Biological effects of drugs in relation to their plasma concentrations

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EDITED BY D.S.DAVIES/B.N.C. PRICHARD

BIOLOGICAL EFFECTS OF DRUGS IN RELATION TO THEIR PLASMA CONCENTRATIONS

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Preface

The concept that the activity of a drug depends not on the dose, but the plasma concentration, was first put forward in the early 1940's. The subsequent discoveries of large inter-individual differences in steady-state plasma concentrations of drugs, largely due to differences in rates of metabolism, added force to the argument that therapy should be controlled by monitoring the concentration of drug in plasma. However, this assumes that the desired pharmacological response is achieved over a relatively narrow range of concentrations in different individuals. In recent years this assumption has been challenged. This appeared to be a particularly appropriate time for the Clinical Pharmacology Section of the British Pharmacological Society to organize its first symposium to examine the relationship between the biological effects of drugs and their plasma concentrations.

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Chairman: Professor C. T. Dollery

ONE

The Value of Correlating Biological Effects of Drugs with Plasma Concentration

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Introduction

The concept that the activity of a drug depends on its plasma concentration was first tested by E. K. Marshall with sulphonamides (Marshall, 1940), but the widespread application of this doctrine to rational drug therapy was firmly established during the clinical screening of antimalarials in World War II by Shannon and associates (Shannon, 1946).

The loss of quinine sources had created a crisis which made it crucial that potential antimalarial drugs be tested accurately using a small number of therapeutic trials. Initial studies revealed that the therapeutic effects of the four cinchona alkaloids could not be related to their dosage. Fortunately, their effects were found to correlate with their plasma concentration, making possible rapid screening for antimalarial activity. Subsequent studies showed a similar relationship between the antimalarial activity of synthetic substances and their plasma levels, and led to the effective use of mepacrine, a well-known compound that had been discarded as ineffective because it previously had been administered incorrectly (Shannon, Earle, Brodie, Taggart & Berliner, 1944).

Therefore the most important achievement of the antimalarial project

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was not the development of new compounds but the development of new principles in drug screening.

Kinetic Considerations Underlying the Use of Plasma Concentrations

A fundamental premise in pharmacology is that a drug response is determined by the quantity of drug fixed to sites of action. Since the concentration of drug in plasma can usually be measured, it is important to know whether changes in this concentration reflect changes in the amount of drug at its active site(s).

For drugs that act reversibly, the formation of drug-receptor complexes obeys the law of mass action. At equilibrium, the rates of formation and dissociation of drug-receptor complexes are equal. In general, the rates of association and dissociation are so high that changes in the number of drug-receptor complexes and in the intensity of response parallel changes in concentration of the drug in tissue water, which in turn is usually in rapid equilibrium with the drug in plasma.

Nevertheless, there are many instances when pharmacological effects are apparently not related to the plasma level of the drug. A therapeutic agent may be inactive itself but act through a bio-transformation product. In this case, the response will be related to the concentration of the metabolite in plasma. Whenever a response is clearly unrelated to the drug concentration in plasma, the possibility must be considered that the action of the drug is mediated through a metabolic product; a number of therapeutic agents have been discovered by the study of such relationships (Brodie, 1964).

In addition, other drugs act non-reversibly, i.e. the quantity of active agent attached to receptors is not related to steady-state plasma concentration. Such drugs often attach to their receptors and then bond covalently with them. A small amount of drug remains attached to these sites long after the rest of the drug has vanished from the body. Certain drugs, such as reserpine, act non-reversibly without bonding covalently, but they also are attached so tightly to receptors that they remain fixed to these sites after the concentration of unbound drug has declined to levels which are unmeasurable by our present analytical techniques.

Non-reversible drugs are inherently dangerous. Even when given in very small daily doses, the effects accumulate even though the drug apparently does not. Thus, they exert a persistent action and recovery depends on regeneration of the sites of action. Since plasma levels are not a guide to therapy, non-reversibly acting drugs must be handled with great care. Kinetic studies in animals will disclose whether a new drug acts non-reversibly; in fact, the clinical pharmacologist should insist on having this information before undertaking human studies.

Extrapolation of Animal Data to Man: Plasma Concentrations as an Explanation of Biological Variability in Drug Response

A major difficulty in drug development is the vast species variability in drug responses. This variability makes it difficult to extrapolate to man experimental results obtained in animals. Not long ago, species variability in drug responses was attributed to intrinsic differences in the responsivity of the target organ. This view was based on the assumption that the same dose of drug (in mg/kg) would attain the same concentration at drug receptor sites in various mammalian species. Recent years, however, have disclosed vast differences in rates of drug metabolism within and between species. This raises the possibility that variations in response may be due to differences in amounts of drug available at sites of action.

Consistent with this view is the fact that most drugs which elicit pharmacological effects of equal intensity after comparable doses in various mammalian species mainly are poorly lipid-soluble compounds which are not dependent on metabolism for elimination. For example, ganglionic blocking agents, many antibiotics, the thiazide diuretics and the adrenergic blocking agent, tolazoline, exert similar biological effects in animals and man. These drugs are disposed of by excretory processes that are essentially the same for all mammalian species. Hence, they attain similar plasma concentrations in most animals and show little species variability in drug response.

Even for drugs whose metabolism does show marked species differences, dependable predictions of activity are usually obtained if drug responses are related to plasma concentration rather than to dosage. This point is well illustrated by a few examples.

Despite great species differences in duration of action and rates of metabolism of several barbiturates, man and other animal species recover from hypnosis at similar plasma concentrations. In addition, variations in metabolism due to strain and sex differences are circumvented if activity is based on plasma levels (Quinn, Axelrod & Brodie, 1958). Similarly, the duration of sedative action of carisoprodol varies in four species from 0·1 h (in mice) to 10 h (in cats), but plasma concentrations are almost identical on recovery from hypnosis (righting reflex). Although hypnosis is three times as long in female as in male rats, and is markedly reduced by phenobarbitone pretreatment, plasma levels on recovery are similar (Gillette, 1971).

The compound ICI 33828 inhibits pituitary gonadotropic function at vastly different doses for a number of species. Despite a 200-fold variation in daily dosage, the inhibitory plasma level of each species is about 3μg/ml (Duncan, 1963).

To protect against glycerol-induced inflammation in the rabbit's eye

requires 300 mg phenylbutazone daily. In man 5–10 mg/kg is required to exert an antirheumatic effect. In both instances, however, the plasma concentrations are 100–150 μg/ml. The marked difference in dosage reflects the biological half-life of 3 h in rabbits compared with 70 h in man (Burns, 1962). Again, the dose of N-isopropylmethoxamine that blocks the epinephrine-induced output of free fatty acids in man and dog is about 10 mg/kg and plasma concentrations are 3 to 6 μg/ml. In mouse and rat, the drug elicits no effects in doses up to 400 mg/kg, but the plasma levels do not rise above 0·5 μg/ml. Despite these apparent species differences, the antilipolytic effects of the drug are equally effective in isolated adipose tissue of rats and dogs (Burns, 1965).

Drug Screening in Animals

As the above examples show, therapeutic agents are often metabolized much more slowly in man than in other animals. This raises the possibility that present methods of screening might well overlook many rapidly metabolized drugs that could be of therapeutic value to man.

The following are examples of drugs discovered in man that earlier animal tests would not have disclosed. Oxyphenbutazone has such a short half-life in animals (about 30 min in dogs compared with 72 h in man) that it would have been discarded if the investigators had not been aware of species differences in metabolism (Burns, 1962). The relatively short half-life of phenylbutazone in animals also caused it to be initially overlooked. The potent antirheumatic action of this drug in man was discovered by chance when it was used as a solubilizing agent for the parenteral injection of amidopyrine (Gsell & Muller, 1950). Likewise the antidepressant action (reversal of reserpine syndrome) of imipramine and its active metabolite desipramine would not have shown in rabbits or mice, since these animals rapidly inactivate both (Dingell, Sulser & Gillette, 1964).

Drug Screening and Development of Optimal Dosage Schedules in Man

It is not generally recognized that a common cause of toxic reactions in man is 'overdosage' because of large person-to-person variability in rates of drug metabolism; in different subjects, the same daily dose of a drug may cure, cause severe toxicity or have no effect whatsoever. Clinical investigators whose experience has been confined mainly to polar drugs, such as the quaternary ammonium compounds and thiazide diuretics, may suspect that the importance of individual differences in metabolism has been grossly exaggerated. In contrast, researchers concerned with drugs having some degree of lipid solubility are aware of the wide divergencies in drug response but until recently have resisted the view that they are due to diver-

gencies in drug metabolism. The individual variability in drug metabolism can indeed be large: bishydroxycoumarin and ethyl biscoumacetate, for example, show a fifteen-fold difference among various individuals. Many other drugs, including diphenylhydantoin, isoniazid, amidopyrine, antipyrine, desipramine, chlorpromazine and quinidine, are metabolized at widely different rates.

With such variability, how can a clinical pharmacologist be expected to evaluate a drug if, unknown to him, the plasma concentration progressively accumulates or oscillates between that which is ineffective and that which is toxic? Early information about the fate of a drug in man is needed to develop dosage schedules that will improve the efficiency of screening and reduce the danger of overdosage. With the imminent availability of ^{13}C-labelled (non-radioactive) drugs and gas chromatography-mass spectrometry techniques, it should soon be possible, based on limited animal-toxicity studies, to evaluate in man the physiological fate of most drugs given in doses of only a few milligrams. From such studies, the degree of absorption of a drug can be determined from its concentration in plasma. If the plasma level is almost identical a few hours after both oral and parenteral administration, it may be assumed that absorption is rapid and complete. After intravenous administration, the biological half-life of the drug can be calculated from the slope of the exponential decline of the plasma concentration after diffusion equilibrium is reached. Such preliminary studies can decide whether a drug should be abandoned either because its absorption is inadequate or its excretion is too rapid.

Several examples show the value of these early studies.

1. A screening programme to find a barbiturate that would be rapidly metabolized in the body led to the discovery of a compound that was extremely unstable in dogs. After detailed and expensive toxicity studies, the compound proved to be the longest lasting barbiturate of all time when finally tested in man (Brodie, 1964).

2. Pethidine at one time was believed not to produce tolerance and addiction in man. This erroneous view arose from studies in dogs in which the drug has a half-life of a few minutes compared with 4 h in man (Burns *et al.*, 1955). The experiments in dogs only proved that it is difficult to produce tolerance and addiction to a drug that is not there.

3. Measurement of plasma levels would have shown that the 'special disease' by which chloramphenicol supposedly killed newborn children was simply overdosage due to chloramphenicol's slow metabolism in the neonate (Weiss, Glazko & Weston, 1960).

When optimal dosage schedules are developed, an attempt is made to maintain a drug at an effective concentration; that is, one that is above the therapeutic and below the toxic plasma concentration. Theoretically, a constant level can be maintained only by continuous intravenous infusion.

With oral administration, a compromise may be achieved by giving a priming dose of drugs large enough to produce the desired therapeutic plasma level followed by maintenance doses given at appropriate intervals.

Thus dosage schedules entail three variables: the size of the priming dose, the size of the maintenance dose and the dosage interval. The size of the priming dose (mg/kg) is calculated by multiplying the experimentally determined effective plasma concentration (mg/l) by the 'apparent' volume of distribution and adding to this value the maintenance dose. The apparent volume of distribution is a measure of the relative tissue to plasma concentration of the drug after equilibration. The maintenance dose and the dosage interval depend on the permissible degree that the plasma level can oscillate and still produce a therapeutic effect without evoking toxicity. The appropriate dosage regimen can be readily calculated from the biological half-life of the drug. Since these kinetics are discussed in detail by other authors, we need not discuss them further.

For certain drugs, the time is approaching when a different dosage schedule for each individual will be needed. Drugs are becoming more effective but also more toxic, and it is often difficult to take advantage of these agents unless dosage schedules are tailored based on the optimal plasma concentration. It must be emphasized, however, that such individualized regimens will be important mainly for drugs with a highly variable person-to-person rate of metabolism. Furthermore, they would be valid only for drugs whose therapeutic effects depend on the steady-state plasma level and would not apply to non-reversibly acting drugs, such as reserpine, alkylating agents and monoamine oxidase inhibitors.

Elucidation of Mechanisms of Drug Interactions

In recent years much concern over drug interactions has evolved because doctors frequently prescribe more than one drug or are unaware that the patient is taking drugs prescribed by other physicians. An important type of drug interaction occurs when one drug alters the plasma concentration of another. For example, a number of drugs in therapeutic doses can stimulate the activity of a wide diversity of microsomal drug-metabolizing enzymes. An especially difficult therapeutic situation can arise when a patient is treated at the same time with a coumarin anticoagulant and a variety of other drugs. For example, various barbiturates accelerate the metabolism of the coumarin drugs (O'Reilly & Aggeler, 1970). If the administration of the barbiturate is discontinued, the coumarin levels rise and can lead to internal bleeding.

These studies also demonstrate, incidentally, that cross-over studies using subjects as their own controls must now be carefully scrutinized,