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BIOAVAILABILITY AND PHARMACOKINETIC ANALYSIS OF DRUG RESPONDING SYSTEMS

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INTRODUCTION

Pharmacokinetics is that branch of pharmaceutical science which provides the mathematical relationships between the dynamic (time-dependent) manner in which a drug is released to enter the body and the time course of the pharmacological effects that ensue. In this context, pharmacokinetics may be described as quantitative pharmacology (1). Once a drug has entered into the body, i.e. when it becomes bioavailable, there is little that can be done, outside of antidotal procedures, to further affect the time course of its effects on the organism. Therefore, bioavailability is of cardinal importance in clinical pharmacology in that it is the control of drug bioavailability which provides the only practical means by which a drug's therapeutic and toxic effects can be controlled in a necessarily routine manner. Despite the many excellent treatments of the topic of bioavailability found in the literature (2–7), confusion still exists as to the precise meaning of the term as well as the relationship of bioavailability to bioequivalency; the introduction of in vitro bioequivalency into the federal regulation of drug products has also added to the confusion (2, 8).

The majority of the published reports on bioavailability are principally oriented to drug product bioavailability/bioequivalency testing and procedures that employ chemical and radiological assay techniques to monitor parent drug and/or metabolite levels in blood and/or urine. The biological, formulation, and manufacturing factors that also affect bioavailability have also been well discussed (9). Therefore, this report seeks to place the concepts of drug bioavailability and bioequivalency in a broader perspective and emphasize the now Food and Drug Administration-accepted, although less familiar, approach of using pharmacological data for performing drug bioavailability analyses. The relative attributes of using direct assay and pharmacological data are compared.

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THE CONCEPT OF BIOAVAILABILITY

Most broadly, *bioavailability* can be considered a generic term relating to the dynamic manner in which a drug and/or its metabolites enter the body to reach the systemic circulation, the site(s) of action, or become released at preabsorption sites into the body. The site(s) of action (biophase) may be accessed either via the drug entities first passing into the systemic circulation or more directly by their absorption from a vicinal site of administration. The latter is the case with drugs intended for local effects as occurs with drugs applied topically to the skin or eyes, inhaled, or implanted into the vagina or uterus. This statement of bioavailability encompasses the various interpretations proposed by different authors (2–6). The definition appearing in the code of federal regulations, "Drug Products: Bioequivalence Requirements and In Vivo Bioavailability Procedures," which appeared in the *Federal Register* on January 7, 1977, describes bioavailability 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 action" (2). It has been argued, however, that the meaning of bioavailability should be restricted to involve only the drug reaching the systemic circulation (5) as defined by the American Pharmaceutical Association Academy of Pharmaceutical Sciences (10). The latter definition is quite narrow and overlooks that measures of site of action (biophasic) drug levels and availability can often be quantitatively determined as readily as systemic bioavailability from the results of monitoring pharmacological data (11–28).

When the operation of any capacity-limited (nonlinear) dynamics in a drug's disposition behavior (29) in the body can be neglected, the time dependence of its distribution, metabolism, binding to tissue and plasma constituents, and excretion can be described by linear mathematics (30–33). In this case it can be shown (14, 33–36) that it is a consequence of linear mathematics that the overall extent of biophasic availability, i.e. the total amount of drug that traverses the site(s) of action is directly proportional to the quantity of systemically bioavailable drug. This is the case irrespective of the percentage of the administered dose absorbed into the body (unchanged or metabolized) and whether the rates and mechanisms of absorption into the body involve the operation of either linear or nonlinear processes. However, the time course of levels of drug appearing in the blood can be quite different from the levels occurring at corresponding times at the site(s) of action even when linear mathematics apply to describing the involved pharmacokinetics. This is especially the case when the site(s) of action occur in "deep" tissue compartments (locations) into which the drug penetrates and is dissipated slowly and/or the pharmacological activity results from a metabolite which is slowly formed from the administered parent drug compound (36). If nonlinear disposition kinetics is involved, the disparity between blood and biophasic drug levels will further increase. In this case, the rates of drug absorption will not only affect the shape of the drug level versus time profiles as is always the case, but can profoundly affect the overall extents of biophasic availability relative to systemic availability. Even more significantly, it has been demonstrated that even when linear disposition kinetics apply, the rates at

which a drug becomes bioavailable can strongly influence the therapeutic utility of a drug in that the time course of the intensities of a sought therapeutic response, relative to the intensities of concomitantly elicited adverse effects, can be severely affected (15). This will generally be the case even when the site(s) of action for the therapeutic and toxic responses share the same biophase compartment, that is, when the time course of the drug's access to the therapeutic and toxic site(s) of action are identical (26). These considerations support the validity of the FDA's definition of bioavailability involving the availability to sites of action in preference to the systemic circulation. However, as pointed out (2, 5), "it is overly optimistic to presume that bioavailability data consisting of estimates of parent drug and/or metabolite concentration in body fluids, rate of excretion, or the measurement of an acute pharmacological effect (other than the sought therapeutic response) provides, as a general rule, an estimate of the availability of the therapeutic moiety at the site of action (2)."

It is common and implicit in all considerations of drug bioavailability that drug input dynamics or the consequences of different drug inputs are being considered in one way or another. Some of the confusion concerning bioavailability in terms of drug inputs arises from the common use of univariate characteristics (2, 37) of drug *response outputs,* i.e. blood level, biophasic drug level, excretion rate, or pharmacological response intensity versus time curves to describe the characteristics of drug bioavailability inputs. For example, 1. the area under such curves is used to describe the relative extents of overall bioavailability (37); this is strictly correct with regard to drug levels only with drugs and biological systems exhibiting linear pharmacokinetic behavior (33, 37–40) and the AUCs are directly proportional to dose (41). With graded pharmacological response data, the intensities of effect must be directly proportional to their corresponding biophasic (site-of-action) drug levels (19–20) or transformed into biophasic drug levels as can be done using dose-effect curves (13, 14, 16, 27, 28, 34). 2. The peak, and 3. time to reach peak drug levels or response intensities are commonly used as indirect indicators of drug input rates. This is valid provided that the concurrent drug distribution, metabolism, and excretion processes are unaffected and independent of the dose and the drug input dynamics (41), i.e. when the systems are linear.

CLASSIFICATION OF BIOAVAILABILITY

In order to mitigate the confusion concerning the generic term *bioavailability,* the classes of bioavailability considerations implicit in its usage have been explicitly defined in terms of drug bioavailability inputs and response outputs (13, 42). A similar classification of bioavailability is outlined as follows:

I. Absolute (drug input) bioavailability
   A. Systemic bioavailability (rates and extents of drug or metabolite)
   B. Biophasic availability
   C. Preabsorption bioavailability
II. Comparative (drug output response) bioequivalency
III. In vitro predicted (input or output response) bioavailability.

ABSOLUTE BIOAVAILABILITY

Absolute bioavailability of a drug or metabolite is defined by the temporal patterns of the rates (differential drug input) and extents (cumulative or integral drug input) at which the chemical entity of interest enters into the body or is released at preabsorption sites to subsequently enter the body. Systemic bioavailability and biophasic availability refer to the drug's entrance into the systemic circulation and to its sites of action, respectively. Systemic bioavailability and biophasic availability are identical when the passage of drug between the systemic circulation (plasma compartment) and sites of action (biophase compartment) is sufficiently rapid that the drug is always in equilibrium between them. When a compartment is defined as a physical space into which a drug can enter or as a different chemical entity into which it is transformed at a measurable rate (43), the plasma and biophase compartments in this case are kinetically indistinguishable and the same. When the drug is administered in a manner intended to elicit a localized response in the vicinity of the site of administration, biophasic availability precedes systemic bioavailability. In fact, in this case the occurrence of appreciable levels of drug in the blood is quite undesirable and would be indicative of a toxic dose or a poorly designed drug product (25, 44–47). For example, in dealing with ophthalmic dosing for local effects, the objective is to design systems that provide a controlled biophasic availability and local therapeutic response while minimizing toxic effects that result from the drug's systemic bioavailability. The systemic bioavailability occurs by absorption through the vascularized sclera or drainage of drug-containing tears by the lacrimal ducts. A scheme that allows both systemic and biophasic availability to be calculated from monitoring changes in pupil diameter has been described and exemplified for carbachol (26). Quantitative computations of local biophasic availability of the mydriatic drugs, tropicamide (16–18) and tridihexethylchloride (34, 47), with regard to the influence of the addition of polymers to the ophthalmic vehicle, have been reported. Such results can be useful in elucidating the mechanisms of the influence of ophthalmic drug adjuvants (48–50) and the mode of drug administration (51). Preabsorption bioavailability always precedes systemic or biophasic availability and can be considered as an in vivo analogue of an in vitro drug dissolution profile. For example, with a drug administered orally as a tablet or capsule, preabsorption bioavailability has been termed *gastrointestinal availability* and refers to the time course of the rates and extent of dissolution of the drug into the gastrointestinal fluids (12–14, 42). The concept has been exemplified with the gastrointestinal bioavailability of chlorpromazine in humans which was reported to be computed from monitoring the time variation of intraocular pressure lowering (12). The results were verified by comparing the computed amounts of drug released into the gut lumen with known amounts given in divided solution doses.

Preabsorption bioavailability profiles can also be applied to describe the temporal patterns of drug release from drug delivery systems intended to elicit localized effects. For example, the release dynamics of an ophthalmic drug delivery system, such as an Ocusert® (46), into the ocular fluids could be studied by this approach. A fraction of the drug that is preabsorptively available to the precorneal fluids is

then transcorneally absorbed to become biophasically available and elicit a localized effect, e.g. such as the lowering of intraocular pressure or changes in pupil size. Recently, preabsorption bioavailability has been calculated for pilocarpine administered ophthalmically as suspensions of bioadhesive, polymer-coated particles (52). The computation of temporal patterns of absolute systemic bioavailability has been described using direct assay (37, 38) and pharmacological data (13, 14).

COMPARATIVE (DRUG RESPONSE) BIOEQUIVALENCY

The importance of this category of bioavailability arises from the fact that although two drug products may contain the same quantity of drug (and, in fact, each have an identical chemical composition) purposeful, inadvertent, seemingly trivial, and often unknown differences in the formulation and manufacture of drug products can render them seriously *bioinequivalent.* Such inequivalencies between drug product formulations can result in therapeutic failures and serious toxicities. This is especially the case for potent drugs having a low therapeutic index. Reports of drug product bioequivalencies (6) have led to the general recognition that the dosage form is as important as the drug in contributing to its properties.

Genetic, environmental, pathophysiological, and other factors can also contribute to the interpatient and intrapatient variability in therapeutic and adverse drug response which is generally seen following the administration of the same dose of a drug given in the same manner. However, in contrast to these biological factors, the hazards and uncertainty in a drug's clinical usage resulting from differences in the bioavailability behavior of multisource "chemically equivalent" drug products (as well as differences between lots of the same manufacturer's product) are controllable. It is therefore the position of the FDA that such differences be minimized, as far as practicable, through the bioequivalency regulation of drug products. For any given drug with a known or potential bioequivalency problem (2), this is accomplished through the implementation of the most sensitive and reliable in vivo or in vitro methodology currently available at any given time.

In vivo methods of ensuring the bioequivalency of drug products that are intended to be used interchangeably as therapeutic agents involve making comparisons of the response versus time profiles elicited in humans, and sometimes animals, by two or more drug products generally employing a complete crossover experimental design (53). One of the products included in comparative drug bioequivalency studies serves as a reference to which the relative bioavailability obtained with the product(s) under test are compared. The safety and therapeutic efficacy of the reference product is generally well established by extensive clinical trials, years of experience, and has been supported by an NAS/NRC DESI (Drug Efficacy Study Implementation) review panel. Most often the reference drug product is that originally marketed by the innovating drug company and the products under test are products proposed for competitive marketing following the expiration of the innovator's patent. If the drug itself is accepted as safe and effective, but the innovator's product is inadequate, then the FDA may require that the reference dose be given as an oral solution or parenterally. A variety of factors such as posture; type and frequency of food intake;

mobility of the human subjects; and pathophysiological conditions, can affect the results of bioequivalency trials (54). Therefore, the bioequivalency of drug products is most therapeutically meaningful when established through in vivo testing conducted under normal, clinical use, conditions employing clinically relevant endpoints, provided of course that sufficiently sensitive clinical criteria are available to quantitatively judge the products being tested.

It most often occurs that because of the large variability seen in patients because of unstable pathophysiology, simultaneous administration of other drugs, psychosomatic-placebo effects as well as other considerations, bioinequivalent drug products can be clinically used and studied for long periods before their clinical differences are reported and unequivocally documented. The difficulties in satisfactorily documenting clinical differences between bioinequivalent drug products does not contradict their existence or minimize their importance. Consequently, in addition to eliminating the ethical consideration of treating patients in need of the drugs with drug products of unproven effectiveness, bioequivalency studies performed using normal human volunteers, which are conducted under rigorously controlled conditions to minimize variation in the results, are often more sensitive and reliable and can appreciably reduce the number of subjects placed at risk in such studies; the results of these studies provide well-defined bioavailability criteria on which the bioequivalency of different drug products can be quantitatively judged. In addition, the pharmacokinetic data derived also provides a sound basis for the development of in vitro drug dissolution tests which can provide in vitro results that predict or correlate with the in vivo bioavailability behavior of different drug products (55–58). In vivo bioavailability/pharmacokinetic studies performed in animals do not generally provide results that quantitatively translate into man (59, 60). This also applies to higher primates (61). Drug products intended for use in man are most reliably evaluated in man. The APhA bioavailability project (4) reviews drug testing procedures used to study the bioequivalency of drug products; a wealth of information has been compiled by this effort.

Seldom, if ever, is absolute bioavailability directly determined by direct experimental observation. Time patterns of absolute drug bioavailability rates and extents in humans must almost always be computed from observed drug response output data using appropriate pharmacokinetic model relationships (12–15, 33, 37, 38). In contrast, judgments of the comparative bioequivalency of drug products are made on the basis of the superimposability (5, 11) of directly observed pharmacological response intensity versus time profiles, biophasic drug level versus time profiles derived from pharmacological data (11, 19, 20) or drug and/or metabolite levels in body fluids (blood, urine, and saliva); comparisons of the individual data points and univariate characteristics reflecting rates (peak times and peak responses) and extents (AUCs) of bioavailability are made by applying statistical methods (53).

Inadequate extents of bioavailability are tantamount to reduced dosage and are therefore always a consideration in judging the bioequivalency of drug products. Rates of bioavailability are most likely to be important for drugs (*a*) that have a low therapeutic ratio (26), (*b*) that are degraded in the gut lumen, wall, or liver prior to absorption (this is especially the case if the degradation processes are saturable)

(41), (*c*) that are absorbed by active or facilitated (capacity limited) processes, and (*d*) for which it is important to rapidly attain therapeutic levels of effects (15) such as with some CNS depressants, hypotensives, analgesics, hypoglycemics, antianginal agents, and antibiotics (6). The magnitude of differences allowed between drug products for them still to be judged bioequivalent should always be specifically determined for each drug on the basis of clinical pharmacology-pharmacokinetic considerations. However, a rule of thumb often applied by the FDA is that the products should not differ by more than 25% using a number of subjects in a crossover experimental design which is sufficient to detect such a difference 80% of the time at a statistical confidence level of 95% (53). Usually, when two products satisfy such criteria, they are considered bioequivalent and inferred to be therapeutically interchangeable. However, this may not always be the case, especially, for example, with drugs that undergo extensive, first pass, saturable gut wall and hepatic metabolism prior to reaching the systemic circulation. Under these conditions the extent to which the intact administered drug is presystemically metabolized will decrease with increasing dose and increasing rates of drug release to the involved capacity limited enzyme systems (54). Therefore, for any given dose, a dosage form of the drug such as a solution would exhibit a greater systemic bioavailability of the intact drug than the same dose of drug administered in the form of a relatively slow-releasing tablet or capsule. However, whether the difference is detected or not depends upon whether the measures used to construct the response profiles to be compared reflect only the parent drug or the metabolites as well. This situation is well exemplified by orally administered chlorpromazine (12, 19, 20, 62–64) and probably other phenothiazines (65–66). The extent of the presystemic metabolism that produces therapeutically inactive as well as therapeutically antagonistic, sulfoxide metabolites of chlorpromazine (67–69) is dependent upon the rates of release of the drug from its dosage form (12, 19, 20, 62–64). The bioequivalency of two drug products can be judged from the extents of systemic bioavailability as reflected by the areas under observed response versus time profiles. For two drug formulations having different release rates, such areas will be different when measurements reflecting only the presence of unchanged chlorpromazine in the body are being made using a chemical assay (41, 62) or a pharmacological measure such as pupillometry (12, 19, 20). Measurements, such as those using a nonspecific assay for the phenothiazine nucleus (70) or intraocular pressure lowering (12, 19, 20), which detect both the drug and its metabolites, will cause chlorpromazine product formulations to appear to be bioequivalent despite the existence of differences in their therapeutic performance (64). For example, using nonspecific measures such as the appearance of chlorpromazine and its metabolites in urine, sustained action dosage forms of chlorpromazine can appear to be bioequivalent to the same dose given repeatedly in a rapidly available dosage form (70). This is apparently the case despite the sustained action product releasing the drug at a rate that does not saturate the presystemic metabolism (41, 62, 63). The consequences of such slow-releasing formulations are the increased formation of inactive or adversely active metabolites. Interestingly, evidence has been reported (12, 19, 20) that pupillometric measures are not only directly reflective of unchanged, therapeutically active, chlorpromazine

blood levels, but they are also apparently antagonized by the presence of therapeutically antagonistic metabolites (12, 67). The sensitivity of this method [approximately 30 times more sensitive than GLC assay of blood samples (12)] allowed the phenomenon to be detected at lower doses where it can be expected to be most pertinent.

IN VITRO PREDICTED OR CORRELATED BIOAVAILABILITY

There is currently considerable interest in in vitro test predictions of in vivo drug product bioavailability as a result of the adoption of in vitro dissolution standards by the USP and the imminent development of in vitro bioequivalency requirements for an increasing number of drug products by the FDA (2, 8). The position of the FDA is that human bioavailability testing of drug products can be minimized by the development of in vitro standards that reflect in vivo drug product performance. The concern is principally with oral products such as tablets, capsules, and suspensions from which the rates and extents of dissolution of the active ingredient after oral ingestion is a limiting factor in its bioavailability.

From among the various chemical and physical tests that can be performed on drug solids, dissolution testing is the most sensitive, reliable, and rational for use in correlating or predicting in vivo drug product bioavailability behavior (8). However, in order for any in vivo significance
cumulative amounts and/or rates of drug dissolved in vitro, some definite relationship between in vitro and in vivo drug availability needs to be observed and established. Confidence in the in vitro tests' predictive capability must also be gained before it can be applied to evaluating drug products with regard to their expected in vivo behavior. This is of cardinal importance in that the degree to which in vitro dissolution test results are related to in vivo drug availability can be sensitively dependent upon the type of apparatus employed and the process variables used (55); the latter are defined by the composition(s) of the dissolution medium, degree of agitation (stirring or flow
which determines the degree to which it becomes saturated with the drug (sink conditions). These process variables are factors extrinsic to the drug product which, if improperly chosen, can either mask important bioavailability differences in drug products or be overly sensitive in detecting in vitro differences that are not significant in vivo (55, 57, 71). Despite the availability of statistical methods of optimal experimental design that allow process variables to be systematically and optimally chosen with a minimum of experimental effort (72, 73), the selection of test conditions has largely been relatively empirical. In any case, no confidence can be placed in the in vivo relevance of an in vitro test whose process variables have not been chosen on the basis of the fidelity with which the test is reflective
behavior of at least one, but generally two or more, drug products having different in vivo drug release properties (57). When no in vivo data are available to base the development of an in vitro dissolution test, the process variables for the test can only be rationally chosen to provide a test which is maximally sensitive in discriminating differences between different manufacturers' drug products or different batches of

the same product. However, when such tests are used in quality control they can cause waste in that lots of drug products may be rejected on the basis of dissolution criteria which have no relevance to their in vivo bioavailability performance. The apparatus most commonly employed in in vitro drug dissolution testing (55) presently consists (74) of the USP rotating basket apparatus (75), FDA paddle method (76), stationary basket-rotating filter apparatus (77), the Sartorius Solubility and Absorption Simulators® (78, 79), and column type flow-through apparatuses (57, 80, 81). Column type methods offer advantages with regard to the definition and standardization of process variables. A collaborative study by the Academy of Pharmaceutical Sciences Committee on Dissolution Methodology is being conducted with the aid of the USP laboratory and the FDA. Its objective is to evaluate and compare the reliability of data obtained with various types of dissolution testing and apparatus by different laboratories using standardized conditions and drug products. The study has not yet been fully completed and no conclusions have yet been reported at the time of this writing.

With relatively few exceptions of multiple time-point correlations between the cumulative amounts and rates of drug systemically absorbed (absolute bioavailability) following oral dosing in vivo, with corresponding amounts and rates dissolved in vitro (26, 42, 79, 82, 84), the relationships most commonly reported between in vitro dissolution and in vivo bioavailability have been of the single point or rank order type (84). These correlations most frequently involve the percentage of drug dissolved up to a given time being shown to be at least approximately related to clinical effects or linearly correlated with some univariate characteristics of the drug products' in vivo response versus time profiles, such as peak response (time to reach peak or 50% of peak) and AUCs (82–85). There is seldom a rational, theoretical basis for expecting such correlations to be linear (86, 87). The selection of in vitro and in vivo drug availability criteria is somewhat arbitrary (86) and the use of single point correlations can be misleading (57). The goodness of single point, linear correlations depends upon the in vitro and in vivo characteristics being correlated as recently reported for prednisone (86).

Ideally, the ultimate objective to be sought by in vitro drug product dissolution testing is the reliable prediction of the time course of pharmacological response or body fluid levels that would be elicited by a panel of human subjects. The feasibility of such an accomplishment has been discussed and the approach exemplified for pharmacological response data by computer simulation (84, 88). More recent reports describe and exemplify (14, 26, 42, 56, 57) approaches to provide in vitro predicted data analogues of in vivo drug response versus time profiles. One method is a control engineering approach to drug dissolution testing that optimally predicts the in vivo bioavailability behavior of drug products (57). This approach utilizes a minimum of in vivo bioavailability data obtained for one or more dosage forms having different drug release characteristics. The required in vivo data are commonly available from the FDA and drug companies. The in vivo data are used to optimize the calibration of a relatively simple computer-controlled, in vitro, continuous flow-through type of apparatus by determining the optimal (*a*) total flow rate, (*b*) programming of a variable composition of the dissolution medium, and (*c*)

programming of a varying recycle flow of dissolution medium back through the dissolution cell to continuously change sink conditions. The performance criteria on which the optimal calibration of the apparatus is based assure that the error between in vivo drug absorption and in vitro drug dissolution is (*a*) minimized, (*b*) uniform for all dosage forms having different drug release properties, and (*c*) uniform over time. When the calibration of the apparatus is accomplished to satisfy these criteria, the apparatus has an optimal capability to predict the in vivo bioavailability behavior of drug products. It can be calibrated to predict with predetermined statistical confidence either (*a*) the drug absorption versus time profiles, (*b*) the blood or urine levels, or (*c*) the pharmacological response versus time profiles that would be seen in the same panel of human subjects from which in vivo data, used to calibrate the apparatus, was obtained. In this way, once calibrated, the apparatus serves as a substitute for this same panel of human subjects. In other words, the average drug absorption characteristics of the panel have been optimally transferred and locked into the programming of the in vitro apparatus. Although all types of in vitro drug dissolution testing certainly have limitations, this type of approach at least provides some mathematical assurance that for any given drug(s) and in vivo data base, a predictive test is achieved.

Unlike single point, in vitro to in vivo correlations, the second approach (14, 56), which is a computational method, utilizes all the data obtained from in vitro and in vivo experiments and maximizes the amount of information obtainable from the conventional type of in vitro dissolution testing which is most commonly employed at present. Whereas the first method employs a systematic approach to adjusting the operating conditions of an in vitro test to directly provide optimally predictive in vitro analogues of in vivo drug input or response versus time profiles, the second approach mathematically transforms in vitro drug dissolution data into computationally predicted in vivo drug response versus time profiles. The successful application of this approach to predicting plasma level versus time profiles from in vitro dissolution profiles was exemplified by the author for different drug products of warfarin (56) and for acetazolamide (90). Fundamentally, the method involves determining a weighting (transfer) function relationship between a drug dissolution versus time profile(s) and the average in vivo drug response versus time profile(s) resulting from studying the same dosage form(s) in a panel of human subjects. The weighting function then allows average in vivo blood level profiles for other dosage forms to be computationally predicted from their observed in vitro dissolution profiles. As additional in vivo and in vitro data become available, the approach provides for its use to update the mathematical relationship between in vitro and in vivo time profiles and improve the fidelity of its predictions. The details and limitation of this promising method are fully described in the original article (56) along with the computer programs that can be used for its implementation. The use of a similar computational method (91), which mistakenly employs division and multiplication instead of correctly using deconvolution and convolution operations in computing in vivo plasma drug profiles from dissolution rates, should be avoided in that it yields incorrect results; the limitations of this approach have been described (92).

The above described two approaches (56, 57) to in vitro predicted bioavailability provide the most rational and rigorous means of establishing in vitro bioequivalency requirements (2, 8). In addition to being used for quality control purposes, such methods when successfully applied can also provide an optimized, in vitro alternative to the expensive and time-consuming in vivo testing which otherwise is generally required to develop drug product formulations to possess optimally sought, controlled drug release dynamics and a maximum therapeutic utility (15, 22, 26, 42). However, judgment and caution must be exercised with regard to the limitations and applications of in vitro dissolution testing for in vivo bioavailability (8, 56, 57).

An awareness of the physiological and physiochemical mechanisms operating to affect the bioavailability of oral drug products is always useful. However, it is futile and unnecessary to attempt to compensate for the complexity of all such factors in designing biologically relevant in vitro drug dissolution tests. Considering that even sleep can be a factor (89), this is obviously an impossible task which should not be complicated more than absolutely necessary to achieve in vitro results which satisfactorily represent average in vivo bioavailability. Most fundamentally it is the predictive fidelity of the in vitro results that is of interest and not how they are obtained. Therefore, a black box, systems analysis approach (57) presents the most generally applicable and versatile means of developing optimally predictive in vitro tests and quantitatively evaluating their performance. In this view, there can be no objection to using a nonaqueous solvent(s) as the dissolution medium for poorly water-soluble drugs such as reserpine. This is, of course, with the provision that the in vitro results obtainable with such solvents are satisfactorily reflective of in vivo bioavailability. Obviously, no claim can be made as to the biological relevance of tests that employ such nonphysiological solvents and have not been specifically developed to reflect in vivo behavior. The inclusion of membranes or membrane filters in the design of in vitro dissolution devices is generally a needless complication except when some of the drug products to be tested are known to contain components that can form soluble, but nonabsorbable or less absorbable, complexes with the drug. For example, such complexation can commonly occur between some amine drugs and anionic polymers. However, if all the dosage forms to be tested contain the same complexing excipients, differences in their bioavailability can likely be ascribed to other manufacturing and formulation factors and the use of membranes is unnecessary. When a membrane is employed in a drug dissolution device, it should at least have a realistic capability of simulating the selective permeability properties of biological barriers. Hydrated membranes composed of cellulose acetate (93) or polysalt complexes (94) appear to offer the most promise in this regard.

In summary, it is suggested that the adequacy of conventional in vitro dissolution tests, such as the FDA paddle method, be judged on the basis of the fidelity with which the dissolution data they provide can be computationally converted into in vitro predicted in vivo response (blood level) versus time profiles. Obviously, a test that does not at least provide single point in vitro to in vivo correlations cannot be expected to predict in vivo response curves. The process variables of tests that fail

to provide adequate predictions of in vivo response curves should be adjusted until satisfactory predictions are obtained. The most systematic and reliable means of achieving optimally predictive tests (57) has been described above. Following this approach, in vitro analogues of in vivo response profiles are obtained that allow the bioequivalency of two drug products to be judged using the same criteria applied to in vivo blood curves. Although fraught with pitfalls this is the nearest that in vitro dissolution tests can become a substitute for human experimentation.

SELECTION OF PHARMACOKINETIC DATA

Direct Assay Data Versus Pharmacological Measures

As exemplified for chlorpromazine (12), the selection of the type of measures to be employed in bioequivalency studies can be critical to their outcome. However, as also demonstrated for chlorpromazine, using pupillometric, intraocular pressure lowering and temperature depression as response variables (12, 42), the type of data employed to compute absolute bioavailabilities in contrast has no influence on computed bioavailability results. This has been shown mathematically to be the case irrespective of whether the measures that are made reflect blood levels of the intact drug, metabolites, or both (14); strictly, however, this is only true with the provision that the system's dynamic behavior can be described by linear mathematics or that corrections can be made for any significant nonlinearities. When output response data are used to infer bioavailability behavior, the bioavailability that such results describe is best defined operationally in terms of the availability of the drug entities being detected to the sites in the body at which their presence is monitored. For example, the bioavailability of drugs that have a first pass effect and that are further metabolized in the lungs would depend upon whether (*a*) venous or arterial blood is sampled and (*b*) an assay procedure specific for the parent drug is used or (*c*) whether the assay is also sensitive to the presence of the metabolites (54).

A decision as to whether pharmacological response, blood level, and/or urinary recovery data should be recorded in a study must be based on the availability of methods, the objectives of the study and a knowledge of what drug entities having what biological activities are being detected by various measurements. Both chemical and radiological assay techniques can be specific for detecting the parent drug, a single metabolite of the parent drug, and/or any number of the metabolites formed in vivo or even degradation products that may have been present in the dosage form prior to its administration. The same consideration applies to the use of pharmacological response data in reflecting parent drug levels, metabolites, or both. In general, pharmacological data reflect the presence, at their sites of action, of all the active chemical entities that contribute to the intensity of the observed pharmacological response. Whether pharmacological data, direct chemical or radiological assay data, or both should be used in any particular study can be judged on the basis of such criteria as 1. The relevance of the measures to therapeutic and toxic effects of clinical interest (Pharmacological response data are generally preferred on this basis

except for drugs such as antibiotics and urinary antiseptics, especially if a microbiological assay using the invading organism is performed. However, pharmacological measures of side effects that are of little clinical interest are in the same category as body fluid, direct assay data in that they merely serve as analytical tools to gauge bioavailability.) 2. Sensitivity of the measure to dosage and therefore to bioavailability differences [An observed dose dependency in temporal response patterns is tantamount to the measure being sensitive to bioavailability differences (2).] 3.Intrasubject and intersubject variability of the data (The lesser the variability, the fewer the number of subjects required.) 4. The stability of placebo baselines. 5. Ease and convenience of recording the data (Pharmacological response measurements that can be made noninvasively and continuously over time are preferred in this regard. In contrast, blood sampling by venipuncture is obviously invasive and intermittent.) 6. Preference of direct measurements, i.e. those not requiring extensive computer processing in the case of pharmacological data (e.g. pupillometry relative to evoked response EEG) or complicated sample preparation for chemical assay. 7. Suitability of the data for quantitative pharmacokinetic computations of absolute bioavailabilities and for mathematical modeling (13–14).

In the absence of a suitably sensitive assay for the drug, clinical testing of drug products is usually resorted to. However, because of such factors as the patients' taking other drugs, pathology-induced instability in the patients' physiological state, the relatively stronger placebo effect in patients relative to normal volunteers, and the difficulty of accurately measuring clinical drug response endpoints, such testing is often quite insensitive and highly variable results can be produced. Therefore, a large number of subjects and considerable expense can be involved in such testing. The viable alternative method of performing bioavailability studies utilizing temporal pharmacological data has often been overlooked.

In addition to generally being noninvasive and more clinically revelant, as well as allowing several effects to be monitored simultaneously, the use of pharmacological data allows bioavailability studies to be performed with drug products containing drug combinations, e.g. with the class of anticholinergic/antispasmodic–sedative/tranquilizer drug products; the effectiveness and bioavailability of many of the drug products in this class have been brought into question by the FDA's Drug Efficacy Study Implementation (DESI) program (96). There is considerable difficulty involved in clinically evaluating the effectiveness of these drug combinations and performing bioavailability studies using chemical assay data. These problems could be mitigated to a large extent through the use of quantitative pharmacological measures. Since the use of pharmacological data is a form of bioassay, it can also be applied to the study of natural product drugs, such as rauwolfia whole root extract tablets, whose chemical composition may not yet have been identified.

Since most drugs elicit more than one effect, two or more pharmacological responses can be simultaneously recorded with very little additional effort. The results of such multiple recordings are useful for corroborating bioavailability differences that might only be suspected from the results of a single response, as well as for providing information concerning the relative potencies of active metabolites of the

drug when blood samples are also taken and assayed for the parent drug and its metabolites. The recording of such combinations of direct assay and pharmacological data can be especially valuable in phase I IND studies. In this case, active metabolites may be detected and/or new indications for the parent drug discovered at the time of its first introduction into man.

Except for a linearization procedure performed on observed pharmacological response intensities which converts them into corresponding biophasic drug levels (25–28), the pharmacokinetic treatment of pharmacological data is identical with direct assay data (26). In addition, pharmacological data permit the determination of biophasic and preabsorption bioavailabilities in circumstances that preclude the use of direct sampling for drug levels in tissues and body fluids. This is especially the case with drugs intended for local effects where, for example, preabsorption or biophasic availabilities of a drug in the eye can be determined from pupil size measurements (16–19, 52) or the percutaneous absorption of steroids from topical vehicles can be studied by monitoring their blanching effect (97).

Because of the general ease and noninvasive nature of pharmacological response monitoring, its inclusion should be considered in bioavailability studies irrespective of whether a suitably sensitive and specific assay for the drug exists or not. In this manner a maximum amount of information can be accrued from the subjects put at risk in such studies with often relatively little, if any, additional expense.

Resolution of Pharmacokinetic Data from Biological Signals

Measures of the activity of, e.g., hypotensives, hypoglycemics, antiglaucoma agents, mydriatics, miotics, β-adrenergics, and anticoagulants can be obtained directly from blood pressure, blood glucose, intraocular pressure, pupil size, heart rate and clotting times, respectively. That such measures can be used for quantitative pharmacokinetic analysis and the computation of absolute bioavailabilities has been well demonstrated (11–22, 25–28, 34, 42, 47, 98–100). The growing sophistication of biomedical recording instrumentation and methods of computerized analysis of biological signals (42, 101, 102) is providing a concomitantly increasing capability for quantitating drug effects when such direct measures do not apply. This is accomplished through the computerized resolution of drug-induced time variations in the characteristics of the signals. The final results of the analysis of drug-affected biosignals are presented as pharmacokinetic response profiles that resemble blood level versus time curves (25, 42). Often several response variable versus time profiles can be resolved from the recording of a single signal such as evoked and spontaneous electroencephalography (EEG), electrocardiography (ECG), plethysmography, electroenterogastrography (EEnG), electromyography (EMG), displacement cardiography (DCG), and phonocardiography (PCG) (42). Information concerning the mechanisms of the drug's actions may sometimes be inferred from the observed changes in the signals (101, 103).

Considerable work has been reported in quantitating the effects of especially such CNS drugs as psychotropics, sedatives, and anesthetics on the human EEG (42, 104–107). Spontaneous EEG changes have been employed in the identification and

classification of new psychotropic drugs and in the performance of bioavailability studies (42, 105, 106). A new method of photically evoked response EEG has been reported to be especially promising for use in bioavailability studies of psychoactive drugs such as the phenothiazines (42).

Of particular current interest are the biological signal measures that have been adopted by the FDA (108, 109) for the bioavailability and pharmacological effectiveness evaluation of organic nitrate, antianginal drug products. A DESI review of this class of drugs has classified especially oral and controlled-release formulations as only possibly effective. Clinical studies with patients have been largely conflicting and inconclusive because of the large variability in response seen with patients and the insensitivity of clinical endpoints. The FDA-recommended bioavailability method for this class of drugs instead quantitates drug-induced physiological changes that underlie their clinical effectiveness through the recording of noninvasive biological signals performed on normal human subjects under rigorously controlled conditions. For example, the effect of sublingual nitroglycerin on the shape of the digital plethysmographic waveform, which is monitored in such studies, is shown in Figure 1. Through computerized analysis, time variations in drug-induced changes in amplitudes, slopes, intercepts, and time intervals are resolved; these variables reflect blood flows, peripheral resistances, and stroke volumes (42, 108, 110). The sensitivity of the approach is exemplified by the differences seen in Figure 2 where the six subject, average, time patterns of the systolic amplitude response intensity are compared with two, supposedly bioequivalent, isosorbide dinitrate sublingual products supplied by two different manufacturers (42, 108).

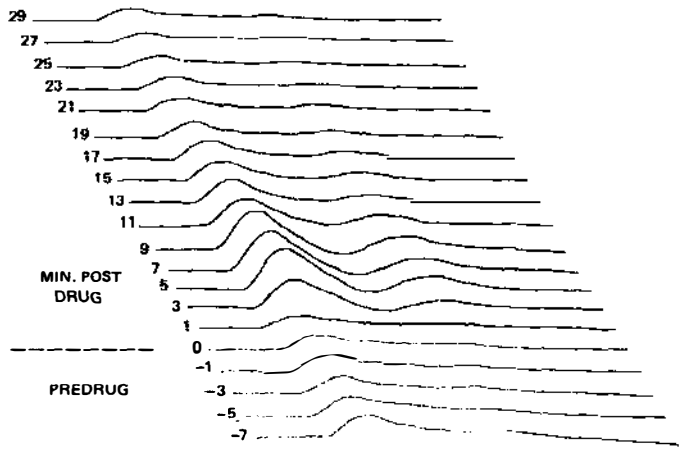

Figure 1 Representative individual digital plethysmographic (DPG) waveforms recorded before and after dosing of a single human subject with 0.9 mg of nitroglycerin administered sublingually. The results exemplify the relatively large magnitude of the drug-induced changes in the characteristics of the DPG signals.

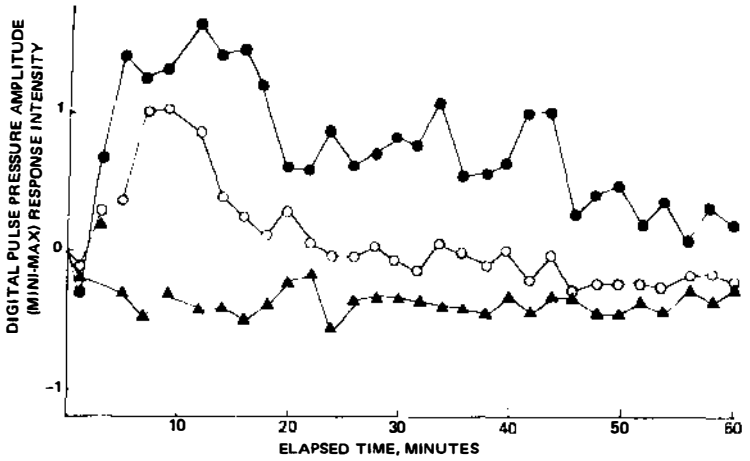

Figure 2 Average digital pulse pressure amplitude response intensity data following dosing of 6 male volunteers with isosorbide dinitrate (ISDN): ▲, placebo, sublingual; ○, 5 mg ISDN, sublingual (Brand A); ●, 5 mg ISDN, sublingual (Brand B).

Drug Bioavailability Input ⇆ Pharmacological Response Output Relationships

The objective of pharmacotherapy is of course to affect physiological states rather than to achieve body drug levels (95). However, the majority of the reported work on the kinetics of drug effects has been concerned with the relationship between body fluids and tissue drug levels and pharmacological response (98–99). Although such relationships are always of research interest (111, 112), they also are of practical clinical significance in that drug levels often reflect intensities of therapeutic and toxic effects and are useful when clinical endpoints are poorly defined and drug levels can be determined more readily. In any event, both the dynamics of body drug levels and pharmacological effects are determined by absolute, drug input bioavailability. Therefore, relationships between drug bioavailability inputs and pharmacological response outputs are of the most fundamental importance in practical applications of pharmacokinetics (12–14). The factors that govern the dynamics of how a drug becomes bioavailable can be controlled entirely, or to effective degrees, by selection, design, or formulation. These factors include (*a*) the dose, regimen, mode, and site of drug administration, (*b*) the drug release properties of dosage forms, (*c*) absorption rates and extents from the site(s) of administration, and (*d*) the design and mode of operation of mechanical or electromechanical drug administration devices whenever such devices might be used.

The establishment of reliable mathematical relationships between drug bioavailability inputs and pharmacological response outputs can provide criteria for rationally exercising control over the manner in which drugs should be allowed to enter

the body. Three modes of application of drug bioavailability input ⇆ pharmacological response output relationships have been described (12). These are

1. Drug Input Optimization
   Hypothetical Time Response → Drug Input
2. Drug Bioavailability Input Analysis
   Experimental Time Response → Drug Input
3. Drug Response Analysis
   Known or Predicted Drug Input → Drug Response Output.

In the first case, where the drug response profile is a hypothetical, ideally sought, optimal response, the objective is to compute the optimal drug input to which it corresponds. Such computed results are useful in establishing criteria for the design of drug delivery systems and the selection of optimal drug dosage regimens. In the second case, where the drug response profile is an experimentally observed result, the corresponding input is computed in order to evaluate the bioavailability behavior of the drug delivery system. Such information is useful for suggesting modifications in the formulation design, or use of drug products that can lead to their improvement. The third use of the input/output relationships is the inverse computation of pharmacological response from drug inputs. Such results can be applied to the prediction of time responses for a given dosage regimen or for drug delivery systems having a priori known inputs. The inputs may be known simply from a proposed schedule of intravenous dosing, the design of a dosage form, or the result of predictive in vitro drug release testing of a drug product (56–57).

Absolute bioavailability is seldom, if ever, obtained directly and must therefore be computed from observed response outputs. The mathematical relationships used for such computations have most commonly been based upon compartment models (30, 31) and have involved the use of blood or urine drug level response data (37, 38). However, the use of compartment models is needlessly complex and unnecessary if the only purpose of the compartment modeling is to compute absolute bioavailability inputs from observed responses or response profiles from drug inputs (12). Recently a generalized, model-independent approach has been described that directly relates pharmacological response outputs to bioavailability inputs (1, 2). This approach, as diagrammed in Figure 3, is equally applicable to biophasic, preabsorption, and in vitro predicted absolute bioavailability determinations in addition to computing systemic bioavailability from either pharmacological, blood, or urine level data. The blocks in the diagram in Figure 3 signify weighting and transduction mathematical functions that interrelate a drug input with each pharmacological response output. When direct assay data are used or the dose effect curve for pharmacological response is a straight line, the transduction function is not needed (13–14). The functions are experimentally determined from the observed response to known drug inputs. Although any type of known input can be used, it is most simple to use impulse inputs. In this case, the biophasic drug level or direct assay drug level response versus time profile observed for an impulse input directly defines the weighting function. The weighting function then, in general, provides the relationship between any drug input entering the site of the impulse input and the

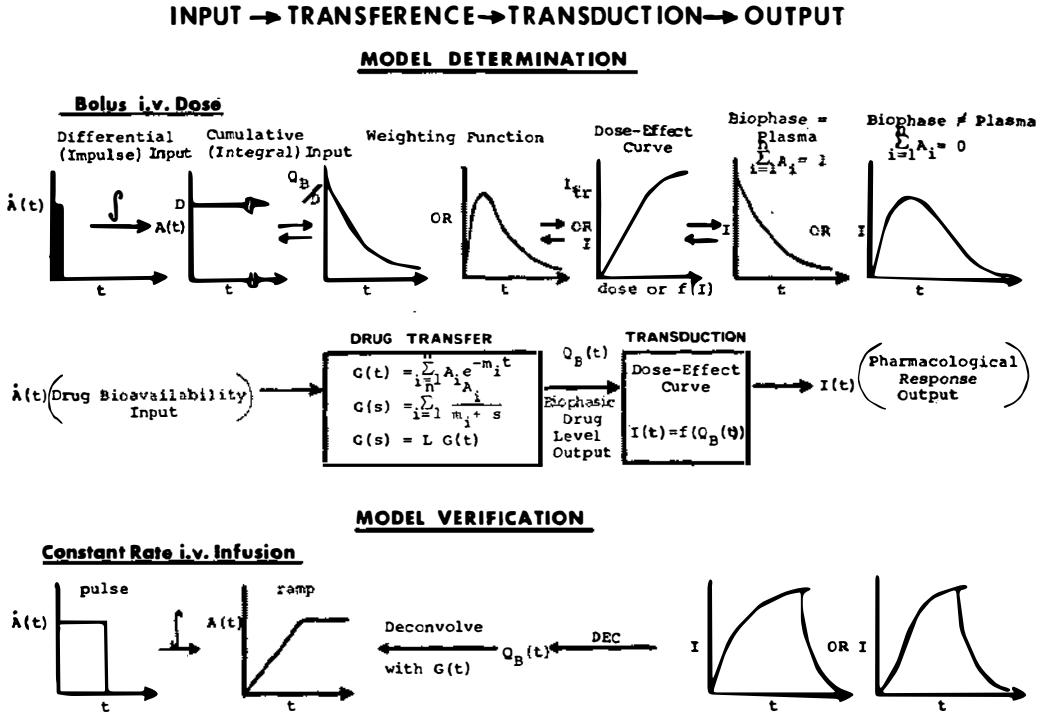

Figure 3 Drug input ≒ pharmacological response output relationships. The upper curve illustrates the process of determining a weighting function (in the time domain, t) or transfer function model (in the complex frequency domain, s) as defined by the relative dose (D) normalized biophasic drug level ($Q_B(t)/D$) versus t response curve to an impulse (bolus i. v. dose) input. The $Q_B(t)$ values are obtained by conversion of observed pharmacological response intensities (I) via the use of the dose effect curve (DEC). The weighting function model is verified for use in absolute bioavailability computations by comparisons of an experimentally known, e. g. constant rate i.v. infusion inputs, with the inputs computed from the observed I versus t output curves which are converted to $Q_B(t)$ and deconvolved with $G(t)$. The DEC is constructed as a plot of I (observed at a constant time, t, after dosing) versus dose.

observed response output. When the systemic bioavailability is of interest, the impulse input would be constituted by a bolus i.v. dose; the weighting function then relates the rates versus time profile for the drug entering the systemic circulation when it is given by any other route or dosage form. Similarly, the weighting function resulting from the administration of a bolus of solution given orally or into the eye relates preabsorption bioavailability input rates into the gut contents or the fluids of the eye (14, 15), respectively. Whether the time of peak response to an impulse occurs at time zero or later depends upon whether the input site is the same compartment as the response data sampling site or not; this is shown in Figure 3 for the case when the biophase and plasma compartment are the same or different compartments.

The transduction function is defined by an observed dose-effect curve which is constructed by plotting the response intensity observed at a consistent time (usually time of peak response) following the administration of doses of increasing magnitude. The dose-effect curve is then used in the manner of a calibration curve to convert observed pharmacological response intensities into their corresponding biophasic (site-of-action) drug levels. Their use in this manner is analogous to using a nonlinear Beer's law plot to convert observed absorbances into plasma level concentrations when using a spectrophotometric assay. The validity of the Beer's law plot is obviously independent of the route and mode of administration as well as the time at which the plasma sample being analyzed is collected. This is also the case for the use of the dose-effect curve to convert observed pharmacological responses into biophasic drug levels. This is, therefore, a quite general method by which, nonlinear, observed pharmacological response variables can be converted into biophasic drug levels which can then be treated by linear mathematics. Since the transduction function is experimentally determined, as the dose-effect curve, it is independent of the assumption of any particular drug-receptor site interaction model (98, 99).

The top of Figure 3 graphically illustrates the method of determining a pharmacokinetic model to describe the relationship between systemic drug inputs and pharmacological response outputs. The graphs at the bottom of the figure illustrate the procedure used for verifying the model. The fidelity of the determined model is evaluated from the results of comparing experimentally known, usually slow intravenous infusion, drug inputs with the drug inputs computed and predicted from the results of monitoring the pharmacological responses to the known inputs: The model previously determined from bolus intravenous doses is used for the computations. Therefore, whether the method applies in any particular case is determined from pharmacological data alone, and this approach can be applied with drugs for which chemical assays do not exist or whose exact chemical composition or active constituent may not even be known. It has been demonstrated that neither the mathematical form of the weighting or transduction form need be explicitly defined in order to compute drug inputs and outputs from one another. As shown with the results in Figure 4, the computations can be performed entirely numerically and in the frequency rather than time domain (13–14). The only assumption involved is that the disposition of the drug in the body is at least approximately linear over the

range of drug inputs being considered. Details of this method have been reported (13–15).

The author has encountered and resolved three problems that can arise with the use of the above-described approach which have not appeared in the literature. The first problem arises when response profiles have multiple peaks without any well-defined maximum occurring at a consistent time which can be used to plot a dose-effect curve. In this case, the area under the response curve (AUC) is plotted versus dose, instead. The resulting plot is linearized by finding some function of the AUC which when plotted versus dose yields a straight line. It is a simple matter to show mathematically that the same function that linearizes AUC versus dose plots also linearizes plots of maximum response intensity versus dose. Therefore, when this function is applied to observed intensities of response, it converts them into the relative biophasic drug levels needed for linear pharmacokinetic analysis.

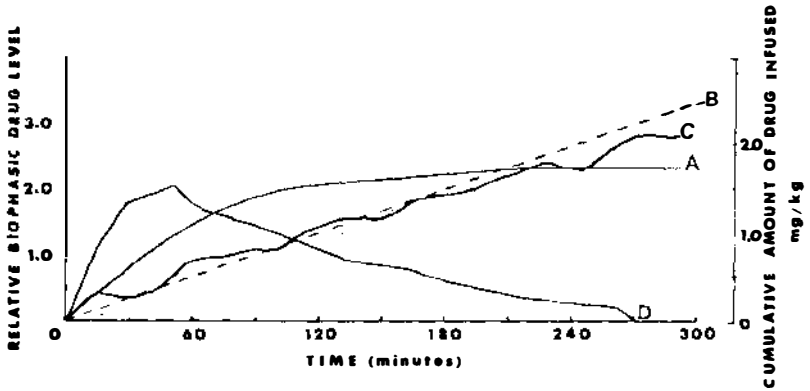

Figure 4 Comparison of the experimentally known cumulative amount of chlorpromazine infused at a zero-order rate of 0.5 mg/kg per min to rabbits as a function of time (curve *B*) with the amounts computed to have been administered (curve *C*) from the results of monitoring the time course of the intensity of observed miotic response. The computation was accomplished by numerical deconvolution performed numerically in the frequency domain using a Hewlett-Packard 5451B/2100S Fourier Analyzer microprogrammable computer system. The weighting function (curve *D*), which represents dose-normalized relative biophasic drug levels resulting from bolus intravenous dosing (impulse response), was deconvolved against the relative biophasic drug level versus time response (curve *A*) corresponding to the slow, zero-order, intravenous infusion (step response) and integrated. Prior to deconvolution, curves *A* and *D* were numerically smoothed, once employing a computer program using the three-point smoothing algorithm:

$$\text{DATA}\,(N) = \frac{\text{DATA}\,(N) + [\text{DATA}\,(N-1) + \text{DATA}\,(N+1)]\ /2}{2}.$$

The close similarity between the experimentally known and computed drug input profiles (curves *B* and *C*, respectively) demonstrated the verity of the approach. The curves were constructed with a Hewlett-Packard 7210 digital plotter. The range of values for the weighting function (curve *D*) is 0–1.0.

The second problem is the occurrence of dose-effect curves which are not monotonic increasing with dose; this causes the difficulty of response intensities corresponding to more than one biophasic drug level. This problem is solved by utilizing a time-tracking program to select the correct values of biophasic drug levels for any observed response intensity (52). The third complication arises when the disposition kinetics of the system is nonlinear. A trend with dose, in the time of peak pharmacological response intensities can indicate that this is the case (21). A general, piecewise, linear approach to circumventing this problem which can always be applied involves the following: 1. constructing the usual dose-effect curve by plotting maximum intensities of response versus dose irrespective of the time of their occurrence and using it to convert the pharmacological response intensity, I, profiles observed for each dose, into corresponding biophasic drug levels, Q_B. 2. Fitting a sum of exponential expressions to each of the Q_B versus time profiles obtained for each impulse input, dose (14); they will be given by Equation 1 where the A_i's and m_i's are equation parameters.

$$Q_B = \sum_{i=1}^{n} A_i e^{-m_i t} \qquad 1.$$

Alternatively, any other empirical expression, such as a polynomial, could be used. In any case, these results define dose-dependent weighting functions. 3. Plotting of the parameters of the dose-dependent weighting functions versus the time average values of Q_B corresponding to each dose, as can be defined by Equation 2, where there are k observations of $Q_{B,p}$ recorded at each p'th time interval following the j'th dose.

$$\overline{Q}_{B,j} = \sum_{p=1}^{k} Q_{B,p} \qquad 2.$$

In this manner, the dependency of the parameters of the weighting function on the intensity of the response output is established. 4. Selecting a set of weighting function parameters from the plots constructed in step 3 which correspond to each of the Q_B data points on a Q_B versus time profile observed to result from the absolute bioavailability input profile which is to be determined by computation. The weighting function parameters are then used to calculate weighting function values which correspond to each of the Q_B values for which the corresponding absolute bioavailability input is being sought. In this manner, the weighting function is continuously adjusted to compensate for its dependency on the magnitude of the Q_B response output at any time. 5. Computation of the sought after absolute bioavailability input by numerical deconvolution (14) of the output adjusted values of the weighting function with their corresponding output response values; this produces the sought after absolute bioavailability rate versus time profile. The extent of absolute bioavailability versus time profile is obtained by integration of the rate profile. Step 1 in this procedure can be omitted and I values used instead of Q_B values. However, the partial compensation for nonlinearity in the gain of the systems (14), which results

from the dose-effect curve conversion of I into Q_B values, has been found by the author to contribute appreciably to the accuracy of the computed absolute bioavailability profiles and is therefore recommended. This piecewise linear approach to computing absolute bioavailabilities for nonlinear systems is also applicable to blood or urine level data which can be treated in an identical manner.

The piecewise linear approach to computing drug inputs from drug-response outputs, or vice versa, has been very successfully applied to hypothermic response to chlorpromazine data obtained in rabbits (21). It provided much improved results (V. F. Smolen and R. J. Cosgrave, unpublished) relative to a straightforward linear systems approach (21). The generalized piecewise linear approach to bioavailability analysis is herein described in some detail because of its considerable significance in allowing absolute bioavailabilities to be computed for nonlinear systems without the need of any knowledge of the mechanisms responsible for the system nonlinearities. Therefore, this method is always applicable and permits nonlinear systems to be treated with the generality of linear systems mathematics. Previously, some knowledge of the mechanisms responsible for the nonlinearities was necessary in order to postulate a system-specific model on which to base any calculations of absolute bioavailability. With the above three described modifications performed as needed, the scheme described in Figure 3 can be applied to nearly any pharmacologically responding system, using either direct assay or pharmacological data.

OPTIMAL DRUG BIOAVAILABILITY INPUTS AND DRUG DELIVERY SYSTEMS

An optimal drug input has been defined on the basis of pharmacological criteria as having a maximum therapeutic utility in that it takes into account the adverse drug effects that can accompany the desired therapeutic activites (15, 25). In this context, an optimal absolute bioavailability is constituted by the time pattern of rates and extents of administered drug which approaches the elicitation of an ideally sought therapeutic response versus time profile as closely as possible without exceeding predetermined safely allowable limits of concomitantly occurring adverse drug reactions (15). The manner of application of time optimal systems analysis methods to compute optimal drug inputs has been described and exemplified (15, 26).

Almost any systemic, drug input–time pattern can be accomplished by programmed intravenous infusion. However, most commonly drug inputs are effected by drug delivery systems that are either chemical, mechanical, or electromechanical devices which are designed to input drugs into the systemic circulation or to specific target sites in the body at predetermined controlled rates. Most commonly, of course, they are drug product formulations such as tablets, suppositories, and solid implants.

However, new and novel approaches to drug delivery are being developed (45, 51). Among the most innovative and promising of new drug delivery systems are feedback controlled, automated, drug administration devices. The best known of these is the artificial pancreas for insulin (113, 114). The problem with such a device, which functions to monitor glucose levels and administer insulin automatically as

needed, has been the development of a suitable electrochemical sensor for glucose which can remain chronically implanted in the body. Not only has this been a difficult problem for glucose, but the general lack of continuous and specific in vivo assay methodologies is, in general, a severe limitation to detecting drugs in the body as well. However, the use of pharmacological response data removes this restriction and can permit automated drug delivery devices to be developed for various classes of drugs such as, for example, hypotensives, anesthetics, skeletal muscle relaxants, and antiarrhythmics (15). Such devices can become quite sophisticated. For example, using methods borrowed from control engineering and signals analysis, adaptive, optimal drug delivery devices have been developed in the author's laboratory which have the capability of automatically compensating for changes in a patient's responsivity to a drug such as may occur through the development of tolerance or as a consequence of changes in the patient's pathophysiological condition (42, 115). With the continuously rapid growth of computer technology and electronics miniaturization, such ultimate drug delivery systems may well represent the next generation of drug products.

CONCLUSIONS

The pharmaceutical sciences and the drug industry are concerned with the marketing of economical drug delivery systems, which are either chemical drug products or electromechanical devices, which elicit optimally desirable drug effects. The quantitative description of drug activities and their relationship to the manner in which drugs can be made bioavailable to the body by drug delivery systems is the practical concern of pharmacokinetics. These problems can be efficiently approached through the direct application of engineering control theory, signals analysis, and optimization techniques.

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