

PHA 5128
HOMEWORK 4

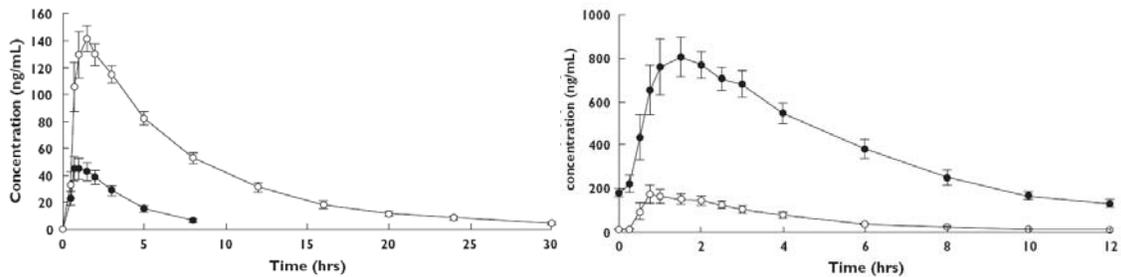
(Phenobarbital/Carbamazepine/Valproic Acid, Phenytoin)
Spring 2008

1. J.T., a 71 kg 65 year old male, suffers seizures, and is given phenobarbital of 2 mg/kg twice a day (BID). After one month, his seizures are not controlled and his physician decided to start a concomitant therapy of carbamazepine. Calculate the daily maintenance dose of carbamazepine to produce a target steady state concentration of 7 mg/L using the immediate release formulation. Later the results come back from the lab and the concentration of carbamazepine was 8.75mg/L. In order to achieve the desired serum concentration, what is your suggestion? (2 points)

2. L.J., a 75 kg male, was admitted to the hospital for the seizures. A loading dose of sodium phenytoin was given to achieve 15 mg/L, and then maintenance dose was given 300mg daily. After a week, a steady-state concentration was measured at 9 mg/L. The physician decided to increase maintenance dose to 350 mg daily. After another week, the concentration of phenytoin at steady-state was at 22 mg/L, which is way too high. The following dose was discontinued until concentration drops to 15 mg/L. How long will it take to achieve this drop from 22 mg/L to 15 mg/L? (3 points)

3. A female patient will take Depakene Syrup (Valproic Acid) chronically. In a previous trial of a single dose of Depakene (500 mg) in this patient, it was found that an initial concentration of 48 $\mu\text{g/ml}$ had been reduced to 14 $\mu\text{g/ml}$ within 24hr. Suggest a dosing regimen for chronic treatment to maintain concentration within range from 50 to 100 $\mu\text{g/ml}$. (3 points)

4. A recent study was performed to investigate the effects of ketoconazole and carbamazepine on the pharmacokinetics of Drug 5128. Drug 5128 was given to the subjects alone, or concomitant administration of ketoconazole or carbamazepine with Drug 5128. The results are presented in the following Figures. Which of the following statement is FALSE? And WHY (Use one sentence)? (2 points)



Figures: Drug 5128 concentration-time Profiles

Left Panel (Drug 5128 alone (close circles), concomitant administration of ketoconazole and Drug 5128 (open circles)); **Right Panel** (Drug 5128 alone (close circles), concomitant administration of carbamazepine and Drug 5128 (open circles))

- A) In this study, ketoconazole increased mean Drug 5128 plasma C_{max} significantly; and Carbamazepine decreased mean Drug 5128 plasma C_{max} dramatically.
- B) Cytochrome P450 3A4 is a primary enzyme responsible for the metabolic clearance of Drug 5128.
- C) Ketoconazole is the strong inhibitor of CYP3A4, and carbamazepine is the strong inducer of CYP 3A4.
- D) Other drugs and ingested natural products that strongly modulate the activity or expression of CYP3A4 would be predicted to change exposure to Drug 5128.
- E) Clearance of Drug 5128 is increased by ketoconazole; and decreased by carbamazepine.