# 國立臺灣大學99學年度碩士班招生考試試題



請寫出計算過程

1. The disposition kinetics of a new angiotensin receptor antagonist used for hypertension treatment follows a one compartment model. The serum concentrations were 10 ug/mL and 5 ug/mL at 4 h and 8 h after 0.5 mg intravenous bolus administration, respectively, in human. Please answer the following questions carefully. **(20 points)**

   a. What is the elimination constant of this drug?

   b. How long does it take for 87.5% of an intravenous bolus to be eliminated?

   c. How long does it take to remove 0.375 mg following a 0.5 mg bolus dose?

   d. Is it appropriate for complete urine collection up to 24 h in order to provide a good estimate of the ultimate amount of drug excreted unchanged? And also give the reason.

   e. Is it correct that the fraction of the administered dose eliminated by a given time is dependent of the size of the dose? Please write down your reason.

2. A newly recombinant protein with polyethylene glycol modification was used to treat a malignant patient after single intravenous and subcutaneous administration of 20 unit/kg on separate occasions. The following table lists some finding in a patient with body weight 40 kg. **(15 points)**

| Rout | Tmax | Cmax (unit/L) | AUC (unit-h/L) | Terminal t1/2 (h) |
|---|---|---|---|---|
| Intravenous | 5 min | 385 | 2500 | 34.6 |
| Subcutaneous | 12 h | 37.5 | 1500 | 55.3 |

   a. What are the clearance and volume of distribution of this drug?

   b. What is the bioavailability of this drug after subcutaneous dose? How do you explain this observation?

   c. What is the factor affecting the lower Cmax after the subcutaneous dose other than its bioavailability?

3. An anti-arrhythmic drug following one-compartment kinetics was administered as an intravenous bolus of 500 mg followed immediately by a constant infusion of 20 mg/h for the duration of the stay. The plasma concentrations were 20 mg/L, 15.2 mg/L, 9.6 mg/L, 8 mg/L, and 8 mg/L at 0 h, 5 h, 20 h, 50 h, and 60 h, respectively. Please estimate the values of volume distribution, half-life, and clearance of this drug. **(15 points)**

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4. A drug (100 mg) was administered by rapid IV injection to a 70-kg healthy adult male. Blood samples were taken periodically after the administration of drug, and the plasma fraction of each sample was assayed and listed in the table:

| Time (hr) | Plasma concentration (μg/ml) |
|---|---|
| 0.25 | 43 |
| 0.5 | 32 |
| 1 | 20 |
| 1.5 | 14 |
| 2 | 11 |
| 4 | 6.5 |
| 8 | 2.8 |
| 12 | 1.2 |
| 16 | 0.52 |

   a. Estimate the equation that can describe the plasma concentration change of this drug **(10 points)**

   b. Explain the equation in question 1a **(5 points)**

5. Population pharmacokinetic analysis is frequently used in clinical drug study. Please describe how to perform the analysis of population pharmacokinetic data **(5 points)**

6. It is known that drug-A is metabolized by CYP2C19. The AUC and AUMC values of drug-A (I.V. bolus, 5 mg) are 278 μg-hr/L and 1390 μg-hr$^2$/L, respectively. Assuming this drug follows one-compartment model.

   a. Calculate the volume of distribution at steady-state (Vdss) of this drug **(5 points)**

   b. Is there a decrease in hepatic clearance of drug-A in a patient who is a CYP2C19 poor metabolizer? Why? **(5 points)**

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7. The following figure describes the plasma concentrations of drug A in a male patient after oral administration.

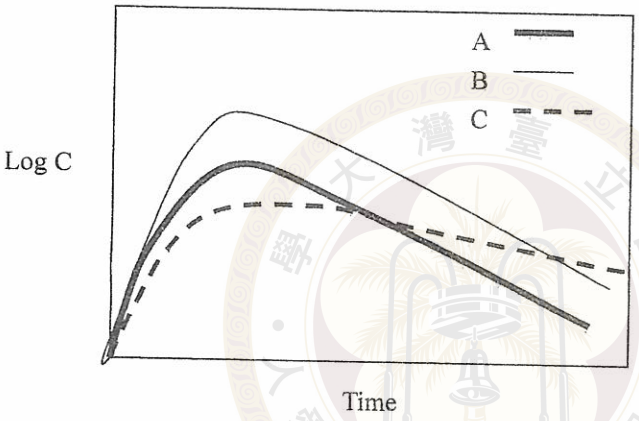
   Line A represents the concentrations of drug A when it was given alone.

   Line B represents the concentrations of drug A when it was concomitantly used with drug B.

   Line C represents the concentrations of drug A when it was concomitantly used with drug C.

   a. Please explain the change of pharmacokinetic parameters and effects of drug B on the pharmacokinetics of drug A. **(5 points)**

   **b.** Please explain the change of pharmacokinetic parameters and effects of drug C on the pharmacokinetics of drug A. **(5 points)**




8. Please explain the pharmacokinetic parameters listed in the following table **(5 points)**

**Table I.** Pharmacokinetic parameters for imatinib 400mg in patients with chronic myeloid leukaemia on day 1 and at steady state (reproduced from Peng et al.,[94] with permission from the American Society of Clinical Oncology)[a]

| Parameter | Day 1 of administration | Steady state (day 28) |
|---|---|---|
| $C_{max}$ (ng/mL) | 1907.5 ± 355.0 | 2596.0 ± 786.7 |
| $t_{max}$ (h) | 3.1 ± 2.0 | 3.3 ± 1.1 |
| $AUC_{24}$ (μg • h/mL) | 24.8 ± 7.4 | 40.1 ± 15.7 |
| $AUC_{\infty}$ (μg • h/mL) | 38.8 ± 15.9 | 81.9 ± 45.0 |
| $t_{1/2\beta}$ (h) | 14.8 ± 5.8 | 19.3 ± 4.4 |
| CL/F (L/h) | 12.5 ± 7.2 | 11.2 ± 4.0 |
| $V_z$/F (L) | 236.0 ± 76.5 | 295.0 ± 62.5 |
| Trough concentration (ng/mL) | Not calculated | 1215.8 ± 750.2 |
| Time above 1 μmol/L (h) | Not calculated | 49.3 ± 17.1 |

9. The followings describe the relationship among three pharmacodynamic parameters and the number of *Klebsiella pneumoniae* (indicated by CFU) in the lungs of neurotroponic mice after 24-hr therapy with cefotaxime.

Please describe the these findings and the PK/PD properties of cefotaxime **(5 points)**

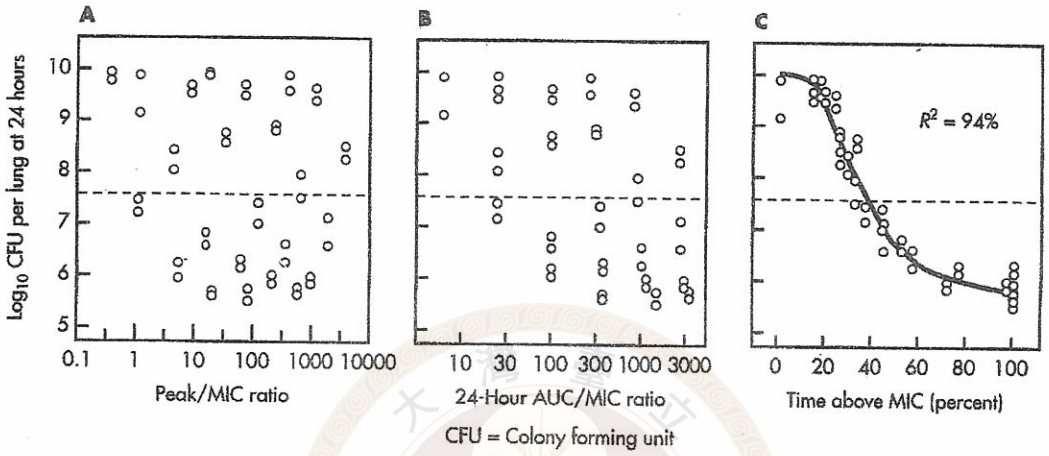



**Figure 19-9.** Relationship between three pharmacodynamic parameters and the number of *Klebsiella pneumonia* in the lungs of neurotroponic mice after 24-hr therapy with cefotaxime. Each point represents one mouse.
From Craig WA, 1995, with permission.