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The value of infusion and injection regimens in assessing efficacy and toxicity of drugs

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There is growing recognition that regimen or rate of drug administration can influence the expression of drug actions. The literature now contains a number of striking examples of regimen-dependent, or schedule-dependent effects[1–11].

Basically, regimen dependence signifies a shift of the dose–response curve to the right or left according to the time-pattern of drug administration. That is, the same total dose of the drug produces different actions when the schedule of its administration changes. Until recently, studies of regimen dependence were infrequently done, except with anticancer drugs where schedule dependence is often observed. In the last few years, the advent of delivery systems has made it practical to design and test various delivery patterns in all phases of drug research. Moreover, rate-controlled dosage forms (delivery systems, therapeutic systems) are now available to apply certain of these patterns in routine therapeutics, as an alternative to the happenstance kinetics of drug release from conventional dosage forms.

The purpose of this paper is to analyse several studies of regimen dependence, and to examine the implications of such work for animal and clinical pharmacology, and for therapeutics. These studies strikingly illustrate how the dose–response of familiar drugs can change with different regimens: in this case, with administration by injection v. continuous, constant-rate infusion.

Regimen dependence of valproate, bleomycin, and other agents

Nau *et al.*[1,2] administered valproic acid (VPA) by two different regimens in the same total dose to pregnant mice from day 7–15 of gestation: by injection once daily and by continuous, constant-rate infusion from implanted miniature osmotic pumps. The once-daily injections caused VPA concentrations in plasma to peak and decline quickly (Fig. 1); in fact, for long periods between injections, the drug was undetectable. Compared with the time-pattern of drug concentrations in the mouse, in humans the peaks are only 1/10 as high, but the trough concentrations are many times higher. These differences reflect the fact that the half-life of this widely used anti-epileptic drug is only 0.8 h in the mouse compared with 8–16 h in humans.

Continuous infusion in mice maintained drug and metabolite levels within a narrow range (Fig. 2). Moreover, Nau found that, with the infusion mode, a higher total dose was required to produce embryotoxicity (resorptions and exencephaly) than with daily injections (Fig. 3). Thus, the infusion regimen shifted the dose–response curve for embryotoxicity to the right (Fig. 4), such that a ten-fold higher dose was required with the infusion regimen to yield the same absorption rate observed with the injection regimen[2].

Sikic *et al.*[3] had previously observed regimen dependence for both the toxic and therapeutic actions of the anticancer drug bleomycin. These workers administered doses of the drug in three different 5-day regimens: injections twice daily, alternate day injections and continuous infusion by implanted osmotic pumps. Results associated with drug infusion differed in two ways from results obtained with either injection regimen: at equal total doses, the infusion reduced the drug's toxicity (Fig. 5A) but increased its anti-tumor efficacy (Fig. 5B). This enhanced efficacy observed with continuous infusion of bleomycin was confirmed by Peng and colleagues[4]. Thus, continuous infusion shifted the dose–response curve for bleomycin toxicity to the right, while shifting the dose–response curve for efficacy to the left. Putting together these two observations leads to the conclusion that bleomycin's therapeutic index is widened by use of the infusion regimen and narrowed by the injection regimen. Subsequent clinical studies also appear to confirm the prediction that the human use of bleomycin may be made both safer and more efficacious by use of a constant-rate infusion regimen[12,13].

Several additional studies in which the action of such agents as parathormone[9],

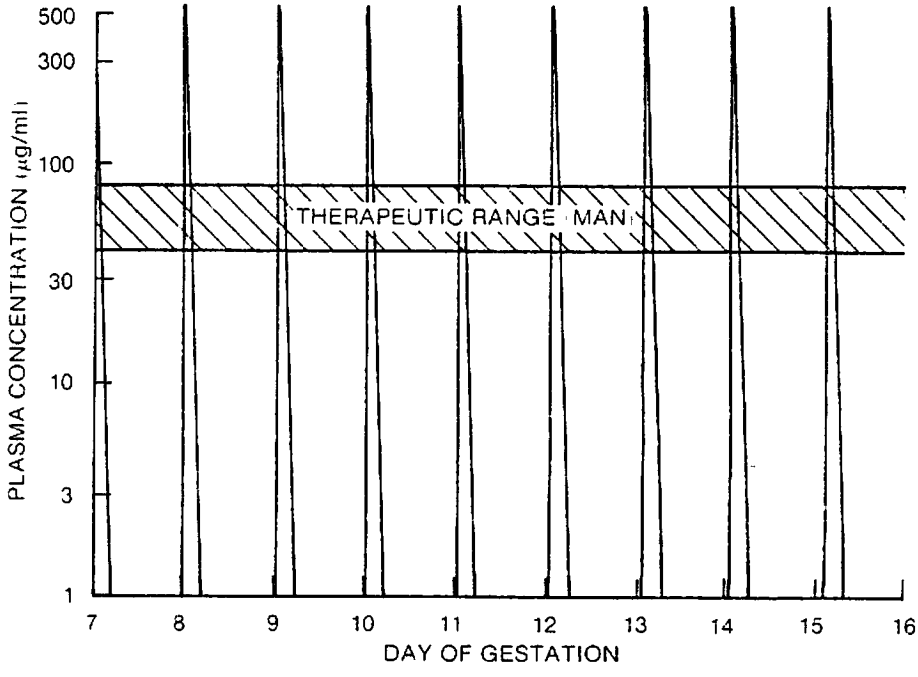

Fig. 1. Concentrations of valproic acid in mice following once daily s.c. administration of the drug (400 mg kg^{-1}) between days 7 and 15 of gestation. The curves show experimentally determined values. The shaded area represents the range of human plasma concentrations observed during pregnancy. (From Nau *et al.*, Ref. 1.)

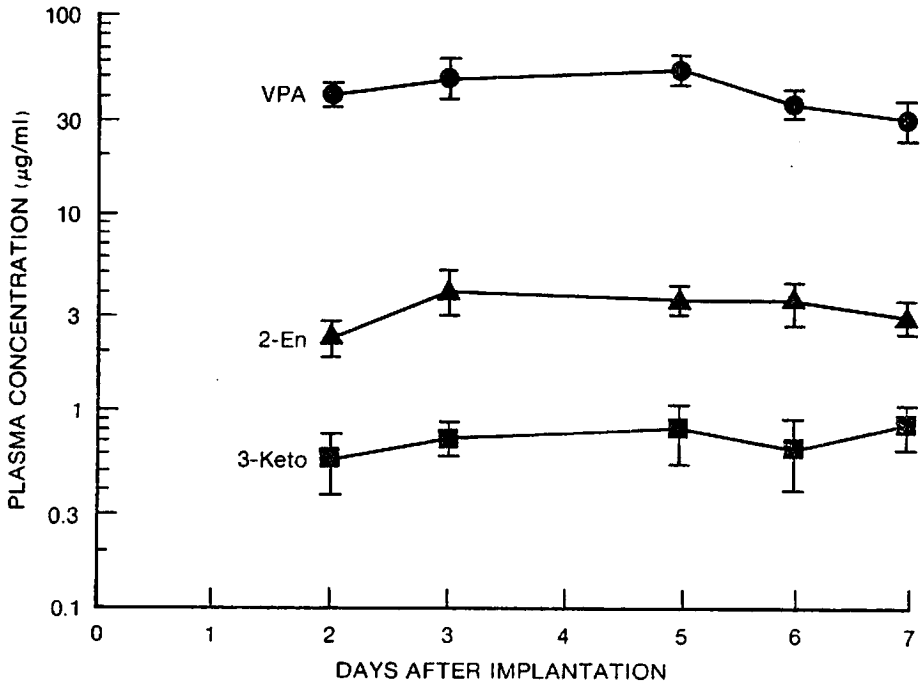

Fig. 2. Valproic acid plasma concentrations in mice following s.c. implantation at day 7 of gestation of two osmotic pumps containing 400 mg sodium valproate per ml water and delivering 1 μl h^{-1} of drug. (From Nau *et al.*, Ref. 1.)

human growth hormone[10], and triiodothyronine[11] were studied in comparative injection–infusion protocols showed similar regimen dependent drug actions.

Pharmacokinetic differences between infusion–injection regimens

Before examining interpretative aspects of the pharmacodynamics underlying these different responses to injections and infusions, it is useful to consider the pharmacokinetic differences between the two regimens. The injection regimen presents the drug in a rapidly absorbable form that usually causes a rapid rise in the concentration of drug in blood and tissues. The concentration peaks usually within an hour or two – and then declines until the next dose is given. If the half-life of the drug is short, and if the interval between injections is relatively long, then the concentrations of drug in blood and tissues may fall to zero between doses. On the other hand, if the drug's half-life is relatively long, and if the interval between its injections relatively short, then the concentrations of drug have less time to decline, and they decline more slowly; therefore, concentrations fluctuate less.

A good rule of thumb is that if the interval between injections is greater than 4 times the drug's half-life, it is reasonable to assume that drug concentrations will fall to zero between doses. Application of this rough rule in planning or analysing experiments, however, requires knowledge and use of the half-life of the drug in the species under study. Drugs generally have much shorter half-lives in small animals than in larger animals and man.

Another rule of thumb is also helpful, namely: the ratio of the half-lives in two species is very roughly proportional to the one-fourth power of the ratio of the average weights of two species. Thus, between a 100 kg human and a 10 g mouse the half-life in the mouse is about one-tenth the value in man: the body weight ratio is 1/10 000 and the 1/4th power of 1/10 000 is 1/10. This estimate, which roughly applies, e.g. to valproate, is worth calculating and noting in designing a regimen for animal testing. The short half-life in the

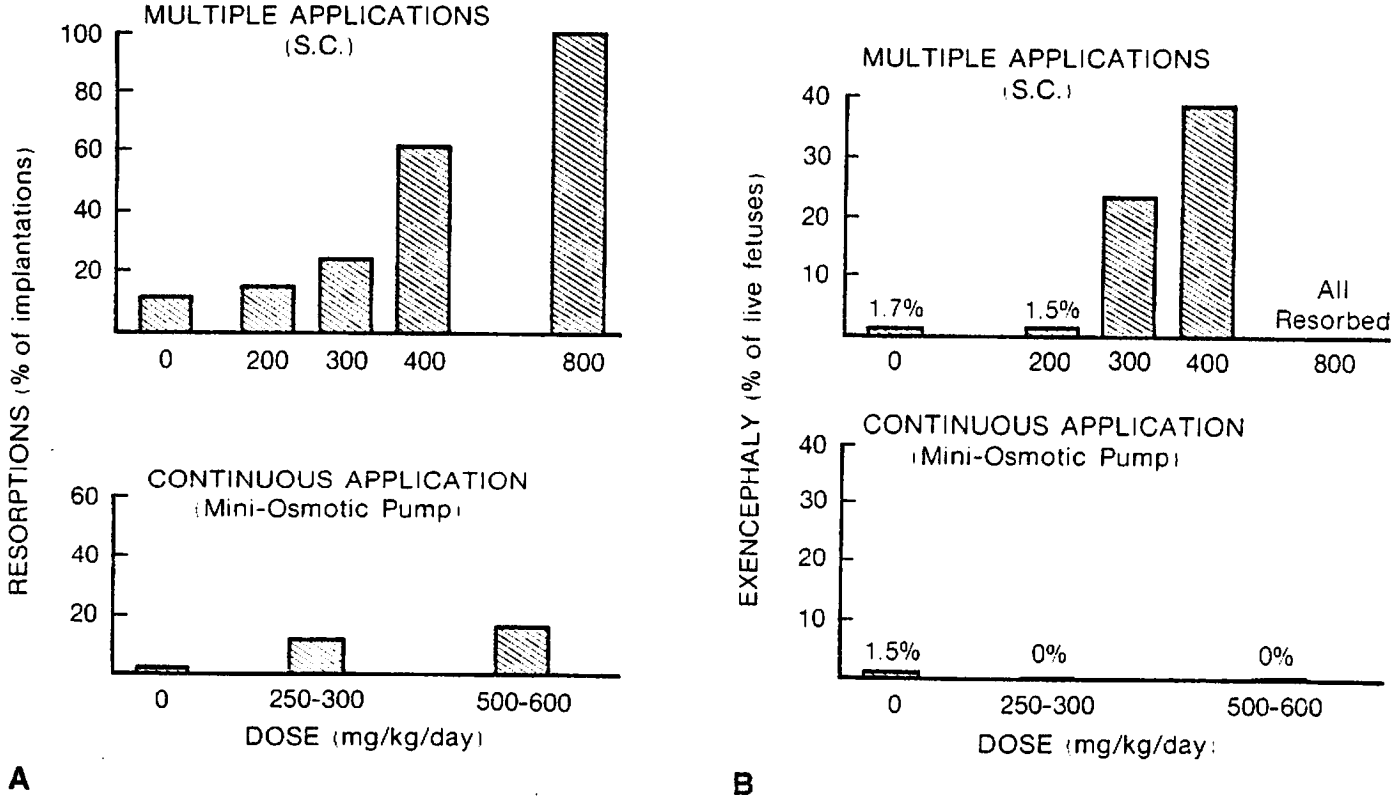

Fig. 3. (A) Percentage of implantation resorptions in mice after administration of valproic acid between days 7–15 of gestation. (From Nau *et al.*, Ref. 1.) *(B) Incidence of exencephaly (% of live fetuses) in mice following administration of valproic acid between gestational days 7–15.* (From Nau *et al.*, Ref. 1.)

mouse means that the regimen should call for reinjection every 4 h to ensure continual presence of the experimental agent in blood and tissues. Otherwise, some hours of 'drug holiday' will occur when no drug is present in the test animal. If drug holidays do not also occur in humans, the long periods with no detectable drug in mice may lead to underestimating its human toxicity. The opposite error in extrapolating data from mouse to man may also arise. Since injections produce much higher peak concentrations in small animals than in human subjects, the human toxicity of a drug may be overestimated.

In contrast, the infusion regimen builds the concentration of drug up to a steady level that is maintained so long as the infusion continues. Reaching that level requires a period of time equal to 4 drug half-lives. Since concentration usually does not 'peak' during an infusion, the pharmacokinetic concept of 'time-to-peak' has no meaning. Since concentration is maintained throughout the duration of the infusion, which can be hours, days, weeks, or months, the pharmacodynamic concept of 'duration of action' also has no meaning. Some fluctuation in concentration may, however, occur during an infusion if, for example, the metabolism or excretion of the drug has a diurnal rhythm. Some fluctuation or drift in drug action may occur if drug receptors increase or decrease in number during the course of the infusion.

A simple relation to use to approximate the maintained concentration of drug during an infusion is this: rate of infusion = concentration × clearance = rate of elimination. Since infusion rate equals elimination rate in the steady state, measurement of the drug's concentration in plasma permits a simple calculation of the drug's clearance value, namely the infusion rate divided by the concentration. (Infusion rate is the product of drug concentration in the infused solution and the vehicle flow rate.) The calculated clearance rate can then be used to estimate what concentrations will prevail with other infusion rates; any day–night variations observed in drug concentration signify day–night variations in clearance, which can be calculated from the concentration measured during day and night. Finally, when infusion is stopped, drug concentration will begin to decline, and will effectively reach zero after a time period equal to four drug half-lives in the species under study.

Pharmacodynamic and therapeutic implications

With these simple pharmacokinetic considerations in mind, let us now look at some possible pharmacodynamic and therapeutic implications of regimen-dependent expressions of drug action. The following interpretations of right and left shifts in dose–response curves are speculative, but they may serve to demonstrate the value of the infusion–injection comparison (IIC) protocol in stimulating new lines of thinking in pharmacodynamics.

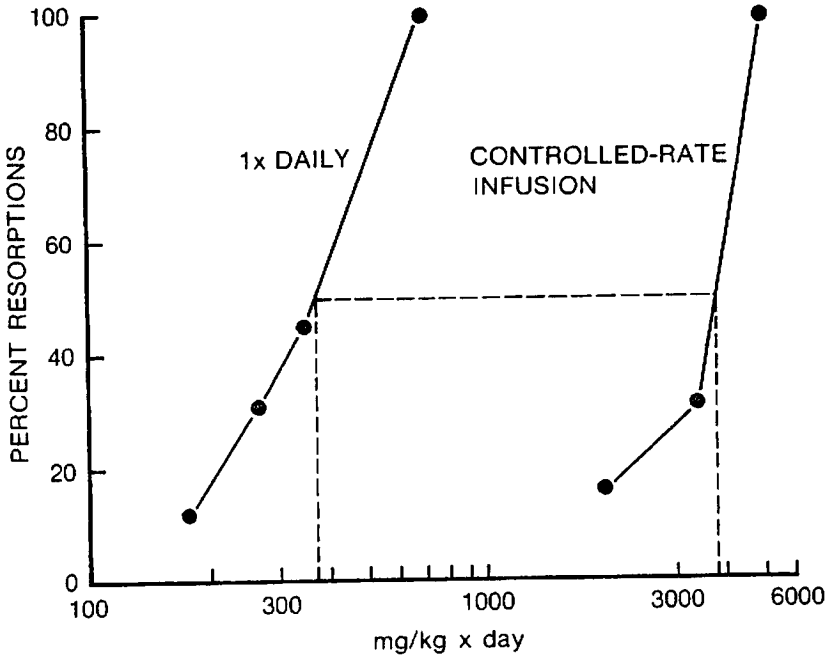

Fig. 4. Fetal reabsorption rate observed when valproic acid is given by single daily injection and by infusion. (From Nau *et al.*, Ref. 2.)

In assessing leftward shifts of the dose–response curve during infusion, one needs to know whether the injection regimen allowed any 'drug holidays'. If so, then one might infer that the continuing presence of some drug during infusion, although not necessarily a high concentration, is an important determinant of the response. (Note that the concept of 'drug holiday' is not restricted to zero concentrations; if a minimum effective concentration for a drug action exists, then any lower concentration would represent a 'drug holiday' for that action.) The leftward shift with infusion also suggests that even the high peak concentrations produced by injections do not compensate for periods of drug absence so far as eliciting the effect in question is concerned.

If, on the other hand, the dose–response curve shifts to the right with infusion, one might infer that a peak concentration plays an important role in eliciting the response. The embryotoxicity of valproate is an example; although ≥18 h of 'drug holiday' occurred in Nau's study with the once-daily injection regimen, embryotoxicity nevertheless occurred with doses that had no such effect when given by constant-rate infusion. Conversely, the low concentration that the infusion continuously maintained failed to elicit exencephaly, or cause fetal death at daily doses that caused 100% fetal death when given by injection.

What does it signify when injection and infusion regimens show little or no difference in dose–response? For example, although Nau showed a statistically significant difference between infusion–injection regimens with respect to fetal weight loss, the absolute difference was small, relative to that observed with exencephaly and fetal death. Here it seems reasonable to suppose that the pharmacodynamically important factor associated with weight loss is quantity of drug reaching the receptor, not the time-pattern of its arrival. Thus, carrying out the IIC protocol is, arguably, the logical first step in the systematic pharmacodynamic study of a drug.

Whether or not these speculations are apt, they suggest that the IIC protocol serves an important purpose. It provides some view of the boundaries of the drug's pharmacodynamics: (1) whether its actions are peak-concentration related; (2) whether 'drug holidays' are important; (3) whether the drug's actions are relatively independent of the time-pattern of drug administration/drug concentrations. These considerations are basic in deciding the best time drug deployment in the body in therapeutic use, i.e. whether continuous presence or a short pulse/long 'holiday' sequence is the preferable time pattern, or whether it does not matter which.

Clinical pharmacological implications

Having this basic pharmacodynamic understanding should be a good guide to how best to administer the drug in human use. In therapy one obviously seeks the

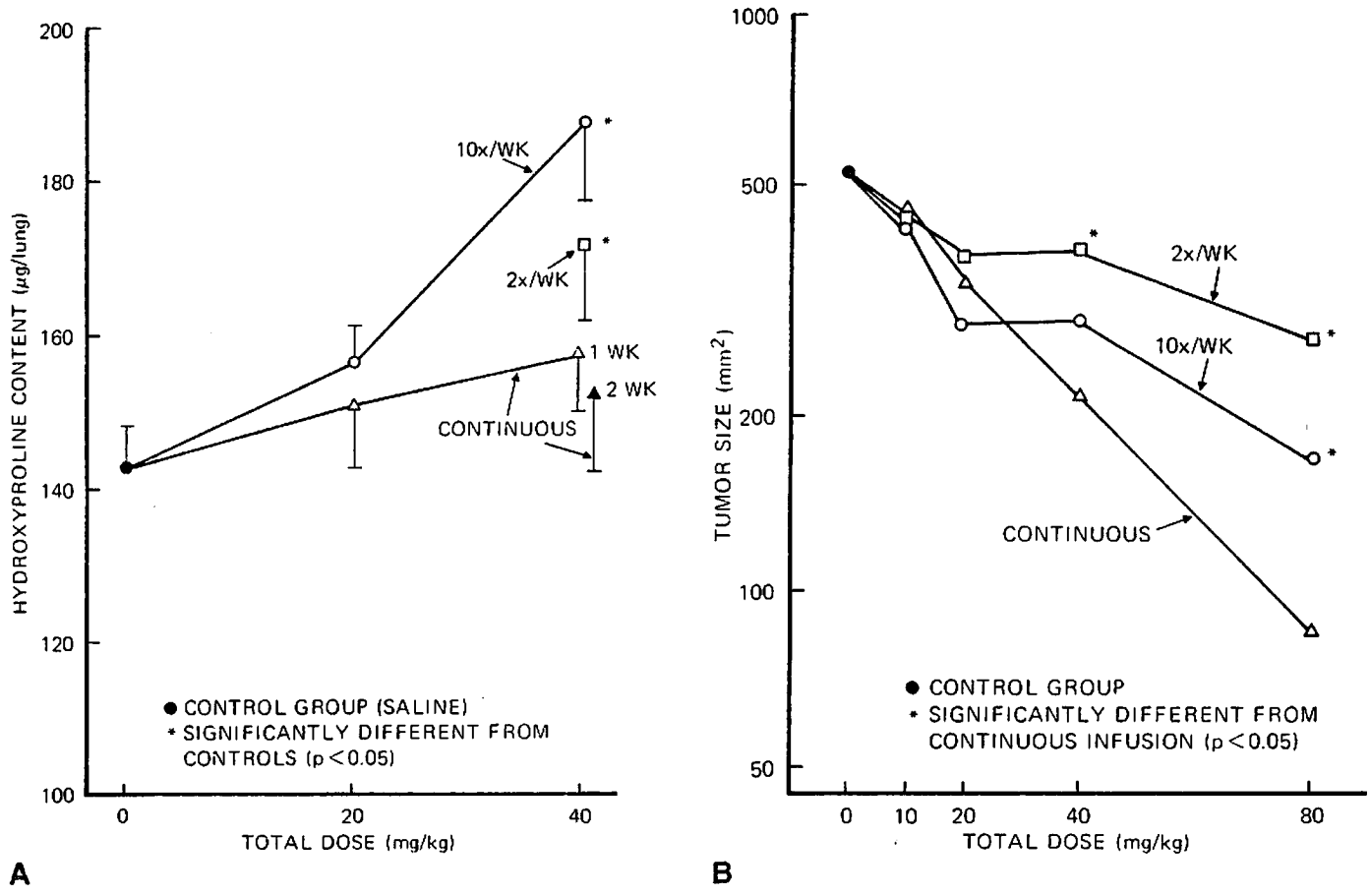

Fig. 5. (A) Effect of various regimens and doses of bleomycin on pulmonary toxicity in nontumored animals, as measured by lung hydroxyproline content 10 wk after treatment. (From Sikic *et al.*, Ref. 3.)

(B) Dose–response curve of bleomycin antitumor effect against Lewis lung carcinoma comparing 3 regimens of administration. These measurements, made on day 15 after implantation, are representative of differences that existed throughout the course of tumor growth. (From Sikic *et al.*, Ref. 3.)

greatest possible degree of selectivity of action. That aim would seem to call for a regimen that places the dose–response curve for the desired action as far to the left as possible, and places the curve for the undesired actions as far to the right as possible.

Comparing the responses to these two regimens should provide a guide as to whether the drug manifests its greatest selectivity of action in humans when it is administered in a multiple-dose pattern or at a constant rate. Achieving the former would require rapidly dissolving, rapidly absorbed dosage forms incorporating the derivative of the drug with the shortest possible half-life. If, on the other hand, constant rate administration provides the best selectivity, then a rate-controlled oral or transdermal form, or an i.v. infusion would be the logical choice.

When the injection–infusion regimens produce different but suboptimal results, then some intermediate time-pattern of drug input may be tried. For example, a short half-life agent administered in a single injection might evoke a brief but useful response; the same agent administered in a constant infusion might evoke a good initial response that fades as the infusion continues. In that case, an injection sequence in which the length of the 'drug holiday' is varied systematically, may prove useful. Use of such a sequence, in fact, is how Knobil and his associates succeeded in working out the remarkable pharmacodynamics of gonadotropin-releasing hormone[5]. Knobil's work, and its subsequent clinical applications[6–10], is a very important object lesson and model for all with interest in pharmacodynamics.

Another way to deal with the 'drug holiday' problem may be to use a combined regimen of injections plus infusion. The injections produce peak concentrations, related to the dose injected; the infusion ensures continuing presence of the drug, at a minimum concentration proportional to the infusion rate that will prevail as long as the infusion continues. Such combined regimens may be particularly useful in the evaluation of antitumor agents.

Conclusion

The studies reviewed here suggest that dose–response studies should be designed to compare results obtained with the injection mode of administration and with the infusion mode. The IIC protocol appears to be a basic first step in the systematic study of a drug's pharmacodynamics. It has practical implications for therapeutics because sometimes one mode of administration provides much greater selectivity of drug action than the other. Such information ought to be taken into account when the initial human studies of the drug are being designed.

Acknowledgement

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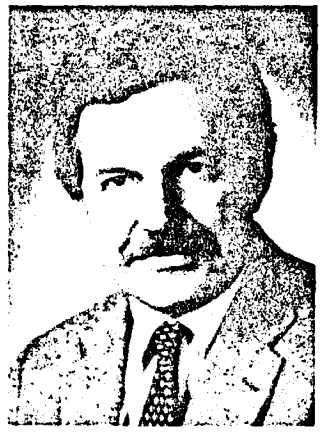

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The pharmacology of Parkinson's disease: L-dopa and beyond

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Introduction

There is little doubt that the introduction of L-dopa treatment of Parkinson's disease was a revolutionary step in neuropharmacology[1]. Not only is it effective and comprehensive in its reversal of many parkinsonian symptoms, its introduction represented a major advance in that it derived directly from neurochemical findings[5]. This surprisingly unserendipitous approach to drug design has paved the way for similar approaches to other neuropsychiatric disorders with, however, rather less success.

L-dopa is widely and successfully prescribed, although it has not totally superseded the anticholinergic drugs which are still employed, particularly in early stages of the disease process. However, much effort has been put into the search for other antiparkinsonian drugs, either to replace L-dopa or improve still further its therapeutic effects.

Optimization of L-dopa by enzyme inhibition

A major problem with L-dopa is that the high dose necessary for an effective central action has substantial, and occasionally intolerable, peripheral side-effects. These side-effects are minimized by the concurrent administration of an inhibitor of dopa decarboxylase, which prevents peripheral formation of dopamine, allowing proportionately more L-dopa to enter the brain and be decarboxylated at the appropriate sites, the dopaminergic terminals of the striatum.

With this advance, antiparkinsonian drug treatment came of age; combined L-dopa and decarboxylase inhibitor treatment has been the mainstay of the parkinsonian patient for several years now[2]. The success of this inhibition in increasing the efficacy of L-dopa treatment has led to other enzyme inhibitors being investigated in an attempt to increase the amount of dopamine available for neurotransmission. It was thought that monoamine oxidase (MAO) inhibitors might have a similar effect since they would be expected to block the oxidative degradation of dopamine. Initial experiments with L-dopa and some unspecific MAO inhibitors were soon abandoned due to intolerable side-effects, although improvements in motor function could be observed.

More recently a relatively new MAO inhibitor, selegiline (deprenyl)[10], has been found beneficial and is now being introduced in several countries, including the UK. Selegiline is unusual in being free of the 'cheese effect', a hypertensive response which other, less selective, MAO inhibitors induce when taken concurrently with some amine-containing foods. Its favourable effects on akinesia, particularly end-of-dose akinesia, and its ability to relieve the rapid ('on-off') oscillations in drug response (reviewed in Ref. 2), are presumed to derive from its specific inhibition of MAO type B, for which dopamine is a substrate (while noradrenaline and 5-hydroxytryptamine are substrates for type A) in human brain[3]. Since selegiline has an L-dopa-sparing effect additional to that due to peripheral decarboxylase inhibitors, it would seem that the resultant MAO inhibition brings about a specific increase in the availability of dopamine at the synapse.

Following the success of selegiline, another MAO inhibitor, tranylcypromine, has been re-examined for the treatment of Parkinson's disease[13]. Although not as specific as selegiline, tranylcypromine is