PLASMA LEVEL STUDIES IN PSYCHOTROPIC DRUG EVALUATION

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Pharmacologists and clinicians have always taken an interest in the disposition and fate of the drugs which they study, but the current enthusiasm for studies of plasma levels of psychotropic drugs in man originated in the mid-sixties, when Dr Bernard Brodie encouraged various workers, including myself, to investigate the idea that at least some interpatient and inpatient variations in responses to psychotropic drugs might relate to variations in drug concentrations in body fluids (Brodie, 1967).

The early experiments led on to more intensive investigations of the tricyclic antidepressants, first by Hammer, and later by Sjoqvist in Sweden, and by various other groups in various parts of the world, of the phenothiazines at The London Hospital and other centres, and of the benzodiazepines by Garattini in Italy (Hammer & Brodie, 1967; Sjoqvist *et al.*, 1971; Curry, 1971). Meanwhile, Schou (1969) in Denmark, and others, were actively investigating lithium concentrations in blood.

It is now possible to attempt an evaluation of the importance of this work, and to set guidelines for greater extension of the investigations. This paper is designed to illustrate the value and potential difficulties of plasma level studies, with a view to facilitating satisfactory interpretation of future data.

Factors affecting drug concentrations in plasma

The plasma level reflects input of drug into the body by administration and absorption, output from the body by metabolism and excretion, and distribution between plasma and tissues (Curry, 1974). Any secondary factor affecting these processes will affect the plasma levels. Table 1 is a listing of some of the known factors, some of which have been extensively studied. One of these factors, geographical location, deserves special attention in this symposium, as drug development is essentially an international enterprise.

A geographical location difference has been observed with chlorpromazine. I have now seen plasma level data for chlorpromazine from a number of centres, mostly either in the U.S.A., or the U.K. Higher doses are usually used in the U.S.A., but it is remarkable that similar concentrations appear to be maintained in similar psychiatric populations in these two countries. Data from two centres are in Table 2.

The plasma level yield per mg of oral dose was three times the U.S.A. figure in the U.K. group, while the yield was more comparable following similar intramuscular doses. The immediate reaction to this is that there is an unusual relation between plasma level and dose for this drug. However, within-patient studies of plasma levels as a function of oral dose show direct proportionality, with a 100% increase in plasma levels for a 100% increase in dose.

Analogous between-patient comparisons in chronically-treated schizophrenics in the U.K. have shown a linear relationship between plasma level and dose, with a 50% increase in plasma levels for a 100% increase in dose above 25 mg. A three-fold increase in dose in the U.K. group, to the U.S.A. dose level, would probably have increased the plasma levels to more than twice those of the U.S.A. group. There is thus good reason to believe in a genuine difference between the two groups.

It is probable that this difference relates to a difference in gastrointestinal function, as it is basically a difference in the divergence of orally and parenterally-induced plasma levels, which is in turn a function of drug metabolism in the intestinal wall. It could be of course a bioavailability phenomenon, but such problems with chlorpromazine have not been

Table 1 Factors affecting drug response by influencing processes of absorption, tissue distribution, metabolism and excretion:

Route of administration
Dose
Food
Pharmaceutical formulation
Presence of other drugs
Motor activity (by affecting absorption)
Age
Sex
Pregnancy
Weight (including distribution and contributing components)
Pathology (especially liver and kidney disease)
Urinary pH
Certain mechanisms of tolerance
Plasma albumin
Geographical location

generally detected, even though they have been sought (Potter, 1971; Curry, 1974).

Plasma level studies in their own right

Plasma level studies are obviously of major importance in themselves, as they are the best means of investigating the persistence of drugs in the body, and of interspecies variations, as well as being important in the search for active metabolites, and in the study of dose-response relationships, tolerance and drug interactions. They are useful as a guide to suitable concentrations for *in vitro* studies of the mode of action of drugs.

In animals, plasma levels are a vital part of a neglected area of study of crucial importance in understanding the role of the plasma level as a determinant of drug response. This is the relationship between tissue levels and plasma levels. Figure 1 shows interesting data of a relevant type, again for chlorpromazine. The drug was given to rats intravenously in radioactive form. Note that the equilibrium concentration ratio between plasma and brain tissue for unmetabolized chlorpromazine was reached before any measurements were made. In general, brain concentrations of highly lipophilic foreign compounds change in parallel with plasma concentrations. This is a vital comment in relation to the interpretation of plasma levels, as it is the basis for the belief that plasma levels of centrally acting drugs *represent* (but do not necessarily *equal*) concentrations at receptors in the central nervous system.

The total radioactivity in this experiment declined more slowly, reflecting the formation of metabolites which persisted in body fluids longer than did unmetabolized chlorpromazine. However, the total radioactivity declined less slowly in brain than in plasma, reflecting the fact that some of the metabolites were too polar to cross the blood-brain barrier. This emphasizes the need for specific assay of a designated compound, a need which is not always recognized. Tissue and plasma levels have been studied in parallel

Figure 1 Concentrations (ng/g) of total radioactivity (S-35) and unmetabolized chlorpromazine (CPZ) in brain and plasma of rats given 10 mg/kg intravenously. Each point is the mean $\pm$ s.e. mean of four to six rats.

with some barbiturates and with diazepam, the general picture being analogous to that of Figure 1 (Brodie, 1952; Garattini, 1973).

In man, plasma levels are important in their own right as a means of basing dosage regimens on known

Table 2 Mean doses and plasma levels of unmetabolized chlorpromazine in two comparable groups of psychiatric patients studied in different geographical locations

Geographical location	Route of administration	Dose (mg)	Plasma levels (ng/ml) at times (h) following dosage						
			1/4	1/2	2	4	7	8	12
U.K. (Southall, Middlesex)	Oral	57.7	28	—	51	52	37	—	—
	Intramuscular	57.7	35	—	101	62	56	—	—
U.S.A. (Palo Alto, California)	Oral	316.7	—	38	42	55	—	46	31
	Intramuscular	89.6	—	64	61	76	—	53	57

Standard errors ranged from 6 to 25% of the mean values. Differences between the U.K. and U.S.A. doses reached statistical significance ($P < 0.05$) as did the oral intramuscular difference in the U.S.A. group ($P < 0.01$). Other comparisons failed to show statistical significance ($P > 0.05$).

pharmacokinetic data, and for the study of intersubject and intrasubject variations (Kruger Thieme, 1960). The scale of these intersubject pharmacokinetic variations is shown by the half-time of disappearance of N-desmethyldiazepam from plasma of six subjects, which varies from 13.2 to 32.4 h, and by many other studies.

Plasma levels as an adjunct to other pharmacological studies

Comparisons between available drugs. Drugs vary in their pharmacokinetic properties, and this usually affects pharmacodynamic properties. Table 3 shows the half-times of disappearance of various benzodiazepines from blood, together with their apparent volumes of distribution, in man. These values were derived from plasma level data (Garattini *et al.*, 1973).

The need to understand the relation between plasma levels and effect. This relation is complex. As one example, and in spite of comments made in the previous section, immediately following intravenous doses of barbiturates there is a brief period varying from a few seconds for thiopentone to an hour for phenobarbitone when the concentration declines in plasma and rises in brain. This is a good general model, although phenobarbitone is an extreme case. During this time, the effect increases while the concentration in plasma falls. Later, both effect and concentration fall in parallel.

Following oral and intramuscular doses, the most perfect relationship would be that of the model in Figure 2, where effect and concentration would rise together, peaking at the same time. Such a relation has been shown for the influence of glutethimide on reaction time (Curry *et al.*, 1971). However, some effects appear to be greatest on the ascending limb of the plasma level curve (Curry & Norris, 1970; Jones & Vega, 1972). This applies with depression of the ability to successfully follow a moving light ('smooth-tracking'), also by glutethimide, and to impairment of various functions by ethanol.

Table 3 Half-times of elimination ($T_{1/2}$) (h) and apparent volumes of distribution (V_d) (l/kg) of six benzodiazepine drugs

	$T_{1/2}$	V_d
Nitrazepam	20–25	1.25
Diazepam	25–30	1.6
N-Desmethyldiazepam	25–30	0.6
Chlordiazepoxide	10–15	0.26
Oxazepam	15–20	—
Demoxepam	35–40	0.4

Figure 2 Model relationship between plasma levels and effect for single dose treatment. The curve is of either drug concentration or effect against time.

Another possibility is development of the effect after the peak concentration is past. This relationship has been particularly noticed with anticoagulant drugs (Nagashima, O'Reilly & Levy, 1969). With some compounds, it is possible to measure an effect only once within any one dosage period, so that the best data that can be obtained are of incidence of an effect in a population. This appears to have been the case so far with the hypnosedative effect of diazepam (Garattini, 1969).

Multiple dosing adds to the complexity of the relation. The model relationship would be that of Figure 3 where effect and concentration would vary together, each with a series of peaks and troughs, one for each dosage period. Variations on this theme would result from changes in effect being less sensitive than might be predicted to changes in concentration, as with antischizophrenic drugs, from the effect occurring only during the early stages of treatment, as with sedation to phenobarbitone, or from the effect developing more slowly than did the elevated plasma levels as might happen with almost any behavioural study. Interestingly, something approaching a model multiple dose relationship apparently occurs with lithium toxicity (Fry & Marks, 1971).

Generally speaking, in addition to the points raised above, it must be remembered that (a) dose-response relationships are not necessarily *linear*, so that a *linear* relationship between plasma level and response should not be expected; (b) many drugs are given prophylactically, so no graded measure of response is available, and the effect can only be assessed in terms of episodes of successful treatment; (c) development of pharmacodynamic tolerance will modify dose-effect and therefore concentration-effect relationships; (d) enzyme induction (drug metabolic tolerance) will modify concentration-dose relationships; (e) normal dose-response relationships do not always prevail with

Figure 3 Model relationship of the type in Figure 2, for multiple dose treatment. The dashed line following the fifth dose interval represents decline when the fifth dose is the last one.

psychotropic drugs, in that some patients respond to placebo, and there is often no dose at which all patients respond; (f) there are some cases, such as reserpine and perhaps monoamine oxidase inhibitors, for which a direct plasma level effect relation should not be expected on pharmacodynamic, chemical or biochemical grounds; and (g) some effects are especially complex; for example in toxicity studies it has been noted that although peak plasma levels and peak depressant effects following lethal doses of phenobarbitone occur in mice at about 1 h after an intraperitoneal dose, death occurs at 6–8 h, when the concentrations have declined, possibly because of the lesser but prolonged depression in the 5–7 h which follow the peak level at 1 hour.

Importance of longitudinal studies. The relation between effects of psychotropic drugs and their plasma levels sometimes appears to change with time. This, again, is shown with chlorpromazine. In the first 8 days following initiation of a fixed dose regimen, the plasma level pattern is of the model type shown in Figure 3. However, from the eighth to the thirty-sixth day a steady decline in the overall level is seen, although there is still the expected rise and fall during each individual dosage period (Sakalis *et al.*, 1972).

Without necessarily quite knowing why, the psychiatrist tends to increase the dose during this time, so that the plasma level may stay elevated, but at a higher dose level. The plasma level yield per unit of dose has become less. This results from an increased rate of chlorpromazine metabolism caused by enzyme induction. The plasma level yield per unit of dose stays approximately constant from the thirty-sixth day onwards. Figure 4 shows plasma level data in three groups of subjects, one group given single 100 mg

doses orally and by intramuscular injection, one group treated for 36 days with about 100 mg three times a day, and sampled during a single dosage period on the thirty-sixth day, and one group treated for about 2 years with about 100 mg three times a day, and studied during a single 100 mg oral dosage period, and during one period in which the dose was 100 mg by intramuscular injection. In the middle group, the levels rose to the 80–120 ng/ml range by the eighth day.

As mentioned earlier, the oral–intramuscular divergence in plasma levels of chlorpromazine is caused by metabolism of the orally administered drug to inactive materials in the intestinal wall.

While the overall levels of chlorpromazine in plasma are rising and falling during the first 36 days, the patients show a response, so that for 8 days improvement occurs while the levels are rising, while improvement is inversely related to level on days 9–36. Later on, with a more-or-less steady level, improvement continues.

Various possible explanations for this complex relationship come to mind. First, there is the conventional active metabolite theory, but studies of chlorpromazine metabolites in plasma have been relatively unsuccessful. The demethylated compounds are only present in quite small quantities. Chlorpromazine sulphoxide is present but it is inactive, and a search for hydroxylated metabolites in plasma of acutely treated responding schizophrenics has been unsuccessful, although 7-hydroxychlorpromazine has been found in long-term patients. Additionally, while chlorpromazine metabolites have pharmacological activity in animals and *in vitro*, it does not exceed that of the parent drug (Buckley *et al.*, 1973; Miller & Iverson, 1974). Concentrations higher than those of the parent drug would therefore be needed if the

Figure 4 Mean concentrations of chlorpromazine in groups of 10 male patients treated with 100 mg single doses, with 100 mg three times a day for 6 weeks, and for about 2 years, tested during conventional oral dosage periods (●—●) and after 100 mg intramuscular test doses in place of oral doses on isolated occasions (●---●).

metabolites were to make a major contribution to the chlorpromazine effect.

The second idea is that receptors for chlorpromazine might be located in some remote pharmacokinetic compartment, such that the active molecules are lost only slowly when residues are cleared from the rest of the body. This is not very likely, as the brain, in which the receptors must lie, is a highly vascular tissue, and remote pharmacokinetic compartments are usually in tissues with relatively poor blood supplies.

A third idea is that chlorpromazine is stored in sites in fat and muscle from which it is released slowly to receptors in brain and plasma before being metabolized or excreted. This storage undoubtedly happens, and the theory that is important in the quantitative relationships is quite plausible, although a very wide plasma level range for a similar effect has to be postulated to accommodate all known data in this theory.

Figure 5 shows mean plasma levels in a group of 20 patients treated with a stabilized dosage regimen for 4 weeks, before receiving 50% of their dose for 2 weeks, and then placebo (0%) for 10 weeks (Pigache & Curry, 1974, unpublished). Samples were taken at a fixed time, corresponding to the time of the peak in the model fluctuating pattern of Figure 3, at fortnightly intervals. Once placebo was established, the concentration settled to a level corresponding to the trough of the fluctuating pattern, but this level was maintained for a very long time, without further dosage.

This is taken as evidence of very slow loss of chlorpromazine from stores, and consequent very slow loss of the drug from the body by metabolism and excretion, which leads to constant bathing of receptors with a small amount of unmetabolized chlorpromazine over a long period of time. The importance of this metabolism and excretion is confirmed by Figure 6, which shows the excretion rate of mixed ether-extractable metabolites in the same group of people. These measurements, too, showed a fixed pattern during dosage with a 90% drop on introduction of placebo. This probably indicates a reduction in the metabolites in the body by 90% at the same time, as the rate of excretion of metabolites is dependent on the amount present in the body, as 'substrates' for excretion. In the weeks following cessation of dosage we see the loss of unchanged drug from the stores to plasma, and its metabolism and excretion in urine.

However, patients do not, of course, relapse immediately dosing stops, even though the drug concentration drops dramatically (Leff & Wing, 1971). I therefore feel the need to put forward a fourth idea, that in the first 8–15 days of treatment, acute schizophrenics require the high concentrations of chlorpromazine which they obtain from the early, relatively small doses. Later on, they have the same concentrations from higher doses, or lower concentrations from the same doses, and if the drug is withdrawn, they maintain a low concentration from no dosage. The later, lower concentrations may be sufficient to maintain in reverse a vicious circle of pathology

Figure 5 Concentrations of chlorpromazine in plasma of schizophrenics at the end of two fortnights of fixed dosage, one fortnight of 50% dosage, and five fortnights of placebo treatment (0%). Data are means of determination from 15–20 patients $\pm$ s.e. mean.

originally put into reverse by the earlier, higher, concentrations. In some circumstances, behavioural and environmental factors might change sufficiently during treatment to permit this improvement to be permanent, even though the final drug residue might be lost. In other cases, relapse might occur at this final stage. This idea is, of course, heresy in terms of standard pharmacological theory, but I would imagine that it is a theory to delight the behavioural therapists. I use it to illustrate the importance of longitudinal studies.

Fallacy of 'steady-state'. The study of so-called 'steady-state' drug concentrations has been popularized in recent years (Davies & Prichard, 1973). The idea is that the drug increases in its concentrations in body fluids until a state is reached in which input (by dosing) equals output (by metabolism and excretion), with an unchanging concentration in the body fluids. The multiple dosing model in Figure 3 shows the fallacy of this. With a fixed dose regimen, the overall concentration rises steadily, but it becomes unchanging only at infinity, a time never reached in therapeutics. Even at infinity, there would still be a rise and fall within each dosage interval. About 90% of the infinity pattern would, of course, be reached after about four half-times of drug elimination, but the so-called 'steady-state' remains at best a pseudo-steady-state, incorporating fluctuation.

It might be thought that the degree of fluctuation would be trivial, but this is only so with those drugs with the longest half-times, or for drugs with unusually low absorption rate constants. As an example, for a drug which is largely absorbed in 3 h during thrice daily administration, with a half-time of 15–16 h, the rise in concentration after each dose will be about 50% of the pre-dosage level. Interestingly, this is approx-

Figure 6 Excretion rates of ether-extractable chlorpromazine metabolites in the urine of the patients of Figure 5. Data are means of determinations from 15–20 patients $\pm$ s.e. mean.

imately the pattern seen with lithium, and it represents a substantial rise and fall between the commonly quoted limits of 0.8 and 1.5 mEq/l for therapeutic effect and toxicity respectively. In such a case, the observed plasma level effect relationship will be heavily dependent on the time of collection of blood samples, and any between-patient correlations will be obscured, unless these changes in the concentrations during the pseudo-steady-state are carefully taken into account.

Diurnal variation. One form of diurnal variation is the fluctuation in plasma levels just discussed. In addition, it should be remembered that pharmacokinetic phenomena can, at least theoretically, exhibit considerable degrees of variation within each 24-h period. For example, the rate of absorption of a particular drug might vary with the time of the day. This would add a daily fluctuation to the dose-by-dose fluctuation pattern. Moreover, pharmacodynamic sensitivity can change within each 24-h period, so that a given dose or plasma level can induce various levels of effect depending on the time of day. The most obvious manifestation of this is the fact that a dose of a hypnotic sufficient to efficiently induce sleep, when taken at 10 pm, may be no more than mildly sedative when taken at 10 am, by a person pursuing a conventional daily timetable. The importance of this for sedatives and tranquillizers could be considerable, but systematic study in this area appears not to have been attempted.

Within patient and between patient comparisons. If a plasma level measurement obtained in con-

Figure 7 Effect of N-desmethyldiazepam (nordiazepam) as a function of its concentration in plasma in five patients treated with placebo (●), diazepam (▲), and clorazepate (○). Psychopathology was assessed by means of the Symptom Rating Test (SRT score). A reduction in the score indicated improvement.

junction with a pharmacodynamic observation is to be properly interpreted, it is essential to appreciate that a clear-cut relationship seen within each individual will not necessarily manifest itself as a relationship across the population. I have examined this with various benzodiazepines. In the experiment, a series of severely anxious relapsing out-patients were entered into a clinical trial comparing placebo, diazepam, and clorazepate in a protocol calling for 2 weeks' treatment with each material, in random order, on a double-blind cross-over basis (Robin, Curry & Whelpton, 1974).

Anxiety was assessed before starting and at the end of each fortnight by means of the Symptom Rating Test of Kellner and Sheffield, in which a reduced score indicated improvement. Drug analysis was for diazepam and N-desmethyldiazepam, in single samples collected at a fixed time on the day of rating. The total drug material in plasma was similar following the two drug treatments, but following diazepam it comprised two-thirds diazepam and one-third N-desmethyldiazepam, while following clorazepate it was all N-desmethyldiazepam. In each subject, a near-perfect inverse relationship between rating and N-desmethyldiazepam concentration was observed. A selection from the data is shown in Figure 7.

However, a variety of readings and changes in reading were compared with the N-desmethyldiazepam concentrations and with the changes in these concentrations in a between-patient correlation study, and among seven relationships tested only one reached significance at the 5% level (Table 4). Thus although a

clear-cut relationship was observed, it was not possible to define a clinically desirable concentration range.

Clinical trials. There are several aspects to the use of plasma level determinations in clinical trials (Curry, 1970). First, there is the purely forensic and very obvious application in detecting the efficiency of consumption of prescribed medicines, but no scientist with any pretensions to original thought will waste his time working on such a purely technical endeavour. Second, there is the detection of carry-over of drug residues from one treatment period into another, or into a placebo period, which could greatly affect the data obtained from a second or later treatment in a crossover trial. The third, and most scientifically satisfying, application would be in attempting to narrow the limits of measurements in clinical trial assessments, in those cases where the limits are a function of within-patient or between-patient variations in pharmacokinetic phenomena.

Table 4 Spearman rank correlation coefficients (r_s) with an estimate of statistical significance (P) for various between-patient comparisons using the data of Figure 7

Comparison	r_s	P
SRT score against nordiazepam concentration at end of clorazepate treatment fortnight	-0.30	>0.05
SRT score against nordiazepam concentration at end of diazepam treatment fortnight	-0.02	>0.05
Difference in SRT scores at end of placebo and clorazepate treatment fortnights against nordiazepam concentration	0.40	>0.05
Difference in SRT scores at end of placebo and diazepam treatment fortnights against nordiazepam concentration	0.78	>0.05
Difference in SRT scores at end of placebo and clorazepate treatment fortnights against difference in nordiazepam concentrations at similar times	0.70	>0.05
Difference in SRT scores at end of placebo and diazepam treatment fortnights against difference in nordiazepam concentrations at similar times	0.90	0.05
Difference in SRT scores at end of clorazepate and diazepam treatment fortnights against difference in nordiazepam concentrations at similar times	0.05	>0.05

As far as I know, this has not yet been attempted, although the benzodiazepine trial mentioned earlier provides a model for an attempt. To put the idea into practice it would probably be necessary to design a trial comparing two doses of each drug under test. This would be no bad thing in a great many trials, as information that one drug is more potent than another is virtually useless without some information as to the maximum obtainable effect from each drug, which is a slightly different but highly relevant comparison. The study of two dose levels in each case would be a step towards satisfying this need, but pharmacokinetic variations would ensure that the variation in response at each dose level of each drug would be great.

A more useful way of presenting data might be as effect against plasma level (or log. plasma level) of each drug, so that for each compound there would be a good chance of spotting the plasma level at which the maximum effect was obtained, together with a graded series of additional points lower down from which a reasonable potency comparison might be made. It is true of course that such an approach might be frustrated by the between-patient variation discussed earlier, but it would be refreshing to see a trial designed as an attempt to take into account, and attempt to allow for, pharmacokinetic influences on this scale.

Drug toxicity. Studies of drowsiness following diazepam, and unwanted effects of lithium, have shown conclusively that, regardless of the implications of plasma levels for therapeutic outcome, incidents of toxicity are often related to plasma levels, and that elimination of such incidents is often possible if pharmacokinetic factors are considered.

The importance of drug metabolites. Some drugs exert their effects through pharmacologically active metabolites. It is obvious that any plasma level assessment must include separate measurement of such materials. However, even inactive metabolites have importance as indicators of drug consumption, in that, increasingly, it is noted that drugs are metabolized in the intestinal wall or portal circulation before they even reach the general circulation. A plasma level determination of unmetabolized drug may imply a lack of tablet-taking efficiency by the patient, or poor absorption of consumed drug, while measurements of metabolites, active or inactive, will give a truer picture of what is happening. Of course, as

mentioned before relationships with effect must only concern active materials.

Hangover and rebound. Sleep studies have shown various effects on various types of sleep depending on the dose of hypnotic drugs, and depending on the time elapsed after fixed doses (Oswald & Priest, 1965; Kupfer *et al.*, 1971). Hangover effects of nitrazepam have been shown during the day following single hypnotic doses, even when plasma levels have dropped quite low (Malpas *et al.*, 1970). Thus the stage at which a plasma level effect relationship study is conducted can be fundamental to the type of relationship observed.

Importance of drug interactions. Any relationship between drug response and drug concentration will be complicated if more than one drug is involved, as the two drugs, pharmacologically speaking, may be antagonistic, additive, or mutually potentiating, with no effects on their respective concentrations. If the concentrations are themselves affected, the problem will involve new dimensions of complexity.

General observations

In this paper I have attempted to present the rationale for the belief that an added degree of sophistication is added to psychotropic drug evaluation when the concentrations of pharmacologically active molecules present in plasma are considered. I have also discussed some of the difficulties and pitfalls involved in the relevant studies.

The general philosophy involved has met a remarkable amount of resistance in recent years. In spite of the fact that the importance of dose-response relationships is generally accepted, and that there is a predictable dose-concentration relationship, many people have experienced difficulty in believing in a concentration-response relationship. However, it is true to say that with almost all pharmacodynamic phenomena, higher doses will lead to more drug in plasma and to more effect. It is the sophisticated variants on this theme that makes the study of the relationship between pharmacokinetics and pharmacodynamics at one and the same time an exciting field of research, and an avenue of exploration of sufficient complexity to deserve the attention of specialist investigators.

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