DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 26

Drug Dynamics for Analytical, Clinical, and Biological Chemists

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DRUGS AND THE PHARMACEUTICAL SCIENCES

A Series of Textbooks and Monographs

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Preface

The purpose of this monograph was to introduce to analysts performing therapeutic drug monitoring the many physiological and biochemical aspects related to drug dynamics or drug action. It became increasingly evident to us that many technicians and analysts working in the areas of clinical chemistry, biochemistry, analytical chemistry, and toxicology, as well as those in some pharmaceutical laboratories, have been generating volumes of drug test results with little or no appreciation for what is involved in a drug's disposition in the patient's body after its administration by the physician.

This monograph was written in a condensed version so as to elucidate the various aspects involved in this ever-growing area. It should be of value to the layman as well as the professional, and covers such subjects as drug administration (routes of entry), principles governing drug absorption and distribution, major pathways of and factors influencing biotransformation of drugs, the elimination of drugs, and the mechanisms of drug action. It is essentially a book on drug dynamics—a basic primer for those performing drug analyses.

Benjamin J. Gudzinowicz
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Introduction

It is not the purpose of this book to delve deeply into various aspects of pharmacology such as biostatistics, drug administration, distribution, biotransformation (metabolism) and elimination, drug interactions, dose-response and dose-time relationships, and so on, since these subjects are more authoritatively presented in many fine reference books [1-31]. Nevertheless, these areas will be discussed briefly in order to place into proper perspective the problems associated with the analysis of drugs and their metabolites in biological fluids or media. A basic understanding of the underlying principles is essential for analytical, clinical, and biological chemists to assist them in the design and conduct of more efficient, meaningful research approaches to problem solving and also to make them more appreciative of the complexity of biochemical analyses in general. On the other hand, the tools by which some pharmacological problems can be solved have been discussed in a three-volume analytical series dealing specifically with gas chromatography (GC) [32], mass spectrometry (MS) [33], and the integrated GC-MS analytical system [34], these instrumental techniques serving as the basis for a seven-volume set of books by Gudzinowicz and Gudzinowicz [35-41] for the analysis of drugs and their metabolic products in varied biological media. As in pharmacology, their fundamentals must also be understood in order to utilize these analytical techniques to their fullest potential.

1

Drug Administration: Routes of Entry

Drugs may be administered into the body by either of two routes, parenteral or enteral. If administered parenterally, the gastrointestinal tract is bypassed, the commonest parenteral routes being intravascular, intramuscular, subcutaneous, topical (percutaneous), intradermal, inhalation, intra-arterial, and intravaginal. On the other hand, the administration of drugs by the enteral route is achieved via a sublingual, oral, or rectal process. Since the purpose of drug administration is to ensure an effective level of the therapeutic agent at its site of action, various factors, such as passage of drugs across body membranes, absorption, distribution of the therapeutic agent in the body, drug metabolism or biotransformation, and rate of excretion or elimination of drugs, influence the attainment of such a level within the human or animal system under study [6].

I. PARENTERAL ROUTES OF ADMINISTRATION

A. Intravascular Administration

Intravenous injection of drugs directly into the bloodstream has several advantages: the rapidity by which the drug can be circulated with a minimum of delay, and the ability to control the rate of drug administration to establish and maintain within rather well-defined narrow limits a plasma plateau via a continuous but controlled infusion. By reducing its rate or stopping

the infusion, local, excessive drug concentrations can be drastically reduced. Permitting a more rapid drug action than can normally be achieved by either subcutaneous or intramuscular administration, the intravenous approach is at times more suitable for therapeutics that are less readily adsorbed from the gastrointestinal tract or tissue depots but more susceptible to possible destruction before appreciable absorption could occur (e.g., protein hormones, blood plasma, plasma substitutes, and whole blood) [1]. On the other hand, possible complications may result using the intravascular route: (a) anaphylactoid reactions resulting from the administration of a therapeutic agent to a sensitized person, (b) embolism by the inadvertent administration of particulate matter into the vein, (c) erythrocyte agglutination or hemolysis as a consequence of hypotonic or hypertonic solution injection, (d) infection by bacterial contaminants, and (e) the fact that once injected, the drug cannot be recalled.

B. Intra-Arterial Administration

In order to achieve a high local concentration in a specific area of the body before the onset of plasma volume dilution, drugs may be injected into the artery. The intra-arterial route is used principally for diagnostic therapeutics; it is rarely used otherwise except for specialized techniques in cancer chemotherapy.

C. Intramuscular Administration

More vascular and less sensitive than subcutaneous tissue and more tolerant to irritant suspensions or solutions, drug absorption is generally rapid when injected in the gluteal or deltoid regions of skeletal muscle. The rate of absorption is nevertheless dependent on many critical factors: (a) ionization of the drug, (b) lipid solubility of the drug, (c) vascularity of the site, and (d) solution osmolality, in addition to many other possible variables.

D. Subcutaneous Administration

The same factors that determine the therapeutic agent's rate of absorption from skeletal muscle influence its absorption from subcutaneous tissues. Its absorption can be retarded by incorporating a vasoconstrictor agent in the drug solution to be administered, by drug implantation in a solid pellet form under the skin, by vasoconstriction initiated by local cooling, by limb immobilization,

or by tourniquet application adjacent to the injection site to impede or block superficially lymphatic flow and venous drainage.

E. Intradermal Administration

Small amounts of isotonic materials can be injected into the skin and, if properly administered superficially at a depth not exceeding several cell layers, a wheal is formed. This drug administration route is used for the introduction of antigens for skin tests and anesthetics to create an insensitive area for subsequent painless, deeper injections of a local anesthetic via a larger needle.

F. Topical (Percutaneous) Administration

Dermatological administration of drugs and their subsequent absorption through the skin barrier, which behaves qualitatively like a cellular membrane (the rate of penetration governed largely by their water-soluble ions, polar molecules, and lipid-water partition coefficients), requires that consideration be given not only to the pharmacological effect of the active agent but additionally to the physical form of the preparation (wet preparations, powders, shake lotions, emulsions, creams, or hydrophilic ointments, pastes, ointments, or direct drug application either as a simple solution, tincture, paint, suspension, or as crystals), which may itself have a therapeutic or adjuvant effect [20]. On the other hand, the pharmacological effects or actions resulting from the form of the topical medication may vary: (a) antipruritic, (b) astringent, (c) keratoplastic, (d) keratolytic, (e) antibacterial, (f) anti-inflammatory, (g) antifungal, or (h) parasiticidal. To facilitate drug penetration through the skin, research efforts have been directed toward the development of pharmacologically inert organic solvents to expand the usefulness of the percutaneous route for drugs with systemic actions [1]. Iontophoresis has also been used to drive by electrical gradients drugs into the skin after an ionized drug in solution is placed in an absorbent material on the skin in contact with an electrode. The drug ions are forced to migrate through the epidermis by applying a galvanic current to this electrode and another placed elsewhere on the body surface.

G. Drug Administration by Inhalation

Inhalation of drugs as aerosols (either liquid or solid particles) enter the circulation by diffusing across the permeable alveolar membranes. The degree of impaction (a term used to describe

the aerosol particles in the respiratory tract) is rate dependent: that of sedimentation, diffusion, and inertial precipitation. For different parts of the respiratory tract, the extent of impaction can be determined for various particle sizes. Furthermore, the rate of drug absorption through the alveolar epithelium is strongly particle size dependent. Under certain circumstances, aerosol therapy (tranquilizers, diuretics, penicillin, glycosides, and digitalis) have been used effectively for systemic effects. However, the unrestricted use of aerosols containing isoproterenol and related bronchodilators can be fatal, as indicated by Speizer et al. [42], who noted a large increase in mortality from asthma in England during a 7-year monitoring period, the death rate paralleling the over-the-counter sales of these aerosols.

II. ENTERAL ROUTES OF ADMINISTRATION

A. Sublingual Administration

Like that of the rest of the alimentary canal, the epithelial lining of the mouth behaves as a lipidlike membrane barrier to the passage of drugs. Drugs in tablet form placed under the tongue (sublingual) between the buccal and gingival mucosa are absorbed from this site and enter the systemic rather than the portal circulation, its absorption being much more rapid than after the drug is swallowed.

B. Oral Administration

The most common drug administration route is via the mouth, it being painless, convenient, and economical. However, as noted by Schanker [43], the oral route of administration has certain liabilities or disadvantages: (a) gastric acid or digestive enzymatic destruction of some drugs; (b) precipitation or insolubility in gastrointestinal fluids of some drugs; (c) formation of drug-food nonabsorbable complexes; (d) variable absorption rates as a consequence of physiological factors such as gastric emptying time, gastrointestinal motility, and mixing; (e) poor effectiveness in an emergency situation if the rate of absorption is too slow; and (f) possible gastric mucosa irritation, with resultant nausea or vomiting. In contrast to a compound administered in aqueous solution, its absorption rate, if administered in solid form, is influenced by its rate of solution. Levy [44] has shown that its rate of solution depends on several factors: (a) particle size, solubility, salt form, and crystallinity of the drug; (b) the disintegration rate of the solid drug in the

gastrointestinal lumen; and (c) gastrointestinal pH, motility, and food content.

C. Rectal Administration

In the form of suppositories or, less commonly, by enema, drugs may be administered rectally either for systemic effects or as local therapy. As in other parts of the alimentary canal, drugs are transported across the rectal mucosa via the same mechanism. Possessing a rather small surface area (being devoid of villi but having a rich lymphatic and vascular supply), drug absorption is usually slow. For this reason, rectal medication is normally used when the oral route is unsatisfactory, especially when orally administered drugs are either destroyed in the intestinal fluids or cause gastric irritation. The inert substances used for suppository preparations include polyethylene glycol, cocoa butter, and glycerinated gelatin.