# SYMPOSIUM

## THE MODIFICATION OF THE DURATION OF DRUG ACTION

### PHARMACOLOGICAL AND CLINICAL CONSIDERATIONS

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THE usual reason for attempting to modify the actions of a drug is to increase its usefulness in the treatment of disease. Sometimes, however, the purpose may be to improve its prophylactic value, or occasionally to provide a more rapid, precise or safer diagnostic agent. Drug action can be modified in a number of ways; by altering its physical properties by adding to it other substances or other drugs, or by modifying its chemical structure.

In considering the modification of drug action for therapeutic purposes, it would be generally true to say that the aim of any kind of treatment is to control the disease process or the symptoms to which it gives rise in the shortest period of time and with the least inconvenience to the patient. The success or failure of modifying the action of a drug can therefore be gauged by whether the patients who receive treatment with the modified drug are cured or relieved of their symptoms more rapidly, more completely, or more frequently than they would with the unmodified drug. There are several important points to observe in making comparisons of this kind but I do not propose to discuss them in detail. I would like to emphasise however the necessity to distinguish pharmacological effects from the effects of suggestion. This is not to underestimate the value of therapeutic suggestion, but rather to point out the danger of drawing the wrong sort of conclusions. For example, if one were to accept all that has been written about new methods of improving drug action, it would seem that no one need suffer headache for more than 3 minutes or lie awake counting sheep—or overdrafts—for more than 5 minutes. The rapid effect obtained after swallowing a capsule would seem to be connected more with the act of taking the capsule rather than with the action of its contents.

Whatever measurements are chosen as an index of pharmacological action, no valid comparison of drug action can be made without them. They can serve to distinguish between a scientific advancement and a sales-promotion gimmick. The nature of the comparison will of course depend on the particular circumstances. It may consist in measuring the relative concentration of the drugs in the blood, cerebrospinal fluid or urine, or in determining by some biochemical tests, the changes produced on the blood sugar level, on the electrolytes excreted in the urine, or in the case of some antibiotics, the antibacterial activity of the serum or urine. Simple clinical measurement of changes in blood pressure, pulse rate, body weight or body temperature may be sufficient or more complicated assessments may be considered necessary, such as measurement of

cardiac output, vital capacity, retention of iodide, differential blood cell counts or the number of parasites killed or eliminated.

The apparatus required may be complex and expensive, or on the other hand, a pen or pencil may suffice to record how many times a patient coughs, how long he sleeps or how frequently or to what extent he has relief of pain.

## Clinical Considerations

Modification of drug action may be required in order to provide (*a*) a more rapid therapeutic effect; (*b*) a more prolonged and sustained action with less frequent administration; or (*c*) a safer or less disturbing therapeutic effect less liable to be accompanied by other actions or side-effects of the drug.

### *Increasing the Onset of Action*

Many of the drugs which are absorbed from the alimentary tract are reasonably well absorbed within 15 to 45 minutes of oral administration, and their action can be expected well within this time range. For many patients this is a convenient and satisfactory form of treatment. There are occasions however where, because of the severity of illness or because the patient is unable to swallow or retain substances given by mouth, some more rapid or alternative method of treatment is necessary. This can often be achieved by temporarily changing the route of administration of sulphonamides or of tetracycline drugs, for example, in the initial stages of treating severe acute infections. Herein lies the importance of providing sterile preparations of the latter suitable for intravenous as well as for intramuscular injection.

Sometimes the onset of action of a drug normally administered by intramuscular or subcutaneous injection is delayed by the presence of gross oedema or adipose tissue, or on account of peripheral vascular failure. Here again a change to intravenous injection, for example, of mersalyl, insulin or of an analgesic such as morphine provides a satisfactory answer to the problem.

The use of hyaluronidase to increase the rate of absorption by increasing the subcutaneous dispersal of fluid, is a valuable therapeutic method of rapidly restoring water and electrolyte balance especially in infants and young children. The advantages afforded by the use of a spreading factor have also been readily appreciated by surgeons and anaesthetists to increase the rate of action of local anaesthetics, though some care must be exercised in controlling the spread of effect and also the resultant decrease in duration of local anaesthesia.

The rapid absorption of iron by intramuscular injection of iron-dextran complex is a notable contribution which might be expected to stimulate further work in this field. For example, a non-irritant intramuscular preparation of aminophylline would be a welcome alternative to intravenous injection—at present the only effective method of giving this valuable drug.

There appears to be a considerable increase in the number of drugs which are prepared for parenteral administration. In the United States

of America during 1957, a total of 496 new products and preparations were introduced of which 52 were for parenteral administration, and 36 more were made available in 1958[1]. Some of these consist of hormones such as gonadotrophins, corticotrophin and oxytocin which can only be administered by injection, others such as antispasmodics, antihistamines, tranquillising drugs and vitamins are more difficult to justify on the basis of a need to increase the speed of action or to facilitate administration.

More use could be made of the sublingual route of administration. The success of nitroglycerin and isoprenaline tablets for the treatment of angina and bronchospasm is well recognised. The rapid relief of symptoms and the ease with which the effective dose can be quickly determined, specially commend this method for emergency treatment. It could with advantage be extended to the study of potent analgesic and cough suppressant drugs. The same could be said of administration of drugs in aerosols.

*Prolonging Duration of Action*

There are several reasons for attempting to prolong the action of a drug, the most important of which is to maintain the therapeutic effect for longer periods than can be obtained after administration of a single dose. Moreoever this might be expected to diminish the waxing and waning of drug action following frequent administration of single doses. Other reasons such as saving the time of the nursing staff, more convenience for the patient, or avoiding reliance on his memory are probably less important and less convincing.

There are a number of outstanding examples where this method of modifying the action of a drug has been successful, notably in the treatment of certain endocrine diseases such as diabetes mellitus, diabetes insipidus, Addison's disease and related conditions requiring supplemental therapy with adrenal cortex hormones. It is significant that in all these instances the drug has been administered parenterally, usually because of its inactivation or inadequate absorption in the gastrointestinal tract.

These therapeutic successes have encouraged the extension of this type of modified preparation to other drugs, the successful outcome of which is more doubtful. There are however many clinical indications where the sustained or prolonged action of a drug is necessary. In the treatment of infections, adequate and continuous action of the chemotherapeutic agent is vital even though the therapeutic programme is restricted to 7 or 10 days. The argument is even greater for treatment with antituberculosis or antileprotic drugs which are required to be given for many months. This also applies to the treatment of a number of tropical diseases and helminthic infections.

Continuous therapy is also necessary in the management of peptic ulceration, which demands continued action of the drug throughout the night and early morning. Antacid or antispasmodic drugs with a prolonged action would therefore be very acceptable additions to the drugs at present available. Longer-acting ganglion blocking and tranquillising

drugs would be useful in the treatment of hypertension, and similar modifications of solanaceous alkaloids and of antihistamine drugs would be valuable in maintaining symptomatic control of Parkinsonism and of some allergic diseases. Severe continuous or intermittent pain is a distressing symptom of a number of diseases and longer acting analgesic drugs would be gladly welcomed. A notable exception to this is the treatment of angina of effort with nitrites where to continuously obscure the warning symptoms of pain, and therefore of over-exertion, would most likely do more harm than good.

The effective symptomatic control of cough is appreciated by the patient and just as often by those in his immediate environment. There is much to be said therefore for the provision of a long acting cough suppressant drug. According to one statement[2] there is now available a preparation containing 5 mg. of dihydrocodeinone, a single dose of which will stop a useless cough for 6000 jet-miles. How many miles have to be travelled before the effect begins may perhaps best be answered by the fellow-travellers.

The success which follows attempts to prolong the action of a drug must be judged by whether the modified drug produces an adequate effect for the desired period without undue delay; this last point is important but not so vital as the others, since if necessary the action can be initiated by administration of the unmodified drug.

Apart from the systemic administration of drugs some attempts have been made to prolong the action of those which are intended only for local administration. The most notable example is the use of adrenaline as a vasoconstrictor to delay absorption and prolong the action of local anaesthetic drugs. Many instances of ischaemic necrosis have resulted from the use both in medical and dental practice of high concentrations of adrenaline. It is noteworthy that there is now fairly general agreement amongst clinicians that for this purpose, the maximum effective concentration consistent with safety is a 1 in 100,000 (0·001 per cent) solution of adrenaline. The use of compressed pellets of hydrocortisone for the treatment of ulcers in the buccal cavity focuses attention on the importance of exploring further this method of prolonging the local action of drugs.

*Pharmacological Considerations*

Intensity and duration of action depend on the concentration of drug on the cells on which it acts and this is determined by its rate of absorption, distribution to and clearance from the tissues. Thus the action of a drug may be prolonged by reducing its rate of absorption, by delaying the rate at which it is inactivated, or if it is excreted unchanged, by retarding its excretion.

In general the most practical and successful methods depend on reducing the rate of absorption and, because of the greater number of variable factors which influence absorption from the gastrointestinal tract, modification of drugs for parenteral administration have produced more satisfactory results than those for oral administration.

*Parenteral Administration*

The more water-soluble the drug the more rapidly it is absorbed; therefore absorption will be delayed when the drug is administered in a relatively water-insoluble form. This can be done by changing the solvent to an oily vehicle or by adding to the aqueous solution a colloid such as gelatin, polyvinylpyrrolidone or dextran. The former has been useful in the earlier days of administering penicillin, vasopressin, and a number of other drugs, but absorption is erratic and the oily vehicle complicates the cleaning of syringes. The use of gelatin has been effective in delaying absorption of corticotrophin but is not reliable for the administration of heparin. Some anxiety has been expressed about the carcinogenic potentialities of polyvinylpyrrolidone but this should not be allowed to preclude its use for short-term therapy, or where the patient already is the victim of malignant disease. It would be interesting to know whether a long acting potent analgesic can be formulated with this substance. More evidence would be relevant regarding the use of dextran in prolonging the action of ganglion-blocking drugs, neostigmine, heparin and analgesic drugs.

These and other methods of delaying absorption such as forming water insoluble salts, esters or protein complexes will be discussed in detail by Dr. Edkins. It is relevant to point out that they apply mainly to drugs such as insulin, corticotrophin, heparin and penicillin which are fairly rapidly cleared from the body. No useful measure is served in extending investigations of this kind to drugs, for example, thyroxine, digitalis glycosides or cyanocobalamin, which though required continuously, are themselves slowly eliminated.

The action of some drugs, notably the stable steroid hormones, can be prolonged by preparing them as compressed or fused pellets. Three methods of administration are being increasingly and successfully explored in medical, dental and veterinary practice. Subcutaneous implantation of DOCA pellets for the treatment of Addison's disease is one of the classical examples; much more frequent use is made of this method of administering oestrogens and androgens. Sublingual absorption of methyl testosterone is another use, and more recently the prolonged local action of hydrocortisone in the buccal cavity. Oral administration of pellets has also promising application in veterinary practice. These different methods of administering pellets doubtless pose a number of problems in formulation.

*Oral Administration*

So far as I am aware, the present fashion for taking medicine only once a day has not spread to the taking of food and I would like to express the hope that the idea of squeezing the most out of a drug, by allowing it to be absorbed slowly and preventing any wasteful excretion of it, does not invade or threaten the pleasure of eating three square meals a day. Until much more is known about the laws that govern the absorption of drugs from the gastrointestinal tract and their subsequent utilisation, there is little prospect of introducing successful automation of the alimentary tract.

There is no harm is trying out these ideas with drugs that don't matter very much, but as Dragstedt[3] has emphasised they should not be applied at present to potent drugs such as digitalis glycosides, antibiotics and ganglion blocking drugs, precise and adequate doses of which are vital if they are to contribute to the wellbeing and life of the patient.

At one time it was considered that ethyl alcohol was the only drug that was effectively absorbed from the stomach, but there is increasing evidence that the stomach is an important site of absorption of drugs. Various factors however influence the extent to which this occurs. One is the ability of the drug to dissolve in the gastric contents; for example, a moderately soluble compound like aspirin is readily absorbed, whilst a poorly soluble one such as dicoumarol is not. Hogben and his colleagues[4] have found that if a drug is partially unionised in the acid gastric contents it is well absorbed, whereas little is absorbed if it is ionised. This is attributed to the fact that the gastric mucosa acts as a lipid barrier which selectively permits passive diffusion of the unionised lipid-soluble form of a drug but prevents the diffusion of the lipid-insoluble ionic form. For example, organic acids such as aspirin and barbiturates with a pKa of 3 or more which are undissociated in acid gastric juice are rapidly absorbed, whilst bases such as quinine, ephedrine and amidopyrine with a pKa greater than 5, which are ionised are not absorbed. Phenazone, a weaker base which in the presence of gastric secretion is not dissociated, is quite well absorbed.

A similar type of pattern seems to condition absorption from the intestine where there is a fairly close relation between the lipid solubility of unionised drug and the rate of intestinal absorption[5]. The idea of a lipid barrier does not satisfy all the requirements for absorption of a drug because it does not account for the passage of inorganic ions and other lipid-insoluble substances which are required for cell metabolism. Doubtless other special transport mechanisms are involved.

There are of course other factors which determine the extent to which drugs are absorbed from the stomach. If a drug is taken with water before a meal, it may remain only for a short time and little of it is absorbed from the stomach. If it is swallowed soon after a meal, the delayed emptying favours absorption but the rate at which this occurs is delayed by the volume of the gastric contents.

Individual variation in the amount of drug absorbed is another important factor; some individuals are relatively poor absorbers. This is common experience but is illustrated by the evidence recently reported by Hogben and his colleagues[4]. Observations were made on three healthy adults of the amount of drug absorbed after its administration by gastric tube. After 20 minutes the amounts of aspirin absorbed by each of the subjects expressed as a percentage of the dose were 31, 42 and 16 respectively.

The phenomenon of individual variation not only in respect to the rate and extent of absorption but also in relation to the response to drugs emphasises the importance of paying due attention to the individual needs of the patient and severely restricts the likelihood of regulating drug therapy by alarm-clock methods of sustained release.

There are two examples in veterinary medicine which illustrate the successful modifications of drug action on the alimentary tract. The first concerns the use of the "cobalt bullet". Cobalt deficiency in ruminants gives rise to a deficiency in the production of vitamin $B_{12}$ by micro-organisms in the rumen. Thus in certain areas of Southern Australia when sheep and cattle are grazed on pasture consisting predominantly of *Phalaris tuberosa*, the animals frequently develop a demyelinating disease, Phalaris staggers, which is often fatal. This can be prevented by oral administration of cobalt which promotes an adequate biosynthesis of vitamin $B_{12}$. Dewey, Lee and Marston[6] have given a fascinating account of how they succeeded in preparing compressed cylindrical pellets containing cobaltic oxide in china clay. The specific gravity of the pellets was such that when swallowed they were transported fairly rapidly to the reticulum, where because of their density, they remained and from them cobalt was released for many weeks. This report is important because it illustrates how a careful study of drug absorption can be carried out both *in vitro* and *in vivo* and it also provides the basis for investigating the prolonged administration of other substances such as anthelminthics to ruminants.

The other example concerns the anthelminthic phenothiazine. Kingsbury[7] and others[8–10] have demonstrated that in the treatment of nematode infections of sheep the particle size of this water-insoluble compound is an important factor in determining its anthelminthic activity and hence its therapeutic efficiency. Extensive studies by these investigators have shown that the most active preparations were those which were prepared from phenothiazine containing a high proportion of particles of $10\mu$ or less. This work illustrates the importance of determining the physical properties of a drug which are necessary for its optimum local action, consistent with low absorption.

*Delaying Inactivation*

Apart from altering its chemical structure there are few practical methods of modifying the rate of inactivation of a drug. One notable example is the inhibition of enzymes involved in the inactivation of drugs. The action and uses of anticholinesterase compounds such as neostigmine depend on their ability to combine with cholinesterase and prolong the action of acetylcholine by delaying its hydrolysis. Various attempts have been made to increase and prolong the action of other drugs, for example morphine, by concurrent use of one of these inhibitors[11].

A new approach to this aspect of prolonging drug action is the discovery of some compounds which by themselves have little or no action but which are able to prolong the action of a variety of other drugs by inhibiting the enzyme systems in liver microsomes which inactivate them[12,13]. $\beta$-Diethylaminoethyl diphenylpropylacetate (SKF525–A), 2,4-dichloro-6-phenylphenoxyethyl diethylamine (Lilly 18947), and isopropyl-2-isonicotinyl hydrazine (iproniazid, Marsilid) have been shown to interfere with the metabolism of barbiturates, amphetamine, acetanilide, pethidine and amidopyrine. These substances have not yet been investigated

sufficiently to establish their therapeutic value but their potential uses are considerable.

There are several examples of drugs whose actions can be prolonged by modification of their chemical structure. The different rates of inactivation of barbiturates provide a selection of compounds varying in duration from two or three hours (quinalbarbitone) to 12 hours or more (phenobarbitone). An anticholinesterase compound can be chosen to provide for diagnostic use the brief action of edrophonium, or for therapeutic purposes the longer action of neostigmine or pyridostigmine. A large series of similarly acting organophosphorus compounds consisting amongst other of dyflos, tetra-ethylpyrophosphate and octamethyl pyrophosphate (OMPA) can produce even more prolonged action but the difficulties of controlling the extent of enzyme inhibition within safe limits have severely restricted their general therapeutic uses.

A formidable amount of information has been collected on the outstanding value of many of these compounds as insecticides[14]. Some of those with low toxicity in mammals, notably malathion and chlorthion, have been formulated as dusting powders for the control of human body louse infections. The beneficial results to the community at large, which have accrued from the careful systematic and coordinated researches on this aspect of drug action are indeed noteworthy.

*Delayed Excretion*

One of the classical methods of prolonging drug action is the curtailment of salt whilst administering bromides. It has been known for many years that the therapeutic benefit of bromide depends on establishing an optimum concentration of it and maintaining this by balancing the amount absorbed and excreted. This drug has been largely discarded but I hope the wisdom of knowing how to use it remains. The excretion of drugs, such as penicillin and aminosalicylate, which are eliminated by tubular excretion can be delayed by concurrent administration of caronamide or probenecid which interfere with transport mechanisms in the renal tubules. The practical problem of conveniently maintaining an effective concentration of the interfering drug has severely restricted the therapeutic usefulness of this method.

The action of some drugs may be prolonged on account of their storage in tissues from which they are slowly released and excreted. This property may be important in the choice of a particular drug from several which have similar pharmacological actions. The fact that chloroquine, after oral administration, is highly concentrated in the liver from which it is gradually released makes it specially valuable for the prophylactic control of malaria. The accumulation of chlorotrianisene (TACE) in the body fat has led to the use of this drug as a long-acting orally administered oestrogen[15,16].

*Reducing the Side Effects*

One of the most important therapeutic tasks is the problem of choosing from a number of drugs with similar actions the one which is likely to be

most suitable for the individual patient. It is a problem which arises from the fact that each patient, in a sense, is a law unto himself and that his response and reactions to drugs cannot be accurately predicted. It is common knowledge that the dose of a drug which is necessary to produce its typical effect in a group of individuals may vary over a four-fold range or more. Because of this wide individual variation in response, many potent and therefore potentially toxic drugs must be administered in such a way that the dose can be adjusted according to the individual need and response. Most experienced clinicians adopt this procedure when prescribing treatment with well established drugs such as digitalis, insulin, salicylates and morphine. Unfortunately this principle seems to be overlooked when newer drugs are used. Thus when a new drug is tried in the recommended dose with little or no therapeutic effect, or if its effect is accompanied by nausea, headache or some other uncomfortable side-effect, instead of adjusting the dose or frequency of administration treatment is too often abandoned in favour of some other drug or mixture of drugs.

This is one of the chief reasons why mixtures of drugs in one preparation have become so popular. A critical examination of many or these however reveals no evidence of any rational pharmacological basis for therapy. The virtue of some appears to lie in the fact that the dose of each constituent is sufficiently small not to give rise to any serious risk of overdose, nor indeed to any significant pharmacological action. Perhaps there is some substance in the remark of the cynic who advocated a policy of basing his therapy on 90 per cent suggestion and 10 per cent pharmacology.

The major criticism of preparations containing mixtures of anti-histamine and amphetamine drugs, amphetamine and barbiturates, antispasmodic and antacid drugs and many others of this nature is the fact that the fixed proportion does not readily permit any adjustment of the dose of each constituent drug. Preparations containing an active drug and one of its antagonists have little to commend them.

A notable exception to these is the use of three sulphonamides instead of one but with the synthesis of less toxic sulphonamides, this may be regarded more as of historical interest.

Hypersensitivity reactions to drugs scarcely come within the province of this discussion. The fact that some individuals respond in a wholly abnormal manner to normal or subnormal doses of a drug should always be anticipated, and when it occurs should be noted and respected by both patient and physician. This applies not only to reactions to penicillin, sulphonamides, barbiturates and many other new drugs, but just as much to aspirin. The only safe modification is to change the drug rather than the patient.

One of the best reasons for encouraging attempts to reach the moon is not so much for what is likely to be found there, but because a considerable increase in the amount of knowledge will be gained in the process of reaching this objective. The same can be said of many investigations which have been pursued on the theme of modifying drug action. This is

meant as a tribute to the ingenuity of pharmaceutical formulation, but it is intended also to convey a plea for a more realistic appreciation of the pharmacological limits which condition such manipulations of drugs.

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