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“An Overview of Bioavailability and Bioequivalence Study in Human Subject”.

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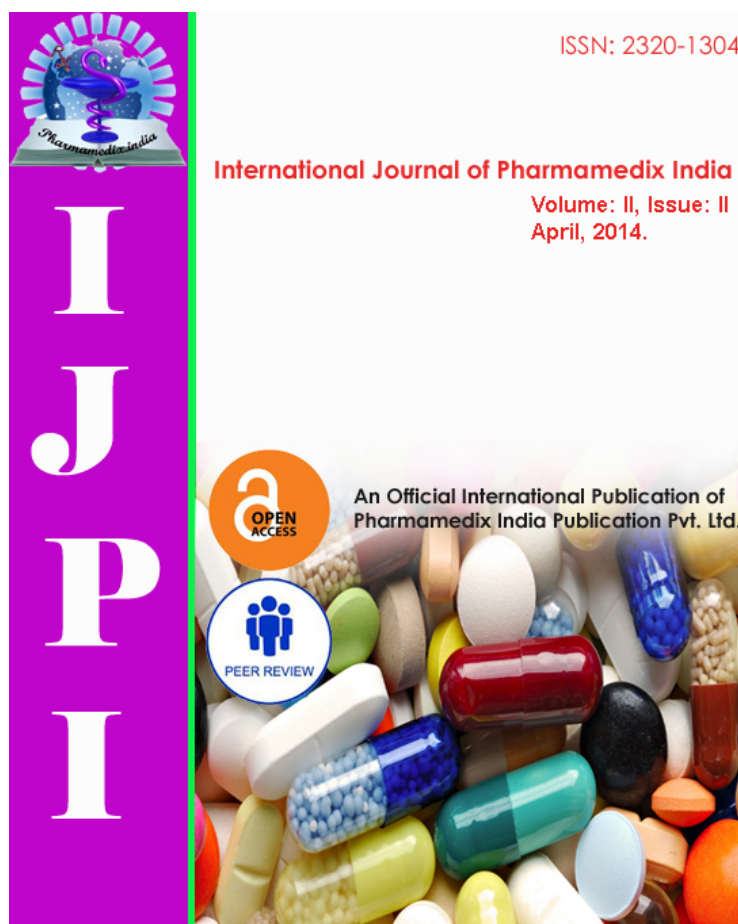
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Abstract:

Currently drug bioavailability has become a subject of interest not only in drug development, but also in the early stages of drug discovery. This is on sequence of the finding that most of the drugs candidate that failed in clinical trials did so because of problems with ADME (absorption, distribution, metabolism, excretion) and toxicology, rather than through lack of efficacy. Efforts are being made in the pharmaceutical industry to improve success rates by taking into account ADME and toxicology aspects in drug discovery from very early one. Therefore, it is not surprising to see that the number of publications on drug bioavailability has been increasing steadily for some time. In this review, attention is focused to briefly discuss some terms of bioavailability, relative bioavailability, bioequivalence, formulation and manufacturing variables that could influence the bioavailability of a drug product, physiologic and other factors affecting bioavailability, characteristics of drugs with the greater potential for a bioavailability problem, assessment of bioavailability from pharmacologic as well as therapeutic response, bioavailability of drugs versus dietary supplements, causes of low bioavailability and different approaches to improve it based on biopharmaceutical classification system. Thus approaches to improve drug solubility as well as drug permeability are the important strategies in order to enhance the bioavailability of drugs.

Keyword: Bioavailability, Bioequivalence, ADME.

Introduction

Life expectancy of patients has increased globally during the last three decades due to the new drug discovery (Patent drugs) as well as generic drug production. It is well known that most health care interventions occur through medication. The rising cost of medication has been contributing to the total overall cost of health care and thus receives considerable attention globally. A major strategy for lowering the cost of medication and thereby reducing its contribution to total health care costs, has been the introduction of generic equivalents of patent drugs (innovator drugs) (Midhal et al., 2005). This strategy has been effective in reducing total prescription cost by 11% without sacrificing (Haas et al., 2005).

With the increased availability and use of generic drug products, healthcare professionals are encountered with a large number of multisource products from which they have to select therapeutically equivalent products. Generic substitution is of concern not only for healthcare professionals but also for pharmaceutical industries, consumers and government officials. Many research papers have pointed out the concern regarding standards for approval of generic products which may not always ensure therapeutic equivalence (Boix et al., 2011; Lamy et al., 1989).

Many guidelines and regulations covering the licensing of generic products have been introduced to ensure that the medicinal

products reaching the market have well-established efficacy and safety profile (Food and Drug Administration (FDA); 1992; Committee for Proprietary Medicinal Products (CPMP); 2000).

1.1 Bioavailability/ Bioequivalence

Bioavailability /Bioequivalence of drug products, and drug product selection have emerged as critical issues in pharmacy and medicine during the last three decades. Concern about lowering health care costs has resulted in a tremendous increase in the use of generic drug products; currently about one half of all prescriptions written are for drugs that can be substituted with a generic product (Miller & Strom, 1990). According to the FDA, "pharmaceutical equivalents" are drug products that contain identical active ingredients and are identical in strength or concentration, dosage form, and route of administration (FDA, 1991). However, pharmaceutical equivalents do not necessarily contain the same inactive ingredients; various manufacturer dosage forms may differ in color, flavor, shape, and excipients. The terms "pharmaceutical equivalents" and "chemical equivalents" are often used interchangeably.

Over 80% of the approximately 10,000 prescription drugs available in 1990 were available from more than one source (*The Food and Drug Letter*, 1990). With the increasing availability and use of generic drug products, health care professionals are confronted with an even-larger array of multi source products from which they must select those that are therapeutically equivalent. This phenomenal growth of the generic pharmaceutical industry and the abundance of multi source products have prompted some questions among many health

professionals and scientists regarding the therapeutic equivalency of these products, particularly those in certain critical therapeutic categories such as anticonvulsants and cardiovascular (Lamy, 1985; Foster, 1991). Inherent in the currently accepted guidelines for product substitution is the assumption that a generic drug considered to be bioequivalent to a brand-name drug would elicit the same clinical effect. As straightforward as this statement regarding bioequivalence appears to be, it has generated a great deal of controversy among scientists and professionals in the health care field. Numerous papers in the literature indicate that there is concern that the current standards for approval of generic drugs may not always ensure therapeutic equivalence (Meyer, 1985; Nuwer et al., 1990). The availability of different formulations of the same drug substance given at the same strength and in the same dosage form poses a special challenge to health care professionals, making these issues very relevant to pharmacists in all practice settings. Since pharmacists play an important role in product-selection decisions, they must have an understanding of the principles and concepts of bioavailability and bioequivalence.

1. Types of Bioavailability

- Comparative bioavailability or Relative bioavailability
- Absolute bioavailability

2.1 Comparative Bioavailability

Comparative or relative bioavailability refers to a comparison of two dosage forms in terms of their relative rate and extent of absorption. In some instances, two pharmaceutical alternatives exhibit markedly different bioavailability, for example, a rapidly absorbed elixir and more slowly

absorbed capsule. In other cases, two different dosage forms (e.g., a tablet and a capsule) may or may not exhibit very similar bioavailability (Darwish et al., 2007).

$$\text{Comparative bioavailability} = \frac{\text{AUC}_{po} \times \text{dose}_{iv}}{\text{AUC}_{iv} \times \text{dose}_{po}}$$

2.2 Absolute Bioavailability

Active pharmaceutical ingredient reaches to the systemic circulation and the range is $F=0$ (No drug absorptions) if the drug is completely absorbed in the systemic circulation is $F=1$. Since the total amount of drug reaching the systemic circulation is directly proportional to the area under curve (AUC), F is determined by comparing the respective AUCs of the test product and the same dose of drug administered intravenously (Darwish et al., 2007).

$$\text{Absolute bioavailability} = \frac{\text{AUC}_{po}}{\text{AUC}_{iv}}$$

3. Pharmacokinetic Parameters

The following pharmacokinetic parameters are usually compared for bioequivalence studies:

3.1 Maximum Plasma Concentration (C_{max})

The peak plasma drug concentration C_{max} represents maximum plasma drug concentration obtained after oral administration of drug. For many drugs, a relationship is found between pharmacodynamic of drug and plasma drug concentration. C_{max} provides indications that the drug is sufficiently systemically absorbed to provide therapeutic response. In addition, C_{max} also provides warning of possible toxic levels of drugs. The units of C_{max} are concentration unit's e.g $\mu\text{g/ml}$, ng/ml (Leon Shargel & Yu A, 1999).

3.2 Time of Peak Plasma Concentration (t_{max})

The time of peak plasma concentration (t_{max}) corresponds to the time required to reach maximum drug concentration after drug administration. At t_{max} peak drug absorption occurs and the rate of drug absorption exactly equals to the rate of drug elimination. Drug absorption still continue after t_{max} is reached, but at a slower rate. When comparing drug products, t_{max} can be used as an approximate indication of drug absorption rate. The value for t_{max} will become smaller (indicating less time required to reach peak plasma concentration) as the absorption rate for the drug becomes more rapid. Units for t_{max} are units of time (e.g, hours, and minutes) (Leon Shargel & Yu A, 1999).

3.3 Area under curve (AUC)

The area under the plasma level time curve (AUC) is a measurement of the extent of drug bioavailability. The AUC is the total amount of active drug that reaches the systemic circulation. The AUC is the area under the drug plasma level-time curve from t to 0 & t to ∞ , and is equal to the amount of unchanged drug reaching the general circulation divided by the clearance. The AUC is independent of the route of administration and processes of elimination as long as the elimination process does not change. The AUC is determined by a numerical integration procedure, such as trapezoid rule method. The units for AUC are concentration time (e.g. $\mu\text{g/hr/ml}$) (Leon Shargel & Yu A, 1999).

3.4 Area under the First Moment Curve (AUMC)

Area under the first moment curve is a parameter that is necessary to calculate Mean Residence Time (MRT) which indicates the time of stay of the drug in the body (Leon Shargel & Yu A, 1999).

3.5 Mean Residence Time (MRT)

The Mean Residence Time (MRT) is the time required to eliminate 63% of the drug from the body. Mean residence time (MRT) represents the average residence time of the drug in the body organs or compartment as the molecules diffuse in and out. MRT is an alternative concept used to describe how long a drug stays in the body. The main advantage of MRT is that it is based on probability and is consistent with how drug molecules behave in the physical world (Leon Shargel & Yu A, 1999).

3.6 Half Life ($t_{1/2}$)

It is the time taken for the amount of drug in the body (or the plasma concentration) to fall by half. The elimination of a drug is usually an exponential (logarithmic) process so that a constant proportion of the drug in the body is eliminated per unit time. It is a composite pharmacokinetic parameter determined by both clearance (CL) and volume of distribution (V). It is increased by an increase in volume of distribution or a decrease in clearance, and vice versa. It is the major determinant of the duration of action after a single dose, the longer the half life the longer the plasma concentration of drug stay in the effective range, the time taken to reach steady state with constant dosing and the frequency. Half life is a reciprocal function of the elimination rate constant.

$$t_{1/2} = 0.693 \cdot V / CL \text{ (Donald , 2002)}$$

3.7 Elimination Rate Constant (K_e)

The elimination of a drug is usually an exponential (logarithmic) process so that a constant proportion of the drug in the body is eliminated per unit time.

$$C_t = C_o \cdot e^{-kt}$$

In this expression C_t is the concentration at various times (t) after the dose, C_o is the initial concentration at zero and k is the elimination rate constant. Therefore, the elimination rate constant (K_e) is proportionality constant expressing the proportion of drug in the body eliminated per unit time and has the units' per hour or mg/hour (Donald, 2002)

$$\text{Elimination rate (mg / hour)} = \text{clearance (L /hour)} \cdot \text{plasma drug concentration (mg /L)}$$

3.8 Volume of Distribution (V_d)

It is not a real volume. It is the parameter relating the concentration of a drug in the plasma to the total amount of the drug in the body. For example, if a drug has plasma concentration of 10mg/L there is 1000mg of drug in the body. The volume of distribution would be 100L. That is, dissolving 1000mg of drug in an imaginary volume of 100L would give a concentration of 10mg/L.

$$V = \text{total amount of drug in body (A)} / \text{plasma drug concentration (C)}$$

The major determinant is the relative strength of binding of the drug to tissues components as compared with plasma proteins. If a drug is very tightly bound by tissues and not by blood, most of the drug in the body will be held in the tissues and very little in plasma, so that the drug will appear to be dissolved in a large volume and V will be large (Donald , 2002).

3.9 Volume of Steady State (V_{ss})

It is also known as steady state apparent volume of distribution. It relates the plasma drug concentration to the amount of drug present in the body. At steady state

condition, the rate of drug entry into the tissue compartment from the central compartment is equal to the rate of drug exit from the tissue compartment into the central compartment. The magnitude of V_{ss} is dependent on the hemodynamic factors responsible for drug distribution and on the physical properties of the drug, which in turn, determine the relative amount of intra and extra vascular drug remaining in the body (Leon Shargel & Yu A, 1999).

3.10 Total Body Clearance (Cl)

Total body clearance is a measure of drug elimination with-out identifying the mechanism or process. Drug clearance refers to the volume of plasma fluid that is cleared of the drug per unit time usually liter per hour or milliliter per minute. Clearance is one of the parameter that determines the maintenance dose rate required to achieve a target plasma concentration and therefore effect at steady state.

$$CL = U \cdot V / P$$

Where U is urine drug concentration, V is urine flow rate and P is the plasma (or blood) concentration of a solute such as creatinine or a drug (Donald, 2002).

4 Pharmaceutical Equivalence & Bioequivalence

With the phenomenal increase in the availability of generic drugs in recent years, the issues of bioavailability and bioequivalence have received increasing attention. In order for a drug product to be interchangeable with the pioneer (innovator or brand name) product, it must be both pharmaceutically equivalent and bioequivalent.

"Bioequivalence" is a comparison of the bioavailability of two or more drug products".

Thus, two products or formulations containing the same active ingredient are bioequivalent if their rates and extents of absorption are the same. When a new formulation of an existing drug is developed, its bioavailability is generally evaluated relative to the standard formulation of the originator. Indeed, a bioequivalence trial against the standard formulation is the key feature of an Abbreviated New Drug Application (ANDA) submitted to the Food and Drug Administration by a manufacturer who wishes to produce a generic drug. For a generic drug to be considered bioequivalent to a pioneer product there must be no statistical differences (as specified in the accepted criteria) between their plasma concentration- time profiles. Because two products rarely exhibit absolutely identical profiles, some degree of difference must be considered acceptable, as will be discussed later. Since the concentration of a drug in blood is used as an assessment of its clinical performance, inherent in the demonstration that two preparations containing equivalent amounts of the same drug produce similar concentrations of the drug entity in blood is the assumption that they will elicit equivalent drug responses. Thus, two products that are deemed to be bioequivalent are also assumed to be therapeutically equivalent, and therefore interchangeable. This principle is fundamental to the concept of bioequivalence and is the basic premise on which it is founded. In general, the FDA considers two products to be "therapeutic equivalents" if they each meet the following criteria.

- They are pharmaceutical equivalents.

- They are bioequivalent (demonstrated either by a bioavailability measurement or an *in vitro* standard).
- They are in compliance with compendia standards for strength, quality, purity and identity.
- They are adequately labeled.
- They have been manufactured in compliance with Good Manufacturing

Practices as established by the FDA (Rockville, MD., 1994.)

5. Criteria for Bioequivalence A generic drug is considered bioequivalent to a reference (branded) drug if the 90% confidence interval (CI) for the AUC and C_{max} of the generic are within 80% to 125% of the AUC and C_{max} of the reference drug, using log-transformed data and two one-sided statistical tests (Figure 1.1).

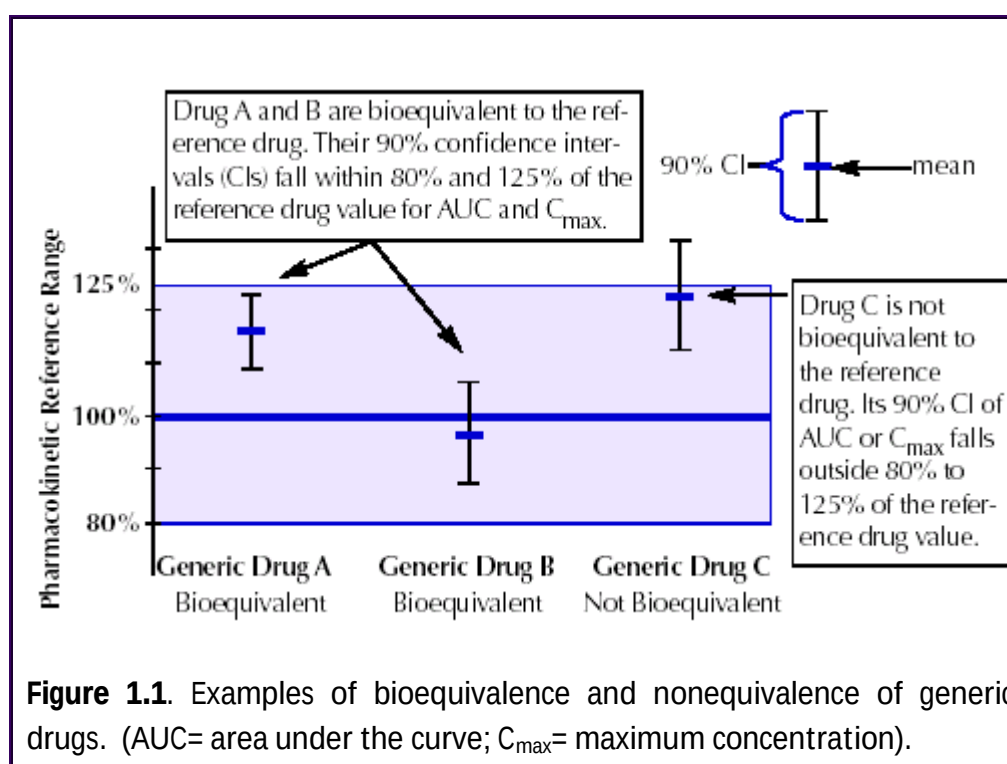


Figure 1.1. Examples of bioequivalence and nonequivalence of generic drugs. (AUC= area under the curve; C_{max} = maximum concentration).

Pharmaceutical Equivalence	Bioequivalence	Therapeutic Equivalence
Same active ingredient same dosage form (tablets vs capsules). Same route of administration. Identical strength or concentration	In normal subjects AUC and C_{max} 90% CI is within 80% to 125% of AUC and C_{max} of reference drug.	Equivalent therapeutic effect on outcome of interest (such as serum TSH)

6. Equivalency Criteria : The FDA's position is that if products are pharmaceutically equivalent and bioequivalent they are

expected to produce the same therapeutic effect. The ability of the generic drug to produce a therapeutic effect equivalent to

that of the branded drug on a pharmacodynamic outcome (Michael et al., 2003) and is shown in (Table 1.1).

AUC= area under the curve

C_{max} = maximum concentration, TSH= thyroid stimulating hormone, CI= confidence interval

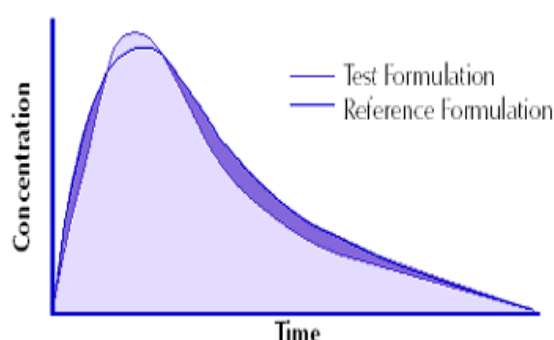


Figure 1.2. Comparison of AUC and C_{max} of a test drug versus a reference drug.

(AUC, area under the curve; C_{max} , maximum concentration).

7. Bioequivalence Background The first intimations of bioequivalence problems with multi-source drug products were given by early investigations of the availability of vitamins, aspirin, tetracycline, and tolbutamide (Melnick & Hochberg, 1945; Donald & Pisano, 1969). In 1974, after an extensive review of the bioavailability of drugs, Koch-Weser concluded, "among drugs thus far tested bioinequivalence of different drug products has been far more common than bioequivalence" (Koch-Weser, 1974). Of particular note were the studies involving digoxin; the findings of these investigations sparked the discussion about bioequivalence assessment that still continues today. Significant differences were seen in the bioavailability of digoxin not only between products supplied by different companies, but also between lots obtained from the same manufacturer (Lindenbaum & Mellow, 1971).

Because of the narrow therapeutic range for this drug, and because the drug is utilized in the treatment of cardiac patients, these findings generated a great deal of concern. Similar reports of bioinequivalence and therapeutic inequivalence appeared for other drugs as well, including phenytoin, phenylbutazone, chloramphenicol, tolbutamide and thyroid (Meyer, 1985).

The clinical significance of these reported differences in bioavailability relates to the therapeutic index of the drug, the dose of the drug and the nature of the disease. In 1973 the Ad Hoc Committee on Drug Product Selection of the American Pharmaceutical Association published a list of drugs with a potential for therapeutic inequivalence based on reported evidence of bioinequivalence (*J. Am. Pharm. Assoc*, 1973).

8. Bioequivalence Regulations

In 1977, the FDA implemented a series of bioavailability and bioequivalence regulations which formed the basis of subsequent discussion, if not controversy, of therapeutic equivalency of drug products (Bioavailability and Bioequivalence Requirements, *Federal Register*, 1977). The regulations are divided into two separate regulations; Subpart B - Procedures for Determining the Bioavailability of Drug Products and Subpart C - Bioequivalence Requirements.

9. Methods to Document Bioavailability and Bioequivalence Studies

Several in vivo and in vitro methods can be used to measure product quality Bioavailability and establish Bioequivalence. In descending order of preference, these include pharmacokinetic, pharmacodynamic, clinical, and in vitro studies (Michael et al., 2003).

10. Controversies and Concerns in Bioequivalence. The design, performance and evaluation of bioequivalence studies have received a great deal of attention over the past decade from academia, the pharmaceutical industry and regulatory agencies. A number of concerns and questions have been raised about the conduct of bioequivalence studies as well as the guidelines and criteria used to determine bioequivalence (Steinijans et al., 1992). Many of these concerns were triggered by the passage of the Drug Price Competition and Patent Term Restoration Act (The Waxman-Hatch Amendments) by Congress in 1984. This Act provided for an expedited approval by the FDA of generic drugs, thereby expanding the potential generic market for prescription generic drugs (Mattison, 1986).

Shortly after the passage of this Act, numerous published reports appeared in the scientific literature questioning the FDA's ability to ensure that generic drugs were equivalent to the brand name drugs they were copying. Most of the concerns of the scientific community centered round adequate standards for evaluation of bioequivalence and correlation between bioequivalence and therapeutic equivalence. At the center of the controversy were the methods and criteria used by the FDA to determine bioequivalence. Assessment of bioequivalence was done on the basis of mean data: mean AUC and C_{max} values for the generic product had to be within +20% of those of the innovator product for approval. A statistical test was employed to assess the power of the test to detect a 20% mean difference in treatments. For drugs that could not meet the statistical criteria because of inherent variability, another rule was used, the so-called "75/75" rule: that in at least

75% of the subjects, the test formulation must fall within the range of 75% to 125% of the reference standard to be considered equivalent (Madan, 1992). It was felt by many that these rules permitted too much variability in the bioavailability of test drugs and could result in therapeutic failure or increased risk of side effects (Colaizzi & Lowenthal, 1986; Barone & Colaizzi, 1985; Barone & Colaizzi 1983). Statistically, the power approach and the 75/75 rules were shown to have poor performance characteristics and bioequivalence evaluation based on these methods was discontinued by the FDA in 1986. In their place, the Agency currently employs the two one-sided tests procedure, as previously discussed. Although the decision of bioequivalence is now made in a more statistically valid way and the associated concerns have diminished somewhat, some important questions and controversies in bioequivalence remain. These are primarily centered on study design, the criteria used to establish or refute equivalence, and the assumption that products that are bioequivalent are therapeutically equivalent. One criticism of bioequivalence testing is that it is almost always done in a panel of young, healthy male volunteers rather than in the target population for which the drug is intended. Clearly, the performance of a drug product in a 20-year-old male will not be the same as in an 85-year-old woman. Serious concerns have been raised that different results would be observed in elderly patients, in women, in patients with diseases of the gastrointestinal tract, and in patients with diminished renal or hepatic function. However, although factors such as age and disease state might affect the actual observed concentrations of drug, the products being compared should be

affected in a similar fashion, and one can still be compared to the other. If two products show an equivalent level in healthy volunteers, their levels should be elevated to the same extent in patients with impaired hepatic function.

Thus, they can still be compared to each other. Healthy male volunteers are generally used in bioequivalence studies to assure a homogeneous study population and to permit focus on formulation factors that might affect bioavailability. In addition, healthy subjects are more likely to remain stable during the study. The condition of actual patients might change due to the disease resulting in greater variability in the data. The FDA does recognize the possibility that some conditions could cause two products that are bioequivalent in healthy subjects to be bioinequivalent in certain patients and is prepared to modify its guidelines if necessary. A study design-related area of concern is average versus individual bioavailability.

Current procedures assess equivalence in terms of average bioavailability, and do not address within-subject equivalence. In recent years, there has been increased interest expressed in the variability of response, particularly variability within an individual. This has given rise to the most recent controversy in bioequivalence assessment, namely whether bioequivalence average is adequate to allow interchangeability of drugs in an individual (Steinijans et al., 1992). Anderson and Hauck believe that a different, more stringent, notion of bioequivalence, referred to as individual bioequivalence, is needed to provide assurance that an individual patient can be switched from one formulation to another (Anderson & Hauck,

1990). The second major area of controversy has focused on the criteria used to determine bioequivalence. Implicit in the FDA guidelines is the assumption that a -20%/ +25% change in mean serum concentration of drugs can be safely tolerated. However, there is little documentation demonstrating whether 20% variation in bioavailability does or does not affect the safety and efficacy of drugs.

There are certain critical therapeutic categories in which minor fluctuations in blood levels may have a substantial impact on therapeutic outcome or toxicity (Carter & Sanderson, 1988; Somberg & Sonnenblick, 1985). In view of this, some scientists believe that the FDA should be more stringent, requiring the mean values for AUC to be within 10% rather than 20% or 25%. The Bioequivalence Task Force, in its 1988 report, concluded that for certain drugs or drug classes, there is clinical evidence that may indicate a need for tighter limits than the then-generally applied +20% rule (FDA Bioequivalence Task Force Report, 1988). The Task Force recommended that the Agency consider using as an "additional non-statistical criterion" a mean difference in AUC of +10%; however, this additional criterion would not be essential to ensuring drug bioequivalence. In general, the choice of the appropriate bioequivalence range should be done on clinical grounds; for a drug with a narrow therapeutic range, more stringent limits should be considered. On the other hand, the current requirements for C_{max} for some drugs may be too stringent, considering the difficulty in accurately estimating this value. For example, it has been suggested that the acceptable bioequivalence range for C_{max} for fast-releasing nifedipine formulations should be 70% to 130%, rather than the usual 80% to 125%. In light of this, many, including

the Pharmaceutical Research and Manufacturers of America (formerly the Pharmaceutical Manufacturers Association [PMA]), feel that the FDA should repudiate its -20% or +25% rule and develop drug-by-drug bioequivalence criteria (Gore & Cost, 1991).

A third source of controversy in bioequivalence is the very foundation on which the whole concept of bioequivalence is based: the central assumption is that if two products are shown to be bioequivalent by currently accepted standards, then they are also therapeutically equivalent, and thus interchangeable. A number of critics have challenged this "bioequivalence = therapeutic equivalence" equation, pointing out that this relationship has not been conclusively established for most drugs (Dettelbach, 1986; Horwitz, 1985; Strom, 1987; Somberg, 1986). These terms are, in fact, not interchangeable; bioequivalence means that two products have basically superimposable blood level curves (within specified limits) while therapeutic equivalence means the products produce similar effects. There may be situations where two products have similar blood concentrations, yet if the drug has a narrow therapeutic range, they may have significantly different therapeutic effects. On the other hand, there may be products, which have widely varying blood level profiles, but exhibit very little difference in their clinical effect. This might be the case for drugs with a wide therapeutic range. In addition, the therapeutic efficacy of some drugs is not necessarily related to their blood levels, e.g., some psychoactive drugs, where the end point of drug effects is psychological and behavioral response (Garrett & Weinstein, 1985). Williams suggests several ways that the integrity of a bioequivalence study as a prediction of therapeutic

equivalence could be assessed. One way involves the performance of specific clinical studies to confirm that products shown to be bioequivalent in healthy subjects would be bioequivalent in the patient population as well. A second way suggested is through post-marketing surveillance of therapeutic response produced by different formulations of the same drug under actual conditions of use. A third method is based on anecdotal reports. Williams point out that none of these methods have been systematically employed to confirm current bioequivalence methodology. Thus, a number of problems remain in the bioequivalence process, which should be addressed. FDA scientists themselves have readily acknowledged the existence of shortcomings in the bioequivalence testing program. However, a great deal of progress has been made in this area in the last twenty years. The improved design of the studies, the interpretation of the data, the increased scientific rigor of the acceptance criteria, as well as the more rigorous auditing and inspection program have made bioequivalence data an appropriate and valid means of approving generic drug products.

11. Aims of Bioequivalence Studies

- Given sufficient data to compare an oral product with another oral product or an IV product, the student will estimate the bioavailability (compare AUC) and judge professional acceptance of the product with regard to bioequivalence (evaluate AUC, and).
- To write a professional consult using the above calculations.
- To calculate the absolute bioavailability of drug products.

- To discuss the various factors affecting bioavailability.
- To discuss the various methods of assessing bioavailability.
- To discuss *In Vivo / In Vitro* Correlations.
- To enumerate FDA requirements regarding bioequivalence.
- To utilize the FDA “Orange Book” to make drug product selections.
- To discuss and utilize reasonable guidelines regarding drug product selections.

12. Bioequivalence of Antibiotics/Antibacterial/Antimicrobials

Antibiotics/Antibacterial/Antimicrobials are widely used to treat the sign and symptoms of respiratory, skin, soft tissue, and urinary tract infections. However, side effects related to gastrointestinal, hypersensitivity, and thrombocytopenias sometime have important clinical limitations on antibacterial use. Cephalosporins are a type of antibiotic in the same class as penicillins (β -lactams), but have a broader spectrum than penicillins. They are used to treat certain bacterial infections such as throat, ear, skin, and urinary tract infections, among many. Cephalexin has weak bond ability to blood protein, has no metabolites, has low toxicity, and is rapidly absorbed following oral administration to give a high serum level and urine concentration. Cephalexin is excreted unaltered by the kidneys, almost all of the dose being recovered within six hours. In clinical chemotherapy the bioavailability of drugs is an important subject. It is obvious that all commercially available products do not show bioequivalency. Therefore, the evaluation of the bioavailability of various solid dosage forms especially where the only generic products are available is necessary.

Cephalexin is specifically bind to penicillin binding proteins (PBP) located in the bacterial cell wall it inhibits the third and last stage of bacterial cell wall synthesis.

Culture and susceptibility tests should be initiated prior to and during therapy. Renal function studies should be performed when indicated. To reduce the development of drug resistant bacteria and maintain the effectiveness of Cephalexin and other antibiotics, Cephalexin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.

13. Conclusion

Nowadays, the use of generic drug products increases to minimize the healthcare cost. With increased availability and use of generic drug products, healthcare professionals are encountered with a large number of multisource products from which they have to select therapeutically equivalent products. Generic substitution is of concern not only for healthcare

professionals but also for pharmaceutical industries. Therefore the present review described the general aspects of bioavailability and bioequivalence studies conducted in human subjects for developing the generic drug.

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