RESPIRATORY CARE PHARMACOLOGY

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CHAPTER 2

Principles of Drug Action

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CHAPTER OUTLINE

The entire course of a drug's action, from *dose* to *effect*, can be understood in three phases of action: the *drug administration* phase, the *pharmacokinetic* phase, and the *pharmacodynamic* phase. This useful conceptual framework, based on the principles offered by Ariëns and Simonis,[1] organizes the steps of a drug's action from drug administration through effect and ultimate elimination from the body. This framework is illustrated in Figure 2-1, and provides an overview of the interrelationship of the three phases of drug action, each of which is discussed.

The Drug Administration Phase

Definition: The drug administration phase describes the method by which a drug dose is made available to the body.

Drug Dosage Forms

The drug administration phase entails the interrelated concepts of drug formulation (e.g., compounding a tablet for particular dissolution properties) and drug delivery (e.g., designing an inhaler to deliver a unit dose). Two key topics of this phase are the drug dosage form and the route of administration. The drug *dosage form* is the physical state of the drug in association with nondrug components such as the vehicle. Tablets, capsules, and injectable solutions are common examples of drug dosage forms. The *route of administration* is the portal of entry for the drug into the body, such as oral (enteral), injection, or inhalation. The form in which a drug is available must be compatible with the route of administration desired. For example, the injectable route, such as intravenously, requires a liquid solution of a drug, whereas the oral route is possible with capsules, tablets, or liquid solutions. Some common drug formulations are listed in Box 2-1 for each of the common routes of drug administration.

Drug Formulations and Additives

A drug is the active ingredient in a dose formulation, but it is usually not the only ingredient in the total formulation. For example, in a capsule of an antibiotic, the capsule itself is a gelatinous material that allows the drug to be swallowed. The capsule material then disintegrates in the stomach, and the active drug ingredient is released for absorption. The rate at which active drug is liberated from a capsule or tablet can be controlled during the formulation process, for example, by altering drug particle size or using a specialized coating or formulation matrix. Aerosolized agents for inhalation and treatment of the respiratory tract also contain ingredients other than the active drug. These include preservatives, propellants for metered dose inhaler formulations (MDIs), dispersants (surfactants), and carrier agents with dry powder inhalers (DPIs). An example of three formulations with differing ingredients for the adrenergic bronchodilator albuterol is given in Table 2-1. In the nebulizer so-

lution, the benzalkonium chloride is a preservative and sulfuric acid adjusts the pH of the solution. In the MDI, the chlorofluorocarbons are propellants and oleic acid is a dispersing agent. Similarly, in the DPI formulation, the lactose acts as a bulking agent to improve uniform dispersion of the drug powder.

ROUTES OF ADMINISTRATION

Advances in drug formulation and delivery systems have yielded a wide range of routes by a which a drug can be administered. In the discussion below, routes of administration have been divided into five broad categories: *enteral, parenteral, inhalation, transdermal,* and *topical.*

ENTERAL

The term *enteral* refers literally to the small intestine, but the enteral route of administration is more broadly applicable to administration of drugs intended for absorption anywhere along the gastrointestinal tract. The most common enteral route is by mouth (oral) because it is convenient, is painless, and offers flexibility in possible dose forms of the drug, as seen Table 2-1. The oral route requires the patient to be able to swallow, and airway protective reflexes should be intact. If the drug is not destroyed or inactivated in the stomach and can be absorbed into the bloodstream, distribution throughout the body and a

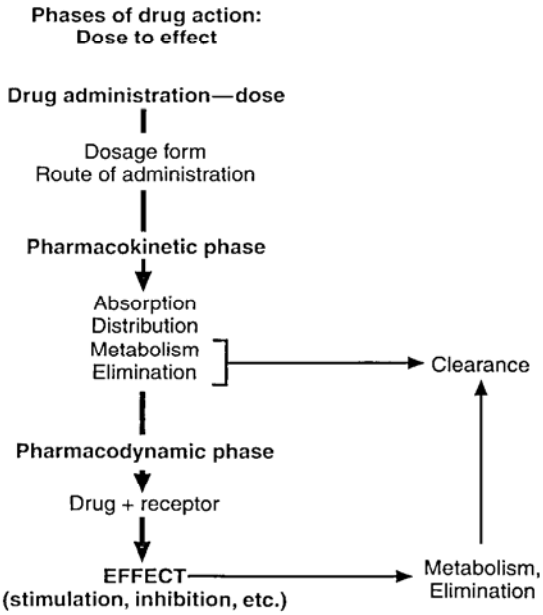

Figure 2-1 The conceptual scheme illustrating the major phases of drug action in sequence, from dose administration to effect in the body. (Modified from Ariëns EJ, Simonis AM: Drug action: target tissue, dose-response relationships, and receptors. In Teorell T, Dedrick RL, Condliffe PG, eds: *Pharmacology and pharmacokinetics,* New York, 1974, Plenum Press.)

Box 2-1 Common Drug Formulations for Different Routes of Administration

Enteral	Parenteral	Inhalation	Transdermal	Topical
Tablet	Solution	Gas	Patch	Powder
Capsule	Suspension	Aerosol	Paste	Lotion
Suppository	Depot			Ointment
Elixir				Solution
Suspension				

Table 2-1
Three different dosage forms for the bronchodilator drug albuterol indicating ingredients other than active drug

DOSAGE FORM	ACTIVE DRUG	INGREDIENTS
Nebulizer solution	Albuterol sulfate	Benzalkonium chloride, sulfuric acid
Metered dose inhaler	Albuterol	Trichloromonofluoromethane, dichlorodifluoromethane, oleic acid
Dry powder inhaler	Albuterol	Lactose

systemic effect can be achieved. Other enteral routes of administration include suppositories inserted in the rectum, tablets placed under the tongue (sublingual), and drug solutions introduced though an indwelling gastric tube.

Parenteral (Injectable)

Technically, the term *parenteral* means "besides the intestine," which implies any route of administration other than enteral. However, the parenteral route is commonly taken to mean injection of a drug. Various options are available for injection of a drug, the most common of which are the following:

Intravenous (IV): Injected directly into the vein, allowing nearly instantaneous access to the systemic circulation. Drugs can be given as a bolus, in which case the entire dose is given rapidly, leading to a sharp rise in the plasma concentration, or a steady infusion can be used to avoid this precipitous rise.

Intramuscular (IM): Injected deep into a skeletal muscle. Because the drug must be absorbed from the muscle into the systemic circulation, the drug effects occur more gradually than with intravenous injection, although typically more rapidly than by the oral route.

Subcutaneous (SC): Injected into the subcutaneous tissue beneath the epidermis and dermis.

Transdermal

An increasing number of drugs are being formulated for application to the skin to produce a systemic effect. The advantage of this route is that it can supply long-term continuous delivery to the systemic circulation. The drug is absorbed percutaneously, obviating the need for a hypodermic needle and decreasing the fluctuations in plasma drug levels that can occur with repeated oral administration.

Inhalation

Drugs can be given by inhalation for either a systemic effect or a local effect in the lung. Two of the most common drug formulations given by this route are gases, which usually are given by inhalation for anesthesia (a systemic effect), and aerosolized agents intended to target the lung or respiratory tract in the treatment of respiratory disease (local effect). The technology and science of aerosol drug delivery to the respiratory tract continues to develop and is described in detail in Chapter 3. A summary of devices commonly used for inhaled aerosol drug delivery is given in Box 2-2. The general rationale for aerosolized drug delivery to the airways for treating respiratory disease is the local delivery of the drug to the target organ, with reduced or minimal body exposure to the drug and hopefully reduced prevalence or severity of possible side effects.

Box 2-2 Devices for Inhaled Administration of Drugs

Vaporizer (anesthetic gases)
Atomizer
Nebulizer, small or large
Metered dose inhaler (MDI), with/without spacer
Dry powder inhaler (DPI)
Ultrasonic nebulizer (USN)

Topical

Drugs can be applied directly to the skin or mucous membranes to produce a local effect. Such drugs are often formulated to minimize systemic absorption. Examples of topical administration include the application of corticosteroid cream to an area of contact dermatitis (e.g., poison ivy), administration of an eye drop containing a β-adrenergic antagonist to control glaucoma, and instillation of nasal drops containing an α-adrenergic agonist to relieve congestion.

The Pharmacokinetic Phase

Definition: The pharmacokinetic phase of drug action describes the time course and disposition of a drug in the body, based on its absorption, distribution, metabolism and elimination.

Once presented to the body, as described in the drug administration phase, a drug crosses local anatomical barriers to varying extents depending on its chemical properties and the physiological milieu of the body compartment it occupies. For a systemic effect it is desirable for the drug to get into the bloodstream for distribution to the body; for a local effect this is not desirable and can lead to unwanted side effects throughout the body. The four topics of absorption, distribution, metabolism, and elimination describe the factors influencing and determining the course of a drug after it is introduced to the body. In essence, *pharmacokinetics* describes what the body does to a drug and *pharmacodynamics* describes what the drug does to the body.

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