Study program: Integrated Academic Studies in Pharmacy

Course title: Pharmacokinetics

Teacher: Nataša P. Milošević, Kosta J. Popović

Course status: Compulsory

ECTS Credits: 7

Condition: General Pharmacology

Course aim

To understand kinetic processes, which affect the drug in the body, the kinetic analysis and mathematical modeling in the making of new drugs and determining dosage regimen for the implementation of rational pharmacotherapy.

Expected outcome of the course:

After passing the examination the student is expected to know Pharmacokinetic processes and factors which have influence on them, to have knowledge of different approaches to pharmacokinetic analysis of data and their mathematical modeling, knowledge of factors affecting the variability of therapeutic response, knowledge of the ways of testing the biological availability and biological equivalence of medicinal preparations. Upon completion of the course, the student is expected to be able to calculate Pharmacokinetic parameters of single and multiple dosing, assess the need for therapeutic drug monitoring, interpret the measured concentrations of drugs, apply the principles of clinical pharmacokinetics

Course description

Theoretical education

1.Introduction to pharmacokinetics 2. Elements of pharmacokinetics 3. Modeling the pharmacokinetics 4. Mathematical modeling methods in pharmacokinetics 5. Basics of system theory and the concept of "black box" 6. Elementary and complex systems 7. Examples of complex systems in the pharmacokinetics 8. The method of least squares 9. Single- compartment models 10. Single-compartment model - pharmacokinetic parameters 11. Excretion from single-compartment model 12. Intravenous infusion in single-compartment model13. Pharmacokinetic parameters for infusion in single-compartment model14. Multiple, intermittent, intravenous bolus dosing in single-compartment model 15. Multiple dosing and initial dose 16. The time it takes to get C_{max}17. Relationship of multiple intermittent dosing and continuous iv infusion 18. Two compartment open models 19. Bateman functions 20. Flip-flop rotation constants 21. Mathematical properties of Bateman functions 22. Pharmacokinetic properties of Bateman functions 23. Important Pharmacokinetic parametersof the simplest model with the absorption 24. Pharmacokinetics analysis by using data on excretion in urine, bile, stools for the simplest model with resorption 25. Two compartment model for drug metabolism 26. Multiple paravascular intermittent dosing for the simplest model with absorption 27. Two compartment model with intravascular drug injection into the first of two compartments 28. Two compartment model with intravascular administering 29. Pharmacokinetic parameters of two compartment models with iv administration of drug 30. Analysis of the process of excretion for two compartment model with iv injection in the first compartment 31. Infusion in Two compartment model32. Three compartment models 33. Četvorokompartmanski models 34. Application of pharmacokinetic parameters in the individual manner of dosing drugs 35. Effect of combined therapy on dosing 36. Influence of age on the dosage regimen 37. The dosage of drugs for children 38. Determination of the initial dose and new dose when the original has nott achieved the desired concentration 39. Dosing interval 40. Examples of drug pharmacokinetics and calculation of the basic parameters - single dose 41. Examplesof multiple administration of drugs with concentrations presented graphically 42. Influenceof pharmacokinetic parameters on the appearanceof pharmacokinetic curves in multiple drug administration 43. Influence of the initial dose onf the drug concentration in multiple drug administration. Distribution of medicines.

Practical education

1. Preparation of samples for pharmacokinetic testing of drug from biological materials. Sampling and storage of biological material for pharmacokinetic analysis. Handling samples. Methods of preparing samples for analysis: Liquid/liquid extraction, supercritical extraction with CO2-SFE, the solid phase extraction - SPE, the hydromatrix extraction, extraction under pressure - Accelerated Solvent Extraction. Selecting the optimal method of sample preparation for analysis. 2. HPLC in pharmacokinetics. Introduction - the application of HPLC analysis Pharmacokinetic investigations. Determination of the concentration of drug X in plasma of experimental animals HPLC method. Construction diagrams of drug concentration X in function of time. Comparing the results of several investigated series. 3. Absorption of drugs. Places of drug absorption (gastrointestinal tract, lungs, skin, mucosa, parentreral administration of medications). Absorption from gastronitestinalnog tract (mouth cavity, stomach, small intestine, colon, rectum). Absorption through the skin and mucous membranes. Parenteral drug administration (subcutaneous, intramuscular and

intravenous administration of medications). Biological availability of drugs 4. Distribution of medicines. The initial distribution of drugs. Redistribution of drugs. The passage of drugs through physiological barriers (hematoencephalic barrier, placenta). Volume of distribution. Interactions of drugs at the level of distribution 5. Metabolism of drugs. Reactions in I and II phaseof drug biotransformations, with examples of the movement of drug in the body (elimination of the drug without changes, subject only to drug reactions phase II of biotransformations, the drug is subject to phase I biotransformations and transformed in the direction of inactive, active or toxic metabolites). 6. The influence of various factors on drug metabolism (genetic factors, gender, age, pathological conditions, environmental). Clinical effects of changes in drug metabolism (induction, inhibition of enzymes which metabolized drugs) 7. The elimination of drugs. Excretion (secretion) and elimination of drugs. Excretion through the kidneys (glomerular filtration, tubular secretion and tubular reabsorption of drugs). Excretion via the liver and bile. Other excretion routes. Drug clearance (kidney, liver, total). Cycle of drugs in the body. Factors affecting the excretion of drugs. 8. Mathematical tasks. Single-compartment model – presentation of pharmacokinetic data, calculating pharmacokinetic parameters (elimination half-time, volume of distribution, clearance), interpretationof the obtained results 9.Ppredicting the concentration of the drug after a certain time interval, calculating the required dose. 10. Mathematical tasks. Ekstravaskularna application of the drug - Calculate the constant resorption and resorption half constructed using graphics 11. Mathematical tasks. Monitoring of drugs and metabolites and determination of pharmacokinetic parameters, Michaelis-Menten kinetics, the determination of parameters of Michaelis-Menten kinetics of various graphical and mathematical procedures. 12. Mathematical tasks. Investigation of drug excretion in the determination of drug concentrations in the urine. Differential and integral method. 13. Mathematical tasks. Studies of pharmacokinetic parameters from data on drug excretion in urine. 14. Mathematical tasks. Graphical presentation and calculationof pharmacokinetic, and interpretation of the results of continuous intravenous infusion. The initial dose and initial infusion. 15. Mathematical tasks. Multiple dosing of medicines, and graphical presentation of a mathematical description, time to achieve a stationary state. Relation of dosing interval and elimination half. The initial dose. 16. Mathematical tasks. Open Pharmacokinetic Model of two compartments - pharmacokinetic presentation of data, calculating pharmacokinetic parameters (elimination half-time, volume of distribution, clearance), interpretation of results, predicting the concentration of the drug after certain time interval, calculating the required dose. 17. Mathematical tasks. Practical examples of pharmacokinetic calculations in clinical practice.

Literature

Compulsory

1. Jambhekar SS. Breen PJ. Basic Pharmacokinetics. London: Pharmaceutical Press, 2009.
2. Winter M. Basic clinical pharmacokinetics, 4th edition. London: Lippincott Williams & Wilkins, 2003.
3. Ritschel W, Kearns G. Handbook of Basic Pharmacokinetics, 6th edition. Washington: APhA Publications, 2004.
4. Bauer LA. Applied clinical pharmacokinetics, 3rd edition. New York: McGraw-Hill Education, 2014.

Number of active classes	**Theoretical classes:** 60	**Practical classes:** 45

Teaching methods

Lectures, practical classes, case studies analysis,

Student activity assessment (maximally 100 points)

Pre-exam activities	**points**	**Final exam**	**points**
Lectures	10	Written	50
Practices	10	Oral	
Colloquium	30		