Principles of Basic Clinical Pharmacokinetic Parameters

Part I

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Background and historical introduction

- Until the 1960s, trial and error was the most common scenario for drug management.

- Even though the guiding principles were usually obtainable and believable to be efficient and safe, majority of practitioners implement dosing in an empirical approach.

- Doses were frequently started at low ranges and increased gradually until an improvement is achieved or, in spite of the guidelines, toxic effects manifested.

Background and historical introduction

- With the realization that **standard dosage regimens** resulted in unreliable patient outcomes, researchers start to find analytical facilities that can more precisely describe the pharmacokinetic characteristics and therapeutic ranges.

- As a consequence, the last three decades showed an obvious growth in the concept of therapeutic drug monitoring (TDM), especially in the area of pharmacokinetics and pharmacodynamics research.

Background and historical introduction

- The main goal of applying clinical pharmacokinetic and pharmacodynamic principle relationship concept was:

Optimizing drug therapy

- Therefore, increased efficacy without unacceptable toxicity or reduced toxicity without compromising efficacy may justify the use of the principles of pharmacokinetics and pharmacodynamics to improve the clinical outcome and drug therapy.

Background and historical introduction

Minimizing the probability of drug toxicity and maximizing the benefit of achieving the desired therapeutic effect

Pharmacokinetics

Absorption

- With respect to oral dosage form, the drug molecules release from the tablet or capsule via dissolution, and the molecules must pass through the various layers of the gastrointestinal tract where they reach blood circulation.

Distribution

- Occurs when drug molecules that have entered the vascular system pass from the bloodstream into various tissues and organs such as the muscle or heart.

Pharmacokinetics

Metabolism

- is the chemical conversion of the drug molecule, usually by an enzymatically mediated reaction, into another chemical entity referred to as a metabolite. The metabolite may have the same, or different, pharmacological effect as the parent drug, or even cause toxic side effects.

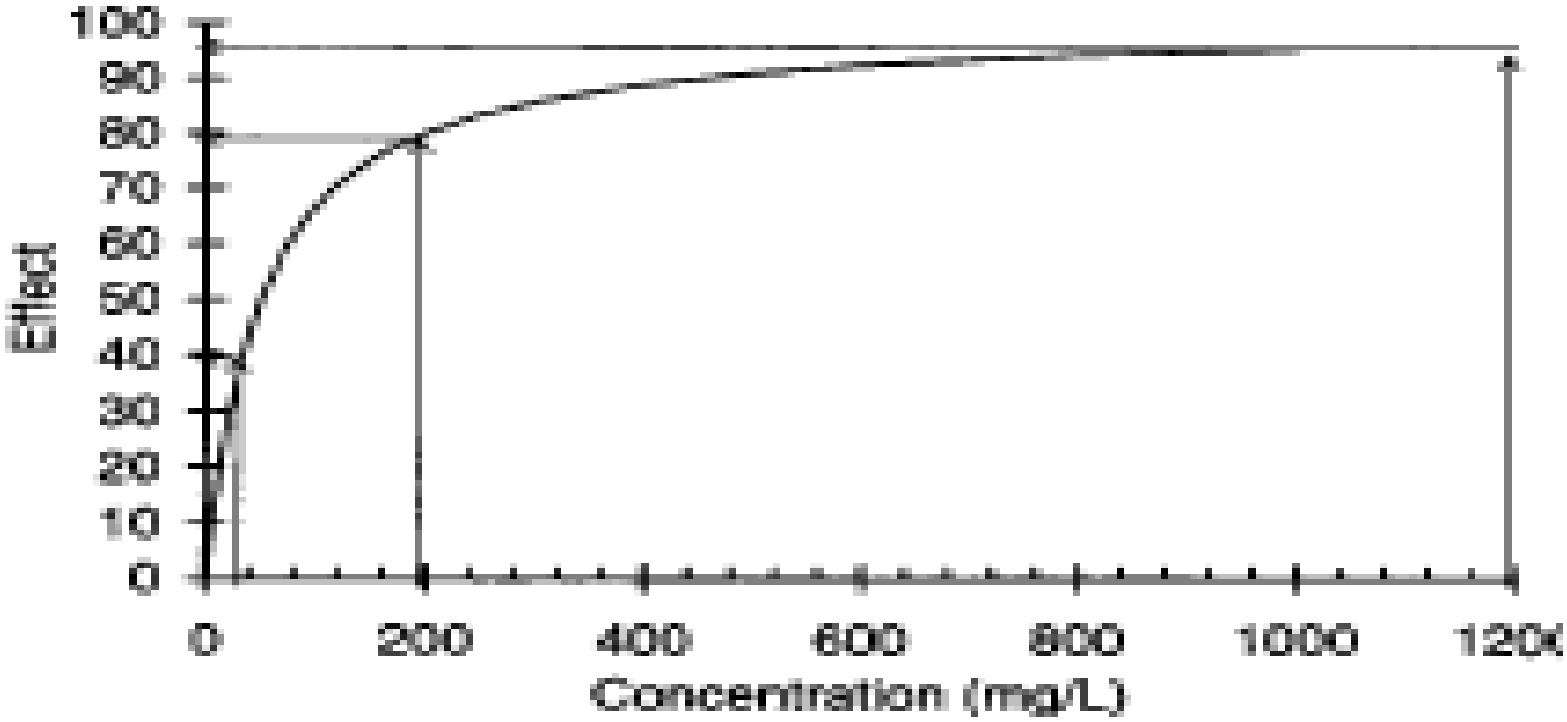
Excretion

- is the irreversible removal of drug from the body and commonly occurs via the kidney or biliary tract.

Pharmacodynamics

- The relationship between drug concentration and pharmacological response.

- It is extremely important for clinicians to realize that the ***change in drug effect is usually not proportional to the change in drug dose or concentration***.

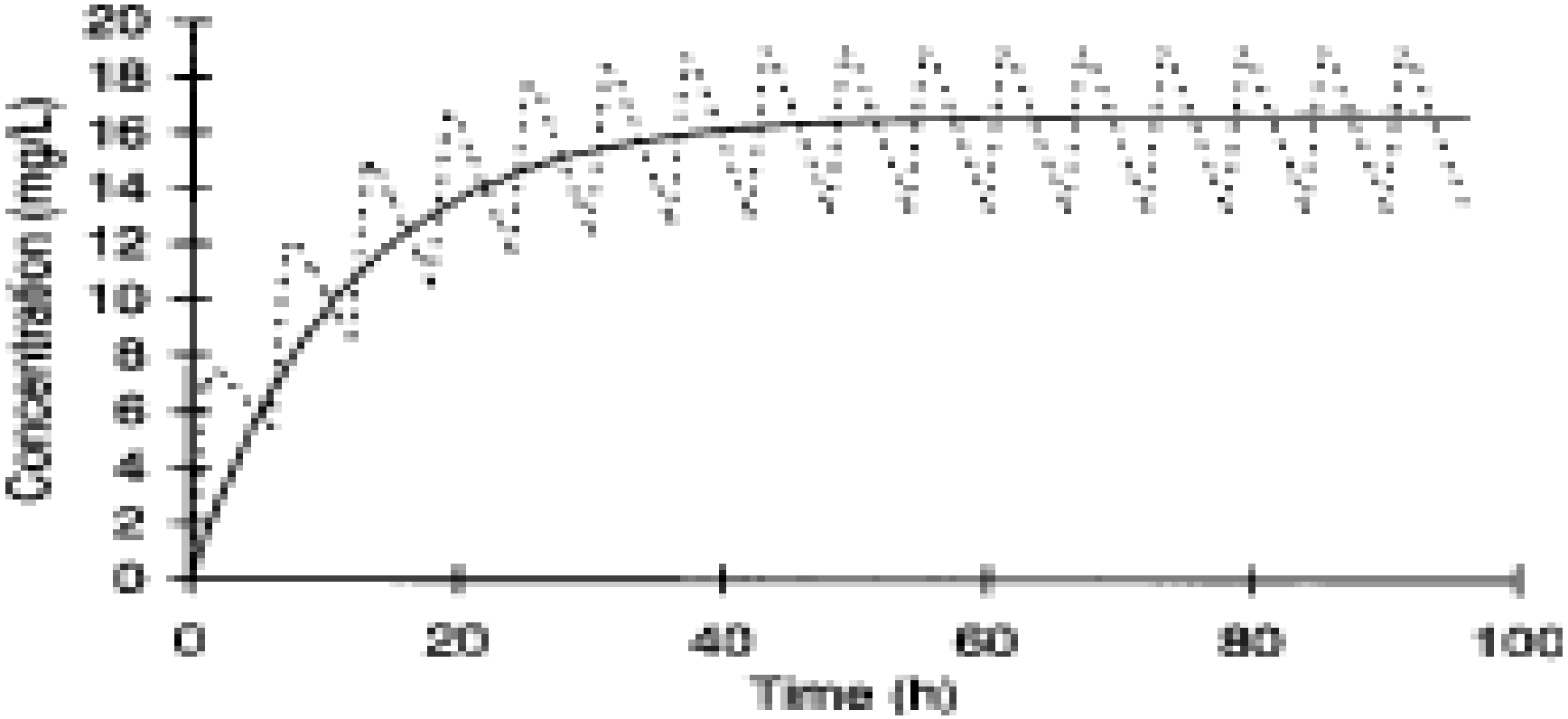


The drug effect changes from 40 to 80 units with a fivefold increase in concentrations from 40 to 200 mg/L, but only 20% (from 80 to 95 units) when the same five-fold increase in concentrations is made at high concentrations (from ~200 to 1000 mg/L).

In clinical situations, patients may need to tolerate some side effects in order to obtain the maximal pharmacological effect of the agent

Linear versus nonlinear pharmacokinetics

- When drugs are given on a constant basis, such as a continuous IV infusion or an oral medication given every 12 hours, serum drug concentrations increase until the ***rate of drug administration*** **equals** ***the rate of drug metabolism and excretion.***



The solid line shows serum concentrations in a patient receiving IV theophylline at a rate of 50 mg/h and oral theophylline 300 mg every 6 hours (dashed line). Since the oral dosing rate (dose/dosage interval = 300 mg/6 h = 50 mg/h) equals the IV infusion rate, the drug accumulation patterns are similar.

Linear versus nonlinear pharmacokinetics

- Regardless of the mode of drug administration, when the rate of drug administration equals the rate of drug removal, the amount of drug contained in the body reaches a constant value.

- This equilibrium condition is known as ***steady-state*** and is extremely important in clinical pharmacokinetics because usually steady-state serum or blood concentrations are used to assess:
  - ***patient response***
  - ***compute new dosage regimens***

Linear versus nonlinear pharmacokinetics

- When the steady-state serum concentrations increase or decrease proportionally with dose, *plot of steady-state concentration versus dose yields a straight line*.

- Hence, the drug is said to follow ***linear pharmacokinetics***.

Concentration (µg/mL)	Dose (mg/h)
10	100
15	150

Linear versus nonlinear pharmacokinetics

- In some cases drug concentrations do not change proportionally with dose.

- Steady-state concentrations change in a disproportionate fashion after the dose is altered, a plot of steady-state concentration versus dose is not a straight line and the drug is said to follow ***nonlinear pharmacokinetics***.

Linear versus nonlinear pharmacokinetics

- When steady-state concentrations increase more than expected after a dosage increase, the most likely explanation is that the processes removing the drug from the body have become saturated.

- This phenomenon is known as saturable or ***Michaelis-Menten*** pharmacokinetics.

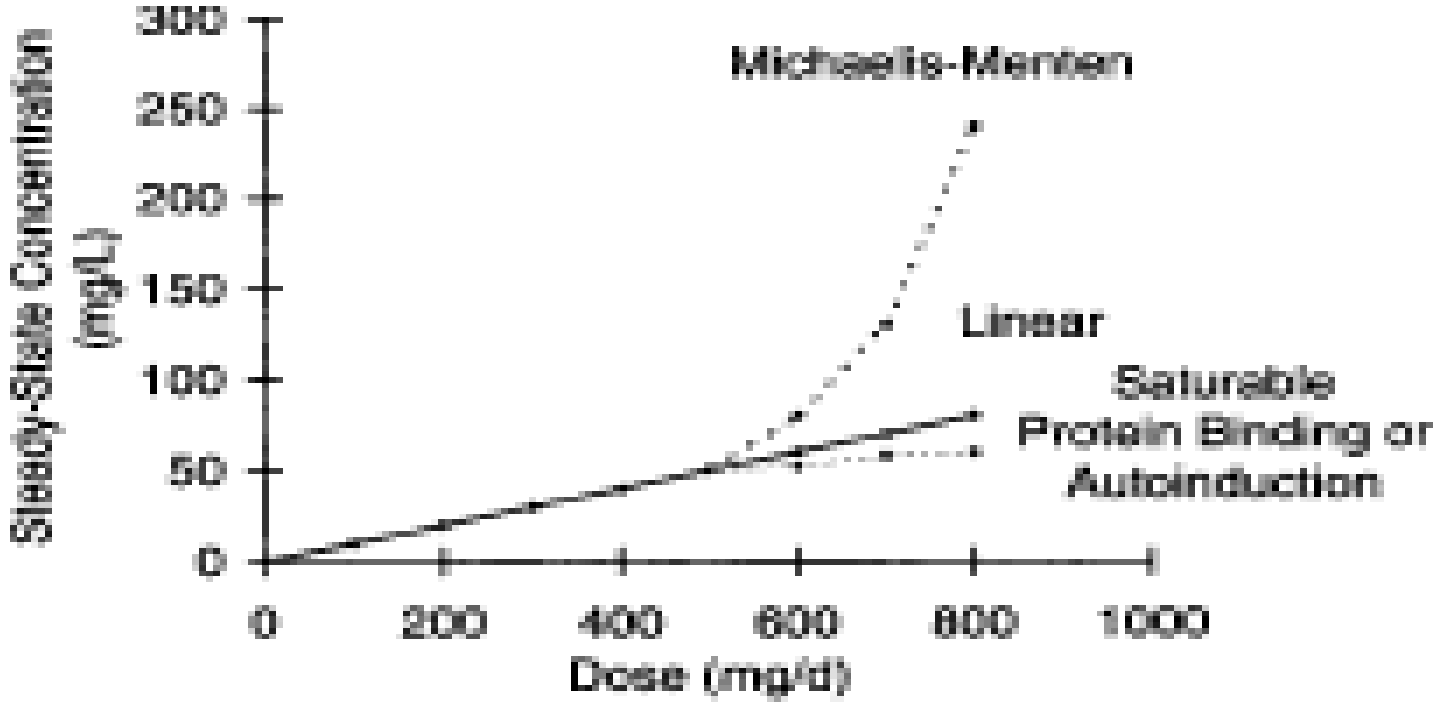
- Both phenytoin and salicylic acid follow Michaelis-Menten pharmacokinetics.

Linear versus nonlinear pharmacokinetics

- When steady-state concentrations increase less than expected after a dosage increase, there are two typical explanations:

➢ **Saturation of protein binding sites** (e.g., valproic acid and disopyramide).

➢ **Autoinduction of drug metabolism** (e.g., carbamazepine).



When doses are increased for most drugs, steady-state concentrations increase in a proportional fashion leading to linear pharmacokinetics (solid line). However, in some cases proportional increases in steady-state concentrations do not occur after a dosage increase. When steady-state concentrations increase more than expected after a dosage increase (upper dashed line), Michaelis-Menten pharmacokinetics may be taking place. If steady-state concentrations increase less than expected after a dosage increase (lower dashed line), saturable plasma protein binding or autoinduction are likely explanations.

Linear versus nonlinear pharmacokinetics

- In either case, the relationship between steady-state concentration and dose for drugs that follow *nonlinear pharmacokinetics* is *fraught with significant intersubject variability.*

- Drugs that exhibit *nonlinear pharmacokinetics* are oftentimes very difficult to dose correctly.

Clearance

- The definition of clearance is the volume of serum or blood completely cleared of the drug per unit time.

- Thus, the dimension of clearance is

volume per unit time (L/h or ml/min)

Clearance

- Clearance (Cl) use to determine the maintenance dose (MD) that is required to obtain a given or a target steady-state serum concentration (Css):

$$MD = Css \cdot Cl$$

Clearance

- Target steady-state concentrations are usually taken from previous studies.

- Theses concentration come as a range;

➢ *minimum effective concentrations*
➢ *maximum effective concentrations* (without toxic side effects)

- This range of steady-state concentrations is known as the *therapeutic range for the drug*.

Clearance

- For example, the therapeutic range for theophylline is generally accepted as 10–20 µg/mL for the treatment of asthma.

- If it were known;

➢ Theophylline clearance for a patient equaled 3 L/h

➢ The desired steady-state theophylline serum concentration was 10 µg/mL

➢ ***MD = Css · Cl***

$$MD = 10\ mg/L \cdot 3\ L/h$$

$$= 30\ mg/h$$

Hepatic clearance

- It can also be recognized based on three physiological factors:

i. **Intrinsic clearance (Cl'_{int}):** intrinsic ability of the enzyme to metabolize a drug

ii. **Free fraction (f_B):** the fraction of drug present in the bloodstream that is not bound to cells or proteins, such as albumin, α1-acid glycoprotein, or lipoproteins. The unbound fraction of drug is the unbound drug concentration divided by the total (bound + unbound) drug concentration

iii. **liver blood flow (LBF)**

Renal clearance

- The physiological determinants of renal clearance are:

  a) ***Glomerular filtration rate (GFR)***
  b) ***Drug free fraction in the blood or serum (f_B)***
  c) ***Drug clearance via renal tubular secretion (Cl_{sec})***
  d) ***The fraction of drug reabsorbed in the kidney (FR)***

- Average glomerular filtration rates in adults with normal renal function are 100–120 ml/min.

Renal clearance

- The aminoglycoside antibiotics and vancomycin are eliminated primarily by glomerular filtration.

- Digoxin, procainamide, ranitidine, and ciprofloxacin are eliminated by both glomerular filtration and active tubular secretion.

- If the renal clearance of a drug is greater than glomerular filtration rate, it is likely that the drug was eliminated, in part, by active tubular secretion.

Renal clearance

- For the purposes of drug dosing, glomerular filtration rate is approximated by measuring or estimating creatinine clearance for a patient.

- Creatinine is a by-product of muscle metabolism that is eliminated primarily by glomerular filtration.