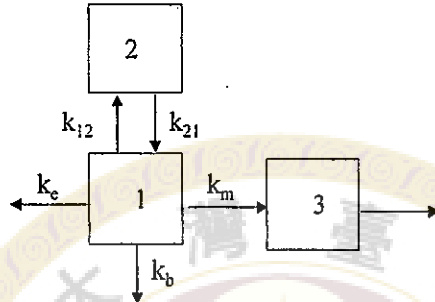


1. A drug is eliminated by renal excretion (k_e), biliary excretion (k_b), and drug metabolism (k_m). In terms of compartment model, the pharmacokinetics of this drug can be described by the following model (compartment 1 is the central compartment):



- (a) Draw a plasma drug concentration versus time profile that fits this model. (the Y-axis is in log scale) (5 分)
- (b) Write an equation that describes the rate of change of drug concentration (dC/dt) in compartment 1. (5 分)

2. A female patient (35 years old, 65 kg) with normal renal function is to be given a drug by IV infusion. The elimination rate constant of this drug is 0.1 hr^{-1} and the apparent volume of distribution is 15 Liter. The pharmacokinetics of this drug assumes a first-order process. The desired steady-state plasma level for this drug is $10 \mu\text{g/ml}$.

- (a) Without loading dose, how long after the start of the IV infusion would it take to reach 95% of the C_{ss} ? (5 分)
- (b) If the total body clearance declined 50% due to partial renal failure, what is the new infusion rate to maintain the desired C_{ss} ? (5 分)

3. An antibiotic is given by IV bolus injection at a dose of 500 mg. The apparent volume of distribution was 21 Liter and the elimination half-life was 6 hours. Urine was collected for 48 hours, and 400 mg of unchanged drug was recovered.

- (a) Calculate hepatic clearance (CL_h) (5 分)
- (b) Explain whether there are renal excretion or reabsorption of this drug. (5 分)

4. Describe the application of population pharmacokinetics in drug development. (10 分)

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5. In order to estimate the renal clearance of a drug in a patient, a 2-hour postdose urine sample was collected and found to contain 200 mg of drug. A midpoint plasma sample was taken (1 hour postdose) and the drug concentration in plasma was found to be 25 $\mu\text{g}/\text{ml}$. Estimate the renal clearance for this drug in the patient. (5 分)

6. Four drugs given in a single intravenous bolus of 280 mg to healthy volunteers separately. The plasma drug concentration data can be described by the following equations. Which drug has the largest volume of distribution? (5 分)

- (a) The plasma concentration of drug-A can be described by $C = 78 e^{-5t}$
- (b) The plasma concentration of drug-B can be described by $C = 39 e^{-5t}$
- (c) The plasma concentration of drug-C can be described by $C = 150 e^{-5t}$
- (d) The plasma concentration of drug-D can be described by $C = 78 e^{-2t}$

7. The f_u values of drug-A, drug-B, drug-C and drug-D are 0.47, 0.3, 0.07 and 0.62, respectively. Explain which drug might be predicted to cause an adverse response in a patient that has severe hepatic disease. (5 分)

8. Explain why does a drug ($F = 0.15$) demonstrate greater differences between patients after oral administration than after intravenous administration (10 分)

9. An adult male (73 years, 65 kg) with diabetes mellitus is placed on hemodialysis. His residual creatinine clearance is $< 5 \text{ ml}/\text{min}$. The patient is given tobramycin at a dose of 1 mg/kg by IV bolus injection. Tobramycin is 90% excreted unchanged in the urine and is less than 10% bound to plasma proteins. The elimination half-life of tobramycin is 2.2 hours in patients with normal renal function. In this patient, tobramycin has an elimination $t_{1/2}$ of 50 hours during the interdialysis period and an elimination $t_{1/2}$ of 8 hours during hemodialysis. The apparent V_d for tobramycin is 0.33 L/kg. For this patient, calculate the plasma drug concentration just after the end of hemodialysis. (15 分)

$$(e^{-1.368} = 0.25 ; e^{-0.693} = 0.5 ; e^{-0.3465} = 0.7 ; e^{-0.0866} = 0.917)$$

10. Describe the roles of membrane transporters in ADME drugs. (20 分)