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Reviews

The Practical Benefits of Pharmacokinetics in the Use of Antineoplastic Agents

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Summary. *Clinical pharmacokinetics has clearly had an important impact on the use of antineoplastic agents, but this influence has primarily been the result of comprehensive analyses conducted at the time of initial clinical trial. Such studies have often determined the dose, schedule, and route of administration, and have provided general guidelines for dose adjustment in patients with organ dysfunction. On the other hand, routine pharmacokinetic monitoring, while a highly effective adjunct to drug therapy in clinical specialties other than cancer, has not yet had an important effect on clinical oncology, with the obvious exception of high-dose methotrexate therapy. A number of potentially important applications of routine monitoring are pointed out in this paper, and will certainly be examined in the future as a means of dealing with pharmacokinetic variability. However, major impediments in this effort are posed by complexity of antineoplastic pharmacology and the lack of suitably sensitive, specific, and rapid assays for routine clinical use. Radioimmunoassays and competitive binding methods offer considerable hope in this effort, but the widespread application of these methods has not yet been realized in clinical practice.*

Introduction

An understanding of pharmacokinetics has become essential to the effective use of many classes of drugs, including antibiotics, cardiovascular agents, and anticonvulsants. In these areas, routine drug level monitoring has become commonplace, and has been of clear benefit in solving specific problems regarding drug delivery, optimization of therapeutic effect, and minimization of toxicity. It is not difficult to convince the average practitioner of the benefits of monitoring such agents as phenytoin or procainamide; it is well established that standard doses of phenytoin (300 mg per day) produce suboptimal plasma concentrations in over 50% of patients, and toxic levels in 16% [43]. Similarly, the original schedules of procainamide administration (every 6 h) have been adjusted to shorter time intervals (every 3 h) to accommodate the brief plasma half-life of this agent [61]. Similar useful applications of pharmacokinetic approaches have been infrequent in the field of antineoplastic therapy, principally because of the extreme chemical reactivity of many of these agents, their activity at low plasma levels, and the lack of suitably sensitive, rapid, and specific assay methods. However, this situation is rapidly changing thanks to major new advances in methods as well as clinical interest in basing therapy on pharmacologic considerations such as drug concentration and exposure duration. It will be the purpose of this review to discuss the impact of comprehensive pharmacokinetic studies and routine drug monitoring on current antineoplastic therapy.

Comprehensive pharmacokinetic investigations of new antineoplastic agents have been conducted for many years, and in many instances have provided useful information. In general, however, these studies were severely limited by the insensitivity of available assay methods, and often had to rely on the use of radioactive drugs. Such studies led to incomplete or mistaken conclusions, for several reasons: (1) Impure radiochemicals were used; (2) the radiolabel, such as labile [^{3}H] atoms, often dissociated from the compound before administration or during transit through the body; and (3) total radioactivity was taken indiscriminately to be a reflection of parent compound, as in the case of studies of melphalan [72] and of methotrexate [37]. The introduction of highly sensitive and specific methods, such as radioimmunoassay, competitive protein binding, high-pressure liquid chromatography, and gas chromatography-mass spectrometry, has greatly altered this situation in the past 5 years, and has al-

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Table 1. Assay methods available for selected antineoplastic agents

Agent	Assay method	References
Methotrexate	CPBA[a], RIA[b]	2, 5, 12, 36, 46, 47, 54, 60
5-Fluorouracil	HPLC[c], GC	15, 22, 23, 48
Cytosine arabinoside	HPLC, RIA	44, 58
6-Thioguanine	HPLC	49
6-Mercaptopurine	HPLC	49
Adriamycin	HPLC	39, 57
Bleomycin	RIA	13, 30
Melphalan	HPLC	20
Chlorambucil	HPLC	45
Cyclophosphamide	GC-MS[d]	34
Hexamethylmelamine	GC	29

[a] Competitive protein-binding assay
[b] Radioimmunoassay
[c] High-pressure liquid chromatography
[d] Gas chromatography-mass spectrometry

lowed precise measurement of parent compound and metabolites for many useful anticancer drugs (Table 1). These assays have been applied in two basic types of studies – comprehensive analyses of pharmacokinetics of new and established drugs, and routine clinical monitoring to aid adjustment of doses and clinical decision making in individual patients.

For the purposes of this discussion, comprehensive pharmacokinetic studies are considered to be detailed studies of drug disappearance in plasma, while routine drug monitoring differs in that a single time point is chosen as a valid reflection of the drug's pharmacokinetic behavior in that patient. For routine monitoring to be useful, comprehensive pharmacokinetic studies must have been completed for that drug.

I. Comprehensive Pharmacokinetic Studies in Antineoplastic Therapy

The primary goals of comprehensive pharmacokinetic studies are to define the absorption, distribution, elimination, and metabolism of a drug, with the ultimate aim of achieving an optimal clinical schedule and dose [31]. The four primary elements of pharmacokinetics set the foundation for a rational approach to drug administration, and, if performed at the time of initial drug trials in man, may profoundly influence subsequent drug usage. The importance of each of these elements will be considered in the following discussion.

Drug absorption studies are critical to the choice of route of administration. Variable or incomplete oral absorption leads to unpredictable or ineffective therapeutic activity. Melphalan and hexamethylmelamine are examples of antineoplastic drugs for which variability in plasma levels after oral administration has been well documented. Both agents are usually administered in fixed doses. Alberts et al. [3] and Tattersall et al. [72] have reported wide interindividual variability in melphalan absorption. Melphalan excretion in feces after oral administration was documented to be between 20% and 50% of the administered dose. The ratio of concentration by time ($C \times T$) for oral versus intravenous administration of melphalan in three patients ranged from 0.3 to 1.0, while one patient showed no plasma melphalan after an oral dose. Even greater variability in plasma levels of hexamethylmelamine has been demonstrated by D'Incalci and co-workers, who found 100-fold differences in the $C \times T$ product in their study of 11 patients [28]. In this case, the variability may be attributable to either erratic absorption or variable first-pass metabolism of the parent compound by the liver. These data imply that the standard dosage regimens often used in the treatment of multiple myeloma and ovarian cancer with these agents may result in inadequate drug bioavailability, and support an increased use of drug level monitoring with dose modification to assure adequate therapeutic exposure.

Knowledge of drug distribution is also an important element in therapeutic decision making for specific tumors and clinical situations. Nitrosoureas are the preferred agents for treatment of central nervous system malignancies because of their high lipid solubility and ability to cross the blood-brain barrier [27]. However, studies of the distribution of non-lipid-soluble drugs such as methotrexate have also yielded unexpected and useful information [9]. The drug levels (above 1 μM) that can be achieved in the cerebrospinal fluid during high-dose systemic infusion have allowed the successful use of this form of treatment for lymphoma metastatic to the central nervous system [64] and led to studies of its use as CNS prophylaxis in the treatment of childhood acute leukemia. Significant levels were also found in third spaces, such as peritoneal and pleural effusions [8]. The subsequent slow efflux of methotrexate from these compartments resulted in prolongation of the half-life of the drug in the systemic circulation, leading to prolonged exposure of normal tissues to low but cytotoxic concentrations of drug, with resultant unexpected toxicity. Recognition that the peritoneal space may selectively retain non-lipid-soluble agents such as methotrexate and 5-fluorouracil has resulted in the novel approach of using peritoneal dialysis as a means of delivering high concentrations of chemotherapy to intraperitoneal tumor, with limited exposure of systemic tissues [41, 65].

Knowledge of drug elimination, which most commonly occurs through renal excretion or hepatic metabolic degradation and biliary excretion, enables dose modification to be made in the face of organ dysfunction, or allows for continuation of maximal doses if this dysfunc-

tion is known not to influence pharmacokinetics. For example, studies of adriamycin elimination have revealed predominant elimination by metabolism in the liver, with subsequent biliary excretion. Toxicity was found to be increased in patients with hepatic compromise who received standard doses of the drug [7]. These findings led to the recommendation of 50% dose reduction for bilirubin levels above 1.5 mg per 100 ml, and 75% for bilirubin above 3 mg per 100 ml. Unfortunately, the available assays for adriamycin are not sufficiently simple or reliable to allow routine patient monitoring, and attempts to correlate blood levels with hepatic function or toxicity have been unsuccessful. Clearly there is a need for routine monitoring capability in the clinical use of adriamycin.

An additional example of the value of pharmacokinetic information is provided by recent studies of the combination of 5-fluorouracil (5-FU) and thymidine. These studies were initiated largely on the basis of the preclinical work of Martin and colleagues, who demonstrated agmented 5-fluorouracil incorporation into tumor RNA and enhanced antitumor activity in several murine systems [50, 51]. Clinical trials of this combination have not answered the question of its therapeutic value, but significant host toxicity has been observed [42, 74, 77]. When 15 g thymidine was administered prior to intravenous injection of 5-fluorouracil, the half-life of 5-fluorouracil was increased from less than 30 min to 6 h [77]. Increases renal clearance of intact drug and decreased [^{14}C]-CO_2 production from labeled drug suggest that this enhanced potency is the result of competition of 5-fluorouracil and thymine (derived from thymidine) for pyrimidine-catabolic enzymes. Additional mechanisms of interaction at the cellular level are not ruled out by these studies, but a plausible explanation for increased clinical toxicity has been provided by pharmacokinetic analysis.

An appreciation of the requirement of certain antitumor agents for activation by hepatic microsomes may influence drug usage. Prednisone [71], hexamethylmelamine [62], cyclophosphamide [25], and imidazole carboxamide (DTIC) [17] are all agents that require metabolic activation by liver microsomes. Intra-arterial administration of any of these drugs is unlikely to confer any therapeutic advantage. The conclusion reached in a recent report of the use of intra-arterial DTIC in an adjuvant protocol for treatment of malignant melanoma was that this therapy does not provide any additional benefit [6]. Although other factors may have contributed to this negative result, the pharmacological considerations would have suggested that no advantage could possibly result from this route of administration as against intravenous therapy.

In spite of the rapid accumulation of pharmacokinetic data about chemotherapeutic agents, a caveat must be recognized because of the nature of the antineoplastic process. Prediction of therapeutic or toxic effects on the basis of plasma pharmacokinetics presupposes that changes in plasma drug levels reflect changes within target tissues. However, the neoplastic process is heterogeneous with respect to differentiation, metabolic activity, clonogenic potential, and degree of vascularity. This heterogeneity may complicate the correlation of therapeutic effect with classic pharmacokinetic parameters such as plasma drug concentration. It may well be that such pharmacokinetic analysis will be useful in predicting toxicity, since the response of normal tissue to given drug concentrations should show less variability. With regard to antitumor effects, it is likely that additional approaches will be needed to define the relationship between drug concentration and therapeutic response, such as the integration of pharmacokinetics with biochemical pharmacology and cell kinetics.

II. Routine Monitoring of Antineoplastic Drugs

The usefulness of drug level measurement in the routine clinical use of antineoplastic drugs depends on the identification during more complete pharmacokinetic studies of a single time point or small number of points reflecting the interindividual variation that may result in increased toxicity or a compromise of therapeutic effect. A few such applications have been demonstrated in the clinical setting, but most remain speculative and must be verified by future studies. Several characteristics of available chemotherapeutic agents make routine drug monitoring a desirable goal. The therapeutic index for most antitumor agents is extremely low. Thus, the likelihood of toxicity or a lack of therapeutic effect developing from fixed dosing is not to be ignored. Routine monitoring could be used to predict toxicity in these cases and so allow the physician to intervene prior to manifestation of clinical toxicity. In many instances, chemotherapeutic agents cause target-tissue toxicity that cannot be detected at an early stage by routine clinical tests. Such is the case with adriamycin cardiotoxicity and bleomycin pulmonary toxicity. Definition of a pharmacokinetic parameter that would predict the toxicity sufficiently early to obviate these toxic effects would allow routine monitoring to be used in these cases. A number of factors may be responsible for interindividual variation in pharmacokinetics and the capricious nature of clinical toxicity, including wide variations in drug absorption, metabolism, or elimination. They may lead to considerable variability in clinical effectiveness of fixed doses. Routine monitoring may allow dose adjustment on a more rational basis than is presently used, i.e., nadir white blood count or platelet count. Renal or hepatic disease, which are often concomitant problems in patients with neoplastic disease, may significantly alter a drug's activity. Monitoring drug levels would allow the safe use

of chemotherapeutic agents in patients with such organ impairment, with adjustment of subsequent doses on a rational basis. The occurrence of saturation kinetics in drug uptake, transport, and elimination may result in severe toxicity with only small increments of drug dose. Although this has not been a recognized problem in the use of antineoplastic agents in the past, recent pharmacological studies of intraperitoneal 5-FU have suggested that saturation of an elimination process may play a role in the level at which toxicity occurs [66]. Drug interactions may significantly alter pharmacokinetics and clinical effects. With the common use of combination chemotherapy, such interactions should be systematically evaluated. Little work has been carried out as yet in this area. Finally, for drugs having a prolonged plasma half-life, patient compliance can be verified by blood level measurement. Certainly, the potential for acute toxicity such as nausea and vomiting may encourage patients to omit doses of oral medication.

While these reasons for monitoring are frequently appreciated in clinical practice, opportunities for the use of routine monitoring are limited by the lack of availability of simple, rapid, and yet dependable assay methods that are sufficiently inexpensive to allow their frequent use in patient care. However, recent years have witnessed a definite increase in reliable clinical pharmacokinetic studies suggesting a more specific role for routine drug level monitoring to improve either the safety or efficacy of antineoplastic therapy. The most thoroughly studied example is the use of methotrexate (MTX) in high-dose infusions. These infusions depend on rapid renal excretion of the drug for safe administration, and the ability of individual patients to excrete MTX is not always predictable on the basis of routine pretreatment screening tests of renal function. Since high-dose MTX infusions have been associated with severe myelosuppression, stomatitis, and a 6% incidence of drug-related fatalities [75], a clear need has been present to carefully monitor drug administration in an attempt to predict which patients are at increased risk for toxicity. This has been greatly simplified by the development of rapid, sensitive radioimmunoassays and competitive enzyme-binding assays for MTX in plasma, which make it possible to report results to clinicians within hours [2, 5, 12, 36, 46, 47, 54, 60]. The careful study of several high-dose MTX regimens has established the value of routine drug level monitoring in predicting toxicity [38, 56, 68, 76]. Stoller and co-workers found that patients treated with a 6-h infusion of 50—250 mg MTX/kg who had a plasma level of greater than 0.9 μM at 48 h had a high likelihood of myelosuppression. This toxicity was not observed in patients with lower 48 h levels. They also determined that the administration of higher doses of leucovorin (100 mg/m^2) effectively prevented this toxicity in some cases despite the continued presence of toxic levels of MTX [68]. Other studies have also suggested that such intensified rescue regimens may prevent toxicity among patients with delayed drug clearance [38]. The importance of adequate hydration and alkalinization of the urine has also been properly emphasized [56].

Although the recommendations of authors vary slightly as to the timing of MTX level determination for optimal clinical utility, monitoring practices for this drug are all based on similar principles. First, there is a critical threshold concentration of MTX for sensitive normal tissues, which must be exceeded before DNA synthesis is inhibited and tissue is damaged [16]. Second, the concentration or dose of leucovorin required to reverse MTX effect in vitro appears to increase with increasing MTX concentrations [59]. This work provides the rationale for escalation of leucovorin rescue in patients at risk for toxicity. Two groups have also shown that leucovorin dosage following high-dose MTX infusion can be minimized, and the rescue of malignant tissue theoretically limited, by basing leucovorin doses on measurement of serum MTX [40, 69]. Finally, there is a critical threshold for duration of exposure required to produce damage to sensitive tissues. Clinical toxicity seems to be correlated with both the duration of time that this threshold is exceeded and the degree of elevation of drug concentration above the threshold. In one study, infusions of up to 36 h resulted in minimal toxicity if adequate leucovorin was begun promptly, whereas longer infusions during which lower plasma MTX levels were maintained resulted in severe toxicity [33].

The measurement of MTX in cerebrospinal fluid (CSF) has become a necessary accompaniment of attempts to effectively treat CNS malignancy with this drug. The syndrome of acute MTX neurotoxicity has been associated with delayed clearance of the drug from the CSF following intrathecal injection [10]. Measurement of CSF levels of MTX may therefore be helpful clinically in distinguishing MTX neurotoxicity from malignant leptomeningitis. The demonstration of poor penetration of MTX into ventricular CSF following intralumbar injections of the drug [63] has provided one explanation for the high relapse rate of leukemic meningitis and has prompted the study of the Ommaya reservoir and other techniques of administration for patients with active CNS malignancy [I, II]. High-dose systemic MTX infusions have been shown to be effective in the treatment of CNS involvement with non-Hodgkin's lymphoma [64], and are currently under study as a mode of therapy for prophylaxis of leukemic and lymphomatous meningitis in high-risk patients. This type of therapy will require monitoring to document achievement of anticipated therapeutic MTX levels in the CSF and to aid in interpretation of the clinical outcome.

Although drug level monitoring has not been established for the routine clinical use of 5-fluoropyrimidines,

existing studies of the use of 5-FU illustrate both the possibilities and the difficulties with this approach. For example, the erratic plasma levels noted following orally administered 5-FU, with peak levels that are lower and delayed compared with the same dose given intravenously [14, 24, 32, 35, 52] has been used as an explanation for the lower response rates seen in some of the clinical trials in which these routes of administration are compared [4, 67]. The prolonged half-life of 5-FU when given with thymidine and the attendant host toxicity provides a second example of a rough correlation between plasma levels of drug and clinical toxicity or drug effect. This gives cause for optimism that the measurement of 5-fluoropyrimidine in plasma may be useful to clinicians.

There are several reasons why this has not occurred which are typical of the situation with most other antineoplastic agents as well. Published studies have been unable to quantitate 5-FU in plasma beyond 3 h [21, 24, 32], while the antimetabolic activity persists for a more prolonged period. It is known that 5-fluorodeoxyuridylate (5-FdUMP), the active metabolite that inhibits thymidylate synthetase, may persist in tissues for several days [18, 19, 55]. The cellular disappearance of 5-FdUMP, and perhaps ribonucleotide forms as well, determines the duration of drug effect and in part the degree of cytotoxicity. Differential sensitivity to 5-FU in two murine tumor lines has been correlated with the cellular clearance of this inhibitor [53]. Therefore, until plasma determination of 5-fluoropyrimidine can be shown to have some relevance to the cellular determinants of drug effect, drug level monitoring will not reach its greatest utility. Finn and Sadee, using an isotope dilution mass spectrometric assay, observed a terminal half-life of 20 h in rats treated with 5-FU [32]. This value correlates more closely with the duration of 5-FU effect, and these authors suggested that this terminal half-life may reflect the elimination of 5-FU-derived nucleotides from tissue. Unfortunately, the assay was not sufficiently sensitive to measure 5-FU in the terminal elimination phase from plasma of human subjects. The development and availability of analytical methods capable of measuring these low concentrations of 5-FU, 5-fluorouridine, and 5-fluorodeoxyuridine would allow this hypothesis to be fully tested and would possibly be very useful in identifying patients at risk for toxicity.

Two additional instances in which drug level monitoring may have a role have been suggested by recent work. Crooke and co-workers have demonstrated that the terminal elimination half-life for bleomycin in patients given an intravenous bolus increases exponentially as the creatinine clearance decreases below 25–35 ml/min [26]. Definite recommendations concerning the dosage modifications of bleomycin that may be necessary in patients with compromised renal failure will not be possible until the incidence and severity of drug toxicity are correlated with drug levels, plasma half-life, or renal function. These studies are of great potential importance and should be forthcoming, since a sensitive and specific radioimmunoassay for bleomycin peptides is available [13, 70].

And finally, a provocative study by van Proojien and co-workers of the pharmacokinetics of ara-C in patients with acute myeloid leukemia (AML) has demonstrated a correlation between plasma half-life and remission induction in a small group of patients treated with 100 mg ara-C/m^2 every 12 h for 10–14 days [73]. Five patients with a second phase half-life of 6.6–10.7 min had a poor treatment response, whereas nine patients with a half-life of greater than 12.7 min had a complete bone marrow remission at 3 weeks. Since many patients with AML are treated by continuous infusion, this study leaves important questions unanswered, but it represents an extremely important attempt acquire pharmacokinetic data with relevance to the therapy of individual patients.

Conclusions

Pharmacokinetics of antineoplastic agents can be considered with respect to comprehensive pharmacokinetic studies and routine drug monitoring. Ideally, the comprehensive studies should be completed in early investigative trials prior to the widespread clinical use of the drug to define the absorption, distribution, elimination, and metabolism of the drug. Only recently, with the development of new technological advances, has this become possible. Therefore, many of the commonly used antineoplastic agents are only now being clearly defined as to their pharmacokinetic behavior. To date, the clinical utility of monitoring has been defined only for MTX. Monitoring of other antineoplastic agents, such as 5-FU, melphalan, and bleomycin, is within the grasp of clinical pharmacology. Other agents, such as adriamycin and its analogs, await the development of facile but specific techniques and the definition of pharmacokinetic parameters that are of predictive importance. Although pharmacokinetics has much to offer in the area of cancer chemotherapy, the heterogeneous nature of the neoplastic process will probably require an integrative approach of pharmacokinetics, biochemical pharmacology, and cell kinetics to predict therapeusis or toxicity.

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