Bioequivalence, Bioequivalence Parameters, Study Types and Situations Which Are/Not Necessary

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Abstract

In this review, short definition of bioequivalence, study types and situations which is/not necessary have been summarized. In the world, it is realized that the most valuable quality control testing is bioequivalence studies and the results of bioequivalence studies have been used as an important indicator by the authors of the subject.

Keywords: Bioequivalence; Parameters; Pharmaceutical

Introduction

The aim of this mini review is definition of bioequivalence, to give some important information on importance of bioequivalence, evaluation parameters and study types, where bioequivalence study is necessary or not necessary.

Bioequivalence

It is based on the principle of two pharmaceutical equivalent products create a similar level of plasma density and it enables to choose between the preparations of any active substance used in the same field according to scientific data [1-3].

The Purpose of Bioequivalence

It is a quality-control test to determine whether the systemic effect of two products containing the same active substance is similar in terms of efficacy and/or safety or to compare the application routes in the treatment. For bioequivalence tests, it is preferred that the products are pharmaceutically equivalent and scientific justification should be written for bioequivalence studies to be conducted with non-pharmaceutical equivalent products [1-6]. Two different products are considered pharmaceutical equivalents; if they contain the same active ingredient(s) in the same amount(s) or in pharmaceutical forms conforming to comparable standards. If the same molar amount of the same active substance(s) is found equally in both products, if it contains the same active substance or therapeutic molecule with another preparation whose chemical equivalence, if efficacy and safety have been determined before and shows the same therapeutic efficacy and safety; There is said to be clinical equivalence [1-6].

Bioequivalence Study Types

Bioequivalence studies are performed in-vivo or in-vitro under appropriate customized conditions. In addition, to compare and link between formulations used in clinical trials and formulations to be marketed and between stability studies and formulations used in clinical trials, bioequivalence studies are needed. Bioequivalence tests are carried out in two periods, the first is clinical (practice) and the other is when necessary analyzes are made (bioanalytical), both of which can be done in the same place or in different places [1-6].

In-Vitro Study

In-vitro bioequivalence studies may contribute to in-vivo studies if:

- Supporting the bioequivalence of the smallest dosage formulation of the product shown for the highest in-vivo bioequivalence dosage,
- To determine the comparability of the reference product and its orally-applicable generic product,
- In-vitro bioequivalence studies are sufficient when a minor formulation change is made in an approved product and it is desired to ensure consistency between batches of a product [1].

In-Vivo Study

In-vivo bioequivalence testing should be planned and conducted as a pharmacokinetic and/or pharmacodynamic study using the most accurate, sensitive and reproducible methods.

- Pharmacokinetic study: In in-vivo tests, by calculating the course of concentrations of the target type of active substance or metabolite(s) in tissues such as appropriate biological fluids (blood, plasma, serum, urine, milk, saliva, bronchial fluid, etc.) over time (urine, milk, etc.), serum/plasma concentration vs. time graph evaluation is made on pharmacokinetic data [1-5].
- Pharmacodynamic study: It can be used when there is no a sensitive analytical method that can determine drug concentration in appropriate physiological materials. Appropriate measurement of the pharmacological effects of the active substance or therapeutic compound or metabolite(s) as a function of time in target species is required in this test. In this approach, it is imperative to demonstrate the dose- response/effect relationship and is the most appropriate method for demonstrating bioequivalence in locally-effective products [3-5].

Such studies are prominent in antihypertensive, diuretic, antidiarrheic, antidiabetic, anticoagulant, hypolipidemic, antiarrhythmic, antipyretics and analgesic drugs. In other words, the presence or absence of the expected effect (such as the amount of urine measured for the diuretic effect, the decrease in the blood pressure for the hypertensive effect) is important. The same issue is the case with drugs with local effects (such as the improvement of the inflammatory condition in the breast tissue in mastitis and in the eye in conjunctivitis) [1-5].

Basic Rules to Consider in Determining Bioequivalence

It is important that the principles of bioequivalence tests to be carried out on pharmacodynamic effects are determined very meticulously by the authors in the protocol beforehand. In the case of assessing bioequivalence over pharmacodynamic trials of two formulations, meticulous determination of differences in other effects is required. The pharmacodynamic effect measured in the bioequivalence study should be direct, rapid and reversible. In cases where drugs are administered for local effects independent of systemic effects (intramammary in mastitis, antiparasitics for gastrointestinal parasites or enteric antibiotics in enteritis), milk for intramammary applications, intestinal content for antiparasitic and other applications are suitable materials and bioequivalence decision should be made based on the analyzes in them [1-6].

For pharmacokinetic studies, it is essential to plot the active substance concentration measured in blood (serum or plasma) or other suitable biological fluids (saliva, urine, milk, etc). The bioequivalence of a product is defined by the rate and amount of active substance that can be utilized at the site(s) of action by entering the systemic circulation. The most important parameters that determine the rate and amount are AUC (Area under the Curve), C_{max} (peak concentration) and t_{max} (time to peak concentration). AUC is also an indicator of the amount absorbed and thus entering the systemic circulation, ie usable and is independent of the rate of absorption. C_{max} and t_{max} are hybrid parameters and have a very close relationship with both the rate of absorption and elimination of the drug. It is defined as the total area (AUC 0-end) between the time point at which the drug is first detected in the blood ($AUC0$) and the last time point at which the drug can be measured (AUC_{last}) after administration. Linear or logarithmic trapezoidal methods are used to calculate AUC. C_{max} and t_{max} can generally be determined by looking directly at the plasma drug concentration-time data plotted for each subject. If the optimal t_{max} for a product is known, or if a pilot study is available, a bioequivalence study with a multiplicity of samples close to t_{max} increases the importance of C_{max} and t_{max} [1-6].

If a method is available for the measurement of primary active metabolites rather than the parent drug and/or the product is in the form of a prodrug rapidly converted to an active metabolite, it is more appropriate to decide on the metabolite data. Performing a bioequivalence study on the concentration of methyl amino antipyrine after the administration of oxyphenbutazone and phenylbutazone, metamizole after oral administration of bakampicillin or oral administration of ampicillin or suxibuzone constitute good examples of this issue.

In cases where there is no suitable analytical method for measurement on blood or plasma data or the sensitivity of the current method is low, bioequivalence assessment can be made based on the measurement of the parent drug or metabolite in the urine. Here, the sampling time is important

and should be at least five times the elimination half-life of the drug used. However, in such cases, it should be noted that the method to be used in the analysis should be of a quality that will allow the detection of both the drug and its metabolite and it should not be forgotten that excretion can occur in other ways than urine.

Situations Where Bioequivalence Studies are Needed

- Products that are not generically designed but contain a known substance or a new substance: When a change is made in the properties, composition or manufacturing processes of a drug's dosage, it must be demonstrated that the new product is bioequivalent in terms of efficacy and/or safety to the reference product given in clinical trials conducted. Only in-vitro bioequivalence is desired if the suitability of changes made by the company in manufacturing processes can be verified by in- vitro studies [1-6].
- Products containing a known new substance designed as a generic: If the reference is an approved product in terms of efficacy and/or safety, its bioequivalence should also be demonstrated [1-6].
- Comparison of application routes: Routes of administration are bioequivalent when the plasma concentration-time profiles of both routes of administration are statistically similar. In some cases, concentration profiles in other biological fluids may be more appropriate than plasma concentration profiles [1-6].

Situations Where Bioequivalence Study are not Necessary: Bioequivalence studies are generally not required for products that meet one or more of the following conditions:
- Contains the same active substance or therapeutic compound as an intravenous solution designed for intravenous administration only and approved for use in target species,
- If it is used as a parenterally or orally-administered solution and contains the same active substance(s) and carriers in the same concentration as a veterinary product recently approved for use in target species,
- If it has the same formulation (same active substance and same physicochemical properties) as the reference product whose bioavailability has been demonstrated in target species,
- If it is designed as an oral form that is undesirable to be absorbed (antacid or radiopaque substance),
- Syrup or other similar solubilized forms, the active substance or therapeutic compound contains the same therapeutic part and active substance in the same concentration as a product approved for use in the target species and does not contain any inactive substance that may significantly affect the absorption of the active substance or therapeutic compound,
- If it is identical to the original product when reformulated by the original manufacturer, excluding those known to be ineffective in bioavailability such as coloring or flavoring agents or preservatives,
- If it is one of the volatile anesthetic solutions used by inhalation,
- If it is from drugs designed for local effect on animals (only animal products) not used in food production [1-5].

Bioequivalence Determination Criterion (Bioequivalence Range) while making the decision of bioequivalence, not only the statistical significance of numerical values, but also the medical significance of intra- and inter-subject variables should be taken into account. The greater variability in bioavailability for some products may be negligible if they do not require a very rigorous dosage regimen because of the therapeutic purpose or the broad therapeutic index of the product. It is recommended by some authorities to extend the acceptance range a little more in the evaluation of bioequivalence of highly variable drugs and endogenous substances used as drugs and products with very long elimination half-lives or chiral substances. In bioequivalence studies of such drugs, it is necessary to use a large number of subjects and if such drugs have a narrow therapeutic index, steady-state study is also important in addition to widening the acceptance range that is the 'castle', in bioequivalence studies [1-6].

The 90% confidence interval is always used in the bioequivalence decision. As a general rule for AUC, the difference should be within the limits of 80-125% when comparing the average of two products and/or treatments. However, further broadening of these limits is recommended for compounds with a wide safety margin, ie compounds with a broad therapeutic index. If the effect of the drug is of a gradual dose-response nature, a 20% difference may not be accepted. For C_{max}, this limit is 80-125%. However, if this parameter shows a very large variability, especially depending on the sampling, the limits of 70-143% are acceptable. By comparing these two important parameters (AUC and C_{max}) with 90% confidence limits (0.8-1.25), bioequivalence can be decided for products that are not pharmaceutically-equivalent but contain the same active substance. For parameters such as time-dependent t_{max}, a relative range of variability (if required) should be chosen, where 20% variability of 10-minute t_{max} cannot mean the same as 20% variability of 120-minute t_{max}. The bioequivalence range for this parameter should be carefully described and verified [3-5].

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Data Analysis

Data analysis should be done in detail. An analysis of variance (including formulation, period, frequency, animals in frequency and, where appropriate, gender and gender-formulation interactions) is required to determine the error of variability to be used in calculating the confidence interval. It is recommended to convert the data to logarithms before performing analysis of variance for AUC and C_{max}. The main purposes here are;

a) Stabilizing the variables,
b) Normalize the parameter distribution,
c) Ensure the contribution of the statistical model used, and
d) To show the bioequivalence range as a ratio or percentage (%).

In the evaluation of time-dependent parameters (such as t_{max}), since this transformation is not appropriate, a non-parametric approach should be considered for statistical analysis. In order to make the bioequivalence decision, the confidence intervals calculated with the determined error variability in the ANOVA table, lower and upper limits should be compared with the predetermined limits. For data converted to logarithm, 80%-125% or 70%-143% limits are taken into account, for unconverted data, 80%-120% or 70%-130% limits are taken into account. Likewise, for drugs with a narrow therapeutic index, narrowing the limits (0.9-1.10 for unconverted logarithm data and 0.9-1.11 for transformed data) is necessary when making bioequivalence decisions based on AUC. In the bioequivalence examinations made according to the AUC parameter, even if the products are not bioequivalent according to all other parameters, all negative hypotheses can be rejected and a decision can be made in favor of bioequivalence. Whether the decision after the bioequivalence study is right or wrong is very important for the producer, consumer (human and/or animal) and the country's economy [3-5].

After a bioequivalence study: For the test product that is actually bioequivalent to the reference product; if the decision is equivalent, it is the right decision, and everyone wins, but if the decision is not equivalent; it is the wrong decision, the supporter loses. Likewise: For the test product that is not bioequivalent to the reference product; if decision is equivalent, it is the wrong decision, and the consumer loses, but it is not equivalent; the right decision, everyone wins. This is enough to emphasize the importance of bioequivalence for all of us [1-6].

Conclusion

As a result, the dissemination of bioequivalence studies which are of great importance especially for the generic drug producer countries/companies and the increase of equivalent (interchangeable) products are of undeniable importance for users as well as physicians and pharmacists and it is in everyone's benefit to increase these studies.

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