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PHARMACOKINETICS OF DRUG ACTION

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Gerhard Levy and Milo Gibaldi

Department of Pharmaceutics, State University of New York at Buffalo, Buffalo, New York

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This is a review of the literature since 1960 on the kinetics of reversible pharmacologic effects in intact animals including man. No claim is made that this is a complete survey. It is practically impossible to conduct an effective literature search on the pharmacokinetics of drug action, since titles of papers and index terms do not usually indicate that the investigations are concerned with the time course of pharmacologic effects in relation to dose or drug concentrations. The kinetics of drug absorption, distribution, and elimination are not included in this review. The literature in this field has been reviewed only recently (1) and this subject has been dealt with in a number of recently published books (2–4). This review will consist of four sections. These will summarize the literature on the relationship between drug concentration and pharmacologic effect, the kinetics of drug action in cases where the body can be characterized as a single compartment, the kinetics of drug action when the body acts as a multi-compartment system, and the kinetics of indirect pharmacologic effects. While there has been some theoretical work on these subjects before 1960, most of the experimental studies and the quantitative correlations between the time course of drug levels in the body and the time course of pharmacologic effects have been carried out since then. These investigations were made possible largely by the extensive progress in analytical and computational methodology as well as in the ability to quantitate certain pharmacologic effects in animals and man.

Drug Concentration and Pharmacologic Effect

The concept of a direct and rapidly reversible pharmacologic effect implies that a given intensity of effect is associated with a particular drug concentration at the site of action. Consequently, there is likely to be a corresponding relationship between the intensity of a pharmacologic effect and the post-distributive concentration of drug in plasma or serum. For example, in studies of individual differences in the effect of drugs in relation to drug concentration in tissues of rats, it has been found that the duration of narcosis produced by a constant dose of pentobarbital sodium differed widely in different rats. However the concentrations of pentobarbital in the brain and serum of these rats upon awakening showed no such differences

and were essentially independent of the duration of effect (5, 6). This was also found with zoxazolamine which produced paralysis lasting from about 100 to 800 minutes under the experimental conditions at a dose of 110 mg/Kg intraperitoneally. Plots of zoxazolamine concentrations in the serum or brain at the time of recovery versus duration of paralysis were essentially horizontal, indicating that the rats eliminated the drug at widely different rates but that the minimum effective concentrations were practically constant (5). Similar effects have been noted under clinical conditions; patients with digoxin intoxication had a mean serum digoxin concentration (±S.D.) of 3.7 (±1.0) ng/ml while nontoxic patients had a mean digoxin concentration of only 1.4 (±0.7) ng/ml (7). There was no significant difference in the mean daily dose, which was 0.36 (±0.19) mg/day for the intoxicated patients and 0.31 (±0.19) mg/day for the nontoxic group, indicating that the toxic effect was due to differences in either absorption or elimination of the drug. A similar relationship between adverse effects and blood levels has been noted in the case of diphenylhydantoin (8).

There are a number of studies that show a semiquantitative correspondence between the time course of pharmacologic effects and the time course of drug levels in the body. The self-estimated degree of intoxication from three different doses of ethanol showed a close relationship with corresponding blood level curves as a function of time (9). The change in heart rate of dogs after oral and intravenous administration of disopyramide phosphate was found to be linearly related to the logarithm of plasma concentration irrespective of the route of administration (10). The decline of the pharmacologic response to propranolol in man following intravenous administration approximately parallels the decline of propranolol concentration in the plasma (11). Four different dosage forms of pentagastrin for subcutaneous injection showed significant differences in in vitro release rates, biliary excretion rates in the rat as a function of time, and in pharmacologic response (secretion of gastric acid) in dogs. There was good agreement between the in vitro data, elimination rate, and pharmacologic effect data (12).

Concurrent determinations of drug levels in the body and pharmacologic activity have been useful in determining whether a drug possesses intrinsic activity or whether this is due to a metabolite. Inhibition of the biotransformation of acetophenetidin to N-acetyl-p-aminophenol in rats by administration of SKF 525-A increased antipyretic activity, while stimulation of the biotransformation process by treatment with 3-methylcholanthrene decreased the antipyretic effect (13). N-acetyl-p-aminophenol does have antipyretic activity of its own (14), but acetophenetidin is apparently more potent. The plasma propranolol concentrations associated with a given degree of blockade of exercise-induced tachycardia were about three times higher after intravenous administration than after oral administration. This suggested the presence of a pharmacologically active metabolite of propranolol

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which is apparently formed only when the drug is administered by mouth (15).

It is sometimes feasible to establish the relationship between the intensity of the pharmacologic effect at a given time after drug administration and the intravenously administered dose over a wide dose range. Intravenous administration of tropicamide to rabbits resulted in rapid appearance of the maximum mydriatic response (16). The effect-dose relationship thus obtained was used as a "reference curve" to determine from pharmacologic effect measurements the time course of drug levels at the site of action under different conditions of drug administration. If the drug distributes practically instantaneously between plasma and the site of action (i.e., plasma and site of action are in the same pharmacokinetic compartment) then the time course of drug levels thus determined reflects also the time course of drug concentrations in the plasma. It has been proposed that the extent of absorption (bioavailability) of a drug administered by routes other than intravenous can be determined from pharmacologic effect data on the basis of the relationship between intensity of effect at a given time and the intravenous dose (16). This presumes however, that there is no apparent minimum effective intravenous dose and that the effect-dose "reference curve" clearly goes through the origin. The practically instantaneous attainment of mydriatic effects after intravenous administration of tropicamide indicated that the site of action of that drug is in the same apparent pharmacokinetic compartment as the plasma. On the other hand, the maximum mydriatic response to tridihexethyl chloride in rabbits occurred some time after intravenous injection, suggesting that with this drug the plasma and site of action are in different compartments (17). The "reference curve" technique was used to determine the rate of access of drug to the biophase and the extent of drug absorption under different experimental conditions but no direct (chemical) determinations were made to verify the bioavailability estimates.

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Single Compartment Kinetics

Pharmacokinetics deals in part with the mathematical description of the time course of drug absorption, distribution, and elimination by means of suitable models. Depending on the drug, the available experimental data, and the purpose for the pharmacokinetic characterization, such models represent the body as a system of one or more apparent compartments. If a drug distributes very rapidly in the body it is usually convenient and feasible to apply single compartment models. Implicit in this pharmacokinetic approach is the assumption that a change in drug concentration in any one tissue (including the site of action) is accompanied by a corresponding change in drug concentration in all other tissues (including the plasma) at the same time. This section will deal with the effects of drugs that have single compartment characteristics.

The process of drug elimination from the body is often describable by first-order kinetics. The intensity of a direct and reversible pharmacologic effect is in many instances approximately linearly related to the logarithm of the concentration or amount of drug in the body. This linear relationship holds reasonably well from at least 20 to 80 percent of the maximum attainable intensity of effect and is therefore applicable particularly under clinical conditions. It has been shown that the intensity of effect of drugs with these elimination and dose-effect characteristics decreases at an essentially constant rate after intravenous injection (18). That rate is equal to $k \cdot m/2.303$ where k is the apparent first-order rate constant for drug elimination and m is the slope of a plot of intensity of effect versus the logarithm of the dose or plasma concentration. A number of examples of such essentially linear decline of effect with time have been noted including the locomotor activity of rats given dextroamphetamine and pseudonorephedrine (19), the inhibitory effect of warfarin on the synthesis of clotting factors in man (20), and the neuromuscular blocking effect of tubocurarine in man (21). As will be noted in the next section, tubocurarine is not a "one-compartment" drug but the decline of drug levels in the first fifteen minutes after intravenous injection is practically monoexponential (22), and therefore one observes an essentially linear decline of effect during this time. It has been pointed out that the averaging of sets of linear data of intensity of effect versus time will result in a curvilinear plot when zero effect values are included (9). Such curves can be mistakenly interpreted as being monoexponential.

There are instances where the intensity of a pharmacologic effect is apparently linearly related to drug concentration rather than to the logarithm of drug concentration. The time courses of pharmacologic effects and drug concentration will be parallel in such case. There is an essentially linear relationship between performance decrement determined by means of a number facility test, a time estimation test, and an eye-hand coordination test, respectively, and the concentration of ethanol in the serum of normal human subjects (23). The slopes of plots of each of these effects against ethanol concentration in the serum are the same, but intercepts on the concentration axes differ appreciably. The ethanol concentrations in the serum as a function of time after ethanol administration and the performance decrements decline in parallel (23). There is a linear relationship between urine flow rate and the excretion rate of ^{203}Hg following subcutaneous injection of ^{203}Hg mercaptomerin sodium, which extrapolates to the normal flow rate of approximately 1 ml/min (24). The intensity of the anticoagulant effect of ^{35}S-labelled sodium heparin in dogs as a function of time parallels the isotope concentration in the plasma, suggesting a linear relationship between heparin concentration and clotting time (25). A more direct indication of this linear relationship has been obtained by determining the clotting time of blood to which various amounts of heparin were added in vitro (26). It has also been found that there is a linear relationship between the maximum extrapolated clotting time in human subjects after intrave-

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nous injection of heparin and the dose of that anticoagulant (27). As a consequence of this linear relationship and of the elimination of heparin by apparent first-order kinetics there occurs a monoexponential decay in clotting time after intravenous injection of heparin in man (27).

It has been found empirically that the decline of pharmacologic activity of a number of drugs is describable by apparent first-order kinetics some time after drug administration. Examples are the mydriatic effect of an anticholinergic agent in mice (28), the pyretogenic effect of d-lysergic acid diethylamide and of d-lysergic acid morpholide in rabbits (29), the antisialogogue effect of tincture of belladonna in man (29), and the heart rate increase after intravenous injection of isoproterenol in dogs (30). The area under the effect versus time curve for mydriasis in mice has been used as a measure of "total drug effectiveness," which in turn was taken as an index of absorption efficiency of oral and subcutaneous doses (28). However, this approach is valid only if there is a linear relationship between the amount of drug in the body and the intensity of effect, and if the elimination kinetics are dose-independent. The pharmacokinetic characteristics of the sympathomimetic effect of isoproterenol in dogs, as reflected by the increase in heart rate, are difficult to interpret. The heart rate effect decreases by apparent first-order kinetics with a half-life of about one minute after intravenous administration, and there is a linear relationship between maximum effect and the logarithm of the dose (30). In other experiments, the steady-state quantities of isoproterenol in the dog during intravenous infusion of the drug at various rates were calculated on the basis of the known rates of infusion and the rate constant for disappearance of the *pharmacologic effect* (30). This data treatment should be valid only if the half-life for the decay of effect equals the half-life of elimination of the drug from the body. The linear relationship between effect and the *logarithm* of dose indicates that this assumption is incorrect, but the results of the calculations are in fact internally consistent in that the relationship between effect and logarithm of the amount of isoproterenol in the body is the same for the single injected doses and for the amounts of drug maintained in the body by constant rates of intravenous infusion (30).

As explained in the previous paragraphs, the shape of the decay curve of pharmacologic effect after intravenous administration of a drug depends on the relationship between effect and drug concentration. Based on classical receptor theory (31) it has been shown that a plot of the logarithm of $R/(R_M - R)$ versus the logarithm of concentration should be linear where R is the intensity of the pharmacologic effect and R_M is the maximum attainable intensity of that effect (32). From this relationship and the assumption that drug is eliminated from the body by apparent first-order kinetics, it has been shown by theoretical calculations that the intensity of the pharmacologic effect after intravenous injection declines in nearly linear fashion in the 20 to 80 percent effect region, but that the total decay curve (i.e., from 100 to 0 percent) has a sigmoid shape (32). The same type of effect decay curve is

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predicted for inhibitory effects by assuming (*a*) that the decrease in the intensity of an effect is proportional to the product of the intensity of that effect and the change in drug concentration, and (*b*) that drug concentration decreases by apparent first-order kinetics (33). This pharmacokinetic approach has been used to describe the time course of the antisialagogue effect of hyoscyamine administered to human subjects in ordinary and sustained-release tablets (34).

Various techniques have been employed to estimate the elimination rate constant of drugs from pharmacologic activity measurements. The rate constant for elimination of atropine in rabbits has been estimated from the constant infusion rate of atropine necessary to maintain the parasympatholytic effect of an initial rapidly injected dose (35). In a single compartment system the rate of infusion (r) required to maintain the effect of a rapidly injected dose (D) is equal to $k \cdot D$. The rate constant for drug elimination (k) can therefore be determined from r and D. Another method of estimating k is to administer a given dose of drug repeatedly at equal intervals until a defined pharmacologic effect is obtained. It is assumed that the appearance of this effect reflects the attainment of a certain amount of drug in the body. That amount is determined by single dose studies. This method has been used to estimate the elimination rate constants of digoxin and acetyldigoxin in cats (36). Assuming a hyperbolic relationship between effect (R) and drug concentration, and elimination of the drug by apparent first-order kinetics, it has been shown that a plot of log $R/(R_T - R)$ versus time should be linear where R_T is the maximum response at infinite drug concentration (37). The slope of that line is $-k/2.303$ where k is the apparent first-order rate constant for drug elimination.

It has been pointed out that a linear relationship may be expected between the duration of a pharmacologic effect and the logarithm of an injected or a relatively rapidly absorbed dose of a drug, provided that (*a*) the intensity of the effect at a given time is a function of the amount of drug in the body at that time, (*b*) drug metabolites are inactive or very rapidly eliminated, and (*c*) the drug is eliminated by apparent first-order kinetics with the rate constant being independent of dose (21, 38, 39). The slope of the line of a plot of duration of effect versus logarithm of dose is equal to $2.303/k$ and thereby permits an estimation of the elimination rate constant (k). This linear relationship has been demonstrated with respect to the hypnotic effect of glutethimide and diallyl-barbituric acid in human subjects who took toxic doses of these drugs (38), the anorexigenic effect of dextroamphetamine sulfate in dogs (40), the general anesthetic effect of ketamine in human subjects (21), the general anesthetic effect of phencyclidine and pentobarbital in monkeys (21), the neuromuscular blocking effect of succinylcholine in man (41), and the anticoagulant effect of heparin in man (26). In the case of succinylcholine and heparin it has been possible to estimate elimination rate constants not only from the duration-log dose rela-

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tionship, but also from the rate of decline of the effect following administration of a single dose (26, 41). The agreement between these two estimates is very good. A linear relationship has also been demonstrated between the duration of local anesthesia and the logarithm of drug concentration or dose (42). For example, such relationships were obtained with respect to the durations of sciatic nerve block in rats and guinea pigs, peridural anesthesia in cats, and corneal anesthesia in rabbits produced by lidocaine and other local anesthetics (43). The slope of the duration-log dose line reflects in these cases the rate constant for removal of drug from the site of action to the general circulation, which acts as an infinite sink.

It has been found that some drugs under certain conditions yield an apparently linear relationship between the *logarithm* of the duration of effect and the logarithm of dose (44). In the case of the effect of hexobarbital in mice it has been demonstrated that this relationship could be rationalized mathematically due to the fact that the elimination rate constant of the drug decreased with increasing dose while the drug concentration in the brain on awakening increased with increasing dose (44). In another study, the relationship between sleeping time and hexobarbital dose in mice was apparently linear in a linear-log plot despite the fact that drug elimination and drug concentration in the brain on awakening were also found to be dose dependent (45). This may have been due to the relatively narrow dose range employed in the study. However, inhibition of drug elimination by pre-treatment with SKF 525A and stimulation of drug elimination by pretreatment with phenobarbital increased and decreased, respectively, the slope of the duration-log dose curve in accordance with theory.

Some consideration has been given to the effect of additional doses administered immediately after cessation of the effect of an initial dose. If drug elimination is apparent first-order, and a certain minimum amount in the body is required to maintain a measurable pharmacologic effect, then the maximum intensity and duration of effect of a second and equal dose administered upon recovery from the effect of the first dose will be greater (21, 46). This is due to the fact that the second dose is superimposed upon the minimum effective amount of drug remaining in the body from the first dose. Third and subsequent equal doses elicit the same intensity and duration of effect as the second dose. The smaller the initial dose, the larger is the increase in effect of second and subsequent doses (21, 46). Since duration of effect is inversely proportional to the elimination rate constant (k) while the rate of decline of an effect after intravenous injection is frequently directly proportional to k, the product of duration and that rate of decline of effect will be independent of the elimination rate constant. Based on these considerations, it has been determined that the longer duration of the neuromuscular blocking effect of succinylcholine in a group of patients in New York relative to the duration of effect in groups of patients in London and Los Angeles is due to slower elimination of the drug from its site

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of action in the New York patients (47). The same pharmacokinetic approach has been used to analyze pronounced inter-subject differences in the effect of succinylcholine in newborn infants (48).

A number of authors have considered the relationship between dose and the total effect of a drug. The total effect has been expressed as the time integral of the response curve over given limits, and the concept of an index of persistence has been developed for the expression of drug potency (49). The relative pharmacologic activity of a drug (i.e., the total area under the effect-time curve divided by the dose) usually changes as a function of dose. This is due to the nonlinear relation between amount of drug in the body and intensity of effect. The relative pharmacologic activity of isoproterenol on the heart rate of dogs increased when the same dose was infused rather than injected rapidly. Decreasing the infusion rate increased the relative pharmacologic activity under the experimental conditions (30). Similarly, the diuretic effect of a constant daily dose of chlorothiazide in human subjects increased when the dose was administered in divided increments (50). The most pronounced increase in total effect was obtained in going from a single daily dose to two doses a day; further increases in effect were obtained when the daily dose was administered in four and eight daily increments. These experimental findings have been rationalized theoretically and it has also been pointed out on theoretical grounds that the increase in total effect obtained by subdividing daily doses is most pronounced with drugs that are rapidly eliminated from the body (32).

The product of concentration and time has been used as an index of the toxicity of drugs in animals exposed to a constant concentration of the drug until the appearance of a toxic effect. It has been shown that constant concentration-time values can be obtained over a wide drug concentration range under certain conditions when fish are immersed in a drug solution (51). This requires that drug absorption proceeds by passive diffusion, that the pharmacologically effective drug concentration in the fish is negligible relative to the drug concentration in the bathing fluid, and that drug elimination from the body of the animal is negligible during the time required to elicit the effect. Under these conditions a plot of the reciprocal of the time of onset of effect is linearly related to the drug concentration in the bathing solution. The slope of that line (and therefore the product of concentration and time) is not only a function of the intrinsic potency or toxicity of the drug but also of its absorption rate constant (51, 52). These relationships have been used to determine the absorption rate constants of different barbiturates (52), the relationship between pH and absorption rate of a weak acid (51), and the effect of complex formation on drug absorption (53). Linear relationships between the reciprocal of the time of onset of pharmacologic effect (usually death) in fish and concentration in the bathing fluid have been demonstrated for many substances including pesticides, and anti-inflammatory, choleretic, and central nervous system depressant agents (51, 54). A method has also been developed to determine the elimination rate

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constant of drugs in fish based on exposure time to a drug solution and the time of recovery after the fish have been transferred to a drug-free medium (55). A linear relationship between the logarithm of overturn time and the logarithm of concentration has been found with goldfish exposed to ethanol. A suitable equation to describe this relationship has been developed by combining occupation and rate receptor theories (56). Apparently the site of action is instantaneously accessible to ethanol so that absorption rate does not influence the onset of effect.

The linear relationship between the reciprocal of the time of onset of effect and concentration is most pertinent to the effects elicited in animals exposed to relatively high drug concentrations in the atmosphere or in an aquatic environment, but this relationship can also be used to determine the gastrointestinal absorption rate of drugs if the doses are relatively large and drug elimination is negligible during the test period (21). Another means of determining gastrointestinal absorption rate constants is applicable when drug elimination is very rapid as compared to absorption. A plot of duration of effect versus logarithm of dose will be linear under these conditions and the slope is inversely proportional to the absorption rate constant rather than to the elimination rate constant as described in a previous paragraph (21, 30).

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Multicompartment Kinetics

Pharmacokinetic studies in recent years have shown that the elimination of many drugs after intravenous injection is not a simple monoexponential process. A plot of the logarithm of drug concentration in the plasma against time often shows a rather steep decline at first, followed by a less rapid linear phase. This is usually an indication that the drug distributes initially into relatively slowly accessible tissues and that the body acts as a multicompartment system with respect to that drug. Pharmacokinetic models consisting of a "central" compartment (which includes the blood plasma) and one or more peripheral ("tissue") compartments are often useful for describing the pharmacokinetics of such drugs. The time course of pharmacologic effects may be related to the drug concentrations in any one of these compartments. The central nervous system depressant effect of sodium pentobarbital in rats has been found to correlate well with drug concentrations in the brain but not with those in the blood (57). The onset and duration of general anesthesia in rats receiving gamma-butyrolactone did not correlate with the concentrations of this compound and its metabolite, gamma-hydroxybutyric acid (GHB), in the blood, but the animals fell asleep and awakened at approximately the same concentrations of GHB in the brain (58). Concentrations of digitoxin and digoxin in the plasma following intravenous administration to man showed a pronounced initial distributive phase, and the maximum cardiac response occurred near the end of this phase, showing that the myocardial tissue is outside the central compartment (59).

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If the site of drug action is part of the central compartment, then the duration of action is sometimes primarily a function of the rate of distribution of the drug into peripheral tissues. Inhibition of thiopental metabolism in dogs and rats by SKF-525A has no apparent effect on the sleeping time produced by the barbiturate, indicating that hepatic metabolism is not important in the termination of the general anesthetic effect (60). Extensive analog simulations have been carried out to analyze theoretically the time course of drug action in multicompartmental systems (61). Three general cases have been considered: (*a*) where access of drug from the blood to the noneffective tissues is more rapid than to the site of action; (*b*) where access of drug from the blood to the noneffective tissues is less rapid than to the site of action; (*c*) where access of drug from the blood to the noneffective tissues as well as apparent drug elimination from the body are more rapid than the access of drug to and its egress from the site of action. The comparative rates of decline of drug concentrations and pharmacologic effects have been determined theoretically under these different conditions (61). Another approach to the compartmental analysis of the time course of drug concentrations and effects involves the transformation of the effect data so that they relate linearly to dose or concentration of the drug. The drug concentrations in the central compartment and the transformed effect data are then used as input for the usual linear multicompartment analysis (62). It was shown by this kind of analysis that the site of action of norepinephrine on the circulatory system of the cat is outside the central compartment.

With sufficiently frequent determinations of drug concentrations and intensities of pharmacologic effect following intravenous injection it is feasible to calculate the time course of drug levels in each of the several compartments of a multicompartment system. If the site of action is part of one of the "tissue" compartments, then one should note identical concentration-effect relationships in the ascending and descending phases of the concentration versus time curve for that "tissue" compartment (63). Such pharmacokinetic analyses require sufficient data during the initial distributive phase since the intensity of pharmacologic effect should relate equally well to drug concentrations in all compartments in the post-distributive phase (63). It may of course be found that the site of action is not part of any of the pharmacokinetic compartments identifiable from drug concentration data.

Particularly useful for clinical applications is a consideration of the relationship of duration of effect to intravenous dose. In the case of drugs that confer upon the body the pharmacokinetic characteristics of a multicompartmental system, it has been pointed out that the duration of effect is *not* linearly related to the logarithm of dose (32, 64). The nature of this relationship depends on whether the site of action is in the central or peripheral compartments. Additional differences between the single compartment and multicompartment systems are (*a*) third and subsequent equal

doses administered upon recovery from the effect of preceding doses produce longer durations of effect than the second dose, and (*b*) apparently linear relationships between duration of effect and logarithm of dose can be obtained in a restricted dose range but the slope of the line is not independent of the intensity of the effect used as the end point (64). Drugs with sites of action located in relatively small and very slowly accessible compartments show a delayed onset and a prolonged duration of effect. The behavior of reversibly acting drugs with so-called hit-and-run characteristics can be rationalized on this basis (64). If the site of action of the therapeutic effect and that of an adverse effect are located in different compartments, then the therapeutic ratio will not be constant but will vary with time (64). There are many cases where the time courses of different effects of a drug do not coincide. For example, the effects of cigarette smoking on blood pressure and heart rate in dogs show different time courses than the effect on knee jerk (65), but this may or may not have a pharmacokinetic basis. The utility of multicompartmental analysis of drug elimination and pharmacologic effects for the solution of clinical problems is exemplified by a recent study of the kinetics of tubocurarine elimination and neuromuscular blocking effect in man (22). Excellent agreement between experimental data and computer predictions of duration of effect was obtained.

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Indirect Pharmacologic Effects

Some pharmacologic responses are indirect and are the net result of a direct effect of a drug and of an opposing or modifying physiologic effect which is not influenced by the drug. A good example is the anticoagulant action of the coumarin drugs that inhibit the synthesis of certain clotting factors. High degrees of correlation were found between plasma concentrations of warfarin at 48, 72, and 96 hours after oral administration of a single dose and the degree of prothrombin complex depression in normal subjects at these times (66). However, the slopes and intercepts of the correlation plots were markedly different at each of these times. It was pointed out that the correlations should not be construed as evidence of a direct, cause-and-effect relationship (66). The time of occurrence of the lethal effect of warfarin in rats was independent of dose in the high dose range and did not show a constant inverse relationship between dose and time of death, as would be expected if the drug acts directly and if drug elimination is negligible in the time before death (67). A direct quantitative correlation between the anticoagulant effect of warfarin and bishydroxycoumarin and the plasma concentrations of these drugs has been achieved in man by converting clotting times to estimates of the degree of inhibition of the synthesis rate of clotting factors (20, 68). A pharmacokinetic analysis by this method of the effect of a barbiturate on the anticoagulant action of warfarin and of bishydroxycoumarin in man has shown that the decreased effect of these drugs during barbiturate administration is due solely to enhanced biotransformation of the coumarin drugs and is not the result of a number

of other possible effects (68, 69). A pharmacokinetic analysis of the potentiating effect of phenylbutazone on the anticoagulant action of warfarin in man has also been carried out (70). The success of these correlations and the lack of direct correlation between clotting time and drug concentration is due to the fact that clotting time is a function of not only the synthesis rate of certain clotting factors but also of their rate of elimination (which is not affected by the coumarin drugs). A similar approach should be useful in principle for relating the antipyretic effect of certain drugs to their concentrations in a body compartment, since body temperature is a function of the rates of heat production and dissipation. It may also be possible in the future to consider the kinetics of pharmacologic effects that are modified by homeostatic or feedback mechanisms in man. The next review of the pharmacokinetics of drug action will perhaps include considerable literature on these subjects.

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