

Chapter 2

Drug Administration

Debra Si Mui Sim

Abstract Many drugs do not make it from bench to bedside because of poor pharmacokinetic properties. Many medicines fail to save lives or achieve their optimal potentials because practitioners are ill equipped in their pharmacokinetic knowledge. Before a drug can produce its desired clinical effect, it must first be able to reach its target site, be it on the body surface or inside the body. The amount of a drug and the rate at which the drug reaches the target site depend in part on the route taken to administer the drug. The choice of the route of drug administration in turn depends on various factors which are related to therapeutic concerns and drug properties. The therapeutic concerns include questions relating to the desired onset rate and duration of drug action, where the drug target site is (readily accessible or not) and whether or not patient compliance is an issue. The drug properties to be taken into account include its physicochemical characteristics (e.g., lipid solubility, molecular size, ionization status) and plasma concentration-time profile. Drugs can be administered by a wide variety of routes, each with its advantages and disadvantages. Therefore making a right choice of route may be the start of a successful therapeutic intervention.

Keywords Pharmacokinetics • Routes of administration • Enteral routes • Parenteral injections • Route of choice • First-pass effect • Local or systemic effect

Introduction

Choosing a drug for treating a clinical condition is often a qualitative decision. It depends on the mechanism of drug action and the goal of the therapeutic intervention. Having made that qualitative decision, we must necessarily consider quantitative aspects to ensure that the drug can get to the target sites to produce the desired effect clinically. Many drugs do not make it from bench to bedside because of poor pharmacokinetic properties. Many medicines fail to save lives or

D.S.M. Sim, B.Sc., Ph.D. (✉)

Department of Pharmacology, Faculty of Medicine, University of Malaya,
50603 Kuala Lumpur, Malaysia

e-mail: debrasim@ummc.edu.my

achieve their optimal potentials because practitioners are ill equipped in their pharmacokinetic knowledge. However, the amount of a drug and the rate at which the drug reaches the target site (be it on the body surface or inside the body) depend in part on the route taken to administer the drug. The choice of that route in turn depends on various factors which are related to therapeutic concerns and drug properties. Therefore making a correct choice of route may be the start of a successful therapeutic intervention.

What Is Pharmacokinetics

Before we consider the various routes of drug administration, let us first look at what pharmacokinetics is. Pharmacokinetics is the study of how drugs move within the body (Fig. 2.1). It describes the processes (rate and extent) by which an administered drug enters the body, gets distributed to the various tissues in the body and then eliminated from the body. There are two ways by which a drug is eliminated from the body: physically by excretion or chemically by metabolism (also known as biotransformation).

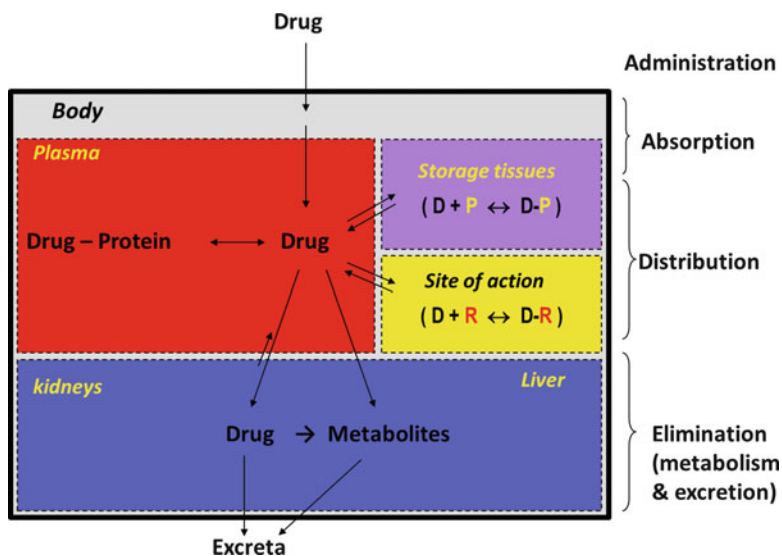


Fig. 2.1 Schematic diagram showing the various pharmacokinetic processes following administration of a drug. *D* drug, *P* protein, *R* receptor

How Pharmacokinetics Influence the Clinical Effect of a Drug

Pharmacokinetic processes, i.e., absorption, distribution, metabolism and excretion (ADME) determine how rapidly (hence, its speed of onset), in what concentration (hence, its intensity of effect), and for how long (hence, its duration of action) a drug will appear at its target tissues (Fig. 2.2).

Drug Administration

For a drug to be able to produce its intended clinical effects, it must first be able to reach its target site of action in the body at an effective concentration. If the drug is to act on some external surfaces, e.g., skin, ears or eyes, it may be applied directly on the affected surface. However, if the drug is meant to produce an effect inside the body, whether it be widespread (e.g., systemic antibiotics) or on some specific tissues (e.g., anti-thyroid agents), then the drug must be administered in such a way that it is able to get into the systemic circulation and be transported to the site (s) where the deranged body function is to be rectified.

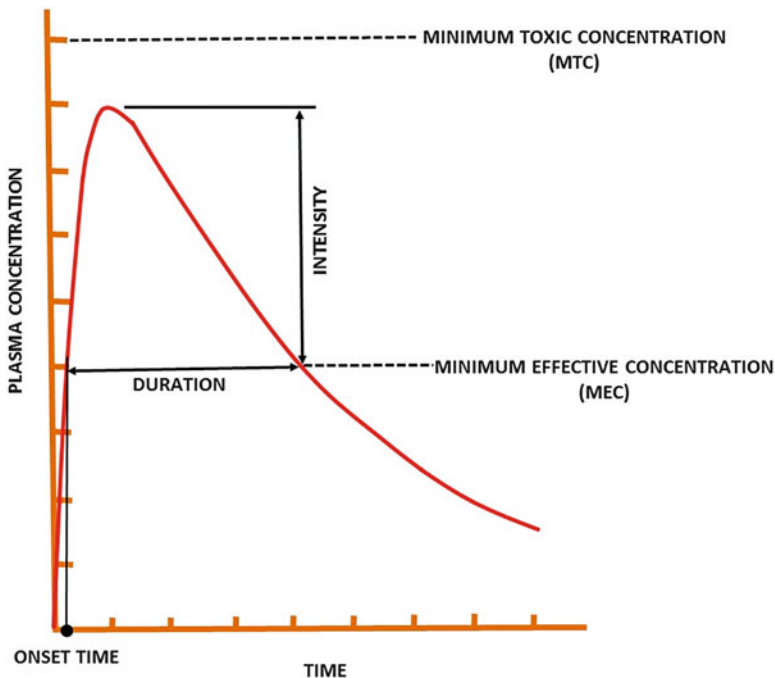


Fig. 2.2 Plasma concentration-time curve showing the onset time, duration of action and intensity of effects

How Drugs Are Administered

Drugs can be administered by a wide variety of routes. These may be generally divided into enteral routes (e.g., sublingual, oral, and rectal), parenteral injections (e.g., subcutaneous, intramuscular, and intravenous), inhalation, topical, transdermal and intranasal. Certain special routes may be used to provide better therapeutic outcomes: intra-arterial route in cancer chemotherapy and intrathecal route for central nervous system infections or for spinal anesthesia. These routes are much more hazardous and would obviously require greater skills and care in administering the drug.

Which Route of Administration

When making decision on the route of administration, two major factors come to mind: therapeutic concerns and drug properties. The therapeutic concerns include questions relating to the desired onset rate and duration of drug action, where the drug target site is (readily accessible or not) and whether or not patient compliance is an issue. The drug properties to be taken into account include its physicochemical characteristics (e.g., lipid solubility, molecular size, ionization status) and plasma concentration-time profile. The advantages and disadvantages of some of the common routes of administering drugs are given in Table 2.1.

Acute or Chronic Condition

In an acute or emergency situation, the route used must allow sufficiently fast absorption to ensure a prompt onset of action. Thus, the parenteral injection (intravenous, intramuscular or subcutaneous) is often the route of choice in acute care. Other routes that may be used in acute situations include intrathecal route for amphotericin B in cryptococcal meningitis, inhalation route for bronchodilators (by nebulizer) in acute bronchial asthma attack, or sublingual route for nitroglycerin in acute angina attack. With young children, the rectal route (as enema or suppository) may also be used, especially when the patient is unconscious or when vomiting occurs. However, for the treatment of chronic illnesses, the onset rate is not so much of a concern, whereas a more convenient route (e.g., oral, transdermal or topical) and simple dosing regimen (e.g., once-daily or once weekly dosing) would ensure better patient compliance. Formulation that can provide controlled release of the drug would be an added advantage especially in situation of poor patient compliance (e.g., severe depression). That is notwithstanding the need to take into account the cost factor. Transdermal route is usually more expensive because of the cost involved in manufacturing the delivery system.

Table 2.1 Advantages and disadvantages of some common routes of drug administration

Route	Advantages	Disadvantages
Intravenous (IV)	Absorption circumvented; prompt onset; Suitable for large volumes and for irritating substances	Most hazardous (embolism, infection, anaphylaxis); Not suitable for oily solutions or poorly hydrophilic substances
Intramuscular (IM)	Absorption may be tailored to needs: prompt, from aqueous solution; slow and sustained, from repository formulations; Suitable for moderate volumes, oily vehicles and some irritating substances	Precluded during anticoagulant therapy; May be painful
Subcutaneous (SC)	Absorption may be tailored to needs: prompt, from aqueous solution; slow and sustained, from repository formulations; Suitable for some poorly soluble suspensions and for instillation of slow-release implants; self-administration is acceptable	Not suitable for large volumes or irritating substances; Possible pain or necrosis from irritating substances
Oral (PO)	Most convenient; Relatively cheap and safe	Variable absorption (potentially slow, erratic and incomplete); First-pass effect may be significant
Rectal (PR)	Partially avoid first-pass effect; Avoid destruction by gastric acid & digestive enzymes	May irritate rectal mucosa; Not a well-accepted route
Sublingual (SL)	Prompt absorption; Bypasses first-pass effect (unless ingested)	Inconvenient for long-term use; Limited to certain types of drugs that can be given in small doses
Inhalation	Almost instantaneous absorption and very rapid onset; Avoid hepatic first-pass effect; May provide localized effect to lungs with minimal systemic side effect	Difficulty in regulating doses (inhaler); Requires special equipment for drug delivery
Transdermal	May provide a sustained effect; Avoid hepatic first-pass effect	Usually very slow onset; Enhanced absorption and risk of toxic effects with inflamed, abraded or burned skin; Drugs must be highly lipophilic

Lipophilic or Hydrophilic Drugs

The suitability of the route chosen also depends on the drug properties (both physical and chemical). Some drugs (e.g., theophylline, phenobarbital, propofol) are not sufficiently aqueous soluble to be given by intravenous injection per se and if needed, these drugs have to be formulated for better aqueous solubility (e.g., aminophylline, phenobarbital sodium) or given as an emulsion (e.g. propofol). On the other hand, most drugs are not sufficiently lipid soluble to be able to

permeate the intact skin. Therefore, only highly lipid soluble drugs such as nitroglycerin, fentanyl, scopolamine, nicotine and estrogen can be formulated for sustained release by transdermal delivery system. Organophosphate insecticides are also very lipid soluble and poisoning can occur through contact with contaminated clothes.

High or Low First-Pass Effect

Some drugs are not stable in the gastric acid environment (e.g., benzylpenicillin) or may undergo extensive hepatic first-pass elimination (e.g., nitroglycerin) and are thus not suitable to be given orally. However some drugs, such as morphine and propranolol, may still be effective orally despite high first-pass effect because of active metabolites, which possess some of the pharmacological actions of the parent drugs.

Vaporized or Atomized Substances

Drugs which are gaseous (e.g., nitrous oxide) or readily vaporized (e.g., isoflurane) may be inhaled. Solid drugs may also be given by inhalation route in the form of aerosols or suspended powder (e.g., salbutamol and beclomethasone). The inhalation route may be used for producing both local (e.g., bronchodilatation in asthma) as well as systemic effects (anesthesia). It is also an important portal of entry for certain drugs of abuse and environmental toxicants. The main disadvantage with the inhalation route for therapeutic use is the difficulty in regulating the dose given and the cost of the delivery system. Intranasal route is usually used for local application (e.g., oxymetazoline for nasal decongestion) but it may occasionally be used for systemic effects (e.g., desmopressin for diabetes insipidus and calcitonin for osteoporosis).

Key Concepts

- For a drug to be clinically useful, it must also have an appropriate pharmacokinetic profile besides having the desired pharmacodynamic action.
- The choice of the route of drug administration depends mainly on two major factors: therapeutic concerns and drug properties.
- Parenteral injection routes are often the routes of choice in acute care while oral route is the most common route used in chronic illnesses.
- The physical and chemical properties of a drug can influence both the dosage form as well as the route(s) by which it may be administered.

Summary

The choice of the route of drug administration depends on various factors which are related to therapeutic concerns and drug properties. The therapeutic concerns include questions relating to the desired onset rate and duration of drug action, where the drug target site is (readily accessible or not) and whether or not patient compliance is an issue. The drug properties to be taken into account include its physicochemical characteristics (e.g., lipid solubility, molecular size, ionization status) and plasma concentration-time profile. Drugs can be administered by a wide variety of routes, each with its advantages and disadvantages. It is important to make the right choice in order to have a successful therapeutic outcome.

Further Reading

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