Handbook of Basic Pharmacokinetics

. . . including Clinical Applications

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Bioavailability and Bioequivalence

Definitions

Bioavailability is defined by the United States Food and Drug Administration (FDA) as the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of drug action. It is unfortunate that this official definition is not precise enough.

First, consider the statement with respect to the site of drug action. Although, in general, we assume that the drug concentration in blood, plasma or serum correlates with the pharmacologic response, it is not applicable to all drugs. Furthermore, the actual bioavailability testing as outlined in the regulation does not attempt to determine the drug concentration at the site of drug action but in systemic circulation. Exception to it is given when it is not possible to measure blood levels; then the bioavailability test is substituted by a pharmacologic or clinical test.

Secondly, this definition does not explicitly include the steadily growing group of prodrugs. As a working hypothesis, we will therefore define bioavailability as follows: bioavailability is both the relative amount of therapeutic moiety in form of a parent drug, active metabolite or active moiety of a prodrug from an administered dosage form which enters systemic circulation and the rate the drug appears in it.

Contrary to the belief of many, bioavailability is *not* a criterion of clinical effectiveness *per se*. Clinical effectiveness is so complex (disease states, nutritional status) and the factors influencing absorption so numerous (food intake/fasting, type and amount of food, circadian rhythm, age, etc.) that a test in a small sample size of the population can only be regarded as a *biologic quality control test* under specified conditions.

A drug product is defined as a finished dosage form; this means a tablet, capsule, solution, suppository, etc. that contains the active drug ingredient generally, but not necessarily in association with inactive ingredients. One has to imply that under active drug ingredient also prodrugs are meant, although not explicitly stated.

Pharmaceutical equivalents are defined as drug products that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety in identical dosage forms, but not necessarily containing the same inactive ingredients, and that meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates.

Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates.

Whereas **bioavailability** is to demonstrate the amount and rate of drug or active moiety appearing in systemic circulation, and has to be determined for any new drug or new drug product, **bioequivalence** is to demonstrate that other drug products are comparable with respect to biologic performance to an already approved drug product.

A bioequivalence problem may arise when two or more pharmaceutical equivalents or pharmaceutical alternatives, which meet all applicable in vitro standards when administered at the same molar dose of the active therapeutic moiety to the same individuals with the same dosage regimen, result in inequivalent bioavailability. In this case, it could either be that the current in vitro standards for the drug products are not adequate to test and assure bioequivalence or that the products are not appropriately labelled according to their different pharmacokinetic behavior of the dosage form.

It is in the public interest that all products containing the same active ingredient be interchangeable which would require that they are bioequivalent or that for special and desired purposes a different labelling, easily recognizable, is required to immediately indicate a different pharmacokinetic

profile.

Bioequivalent drug products are defined as pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the therapeutic moiety, under similar experimental conditions, either single dose or multiple dose.

Some pharmaceutical equivalents or pharmaceutical alternatives may be equivalent in the extent of their absorption but not in their rates and, yet, may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labelling, are not essential to the attainment of effective body drug concentrations on chronic use, or are considered medically insignificant for the particular drug product.

In order to demonstrate bioequivalence, the Food and Drug Administration has imposed *bioequivalence requirements* for in vitro and/or in vivo testing of specified drug products which must be satisfied as a condition of marketing.

Factors Modifying Bioavailability

In all cases, except when a drug is administered intravenously in form of a true solution, the drug has to be released from the dosage form and then be absorbed into systemic circulation by passing through various membranes.

A drug given in different dosage forms or by different routes of administration will yield varying amounts of drug absorbed and, hence, differences in onset, intensity, and duration of the pharmacologic or clinical effect.

These variations are primarily due to differences

in the efficiency and rate of absorption which may originate either with the patient or the dosage form. In the first case, we call it a **physiologically modified bioavailability** and in the second case, a **dosage form modified bioavailability.**

In testing of bioavailability and bioequivalence one has to carefully design the study protocol in order to exclude physiologically based modifications of bioavailability. These include age, sex, physical state of the patient, time of administration, stomach emptying rate, type and amount of food, *pH* and enzyme variations in the gastro-intestinal tract, motility of the gastro-intestinal tract, blood flow, liver function, kidney function, body weight, psychological factors such as stress, etc. It is imperative that any design must be able to either exclude such factors or to allow their proper evaluation. The logical consequence is a true cross-over design.

The bioavailability or bioequivalence problems as specified in the new regulation are, therefore, those which depend on the physico-chemical characteristics of the drug or the dosage form. These factors are particle size, polymorphic form, presence of a solvate or a hydrate, chemical presentation in salt, ester, ether, complex, *p*H of dosage forms, environment, solubility characteristics, type and amount of vehicle substances present, the manufacturing method employed for preparing the dosage forms such as type of granulation, change in manufacturing practices, change in blending and mixing practices, improper drying conditions, high-speed tableting, variation in compression force, and instability.

Bioavailability of New Drugs

In the past, clinical pharmacologists and toxicologists have paid too little attention to biopharmaceutical evaluation of new drug products to be tested in man during Phase I studies.

It is well known that the LADMER-system (liberation, absorption, distribution, metabolism, elimination, response) applies also to the first administration of a new drug to man with all its implications of physicochemical parameters of the drug and the product. It is very likely that if one would reanalyze under our present understanding of biopharmaceutics and pharmacokinetics all those drugs which have been abandoned during the past decades as being ineffective in the first clinical trial, one would find quite a number of useful drugs.

The regulation on bioavailability requires that any new drug application submitted in the United States to the FDA must have a complete biopharmaceutical and pharmacokinetic evaluation, including the determination of bioavailability.

Bioequivalence Requirements

According to the regulation, the FDA on its own or in the response to a petition by an interested person, may identify specific pharmaceutical equivalents or pharmaceutical alternatives that are not or may not be bioequivalent drug products and determine whether to propose or promulgate regulation to establish a bioequivalent requirement for these products.

The criteria and the evidence when bioequivalence requirements have to be established are listed

Table 36-1. Criteria and Evidence to Establish a Bioequivalent Requirement

1. Difference in therapeutic effects.
2. Bioinequivalence demonstrated.
3. $LD_{50}/ED_{50}<2$ or $C_{min\ tox.}/MEC<2$.
4. If bioinequivalence would be of serious consequence.
5. If solubility <0.5 %, or if <50 % dissolved in 30 min, or if particle size is critical, or if drug forms polymorphs, solvates, hydrates, complexes of decreased dissolution, or if drug/excipients <1/5, or if ingredients might interfere with absorption.
6. If absorption from localized site, or f[1] <0.5, or FPE[2], or β[3] or k_m[4] is extremely fast, or if buffers, enteric- or film-coatings are required, or if dose dependent kinetics are in or near therapeutic range.

[1]fraction of drug absorbed
[2]first-pass effect
[3]terminal elimination rate constant
[4]rate constant of metabolism

in Table 36-1.

Inspecting Table 36-1, it is quite obvious that for many drugs such a bioequivalent requirement exists *a priori* due to low solubility of the active ingredient or the fact that they appear in form of polymorphs, in hydrous and anhydrous form, as complexes, solvates, etc.

A bioequivalent requirement may be one or more of the following as specified by the FDA, namely, an in vivo test in humans, an in vivo test in animals other than humans that has been correlated with human in vivo data, or in an animal model without correlation with human in vivo data, or an in vitro test which either has been correlated with human in vivo bioavailability or for which no correlation has been established. In vivo bioequivalence requirement in man is mandatory, if there is documented evidence that pharmaceutical equivalents or pharmaceutical alternatives do not give comparable therapeutic effects or are not bioequivalent, or

Table 36-2. Criteria for Waiver of in vivo Bioavailability

1. I.V. solution, solution, topical product for local effect, drugs not intended for P.O. absorption, inhalation product similar to approved one.
2. P.O. (except enteric coated or controlled release) dosage form similar to approved one except for **some** drugs of the following groups: antiarrhythmics, anticoagulants, anticonvulsants, antihypertensives, antimalarials, antineoplastics, antithyroids, antituberculars, bronchial dilators, carbonic acid inhibitors, cardiac glycosides, corticoids, estrogens, hypoglycemics, thyroid supplements, tranquilizers, vitamin K.
3. Or otherwise waiver is granted.

where the ratio of LD_{50}/ED_{50} is less than 2, or the ratio of the minimal toxic concentration to the minimal effective concentration is less than 2.

The new regulation also specifies criteria for waiver of evidence of in vivo bioavailability under certain conditions which are listed in Table 36-2.

General Guidelines for the Determination of in vivo Bioavailability

The in vivo bioavailability of a drug product is demonstrated by both the rate and extent of absorption of the active ingredient or therapeutic moiety. In principle there are four possible approaches to measure the bioavailability, namely:

1. Blood Level Data.
2. Urinary Excretion Data.
3. Pharmacologic Data.
4. Clinical Data.

Whenever possible blood level studies should be carried out and are preferable to all other studies. If such studies are not feasible, they can be substituted by urinary excretion studies. Only if neither one can be done, particularly if the drug cannot be assayed accurately in biological fluid but the pharmacologic response can be measured, a pharmaco-

logic method can be used to substitute for blood level or urinary excretion studies. In the case where it is difficult or impossible to quantify a given pharmacologic response, clinical studies in patients are permissible to substitute for a blood level or urinary excretion study.

The latter approach can also be used for dosage forms intended to deliver the therapeutic moiety locally such as, for topical preparations for the skin, ear, eye, mucous membrane, oral dosage forms not intended to be absorbed, and also for bronchodilators administered by inhalation. Although clearly specified in the law, this specific reference seems to be in contradiction to the definition of bioavailability. However, it means that controlled clinical studies may be submitted if low systemic absorption is expected and the bioavailability is substituted by a local availability test where the drug apparently does not enter systemic circulation.

Selection of a Standard for Bioavailability Testing

The previous practice that the inventor's product is considered as the standard has been abandoned. The change is legitimate because otherwise it might hinder progress. In general, an aqueous true solution of the drug, an aqueous solubilized system of the drug, or an aqueous suspension of the micronized drug will, for most instances, be considered as the standard. However, no strict regulation can be applied since there are drugs which are absorbed solely from the duodenum. In that case, the transition time through the duodenum might be too short for the drug to be quantitatively absorbed.

The selection of the standard for the various categories of bioavailability testing depends on the

Table 36-3. Selection of Standard

CATEGORY	PARAMETERS TO BE DETERMINED	STANDARD	ROUTE OF ADMINISTRATION FOR STANDARD
New drug in any drug product	Extent and rate of absorption: elimination half-life, rate of metabolism and/or excretion; dose proportionality after single and multiple dosing	Solution or suspension of drug in single dose study	Same as drug product unless drug is poorly absorbed. In the latter case additional I.V. route
New formulation of marketed product	Extent and rate of absorption; pharmacokinetic parameters of new formulation	Current batch of approved drug product on the market in single dose study	Same as drug product
Controlled release formulation	Extent and rate of bioavailability: pharmacokinetic performance of dosage form	Solution or suspension of drug and/or currently marketed non-controlled release and/or controlled release product in single and multiple dosing study	Same as drug product
Combination drug product	Rate and extent of absorption of one, more or all active drugs	Two or more single-ingredient drug products in single dose study	Same as drug product
Any drug product when drug concentration is not determined in biological fluid	Pharmacologic effect or clinical response	Placebo in single or multiple dose study	Same as drug product

type of drug product and the questions to be answered. It can be broken down into the following categories, namely: bioavailability testing for a new drug in any new drug product, for any new formulation of a known and marketed product, for a controlled release formulation, for a combination drug product containing two or more drugs, and for any drug product when the drug concentration cannot be determined in biological fluid. The parameters to be determined in each of these categories, the

Table 36-4. Possible Methods to Assess Bioavailability

SEQUENCE OF EVENTS UPON ADMINISTRATION OF A DRUG PRODUCT	METHOD OF EVALUATION	EXAMPLE
Drug liberation and dissolution at administration or absorption site	Dissolution rate	In vitro: water, buffer, artificial gastric fluid, artificial intestinal fluid, artificial saliva, artificial rectal fluid
Free drug in systemic circulation	(1) Blood level-time profile (2) Peak blood level (3) Time to reach peak (4) Area under blood level-time curve	In vivo: whole blood, plasma, serum
Pharmacologic effect	(1) Onset of effect (2) Duration of effect (3) Intensity of effect	In vivo: discriminate measurement of pharmacologic effect (blood pressure, blood sugar, blood coagulation time)
Clinical response	(1) Controlled clinical blind or double blind study (2) Observed clinical success or failure	In vivo: evaluation of clinical reponses
Elimination	(1) Cumulative amount of drug excreted (2) Maximum excretion rate (3) Peak time of excretion	In vivo: urine

standards and route of administration to be used are listed in Table 36-3. FDA should be consulted prior to applying the standard to any study.

In Vitro — In Vivo Methods for Bioavailability Testing

Possible methods to access bioavailability include determination of the drug liberation and dissolution at the administration or absorption site, determination of the free drug in systemic circulation, mea-

suring the pharmacologic effect or clinical response, or to determine the urinary excretion of the drug.

The methods of evaluation and examples are listed in Table 36-4.

Regarding the question whether or not bioavailability may be measured by some in vitro methods, a personal remark should be voiced. In a true meaning and sense of *bio*availability, no in vitro method can be substituted for a biologic test. An in vitro bioavailability is a contradiction *per se*. However, in vitro methods are necessary to simulate and understand physicochemical processes of absorption, in dosage form development, and as in vitro quality control tests to guarantee batch-to-batch consistency.

Since bioavailability is most precisely determined from either blood level or urinary excretion data, we will discuss the scientific aspects of bioavailability testing based on blood sampling or urine sampling studies only.

Types of Bioavailability

From a scientific point of view, we distinguish between four different types of bioavailability, depending on the purpose of the study and the scientific question to be solved. If new drugs are to be studied probably all four types should be applied, whereas for existing approved drugs only the third or fourth type will be necessary, if a test for bioequivalence is required.

Absolute Bioavailability or Fraction of Drug Absorbed f

The principle of determining the absolute bioavailability is shown in Figure 36-1.

The fraction of drug absorbed f allows determina-

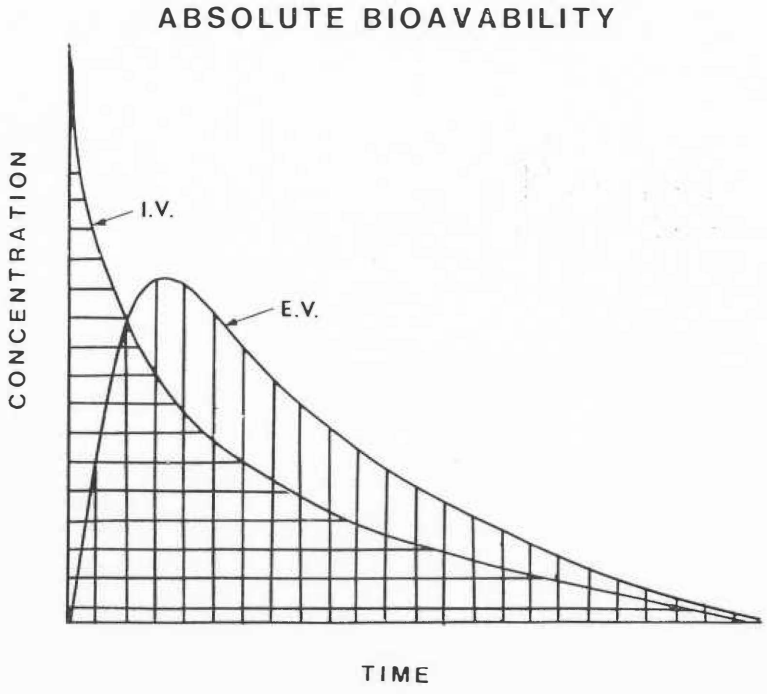

Figure 36-1. Schematic diagram to determine absolute bioavailability from the areas under the curve upon I.V. and E.V. administration of identical dose sizes.

tion of the absolute amount of drug absorbed from an extravascularly administered drug product. It is, therefore, essential that the drug be also administered intravenously. However, it is not required to give the same dose I.V. as is administered extravascularly. For a valid study, both the intravenously and extravascularly administered drug must be given to the same subjects in a cross-over design. The fraction of drug absorbed f is the ratio of the total area under the blood level-time curve upon extravascular route of administration to the total area under the blood level-time curve upon intravenous administration, corrected for the difference in the dose size as given in Equation 36.1:

$$f = \frac{AUC^{0\rightarrow\infty}_{extravascular}\,[(mg/ml)\cdot h]\cdot D_{I.V.}\,[mg]}{AUC^{0\rightarrow\infty}_{I.V.}\,[(mg/ml)\cdot h]\cdot D_{extravascular}\,[mg]}$$

Eq. 36.1

Since the elimination rate constants may vary inter- and intra-individually for the same drug and upon different routes of administration, correction for the observed terminal elimination rate constant data and also for the individual body weight should be made as shown in Equation 36.2:

$$f = \frac{AUC^{0\rightarrow\infty}_{extravascular}\,[(mg/ml)\cdot h]\cdot \dfrac{D_{I.V.}\,[mg]}{BW_{I.V.}\,[kg]\cdot \beta_{I.V.}\,[h^{-1}]}}{AUC^{0\rightarrow\infty}_{I.V.}\,[(mg/ml)\cdot h]\cdot \dfrac{D_{extravasc.}\,[mg]}{BW_{extravasc.}\,[kg]\cdot \beta_{extravasc.}\,[h^{-1}]}}$$

Eq. 36.2

If instead of blood level, urinary excretion data are used, the fraction of drug absorbed f is determined from the ratio of the total amount of unchanged drug excreted into urine upon extravascular administration to that upon intravenous administration, corrected for the dose size as shown in Equation 36.3:

$$f = \frac{Ae^{\infty}_{extravascular}\,[mg]\cdot D_{I.V.}\,[mg]}{Ae^{\infty}_{I.V.}\,[mg]\cdot D_{extravascular}\,[mg]}$$

Eq. 36.3

Bioavailability in Presence of First-Pass Effect

Drugs showing a first-pass effect may result in considerable lower blood level versus time curves

even though all of the parent drug was absorbed from the site of administration, yet did not reach systemic circulation in unchanged form. A drug given I.V., I.M., S.C. or orally will eventually pass through the liver, too. However, it is first distributed in systemic circulation and probably, at least in part, throughout the volume of distribution before being exposed to the liver. At any given time about 80 percent of the blood volume is metabolically inactive.

The fraction of a peroral (P.O.), or in part rectal, dose reaching systemic circulation f_{FPE}, under the assumption of otherwise linear kinetics, can be described by Equation 36.4:

$$f_{FPE} = \frac{D_{I.V.}\,[mg] \cdot AUC_{P.O.}^{0\rightarrow\infty}\,[(mg/ml) \cdot h]}{D_{P.O.}\,[mg] \cdot AUC_{I.V.}^{0\rightarrow\infty}\,[(mg/ml) \cdot h]} \qquad \text{Eq. 36.4}$$

Under the assumption that only first-pass effect is involved and the drug is completely absorbed to specifically describe the fraction of a peroral or rectal dose reaching systemic circulation f_{FPE}, Equation 36.5 can be used where f_m is the fraction of drug metabolized in the liver. LBF is the liver blood flow rate, and λ is the ratio of the concentration of the drug in whole blood to that in plasma.

$$f_{FPE} = 1 - \frac{D_{I.V.} \cdot f_m}{LBF \cdot AUC_{I.V.}^{0\rightarrow\infty} \cdot 60 \cdot \lambda} \qquad \text{Eq. 36.5}$$

If the numeric value of f_{FPE} according to Equation 36.4 is less than that obtained with Equation 36.5 then either absorption is incomplete or FPE can be assumed. If the numeric value of f_{FPE} obtained with Equation 36.4 is greater than that obtained with Equation 36.5 it can be assumed that the drug concentration in the portal vein upon P.O. dosing is high enough to saturate the drug

metabolizing enzyme systems.

It is possible to predict the fraction of drug reaching systemic circulation upon P.O. dosing from I.V. data. In this case one determines the total area under the curve upon the I.V. administration and calculates the f_{FPE} according to Equation 36.6, knowing the dose administered I.V. and assuming a liver blood flow of 1.53 ($l \cdot min^{-1}$):

$$f_{FPE} = 1 - \frac{D_{I.V.}}{LBF \cdot AUC_{I.V.}^{0 \rightarrow \infty} \cdot 60} \qquad \text{Eq. 36.6}$$

For differentiation between incomplete absorption and first-pass effect see Chapter 13.

Relative Bioavailability EBA and RBA, and Bioequivalence

The principle for determination of relative bioavailability is shown in Figure 36-2.

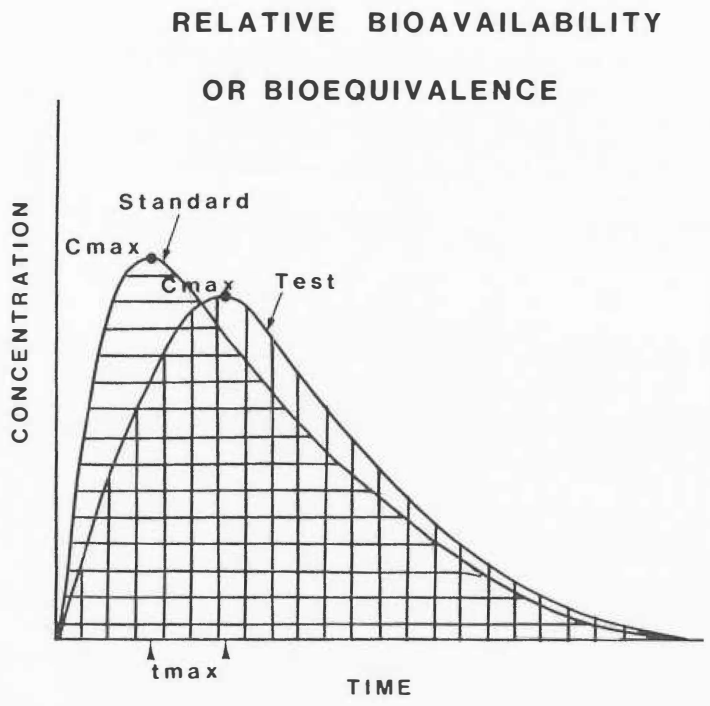

Figure 36-2. Schematic diagram to determine relative bioavailability from the areas under the curve from two different drug products given E.V. by the same route of administration in identical dose sizes.

The relative bioavailability is the *extent* EBA and *rate* RBA of the bioavailability of a drug from two or more different dosage forms given by the *same* route of administration. According to the new FDA regulation the standard used in this procedure is either an approved marketed drug product, or a solution of the drug, or suspension of the micronized drug.

For determination of EBA and RBA either blood level or urinary excretion data upon single or multiple dosing can be used. For valid studies a crossover design has to be used, whereby differences in clearance and/or terminal disposition rate constants should cancel out. For a single dose blood level study EBA is calculated according to Equation 36.7 where the indices tdp and sdp mean "test drug product" and "standard drug product," respectively.

$$\text{EBA} = \frac{\text{AUC}_{\text{t.d.p.}}^{0\rightarrow\infty}\ [(\text{mg/ml}) \cdot \text{h}] \cdot D_{\text{s.d.p.}}\ [\text{mg}]}{\text{AUC}_{\text{s.d.p.}}^{0\rightarrow\infty}\ [(\text{mg/ml}) \cdot \text{h}] \cdot D_{\text{t.d.p.}}\ [\text{mg}]} \cdot 100 \qquad \text{Eq. 36.7}$$

In case of multiple dosing EBA can be determined from the blood level-time curve within a complete dosing interval τ at steady state using Equation 36.8:

$$\text{EBA} = \frac{\text{AUC}_{\text{t.d.p.}}^{\tau_n\rightarrow\tau_{n+1}}\ [(\text{mg/ml})\cdot\text{h}]\cdot D_{\text{s.d.p.}}\ [\text{mg}]}{\text{AUC}_{\text{s.d.p.}}^{\tau_n\rightarrow\tau_{n+1}}\ [(\text{mg/ml})\cdot\text{h}]\cdot D_{\text{t.d.p.}}\ [\text{mg}]} \cdot 100 \qquad \text{Eq. 36.8}$$

In the case of urinary excretion data, the total amount of unchanged drug excreted into urine upon single dose administration is used applying Equation 36.9 to determine EBA:

$$EBA = \frac{Ae^{\infty}_{t.d.p.}\,[mg] \cdot D_{s.d.p.}\,[mg]}{Ae^{\infty}_{s.d.p.}\,[mg] \cdot D_{t.d.p.}\,[mg]} \cdot 100 \quad \text{Eq. 36.9}$$

In the case a urinary excretion is carried out upon multiple dosing Equation 36.10 is applicable:

$$EBA = \frac{Ae^{\tau_n \rightarrow \tau_{n+1}}_{t.d.p.}\,[mg] \cdot D_{s.d.p.}\,[mg]}{Ae^{\tau_n \rightarrow \tau_{n+1}}_{s.d.p.}\,[mg] \cdot D_{t.d.p.}\,[mg]} \cdot 100 \quad \text{Eq. 36.10}$$

Bioequivalence is given if there is no significant difference in extent and rate of relative bioavailability of a test product when compared to the approved standard.

Relative Optimal Bioavailability $EBA_{rel.\ opt.}$

The term *relative optimal bioavailability* has been suggested in 1970 for optimizing extent and rate of bioavailability for a drug product during the development phase. For determination of $EBA_{rel.\ opt.}$ the active drug is administered in aqueous solution without addition of any further excipient by the same route which is intended for the drug product under development. In the case the drug is not water soluble an aqueous-organic solvent, such as, glycerol, propylene glycol, alcohol, or polyethylene glycol-water mixture is used. The total AUC and the absorption rate constant k_a are determined from blood level-time data.

The $EBA_{opt.\ rel.}$ is termed optimal because the first step in the sequence of events responsible for bioavailability, the drug liberation, is omitted since the drug is already in aqueous solution, hence, in absorbable optimal form. However, it is relative,

because the bioavailability might be further increased by the addition of buffers to either prevent decomposition or inactivation, or to increase the nonionized moiety, or by addition of sorption promoting agents. It is further relatively optimal, because the assumption that a drug in aqueous solution is always "better" absorbed may not be valid in all cases. It is well known that if a drug is absorbed exclusively from the duodenum the transit time of the drug in solution might be too short to permit complete absorption.

The absorption rate constant obtained with the solution is termed "true" rate constant for this particular route of administration, whereas the rate constant for absorption obtained with the drug product will only be an *apparent* one which is overlapped by the process of drug liberation and dissolution. If one determines the blood level-time profiles and absorption rate constants upon administration of the drug in solution, drug in powder form filled into gelatin capsules, then of the drug in powder form with the addition of the anticipated excipients filled into gelatin capsules, followed by administration of the granules filled into gelatin capsules, and finally of the tablet, or any other dosage form, it is possible to pinpoint whether a bioavailability problem may be associated with the drug, the excipients, or the manufacturing method.

The $EBA_{rel.opt.}$ is determined according to Equation 36.11:

$$EBA_{rel.opt.} = \frac{AUC^{0\rightarrow\infty}_{(drug;\ +\ vehicle;\ granules;\ tablet)}}{AUC^{0\rightarrow\infty}_{(solution)}} \cdot 100 \qquad \text{Eq. 36.11}$$

The method of optimal relative bioavailability will definitely be determined in animal models and

not in man. It constitutes a useful tool in drug product development.

For determination of area under the concentration-time curve see Chapter 20.

Determination of Rate of Bioavailability RBA

The rate of bioavailability is actually the apparent absorption rate constant of the drug from the drug product. Even if the extent of bioavailability is identical for two or more products it does not necessarily mean that they result in comparable blood level curves, because it is the rate which determines the time and height of the peak in case of complete absorption and constant elimination rate as shown in Figure 36-3.

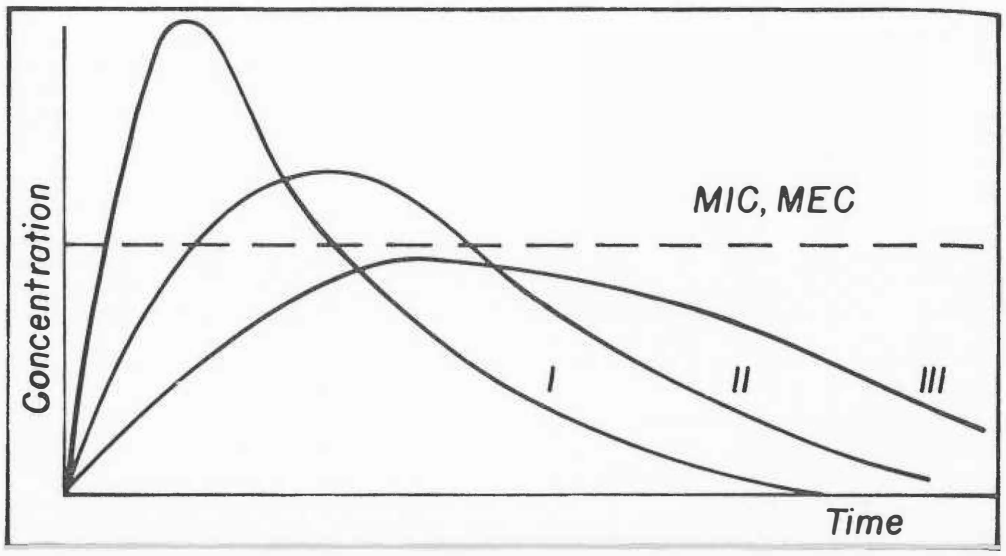

Figure 36-3. Extent of bioavailability and clinical effectiveness. All three curves have identical AUCs, yet one curve does not reach the required minimum effective concentration.

All three curves in Figure 36-3 have the same area under the curve. However, only curves I and II will be clinically effective, since at least a portion of the blood level curve is above the minimum ef-

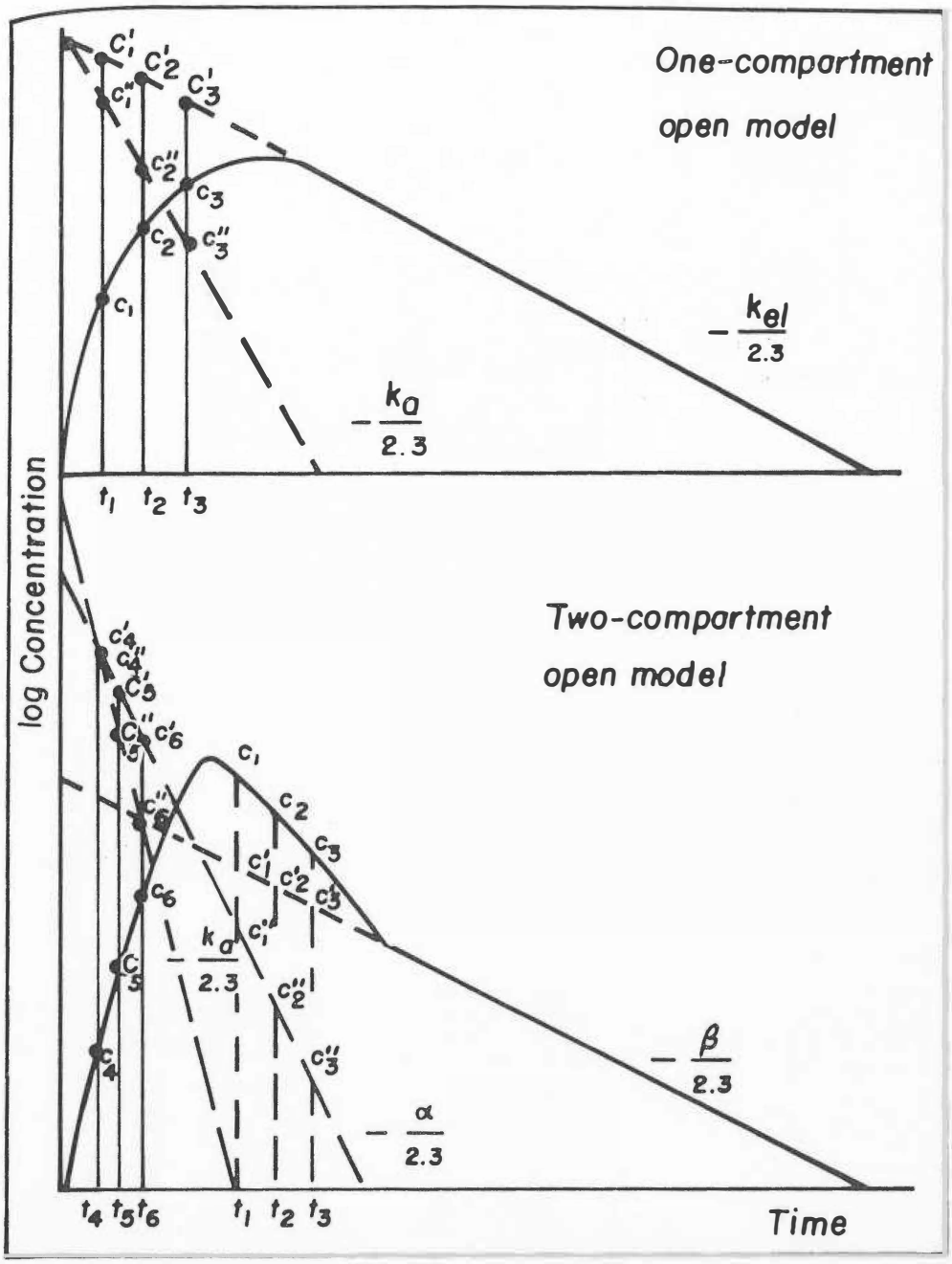

Figure 36-4. Determination of rate of bioavailability by the residual method.

Top:

C_{index} = actual blood concentrations during absorptive phase at corresponding sampling times t_{index}

C'_{index} = concentrations on back-extrapolated: k_{el}-slope at times t_{index}

C''_{index} = differences between C'_{index} and C_{index}

k_{el} = elimination rate constant

k_a = absorption rate constant

Bottom:

$C_{1,2,3}$ = actual blood concentrations during distributive phase at corresponding sampling times $t_{1,2,3}$

$C'_{1,2,3}$ = corresponding concentration values on back-extrapolated terminal disposition slope β

C''_{index} = differences between C'_{index} and $C_{1,2,3}$

$C_{4,5,6}$ = actual blood concentrations during absorptive phase at corresponding sampling times $t_{4,5,6}$

$C'_{4,5,6}$ = corresponding concentrations on fast disposition slope α

$C''_{4,5,6}$ = difference between $C'_{4,5,6}$ and $C_{4,5,6}$

β = terminal disposition rate constant

α = hybrid distribution rate constant

k_a = absorption rate constant

fective MEC or minimum inhibitory concentration MIC, whereas curve No. III does not even reach this minimum therapeutic concentration. Also onset and duration may depend on the rate of bioavailability. The determination of RBA is model dependent, since the blood level-time curve upon extravascular administration is a composite of at least a biexponential or higher exponential process. A number of methods have been described for determination of the RBA. Following we will discuss the residual method only as a typical example and most widely used method.

The drug concentration data are plotted on a log scale versus time. In the case of a one-compartment open model (See Figure 36-4 top) the monoexponential elimination slope is back-extrapolated to the ordinate. Using the intercept B the differences between the actual blood level points during the absorptive phase and the concentrations on the back-extrapolated monoexponential line at the same time are plotted on the same graph. Combining these different points a straight line is obtained by using a least square fit, and the slope of this line is the absorption rate constant k_a.

In the case the two-compartment open model is applicable, first the fast disposition slope α is de-

termined by the residual method as the differences between the descending curved part of the curve and the back-extrapolated monoexponential terminal slope data, and the corresponding concentrations at the identical time of the β slope. Then the residuals are determined between the differences of the actual blood level data during the absorptive phase and the concentrations on the α-slope, the corresponding concentrations on the α-slope at the same times, as shown in Figure 36-4, bottom graph. A least square fit of the difference points will yield the absorption rate constant k_a.

The same procedure for determination of absorption rate constant can also be applied to a plot of log mean excretion rate versus midpoint time obtained from a cumulative urinary excretion study. The mean excretion rate versus midpoint time plot is the identical image to the corresponding blood level curve and is suitable for determination of terminal disposition rate constant, time of peak for the drug concentration in the blood, and determination of absorption rate constant.

Evaluation of Bioavailability Studies

The most precise evaluation of extent and rate of bioavailability is obtained from single dose or multiple dose blood level studies followed by single dose or multiple dose urinary excretion studies.

Single Dose Studies

In case of blood level studies the following three parameters characterize rate and extent of bioavailability:

- Area Under Curve ($AUC^{o\rightarrow\infty}$);
- Actual Peak Height (C_{max});
- Time to Reach the Peak (t_{max}).

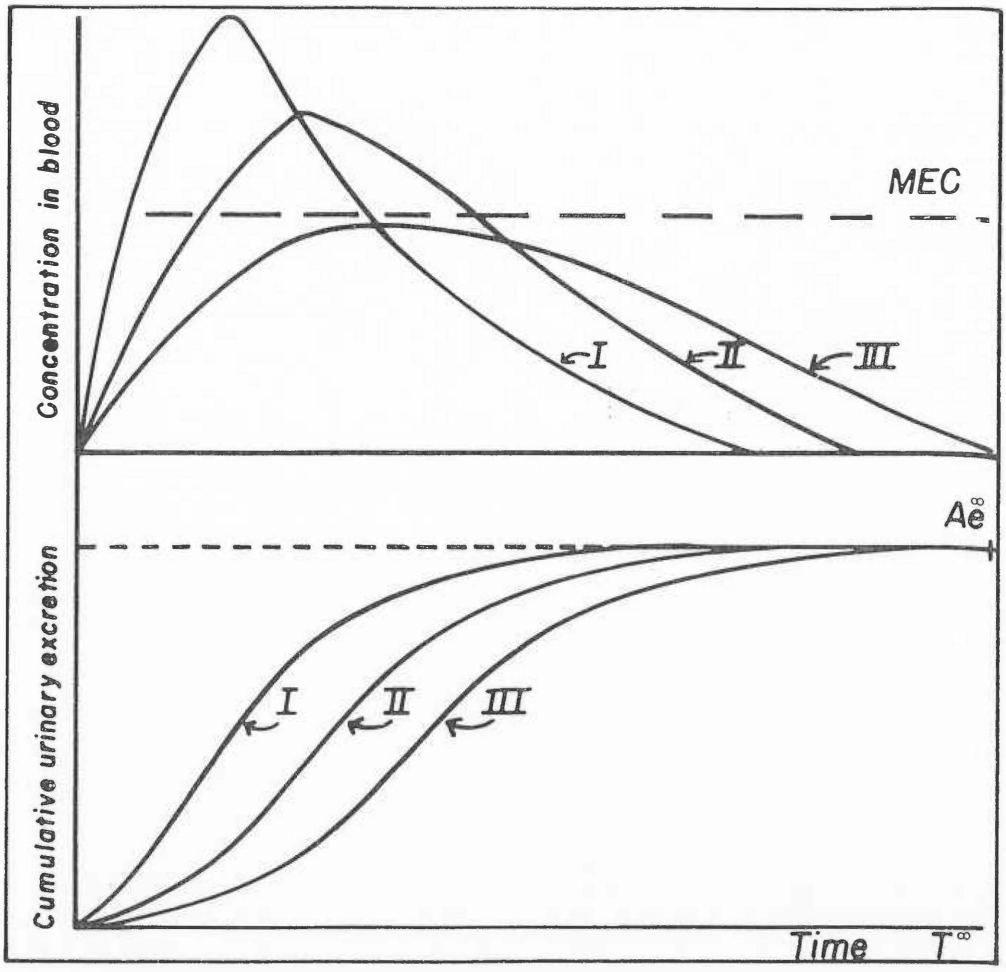

Figure 36-5. Blood level **versus** time curve for three drug products with identical extent of bioavailability but different rates of bioavailability (top), and the corresponding cumulatve urinary excretion curves (bottom): Ae^{∞} = total amount of unchanged drug eliminated in urine at infinite time T^{∞}.

In case of urinary excretion studies the three parameters characterizing the rate and extent of bioavailability are the following:

- Total Amount of Drug Excreted in Infinite Time in Unchanged Form (Ae^{∞});
- Actual Peak Height (C_{max}) determined from the log excretion rate *vs.* midpoint time curve;
- Time to Reach the Peak (t_{max}) determined from a log excretion rate *vs.* midpoint time plot.

Considering the AUCs from blood level studies, or Ae^{∞} from urinary excretion studies, only is not appropriate since two different drug products may result in the same AUC or Ae^{∞} and yet, may not be therapeutically equivalent. A hypothetical example is given in Figure 36-5.

As seen from Figure 36-5, all drugs give the same areas under the curve. Yet drug product I is clearly superior since the peak is above the MEC, whereas drug product III does not even reach the minimum effective concentration. The two drug products differ in C_{max} and t_{max}. Drug product II may even be superior to product I although $C_{max\ II}$ is less than $C_{max\ I}$ but still above the MEC. However, the duration is longer than with product I, as seen from top of Figure 36-5. The corresponding amount of drug Ae^{∞} totally excreted at time T^{∞} is the same for all three drug products as seen on bottom of Figure 36-5. However, the course of the different curves has to be used for determination of the rate of bioavailability.

Multiple Dose Studies

Multiple dose studies are carried out for one dosing interval at steady state. Two parameters characterize rate and extent of bioavailability:

- Area Under Curve During Dosing Interval $AUC^{\tau n \rightarrow \tau n+1}$
- Percent fluctuation

$$\% \text{ Fluctuation} = 100 \cdot \left(\frac{C^{ss}_{max} - C^{ss}_{min}}{C^{ss}_{min}}\right) \qquad \text{Eq. 36.12}$$

Steady state should be verified by taking trough levels on two consecutive days at the same time. It

is not advisable to take trough levels of two consecutive dosing intervals (if <24 h) because a difference may occur due to circadian rhythm even when steady state is reached. Switching from one product to another, the new steady state should be verified.

In case of urinary excretion studies the urine is collected for one entire dosing interval at steady state.

The AUCs can be determined either from the blood level equation after curve-fitting or by the trapezoidal rule (see Chapter 20).

Bioavailability should be evaluated by 90 percent confidence interval based on the two one-sided t-test approach. This approach involves determination of confidence interval for the ratio of means using a modified t-test method. The previously used 75/75 decision rule is no longer acceptable.

In evaluation of bioavailability data one should not plot all data from all volunteers together and determine the parameters as an average from all cumulative data. Instead, one should evaluate either the blood level data or cumulative urinary excretion data separately for each individual and compare these with those of the standard, then determine the average and standard deviation for each parameter.

The question of how many subjects should be used is a difficult one to answer. There is no magic number. It depends on the statistical design of the study and the degree of variations obtained. However, in general, 12 to 18 volunteers will be sufficient to make a statistical evaluation.

From a clinical point of view we may ask: what

is the clinical significance of bioavailability studies? This question clearly goes beyond the scope of bioavailability testing as outlined in the FDA regulation but is, nevertheless, a very valid question. Without doubt we should strive for drug products which are bioequivalent and are, therefore, interchangeable unless otherwise stated that a drug product might be indicated for a desired purpose. Bioavailability should not be considered as a test which generates an imaginary number for a given drug in a given dosage form for a given route of administration, but should be a guarantee for in vivo quality.

For most of the drugs we assume that the drug concentration in blood, plasma or serum is directly related to the therapeutic response. Even if the biophase, the locus of interaction between the drug and the cell or cell component, is not in the systemic circulation but somewhere in the tissue, the drug concentration in systemic circulation may correlate with the therapeutic response, since the transfer of free, nonprotein bound drug from the circulation to the tissue depends on the concentration gradient and can be described mathematically. Exceptions are cases where active transport is involved.

The question of bioavailability should also be considered from a point of view of drug-receptor interaction. (For receptor theories see Chapter 5.)

In relation to bioavailability we may therefore conclude that if a drug exerts its pharmacologic effect according to the occupation theory, then one could assume that the amount of drug available systemically would be the most important parameter. If a drug exerts its pharmacological effect according to the rate theory, then one could assume

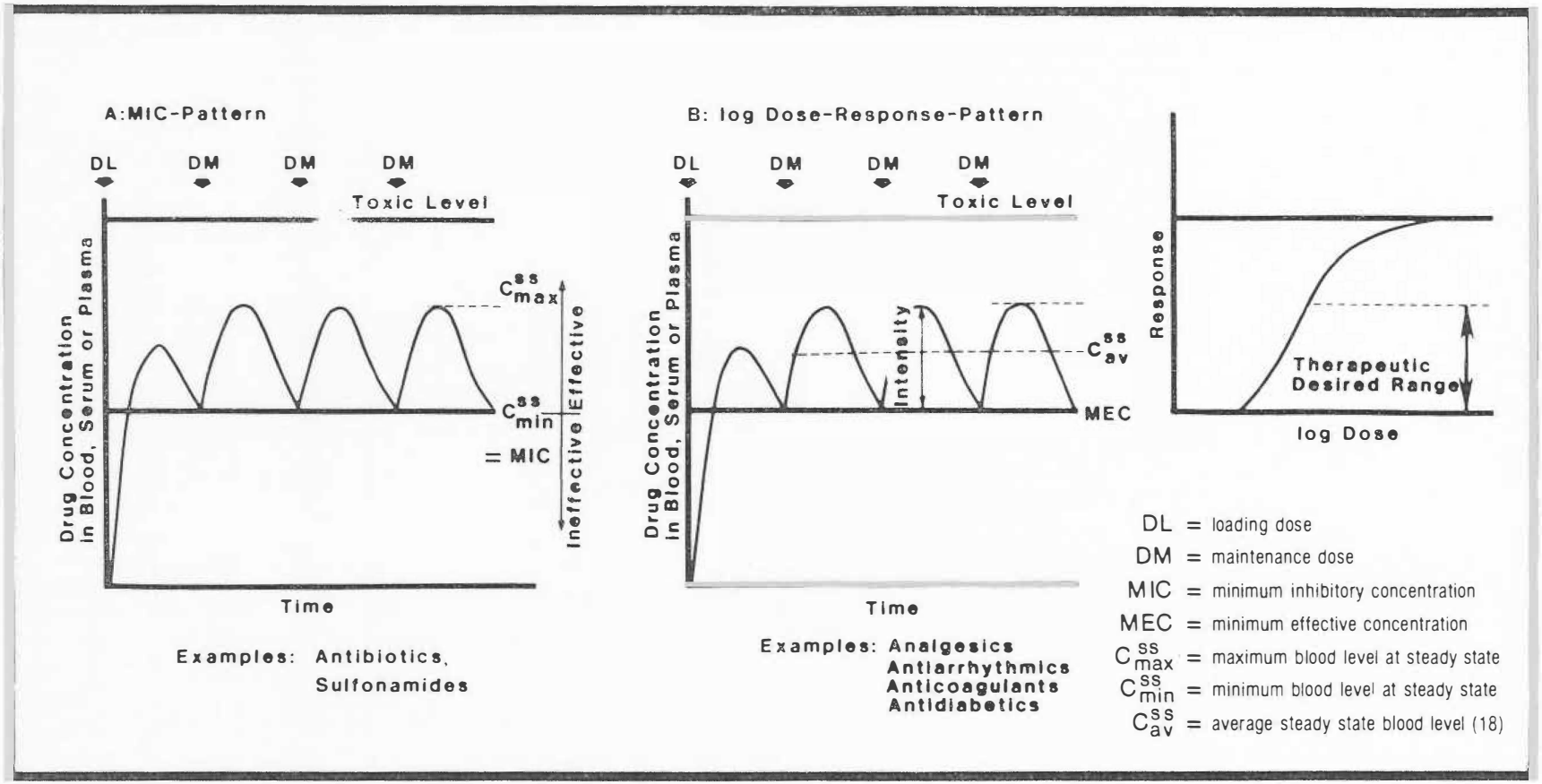

Figure 36-6. Schematic diagram for pharmacokinetic classification with respect to dosage regimen calculation and bioavailability evaluation for drugs following the MIC pattern (A) or the log dose response pattern (B).

the rate and extent of bioavailability would be the most decisive parameters. However, the rate of bioavailability is also important when the drug follows the occupation theory. This is true, because the extent of bioavailability may be the same for different products and yet one may be ineffective due to a low rate of bioavailability which may not permit the drug to reach a concentration in blood above threshold or minimum effective level.

From a point of view of bioavailability, drugs can be classified according to two basic response patterns:

- the response is based on the log dose-response curve;
- the response is based on the minimum effective or minimum inhibitory concentration.

The two patterns are shown in Figure 36-6.

For the log dose-response pattern it is desirable to maintain the drug concentration within the therapeutic range. The higher the EBA is within this range the greater will be the intensity of the pharmacologic effect.

Levy demonstrated that a given degree of change of extent of drug absorption will not necessarily be directly proportional to the change in pharmacologic effect due to the approximately log-linear character of most dose-response relationships as seen from Figure 36-7.

The loss of pharmacologic effectiveness increases disproportionally, the steeper the log-dose response curve is and the deeper the therapeutic dose is located on that curve.

For the MIC-Pattern it is desired to maintain the drug concentration during the entire course of therapy above the minimum inhibitory or minimum

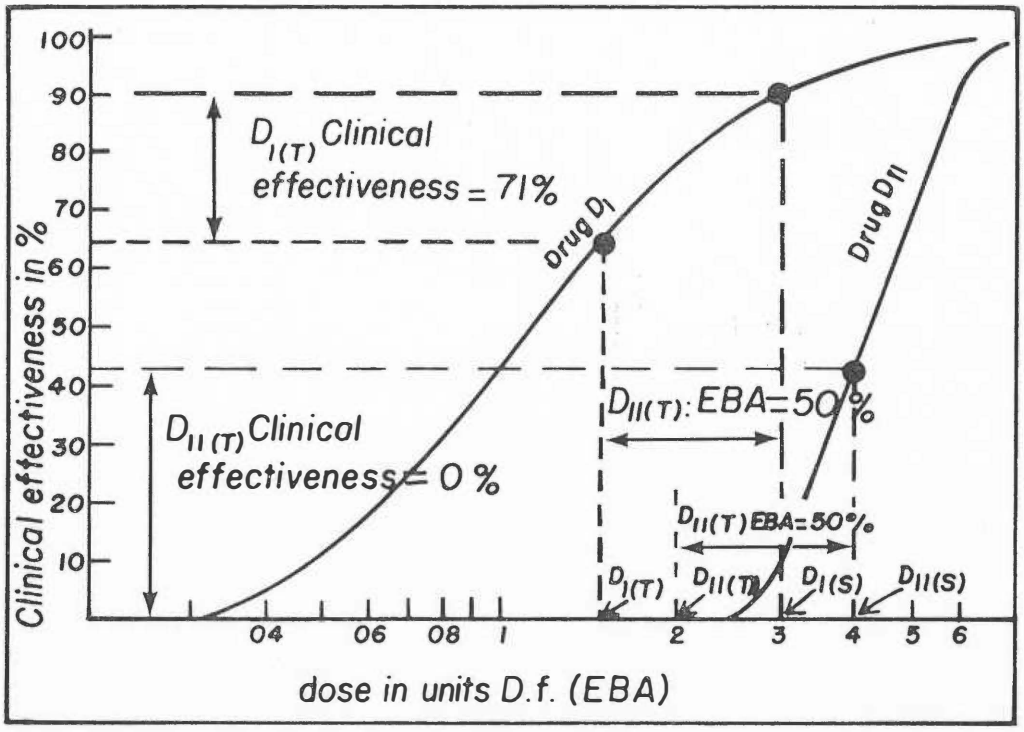

Figure 36-7. Schematic diagram demonstrating disproportional decrease in clinical effectiveness with decrease in extent of bioavailability for drugs following the log dose response pattern.
D_I, D_{II} log dose-response curves for drugs I and II: $D_{I(a)}$, $D_{II(a)}$ = doses of standard for drug I and II: $D_{I(T)}$, $D_{II(T)}$ = doses of test product showing only 50% extent of bioavailability: EBA = extent of bioavailability = D.f.

effective concentration which will differ with each type of microorganism and its sensitivity. The drug will be effective as long as the concentration is above the MIC, regardless of the actual peak height. In this case it is indicated to estimate whether or not a given drug product results at steady state in a blood level at the end of each dosing interval above the required MIC. As long as the steady state concentration is above the MIC the actual extent of bioavailability seems not to be of any clinical significance.

The testing of bioavailability adds a new dimension towards the development of uniform standards

of performance and improvement of the health care delivery system.

Estimate on Bioavailability from in vitro and Extravascular Data Only

Certain drugs cannot be given intravenously, or I.V. blood level-time data are not available. Under the assumption of identical drug disposition upon I.V. and extravascular route of administration, and absence of dose dependency, it should be possible to predict the fraction of drug absorbed, f, by comparing the $AUC^{0\rightarrow\infty}$ from the E.V. administration with the generated $AUC^{0\rightarrow\infty}$ for I.V. administration based on the relationship between volume of distribution, apparent partition coefficient and extent of protein binding (Ritschel-Hammer method). For relationship see Chapter 16.

The $AUC^{0\rightarrow\infty}$ for the hypothetical I.V. administration can be estimated for the one- and two-compartment model according to Equations 36.13 and 36.14 using k_{el} or k_{13}, respectively, from the extravascular concentration-time profile:

$$AUC_{I.V.}^{0\rightarrow\infty} = \frac{D}{(0.0955 \cdot APC + 1.2232) \cdot (1-p) \cdot BW \cdot k_{el}} \qquad \text{Eq. 36.13}$$

$$AUC_{I.V.}^{0\rightarrow\infty} = \frac{D}{(0.0397 \cdot APC + 0.0273) \cdot (1-p) \cdot BW \cdot k_{13}} \qquad \text{Eq. 36.14}$$

The fraction of drug absorbed is calculated by Equation 31.15:

$$f = \frac{AUC_{extravasc.}^{0\rightarrow\infty}}{AUC_{I.V.}^{0\rightarrow\infty}} \qquad \text{Eq. 36.15}$$

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