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BIOAVAILABILITY AND BIOEQUIVALENCE

Many drugs are marketed by more than one pharmaceutical manufacturer. The study of biopharmaceutics gives substantial evidence that the method of manufacture and the final formulation of the drug can markedly affect the bioavailability of the drug. Because of the plethora of drug products containing the same amount of active drug, physicians, pharmacists, and others who prescribe, dispense, or purchase drugs must select generic products that produce an equivalent therapeutic effect to the brand product. To facilitate such decisions, guidelines have been developed by the United States Food and Drug Administration (FDA). The guidelines are available on the Internet (http://www.fda.gov). Some of the guidelines also appear in the United States Pharmacopeia/National Formulary (USP-NF). These guidelines and methods for determining drug availability are discussed in this chapter.

DEFINITIONS

- *Bioavailability.* Indicates a measurement of the rate and extent (amount) of therapeutically active drug that reaches the systemic circulation and is available at the site of action.
- *Bioequivalence requirement.* A requirement imposed by the Food and Drug Administration (FDA) for *in vitro* and/or *in vivo* testing of specified drug products which must be satisfied as a condition for marketing.
- *Bioequivalent drug products.* Bioequivalent drug products are pharmaceutical equivalents that have similar bioavailability (ie, are not significantly different with respect to rate and extent of absorption) when given in the same molar dose and studied under similar experimental conditions. Some drugs may be considered bioequivalent that are equal in the extent of absorption but *not* in the rate of absorption; this is possible if the difference in the rate of absorption is considered clinically insignificant, is not essential for the attainment of effective body drug concentrations on chronic use, and is reflected in the proposed labeling. For example, aspirin and acetaminophen are well-absorbed drugs, and small differences in the rate of absorption are of very little clinical consequence. Bioequivalence

may sometimes be demonstrated using an *in vitro* bioequivalence standard, especially when such an *in vitro* test has been correlated with human in vivo bioavailability data. For some products, other *in vivo* tests may be appropriate, including comparative clinical trials or pharmacodynamic studies.

- *Brand name.* Trade name of the drug. This name is privately owned by the manufacturer or distributor and is used to distinguish the specific drug product from competitors' products (eg, Tylenol, McNeil Laboratories).
- *Chemical name.* Name used by the organic chemist to indicate the chemical structure of the drug (eg, N-acetyl-*p*-aminophenol).
- *Drug product.* The finished dosage form (eg, tablet, capsule or solution) that contains the active drug ingredient, generally, but not necessarily, in association with inactive ingredients.
- *Drug product selection.* The process of choosing or selecting the drug product in a specified dosage form.
- *Drug substance.* A drug substance is the active pharmaceutical ingredient (API) or component in the drug product that furnishes the pharmacodynamic activity.
- *Equivalence.* Relationship in terms of bioavailability, therapeutic response, or a set of established standards of one drug product to another.
- *Generic name.* The established, nonproprietary, or common name of the active drug in a drug product (eg, acetaminophen).
- *Generic substitution.* The process of dispensing a different brand or unbranded drug product in place of the prescribed drug product. The substituted drug product contains the same active ingredient or therapeutic moiety as the same salt or ester in the same dosage form but is made by a different manufacturer. For example, a prescription for Motrin brand of ibuprofen might be dispensed by the pharmacist as Advil brand of ibuprofen or as a nonbranded generic ibuprofen if generic substitution is permitted and desired by the physician.
- *Pharmaceutical alternatives.* Drug products that contain the same therapeutic moiety but as different salts, esters, or complexes. For example, tetracycline phosphate or tetracycline hydrochloride equivalent to 250 mg tetracycline base are considered pharmaceutical alternatives. Different dosage forms and strengths within a product line by a single manufacturer are pharmaceutical alternatives (eg, an extended-release dosage form and a standard immediate-release dosage form of the same active ingredient).
- *Pharmaceutical equivalents.* Drug products that contain the same active drug ingredient (same salt, ester, or chemical form) and are identical in strength or concentration, dosage form, and route of administration (eg, diazepam, 5 mg oral tablets). *Chemical equivalents* are pharmaceutical equivalents. Pharmaceutical equivalent drug products must meet the identical standards (strength, quality, purity, and identity), but may differ in such characteristics as color, flavor, shape, scoring configuration, packaging, excipients, preservatives, expiration time, and (within certain limits) labeling.
- *Pharmaceutical substitution.* The process of dispensing a pharmaceutical alternative for the prescribed drug product. For example, ampicillin suspension is dispensed in place of ampicillin capsules, or tetracycline hydrochloride is dispensed in place of tetracycline phosphate. Pharmaceutical substitution generally requires the physician's approval.
- *Therapeutic alternatives.* Drug products containing different active ingredients that are indicated for the same therapeutic or clinical objectives. Active ingredients in therapeutic alternatives are from the same pharmacologic class and are ex-

pected to have the same therapeutic effect when administered to patients for such condition of use. For example, ibuprofen is given instead of aspirin; cimetidine may be given instead of ranitidine.

- *Therapeutic equivalents.* Therapeutic equivalents are drug products that contain the same therapeutically active drug that should give the same therapeutic effect and have equal potential for adverse effects under conditions set forth in the labels of these drug products. Therapeutic drug products may differ in certain characteristics, such as color, scoring, flavor, configuration, packaging, preservatives, and expiration date. Therapeutic equivalent drug products must be (1) safe and effective, (2) pharmaceutical equivalents, (3) bioequivalent, (4) adequately labeled, and (5) manufactured in compliance with current good manufacturing practices.
- *Therapeutic substitution.* The process of dispensing a therapeutic alternative in place of the prescribed drug product. For example, amoxicillin is dispensed for ampicillin or acetaminophen is dispensed for aspirin.

PURPOSE OF BIOAVAILABILITY STUDIES

Bioavailability studies are performed for both approved active drug ingredients or therapeutic moieties not yet approved for marketing by the FDA. New formulations of active drug ingredients or therapeutic moieties must be approved prior to marketing by the FDA. In approving a drug product for marketing, the FDA must ensure that the drug product is safe and effective for its labeled indications for use. Moreover, the drug product must meet all applicable standards of identity, strength, quality, and purity. To ensure that these standards are met, the FDA requires bioavailability/pharmacokinetic studies and where necessary bioequivalence studies for all drug products.

For unmarketed drugs which do not have full new drug application (NDA) approval by the FDA, *in vitro* and/or *in vivo* bioequivalence studies must be performed on the drug formulation proposed for marketing as a generic drug product. Furthermore, the essential pharmacokinetics of the active drug ingredient or therapeutic moiety must be characterized. Essential pharmacokinetic parameters including the rate and extent of systemic absorption, elimination half-life, and rates of excretion and metabolism should be established after single- and multiple-dose administration. Data from these *in vivo* bioavailability studies are important to establish recommended dosage regimens and to support drug labeling.

In vivo bioavailability studies are performed also for new formulations of active drug ingredients or therapeutic moieties that have full NDA approval and are approved for marketing. The purpose of these studies is to determine the bioavailability and to characterize the pharmacokinetics of the new formulation, new dosage form, or new salt or ester relative to a reference formulation.

After the bioavailability and essential pharmacokinetic parameters of the active ingredient or therapeutic moiety are established, dosage regimens may be recommended in support of drug labeling.

In summary, clinical studies are useful in determining the safety and efficacy of the drug product. Bioavailability studies are used to define the effect of changes in the physicochemical properties of the drug substance and the effect of the drug product (dosage form) on the pharmacokinetics of the drug. Bioequivalence studies are used to compare the bioavailability of the same drug (same salt or ester)

from various drug products. If the drug products are bioequivalent and therapeutically equivalent (as defined above), then the clinical efficacy and the safety profile of these drug products are assumed to be similar and may be substituted for each other.

RELATIVE AND ABSOLUTE AVAILABILITY

The area under the drug concentration–time curve (AUC) is used as a measure of the total amount of unaltered drug that reaches the systemic circulation. The AUC is dependent on the total quantity of available drug, FD_0, divided by the elimination rate constant, k, and the apparent volume of distribution, V_D. F is the fraction of the dose absorbed. After IV administration, F is equal to unity, because the entire dose is placed into the systemic circulation. Therefore, the drug is considered to be completely available after IV administration. After oral administration of the drug, F may vary from a value of 0 (no drug absorption) to 1 (complete drug absorption).

Relative Availability

Relative (apparent) availability is the availability of the drug from a drug product as compared to a recognized standard. The fraction of dose systemically available from an oral drug product is difficult to ascertain. The availability of drug in the formulation is compared to the availability of drug in a standard dosage formulation, usually a solution of the pure drug evaluated in a crossover study. The relative availability of two drug products given at the same dosage level and by the same route of administration can be obtained with the following equation:

$$\text{Relative availability} = \frac{[\text{AUC}]_A}{[\text{AUC}]_B} \qquad \textbf{(10.1)}$$

where drug product B is the recognized reference standard. This fraction may be multiplied by 100 to give *percent* relative availability.

When different doses are administered, a correction for the size of the dose is made, as in the following equation:

$$\text{Relative availability} = \frac{[\text{AUC}]_A/\text{dose } A}{[\text{AUC}]_B/\text{dose } B}$$

Urinary drug excretion data may also be used to measure relative availability, as long as the total amount of intact drug excreted in the urine is collected. The percent relative availability using urinary excretion data can be determined as follows:

$$\text{Percent relative availability} = \frac{[D_u]_A^\infty}{[D_u]_B^\infty} \times 100 \qquad \textbf{(10.2)}$$

where $[D_u]^\infty$ is the total amount of drug excreted in the urine.

Absolute Availability

The absolute availability of drug is the systemic availability of a drug after extravascular administration (eg, oral, rectal, transdermal, subcutaneous). The absolute availability of a drug is generally measured by comparing the respective AUCs

after extravascular and IV administration. This measurement may be performed as long as V_D and k are independent of the route of administration. Absolute availability after oral drug administration using plasma data can be determined as follows:

$$\text{Absolute availability} = \frac{[\text{AUC}]_{\text{PO}}/\text{dose}_{\text{PO}}}{[\text{AUC}]_{\text{IV}}/\text{dose}_{\text{IV}}} = \frac{F}{z} \tag{10.3}$$

Absolute availability using urinary drug excretion data can be determined by the following:

$$\text{Absolute availability} = \frac{[D_u]^{\infty}_{\text{PO}}/\text{dose}_{\text{PO}}}{[D_u]^{\infty}_{\text{IV}}/\text{dose}_{\text{IV}}} \tag{10.4}$$

The absolute bioavailability is also equal to F, the fraction of the dose that is bioavailable. Absolute availability is sometimes expressed as a percent, ie, $F = 1$, or 100%. For drugs given intravascularly, such as by IV bolus injection, $F = 1$, because all the drug is completely absolved. For all extravascular routes of administration, $F \leq 1$. F is usually determined by Equations 10.3 or 10.4.

PRACTICE PROBLEM

The bioavailability of a new investigational drug was studied in 12 volunteers. Each volunteer received either a single oral tablet containing 200 mg of the drug, 5 mL of a pure aqueous solution containing 200 mg of the drug, or a single IV bolus injection containing 50 mg of the drug. Plasma samples were obtained periodically up to 48 hr after the dose and assayed for drug concentration. The average AUC values (0 to 48 hr) are given in the table below. From these data, calculate (1) the relative bioavailability of the drug from the tablet compared to the oral solution and (2) the absolute bioavailability of the drug from the tablet.

Drug Product	Dose (mg)	AUC(μg hr/mL)	Standard Deviation
Oral tablet	200	89.5	19.7
Oral solution	200	86.1	18.1
IV bolus injection	50	37.8	5.7

Solution

The relative bioavailability of the drug from the tablet is estimated using Equation 10.1. No adjustment for dose is necessary.

$$\text{Relative bioavailability} = \frac{89.5}{86.1} = 1.04$$

The relative bioavailability of the drug from the tablet is 1.04, or 104%, compared to the solution. In this study, the difference in drug bioavailability between tablet and solution was not statistically significant.

The absolute drug bioavailability from the tablet is calculated using Equation 10.3 and adjusting for the dose.

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