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Editorial

Pharmacokinetic Modelling—A Prelude to Therapeutic Drug Monitoring for All Cancer Patients?

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THERE IS currently a great cleal of interest in pharmacokinetic modelling in relation to anticancer drugs and in the subsequent use of pharmacokinetic information to individualise dosing. Two examples are given in this issue (Peng and associates (pages) and Holz and associates (pages)), illustrating how different methods can be used to develop limited sampling strategies, which allow an accurate prediction of drug exposure to be made on the basis of only one or two blood samples. The multiple sampling required to define fully an individual plasma elimination profile could not be applied routinely whereas, in principle, limited sampling could allow pharmacokinetic monitoring to be extended to standard therapy. Hence, the question must be asked "how should the information obtained be used?"

The study of pharmacokinetics is rightly an integral part of the development of a new drug. Although preclinical models can never predict completely the behaviour of a drug in man, phamacokinetic information enables correlations to be drawn between the plasma concentrations associated with both toxicity and efficacy, i.e. pharmacodynamics. Usually the specific pharmacokinetic parameter which affords the best correlation with these is the area under the concentration × time curve, or AUC [1], but occasionally peak plasma concentration or time above threshold will be more appropriate, depending on the mechanism of action of the drug. Such investigations will be helpful in determining the most appropriate dose and schedule to be tested in phase II and III clinical trials. Furthermore, the impact of impaired kidney or liver function and interactions with other agents need to be studied if a drug is to be used safely.

There are a number of examples of cytotoxic agents whose dosage may require considerable adjustment in the case of impaired organ function, e.g. epirubicin [2], carboplatin [3, 4], etoposide [5]. In the case of carboplatin, for which clearance is largely due to glomerular filtration, formulae have been derived for the calculation of dose according to renal function, which result in a much more accurate prediction of drug exposure than prescription according to body surface area [3, 6]. The most accurate measurement of renal function is provided by radioisotope methods, in which the clearance of a marker such as [^{51}Cr]EDTA is used to give an indication of glomerular filtration rate (GFR). It has been shown that formulae, such as that of Calvert, do not give accurate information if GFR is calculated from plasma creatinine [7].

Although carboplatin is an example where a surrogate for carboplatin clearance, i.e. GFR, is used to estimate drug exposure, methotrexate remains the only example of a drug where pharmacokinetic monitoring is part of routine practice [8, 9]. Methotrexate clearance is saturable with a long terminal phase. High dose methotrexate requires the use of folinic acid rescue, the duration of which is determined by monitoring methotrexate elimination. Although avoidance of toxicity is the prime consideration, as with carboplatin, it is also the case that interpatient variability may lead to underdosing. Horwich and associates [10] analysed their results with carboplatin in patients with testicular cancer who had been dosed according to body surface area. They calculated carboplatin AUC retrospectively from a knowledge of renal function at the time of treatment and showed that patients receiving a carboplatin AUC of < 4 mg/ml.min had a higher chance of relapse. Similar data have been produced for ovarian cancer [11].

However, it remains the case that, for the majority of cytotoxic agents, pharmacokinetically guided dosing has not been performed outside phase I trials. Should this be the case? It is universally acknowledged that the current generation of anticancer drugs is characterised by a low therapeutic index, i.e. the ratio between a toxic and an effective dose. It is less widely known that current dosing procedures result in wide variations in drug exposure owing to our incomplete knowledge of clearance mechanisms and their variability between patients, e.g. 3- to 4-fold variation in AUC in the case of carboplatin if prescribed according to body surface area (see Peng and colleagues (pages)). One solution to this dilemma is to assume that cytotoxics have to be given at the maximum tolerated dose (MTD), i.e. toxicity must be observed, if necessary, using haemopoietic growth factors to allow "optimum doses" to be delivered. Unfortunately, this approach has not yet been shown in randomised trials to improve results and the guidelines of the American Society of Clinical Oncology [12] are quite clear in stating that growth factors should not be used to facilitate dose escalation outside the context of clinical trials.

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The other, more scientific, approach is to decide what level of drug exposure is optimal and to use pharmacokinetic information to ensure that this is delivered. Studies of methotrexate pharmacokinetics in children with acute leukaemia undergoing remission induction therapy with high dose methotrexate demonstrated that there was a correlation between a high methotrexate clearance and an increased likelihood of relapse [13]. Subsequent investigations showed that maintenance of a steady state methotrexate concentration above 16 μmol/l was associated with an improved outcome [14], leading to an evaluation of test dose of methotrexate followed by individualised dosing to try and ensure that the target steady state level is reached.

There have been a number of other examples showing that pharmacokinetic monitoring with subsequent adjustment of dosage, i.e. adaptive control, is feasible. For this to be practical, it is necessary to limit the number of blood samples required in order to predict the pharmacokinetic behaviour of the drug in a particular individual. The development of such a limited sampling strategy requires the acquisition of a sizeable data set using multiple blood sampling, termed the training set, followed by pharmacokinetic modelling to predict which samples are necessary to define the elimination profile. Different methods may be employed to generate a limited sampling strategy. The iterative two stage approach to population kinetics uses initial estimates from the training set which are then applied prospectively while the data generated are used to modify the original estimates. This method of incorporating existing and new information is usually referred to as Bayesian estimation after the English mathematician T. Bayes [15, 16]. This is time consuming and requires the use of computer programmes which are not particularly "user friendly", e.g. ADAPT II [17]. It is also unclear at what stage the process of refining the model should be regarded as complete. A more comprehensive method is known as non-linear mixed effects modelling which employs the programme NONMEM. This can cope with incomplete data sets from a large number of patients from which a population model can be constructed. A much simpler strategy is that of stepwise forward multiple regression. This uses detailed information forming the training set and involves univariate analysis of time point data compared with the AUC, followed by stepwise forward regression to develop models which can then be compared by the F-test and subsequently be validated. Theoretically, this method is limited in that only one parameter is calculated and the model developed cannot be applied to other schedules of administration.

So, having achieved the initial goal of developing a reliable pharmacokinetic model, generating a limited sampling strategy which enables the pharmacokinetics of the agent to be accurately described from only one or two plasma samples, and demonstrating that drug exposure can be determined more accurately by its use, what then? Should monitoring be applied to all cytotoxic agents in every situation? Ideally yes, but this is currently impractical owing to limited rescources and sometimes lack of suitable methodology. However, therapeutic drug monitoring is now an accepted part of management in many areas of medicine such as the management of epilepsy, cardiac arhythmias and mental illness, should it not be accepted in oncology where all the drugs have a narrow therapeutic range? It must be acknowledged that the problem is more complex given the intermittent nature of cytotoxic therapy compared with chronic oral administration where steady state levels are meaningful.

It has been shown that clear relationships can be established between pharmacokinetic parameters and toxicity or response, i.e. pharmacodynamics. Furthermore, dosing schemes using therapeutic monitoring have been developed which have sucessfully limited the toxicity of new agents such as suramin [18] and improved the therapeutic index of established agents such as 5-fluorouracil (5-FU) [19] and etoposide [20]. A positive correlation has also been shown between 5-FU AUC and survival [21]. Where should one concentrate efforts to deliver optimal drug exposure? One obvious situation is when there is a risk of overdosing, as in patients with organ dysfunction. Another is in the context of genetic variations in drug metabolism where loss of the normal catabolic pathway can lead to excessive toxicity as in the case of 5-FU and deficiency of the enzyme dihydropyrimidine dehydrogenase [22], or 6-mercaptopurine and thiopurine methyltransferase [23]. In the latter case, monitoring has also been helpful in ascertaining levels of compliance, something that may be a problem with chronic oral dosing. However, numerically it is more important to consider the problem of inadvertant underdosing. Where dose intensity has been considered in prospective randomised trials, it has been shown that while dose escalation does not necessarily produce better results, there appears to be a threshold which must be exceeded [24]. Where treatment is being given with curative intent, particularly in paediatrics, every effort should be made to minimise interpatient variability in drug exposure in order to maximise the benifit while keeping the risk of serious side-effects at an acceptable level. The use of pharmacokinetic modelling to develop limited sampling strategies and their subsequent use in therapeutic drug monitoring with dose adjustment, i.e. adaptive control, may offer the best way to achieve this goal with the current generation of cytotoxic agents. What is now required is further prospective validation of this approach in a controlled manner in order to prove that the necessary investment is justified.

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