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Reviews

Dose-dependent Pharmacokinetics and Cancer Chemotherapy

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Summary. *Dose-dependent pharmacokinetics have been reported more frequently for anticancer drugs than for other drugs, probably because anticancer drugs are studied over a wide range of doses during early evaluation and because of the increasing use of anticancer drugs at very high doses. Dose-dependent pharmacokinetics are reflected most commonly as an increase in the biological half-life of a drug and a greater than proportional increase in plasma concentration of the drug and in area under the drug concentration-time curve with increase in dose. Occasionally the rate of drug removal increases with increasing dose. These nonlinear changes in drug concentrations with dose may lead to increases in toxicity out of proportion to increases in dose. Appreciation of the possibility of dose-dependent pharmacokinetics is important in the clinical pharmacologic evaluation of new drugs, and may be essential for the design of effective therapeutic regimens.*

Elimination of most drugs from the body typically follows first-order kinetics, and pharmacokinetic parameters describing elimination of a drug do not change over the therapeutic dose range. A limited number of drugs exhibit dose-dependent pharmacokinetics (also called nonlinear pharmacokinetics), where pharmacokinetic parameters depend upon the dose of drug employed. In some cases pharmacokinetic parameters may change during elimination of a single dose of drug as a function of drug concentration in the body. The theoretical basis for dose-dependent pharmacokinetics has received extensive treatment [48, 69, 75, 113]. This report reviews major types of dose-dependent pharmacokinetics and specifically addresses dose-dependent pharmacokinetic behavior of anticancer drugs in humans.

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Types of Dose-dependent Pharmacokinetics

A major cause of dose-dependent pharmacokinetics is saturation of the capacity of an enzyme or carrier system for drug biotransformation or excretion. The kinetics of these processes can often be described by the Michaelis-Menten equation:

$$\frac{-dC}{dt} = \frac{VmC}{Km + C};$$

where $-dC/dt$ is the rate of decline of drug concentration C, at time t, Vm is the theoretical maximum rate of the process, and Km is the Michaelis constant. When C is greater than Km, the rate of the reaction approaches Vm and is independent of the plasma concentration of the drug (that is, a zero-order process). As the concentration falls and C becomes considerably smaller than Km, elimination becomes first-order. Elimination of drug at high doses is characterized initially by a zero-order process followed by first-order elimination as the concentration falls. At lower doses only first-order elimination is observed . The first-order rate constant and $t_{1/2}\beta$ (the biologic half-life) is the same at all doses. The T50% (time to eliminate 50% of the dose), however, increases with dose. Drugs whose biotransformation becomes capacity-limited at high doses in humans include ethanol [78], salicylate [74], diphenylhydantion [3, 46, 57], sulfamethazine [32, 86], and possibly propranolol [39]. Dose-dependent pharmacokinetics of propranolol have not been found by all workers [50]. Capacity-limited renal tubular excretion may be responsible for dose-dependent pharmacokinetic behavior of chlorthalidone [41] and piperacillin [6]. Saturation of biliary excretion has been implicated in the dose-dependent pharmacokinetic behavior of rifampicin [1].

The pharmacokinetic consequences of plasma protein binding of drugs has received considerable

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attention [19, 70, 79, 100]. If drug elimination is principally a function of free (unbound) drug concentration, then as the capacity of plasma proteins to bind drug is saturated at high drug concentrations, the plasma concentration of free drug and the rate of drug elimination increase. In general, because of the increased rate of elimination of free drug, as the dose of drug is increased the plasma concentration of total drug and the area under the concentration-time curve (AUC) do not exceed a constant (plateau) value. This phenomenon has been observed for several drugs that bind extensively to plasma proteins, such as phenylbutazone [12], naproxen [99], and disopyramide [28, 80]. It should be emphasized that concentration-dependent binding of a drug to plasma proteins over the therapeutic range does not necessarily lead to dose-dependent pharmacokinetics. For example, the binding of lidocaine to plasma proteins is dose-dependent over the range of therapeutic plasma concentrations. Despite this, lidocaine does not show dose-dependent plasma elimination because both free and protein-bound lidocaine are efficiently metabolized by the liver [80].

Binding of drug to tissue proteins can result in dose-dependent pharmacokinetic behavior similar to that for drugs that bind to plasma proteins provided the capacity of tissue binding sites is saturated over the therapeutic range. Prednisolone exhibits an increase in the apparent volume of distribution (Vd) as the dose is increased [90, 98, 108] without a concomitant change in plasma protein binding [108]. Increased binding to tissues with increasing dose has been proposed to account for this dose-dependent effect on the Vd of prednisolone [98, 108].

Absorption is another factor that might influence the pharmacokinetics of an orally administered drug. It has been suggested that a dose-dependent decrease in the rate of absorption contributes to the nonlinear pharmacokinetics of sulfamethazine [32].

Dose-dependent pharmacokinetics may result when a metabolite inhibits processes responsible for biotransformation of parent drug. This occurs when a slowly eliminated metabolite capable of inhibiting an enzyme that metabolizes the parent compound reaches inhibitory concentrations at a time when the concentration of the parent drug is lower than its *Km* for the enzyme. Theoretical aspects of product inhibition on the kinetics of drug elimination have been reviewed by Perrier et al. [89]. An intriguing aspect of product inhibition is that drug concentrations decline more slowly over a given range of concentrations following a high dose of drug than following a low dose of drug. Drug elimination appears to be first-order and $t_{1/2}\beta$ increases with increasing dose. This phenomenon has been termed the dose-dependent 'memory' effect. It has been suggested [4, 48] that this type of dose dependency is seen in humans following administration of dicoumarol [87] and diphenylhydantoin [3].

Several drugs show dose-dependent pharmacokinetics in humans, mediated by mechanisms which have not been established with certainty. These include heparin [10], theophylline [67, 115], disopyramide [60], carbamezepine [9], and chloroquine [42]. Chronic administration of chloroquinone produces remarkable changes in pharmacokinetic parameters. As the dose is increased from 250 to 1,000 $mg \cdot kg^{-1} \cdot day^{-1}$ there is an increase in $t_{1/2}\beta$ from 3–312 min, and a 1,000-fold increase in the AUC normalized for dose.

Dose-dependent Pharmacokinetics of Anticancer Drugs

In initial human studies anticancer drugs are frequently administered over a wide range of doses. It is not surprising that dose-dependent pharmacokinetic behavior has been noted for many anticancer drugs. Dose-dependent pharmacokinetics is suggested when the plasma concentration of drug or AUC does not vary linearly with dose and when the fraction of drug or metabolites excreted in the urine over time varies with dose.

High-dose Cancer Chemotherapy

Some anticancer drugs are administered at doses sufficiently large to saturate processes with limited capacity, such as metabolism and renal tubular secretion. Methotrexate is conventionally administered at doses of about 30 mg/m^2. When therapy is followed by 'rescue' courses of leucovorin, methotrexate has been given at doses up to 12 g/m^2. High-dose methotrexate has been reported to exhibit dose-dependent pharmacokinetics characterized by increasing apparent initial volume of distribution and decreasing urinary clearance with increasing dose [73, 96]. Over 90% of IV administered methotrexate is excreted in the urine unchanged [59, 64, 94, 114]. It has been suggested that methotrexate is filtered at the glomerulus and actively secreted by renal tubular cells [11]. Reich [95] has recently developed an operational pharmacokinetic model incorporating renal tubular secretion with Michaelis-Menten kinetics for high-dose methotrexate infusion. The apparent *Km* obtained by curve-fitting the plasma concentrations of methotrexate in three patients receiving a 24-h infusion of methotrexate in doses between 1.5

and 4 g/m^2 was 5×10^{-5} *M* to 10^{-4} *M*. On the basis of these data, dose-dependent pharmacokinetics would not be expected until plasma methotrexate concentrations exceed 10^{-4} *M*. Concentrations greater than 10^{-4} *M* are achieved in patients with normal renal function at doses of methotrexate greater than 5 g/m^2 given over 24 h [58, 95], and concentrations in excess of 10^{-3} *M* are attained when large doses of methotrexate are given rapidly [20, 61, 105]. Monjanel et al. [81] have used a linear pharmacokinetic model to predict plasma concentrations of methotrexate in patients receiving 1.5 g/m^2 over 36 h (plasma levels of about 10^{-5} *M*), with apparent success. Goh et al. [49] studied children receiving methotrexate at a dose of 25–150 mg/kg (0.45–4.5 g/m^2) by 24-h infusion. Their results show more rapid elimination of methotrexate at serum concentrations greater than 10^{-4} *M*. Not all studies have found dose-dependent pharmacokinetics after high-dose methotrexate therapy. Pratt et al. [94] gave children methotrexate at 100–500 mg/kg over 6 h and reported serum levels up to 10^{-3} *M*. There was, however, no change in the half-life of the elimination of drug from serum with increase in dose, and they concluded that the capacity for clearing methotrexate from blood was not saturated at these doses. The mean half-life, 157 min, observed by Pratt et al. [94], was similar to the half-life reported by others at much lower doses of methotrexate, 134 min at a dose of 10 mg/kg [55] and 210 min at 30 mg/m^2 [59]. Stoller et al. [105] reported a similar initial half-life of 126 min after methotrexate administration at 50–200 mg/kg over 6 h.

Thymidine has been administered in high doses up to 128 g/m^2 over 24 h [35], achieving millimolar plasma concentrations [17, 117]. At these concentrations, thymidine has been reported to have a selective cytotoxic effect on tumor cells [72]. Thymidine is eliminated by metabolism, renal glomerular filtration, and renal tubular secretion [117]. Metabolism and renal secretion are saturated at high doses. At lower doses of thymidine, 8 g/m^2 over 24 h, the half-life of plasma thymidine after cessation of infusion was 10 min. The calculated total-body clearance was 16.0 l/min per m^2, and less than 2% of the total dose was excreted in the urine as unchanged thymidine [34]. At high doses, 75 g/m^2 over 24 h, the half-life was 100 min. Total-body clearance was 0.1 l/min per m^2, and only 39% of the dose was removed by metabolism [17, 117]. Woodcock et al. [116] have studied the pharmacokinetics of thymidine in humans receiving a fixed dose of 5-fluorouracil preceded by increasingly large doses of thymidine given by rapid infusion. As the dose of thymidine was increased from 3–45 g, the post-distributive half-life of thymidine elimination increased progressively from 7–98 min. Zaharko et al. [117] suggested that renal secretion of thymidine is partially saturated at millimolar concentrations, because of their findings that the renal clearance of thymidine is only slightly greater than creatinine clearance at high doses of thymidine but almost four times greater than creatinine clearance at low doses of thymidine [34]. Thymidine is metabolized by the liver and other tissues [117]. Ensminger and Frei [35], using direct infusion of thymidine into the hepatic artery, have shown that the hepatic extraction of thymidine decreases from a maximum of 99% at 8 g/m^2 per 24 h to a minimum of 54% at 32 g/m^2 per 24 h.

Conventional Dose Chemotherapy

Dose-dependent pharmacokinetics have been shown for other anticancer drugs administered over more limited ranges of dose. An early example is a report by Fujita [43] that mitomycin C is cleared more rapidly after low doses than after high doses. The plasma half-life of mitomycin C calculated from Fujita's data is less than 6 min after a total dose of 2 mg and more than 20 min after a total dose of 30 mg. Mitomycin C is metabolically activated in vivo [63] and is cleared from the plasma primarily by metabolism [43]. Changes in metabolism of mitomycin C dependent upon dose could affect the drugs toxicity and antitumor activity.

5-Fluorouracil (5-FU) also exhibits dose-dependent pharmacokinetics. An early report by Clarkson et al. [18] suggested that 5-FU administered by continuous IV infusion at 5 or 30 mg · kg^{-1} · day^{-1} was subject to more metabolic degradation than 15 mg/kg administered as an IV bolus. More recently Garrett et al. [45] demonstrated a decrease in total-body clearance of 5-FU at a total dose of 1,000 mg compared with 500 mg. Ensminger et al. [36] found a decrease in total-body clearance of 5-FU and no change in hepatic clearance as the dose of 5-FU infused was increased from 5.6–22.4 mg · kg^{-1} · h^{-1}. Speyer et al. [103] reported pharmacokinetics for 5-FU administered IP. Their data indicated a decrease in total-body clearance of 5-FU at high doses. This was most marked in one patient in whom clearance declined from 4.1–0.9 l/min as the IP concentration was increased from 5–8 m*M*. Cano et al. [14] reported a lower total-body clearance of 5-FU, 1.1 l/min, when 5-FU was administered as an IV bolus of 15 mg/kg than when the same dose was infused over several hours, when the total-body clearance was 27.1 l/min. These authors reported a flow-limited model for the elimination of 5-FU based on the assumption of modulation of 5-FU metabolism

by pool size of dihydro-5-fluorouracil (5-FUH_2). The first and rate-limiting step in the catabolism of 5-FU is reduction to 5-FUH_2 [82]. Inhibition of the enzyme catalyzing this reduction, dihydrouracil dehydrogenase, has been reported to potentiate toxicity and antitumor activity in animals [23]. Collins et al. [22] have recently proposed a physiological pharmacokinetic model for 5-FU incorporating a saturable term for whole-body clearance (which includes metabolism and renal secretion) with a calculated *Km* of 15 μM.

Adriamycin might exhibit dose-dependent pharmacokinetics. Mathematical models for adriamycin distribution have generally assumed linear pharmacokinetics [16, 54, 97]. The liver is the primary site for elimination of adriamycin, and over the narrow dose range of 30–40 mg/m^2, there is no alteration in hepatic extraction of adriamycin infused into the hepatic artery [44]. Creasey et al. [24], however, have reported that closely spaced IV doses of adriamycin, 15 mg/m^2 every 8 h, are associated with increased toxicity and higher plasma concentrations of adriamycin and metabolites after the sixth compared with the first dose. Their data also show a longer terminal half-life after a single IV dose of 90 mg/m^2 than after 22.5 mg/m^2. Gercovich et al. [47] reported a terminal half-life of 39 h for adriamycin following 60 mg/m^2 infused over 10 h, compared with a half-life of 27 h for the same dose given as a rapid infusion. Dose-dependent pharmacokinetics are not apparent in the results of a study by Bachur et al. [5], when adriamycin was administered at doses of 15–60 mg/m^2.

Arabinosyl-cytosine (AraC) is an anticancer drug that undergoes extensive deamination to form arabinosyl-uridine (AraU) [40]. The *Km* of AraC for deaminase in human liver is 1.4×10^{-4} *M* [13], which is similiar to, or below the plasma concentration of AraC following doses of 100 mg/kg [31, 111]. Dedrick et al. [31] incorporated a term for saturable (Michaelis-Menten) metabolism in a physiological pharmacokinetic model for AraC. Their limited experimental data in patients receiving 1.2 and 8.6 mg AraC/kg suggest that the plasma concentration of AraC increases out of proportion to the increase in dose, raising the possibility that the deaminase is saturated at high doses of AraC.

3-Deazauridine (3-DAU) presents an interesting example of an anticancer drug whose removal appears to increase as the plasma concentration increases. Creaven et al. [27] presented data suggesting that the plasma half-life of 3-DAU decreased from 11 h to about 4 h as the total dose of 3-DAU was increased from 10 mg to 1500 mg. Benvenuto et al. [8] noted that the plasma pharmacokinetics of 3-DAU were dependent upon its rate of infusion. After rapid (15–30 min) infusion of 3-DAU at doses between 1.5 and 5.3 g/m^2, the half-life of plasma elimination was 4.4 h. Following 5 days of continous infusion of 3-DAU at 1.0–3.0 g/m^2 per day the half-life of plasma elimination was 21.3 h. A decrease in plasma half-life of 3-DAU with increasing dose has been reported in mice [29].

It is probable that cis-dichlorodiammineplatinum (CDDP) exhibits dose-dependent pharmacokinetics. Hall et al. [53] reported that the terminal half-life for elimination of total plasma CDDP was between 17.3 and 34.7 h following continuous infusion of CDDP at 20 mg/m^2 for 5 days. Gormley et al. [51] reported a half-life of plasma elimination of CDPP of 57 h following a 1-h infusion of CDDP at 40 mg/m^2. In contrast, DeConti et al. [30] found no differences in pharmacokinetic parameters of radioactively labeled CDDP at doses between 0.07 and 3.1 mg/kg administered as an IV bolus. The initial half-life ranged from 25.5–49.0 min and was followed by a slower half-life ranging from 58.0–73 h. CDDP is bound extensively to protein. Patton et al. [88] measured plasma concentrations of filterable (free) CDDP after slow and rapid IV administration. They reported a significantly shorter half-life, 26 min versus 44 min, and increased urinary excretion, 75% versus 49%, after CDDP at 100 mg/m^2 by 6-h infusion than after the same dose given as an IV bolus. The same group found no differences in the pharmacokinetic parameters of total CDDP and free CDDP when CDDP was administered as an IV bolus at a dose of 50 mg/m^2 [7].

Clinical Trials of New Anticancer Drugs

Clinical phase I trials involve planned dose escalations of new anticancer agents to determine the maximum tolerable dose dose in humans. As doses are increased pharmacokinetic parameters may change in a manner that affects drug toxicity. Work in our laboratory has shown a decrease in total body clearance of a new investigational anticancer drug L-2-amino-3-(N-hydroxy,N-nitrosamino)propionic acid (L-alanosine) as the dose is escalated [92] (Table 1). L-alanosine, an amino acid analogue, is extensively metabolized in humans. Less than 6% of the total dose is excreted unchanged in the urine in 24 h [92]. The major pathway for metabolism of L-alanosine in animals is transamination [66]. We have found evidence suggesting that transamination occurs in humans (G. Powis, 1981, unpublished observations). It is possible that the decreased clearance of L-alanosine at high doses results from saturation of the transamination pathway. We have

Table 1. Plasma clearance (Cl) of L-alanosine

	Dose (mg/m^2)					
	250	375	500	800	1,200	1,500
Cl ($ml \cdot min^{-1} \cdot kg^{-1}$)	24.5	33.3	12.2	13.9	5.2	6.8

L-alanosine was administered to groups of three patients at the doses shown, over 10 min or for the 1,200 and 1,500 mg/m^2 dose levels, over 30 min

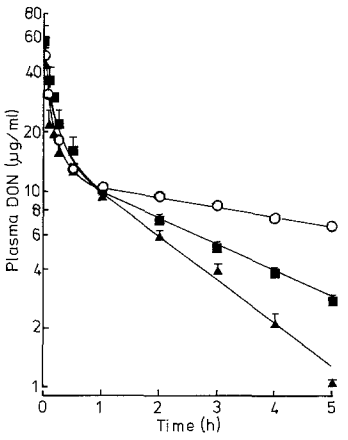

Fig. 1. Plasma levels of DON following IV administration of DON at doses of ▲, 300 mg/m^2 (three patients); ■, 450 mg/m^2 (three patients); and O, 550 mg/m^2 (one patient). Further patients could not be studied at the highest dose level because of unacceptable toxicity. *Bars* represent SEM. The *continuous lines* are computer fits to the data

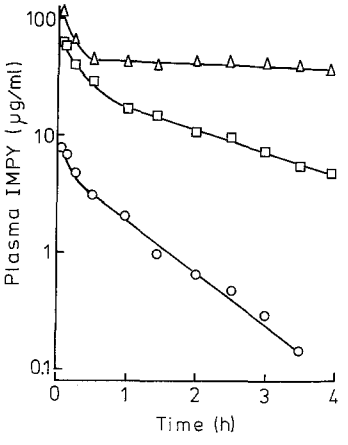

Fig. 2. Plasma levels of IMPY in rabbits following rapid IV administration of IMPY: O, 5 mg/kg; □, 25 mg/kg; and △ 150 mg/kg. From Ames et al. [2]

also studied another amino acid analogue, 6-diazo-5-oxo-L-norleucine (DON), in a phase I clinical trial. DON is extensively metabolized in humans, with little or no unchanged drug appearing in the urine [91, 93]. Removal of DON from plasma is dependent on the dose (Fig. 1). Although limited, the data are compatable with a dose-dependent memory effect such as that produced by metabolite inhibition of biotransformation of parent compound. Confirmation of this hypothesis will require identification of metabolic products of DON and the demonstration that they inhibit metabolism. A drug we have studied in animals, although not in man, is 2,3-dihydro-I-H-imidazol[1,2B]pyrazole (IMPY). Removal of IMPY from plasma in the rabbit is dose-dependent (Fig. 2). The half-life of plasma IMPY is 45 min at a dose of 5 mg/kg and 640 min at 150 mg/kg administered as an IV bolus [2]. Dose dependency has been reported in humans by Staubus et al. [104], with a more prolonged terminal half-life at higher doses. This might explain the sudden onset of serious toxicity reported for IMPY as the dose is escalated [83].

There is limited evidence that the pharmacokinetics of other anticancer drugs exhibit dose dependency, including 5-azacytidine [62] and 6-mercaptopurine [76]. The blood levels and half-life of spirogermanium have been reported to increase considerably after repeated daily administration [71]. ICRF-159 exhibits dose-dependent absorption, with less drug absorbed when administered as a single oral dose of 3 g/m^2 than when the same total dose is divided into three equal portions and administered orally every 6 h [26]. 2-Amino-1,3,4-thiadazole is an experimental anticancer agent, which exhibits dose-dependent pharmacokinetics due to saturation of metabolism in dogs and monkeys [33, 68]. A decreased urinary excretion of N-(phosphonacetyl)-L-aspartic acid (PALA) has been reported in mice by Chadwick et al. [15], which was suggested to be due to saturation of binding sites for PALA, possibly in bone. Studies in humans, however, have shown no convincing evidence for dose-dependent PALA pharmacokinetics [37, 77].

Not all anticancer drugs given in relatively high doses exhibit dose-dependent pharmacokinetics. For example, cyclophosphamide has been administered over a wide range of doses, 1–80 mg/kg. The major pathway for cyclophosphamide elimination is hepatic metabolism [110]. The *Km* for hepatic metabolism is over 1 m*M* [21, 102], which is considerably in excess of plasma concentrations even at high doses [65] and probably accounts for the fact that cyclophosphamide does not show dose-dependent pharmacokinetics [52].

It should also be emphasized that the pharmacokinetic behavior of one drug may be profoundly altered by the presence of other drugs. A striking example is the effect of thymidine upon the plasma elimination and urinary excretion of 5-FU. Wood-

cock et al. [116] reported that administration of thymidine to humans at 7.5 g increased the plasma half-life of 5-FU from 6–135 min and that 15 g thymidine increased the plasma half-life to 188 min. They provided evidence that thymidine all but eliminates oxidative metabolism of 5-FU, resulting in renal clearance becoming the primary route of elimination of 5-FU in the presence of thymidine, as against elimination by metabolism when 5-FU is administrered alone. This phenomenon is akin to decreases seen in elimination of parent drug secondary to inhibition of metabolizing enzymes by metabolite of the parent drug, in that thymine, a metabolite of thymidine, competes with 5-FU for catabolic enzymes.

Consequences of Dose-dependent Pharmacokinetics

Several recent studies suggest that for some anticancer drugs known to exhibit dose-dependent pharmacokinetics saturation of elimination and/or uptake plays an important role in determining the occurrence of drug toxicity [24, 26, 47, 85, 103, 106] and, more provocatively, the occurrence of therapeutic effect [14, 56, 112]. Current approaches to cancer chemotherapy present unique opportunities to study the pharmacokinetic behavior of foreign compounds of widely differing chemical structure, because of the range of drug concentrations routinely used to establish the maximal tolerable dose in the early stages of drug development. We anticipate that as methods for 'rescuing' patients from unacceptable drug toxicity are improved, there will be an increasing trend to use very high-dose therapy to enhance entry of drugs into resistant cells and into pharmacological sanctuaries. As wider ranges of drug doses are studied it is to be expected that dose-dependent pharmacokinetic behavior of many anticancer drugs will be noted and will receive detailed study.

Such information may permit rational design of regimens that minimize toxicity and maximize therapeutic effect. Several examples have been provided of drugs whose metabolism and pharmacokinetic parameters change considerably depending on whether the dose is given by IV bolus or as an infusion. Increasingly anticancer drugs are being given in very large doses. Methotrexate was the first drug to be used at very high doses to maximize entry into tumor cells [11] and into tumor sanctuaries such as the central nervous system [101]. Thymidine is being given in high doses to achieve cytotoxic concentrations in the blood [117] and to modulate the metabolism of other cytotoxic agents [116]. It is probable that soon other drugs will be given in much higher doses than are currently used as new techniques, such as IP administration [103], transplantation of heterologous bone marrow [107] or autologous bone marrow [109], and rescue with specific pharmacologic agents, are more fully developed.

The application of pharmacokinetic principles to the improvement of cancer chemotherapy is in an early stage of development and will be pursued vigoously in the future [25, 38, 84]. In this review we have attempted to show that dose-dependent pharmacokinetic behavior of anticancer drugs is likely to be of special relevance to the development of more effective therapeutic regimens.

References

1. Acocella G (1978) Clinical pharmacokinetics of rifampicin. Clin Pharmacokinet 3: 108–127
2. Ames MM, Powis G, Kuehn P (1979) Determination of pyrazoloimidazole in plasma and urine by gas-liquid chromatography using nitrogen-phosphorus detection. J Chromatogr 169: 412–415
3. Arnold K, Gerber N (1970) The rate of decline of diphenylhydantoin in human plasma. Clin Pharmacol Ther 11: 121–134
4. Ashley JJ, Levy G (1972) Inhibition of diphenylhydantoin elimination in rats by its major metabolite. Res Commun Chem Pathol Pharmacol 4: 297–304
5. Bachur NR, RIggs CE Jr, Green MR, Longone JJ, Vunakis HV, Levin L (1977) Plasma adriamycin and daunorubicin levels by fluorescence and radioimmunassay. Clin Pharmacol Ther 21: 70–77
6. Batra VK, Morrison JA, Lasseter KC, Joy VA (1979) Piperacillin kinetics. Clin Pharmacol Ther 26: 41–53
7. Belt RJ, Patton TF, Himmelstein KJ, Taylor S, Repta A, Sternson LA (1980) Pharmacokinetics of cis-platin in humans. (Abstract) Am Assoc Cancer Res 21: 193
8. Benvenuto JA, Hall SW, Farquhar P, Stewart DJ, Benjamin RS, Loo TL (1979) Pharmacokinetics and disposition of 3-deazaurdine in humans. Cancer Res 39: 349–552
9. Bertilsson L (1978) Clinical pharmacokinetics of carbamazepine. Clin Pharmacokinet 3: 128–143
10. Bjornsson TD, Levy G (1979) Pharmacokinetics of heparin. I. Studies of dose dependence in rats. J Pharmacol Exp Ther 210: 237–242
11. Bleyer WA (1978) The clinical pharmacology of methotrexate: New applications of an old drug. Cancer 41: 36–51
12. Brodie BB, Lowman JJ, Burns JJ, Lee PR, Chenkin T, Goldman A, Weiner M, Steele JM (1954) Observations on the antirheumatic and physiologic effects of phenylbutazone (Butazolidin) and some comparisons with cortisone. Am J Med 16: 181–190
13. Camiener GW (1967) Studies of the enzymatic deamination of cytosine arabinoside-II. Properties of the deaminase of human liver. Biochem Pharmacol 16: 1681–1689
14. Cano JP, Aubert C, Rigault JP, Seitz JF, Carcasone Y (1980) Pharmacokinetic studies of 5-fluorouracil (5FU) in cancer patients: Relation with clinical response and implication of measurement of 5,6-dihydro-5-fluorouracil (FUH_2). (Abstract) Am Assoc Cancer Res 21: 152
15. Chadwick M, Silveira DM, McGarrigle PL, Liss RH, Schepis J (1979) Distribution of PALA in tissues and tumors of mice

after intravenous administration. (Abstract) Am Assoc Cancer Res 20: 241
16. Chan KK, Cohen JL, Gross JF, Himmelstein KJ, Bateman JR, Tsu-Lee Y, Marlis AS (1978) Prediction of adriamycin disposition in cancer patients using a physiologic pharmacokinetic model. Cancer Treat Rep 42: 1161–1171
17. Chiuten DF, Wiernik PH, Zaharko DS, Edwards L (1980) Clinical phase I-II and pharmacokinetic study of high dose thymidine given by continuous intravenous infusion. Cancer Res 40: 818–822
18. Clarkson B, O'Connor A, Winston L, Hutchinson D (1964) The physiologic disposition of 5-fluorouracil and 5-fluoro-2′-deoxyuridine in man. Clin Pharmacol Ther 5: 581–610
19. Coffey JJ (1972) Effect of protein binding of drugs on areas under plasma concentration time curves. J Pharm Sci 61: 138–139
20. Cohen HJ, Jaffe N (1978) Pharmacokinetic and clinical studies of 24-h infusions of high-dose methotrexate. Cancer Chemother Pharmacol 1: 61–64
21. Cohen JL, Jao JY (1970) Enzymatic basis of cyclophosphamide activation by hepatic microsomes of the rat. J Pharmacol Exp Ther 174: 206–210
22. Collins JM, Dedrick RL, King FG, Speyer JL, Myers CE (1980) Nonlinear pharmacokinetic models for 5-fluorouracil in man: Intravenous and intraperitoneal routes. Clin Pharmacol Ther 28: 235–246
23. Cooper GM, Dunning WF, Green S (1972) Role of catabolism in pyrimidine utilization for nucleic acid synthesis in vivo. Cancer Res 32: 390–394
24. Creasey WA, McIntosh LS, Brescia T, Odujinrin O, Aspnes GT, Murray E, Marsh JC (1976) Clinical effects and pharmacokinetics of different dosage schedules of adriamycin. Cancer Res 36: 216–221
25. Creaven PJ (1979) Pharmacokinetic parameters potential for and problems with the use as predictors of response to cancer chemotherapeutic agents. Bull Cancer (Paris) 66: 85–88
26. Creaven PJ, Allen LM, Alford DA (1975) The bioavailability in man of ICRF-159, a new oral antineoplastic agent. J Pharm Pharmacol 27: 914–918
27. Creaven PJ, Rustum YM, Slocum HK, Mittelman A (1978) Clinical pharmacokinetics of 3-Deazauridine, a new antineoplastic agent. In: Siegenthaler W, Luthy R (eds) Current chemotherapy. American Society Microbiology, Washington, pp 1208–1210
28. Cunningham JL, Shen DI, Shudo I, Azarnoff DL (1977) The effect of urine pH and plasma protein binding on renal clearance of disopyramide. Clin Pharmacokinet 2: 373–383
29. Cysyk RL, Gormley PE, D'Anna ME, Adamson RH (1978) The disposition of 3-deazauridine in mice. Drug Metab Dispos 6: 125–132
30. DeConti RC, Toftness BR, Lange RC, Creasey WA (1973) Clinical and pharmacological studies with cisdiamminedichloroplatinum (II). Cancer Res 33: 1310–1315
31. Dedrick RL, Forrester DD, Ho DHW (1972) In vitro-in vivo correlation of drug metabolism – deamination of 1-β-D-arabinofuranosylcytosine. Biochem Pharmacol 21: 1–16
32. du Souich P, Lalka D, Slaughter R, Elvin AT, McLean AJ (1979) Mechanisms of nonlinear disposition kinetics of sulfamethazine. Clin Pharmacol Ther 25: 172–183
33. El Dareer SM, Tillery KF, Hill DH (1978) Distribution and metabolism of 2-amino-1,3,4-thiadiazole in mice, dogs, and monkeys. Cancer Treat Rep 62: 75–83
34. Ensminger WD, Frei E III (1977) The prevention of methotrexate toxicity by thymidine infusions in humans. Cancer Res 37: 1857–1863
35. Ensminger WD, Frei E III (1978) High-dose intravenous and hepatic artery infusions of thymidine. Clin Pharmacol Ther 24: 610–615
36. Ensminger WD, Rosowsky A, Raso V, Levin DC, Glode M, Come S, Steele G, Frei E III (1976) A clinical-pharmacologic evaluation of hepatic arterial infusions of 5-fluoro-2′-deoxyuridine and 5-fluorouracil. Cancer Res 38: 3784–3792
37. Erlichman C, Stron JM, Chabner BA (1980a) Application of simple competitive protein-binding assay technique to the pharmacokinetics of N-(phosphonacetyl)-L-aspartate in humans. Cancer Res 40: 1902–1906
38. Erlichman C, Donehower RC, Chabner BA (1980b) The practical benefits of pharmacokinetics in the use of antineoplastic agents. Cancer Chemother Pharmacol 4: 139–145
39. Evans GH, Shand DG (1973) Disposition of propranolol. V. Drug accumulation and steady-state concentrations during chronic oral administration in man. Clin Pharmacol Ther 14: 487–493
40. Finkelstein JZ, Shern J, Karon M (1970) Pharmacologic studies of tritiated cytosine arabinoside (NSC-63878) in children. Cancer Chemother Rep 54: 35–41
41. Fleuren HL, Verwey-van Wissen C, Van Rossum JM (1979) Dose-dependent urinary excretion of chlorthalidone. Clin Pharmacol Ther 25: 806–812
42. Frisk-Holmberg M, Bergkvist Y, Domeij-Nyberg B, Helstrom L, Jansson F (1979) Chloroquine serum concentration and side effects: evidence for dose-dependent kinetics. Clin Pharmacol Ther 25: 345–350
43. Fujita H 61971) Comparative studies on the blood level, tissue distribution, excretion and inactivation of anticancer drugs. Japanese Journal of Oncology 12: 151–162
44. Garnick MB, Ensminger WD, Israel M (1979) A clinical-pharmacological evaluation of hepatic arterial infusion of adriamycin. Cancer Res 39: 4105–4110
45. Garrett ER, Hurst GH, Green JR Jr (1977) Kinetics and mechanisms of drug action on microorganisms. XXIII. Microbial kinetic assay for fluorouracil in biological fluids and its application to human pharmacokinetics. J Pharm Sci 66: 1422–1629
46. Gerber N, Wagner JG (1972) Explanation of dose-dependent decline of diphenylhydantoin levels by fitting to the integrated form of the Michaelis-Menten equation. Res Commun Chem Pathol Pharmacol 3: 455–466
47. Gercovich FG, Praga C, Beretta G, Morganfeld M, Muchnik J, Pesce R, Ho DHW, Benjamin RS (1979) Ten-hour continuous infusion of adriamycin. (Abstract) Am Soc Clin Oncol 20: 372
48. Gibaldi M, Perrier D (1975) Nonlinear pharmacokinetics. In: Gibaldi M and Perrier D Pharmacokinetics. Dekker, New York, pp 215–228
49. Goh TS, Won KY, Lampkin B, O'Leary J, Gnarra P (1979) Evaluation of 24-hour infusion of high-dose methotrexate. Pharmacokinetics and toxicity. Cancer Chemother Pharmacol 3: 177–180
50. Gomeni IR, Blanchetti G, Seager R, Marselli PL (1977) Pharmacokinetics of propranolol in normal healthy volunteers. J Pharmacokinet Biopharm 5: 183–192
51. Gormley PE, Bull JM, LeRoy AF, Cysyk R (1979) Kinetics of cis-dichloroammineplatinum. Clin Pharmacol Ther 25: 351–357
52. Grochow LB, Colvin M (1979) Clinical pharmacokinetics of cyclophosphamide. Clin Pharmacol 4: 380–394
53. Hall SW, Salem P, Benjamin RS, Lu K, Loo TL, Murphy WK, Wharton J, Bedey GO (1978) Continuous intravenous infusion (CIVI) of cis-diamminechloroplatinum (II) (IDDP): A clinical, toxicologic and pharmacologic study. (Abstract) Am Assoc Cancer Res 19: 417

54. Harris PA, Gross JF (1975) Preliminary pharmacokinetic model for adriamycin (NSC-123127). Cancer Chemother Rep 59: 819–826
55. Henderson ES, Adamson RH, Oliverio VT (1965) The metabolic fate of tritiated methotrexate. II. Absorption and excretion in man. Cancer Res 25: 1018–1024
56. Hillcoat BL, McCulloch BP, Figueredo AT, Ehsan MH, Rosenfeld JM (1978) Clinical response and plasma levels of 5-fluorouracil in patients with colonic cancer treated by drug infusion. Br J Cancer 38: 719–726
57. Houghton GW, Richens A (1974) Rate of elimination of tracer doses of phenytoin at different steady-state serum phenytoin concentrations in epileptic patients. Br J Clin Pharmacol 1: 155–161
58. Howell SB, Ensminger WD, Krishnan A, Frei E III (1978) Thymidine rescue of high-dose methotrexate in humans. Cancer Res 38: 325–330
59. Huffman DH, Wan SH, Azarnoff DL, Hoogstraten B (1973) Pharmacokinetics of methotrexate. Clin Pharmacol Ther 14: 572–579
60. Ilett KF, Madson BW, Woods JD (1979) Disopyramide kinetics in patients with acute myocardial infarction. Clin Pharmacol Ther 26: 1–7
61. Isacoff WH, Townsend CM Jr, Eilber FR, Forster T, Morten DL, Block JB (1976) High-dose methotrexate therapy of solid tumors: Observations relating to clinical toxicity. Med Pediatr Oncol 2: 319–325
62. Israili ZH, Vogler WR, Mingioli ES, Pirkle JL, Smithwick RW, Goldstein JH (1976) The disposition and pharmacokinetics in humans of 5-azacytidine administerd intravenously as a bolus or by continuous infusion. Cancer Res 36: 1453–1461
63. Iyer VN, Szybalski W (1964) Mitomycins and porfiromycin: Chemical mechanism of activation and cross-linking of DNA. Science 145: 55–57
64. Jacobs SA, Stoller RG, Chabner BA, Johns DG (1976) Hydroxymethotrexate as a metabolite in human subjects and rhesus monkey receiving high-dose methotrexate. J Clin Invest 57: 534–538
65. Jardine I, Fenselau C, Appler M, Kan M-N, Brundrett RB, Colvin M (1978) Quantitation by gas chromatography-chemical ionization mass spectrometry of cyclophosphamide, phosphoramide mustard, and nornitrogen mustard in the plasma and urine of patients receiving cyclophosphamide therapy. Cancer Res 38: 408–415
66. Jayaram HM, Tyagi AK, Anandaraj S, Montgomery JA, Kelley JA, Kelley J, Adamson RH, Cooney DA (1979) Metabolites of alanosine, an antitumor antibiotic. Biochem Pharmacol 28: 3551–3566
67. Jenne JW, Wyze MS, Rood FS, MacDonald FM (1972) Pharmacokinetics of theophylline. Clin Pharmacol Ther 13: 349–360
68. King FG, Dedrick RL (1979) Pharmacokinetic model for 2-amino-1,3,4-thiadiazole in mouse, dog, and monkey. Cancer Treat Rep 63: 1939–1947
69. Krüger-Thiemer E (1968) Nonlinear dose-concentration relationships. Farmaco [Sci] 23: 716–721
70. Krüger-Thiemer E, Diller W, Bunger P (1965) Pharmacokinetic models regarding protein binding of drugs. Antimicrob Agents Chemother 1965: 183–191
71. Larsson H, Tropé C, Mattsson W, Orbert B (1980) Clinical pharmacokinetics of intravenously administered spirogermanium. (Abstract) Am Soc Clin Oncol 21: 334
72. Lee SS, Giovanella BC, Shehlin JS Jr (1977) Selective lethal effect of thymidine on human and mouse tumor cells. J Cell Physiol 92: 401–406
73. Leme PR, Creaven PJ, Allen LM, Berman M (1945) Kinetic model for the disposition and metabolism of moderate and high-dose methotrexate (NSC740) in man. Cancer Chemother Rep 59: 811–817
74. Levy G (1965) Pharmacokinetics of salicylate elimination in man. J Pharm Sci 54: 959–967
75. Levy G (1968) Dose-dependent effects in pharmacokinetics: In: Tedeschi DH, Tedeschi RG (eds) Importance of fundamental principles in drug evaluation. Raven Press, New York, pp 141–172
76. Loo TL, Luce JK, Sullivan MP, Frei E III (1968) Clinical pharmacologic observations on 6-mercaptopurine and 6-methylthiopurine ribonucleoside. Clin Pharmacol Ther 9: 180–196
77. Loo TL, Friedman J, Moore EC, Valdivieso M, Marti JR, Stewart P (1980) Pharmacological disposition of N-(phosphonacetyl)-L-aspartate in humans. Cancer Res 40: 86–90
78. Lundquist F, Wolthers H (1958) The kinetics of alcohol elimination in man. Acta Pharmacol Toxicol (Copenh) 14: 265–289
79. Martin BK (1965) Kinetics of elimination of drugs possessing high affinity for the plasma proteins. Nature 207: 959–960
80. Meffin PJ, Robert EW, Winkle RA, Harapat S, Peters FA, Harrison DC (1979) Role of concentration-dependent plasma protein binding in disopyramide disposition. J Pharmacokinet Biopharm 7: 29–46
81. Monjanel S, Rigault JP, Cano JP, Carcassone Y, Favre H, Baratier F (1979) High-dose methotrexate: Preliminary evaluation of a pharmacokinetic approach. Cancer Chemother Pharmacol 3: 189–196
82. Mukherjee KL, Heidelberger CC (1960) Studies on fluorinated pyrimidines. IX. The degradation of 5-fluorouracil-6-^{14}C. J Biol Chem 235: 433–437
83. Neidhart JA, Staubus AE, Young P, King GW, Malspeis L (1980) Clinical toxic effects of 2,3-dihydro-1H-imidazol1,2Blpyrazole (IMPY) with relevant pharmacokinetic parameters. Cancer Treat Rep 64: 251–256
84. Nichol CA (1977) Pharmacokinetics: Selectivity of action related to physiochemical properties and kinetic patterns of anticancer drugs. Cancer 40: 519–528
85. Ohnuma T, Hart R, Roboz J, Andrejczuk JF (1979) Clinical and pharmacological studies with phosphonacetyl L-aspartate (PALA). (Abstract) Am Soc Clin Oncol 20: 344
86. Olson W, Miceli J, Weber W (1978) Dose-dependent change in sulfamethazine kinetics in rapid and slow isoniazid acetylators. Clin Pharmacol Ther 23: 204–211
87. O'Reilly RA, Aggeler PM, Leonge LS (1964) Studies on the coumarin anticoagulant drugs: A comparison of the pharmacodynamics of dicoumarol and warfarin in man. Thrombosis et Diathesis Haemorrhagica 11: 1–22
88. Patton TF, Himmelstein KJ, Belt R, Bannister SJ, Sternson LA, Repta AJ (1978) Plasma levels and urinary excretion of filterable platinum species following bolus injection and IV infusion of cis-dichlorodiammineplatinum (II) in man. Cancer Treat Rep 62: 1359–1362
89. Perrier D, Ashley JJ, Levy G (1973) Effect of product inhibition on kinetics of drug elimination. J Pharmacokinet Biopharm 1: 231–242
90. Pickup MD, Lowe JR, Leatham PA, Rhind VM, Wright V, Downie WW (1977) Dose-dependent pharmacokinetics of prednisolone. Eur J Clin Pharmacol 12: 213–219
91. Powis G, Ames MM (1980) Determination of 6-diazo-5-oxo-L-norleucine in plasma and urine by reversed-phase high-performance liquid chromatography of the dansyl derivative. J Chromatogr 181: 95–99
92. Powis G, Creagan ET, Ames MM, Kovach JS (1980a) Dose-dependent pharmacokinetic behavior and toxicity of

L-alanosine in humans. (Abstract) Am Assoc Cancer Res 21:133

93. Powis G, Eagan RT, Kovach JS (1980b) Pharmacokinetics and toxicity of 6-diazo-5-oxo-L-norleucine (DON) in humans. (Abstract) Am Soc Clin Oncol 21:329
94. Pratt CB, Roberts D, Sharks EC, Warmath (1974) Clinical trials and pharmacokinetics of intermittent high dose methotrexate – "leucovorin rescue" for children with malignant tumors. Cancer Res 34:3326–3331
95. Reich SD (1979) Mathematical modeling guide to high-dose methotrexate infusion therapy. Cancer Chemother Pharmacol 3:25–31
96. Reich SD, Bachur NR, Goebel RH, Berman M (1977) A pharmacokinetic model for high-dose methotrexate infusions in man. J Pharmacokin et Biopharm 5:421–433
97. Reich SD, Steinberg F, Bachur NR, Riggs CE, Goebel R, Berman M (1979) Mathematical model for adriamycin (doxorubicin) pharmacokinetics. Cancer Chemother Pharmacol 3:125–131
98. Rose JQ, Jusko WJ, Nickelsen JA, Green OC (1979) Prednisolone pharmacokinetics in relation to dose. (Letter) J Pediatr 94:1014–1015
99. Runkel R, Forchielli H, Sevelius M, Chaplin M, Segre E (1974) Nonlinear plasma level response to high doses of naproxen. Clin Pharmacol Ther 15:261–266
100. Schoenemann PT, Yesair DW, Coffey JJ (1973) Pharmacokinetic consequences of plasma protein binding of drugs. Ann NY Acad Sci 226:162–171
101. Skarin AT, Zuckerman KS, Pitman SW, Rosenthal DS, Moloney W, Frei E III, Canellos GP (1977) High-dose methotrexate with folinic acid in the treatment of advanced non-Hodgkin lymphoma including CNS involvement. Blood 50:1039–1047
102. Sladek NE (1971) Metabolism of cyclophosphamide by rat hepatic microsomes. Cancer Res 31:901–908
103. Speyer JL, Collins JM, Dedrick RL, Brennan MF, Buckpitt AR, Londer H, DeVita VT Jr, Myers CE (1980) Phase I and pharmacological studies of 5-fluorouracil administered intraperitoneally. Cancer Res 40:567–572
104. Staubus AE, Kerr TA, Balcerzak SP, Randall G, Neidhart JA (1979) Pharmacokinetics of pyrazoloimidazole (IMPY, NSC 51143) in humans. Am Soc Clin Oncol 20:366
105. Stoller RG, Jacobs SA, Drake JC, Lutz RJ, Chabner BA (1975) Pharmacokinetics of high-dose methotrexate (NSC-740). Cancer Chemother Rep 6:19–24
106. Stoller RG, Hande KR, Jacobs SA, Rosenberg SA, Chabner BA (1977) Use of plasma pharmacokinetics to predict and prevent methotrexate toxicity. N Engl J Med 297:630–634
107. Storb R, Thomas ED (1979) Human marrow transplantation. Transplantation 28:1–3
108. Tanner A, Bochner F, Caffin J, Halliday J, Powell L (1979) Dose-dependent prednisolone kinetics. Clin Pharmacol Ther 25:571–578
109. Tobias JS, Weiner RS, Griffiths CT, Richman CM, Parker LM, Yankee RA (1977) Cryopreserved autologous marrow infusion following high dose cancer chemotherapy. Eur J Cancer 13:269–277
110. Torkelson AR, LaBudde JA, Weikel JH Jr (1975) The metabolic fate of cyclophosphamide. Drug Metab Rev 3:131–165
111. Van Prooijen HC, Vierwinden, Van Egmond J, Wessels JMC, Haan C (1976) A sensitive bio-assay for pharmacokinetic studies of cytosine arabinoside in man. Eur J Cancer 12:899–905
112. Van Proojien R, Van der Kleijn E, Haanen C (1977) Pharmacokinetics of cytosine arabinoside in acute myeloid leukemia. Clin Pharmacol Ther 21:744–750
113. Wagner JG (1971) Biopharmaceutics and relevant pharmacokinetics. Drug Intelligence, Hamilton, pp 302–317
114. Wan SH, Huffman DH, Azarnoff DL, Stephens R, Hoogstraten B (1974) Effect of route of administration on effusions on methotrexate pharmacokinetics. Cancer Res 34:3487–3491
115. Weinberger M, Ginchansky E (1977) Dose-dependent kinetics of theophylline disposition in asthmatic children. J Pediatr 91:820–824
116. Woodcock TM, Martin DS, Damin LAM, Kemeny NE, Young CW (1980) Combination clinical trials with thymidine and fluorouracil: A phase I and clinical pharmacologic evaluation. Cancer 45:1135–1143
117. Zaharko DS, Botter BJ, Chiuten D, Wiernik PH (1979) Pharmacokinetic studies during phase I trials of high-dose thymidine infusions. Cancer Res 398:4777–4781

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