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IDEALIZED APPROACH TO THE OPTIMAL DESIGN, DEVELOPMENT AND EVALUATION OF DRUG DELIVERY SYSTEMS I: DRUG BIOAVAILABILITY INPUT-PHARMACOLOGICAL RESPONSE OUTPUT RELATIONSHIPS

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ABSTRACT

The marketing of drug delivery systems possessing an optimal therapeutic utility is the principal concern of the drug industry. It is necessary and useful in systematically pursuing the rational design and development of optimal drug delivery systems, to establish performance criteria upon which to base their evaluation and gauge the success of these efforts at any stage of the development. This first communication discusses the drug bioavailability input-pharmacological response output relationships which provide the means for establishing such guidelines. Part II discusses the application of these relationships and presents a rational, although idealized, approach to the development of drug products designed to elicit optimally sought pharmacological response behavior. The role of a new method of in-vitro drug product testing which is optimally predictive of in-vivo bioavailability, is presented. Examples are drawn from ongoing research in the authors' laboratories. The limitations within which the general ideals of ultimately optimal behavior of drug delivery systems are applicable and practical to achieve are discussed.

INTRODUCTION

Any general scheme for defining and developing drug delivery systems to possess optimal therapeutic performance characteristics would at the present time obviously need to be considered idealized and merely present a framework within which such practical difficulties as quantitatively defining pharmacological effects, biological variation, and the unique physicochemical, pharmacological and toxicological properties of individual drugs can be viewed. However, the handling of such problems may be anticipated to continue to be ameliorated through communication and the strongly synergistic interdisciplinary collaboration which results from the interaction of pharmacologically, physicochemically and engineering oriented pharmaceutical scientists. The application of engineering principles to pharmaceutics, the availability of miniaturized and inexpensive computers, the ever increasing sophistication in bioinstrumentation and data analysis for the quantitation of recorded drug responses, as well as the innovative implementation of biophysical and polymer chemistry principles are permitting approaches to drug delivery which seemed only visionary in the very near past to become feasible for the very near future.

CONTROL OF DRUG BIOAVAILABILITY INPUTS

A drug delivery system may be defined as a chemical or electromechanical device designed to input drug(s) to the systemic circulation or to specific target sites in the body at predetermined controlled rates. Based on this definition, drug delivery systems can therefore be differentiated from "Drug dump systems" which release the drug to the body in an uncontrolled, unplanned, manner at rates which are mostly fortuitous in that they were not specifically designed or chosen a priori and accomplished by the design and mode of operation of a device or through the chemical formulation of a drug product.

The factors which determine drug bioavailability inputs include: 1) the mode and site of administration, 2) the dosage regimen, 3) absorption rates from the site(s) of administration, and 4) design and mode of operation of electromechanical drug administration devices, if these should happen to be used. Each of these factors can be controlled entirely or to effective degrees by either mere selection, design, or formulation.

The rates of drug bioavailability which a drug delivery system should be designed or set to provide can most rationally be determined only on the basis of the corresponding dynamic pharmacological response behavior it should elicit. The corresponding levels of drug in body fluids such as blood and urine, are only of interest in this regard in that they may be related to pharmacologic effects. In other words, how much drug is in the body is not as important as what it does when it's there. Pharmacokinetic relationships between drug bioavailability inputs and pharmacological response outputs are therefore of the most fundamental and practical interest and importance to the design, testing, and ultimate optimization of the therapeutic performance of drug delivery systems. Relationships between drug inputs and drug blood or urine levels are only of interest in this context when the body fluid drug levels can be directly related to pharmacological activity.

SYSTEMIC AND BIOPHASIC DRUG INPUTS

Figure 1 illustrates the familiar type of simplified representation of the body as a compartmented system; in the diagram the compartments are represented by the rectangles and the various drug transport processes are described by the arrows. The heavy arrows indicate drug input and response processes; in such models, compartments are analogous to well stirred tanks and represent a space or

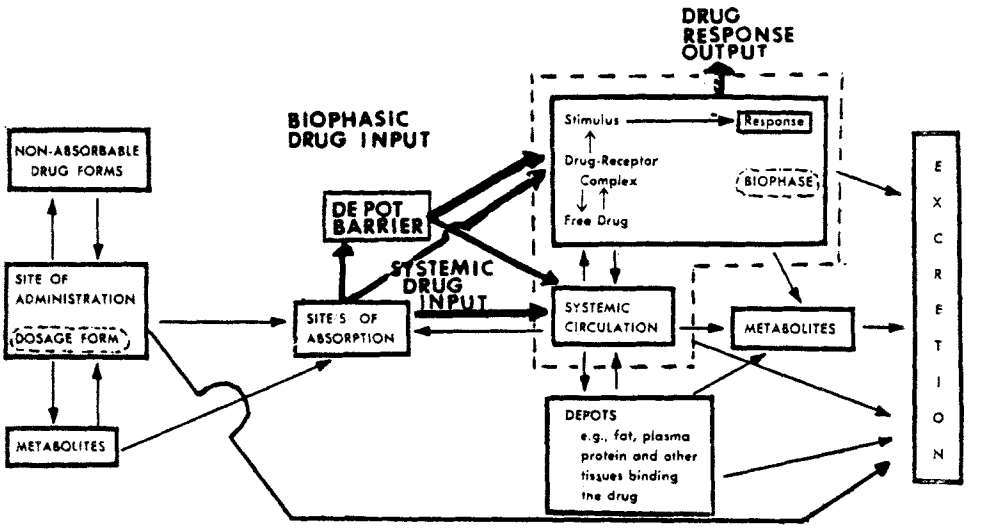


FIGURE 1

Simplified compartmental representation of the processes influencing drug response characteristics.

solubility volume into which the drug can enter or a chemical entity into which it can be metabolically transformed. The biophase is a compartment into which the drug enters to induce its effects. The dashed lines in the diagram shown encircling the biophase and central systemic compartment are meant to signify that these two compartments may or may not be one and the same depending upon the rapidity with which the drug can penetrate to its sites of action from the blood. It is also possible that the sites of action are physically contained in the systemic blood compartment yet the biophase will be in a separate compartment if the active entity is a metabolite of the administered compound into which it is slowly transformed. When the biophase and plasma compartments are the same, the intensity of pharmacological effect

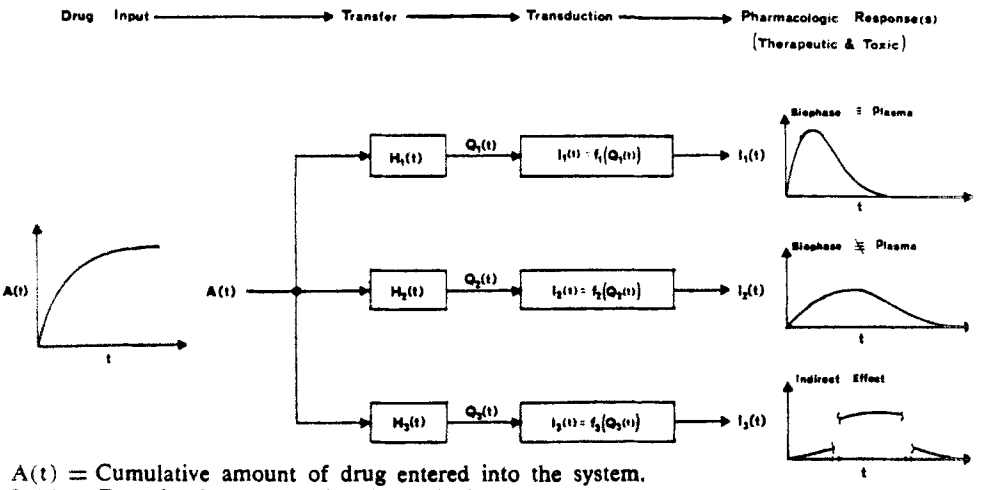
and blood levels will peak at the same time and may be directly proportional or often semilogarithmically related over an appreciable range. When this is not the case a causal relationship still exists, but it will be more complex.

Figure 1 indicates two types of drug inputs: in one case the drug enters the systemic circulation either directly, or indirectly via a depot barrier compartment, and is subsequently distributed to its biophase. This is what occurs with oral and parenteral administration. In the other case the drug is absorbed into its biophase prior to entering the systemic circulation. This is the base when a localized effect of the drug is sought by means of, for example, ophthalmic dosing, topical application to the skin, or by intrauterine or vaginal implantation. In these cases the presence of the drug in the blood is undesirable and its detection in the blood in any appreciable concentrations would indicate a toxic dose or a poorly designed drug "dump" system.

TRANSFER AND TRANSDUCTION FUNCTIONS

In designing drug delivery systems intended for providing either systemic or biophasic drug inputs we are primarily concerned only with the dynamic relationships between the drug inputs and drug response outputs. Therefore, the development of compartment models in which some biophysical significance is ascribed to each compartment is an often unrealistic and needlessly complex model description of the system if the only purpose of the model is to relate drug inputs to drug response outputs. The application of control theory principles most commonly used in engineering practice allows a much simplified and more powerful approach to this problem.

Figure 2 illustrates the principles of an approach[1-11] which is valid for a majority of drugs. A block diagram illustration



$A(t)$ = Cumulative amount of drug entered into the system.
$Q_i(t)$ = Drug levels at sites of action (biophase).
$I_i(t)$ = Pharmacologic response intensity (therapeutic or toxic).

FIGURE 2

Block diagram characterization of the dynamics of drug action.

of the relationships between drug bioavailability inputs and drug response outputs is shown. The relationships are valid irrespective of: 1) whether the inputs are directly into the biophase or reach the biophase via the systemic circulation. 2) Whether the biophase and systemic compartments are the same or not. An intensity of pharmacological response observed at any time is the result of all active drug entities present or which have been present earlier at their sites of action in the biophase compartment. The blocks in the diagram indicate the two functional relationships which are most usually required to establish the inter-relationships between drug inputs and each pharmacological time response output elicited by the drug. The first relationship is the transfer function which relates the time course of change of biophasic drug levels to their corresponding

drug inputs. In this scheme, a linear relationship, i.e., linear in the sense of the superposition principle[12] is assumed between the input and biophasic drug level response; this is most commonly a valid assumption. The intensity of the pharmacological response can be assumed to be a single valued function of its corresponding biophasic drug levels. Since biophasic drug levels are linear variables, the response intensity will therefore also be linear in its dynamical behavior, but because of threshold and saturation effects it will not generally be linear in magnitude. In other words, if a transfer function were written to directly relate drug inputs to pharmacological response outputs, the time constants in the transfer function would be invariant with dose, but the gains would be dose dependent. The transduction function, symbolized by the second block in the diagram, corrects for this dose dependence and serves to fully linearize the drug input/output pharmacological response behavior of the system. Whether the assumptions upon which the drug bioavailability input-pharmacological response output relationships are based are valid or not in any particular case can be determined using tests[2,5,7,9] requiring only pharmacological data alone without any need for direct assay data. Therefore this approach can be applied with confidence to drugs for which direct chemical or radiological assays are difficult or nonexistent or to natural product drugs whose exact chemical composition may not even be known.

CHARACTERISTICS OF PHARMACOLOGICAL DATA

A commonly occurring cumulative drug input and three types of drug response vs. time profiles are shown in Figure 2. The top curve is characterized by the relatively rapid appearance of a peak which coincides with a peak in blood levels; in this case the plasma

and biophase compartments are the same. The middle curve exemplifies the case where the peak response occurs later than the peak in blood levels due to the plasma and biophase being different comaprtments. Such cases occur when the drug must slowly penetrate to a tissue site outside the systemic circulation and/or be converted to a metabolite in order to exert its response. The lowermost curve exemplifies an indirect effect such as elicited by reserpine on blood pressure or warfarin on prothrombin complex activity where the response may be prolonged even beyond the time the dose is effectively cleared from the plasma.

Figure 3 exemplifies the case where the biophase and plasma compartments are the same. The maximum mydriatic response intensity to the drug tropicamide is seen to occur nearly immediately after

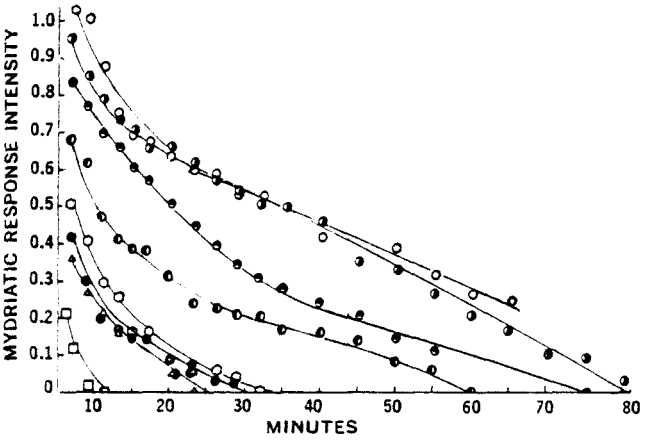


FIGURE 3

Time course of mydriatic response intensity for rapidly administered intravenous doses of tropicamide. Each point is the average of a minimum of four determinations on four rabbits. The doses represented are 13.7 (□), 25.0 (△), 50.0 (●), 66.7 (⬡), 167 (◐), 250.5 (◓), 334 (◑), and 416.5 (○) mcg./kg.

the administration of each bolus i.v. dose. This behavior can be contrasted to that of another mydriatic drug tridihexethyl chloride, shown in Figure 4. where the maxima in the mydriatic responses to rapid i.v. doses occur nearly twenty minutes after dosing. The difference in peak times for the two mydriatic drugs can be attributed to the rapid ability of the unionized tropicamide to permeate tissue barriers to reach its sites of action relative to the ionized tridihexethyl chloride which is a quaternary ammonium compound and therefore passes such barriers more slowly.

The third case is exemplified by the effect of chlorpromazine (CPZ) on rabbit body temprature shown in Figure 5. Although CPZ is rapidly cleared from the blood and may even act quickly to affect the temperature regulating center in the hypothalamus, the slow

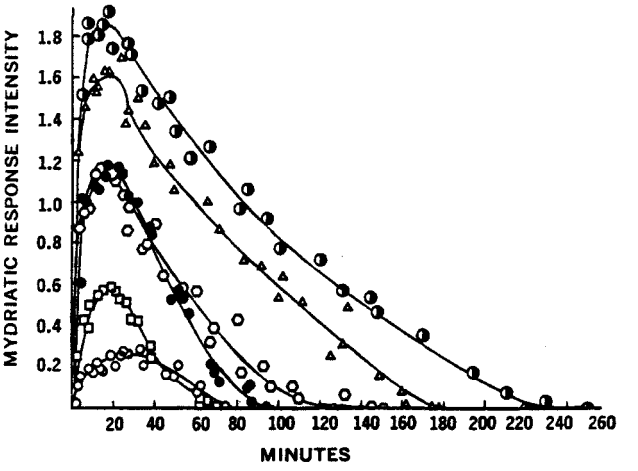


FIGURE 4

Time course of mydriatic response intensity for several intravenously administered doses of tridihexethyl chloride. Each curve is the result of measurements on a minimum of three separate rabbits. The intravenous doses employed, in mg./kg., were 0.17 (-○-), 0.22 (-□-), 0.30 (-●-), 0.45 (-◐-), 0.95 (-△-), and 1.60 (-◑-).

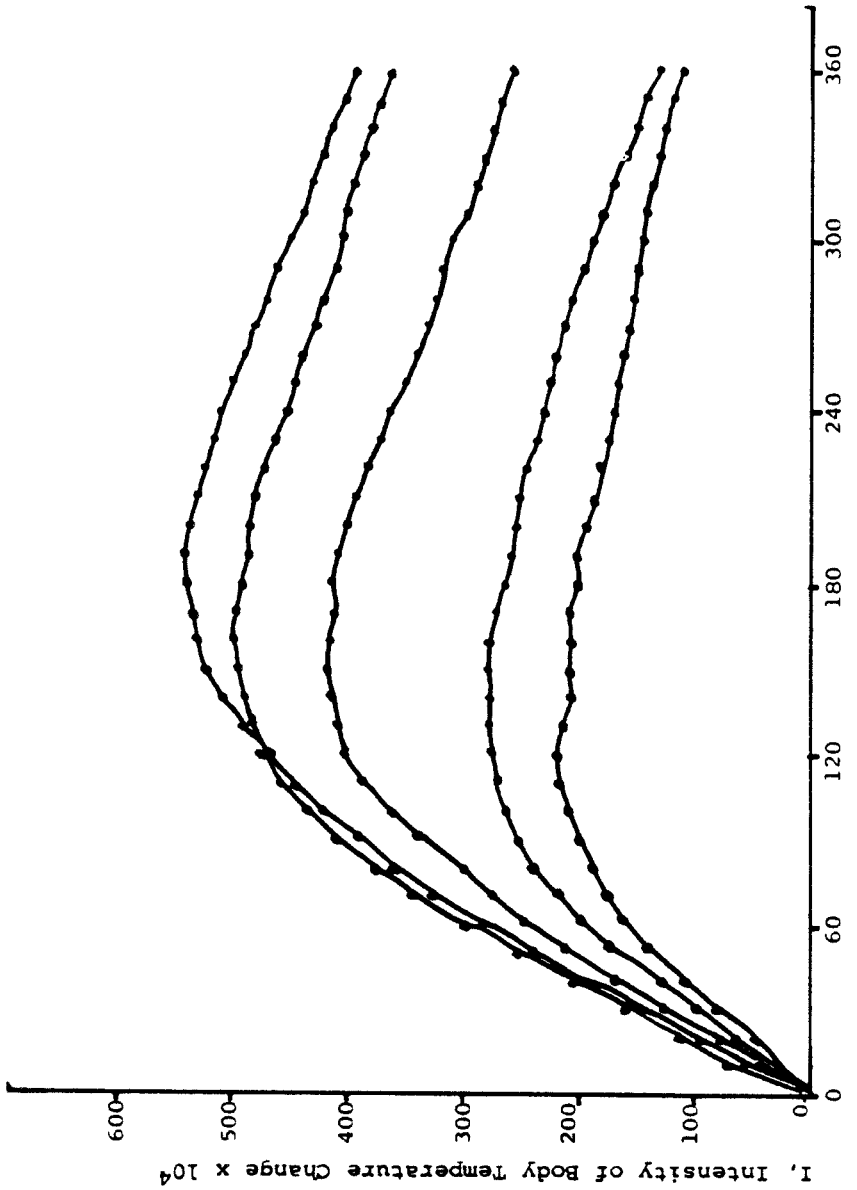


FIGURE 5. Time variation of body temperature response intensity following rapid intravenous doses of 0.5, 1.0, 2.0, 3.0, 4.0 mg./kg. Each point is the average of 8 to 12 determinations on different rabbits; I = (predrug temp.) - (postdrug temp.)/(predrug temp.).

onset and prolonged duration can primarily be attributed to the heat capacity of the body. In contrast, the miotic effects of CPZ, shown in Figure 6, can be expected to be more rapidly responsive to the instantaneous levels of the drug at its sites of action. This is demonstrated by the earlier appearance of the maxima. The smoothness of the temperature response curves relative to the miotic and intraocular pressure curves, can also be attributed to the heat capacity of the body acting analogously to a low pass filter to smooth the temperature response data.

Most drugs, like CPZ, induce multiple responses. When delays in the peaks of simultaneously induced therapeutic and toxic effects occur, they may be used to advantage in minimizing toxic effects by optimizing drug delivery inputs. To achieve a maximum therapeutic utility for a drug it is sought to obtain an ideal therapeutic time response profile while maintaining toxic effects below safely tolerable limits. In order to compute optimal drug inputs, it is first necessary to have a capability of quantitating and recording the therapeutic and toxic drug responses that are to be controlled. Overall evaluations of the clinical effectiveness of a drug input are seldom sufficiently well defined to be useful for the required quantitative computations. However many drug effects such as changes in pupil size, intraocular pressure, blood pressure, skin and body temperature, for example, reflect therapeutic or toxic effects of various classes of drugs and can be directly monitored quite easily with a very often acceptable degree of precision. When responses such as these are not themselves the therapeutic or toxic effects of interest, but merely correlate with such effects their usefulness for drug input

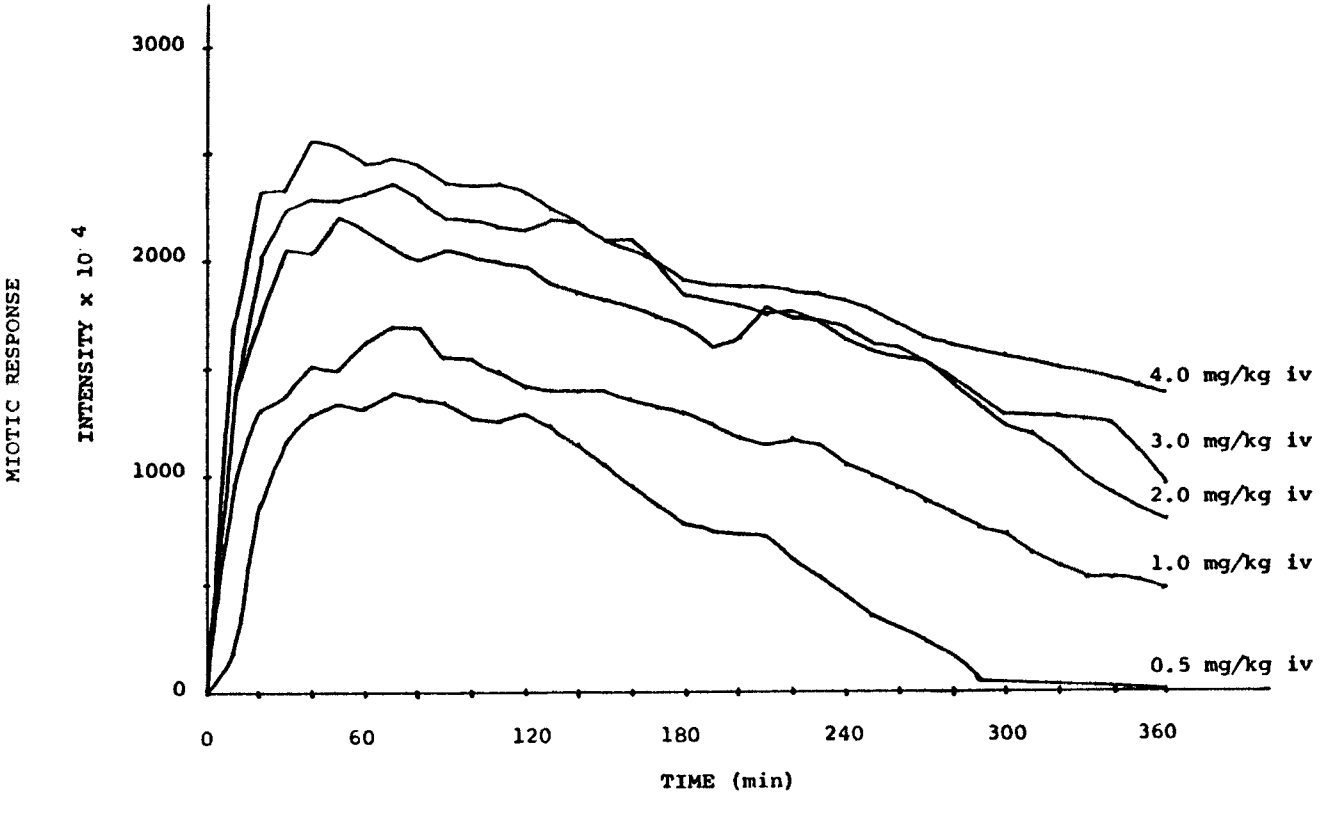


FIGURE 6

Time course of chlorpromazine induced miotic response intensity following rapid intravenous dosing of rabbits with chlorpromazine. Each point is the average of eight determinations.

optimization is then in the same category with blood and urine drug level data.

When it is not possible to directly monitor drug effects of interest, it may be feasible to resolve drug induced time varying changes in the patterns of biological signals such as EKG, spontaneous and evoked response EEG, EMG, and pupil noise. Work in the authors' laboratories has begun to explore the use of biological signals with the intent that this approach could be particularly useful for psychotropic and cardiovascular drugs whose clinical actions correlate with EEG and EKG signal changes. Since chlorpromazine affects both EEG and EKG we chose it as our first drug to be studied in this manner.

Figure 7 shows the effects of chlorpromazine on EKG. The wave forms are averaged representations of the EKG signal recorded at various times before and after dosing. The signal has been corrected for variations in heart rate by computerized processing. Close inspection of the waveforms reveals time varying changes in P-R and Q-T intervals, and an increase in the width of the T wave. These drug induced changes become more apparent in Figure 8 which shows the results of normalizing an averaged pre-drug and post-drug EKG waveforms for heart rate, superimposing them, and plotting their difference. Statistical analyses of these drug induced differences indicate that they are significant and that changes in EKG time intervals and integrated areas of differences between pre-drug and post-drug EKG wave patterns could be useful in monitoring the effect of drugs on the heart.

Figure 9 exemplifies effects of chlorpromazine on the power spectral density of the EEG signal recorded cortically from chroni-

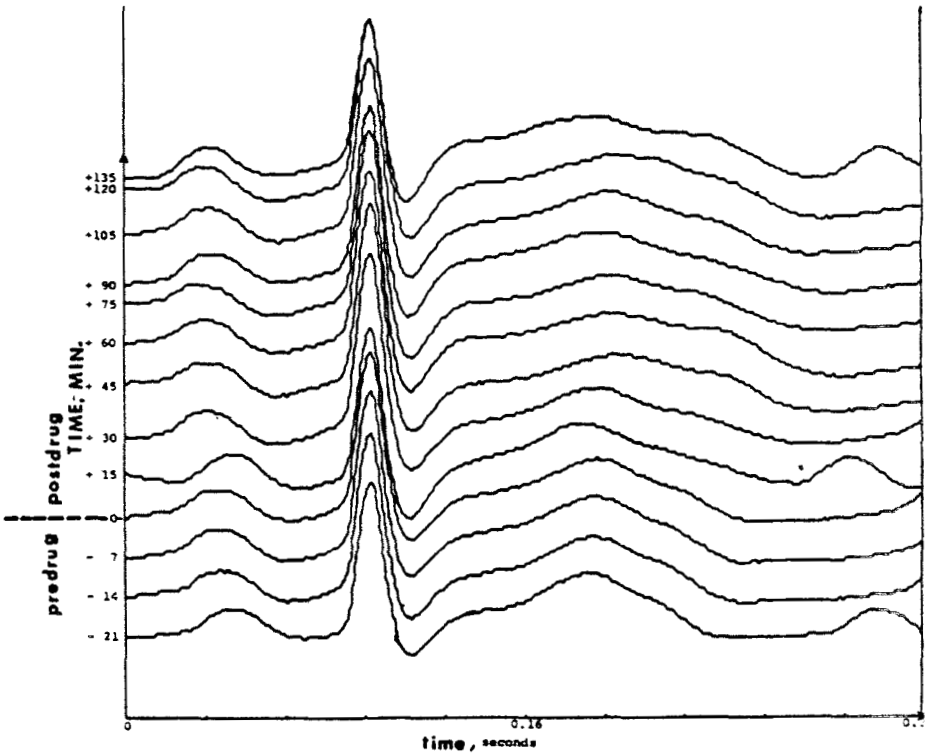


FIGURE 7

Chlorpromazine induced changes in rabbit EEG by a 4 mg./kg. dose given by slow i.v. infusion over 30 minutes.

cally implanted electrodes placed onto the hippocampus of rabbits. Similar results have been obtained from scalp recording on humans. The power spectral density plots appear to indicate that the drug induces changes in the peak height at very low frequency and changes the power in the 10-15 Hz band width. Although these drug effects on the power spectrum of the spontaneous EEG signal are real, their large variance renders it unlikely that they will prove to be quantitatively useful. Therefore, studies have been recently initiated

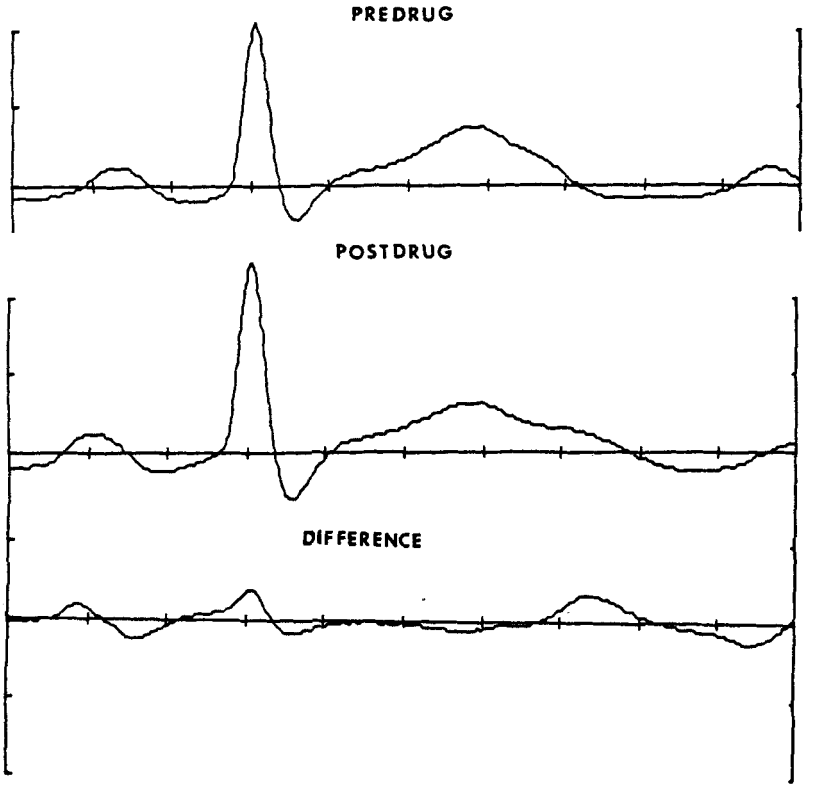


FIGURE 8

Comparison of a computer averaged normal, predrug, electrocardiogram waveform with a waveform recorded approximately 30 minutes after rapid intravenous dosing of a rabbit with 4 mg./kg. of chlorpromazine. The lowest curve represents a point by point difference between the predrug and postdrug waveforms.

using a sensitive method of visually evoked response EEG. Preliminary results observed in humans indicate this to be a considerably more sensitive and reliable method. Such results are shown in Figure 10. Figure 11 further illustrates some time responses for various effects of chorpromazine studied on rabbits. Figure 12 shows

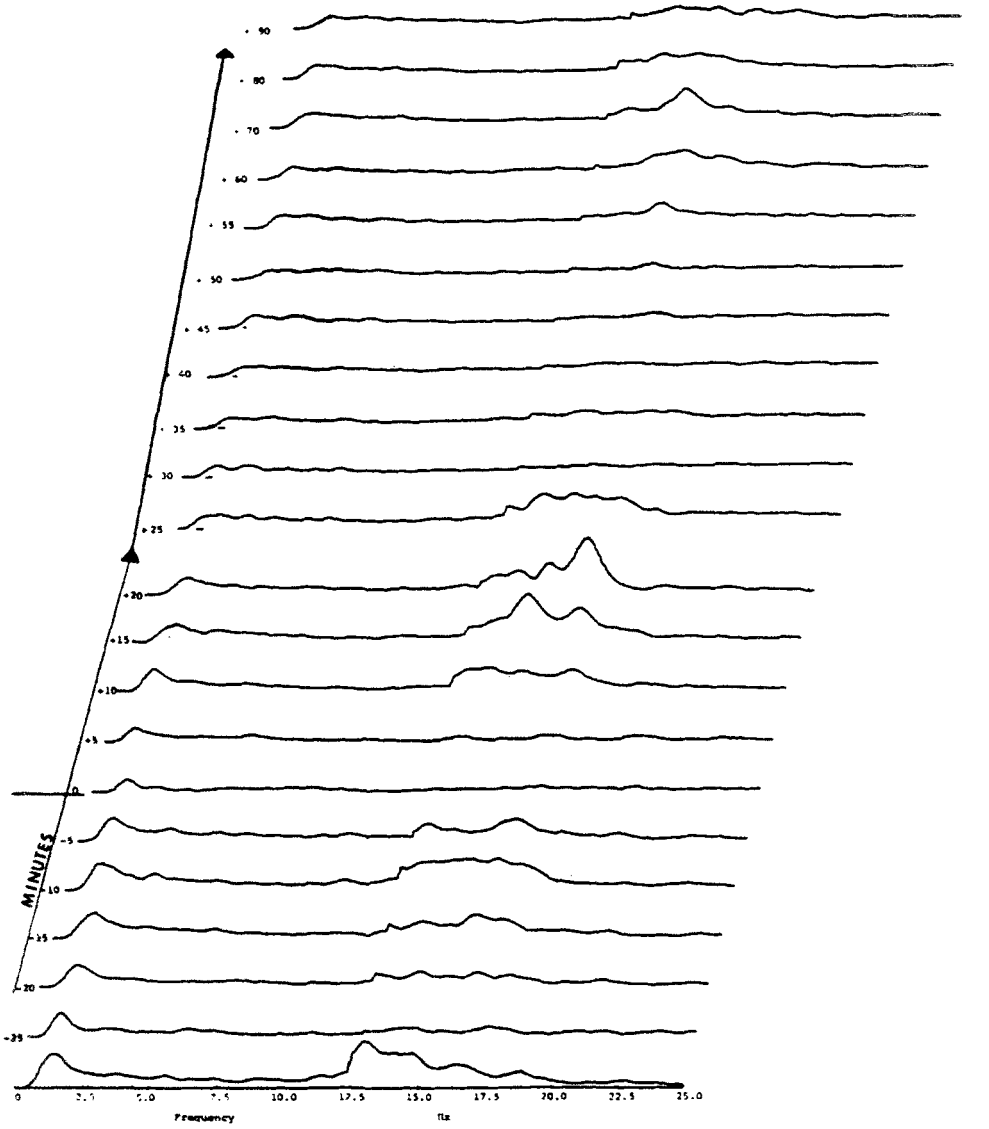


FIGURE 9

Power spectral density plots of the electroencephalographic signals recorded at various times from a rabbit before and after dosing with a 4 mg./Kg. bolus intravenous dose of chlorpromazine.

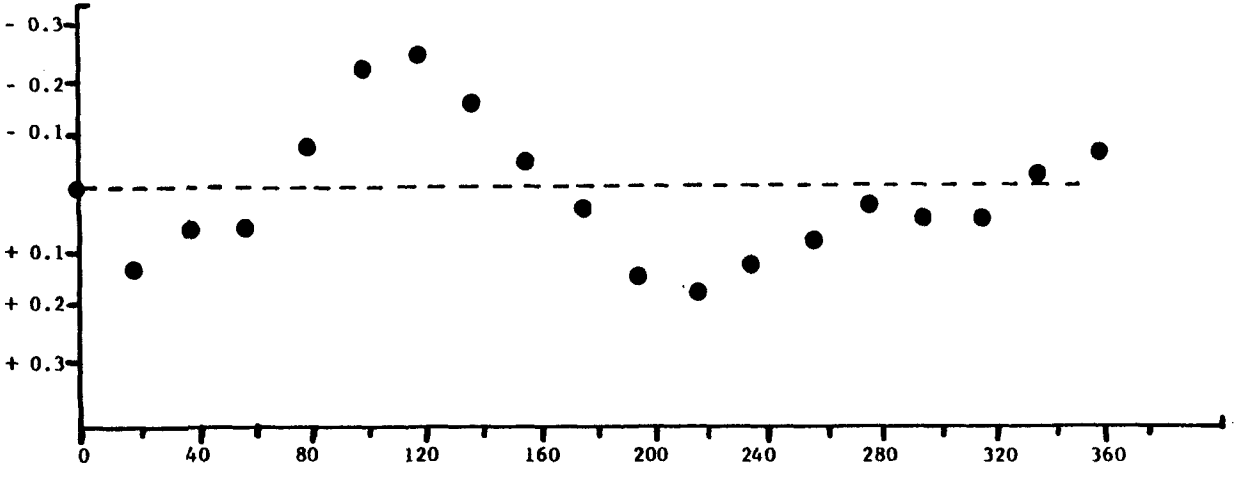


FIGURE 10

Time course of chlorpromazine induced fractional change in the magnitude, relative to predrug values, of the averaged 8 Hz component of occipital. monopolar, EEG signals recorded from humans having received 25 mg./70 Kg. oral doses of chlorpromazine syrup. The EEG signals were recorded while the subjects were being visually stimulated with a 4 Hz sinusoidally varying bar pattern appearing on an oscilloscope. The magnitudes of the maxima and minimum in the plot are dose dependent. Each point is the average of determinations made on three different male human subjects.

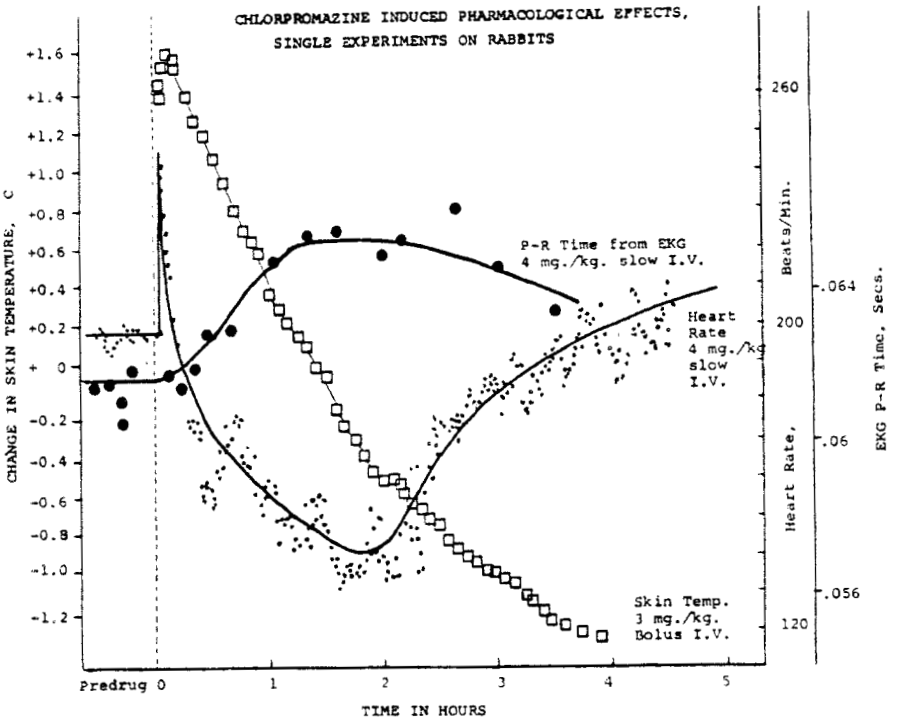


FIGURE 11

Examples of time variations in pharmacological effects of chlorpromazine observed in rabbits following rapid intravenous dosing. Each curve represents the results of a single experiment. The heart rate change (- • -) and P-R time interval in the EKG waveform (-●-) resulting from 4 mg./Kg. doses infused over a 30 minute period and skin temperature change (-□-), after a 3 mg./Kg. bolus i.v. dose, are represented.

the time variation of miotic response induced by varying oral doses of chlorpromazine given to human subjects; the results in Figure 12 are of very practical interest to the bioavailability evaluation of CPZ oral products. This is evident when it is considered that even for 200 mg oral doses blood levels of CPZ cannot be detected reliably using the most sensitive, GLC

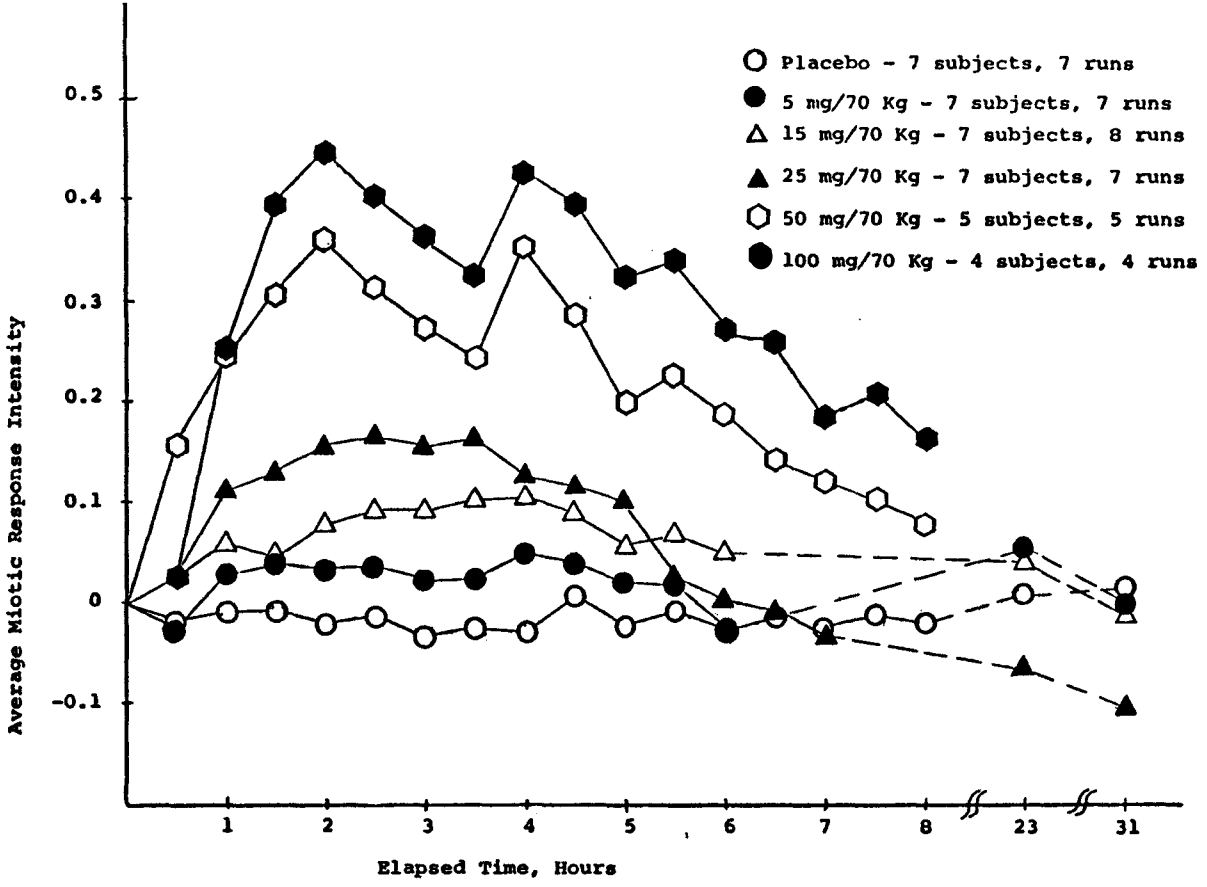


FIG. 12. Time variation of miotic response intensity following the oral dosing of human subjects with chlorpromazine syrup.

assay[13-14]. In contrast, the use of pharmacological data, such as miotic and intraocular pressure change activity, for example, permits the reliable detection of 5 mg oral doses in individual human subjects.

DRUG INPUT-OUTPUT RESPONSE RELATIONSHIPS

In designing drug delivery systems it is necessary to consider how drug responses are quantitatively related to drug-inputs and how drug inputs may be optimized. As mentioned previously, a transfer function and a transduction function are required. As shown in Figure 13, the transfer function is merely the biophasic drug level time response to a unit impulse drug input. If the impulse input is a bolus unit i.v. dose the transfer function will relate biophasic drug levels to the time course of the rates of drug entering the blood. If the impulse input is constituted by a solution of the drug rapidly given orally, injected into the aqueous humor of the eye, or placed in the uterus, then the transfer function will relate biophasic drug levels to the rates of drug release into the gut as occurs from an oral dosage form, the rates of transcorneal passage of an ophthalmic drug into the aqueous humor, or the in-vivo release rates of a drug from an intrauterine implant, respectively. In other words, the relationships are entirely general for linear systems irrespective of the route of administration and whether the drug enters the systemic circulation prior to reaching its sites of action.

The transduction function is required to relate biophasic drug levels to observed pharmacological response intensities; it is simply defined in each case by the drug's dose-effect curve. The basis for using dose-effect curves for this purpose can be

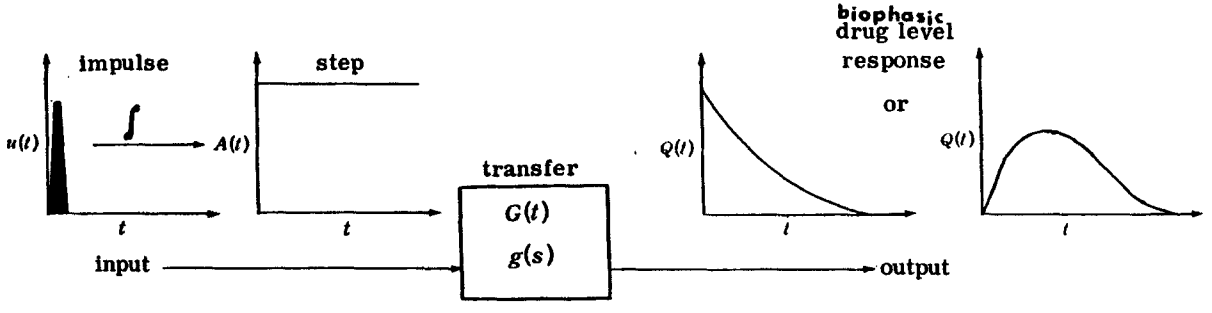


FIGURE 13

Drug input-biophasic drug level response output relationships for a rapidly injected, u(t) (impulse function), drug input to the drug transfer system, i.e., the body. The drug level versus time profile represents the impulse response (weighting function, G(t), in the time domain or transfer function, g(s), in the frequency domain of the system). Subsequently, the cumulative amounts of drug input to the system at any time, A(t), following dosing by other modes of administration are computed as the convolution of the reciprocal of the integral of G(t) and their corresponding observed drug level response, Q(t): i.e., $A(t) = \int_0^t G(t)^{-1} * Q(t)$.

understood from the following considerations: 1) The kinetics of disposition of the drug in the system (body) are assumed linear. Therefore the biophasic drug levels, Q_B, following bolus dosing or dosing by a route where the drug is absorbed by a dose independent process are given by equation 1, where the m_i's and A_i's are constants, t is time, and D is the dose.

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

At any reference time, t_r, Q_B is given by equation 2, where β_{t_r} is defined by: $\beta_{t_r} = \sum_{i=1}^{n} A_i e^{-m_i t_r}$.

$$Q_B = \beta_{t_r} D \qquad (2)$$

Since β_{t_r} is a constant, D is directly proportioned to Q_B and therefore must be a relative biophasic drug level or equal to Q_B when $\beta_{t_r} = 1$. 2) The intensity of pharmacological response, I, is assumed a single-valued, monotonic increasing function of $Q_B = \beta_{t_r} D$. Therefore it can easily be seen that a dose effect curve constructed by plotting I_{t_r}, i.e., values of I observed at t_r following dosing) vs. D is also a transduction function relating Q_B to I; it is only necessary to relabel the coordinates, I_{t_r} vs. D, to I vs. $Q_B/\beta_{t_r} = f(I)$ = relative biophasic drug level. Figure 14 illustrates a dose-effect-time surface for the mydriatic drug tropicamide.[2] A dose-effect curve is simply obtained as the projection of the surface onto an intensity-dose plane placed anywhere along the time axis. For very practical purposes, the time is best chosen as the time of maximal response. Dose-effect curves observed by the authors for various drugs and responses are exemplified in Figure 15. It has been demonstrated by the authors[3,4] that dose-effect curves can alternative-

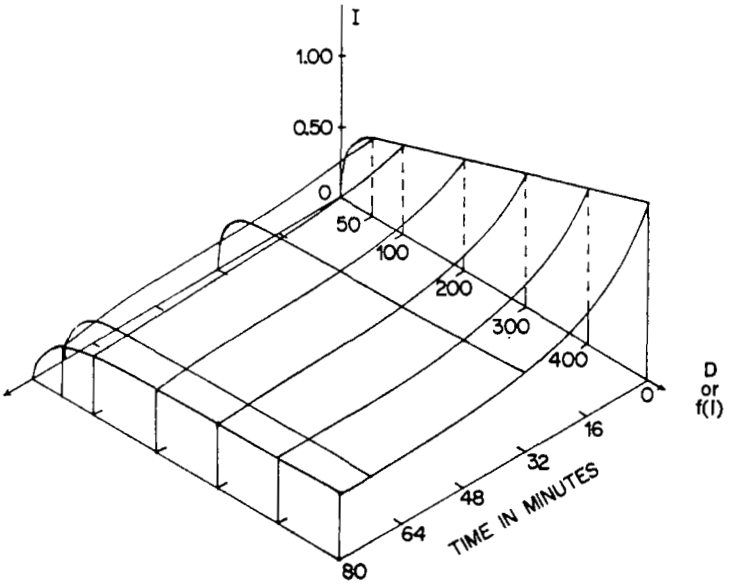


FIGURE 14

Dose-response (I) - time surface for the mydriatic drug tropicamide. The dose, D, axis is equivalent to the relative quantity of drug in the biophase, f(I), axis.

ly be constructed from the results of a single dose if the biophase compartment can be directly sampled for its content of drug while simultaneously recording the corresponding response intensities.

The reliability which can be achieved in computing drug inputs from pharmacological data is exemplified with the results shown in Figure 16 using the mydriatic response of tropicamide.[7,8] The percent of the dose computed from measured pupil diameters to have been administered by slow i.v. infusion at any time is compared to the corresponding experimentally known amounts of drug. The linear correlation coefficient of the line is 0.996. A perfect correspondence between the experimentally known input

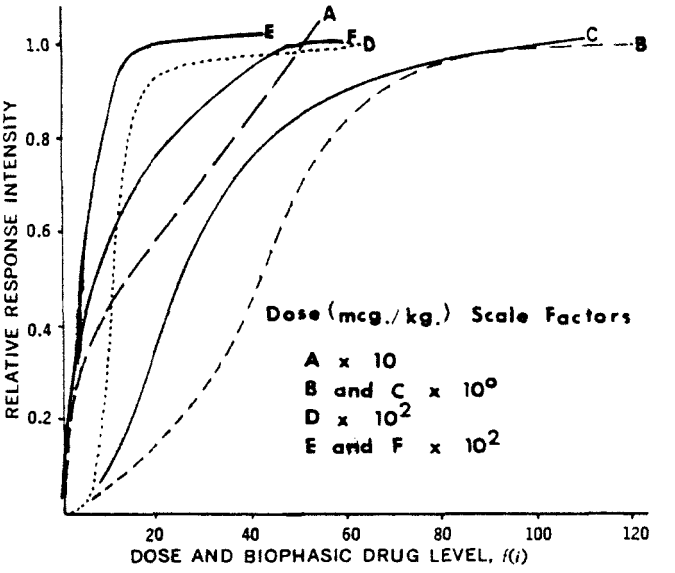


FIGURE 15

Intravenous dose-effect curves for rabbits. Key: A, mydriatic response of tropicamide; B, miotic response to carbachol; C, intraocular pressure response to carbachol; D, mydriatic response to tridihexethyl chloride; E, miotic response to chlorpromazine; and F, body temperature response to chlorpromazine. The curves define the functional relationship between the intensity of drug effect and relative biophasic drug levels.

and the drug input computed from measured pupil diameters would result in all the points lying exactly on the line. Figure 17 shows a similar comparison for chlorpromazine. The straight line represents an experimentally known slow i.v. infusion of the drug. The open circles represent the same drug input computed from rectal temperature measurements. The transfer function, defined by the dose normalized biophasic drug levels, and the temperature response to the slow infusion are also shown in Figure 17; these results were used in the computation of the input.

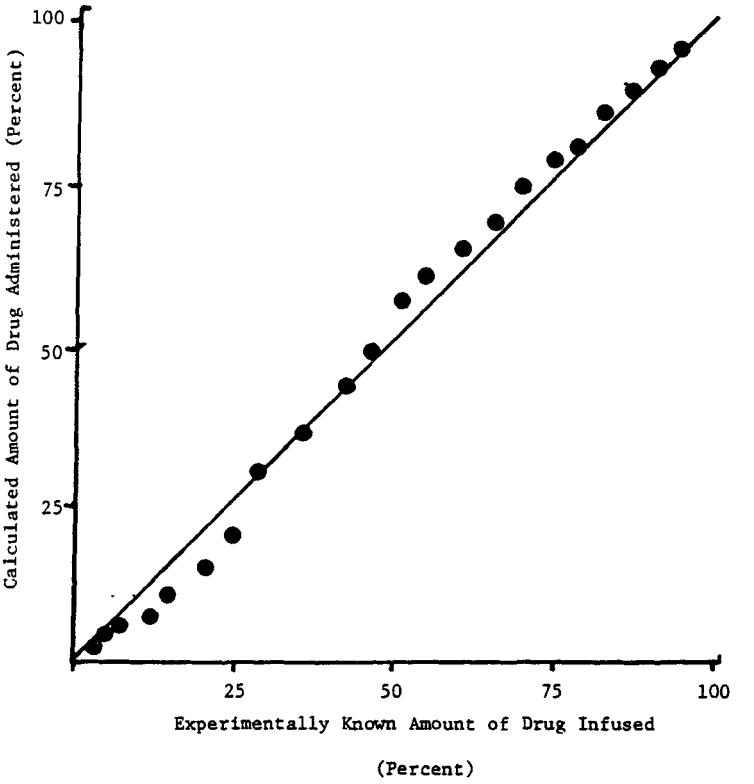


FIGURE 16

A comparison of actual cumulative amounts of tropicamide administered to rabbits by slow continuous intravenous infusion to amounts calculated from pharmacological data (pupillary diameter measurements) on the basis of a linear system model. A perfect correspondence would result in each point residing on the line having a slope of unity. The linear correlation coefficient is 0.996. The results represent the average of four replications on different animals.

The staircase-like plot in Figure 18 represents the cumulative input of CPZ to the alimentary tract achieved by giving five 5 mg doses of CPZ oral syrup to four human subjects at 1/2 hour intervals. The closed hexagons represent the amounts of drug computed to have been given from the results of monitoring intraocular pressure (IOP)

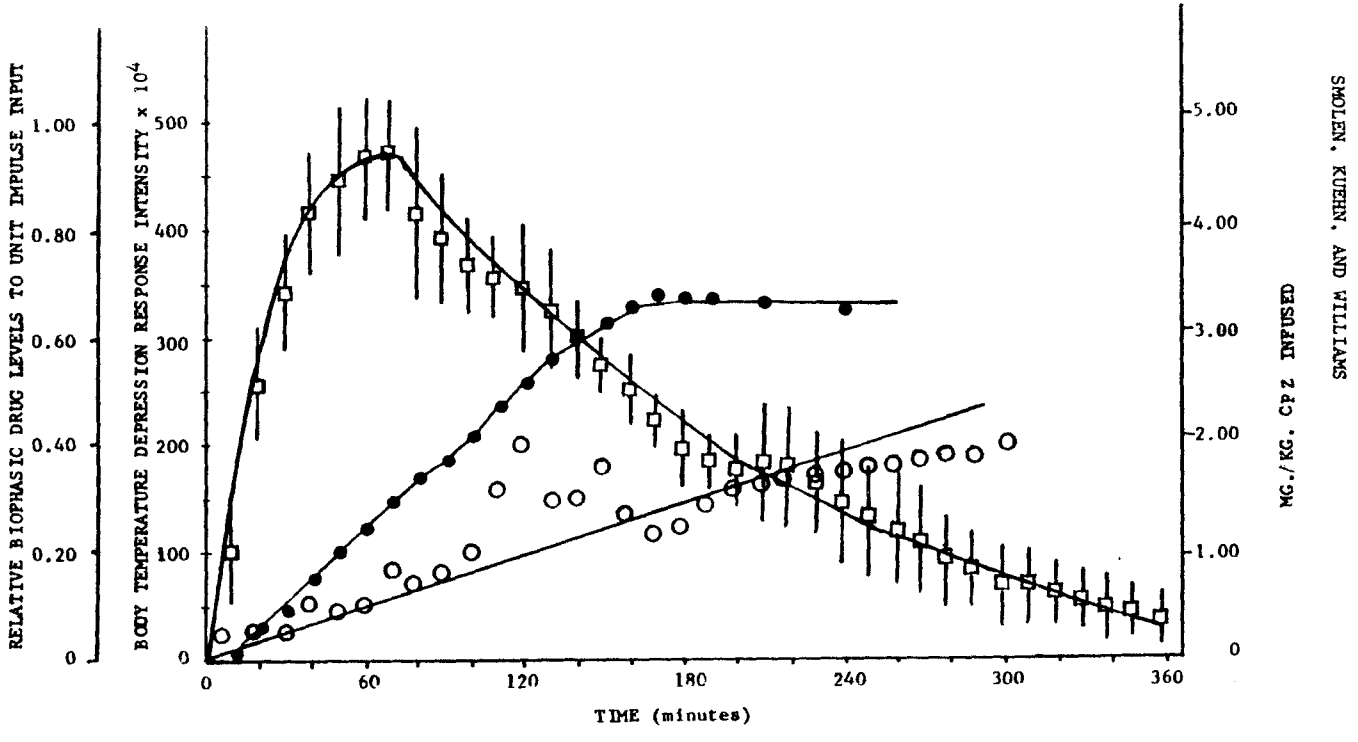


FIGURE 17

The straight line represents the cumulative amount of chlorpromazine given to rabbits by slow intravenous infusion, which can be compared to the amounts computed to have been administered (-○-) from the results of monitoring rectal body temperature (-●-). The relative biophasic drug levels (-□-) represent a time plot of the transfer function of the system which is used in the computation of the input. The points are plotted with their standard deviation. Each point represents the average data from 8 to 12 rabbits.

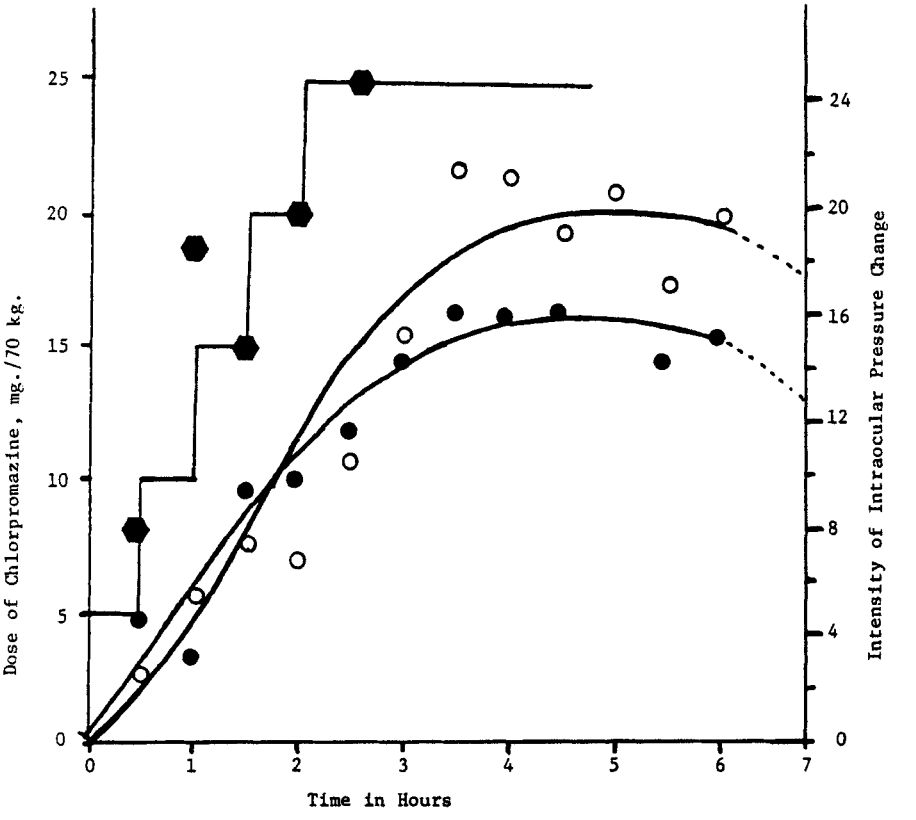


FIGURE 18

The staircase represents the experimentally known cumulative amount of chlorpromazine administered to four human subjects in the form of 5 mg./70 kg. of oral syrup given every 1/2 hour for 2-1/2 hours. The staircase can be compared to the amounts (- ● -) of the drug computed to have been given from the results of monitoring the intraocular pressure (IOP) response of the drug by applanation tonometry. The IOP response intensity to a single 25 mg./70 kg. dose given at time zero (- ● -) and to the staircase input (- ○ -) response curves are described by the weighted, biexponential, least squares fits to the data points used in the calculation of the computed staircase input values.

changes in the subjects. The impulse IOP response to a single 25 mg oral dose of syrup given at time zero (which defines the transfer function for the system) and the response to the divided 25 mg

staircase input, which were used to compute the predicted staircase input, are also shown in the Figure. Interestingly, many of the oral and i.v. dose effect curves observed for CPZ in humans are linear over a considerable dose range. When this is the case, they are not needed as transduction functions and the observed pharmacological response intensities can be used in pharmacokinetic computations in the exact same manner which would be employed with direct assay data. Although the correspondence between the theoretically predicted and experimentally known drug inputs is not always exact, it is well within the limits of biovariation and demonstrates that drug input/output relationships can be established using pharmacological data without the necessity of detecting the drug in the body by direct assay methods; for chlorpromazine such methods are quite difficult and unreliable.[13,14]

SUMMARY AND CONCLUSIONS

Three principal uses can be envisaged for drug input/pharmacological response output relationships. 1) When the drug response vs. time profile is hypothetical and represents ideally sought response characteristics for the drug, the computation of the corresponding drug input profile provides criteria on which to design the in-vivo drug release behavior of drug delivery systems which are to be developed for the drug. 2) When the drug response profile, which may be described by either pharmacological or direct assay data, is an experimentally observed result, the computation of the corresponding drug input is useful for evaluating the drug bioavailability of the drug delivery system which produced it. Such information is useful for suggesting modifications in the formulation, design, or use of the drug delivery system which may lead to an improvement in its therapeutic utility. 3) Pharmaceological responses

can be computed from drug inputs. Such results can be applied to predict drug response vs. time profiles for drug delivery systems whose input characteristics are known. The inputs may be known from the manner in which the drug is administered, the drug delivery system is designed, or primarily for oral drug products, from the results of predictive in-vitro drug release testing. Part II of this communication will describe an apparatus[15] and its operation as an in-vitro drug release test which provides results which are optimally predictive of in-vivo bioabailability vs. time profiles. The manner in which the use of such in-vitro drug release testing fits into an idealized overall scheme for approaching the development of drug products possessing optimal therapeutic utility will be discussed.

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