research strategies?

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..... (a) Assignment

..... (b) Selection of cases to be studied

..... (c) Participant observation

..... (d) Field research.

26. Which of the following is unique to the experimental research strategy?

..... (a) Assignment

..... (b) Selection of cases to be studied

..... (c) Definition of population

..... (d) Field research.

27. If, after a twelve month program, a group of children with reading problem had improved their reading ages by an average of nine months, a viable alternative explanation for the results other than effectiveness of the program would be .....

..... (a) regression to the mean

..... (b) maturation

..... (c) history

..... (d) assignment error.

28. If a well designed study demonstrates a convincing advantage of one therapeutic technique over another but is based on a sample of five people in the two groups, the study is likely to have.....

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..... (a) high internal and low external validity

..... (b) high external and low internal validity

..... (c) low internal and external validity

..... (d) high external and internal validity.

29. Patients who receive inert treatment in a control comparison group, but respond as if they receive real treatment are demonstrating.....

..... (a) the placebo effect

..... (b) external validity

..... (c) internal validity

..... (d) regression to the mean.

30. The placebo effect

..... (a) occurs only in drug studies

..... (b) occurs in experimental as well as control groups

..... (c) is another name for relaxing subject

..... (d) occurs only if you don't have double blinding.

31. Which of the following is most representative of a placebo effect?

..... (a) Headache is reduced when an antidepressant is administered.

..... (b) Headache is reduced one second after swallowing an analgesic.

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..... (c) Headache is increased after a fierce argument with the boss.

..... (d) Headache is decreased after the use of biofeedback.

32. Which of the following is/are true?

(i) A quasi-experimental design does not permit the investigator to control the time at which a treatment is introduced or withdrawn.

(ii) Time-series designs involve the repeated observation of subjects before and after treatment.

(iii) A quasi-experimental design afford greater control over extraneous variables compared to an experiment.

(iv) An important difference between experimental and quasi-experimental designs is that in a quasi-experimental study the subjects are not assigned into treatment groups by the investigators.

..... (a) (i) and (iii) only

..... (b) (ii) and (iv) only

..... (c) (i), (ii) and (iii) only

..... (d) (iv) only.

33. An appropriate design for an investigation will be one which.....

..... (a) minimize all possible sources of error

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..... (b) is experimental

..... (c) give you the answer you expect

..... (d) use sophisticated instrumentation.

34. Which of the following statements is/are true?

(i) Statistical procedures can be used to aid the researcher in choosing an adequate sample size.

(ii) Given that a placebo is an inert substance, its administration has no effects on the subject behaviors.

(iii) The effects of subject and experimenter expectancies is reduced by blinding.

(iv) The random assignment of subject in always preferable to assignment by matching.

..... (a) (i) and (iii) only

.... (b) (ii) and (iv) only

.... (c) (i), (ii) and (iii) only

.... (d) (iv) only.

Questions 35 - 37 refer to the following case.

A researcher is studying the effect of a new drug on healing of ulcers. Patients are assigned randomly, by the physician who treats them, to receive either the standard treatment or the new drug. Patients are informed that they are being

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studied, but they do not know which treatment they are getting. The measure of rate of healing is the number of days until the ulcer is completely healed.

35. Which of the following is the independent variable in the study?

..... (a) Ulcers

..... (b) The new drug

..... (c) Type of treatment

..... (d) Rate of healing.

36. Which of the following is the dependent variable?

..... (a) Ulcer

..... (b) The new drug

..... (c) Type of treatment

..... (d) Rate of healing.

37. This study is .....

..... (a) double blind because the patients do not know the treatment they get.

..... (b) double blind because neither the researchers nor the patients know the treatment.

..... (c) single blind because only the patient and the physician who know which treatment is given.

..... (d) non-blinded as the patients know they are being studied.

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38. Which of the following is true regarding post antibiotic effect of aminoglycosides?

..... (a) It is the toxic effect associated with high post aminoglycoside concentrations.

..... (b) It correlates with the extent of peak concentration above the minimum inhibitory concentration.

..... (c) It is the toxic effect associated with high pre aminoglycoside concentration.

..... (d) It can be prevented by giving single daily doses.

39. Which of the following is/are true regarding drug metabolism?

(i) Administration of phenobarbitone to a pregnant mother may result in increased drug metabolism in neonates.

(ii) Antipyrine is not useful as a model to estimate hydroxylation kinetics of drugs.

(iii) Rifampicin is a metabolic inducer.

(iv) Non-linearity is seen with phenytoin kinetics at therapeutic doses.

..... (a) (i) only

..... (b) (i) and (ii) only

..... (c) (i), (ii) and (iii) only

..... (d) (i), (ii), (iii) and (iv).

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40. Which of the following contributes to the variability in phenytoin plasma concentrations?

(i) Nonlinear kinetics
(ii) Bioavailability
(iii) Drug Interactions
(iv) Non compliance.

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

41. Which of the following influences theophylline metabolism?

(i) Age
(ii) Weight
(iii) Diet
(iv) Cigarette smoking.

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

...20/-

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42. Which of the following is/are true regarding digoxin pharmacokinetics?

(i) The time course of digoxin following an intravenous administration follows a biexponential equation.
(ii) Digoxin is actively absorbed from the intestine.
(iii) When changing from a tablet to an elixir dosage form of digoxin, the dose should be reduced.
(iv) Digoxin is completely renally excreted.

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

Question 43 - 45 refer to the following case

In a study involving 20 patients given 500 mg oral theophylline, plasma sample were obtained at 0.5, 1, 2, 4, 8, 16, 24 hour post dose. The results were then pooled and analysed using a 2- compartment open model to derive population pharmacokinetic parameters for theophylline.

43. The design of the study is called ....
..... (a) The naive pooled approach
..... (b) Bayesian fitting
..... (c) Standard two-steps method

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..... (d) Population optimization.

44. The study would ...

(i) yield a very good estimate of V_d, k_e and Cl for the population studied.

(ii) yield a very good estimate of oral bioavailability of theophylline.

(iii) be useful in estimating dosage regimens for neonatal apnea.

(iv) be meaningless and should be thrown away.

..... (a) (i) and (ii) only

..... (b) (i), (ii) and (iii) only

..... (c) (iii) only

..... (d) (iv) only

45. The study ...

(i) suffers from lack of a control group

(ii) should be reanalysed using the standard two stage method.

(iii) will underestimate k_e if $k_a < k_e$

(iv) should not have been done at all

..... (a) (i) and (ii) only

..... (b) (i), (ii) and (iii) only

..... (c) (iii) only

..... (d) (iv) only.

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46. Which of the fcllowing is not an observational study design used in epidemiological research?

..... (a) cross-sectional study
..... (b) randomised trial
..... (c) cohort study
..... (d) case-control.

47. Which of the following is/are features of a good clinical trial ?

(i) Randomization
(ii) Blinded
(iii) Prospective
(iv) Retrospective.

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

48. Which of the following is not a limitation of clinical trials?

..... (a) they are not exploratory
..... (b) they require extensive planning

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..... (c) they are concentrated on expected therapeutic effects and adverse reactions

..... (d) none of the above.

49. Which of the following is/are feature(s) of a "Cohort Studies"?

(i) Groups of individuals are randomised into drug and placebo treated groups.

(ii) Investigator has no control over who receives what kind of drug.

(iii) The study can only be done prospectively.

(iv) Groups of individuals are identified, characterised and followed over time.

..... (a) (i) and (iii) only

..... (b) (ii) and (iv) only

..... (c) (i), (ii) and (iii) only

..... (d) (iv) only.

50. A study in which drug exposure and disease status or symptoms are determined at the same point in time is called a ....

..... (a) case-control study

..... (b) cohort study

..... (c) cross-sectional study

..... (d) clinical trial

(50 marks)

SECTION (B)

1. (A) Discuss the processes involved in planning a clinical research project and the guidelines useful to avoid the common pitfalls of conduct research in the clinical setting.

(15 Marks)

(B) A researcher wishes to study the effectiveness of a new anti-arthritic drug. The population of interest are patients diagnosed as having arthritis in a clinic at a general hospital. A number of arthritic symptoms are to be assessed using a checklist of seven items.
Design a method of assessment using a checklist of seven items.
Design a method of true experimental design for this research to minimise the threats to internal validity.

(10 Marks)

2. The following data was obtained after a rapid IV bolus injection of 100 mg gentamicin in a 45 year old male weighing 50 kg.

Time after dose (h)	Plasma Concentration (µg/ml)

0.5	7.66
2.5	6.44
4.0	5.65
8.0	4.00
12.0	2.82

Assuming monoexponential decay :

A) Graphically estimate the relevant pharmacokinetic parameters for this patient

(5 Marks)

(B) Design a dosage regimen for this patient to achieve a peak plasma gentamicin concentration of 8 µg/ml and a trough concentration of less than 2 µg/ml.

(5 Marks)

(C) Explain your assumptions made in arriving at (B)

(5 Marks)

(D) Describe a protocol that you would use to determine population pharmacokinetic parameters for gentamicin in your hospital patients.

(10 Marks)

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