PHA 5127 Dose Optimization I

Case Study VI

1. A hypertensive patient is going to receive long-term medication of drug A. Drug A can only be administered via IV-bolus injection due to its low oral bioavailability. The volume of distribution and clearance of drug A are 120 L and 10 L/h, respectively. Drug A's plasma protein binding is 30%. Drug A is known to show severe side effects if its free plasma concentration is higher than 5µg/mL. In order to avoid these side effect and to reach an antihypertensive effect, the Drug A's maximum free drug concentration at steady state should be 20% less than 5µg/mL. The patient has agreed to come twice a day to hospital for the administration of the drug. The physician asks you as a clinical pharmacist to calculate the dose that should be administered to the patient. Which assumptions did you make to ensure that your calculations are valid?

2. Another patient receives the same drug (drug A) as a single-dose IV-bolus injection to treat his hypertensive crisis. A metabolite of drug A is known to counteract the effect of another drug that the patient receives. Thus, a physician asks you as a clinical pharmacist to predict the plasma concentration of the metabolite 6 hours after the administration of the drug A. Assume that 500 mg of drug A will be administered and that the elimination rate constant of the metabolite after IV-bolus injection is 5 h^{-1} (k_{met} = 0.04 h^{-1}, VD_M = VD).

   Calculate the total amount of metabolite that has been eliminated. Assume the metabolite is solely cleared by the kidney (no further metabolism).

   Sketch a semi-logarithmic plot of the plasma concentration time profile of drug A and its metabolite.

   Would this sketch change tremendously if the elimination rate constant of the metabolite was doubled? If yes, sketch the new semi-logarithmic plot of the plasma-concentration-time-profile.

3. A company has invented a formulation technique that has increased the oral bioavailability of drug A to 15%. Due to this new possibility two differently formulated tablets have come on the market. The absorption rate constants of formulation FAST and SLOW are 1 h^{-1} and 0.02 h^{-1}, respectively. Plot the concentration-time-profile from 0-24 h for both formulations. Which formulation shows a "flip-flop"-kinetic?

4. TRUE (T) or FALSE (F)

For multiple-dosing, the free plasma concentration at steady state is always dependent on the clearance of the drug

T F

It generally takes about five half-lives for a drug to be cleared from the body after steady state has been reach.

T F

For multiple-dosing, the peak-through-fluctuation is independent of the dose only after oral administration of the drug

T F

The average concentration at steady state can be calculated as

$$\frac{Dose}{VD * F}$$

T F

For a one compartment body model and oral administration, K_e cannot be calculated as

$$\frac{C_0}{AUC_\infty}$$

T F

After oral administration, T_{max} can always be calculated as

$$\frac{ln\left(\frac{k_e}{k_a}\right)}{k_e - k_a}$$

T F