REVIEW

Basic concepts of bioavailability

RC Li, AHL Chow, MS Yip, K Raymond

Although scientific evaluations for product bioavailability performance have been routinely employed in most European and North American countries, debate continues on the potential problems of bioavailability and bioequivalency of pharmaceutical products in Hong Kong. Data obtained from these evaluations not only confirm the quality of the drug products in the market, but also permit a more rational selection of pharmaceutical products to achieve cost-effectiveness. It is well known that chemical equivalency may not necessarily imply bioequivalency due to the interplay of various formulation, pathophysiological and physicochemical factors. This paper discusses some of the basic concepts and implications of these evaluations.

HKMJ 1995;1:63-8

Keywords: Bioavailability; Bioequivalency; Definitions; Pharmacokinetic parameters

Introduction

For the treatment of diseases requiring the use of non-injectable pharmacological agents, a drug is likely to be administered as some formulated dosage rather than in the form of a pure drug powder. Of the different routes of drug administration possible, the oral route is perhaps the most common and widely accepted. However, for an orally administered drug, a frequent problem is the variability in apparent drug absorption observed between individuals i.e. differences in systemic bioavailability.[1,2]

Bioavailability is a numerical parameter used to reflect the degree of drug availability in the systemic circulation after a certain dose of a pharmacological agent has been administered to a human subject. This parameter applies to oral formulations and other dosage forms, such as rectal suppositories, medicated skin preparations, sublingual tablets, and aerosols.[3] Nevertheless, the term bioavailability has been used loosely in the literature to describe the different plasma drug profiles arising from formulation, pathophysiological and physicochemical factors. This paper aims to explain some of the basic concepts of bioavailability with particular reference to its application in the pharmaceutical industry. The relationship between bioavailability and bioequivalency is also discussed.

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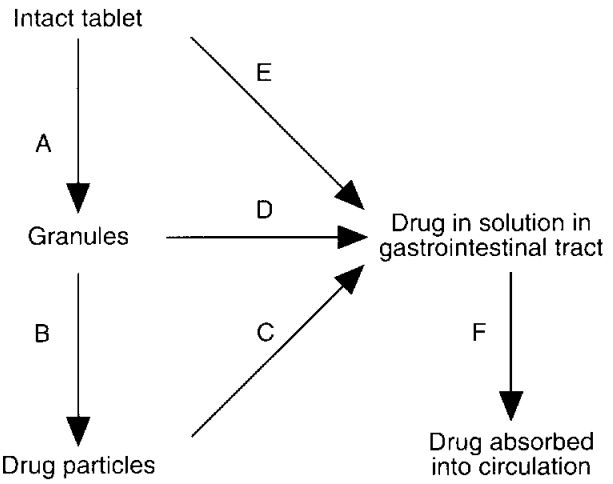


Fig 1. The various processes that take place between ingestion of a tablet containing the active ingredient and the absorption of the ingredient in the GI tract. Steps A and B: disintegration to coarse and fine particles, respectively; Steps C, D and E: drug dissolution with rate C > D > E; Step F: drug adsorption.

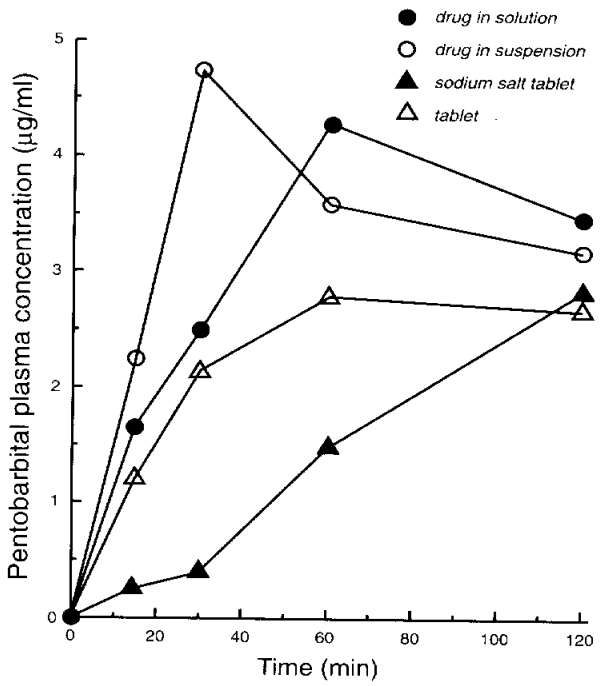
Bioavailability differences among common oral formulations

There are various formulation factors which affect bioavailability. For any oral dosage form in which a drug is incorporated, the ultimate goal is the release of the drug into the gastrointestinal (GI) tract for absorption and subsequent delivery to the target organ via the bloodstream. If one considers the simple case of a conventional tablet, tablet disintegration is the first important step which follows its intake. Once the tablet disintegrates, the surface area of the GI tract exposed to drug particles is greatly increased. The disintegration process increases the exposure area of the tablet mass for subsequent dissolution and release of its contents to the absorption site. The time for tablet disintegration directly affects the speed of dissolution of the active ingredient in the GI tract. The key steps which occur between oral intake of a tablet and the ultimate absorption of the drug in the form of a solution are shown in Fig 1. Provided that the dissolved drug can be freely absorbed by the GI tract, the drug concentration in the blood and target organ will increase accordingly (e.g. an antiepileptic agent in the brain). In many cases, the latter is a prerequisite for the expression of the desired therapeutic drug response.

Depending on the type of formulation, the disintegration and dissolution steps described above can be improved and sometimes omitted altogether. For instance, the active drug ingredient and the excipient in a capsule dosage form already exist in the powder form. Disintegration or splitting of the capsule shell becomes the limiting factor for the release of its active contents into the GI tract. However, capsule splitting in the GI tract is a relatively rapid process which generally requires less time than does tablet disintegration. The lack of a high compression force during manufacturing generally favours the capsule dosage forms over tablets in terms of disintegration. Similarly, for an oral suspension, the disintegration process becomes obsolete. How rapidly the drug dissolves becomes a controlling factor for drug absorption. When a drug is given in the form of an aqueous solution, both the disintegration and drug dissolution processes are bypassed. Hence, administration of an aqueous drug solution should, in theory, yield a more immediate desired drug response when compared to other oral dosage forms.

Pharmacokinetic parameters defining bioavailability

As outlined, it is possible to obtain different degrees of drug absorption when the same drug is formulated into different dosage forms.[4] The different absorption profiles of pentobarbital given as either aqueous solution, suspension, tablet, and tablet containing a more soluble sodium salt are shown in Fig 2. Closer inspection of these profiles show that two variables change significantly among different formulations. The most obvious are the differences in peak blood drug concentration and the time at which the peak is achieved following oral dosing. These two variables are commonly referred to as C_{max} and T_{max} respectively (Fig 3). Another important variable indicating the degree of drug absorption is the area under the concentration versus time curve which is usually abbreviated as AUC. The AUC is actually the numerical computation of the geometrical area bounded by the plasma drug concentration curve and the time- or the x-axis (shaded area in Fig 3).



Source: Sjögren J, et al. Acta Med Scand 1965.[4]

Fig 2. The absorption plasma concentration profiles of pentobarbital after the administration of 200 mg of the drug in various dosage forms

These three variables in combination can be used to describe both the rate and extent of drug absorption. If a drug is being absorbed into the systemic circulation more rapidly, the pharmacokinetic profiles will show a higher C_{max} and shorter T_{max}. Although not exact, the slope of the ascending phase, (this is the slope of the line back-extrapolating from C_{max} to the zero drug concentration on the x-axis), reflects the rate of drug absorption. As soon as a drug is absorbed, distribution of the drug via the blood to various body

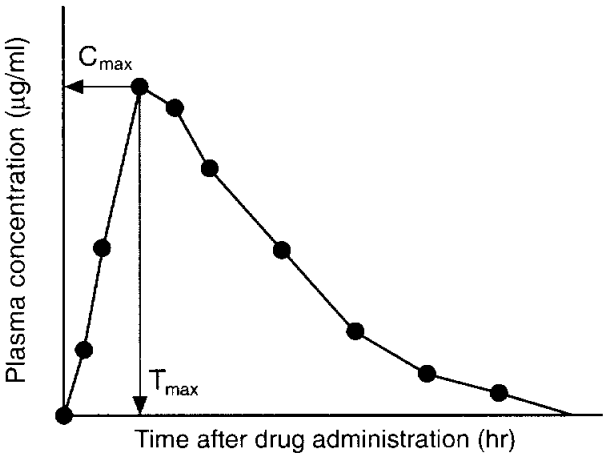


Fig 3. A typical pharmacokinetic profile following oral drug administration. The graphical representation of the three bioavailability parameters, C_{max}, T_{max} and AUC, are shown in the diagram. The AUC is the area bounded by the time axis and the plasma concentration curve.

organs commences immediately. As the circulating drug comes into contact with elimination organs such as the kidney and liver, part will either be excreted unchanged or converted to its metabolite(s) for elimination. For individuals with similar organ functions and body weights, how much drug reaches the circulation and how long the drug will stay in the body should, in part, be a function of the rate and amount of drug absorbed. Accordingly, when a larger amount of drug is absorbed, the drug concentration versus time profile will be elevated upwards, resulting in a proportional increase in the AUC estimate.

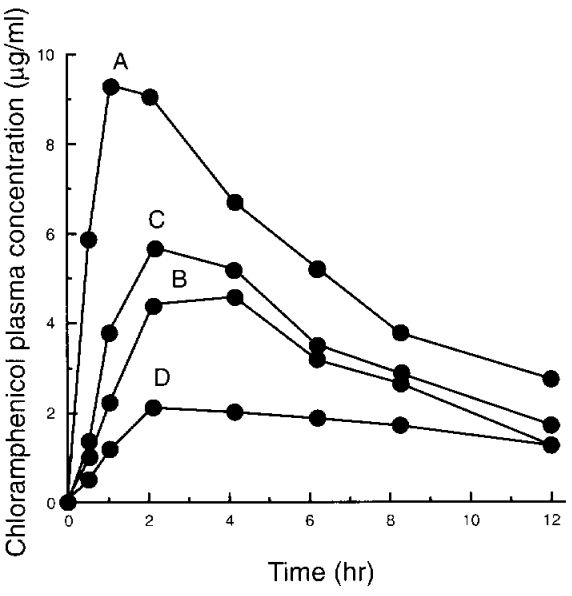
A drug entering the systemic circulation after absorption is commonly eliminated by the kidneys. Because of this, most investigators conducting bioavailability studies also collect urine samples over a rather long period of time in order to recover as much as possible of the drug being excreted by the kidneys. Likewise, the higher the bioavailability of a drug product, the higher the urinary recovery of a drug will be and proportional changes of these two variables are often observed.[5] However, due to the impracticality of prolonged periods of urine collection, especially for drugs with a long half life (at least four to five times the half life of a drug is required for complete urinary drug recovery) and the frequent technical difficulty in assaying urinary drug levels, renal excretion data are not weighted as heavily as are plasma data in bioavailability studies. The exception is when plasma drug concentration data are unavailable.[6] When comparing bioavailability data of certain formulations, C_{max}, T_{max} and AUC are the three parameters that should be vigorously defined.

Relative bioavailability

The term bioavailability should be more correctly referred to as relative bioavailability. It is unrealistic to expect that products containing the same amount of active ingredient will show the same bioavailability relative to one another. This can be seen in Fig 4 which shows a wide variation in relative bioavailability for four different commercial chloramphenicol products.[7] Traditionally, relative bioavailability has been assessed by comparing the AUC estimates or the AUC ratio of the two products under evaluation. When both products contain the same amount of an active ingredient, the following equation demonstrates the mathematical relationship between relative bioavailability and the AUC ratio of the two products:

$$\text{Relative bioavailability } (F_r) = \frac{\text{AUC}_{\text{test product}}}{\text{AUC}_{\text{reference product}}}$$

However, such a comparison is not complete if the rate of drug absorption has not been considered. Even when the two products show identical AUC values, the extent of drug absorption is the only variable that can be regarded as equivalent between these two products. They cannot be considered as truly bioequivalent if the rate of drug absorption differs significantly. For two products which exhibit different release rates due



Source: Glazko AJ, et al. Clin Pharmacol Ther 1968.[7]

Fig 4. Mean plasma concentration versus time profiles for four different commercial preparations (A-D) of chloramphenicol. Each point is the mean concentration obtained from 10 subjects.

to differences in disintegration and/or dissolution, the C_{max} and T_{max} values may vary substantially during in vivo testing. For example, a drug which can be readily absorbed in the GI tract, may release its entire drug content within 30 minutes by one formulation and three hours by another. This can result in profound differences between the drug concentration versus time profiles for the two formulations. Although the AUC values of the two products are similar when the same amount of drug is released and ultimately absorbed, the C_{max} will be much lower and the T_{max} much longer for the latter formulation.

Should expression of drug effect require the drug concentrations in the blood or in the target organ to fall within a certain optimal range, the latter formulation will be totally ineffective (product C in Fig 5). However, if absorption is too rapid, resulting in the drug blood/plasma level exceeding the upper limit of the therapeutic window, the use of such a product may cause drug toxicity (product A in Fig 5). When compared with a reference product, for any other product to be regarded as truly bioequivalent, it must show not only a similar AUC, but also C_{max} and T_{max} values. The plasma concentration versus time profiles generated from both the test and reference products should essentially be superimposable. For this reason, when assessing the performance of different pharmaceutical products, it is essential to distinguish the difference between bioavailability and bioequivalency. Simple comparisons between the contents of active ingredients, without assessing pharmacokinetic profiles and the degree of pharmacological response, is certainly inadequate from both a product safety and efficacy perspective.

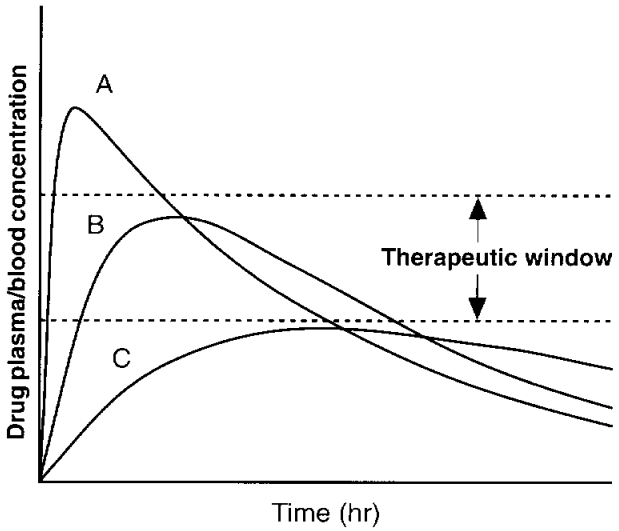


Fig 5. An illustration of the impact of bioavailability on the therapeutic efficacy of a pharmaceutical preparation. The therapeutic window is bound by the two horizontal dotted lines with the lower and upper lines representing the minimal effective level and toxic level, respectively.

Absolute bioavailability

Conclusions drawn in relative terms with any assessment can at times be misleading. In many cases, the amount of drug released by both the generic and brand name products can be low but the bioavailability of one product relative to another can be high. This controversial phenomenon can be readily demonstrated by comparing two products for which each releases 20% of the dose for absorption. Assuming complete absorption of the 20% dose released in the GI tract, the relative bioavailability of these two products is thus 100%. Therefore, relative bioavailability evaluations, although performed separately for the two products, do not necessarily present a true picture of drug availability. As a result, another definition of bioavailability—absolute bioavailability—is employed to describe the actual or absolute amount of drug absorbed from a certain formulation.

Clinical trials on absolute bioavailability are frequently conducted by research-based pharmaceutical companies during the course of development of a new drug. Due to the drug and its formulation being new, this type of assessment is not directed to the comparison with a generic product but rather to define the absorption characteristics of the formulation and its pharmacokinetic behaviour. To permit estimation of the amount of drug subsequently available to the body following absorption, absolute bioavailability assessment must involve the use of an intravenous dose of the same drug under evaluation. This is because the intravenous dose is considered to be 100% bioavailable. In fact, absolute bioavailability assessment involves comparing the new drug product with an intravenous dose of the same drug. The AUC of the new drug product relative to that of an intravenous dosing of the drug at the same dose can be calculated by:

$$\text{Absolute bioavailability (F)} = \frac{AUC_{\text{test product}}}{AUC_{\text{intravenous dose}}}$$

Similarly, the two parameters, C_{max} and T_{max}, obtained from the pharmacokinetic profile of the new product can be used to indicate the rate of drug absorption from the GI tract after oral dosing. Absolute bioavailability, as indicated by the AUC ratio of the above equation, reflects the absolute amount of drug that is available to the body after dosing. This

bioavailability estimate is a hybrid parameter dictated by the fraction of dose absorbed by the GI tract and the fraction of dose that escapes first-pass metabolism by the liver. Hence, variations in liver function can affect the bioavailability of drugs which are extensively metabolised by the liver. Increased bioavailability has been observed in patients with liver dysfunction for various drugs, including meperidine, pentazocine, salicylamide, propranolol, and chlormethiazole.[8-10] Increases in bioavailability can be substantial, approaching three-fold for pentazocine and ten-fold for chlormethiazole.

The need for an intravenous formulation of a new drug creates problems in absolute bioavailability assessments. Deterrants include the rather high production cost, sterility concerns, drug stability in an aqueous vehicle, and the inconvenience associated with intravenous dosing. Therefore, it is not unusual for a drug company to focus on the development of an oral formulation without showing much interest in formulating an intravenous preparation. When a drug is unavailable in the solution form, an intramuscular injection of the drug in suspension can be used as the reference preparation. In many cases, absolute bioavailability data are obtained from preclinical animal studies, conducted during the early stages of the new drug research and development programme. As required by most regulatory agencies in many countries, collection of human data on absolute bioavailability of the new drug product is necessary but may be delayed well beyond the initial clinical phase. Nevertheless, absolute bioavailability data are a gauge for characterising the formulation performance of the new drug under development and may further improve the drug before it reaches the market.

Conclusion

From the viewpoint of the generic-based pharmaceutical industry, the most important and relevant bioavailability assessment is relative bioavailability. This is an important requirement for establishing bioequivalency of a product when compared with other brand name products. Research-based ethical drug companies should conduct studies to define the absolute bioavailability of their new drug products. Studies of this type not only help to define the absorption characteristics of a new drug in the formulation intended for marketing, but also elaborate the pharmacokinetic behaviour of the new drug itself. Although not a primary goal, the pharmacokinetic data generated from absolute bioavailability assessments can assist in dose selection. At present, most clinical studies are performed in Caucasian populations. There is absolutely no reason to assume that both the bioavailability and pharmacokinetic data obtained in Caucasians can be directly applied to other races.

In addition to possible ethnic differences in bioavailability and pharmacokinetic characteristics, it is not known if therapeutic drug responses also differ between different races. A good example is propranolol. Chinese are known to eliminate this ß-blocker more rapidly than do Caucasians, however, they are also more sensitive to its ß-blockade effects.[11,12] The United States Food and Drug Administration has been requesting pharmaceutical companies to provide more clinical data on different races, when submitting a new drug application, especially when the new drug is to be consumed by a significant number of patients from different races. There has been a move to harmonise the regulatory requirements for conducting drug studies between the countries in the European Community, Japan and North America.[13-16] If details can be worked out, this will reduce the repetition of similar studies conducted by the pharmaceutical industry in different countries. Nevertheless, compliance with this new policy does not solve the intrinsic problem of racial differences in drug responses. Additional cost and resources will necessarily be involved if studies on different races have to be included in the drug development process. It is important to watch for any anomalies in clinical safety and efficacy data so as to determine if additional bioavailability and pharmacokinetic studies are necessary for a particular population.

By performing more clinical studies including absolute bioavailability and pharmacokinetic assessments in the Hong Kong Chinese population, a more rational use of drug products in the local patient population can undoubtedly ensue. Ideally, all drug products—either generic or brand name—should at least demonstrate adequacy in drug bioavailability in the Hong Kong Chinese population before being eligible for registration in Hong Kong. Such practice should be considered a safeguard for proper drug utilisation in Hong Kong.

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