Therapeutic Drug Monitoring (TDM)
5th Stage, 2nd Semester

Reference Texts: Applied Clinical Pharmacokinetics, by Larry A. Bauer. (Latest edition)

Additional references include but not limited to: Clinical Pharmacokinetics Concepts and Applications, by Malcolm Rowland and Thomas Tozer (Latest edition)

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Syllabus

No	Lecture Title	Hour(s)
1	Problems in basic Pharmacokinetics (PK)	2
2	Problems in basic pharmacodynamic (PD)	2
3	Clinical PK equations and calculations	2
4	Clinical PK in special population and cases	2
5	Problems in Clinical PK for Antibiotics (e.g., Aminoglycosides, Vancomycin)	4
6	Problems in Clinical PK/PD for Cardiovascular agents (e.g., Digoxin, Lidocaine, Procainamide/N-Acetyl Procainamide)	4
7	Problems in Clinical PK/PD for Anticonvulsants (e.g., Phenytoin, Carbamazepine, Valproic Acid, Phenobarbitone/Primidone, Ethosuxsimide)	6
8	Problems in Clinical PK/PD for Immunossprasants (e.g., Cyclosporine, Tacrolimus)	2
9	Clinical PK/PD of other drugs (e.g., Lithium, Theophylline, Anticancer agents, Anticoagulats	6

Lab. 1

Problems in Basic Pharmacokinetics

- **Clinical pharmacokinetics:** **is the application of pharmacokinetic concepts and principles in humans in order to design individualized dosage regimens which optimize the therapeutic response and minimize the adverse drug reaction.**

- **TDM is the clinical laboratory measurement of drug concentrations in plasma, serum or blood and using this information to individualize the dosage and maintain the drug concentrations within a target therapeutic range.**
- **Laboratories routinely measure patient serum or plasma samples for many drugs, including antibiotics (eg, aminoglycosides and vancomycin), antiepileptics (eg, phenytoin, carbamazepine, valproic acid, phenobarbital, and ethosuximide), antiarrhythmics (eg, lidocaine, procainamide ,quinidine and digoxin), immunosuppressants (eg, cyclosporine and tacrolimus), and others (theophylline, lithium).**

Basic Pharmacokinetics Terms

- **a. absorption : Passage of drug molecules through physiological/biological barriers before reaching the vascular system.**
- **b. distribution: Passage of drug molecules from the bloodstream into tissues and organs.**
- **c. metabolism: Chemical conversion of a drug molecule into a metabolite.**
- **d. elimination: Irreversible removal of drug from the body.**
- **E. steady state: Rate of drug administration equals the rate of drug removal so that serum concentrations and amount of drug in the body are constant.**
- **f. linear or first-order pharmacokinetics: Situation where steady-state serum concentration or area under the serum concen tration/time curve (AUC) changes proportionally with dosage changes.**

Basic Pharmacokinetics Terms

- **g. nonlinear pharmacokinetics:** Situation where steady-state serum concentration or area under the serum concen tration/time curve (AUC) changes disproportionally with dosage changes.
- **h. saturable or Michaelis-Menten pharmacokinetics:** Type of nonlinear pharmacokinetics where an increase in dose results in a dispro portionally large increase in steady-state serum concentration or area under the serum concentration/time curve. Results from overwhelming or "saturating" the enzymes'ability to metabolize the drug.
- **i. autoinduction:** Situation where a drug increases its own rate of metabolism by inducing more drug metabolizing enzyme to be produced.
- **j. therapeutic range:** Minimum and maximum serum or blood concentrations that produce the desired pharmacological effect without producing unwanted adverse effects

Basic Pharmacokinetics Terms

- **k. zero-order pharmacokinetics:** A constant amount of drug is eliminated per unit time usually due to complete saturation of the enzyme system responsible for the metabolism of the drug
- **l. bioavailability:** Fraction of administered dose that is delivered to the systemic circulation.
- **m. bioequivalent:** A dosage form for a drug that produces the same serum concentration/time profile as another dosage form of the same drug. Usually measured by showing that the two dosage forms have the same area under the serum concentration/time curve (AUC), maximum serum concentration (Cmax), and time that maximum serum concentration occurs (Tmax) values within statistical limits
- **n. clearance:** Volume of serum or blood completely cleared of drug per unit time.
- **o. volume of distribution:** Proportionality constant that relates serum concentrations to amount of drug in the body.
- **p. half-life:** Time required for serum concentrations to decrease by one-half after absorption and distribution phases are complete.
- **q. elimination rate constant:** Terminal slope (using an ln C versus time plot) of the serum concentration/time curve after absorption and distribution phases are complete

- Problem 1/ Two new antibiotics are marketed by a pharmaceutical manufacture. Reading the package insert, you find the following information:

DOSE	CURACILLIN STEADY-STATE CONCENTRATIONS (mg/L)	BETTERMYCIN STEADY-STATE CONCENTRATIONS (mg/L)
0	0	0
100	15	25
250	37.5	62.5
500	75	190
1000	150	510

What type of pharmacokinetics do each of these drugs follow?

- A plot of steady-state concentration versus doses is a straight line for Curacillin, but a curved line for Bettermycin .
- Since this relationship is a straight line for Curacillin, it follows linear or first-order pharmacokinetics.
- Because the steady-state concentration versus dose plot is curved upward indicating dispropor tionally large increases in concentration after a dosage increase, Bettermycin follows nonlinear pharmacokinetics. The type of nonlinear pharmacokinetics is Michaelis Menten or saturable pharmacokinetics.

- **Problem 2/ A patient with liver failure and a patient with heart failure need to be treated with a new antiarrhythmic drug. You find a research study that contains the following information for Stopabeat in patients similar to the ones you need to treat: normal subjects: clearance = 45 L/h, volume of distribution = 175 L; liver failure: clearance = 15 L/h, volume of distribution = 300 L; heart failure: clearance = 30 L/h, volume of distribution = 100 L. Recommend an intravenous loading dose (LD) and continuous intravenous infusion maintenance dose (MD) to achieve a steady-state concentration of 10 mg/L for your two patients based on this data and estimate the time it will take to achieve steady-state conditions.**

- **The liver failure patient would likely have pharmacokinetic parameters similar to the liver failure patients in the research study (Cl = 15 L/h, V = 300 L):**
- **LD = V · Css, LD =(300 L)(10 mg/L) = 3000 mg intravenous bolus;**
- **MD = Cl · Css, MD = (15 L/h) (10 mg/L) = 150 mg/h intravenous infusion.**
- **The half-life would be estimated using the clearance and volume of distribution: t1/2 = (0.693 V)/Cl, t1/2 = [(0.693)(300 L)] / (15 L/h) = 13.9 h.**
- **Steady state would be achieved in 3–5 t1/2 equal to 42–70 hours.**

- **The heart failure patient would likely have pharmacokinetic parameters similar to**
- **the heart failure patients in the research study (Cl = 30 L/h, V = 100 L):**
- **LD = V · Css, LD =(100 L)(10 mg/L) = 1000 mg intravenous bolus;**
- **MD = Cl · Css, MD = (30 L/h) (10 mg/L) = 300 mg/h intravenous infusion.**
- **The half-life would be estimated using the clearance and volume of distribution: t1/2 = (0.693 V)/Cl, t1/2 = [(0.693)(100 L)]/ (30 L/h) = 2.3 h.**
- **Steady state would be achieved in 3–5 t1/2 equal to 7–12 hours.**

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