DRUG BIOAVAILABILITY

- ITS IMPORTANCE
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- CLINICAL EFFICACY OF DRUGS
- ADVERSE DRUG REACTIONS

By

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'Bioavailability' of a drug product, is the relative ability of a drug product to deliver a drug or active ingredient into a living system. Precisely a drug might not act upon a definite target organ unless it has an access to it through the circulatory system. A biopharmaceutic expert would define it as—'the rate and extent to which the ingredient is absorbed from the drug product into the body or to the site of action'. It is measured by blood, serum or plasma levels or from urinary excretion data.

In 1968, a school of thought (representing the pharmaceutical organizations) advocated that—'where there is chemical as well as physical equivalency, one can expect to have therapeutic equivalency'.[1] Lasagna (1969)[2] contradicted the above views and claimed that—'the chemical equivalency does not necessarily guarantee therapeutic equivalency'.

Whenever a drug product is prescribed, it is picked up from one of the many classes of drugs viz; antimalarial, diuretics, antihypertensives, contraceptives, antihistamins, analgesics, local anaesthetics, antibiotics, sulphonamides, hypnotics, tranquillizers and the like. The choice of drug solely depends on the desired therapeutic effect and on other supporting factors such as past experience with the drug and history of the patients disease. The prescribed drug is nothing but a pure chemical compound. In other words, a definite amount of pharmacologically active ingredient put into a 'dosage-form' of delivery system. The choice of this dosage-form is of greater importance for effective therapy than the choice of the active ingredient itself.

Its Importance

There are three major factors which govern the efficacy of a dosage-form; these are:—

a) On-set of therapeutic activity;
b) Intensity of the therapeutic effect; and
c) Duration of the therapeutic activity.

The above three factors are mainly responsible for the rate of absorption of the drug, the distribution of the drug throughout the circulatory system and above all the elimination of the active principle from the body.

None of the national Pharmacopoeias and neither the International Pharmacopoeia have yet recognized any accepted specification for the determination of bioavailability for regulatory purposes.

The bioavailability of drugs its principles together with the problems associated with it has been a topic of active discussion at the international level at the WHO Scientific Group.[3] It has been widely accepted that the bioavailability of a drug through a route of administration other than the intravenous one may be altered either by the characteristics of the drug dosage-form or by physiological differences among individual patients.

Official quality control methods adopted e.g., disintegration time, dissolution rate, do not give ample therapeutic equivalence among drug products belonging to the same class. Moreover, even the product of the same manufacturer may have varying degree of bioavailability in different batches. Therefore, it has become quite necessary to introduce comparative bioavailability studies and skillfully designed fool-proof clinical tests of therapeutic equivalence as the effective true remedial measure of the ultimate performance of drug products.

In cases, where measurement of blood levels is either not feasible or highly impractical, a definite pharmacological response (in animal models) may be utilised as a yard-stick in place of blood levels provided there exists a specific correlation between the degree of absorption of the drug and the intensity of its pharmacological response.

However, the most reliable and convincing direct method of establishing the bioavailability of a drug product in question would be the clinical therapeutic trial. Normal adult volunteers receive both the test product and the reference product under controlled standardized conditions. Subsequently, blood levels and/or urinary excretion of the drug are measured at regular intervals. However, the efficacy may be assumed for the test product with sufficient bioavailability only when there is evidence of efficacy for the chemically equivalent reference drug preparation.

In 1968, as many as fifty-one patients suffered from an 'epidemic' of anticonvulsant intoxication in Brisbane. A

thorough investigation conducted by Tyrer *et al* [4] spotted the intoxication caused by altering one of the excipients from calcium sulfate to lactose in the drug product Phenytoin capsule without adequate pre-testing by the manufacturer. This 'minor change' of excipient was sufficient to bring about a 'major change' in enhancing the bioavailability of the active principles to abnormally high levels in the affected patients.

A Question of Quality

It has now been accepted beyond doubt that quality of a drug product cannot be imparted by inspection or analysis, but has to be built into, from the very beginning of manufacture of a drug. Besides effective quality control measures exercised in every aspects of production including environment, screening of raw materials, process controls, intermediates, shelf-life of finished products the most important aspect is to assess the bioavailability of the active principle.

Difference in bioavailability, particularly in drugs with low solubility, as ascertained by blood-level attainment studies, appears to be caused by a number of formulation variables e.g., particles size, crystalline structure, binding or disintegrating agent, excipient etc., on the release of the drug from its dosage-form. For instance, the rate of dissolution of the drug in a 'tablet' or 'capsule' in the gastrointestinal fluids.[5]

As the original manufacturer of a drug is normally responsible and credited with most up-to-date clinical experience, it may be a natural urge to accept the brand name product as the standard for bioavailability studies. In cases, where a generic product with equivalent blood level in normal healthy subjects can be readily acceptable by the quality control authorities, it would perhaps be rather difficult to reject outright a product which may not meet the requirement of the reference material unless the degree of physiological or biological activity can be equated with therapeutic efficiency. Right now, only the physicians can assess the therapeutic efficiency of a specific brand name or generic product by their actual clinical experience on patients who are sick and may, therefore, have impaired physiological and metabolic activities.

Clinical Efficacy of Drugs

In U.S.A., the Food and Drug Administration (FDA) undertook a detailed study of bioavailability of tetracycline capsules (250 mg), collected from nine different firms, in healthy volunteers.[6] Results revealed that some products exhibited peak values of 1 *u*g/ml while others 2 *u*g/ml. This variation in bioavailability might have been attributed either due to formulations or processing methods. One may raise an important query at this point—"How does it matter as far as therapeutic effectiveness is achieved by a peak level of 0.5 *u*g/ml of tetracycline?" A physician may raise a serious objection for the excess dosage marketed whereas a 125 mg capsule of tetracycline might have given the same clinical efficacy positively substantiated by the facts that there would be less possible chances of toxic as well as side effects. In short, the medical world and also the public will think of being cheated altogether. Medical scientists solely rely on the measurement of bioavailability of a drug as a positive indicator of therapeutic equivalent, because clinical efficacy for orally administered drugs depends on the degree of absorption and the presence of the active ingredient in the blood stream.

Technical information based on *in vitro* standards and specifications are generally incorporated in various official compendium. Hence, in order to record a legitimate assessment of bioavailability, *in vivo* test is an absolute must and the relevant data obtained therefrom should form an integral part of the standard specifications in the official standard.

Adverse Drug Reaction

Any dosage-form can produce adverse drug reactions. Therefore, a constant feed-back of relevant information on such adverse reactions from the medical practitioners to the appropriate regulatory authorities and the concerned manufacturers would not only help to intensify better safety measures but also widen the scope to improve 'drug-design' by meticulous research scientists all over the globe.

In 1975, a US estimate reveals that 1.5 million patients usually get admitted in various hospitals a year on account of drug-induced illness. This is further supported by statistical facts that 13% suffer from errors in drug administration, 10% having the incidence of complication in medication and 5% from serious drug reactions.

A computerized report[7] from the U.K. Committee on Safety of Drugs in 1970, recorded 137 different cases of adverse reactions from a commonly used analgesic 'Aspirin'. Increased gastric damage and subsequent bleeding caused by some aspirin formulations has been specifically attributed to the slowly dissolving aspirin particles in the stomach. However, both effervescent and highly buffered dosage-forms (antacid aspirintablet) which help in maintaining the aspirin in solution have been found to minimise gastro-intestinal toxicity.[8]

Likewise, some sparingly soluble broad-spectrum antibiotics like Chloramphenicol and Tetracycline damage the gastro-intestinal epithelium and also change the normal micro-flora in the G.I. tract which are required for normal good health. In other words, bioavailability considerations from the view point of adverse drug reactions is a very important aspect which needs deeper probe. World Health Organisation (WHO) has been charged with a big responsibility to warn and alert the health and regulatory authorities of various member countries about all specific information on adverse drug reactions and eventual withdrawal of such drugs, if any, from the world market.

In conclusion, it may be stated that the pharmacist, as a professional, may have to shoulder the very responsibility not only confined to formulation but also in dispensing the best quality drugs. He should maintain meaningful-liaison with the medical profession so that he can offer his expertised—knowledge and specialized-service in the ideal selection of drugs for the benefit of the suffering mankind. With the advanced knowledge regarding the principles and means of bioavailability evaluation amalgamated with logical scientific command a pharmacist can confidently pick-up from a host of identical drug products the ones which may be *clinically interchangeable.*

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