UNIT

XIX

LINEAR PHARMACOKINETICS

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Ch.Id:-ASU/NSP/EB/BAP/2022/Ch-19

DOI: https://doi.org/10.52458/9789391842451.nsp2022.eb.asu.ch-19

LINEAR PHARMACOKINETICS

The study of the time course of drug absorption, distribution, metabolism, and excretion is known as pharmacokinetics. The application of pharmacokinetic concepts to the safe and effective therapeutic management of drugs in an individual patient is known as clinical pharmacokinetics. Clinical pharmacokinetics focuses on improving the efficacy and reduces the toxicity of a patient's drug therapy. The discovery of robust connections between drug concentrations and pharmacologic reactions has allowed clinicians to apply pharmacokinetic principles to real-life patient settings.

Multiple processes (such as absorption, distribution, metabolism, and elimination) act together to change drug concentrations in tissues and fluids. To forecast a drug's activity in the body, simplifications of physiologic systems are required. Applying mathematical principles to the various processes is one technique to achieve these simplifications. In pharmacokinetic analysis, a variety of mathematical approaches have been proposed, including the use of linear and nonlinear compartmental models, physiologically based models, statistical models, recirculation models, and linear and nonlinear system approaches. Although pharmacokinetic analysis can be performed without specifying any mathematical models (noncompartmental approaches), such models can be useful in therapeutic decision-making. Drugs with linear pharmacokinetics have several essential properties.

In pharmacokinetics, a LINEAR system approach is described as a system approach that mathematically models a general LINEAR PROPERTY of the pharmacokinetic system without modelling the individual kinetic processes responsible for the LINEAR property in question. In pharmacokinetics, a NONLINEAR system approach is described as a system approach that mathematically represents a generalized NONLINEAR PROPERTY of the pharmacokinetic system without describing the particular kinetic processes for the nonlinear property under consideration.

This means that the rate of change in drug concentration is solely determined by the current concentration. No matter how high the concentration is, the half-life will remain constant.

ISBN- 978-93-91842-45-1

The simplest linear pharmacokinetic model is

$$C(t) = \frac{Dose}{V}(e^{-kt})$$

The drug is given as an immediate bolus, and its total distribution is also instantaneous, according to this concept.

These assumptions are frequently incorrect. If the drug is given as a gradual bolus or infusion, the model must be adjusted to account for the duration of the infusion. The concentration of the medicine increases as it is administered:

$$C(t) = \frac{Dose}{VKT}(1 - e^{-kt})$$

The drug concentration decays at the same rate as if it had been given as an immediate bolus once the infusion is stopped. As a result, if T is the infusion period, the post-infusion drug concentrations can be expressed as

$$C(t) = C(T)e^{-k(t-T)}$$

For pharmacokinetic analysis, a wide range of software is available. Hands-on experience with such programmes is likely to assist the interested reader. For the casual reader, there are a few things to keep in mind. The quality of the data entered into the model determines the validity of pharmacokinetic modelling to a great extent. As a result, drug infusions must be carefully timed, plasma samples taken on time, and analytical procedures must be sensitive and specific. To reduce bias due to the increased likelihood of analytical errors at drug concentrations approaching the assay's detection limit, the results must be properly weighted.

Results from a particular model should be compared to results from noncompartmental approaches. Extrapolation of models beyond known time points requires extreme caution.

In most circumstances, pharmacokinetic processes, such as absorption, distribution, binding, metabolism, or excretion, are proportionate to the dose and are referred to as first-order or linear kinetics.

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The concept of superposition states that all semilog graphs of C versus t for different doses are superimposable.

The dose has no effect on the essential pharmacokinetic parameters F, K_a, K_E, V_d, Cl_R, and Cl_H, which define the time-course of a drug in the body, i.e. the pharmacokinetics parameters are dose-independent.

NON-LINEAR, MIXED-ORDER, OR CAPACITY-LIMITED PHARMACOKINETICS

a) When pharmacokinetic processes such as absorption, distribution, binding, metabolism, or excretion rely on substrate-specific carriers or enzymes with specified capabilities and are susceptible to saturation at high drug concentrations.

b) In such circumstances, the pharmacokinetic parameters F, K_a, K_E, V_d, Cl_R, and Cl_H change with the amount of the administered dose, and are considered to be dose-dependent.

HOW TO DETECT NON-LINEARITY

1. Establishing steady-state plasma concentrations at various dosages. The kinetics are linear if the steady-state concentrations are directly proportional to the dose.
2. Determination of a number of essential pharmacokinetic parameters at various medication dosages. Nonlinearity is defined as a change in these parameters, which are generally constant.

CAUSES OF NONLINEARITY

Drug absorption, distribution, metabolism, and excretion can all have nonlinearities.

a) Absorption of drugs

- When absorption is restricted by solubility or dissolution rate, as with griseofulvin.
- When riboflavin, ascorbic acid, cyanocobalamin, and other carrier-mediated transport mechanisms are involved in absorption.

ISBN- 978-93-91842-45-1

- When the presystemic gut wall or hepatic metabolism reaches saturation, such as with propranolol, hydralazine, or verapamil.

F, K_a, C_{max}, and AUC are the parameters that will be affected. In the first two cases, these parameters decrease, but in the third case, they increase.

b) Drug Distribution

- Nonlinearity in the distribution of drugs administered at large doses could be caused by —Binding sites on plasma proteins, such as phenylbutazone and naproxen, are saturated.
- Thiopental and fentanyl saturation of tissue binding sites
- The free plasma drug concentration increases in both circumstances, but Vd rises only in the first, whereas it falls in the second. Clearance is also affected by the drug's extraction ratio.

c) Drug Metabolism

Capacity-limited metabolism is the most clinically important nonlinear kinetics because minor changes in dose administered can result in substantial fluctuations in plasma concentration at steady-state. Nonlinearity in metabolism is caused by two major factors:

a) Metabolism is capacity-limited due to enzyme and/or cofactor saturation. Phenytoin, alcohol, theophylline, and other drugs are common examples.

b) Enzyme induction, such as with carbamazepine, in which a reduction in peak plasma concentration has been observed with repeated dosing over time. The dose-dependent autoinduction observed in this situation.

When an enzyme becomes saturated, it produces less Cl_H and thus more Css. For enzyme induction, the inverse is true.

d) Drug Excretion

The two saturable active mechanisms in renal drug excretion are:

a) Active tubular secretion, e.g. penicillin G. Renal clearance decreases after the carrier system has been saturated.

b) Active tubular reabsorption of water-soluble vitamins and glucose, for example. Renal clearance increases when the carrier system has been saturated.

Forced diuresis, changes in urine pH, nephrotoxicity, and binding site saturation are all contributors of nonlinearity in renal excretion. Tetracycline and indomethacin, which are both active processes, can cause biliary secretion to become saturated.

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