

Design of dosage regimens

Introduction to Dosage Regimens

- The design of dosage regimens involves determining the right dose, dosing interval, and duration of drug therapy to ensure therapeutic effectiveness with minimal side effects.
- It is based on both pharmacokinetics (how the body affects the drug) and pharmacodynamics (how the drug affects the body).

Key Elements

1. Loading Dose (LD):

- Given to rapidly achieve therapeutic drug concentration.
- Depends on **volume of distribution (Vd)** and **target concentration**.

2. Maintenance Dose (MD):

- Keeps drug concentration within therapeutic range.
- Based on **clearance (Cl)** and **dosing interval**.

3. Dosing Interval (τ):

- Time between doses.
- Determined by **half-life ($t_{1/2}$)** and desired peak/trough levels.

Factors Affecting Regimen Design

- **Patient-specific:** Age, weight, organ function (renal/hepatic), comorbidities
- **Drug-specific:** Half-life, therapeutic index, bioavailability
- **Route of administration:** Oral, IV, IM, etc.
- **Special populations:** Elderly, pediatric, obese, renal/hepatic impairment

Clinical Tools Used

- **Nomograms:** Graphical tools to estimate doses
- **Tabulations:** Reference tables with dose recommendations
- **Pharmacokinetic equations:** For calculating LD, MD, and τ

Goals

- Maintain **steady-state concentration**
- Avoid **subtherapeutic or toxic levels**
- Customize therapy to **individual needs**

Nomograms in designing dosage regimen

Definition

- A **nomogram** is a graphical calculating device or chart that simplifies complex pharmacokinetic calculations.
- It integrates multiple variables into a visual format to facilitate rapid and practical estimation of parameters like dose, volume of distribution (Vd), clearance (Cl), and elimination half-life ($t_{1/2}$).

Types of Nomograms

1. **Two-variable nomograms** – connect two known parameters to find a third.
2. **Three-variable nomograms** – allow interpolation of values between multiple parameters.
3. **Drug-specific nomograms** – pre-designed for certain medications (e.g., theophylline, digoxin, vancomycin, aminoglycosides).

Types and Examples

1. Vancomycin Nomogram:

- Based on creatinine clearance (CrCl) and actual body weight.
- Used to determine initial dosing (e.g., mg/kg) and frequency of dosing (e.g., every 12 hours).
- Adjusts for renal function, which is critical for a drug like vancomycin that is renally cleared.

2. Heparin Nomogram:

- Tailored for activated partial thromboplastin time (aPTT) results.
- Guides the initial bolus and infusion rates.
- Adjusts therapy in real-time based on monitoring results.

3. Aminoglycoside Nomogram (e.g., Hartford Nomogram):

- Used for once-daily (extended-interval) dosing of drugs like gentamicin.
- Accounts for renal function and plasma concentrations measured after dosing.
- Helps avoid nephrotoxicity and ototoxicity associated with aminoglycosides.

Construction

- Based on population pharmacokinetic models.
- Includes axes for variables such as **body weight, renal function (e.g., CrCl or eGFR), desired plasma concentration, and dose**.
- Lines or curves intersecting various parameters guide users to an appropriate dose or interval.

Applications

- Estimating **loading and maintenance doses**

- Adjusting doses in **renal or hepatic impairment**
- Switching from **IV to oral dosing**
- Predicting **steady-state concentrations**
- Interpreting **therapeutic drug monitoring (TDM)** data

Advantages

- Quick and user-friendly
- Reduces the need for complex math
- Useful at bedside or in clinical settings

Limitations

- Limited to average population values
- May not account for **individual variability**
- Can be outdated as drug data evolves

Tabulations in designing dosage regimen

Definition

- Tabulations involve the use of **reference tables** that list drug dosing recommendations based on specific patient characteristics like:
 - **Age**
 - **Weight**
 - **Renal function (e.g., creatinine clearance)**
 - **Liver function**
 - **Comorbid conditions**

Common Tabulated Parameters

- Creatinine Clearance ranges **vs.** Recommended Dose/Interval.
- Body weight categories **vs.** Pediatric doses.
- Liver function status (Child-Pugh score) **vs.** Adjusted dose.

Example: Vancomycin Dose Table Based on CrCl

Creatinine Clearance (mL/min)	Dose (mg/kg)	Dosing Interval
> 90	15	Every 8–12 hrs
60–89	15	Every 12 hrs

30–59	15	Every 24 hrs
< 30	15	Every 48 hrs

Uses

- Quick reference for clinicians.
- Widely used in clinical guidelines and institutional protocols.
- Often integrated into **electronic medical records (EMR)** systems or clinical decision support systems (CDSS).

Applications

- **Dose selection** based on renal function (e.g., tables showing dose adjustments for various levels of CrCl)
- **Pediatric dosing** tables that provide weight-based or body surface area (BSA)-based doses
- **Therapeutic range tables** used in TDM (e.g., for lithium, phenytoin)

Sources of Tabulated Data

- Drug labels (FDA-approved)
- Clinical guidelines (e.g., Sanford Guide, Lexicomp, Micromedex)
- Pharmacology textbooks

Benefits

- Easy reference for quick clinical decisions
- Helps in standardizing therapy
- Often includes **initial dosing and adjustment protocols**

Limitations

- May not fit patients with **unique physiology**
- Doesn't replace **clinical judgment**
- Can be conservative, not optimized for all patient profiles

Conversion from Intravenous to Oral Dosing

Introduction

- The conversion from intravenous (IV) to oral (PO) dosing is a vital step in pharmacotherapy, especially in hospitalized patients.
- It helps maintain therapeutic efficacy while reducing hospital stay, lowering treatment costs, minimizing IV-related complications (like phlebitis or catheter infections), and improving patient comfort and mobility.

- Transitioning from IV to oral therapy is not a simple switch; it requires consideration of pharmacokinetics (like bioavailability), drug characteristics, patient-specific factors, and clinical condition.

Benefits of Conversion

A. Clinical Benefits:

- Reduces IV line-associated risks (e.g., infections, thrombophlebitis)
- Increases patient mobility
- Enhances patient comfort and satisfaction
- Facilitates earlier discharge

B. Economic Benefits:

- Reduces medication and equipment costs
- Decreases nursing workload and infusion system demands

C. Patient Safety:

- Reduces risk of IV dosing errors
- Encourages return to normal oral intake and outpatient care

Key Pharmacokinetic Concepts

Bioavailability (F)

- **Definition:** Fraction of the oral dose that reaches systemic circulation in active form.
- **IV Drugs:**
 - 100% bioavailability ($F = 1$).
- **Oral Drugs:** Often have lower bioavailability due to:
 - First-pass metabolism
 - Poor GI absorption
 - Chemical degradation in the GI tract
- **Oral Dose Calculation:**

$$\text{Oral Dose} = \frac{\text{IV Dose}}{F}$$

- **Example:**
 - If IV dose = 100 mg, and $F = 0.5$

$$\text{Oral Dose} = \frac{100}{0.5} = 200$$

First-Pass Metabolism



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