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DOSAGE AND THE PHARMACOKINETICS OF CYTOTOXIC DRUGS

It is now widely accepted that the dose of most cytotoxic drugs is critical and successful therapy depends on steering a course between maximum effect on the tumour and serious drug toxicity. This is particularly true when anti-cancer agents are tested in animal tumour systems where for most agents there is a steep dose-response curve. For example, Frei & Freireich (1965) have shown that in L1210 leukaemia reduction of the dose of cyclophosphamide to one-eighth made it less effective in terms of cell kill by a factor of 5 logs. Over the last few years, using mainly mouse leukaemia models, it has been possible with a number of cytotoxic agents to relate tumour cell kill to both the concentration of the drug and to duration of exposure. In addition, similar data can be obtained for normal tissue, particularly bone marrow. Provided there are differences in the sensitivity and rates of recovery from cytotoxic drugs between malignant and normal cells, treatment schedules can be designed which result in maximum destruction of malignant cells with minimal damage to normal cells (Bruce & Valeriote, 1969; Nichol, 1977).

It might be thought that if this information were applied to the treatment of human cancer optimal therapeutic results would be obtained. Models have been produced which combine the growth kinetics of tumour cells and their modification by cytotoxic drugs with the drug's pharmacokinetic properties (Himmelstein & Bischoff, 1972; Jusko, 1971, 1973). At a less theoretical level, the current use of multi-drug pulsed dosage regimes which are based on similar experimental data has produced much better results in the treatment of lymphomas and leukaemias than previous schedules of treatment.

There is, however, some doubt as to whether these principles are always so effective when applied to many types of human cancer and the subject has recently been reviewed by Tattersall & Tobias (1977). They divide human cancers into three groups, those which are highly sensitive to chemotherapeutic agents, those which are moderately sensitive and those which are relatively insensitive. They show that in all groups there are conflicting results, and that in many types of cancer the relationship between dose and therapeutic response is not clear cut and differs from the precise relationship found in animal models.

It is perhaps not surprising that variable results should be obtained with the standard dose regimes of cytotoxic drugs in human cancer and it is likely that there may be both pharmacokinetic and biokinetic variables involved. In terms of pharmacokinetics, some progress has been made in understanding these variables. Advances in analytical techniques have now made it possible to measure the plasma levels of many cytotoxic drugs and to obtain such classical pharmacokinetic parameters as the rate and extent of absorption from the gut, plasma peak concentration and plasma half-life, plasma clearance and elimination rates and to define some of the factors which might alter these parameters (Chabner, Myers & Oliverio, 1977; Spreafico & Rossi, 1977).

Pharmacokinetics studies have produced helpful guidelines in the use of some cytotoxic drugs: a good example is methotrexate where it has been possible to provide a logical basis for various dosage regimes (Bleyer, 1977a). For example, measurement of plasma concentration/time profiles have shown that up to an oral dose of 30 mg/m^2 absorption is almost complete, whereas at higher doses it is erratic and incomplete, suggesting that the oral route is only suitable for low doses.

After intravenous injection the plasma concentration falls in a triphasic fashion, the last prolonged phase with a half-life of about 10 h being particularly important in terms of bone marrow depression as the toxicity of methotrexate is related to the duration of exposure to the drug as well as its peak plasma concentration. Consideration of this pharmacokinetic characteristic of methotrexate has formed the basis of folinic acid rescue where the potential toxic effects of a large dose of the drug are reversed by folinic acid after an appropriate interval. It is also possible to predict from pharmacokinetic data those patients in whom slowed plasma clearance may require intensified rescue (Isacoff, Morrison, Aroesty, Willis, Block & Lincoln, 1977).

The results of pharmacokinetic investigation have also been used to design treatment regimes for cytarabine. This drug is notorious in that its plasma half-life is very variable, a possible factor in treatment failure or unforeseen toxicity. Following single dose plasma concentrations studies it has been possible to calculate the dose for constant infusion to maintain a suitable plasma concentration (Ho, Brown, Benvenuto, McCredie, Buckels & Freireich, 1977).

The measurement of drug concentration in plasma and in other tissue fluids is also useful in determining its penetration into important areas such as the cerebro-spinal fluid (Mellett, 1977), and also in determining the plasma concentration when drugs are given by unusual routes. For example, intrathecal methotrexate diffuses from the cerebro-spinal fluid into the plasma, producing appreciable plasma levels (Bleyer, 1977b; Bleyer & Dedrick, 1977). This can

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under certain circumstances become dangerous and severe methotrexate toxicity has been reported in a patient with renal failure who received 20 mg/m^2 of methotrexate intrathecally (Cadman, Lundborg & Bertino, 1976). Recently the pharmacokinetics of intraperitoneal cytotoxic drugs has been reviewed (Dedrick, Myers, Bungay & De Vita, 1978). The differences between peritoneal fluid and plasma levels has been defined and general principles of treatment defined.

With many drugs there is a direct relationship between the plasma concentration of a drug and its pharmacological effects. To obtain this, it is necessary that the drug has easy access to its site of action: with cytotoxic drugs this situation is unlikely. Although the distribution of a cytotoxic drug within the body depends on its pharmacokinetic properties there are many factors which will modify its action on malignant cells. The concentration of the drug in the tissue is important but much more so is the concentration/time profile within the tumour and with many drugs within the cancer cell itself. When the variation in size, composition and blood supply of tumours is considered together with the factors which affect penetration of the drugs into and out of the cells, the problem becomes very complex.

As far as tissue concentration and penetration is concerned, classical pharmacokinetics has dealt largely with volumes of distribution which are abstractions and not related to anatomical division and are thus of little use in measuring drug concentrations within organs. Fairly recently a different approach has been proposed by Bischoff, Dedrick, Zaharko & Longstreth (1971). This technique consists of building up a computer model of the distribution and elimination of a drug in animals by direct measurement of tissue/plasma equilibrium of the drug, drug clearance across organs, tissue binding and plasma concentrations and by such physiological data as organ weight and plasma flow. The next stage is to scale up the data to man which can apparently be done without undue loss of biological consistency. This method has already been applied to methotrexate with some success. At present this technique is mathematically very complex and it may be that the computer model is not generally applicable to man owing to the considerable variation of characteristics among the population studied. At the best, this method requires a lot of refining and as yet it has not been able to give the concentration of the drug within the tumour.

A further difficulty is that some cytotoxic drugs are activated *in vivo* and this gives another situation in which measurement of blood levels can be misleading. For example, cyclophosphamide itself is inactive but is changed to cytotoxic metabolites in the liver. Juma, Rogers & Trounce (1979) have recently shown that the formation of these metabolites is modified by the route of administration. There appears to be a moderate first-pass effect so that oral dosage produces a higher blood level of *in vitro* alkylating activity than intravenous injection. Their assay of total alkylating capacity in the plasma as an index of metabolite production does not, however, enable them to say how much of the metabolite production is made up of active cytoxic agents. It is possible that other factors which might interfere with metabolism of cyclophosphamide could modify the production of therapeutically active substances. Similarly the effective action of 5-fluorouracil depends on factors other than drug concentration ambient to the malignant cell, and the situation has been well reviewed by Sadee & Wong (1977). The therapeutic effect of 5-fluorouracil probably depends on the formation of the nucleotide 2-deoxy-5-fluorouridine 5-monophosphate (FdUMP) within the cell as this substance is a major inhibitor of thymidylate synthetase. Not only does the formation of this and other nucleotide metabolites show no correlation with plasma levels of 5-fluorouracil, but the metabolites themselves are largely trapped within the cell and thus not available for estimation in the plasma. It seems probable that similar problems exist with other antimetabolite cytotoxic agents where complex intracellular activation plays an important part in their biological activity.

It is apparent, therefore, that with a number of cytotoxic drugs in which biotransformation is required before the drug becomes an effective cytotoxic agent, estimation of the concentration of the drug in the plasma will give little indication of its anti-tumour activity.

A most important cause of variability in response to cytotoxic drugs is the considerable differences in sensitivity which seem to occur between cancer cells of the same morphology but from different patients. Harris, Potter, Bunch, Boutagy, Harvey & Grahame-Smith (1979) have shown enormous differences in plasma concentration/time profile of cytarabine required to reduce numbers of blast cells in the peripheral circulation in acute myeloblastic leukaemia. In this disease access to malignant cells should not be so variable as with solid tumours as the majority of malignant cells will be in direct contact with the plasma and indeed the situation is analogous with the much used mouse leukaemia model. In spite of this, classical pharmacokinetics correlated very poorly with therapeutic response.

Not only may differences of cell sensitivity occur between tumours, but they may also occur within the same tumour. The question of cell kinetics and sensitivity to cytotoxic drugs has now become the scene of an enormous amount of work, but in general it can be stated that tumours with a high growth fraction and a small number of quiescent cells are usually the most susceptible to treatment by radiotherapy or chemotherapy (Tubiana & Malaise, 1976). This is because the quiescent cells appear

resistant to cytotoxic drugs and they are a major obstacle to successful treatment. Instead of having a homogeneous population of 'receptors' as is the case with many drugs, the situation is more akin to that found with antimicrobials where there may be resistant organisms within the population or where resistant strains may emerge. This makes correlation between plasma levels and effectiveness more complicated for the minimal lethal concentration/time profile may vary from cell to cell.

The improvements in analytical techniques which have occurred during the last few years are leading to increased pharmacokinetic investigation of cytotoxic drugs and no doubt attempts will be made to control dosage by measurement of plasma levels of these agents. This should be useful in determining whether the patient suffers from any major abnormality in the handling of the drug and will enable the dose to be calculated and the drug used more precisely in the face of such problems as absorption defects, gross liver disease or renal impairment. It may also bring to light differences in metabolism of the drug due to disease or genetic factors, or to interactions with other drugs, a hazard which is already beginning to emerge (Warren & Bender, 1977). Classical pharmacokinetic studies are unlikely to provide much information concerning the concentration/time profile of a drug at its actual molecular site of action, and may thus correlate poorly with its therapeutic effect. It would seem that there is a great deal of thinking to be done before it is possible to use cytotoxic drugs with maximum efficiency in man, and there is room for fresh approaches to their pharmacokinetic analysis.

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