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Mitomycin C pharmacokinetics in rats — effect of dose size

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Summary

The pharmacokinetics of mitomycin C was studied following intravenous administration of the drug at three different dose levels to rats. A rapid high-performance liquid chromatographic assay was developed for the determination of mitomycin C in plasma and urine. Analysis was performed using a reversed-phase octadecyl silane column and precolumn. The mobile phase consisted of 30% (v/v) methanol in water (apparent pH of 4.5) containing 1.0 mM octane sulfonic acid–sodium salt delivered at a rate of 1.0 $ml \cdot min^{-1}$. The eluent was monitored at 360 nm. Under the conditions, mitomycin C and the internal standard had capacity factors of 1.6 and 3.0, respectively. Samples (50 μl) of plasma or urine were prepared by alkalinizing the sample with 50 μl of 0.1 M phosphate buffer solution and extracting with four volumes of 1 : 1 (v/v) chloroform : 2-propanol mixture. The detection limit was 0.01 $\mu g \cdot ml^{-1}$. Over the plasma concentration range of 0.01–10.0 $\mu g \cdot ml^{-1}$, the within-day coefficient of variation (CV) ranged from 5 to 16%. The between-day CV ranged from 2 to 18%. The assay was used for pharmacokinetic studies in rats. Logarithm of the plasma concentration–time profiles suggest a biphasic behavior with rapid distribution and dose-dependent elimination phases. At dose levels of 2.5 and 5.0 $mg \cdot kg^{-1}$, the effective half-lives, mean residence times and total plasma clearance did not show any significant dose dependency. However, at 10 $mg \cdot kg^{-1}$ dose level, significant increase in effective half-lives, mean residence times and a significant decrease in total plasma clearance were observed. Only 2–8% of the administered dose appeared as intact drug in the urine, whereas no fecal excretion of the drug was observed. At different dose levels, the disposition is linear with the half-lives becoming longer after the higher doses. This finding may either be attributed to the inhibition of the NADPH-linked cytochrome reductase system or to the rapid tissue uptake followed by slow release of the drug from tissue storage site.

Introduction

Mitomycin C is a highly toxic antitumor antibiotic that has demonstrated activity against a number of human neoplasms including advanced metastatic breast (Godfrey and Wilbur, 1972), gastric (Comis and Carter, 1974) and adenocarcinoma of the lung (Samson et al., 1978). Two major problems encountered with the mitomycin C therapy are delayed cumulative myelosuppression and rapid emergence of resistance. With the development of high-dose intermittent schedule, the myelosuppression has become manageable and renewed interest in both basic and clinical research involving this antitumor agent has become evident (Carter and Crooke, 1979).

The pharmacokinetic knowledge of mitomycin C in animals and humans has been very limited,

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mainly due to the lack of a sensitive and specific analytical method. Recently, preliminary pharmacokinetics of mitomycin C have been reported in humans and rabbits (van Hazel and Kovach, 1982) and in dogs (Barbhaiya et al., 1984). Both normal phase (Barbhaiya et al., 1984) and reversed-phase (Edwards et al., 1979, Buice et al., 1984) high-pressure liquid chromatographic methods have been developed recently for the determination of mitomycin C in plasma.

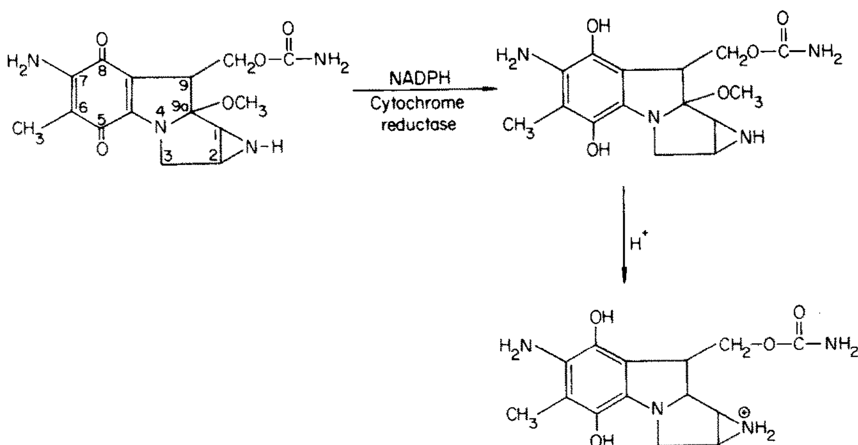
The drug requires metabolic activation, i.e. NADPH-linked cytochrome reduction, to become effective as an alkylating and DNA crosslinking agent (Iyer and Szybalski, 1964) but no information on the in vivo formation and identification of metabolites is available to date. Moreover, a high dose intermittent schedule is recommended at the present time for optimum therapeutic efficacy and lower toxicity (Carter and Crooke, 1979) but no studies using precise and specific analytical methods like high-pressure liquid chromatography have been conducted to examine the effect of dose size on mitomycin C pharmacokinetics. Fujita (1971), using a microbiological assay, studied the plasma elimination of mitomycin C in cancer patients administered with different dose levels of mitomycin C. The study concluded that plasma elimination half-life increased with higher doses and that intermittent administration of a larger dose of mitomycin C results in a higher total amount of drug in the blood than does frequent administration of small doses. Although mitomycin C is absorbed after oral administration, the absorption is too low and variable to allow effective blood levels (Crooke et al., 1976). Intravenous route is the preferred mode of mitomycin C administration.

Therefore, in the present study, the pharmacokinetics of mitomycin C has been evaluated following intravenous bolus administration of the drug at three dose levels. Attempts have been made to analyze urine and feces samples for any intact drug as well as any possible metabolites.

Materials and Methods

Materials

Mitomycin C was obtained as a gift from Bristol-Myers Co., Syracuse, NY (Lot No. S 85C067) and was used as received. Spectral grade 2-propanol, chloroform and methanol (Mallinckrodt, Paris, KY) were used without further purification. Octane sulfonic acid–sodium salt was obtained from Eastman Chemical Co., Rochester, NY. All other reagents were of analytical grade and used as such. Distilled deionized water was used throughout for the preparation of buffers, drug solutions and mobile phases.



Scheme 1.

Animals

Male Sprague–Dawley rats of 200–250 g weight were obtained from the Harlan Co., Indianapolis, IN and were housed individually in stainless steel metabolism cages (Acme Metal Products, Chicago, IL) with free access to food (Rodan Blox, Wayne, St. Louis, MO) and water.

The rats were implanted with a cannula in the right jugular vein. The cannula was made up of silastic and polyethylene tubes joined together by glue with the silastic implanted inside the vein and the polyethylene coming out of the dorsal side of the rats. The surgery was performed under light ether anesthesia 1 day prior to the drug study. The preparation of the cannulas and the surgical procedures were performed according to Harms and Ojeda (1974).

Pharmacokinetic studies

Animals were divided into three groups, each group consisting of 5 rats. Three different dose levels, i.e. 2.5, 5.0 and 10.0 $mg \cdot kg^{-1}$ of mitomycin C dissolved in normal saline were administered intravenously through the jugular cannula. The volume of the administered solution ranged from 0.5 to 0.6 ml and the solution was administered over a 30 s time period. Following the administration of each dose, the cannula was flushed with 0.1 ml of normal saline. Serial blood samples (0.10–0.12 ml each) were withdrawn at 2, 4, 8, 10, 15, 20, 35, 50, 65, 75, 100 and 120 min post dose, with the help of 0.25 ml heparinized collection tubes (Natelson Capillary Tubes, American Hospital Supply, McGaw Park, IL). Prior to collection of each blood sample 0.10 ml of blood/heparinized saline was drawn and discarded. After collection of each blood sample, 0.12 ml of normal saline containing heparin solution (10 USP U/ml) was introduced to flush the cannula and to replace the lost volume. Blood samples were centrifuged (Damon Centrifuge, I.E.C., Fisher Scientific) immediately at 3000 rpm for about 20 min. The plasma was separated, frozen immediately and stored at $-5°C$.

Urine and feces were collected quantitatively at 24 and 48 h postadministration. Urine samples were collected at temperatures of 0 to $-5°C$ to prevent any degradation of mitomycin C. At each urinary collection time, the animals were induced to empty bladder by ether inhalation. Feces samples were homogenized (Thermolyne, Sybron, Rochester, NY) in distilled water. Aliquots of urine and feces homogenates were frozen immediately.

Sample preparation

An aliquot (50 μl) of the plasma or urine sample was added to 50 μl of 0.1 M phosphate buffer solution (pH 8.5) containing 1.0 $\mu g \cdot mL^{-1}$ of the internal standard, porfiromycin, in a screw-capped centrifuge tube with a polytef-lined screwcap. The solution was immediately extracted by vortexing for 2 min with 400 μl of 1 : 1 (v/v) chloroform : 2-propanol mixture. Following centrifugation at 3000 rpm for 10 min, an aliquot (300 μl) of the organic layer was carefully removed and placed in 1/2 dram sample vials and was evaporated to dryness under nitrogen. The residue was reconstituted in 50 μl of methanol and a 15 μl volume was injected onto the high pressure liquid chromatograph.

Chromatography

Similar high-pressure liquid chromatographic techniques were applied to plasma, urine and feces samples. The chromatographic system comprised of a solvent delivery module (M 510A, Waters Associates, Milford, MA), a U-6K universal injector (Waters Associates), a 5 μ 15 cm spherical packing octadecyl silane column (Resolve C_{18} column, Waters Associates), a UV-visible variable wavelength detector (Model 481, Waters Associates) set at 360 nm, a guard column (2.54 cm long packed with 37–50 C_{18} packing material, Waters Associates) fitted just prior to the inlet junction of the analytical column and an integrator (Shimadzu, C-R3A, Chromatopac) for accurate determination of peak areas. The mobile phase consisted of 30% (v/v) methanol in water containing 1 mM octane sulfonic acid–sodium salt. The apparent pH of the mobile phase was adjusted to 4.5 with dilute hydrochloric acid. The solvent flow was maintained at 1.0 ml/min which generated a column pressure of about 2000 p.s.i. The chromatographic analyses were performed at ambient temperature.

Standard curves

Standard plasma and urine samples were prepared by adding 50 μl of the appropriate working standard solution to 50 μl of plasma or urine in a screw-capped centrifuge tube to produce concentration of 0.01–10.0 $\mu g \cdot ml^{-1}$. Standard samples were treated as described above. Standard curves were constructed by plotting the peak area ratios of mitomycin C to the internal standard versus mitomycin C concentration with the equation of best-fit line obtained by linear regression analysis.

Recovery studies

The recovery of mitomycin C from plasma and urine was determined by comparing the peak area ratios of mitomycin C to the internal standard obtained with the spiked plasma or urine samples to the ratios obtained with the injection of equivalent amounts of each compound dissolved in water.

Stability studies

Plasma and urine samples spiked with mitomycin C were stored in 1.5 ml screw-capped centrifuge tubes at $-5°C$ and assayed at various times for up to 72 h to assess how long the specimens could be stored prior to assay. The stability of mitomycin C in methanolic solution was also evaluated for 6 h at ambient temperature.

Pharmacokinetic calculations

Since plasma mitomycin C concentration–time profiles appear to exhibit rapid distribution and dose-dependent elimination phases, a non-compartmental approach based on statistical moment theory would probably be a better method for the estimation of pharmacokinetic parameters. The mean residence time (MRT) in the body and the steady-state volume of distribution ($V_{d_{ss}}$) were calculated by model-independent methods (Benet and Galeazzi, 1979) as given by Eqns. 1 and 2, respectively.

$$MRT = [AUMC]/[AUC] \tag{1}$$

$$V_{d_{ss}} = \text{i.v. Dose } [AUMC]/[AUC]^2 \tag{2}$$

Over the sampling interval, the area under the plasma concentration–time curve, i.e. [AUC] was determined by the trapezoidal rule (Gibaldi and Perrier, 1975). The first moment of the plasma concentration–time profile, i.e. [AUMC] was determined similarly, after multiplying each concentration by its time (Benet and Galeazzi, 1979). The AUC beyond the last plasma concentration value (AUC_t) and the AUMC beyond that point ($AUMC_t^{\infty}$) were calculated by employing Eqns. 3 and 4, respectively. The terminal slope (β) was obtained from the log-linear least-squares fit of the terminal portion of the serum concentration versus time curves (3–4 data points).

$$[AUC]_t^{\infty} = \frac{C_{pl}}{\beta} \tag{3}$$

$$[AUMC]_t^{\infty} = \frac{C_{pl} \cdot t_l}{\beta} + \frac{C_{pl}}{\beta^2} \tag{4}$$

The terminal slope (β), the last plasma concentration (C_{pl}) and the time (t_l) when C_{pl} occurred were used in the above equations. Moreover, the plasma concentration time data then fitted into a non-linear least-squares parameter optimization computer program, NONLIN 84, represented a two-compartment open model with elimination occurring from the central compartment. The purpose of using a model-dependent approach was mainly to obtain estimates of distribution and elimination half-lives.

The total plasma clearance (Cl_p) was calculated according to Eqn. 5.

$$Cl_p = \text{i.v. dose}/[AUC] \tag{5}$$

The MRT of a drug after intravenous bolus administration provides a useful estimate of the persistence time in the body and can also be used as a parameter to denote dose-dependent elimination. Inhibition of metabolic pathways would tend to increase the residence time of a drug in the body. The mean residence time of a drug like mitomycin C that requires multicompartment analysis, is a complex function of the model-dependent rate constants for distribution and elimination. However, as suggested by Gibaldi (1984), an effective

rate constant ($\bar{k}$) can be obtained according to Eqn. 6 which can be related to MRT by Eqn. 7.

$$\bar{k} = Cl_p/Vd_{ss} \quad (6)$$

$$MRT = 1/\bar{k} \quad (7)$$

The ratio of 0.693 to $\bar{k}$ has been defined as the effective half-life of the drug which is greater than model dependent, terminal half-life because for drugs requiring multicompartment characterization, $\bar{k} > \beta$.

Results and Discussion

Representative chromatograms depicting blank plasma samples and samples containing mitomycin C and the internal standard have been illustrated in Fig. 1. Adequate separation could be achieved with capacity factors of 1.6 and 3.0 for the drug and the internal standard, respectively, which generates a value of 1.9 for the separation factor. Excellent linearity ($r > 0.995$) was observed between the peak area ratios and mitomycin C concentration over three orders of magnitude ranging from 0.01 to 10.0 $\mu g \cdot ml^{-1}$.

Assay sensitivity defined as greater than three times the area of the noise level was 0.01 $\mu g \cdot ml^{-1}$. At this concentration, the coefficient of variation was < 15% making it an acceptable detection limit.

As shown in Table 1, the precision of the assay for mitomycin C in rat plasma over the concentration range of 0.01–10.0 $\mu g \cdot ml^{-1}$ ranged from 1 to 15% and from 1 to 18% for the within- and between-day coefficients of variation, respectively.

Assay specificity was verified by injecting plasma samples under a variety of mobile phase conditions (varying methanol concentration, changing from methanol to acetonitrile, varying apparent mobile phase pH from 4.0 to 8.0) and single peak was observed for mitomycin C. No indications of an underlying component was detected, e.g. peak shoulders.

The recovery of mitomycin C from spiked rat plasma and urine samples is summarized in Table

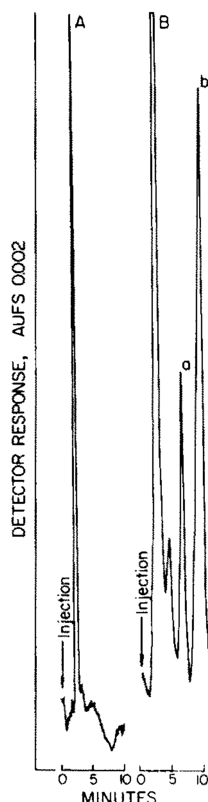


Fig. 1. Chromatograms of plasma extracts. A, blank plasma; and B, plasma spiked with 0.4 $\mu g \cdot ml^{-1}$ of mitomycin C (a) and 1 $\mu g \cdot ml^{-1}$ of porfiromycin (b).

2. The recovery was in the range of 65–70%.

Plasma and urine samples spiked with known concentrations of mitomycin C were stored at

TABLE 1

INTRA-DAY AND INTER-DAY REPRODUCIBILITY OF THE ASSAY OF MITOMYCIN C IN RAT PLASMA

Amount added ($\mu g \cdot ml^{-1}$)	Coefficient of variation (%)	
	Intra-day [a]	Inter-day [a]
0.01	15.7	18.2
0.05	12.9	16.7
0.1	11.8	15.3
0.5	12.1	14.8
1.0	8.6	9.5
5.0	7.7	5.1
10.0	6.5	2.2

[a] n = 6.

TABLE 2

RECOVERY OF MITOMYCIN C FROM SPIKED SAMPLES OF RAT PLASMA AND URINE

Amount added ($\mu g \cdot ml^{-1}$)	Recovery (%)	
	Plasma [a]	Urine [a]
0.01	65.5 ± 4.9	68.9 ± 3.2
0.05	67.7 ± 6.2	65.4 ± 4.1
0.1	71.0 ± 7.5	69.7 ± 3.5
0.5	70.2 ± 3.8	66.5 ± 2.9
1.0	72.5 ± 2.1	70.2 ± 3.6
5.0	73.5 ± 6.6	71.5 ± 5.9
10.0	70.1 ± 1.2	73.2 ± 2.3

[a] Mean ± S.D.; n = 6.

−5°C to assess their stability on storage. When analyzed periodically over 72 hours, no loss of drug was observed; however, all plasma sample were worked up the same day the experiments were conducted. In methanolic solution mitomycin C did not show any degradation for 6 h at ambient temperatures. Therefore the developed assay procedure is a simple and rapid HPLC method for the analysis of mitomycin C in plasma and urine. The method is specific with good precision and reproducibility and has been found to be sensitive enough for pharmacokinetic studies in rats.

Fig. 2 is a representative plot of plasma mitomycin C concentration versus time following intravenous administration of three different dose levels, i.e. 2.5, 5.0 and 10.0 $mg \cdot kg^{-1}$ of the drug to male Sprague–Dawley rats. The plots definitely show multiexponential behavior with decreasing

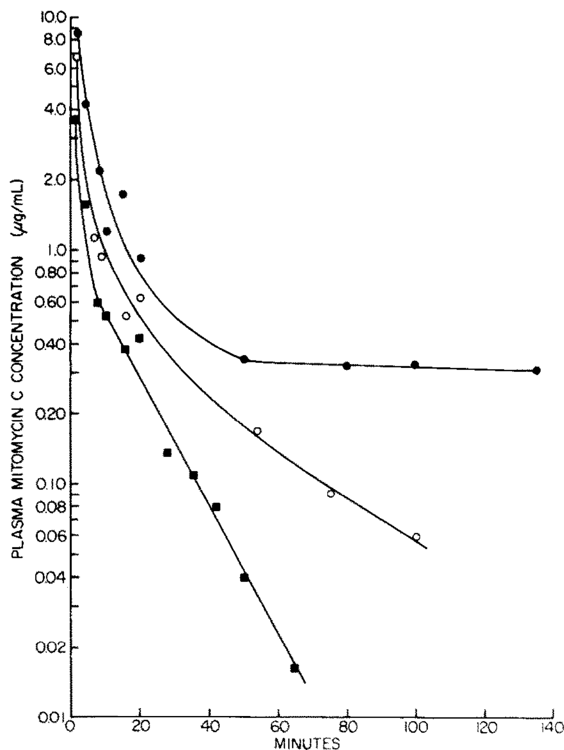


Fig. 2. Semilogarithmic plots of typical mitomycin C plasma concentration–time profiles following intravenous bolus administration of various doses. Key: ●, 10 $mg \cdot kg^{-1}$; ○, 5.0 $mg \cdot kg^{-1}$; ■, 2.5 $mg \cdot kg^{-1}$.

TABLE 3

PHARMACOKINETIC PARAMETERS OF MITOMYCIN C FOLLOWING VARIOUS i.v. DOSES IN THE RAT

Parameter (n = 5)	Dose of mitomycin C ($mg \cdot kg^{-1}$)		
	2.5	5.0	10.0
MRT (min)	16 ± 6.2	12 ± 1.6	166 ± 32 [a]
$V_{d_{ss}}$ ($l \cdot kg^{-1}$)	1.12 ± 0.45	0.82 ± 0.26	0.86 ± 0.37
Cl_p ($l \cdot h^{-1} \cdot kg^{-1}$)	4.21 ± 0.12	4.08 ± 1.12	(3.01 ± 0.76) × 10^{-3} [a]
$\bar{k}$ (h^{-1})	4.35 ± 2.22	5.18 ± 1.38	(3.96 ± 1.98) × 10^{-3} [a]
$t_{1/2},\bar{k}$ (h)	0.18 ± 0.06	0.14 ± 0.03	201 ± 19.84 [a]
$t_{1/2},\alpha$ (h)	0.03 ± 0.01	0.02 ± 0.01	0.01 ± 0.003
$t_{1/2},\beta$ (h)	0.19 ± 0.02 [b]	0.52 ± 0.17 [b]	331 ± 54 [b]

All values are tabulated as mean ± S.D.

[a] Statistically significant at 95% confidence limit. Multiple comparisons were made using Student-Newman Keuls procedure with log-normal transformation. Parameters at 10 $mg \cdot kg^{-1}$ dose level were different from those of the 2 lower doses.

[b] Statistically significant at 95% confidence limit for all three different dose levels using log-normal transformation.

apparent terminal elimination rate constants with increasing dose size. An inspection of the pharmacokinetic parameters in Table 3 would clearly establish the dose-dependent pharmacokinetics of mitomycin C.

The mean residence time (MRT) of the drug in the body calculated from the area under the first moment of the plasma concentration–time curve and the area under the plasma concentration–time curve according to Eqn. 1 shows a dramatic increase, i.e. from 12 to 166 min when the dose level has been increased from 5.0 to 10 $mg \cdot kg^{-1}$, suggesting slower elimination of the drug at higher doses. Although statistical analyses by Student's Newman-Keul's method have suggested significant difference ($P < 0.05$) in persistence time of mitomycin C given at 2.5 or 5.0 and 10.0 $mg \cdot kg^{-1}$ dose levels, no significant difference ($P < 0.05$) has been observed between 2.5 and 5.0 $mg \cdot kg^{-1}$ dose sizes. Similarly, total plasma clearance (Cl_p) and non-compartmental effective half-lives ($t_{1/2}$, $\bar{k}$) show significant differences between 2.5 or 5.0 and 10.0 $mg \cdot kg^{-1}$ dose levels but no significance can be attributed between the 2.5 and 5.0 $mg \cdot kg^{-1}$ dose levels. The non-compartmental steady-state volume of distribution ($V_{d_{ss}}$) calculated according to Eqn. 2 does not show any significant changes at different dose levels confirming the earlier observation that decreased plasma clearance at 10.0 $mg \cdot kg^{-1}$ dose is due to slower elimination of the drug. The steady-state volume of distribution ranges from 0.82 to 1.12 l/kg which suggests that the drug probably distributes to deep tissues. This distribution behavior of mitomycin C might be responsible for the therapeutic activity of the drug in deep-seated tumors of the breast, G.I. or lung tissues.

Compartmental analysis by the computer program NONLIN 84 has suggested a two-compartment open model with elimination occurring from the central compartment. The distribution half-lives ($t_{1/2}$, α) of about 1–2 min suggest a rapid equilibration between plasma and tissues. The terminal elimination half-lives ($t_{1/2}$, β) at 2.5 and 5.0 $mg \cdot kg^{-1}$ dose levels are 11 and 31 min. As steady-state volume of distribution ($V_{d_{ss}}$) values were similar at each dose level, terminal half-lives ($t_{1/2}$, β) suggest a rapid clearance at low dose levels and relatively slower plasma clearance at high dose levels. There is a statistically significant difference ($P < 0.05$) between 2.5 and 5.0 $mg \cdot kg^{-1}$ dose levels as far as this particular parameter is concerned, but effective elimination half-lives ($t_{1/2}$, $\bar{k}$) based on non-compartmental analysis does not show such difference. It must be recognized that $\bar{k}$ is a time-averaged effective elimination rate constant which takes into account the entire concentration–time profile.

The dose-dependent elimination of mitomycin C may not be attributed to saturable enzymatic metabolism resulting in non-linearity. If such an elimination mechanism were operative, logarithm of plasma concentration time plots would show curving (zero-order kinetics) at higher plasma concentrations followed by linear phases (first-order kinetics) at lower plasma mitomycin C concentrations. At different dose levels, the disposition is linear (no curving downward) with terminal linear phases (first order disposition) showing longer half-lives after the higher doses. These findings may not be clearly explained with the current knowledge of mitomycin C distribution but may be described by either one or both of the following two reasons.

(1) Inhibition of the NADPH linked cytochrome reductase activity responsible for metabolism of mitomycin C by the drug itself and/or the reduced metabolic product.

(2) Rapid uptake of the drug to tissue storage site followed by slow release into the blood circulation.

Either of these two mechanisms would cause a slowing of the disposition but would retain first-order kinetics. More work would be needed to establish any one of the two mechanisms.

The liver is thought to be the major organ of biotransformation, but most other tissues like the kidney, lungs, brain, heart, spleen and testis have high capacities for metabolizing mitomycin C (Fujita, 1971). Although no definitive pharmacokinetic studies have been reported so far to establish the dose-dependent elimination of mitomycin C in humans, Fujita (1971) using a microbiological assay, studied the plasma elimination of mitomycin C in cancer patients following administration of different doses of the drug. The studies

TABLE 4

URINARY EXCRETION OF INTACT MITOMYCIN C AFTER INTRAVENOUS ADMINISTRATION AT THREE DIFFERENT DOSE LEVELS

i.v. Dose $mg \cdot kg^{-1}$ (n = 5)	Cumulative percentage of administered dose excreted as unchanged drug in urine till time infinity (infinity is 48 hr)
10.0	8.5 ± 0.1
5.0	6.72 ± 1.31
2.5	2.23 ± 0.38

Data tabulated as mean ± S.D.

concluded that intermittent administration of a large dose of mitomycin C results in a higher amount of drug in the blood than does frequent administration of small doses. Some years prior to Fujita's observation, Hata et al. (1961) noted that a single high dose administration of mitomycin C appeared to be superior to repeated smaller doses in the Ehrlich ascites murine model. Similarly, Kenis et al. (1964) also reported that "massive" doses were more effective than smaller doses in human patients.

The cumulative amount of intact mitomycin C excreted in the urine is given in Table 4. Only 2–9% of the administered dose appears in the urine suggesting that urinary excretion does not appear to be a major route of elimination. The urinary excretion data appears to show the trend that as the dose level is higher, a greater percentage of drug is excreted in the urine. This finding is consistent with the observation of dose-dependent kinetics whereby higher and prolonged levels of the intact drug in the plasma causes more drug to be filtered through the kidney. Therefore, both renal and liver functions in patients taking high dose intermittent therapy are important determinants for drug levels in the body.

Feces samples collected at 24 and 48 h following intravenous administration at all dose levels did not show any trace of intact mitomycin C. Therefore, fecal excretion of unchanged drug is not a likely pathway for mitomycin C elimination. A large fraction, about 91–98% of the intravenously administered dose, is probably metabolized and inhibition of the metabolic pathway can lead to significantly higher and sustained levels of the drug in the body. If these findings can be extrapolated to humans, then it can be suggested that intermittent high dose scheduling of mitomycin C would likely cause significantly higher and sustained levels of the drug improving the efficacy of the antitumor agent in cancer patients. However, monitoring of plasma levels during therapy and especially prior to next dosing are recommended so that the dosage calculation can be based on individual pharmacokinetic parameters of the patient. Otherwise, successive high dosing may cause rapid and significant accumulation of the drug in the body resulting in severe toxicity.

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