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Pharmacokinetics of Mitomycin C in Humans[1]

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ABSTRACT

This paper describes an investigation into the pharmacokinetic behavior of mitomycin C (MMC) in 36 patients receiving either single-agent chemotherapy (10 to 20 mg/sq m), or a combination regimen including MMC (5 to 10 mg/sq m).

A high-performance liquid chromatographic assay of MMC was applied for the analysis of plasma, urine, bile, and ascites fluid samples. The detection limit is 1 ng/ml sample. Most patients were given short-term i.v. infusion, although other methods of administration were used as well. Most plasma concentration-time curves fit a two-compartment model.

Pharmacokinetic parameters revealed large interindividual variations. Median terminal half-lives in single-agent chemotherapy and combination chemotherapy were 50 and 42 min, respectively. The apparent volume of the central compartment was 7 liters/sq m in both groups. The volume of distribution was 22 liters/sq m in single-agent chemotherapy, and 25 litres/sq m in combination chemotherapy. Linear regression analysis of the area under the plasma concentration-time curve *versus* the dose did not produce any evidence that the pharmacokinetics was dose dependent. However, differences were observed between patients receiving MMC alone and those on combination chemotherapy, in particular with regard to the total body clearance: 18 liters/hr/sq m for single-agent chemotherapy and 28 liters/hr/sq m for combination chemotherapy. Urinary recovery was limited to a maximum of 15% of the administered dose. In one patient studied, MMC was found to be present in the bile. There is evidence for enterohepatic circulation of MMC, and MMC was also found to penetrate into the ascites fluid.

INTRODUCTION

The antitumor antibiotic MMC[3] has shown clinical activity in a number of cancers, including stomach cancer, breast cancer, and cervical cancer (1, 2, 6). The drug acts through bioreductive alkylation and seems to be selectively toxic to hypoxic cells (8). Interest in the drug has been limited for a long time because severe bone marrow toxicity was observed with the daily treatment schedule that was applied originally. However, since the introduction of the high-dose intermittent schedule, there has been a revival of interest in the drug. There have been very few clinical pharmacokinetic studies on MMC, mainly because of the lack of sensitive assays. Early studies in animals (11) and humans (4) in which a biological assay with a detection limit of 100 ng/ml plasma was applied failed to produce detailed pharmacokinetic data, as MMC levels could not be followed for more than 2 hr after drug administration. Reevaluation of the initial data showed a biphasic decline of plasma concentrations; it has been speculated that an additional disposition phase may exist beyond the 120-min time point (10). Half-lives of the elimination phase appeared to be longer at the higher dose levels, suggesting nonlinear pharmacokinetics (6, 10).

We recently reported on a sensitive high-performance liquid chromatographic assay for MMC which has a detection limit of 1 ng/ml sample (3). In this report, pharmacokinetic behavior of MMC is described for 36 patients who received an i.v. or i.a. push injection, or an i.v. infusion of the drug. MMC was administered either as a single agent or in a combination regimen. In a limited number of cases, urine, bile, and ascites samples were evaluated, in addition to plasma samples. Attempts have been made to correlate MMC pharmacokinetics to type of therapy, method of administration, comedication, and biochemical and clinical parameters.

MATERIALS AND METHODS

Drugs. MMC for clinical use was obtained from Kyowa Hakko Kogyo Co. (Tokyo, Japan). MMC, used as reference material in the analysis, was a gift from the Bristol-Myers Co. (Syracuse, N. Y.). Porfiromycin was kindly supplied by Dr. D. B. Borders (Lederle Laboratories, Pearl River, N. Y.). All other chemicals were obtained from standard chemical sources and were of analytical reagent grade.

Patients. Thirty-six patients, 23 males and 13 females, aged 40 to 79 years, with advanced solid tumors, including breast cancer, prostate cancer, bronchial adenocarcinoma, and cervical cancer, were entered on the study. Some of the patients had been heavily pretreated. Renal and hepatic functions were in the normal range for all but 3 patients, who showed slight kidney or liver malfunction.

Pretreatment studies included hematology, blood biochemistry, and urine analysis. In the majority of cases, these analyses were repeated at weekly intervals.

Treatment. MMC was administered either as a single agent (Group A) or in a combination regimen (Group B). The methods of administration included short-term i.v. infusion (i.v. push), short-term i.a. hepatic infusion (i.a. push), 3-hr i.v. infusion, and 24-hr i.v. infusion (Table 1), depending on the treatment protocol. The drug was dissolved in distilled water and infused i.v. for 1 to 15 min, depending to some extent on the quality of the veins. Two patients received i.a. infusions, one in 9 min and the other in 22 min.

For infusions lasting 3 and 24 hr, the drug was prepared in 5% dextrose and delivered with an infusion pump. The total volume infused was 250 ml/3 hr.

Sampling. Blood samples were collected from the arm opposite to the infusion site through a cannula inserted into a vein, prior to MMC infusion and at the following time points after infusion: 0, 1, 2, 3, 4, 5, 10, 20, 30, 60, 90, 120, 180, 240, 300, 360, and 420 min. Samples were collected in heparinized tubes. The tubes were cooled in an ice bath and centrifuged as soon as possible. Plasma was separated and stored at −25° prior to analysis. Similar precautions were taken when sampling from patients receiving long-term i.v. infusions. In these cases, samples

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[3] The abbreviations used are: MMC, mitomycin C; i.a., intraarterial(ly); AUC, area under the plasma concentration-time curve.

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Table 1

Division of patients according to therapy, route of administration, and dose

	Dose (mg/sq m)	Single agent	+ VCR,[a] Bleo, CDDP[b]	+ ADM, 5-FUra[c]	+ ADM, CDDP[d]	+ 5-FUra, hydroxy-urea[e]
i.v. push	10	$n = 6$				
	12	$n = 4$				
	15	$n = 5$				
	16	$n = 1$				
	20	$n = 2$				
i.a. push	20	$n = 2$				
i.v. 3-hr infusion	16	$n = 1$				
i.v. 24-hr infusion	10	$n = 1$				
	16	$n = 4$				
i.v. push	6		$n = 2$			
i.v. push	5				$n = 1$	
	8				$n = 2$	
	10				$n = 3$	
i.v. push	10			$n = 1$		
i.v. push	10					$n = 1$

[a] VCR, vincristin; Bleo, bleomycin; CDDP, cisplatin; ADM, Adriamycin; 5-FUra, 5-fluorouracil.

[b] VCR (1 mg/sq m i.v. push, Day 1); Bleo (10 mg/sq m i.v. 24-hr infusion, Days 2 and 3); MMC (6 mg/sq m i.v. push, Day 3); CDDP (50 mg/sq m i.v. 3-hr infusion, Day 4).

[c] ADM (30 mg/sq m i.v. push, Day 1); MMC (10 mg/sq m i.v. push, Day 1); 5-FUra (600 mg/sq m i.v. push, Day 1).

[d] MMC (5 to 10 mg/sq m i.v. push, Day 1); ADM (20 to 40 mg/sq m i.v. push, Day 1); CDDP (60 mg/sq m i.v. 3-hr infusion, Day 1).

[e] 5-FUra (500 mg/sq m i.v. push, Day 1); MMC (10 mg/sq m i.v. push, Day 1); hydroxyurea (1 g/sq m p.o., Day 1 to 14).

were also collected during infusion, *e.g.*, every hr. In 9 patients, urine was collected for 24 hr after i.v. push injection, and aliquots were frozen for subsequent analysis. In one patient, bile was sampled via a T-drain inserted in the bile duct. From 2 patients, ascites fluid samples were collected from an indwelling catheter. These samples were also frozen at −25° prior to analysis.

Analysis. The samples were analyzed by a high-performance liquid chromatographic assay with a sensitivity of 1 ng/ml, using a 1-ml specimen. The method for the analysis of plasma samples has been reported in detail (3). For the extraction of MMC from bile or ascites fluid, 0.1 ml bile or 1.0 ml ascites fluid was mixed with 10 volumes of 50% chloroform in propan-2-ol and then treated in the same way as the plasma samples. For urine analysis, a 0.1-ml sample was extracted twice with 1.0 ml chloroform; then the organic layers were mixed and processed in the same way as the other samples. The internal standard used in the analytical method was porfiromycin, a structure analogue of MMC. Recoveries after extraction were more than 90%. MMC concentrations in the biological samples were calculated from calibration curves obtained by simultaneous analysis of spiked samples of the same biological matrix. All analyses were performed in duplicate.

Pharmacokinetic Data Analysis. Inspection of the drug concentration-time data plotted on semilogarithmic paper revealed in most cases a biexponential decline, suggesting that disposition of MMC in the body can be described in terms of an open 2-compartment model. Because the half-life of the distribution phase turned out to be of the same order of magnitude as the infusion time, an equation was applied which takes into account the time during which the drug was infused (5). Terminal half-life ($t_{½\beta}$) was calculated by a least-squares regression analysis of those data points which appeared to belong to the elimination phase. Curve stripping by application of the method of residuals was used to determine the half-life of the distribution phase ($t_{½\alpha}$). The distribution volume of the central compartment (V_C), the volume of distribution at steady state (V_{ss}), and the volume of distribution (V_β) were calculated by standard methods (5). Total body clearance (Cl_{tot}) was obtained by dividing the dose (D) administered by the AUC, calculated by means of the trapezoidal rule from the onset of the administration until the last observed plasma concentration. For long-term infusions, Cl_{tot} was calculated from the infusion rate divided by the steady-state plasma concentration. In a number of cases, a nonlinear curve-fitting program, according to Nielsen-Kudsk (9), was used to obtain the pharmacokinetic parameters. These values appeared to compare well with those obtained by the curve-stripping method.

RESULTS

Chart 1 shows a number of typical log plasma concentration-time curves after i.v. push administration of MMC, either as a single agent or in combination with Adriamycin and cisplatin. Peak plasma concentrations varied between 0.4 and 3.2 μg/ml plasma, depending on dose and infusion time. In single-agent chemotherapy, the maximum value and the plasma concentrations during distribution and elimination phase were higher than in combination chemotherapy because of the higher dose administered. The plasma disappearance curve after i.a. hepatic injection has the same profile as after an i.v. administration. With long term i.v. infusion of MMC (16 mg/sq m), steady-state levels were reached after 2 to 3 hr; these were 150 ng/ml plasma for 3-hr infusion, and 10 ng/ml plasma for 24-hr infusions. After the infusion was discontinued, the MMC plasma concentration dropped in the same way as after an i.v. push injection. Table 2 shows the median values and the ranges of the most characteristic pharmacokinetic parameters after an i.v. push injection. The data for Groups A and B have been analyzed separately.

The parameters for i.a. push injection are shown in Table 3. Parameters for 24-hr infusions could not be calculated. The data for the 3-hr i.v. infusion proved to be sufficiently significant to derive the pharmacokinetic parameters (Table 3).

In urine, MMC could be detected only during the 8 hr following drug administration. Cumulative urinary recovery was deter-

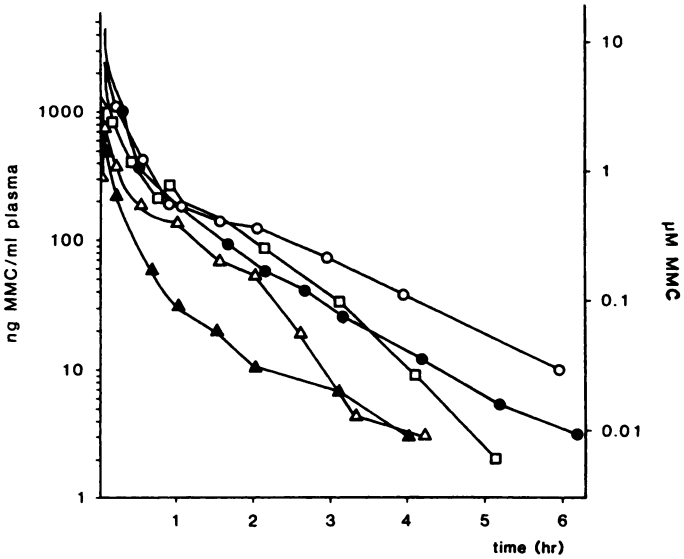

Chart 1. Plasma concentration-time curves after i.v. push injections, single-agent, and combination chemotherapy. ○, Patient S, male, 36 mg MMC (20 mg/sq m), single agent; □, Patient V, male, 38 mg MMC (20 mg/sq m), single agent; ●, Patient V, 30 mg MMC (15 mg/sq m), single agent; △, Patient M, male, 13 mg MMC (7.5 mg/sq m), combination therapy (Adriamycin and cisplatin); ▲, Patient O, male, 17 mg MMC (10 mg/sq m), combination therapy (Adriamycin and cisplatin).

Table 2
Pharmacokinetic parameters of MMC after i.v. push injection

	No. of patients	Dose (mg/sq m)	Single-agent therapy, Group A	Combination therapy, Group B
$t_{1/2}\alpha$ (min)	18	10–20	5.2 (2.9–12.4)[a]	
	10	5–10		4.6 (2.6–7.0)
$t_{1/2}\beta$ (min)	18	10–20	50 (30–70)	
	10	5–10		42 (26–70)
V_C (liter/sq m)	18	10–20	7 (4–13)	
	10	5–10		7 (6–13)
V_β (liter/sq m)	18	10–20	22 (14–47)	
	10	5–10		25 (18–60)
V_{ss} (liter/sq m)	18	10–20	18 (10–30)	
	10	5–10		18 (14–33)
Cl_{tot} (liter/hr/sq m)	18	10–20	18 (11–31)	
	10	5–10		28 (15–46)
AUC (μg·hr/liter)	6	10	388–874	
	4	12	382–880	
	6	15	477–1050	
	2	20	811–1031	
	1	5		177
	2	6		177–248
	2	8		265–379
	5	10		219–654

[a] Numbers in parentheses, range.

Table 3
Pharmacokinetic parameters of MMC after i.a. push injection and after 3-hr i.v. infusion

	No. of patients	Dose (mg/sq m)	i.a. push	3-hr i.v. infusion
$t_{1/2}\alpha$ (min)	2	20	6.5–9.1	
	1	16		1.9
$t_{1/2}\beta$ (min)	2	20	50–54	
	1	16		41
V_C (liter/sq m)	2	20	6–9	
	1	16		11
V_β (liter/sq m)	2	20	22–24	
	1	16		36
V_{ss} (liter/sq m)	2	20	15–17	
	1	16		32
Cl_{tot} (liter/hr/sq m)	2	20	18–18	
	1	16		37
AUC (μg·hr/liter)	2	20	1105–1063	
	1	16		416

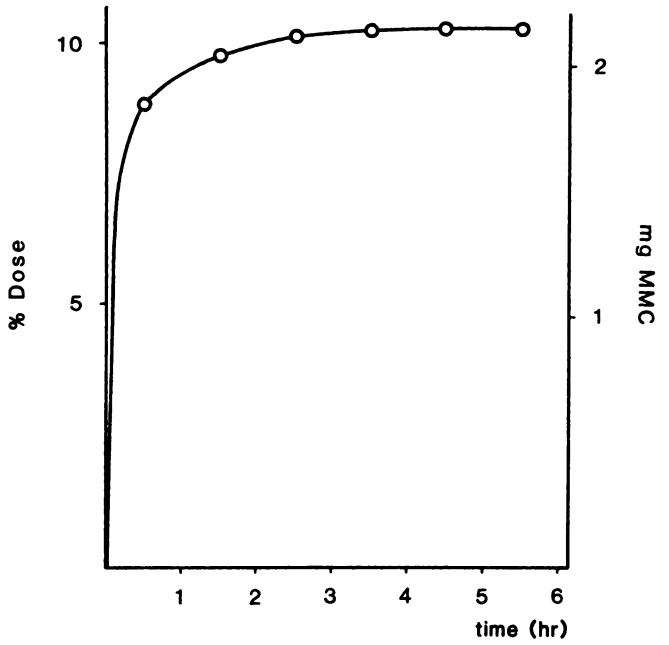

Chart 2. Cumulative urinary excretion curve. Patient R, male, 21 mg MMC (12 mg/sq m), single-agent chemotherapy.

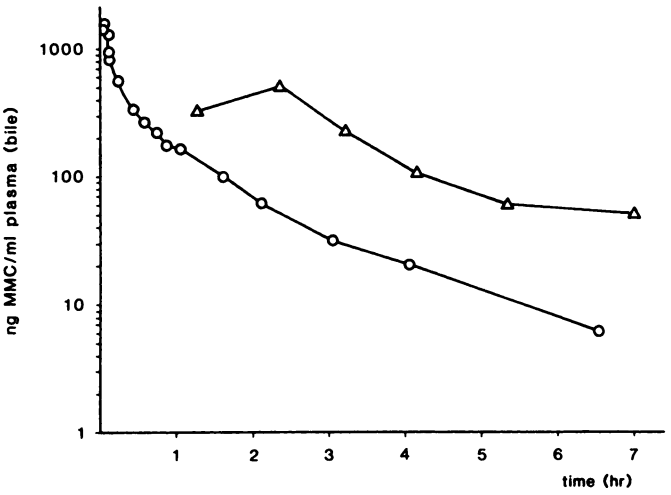

Chart 3. Semilogarithmic plot of MMC concentration in plasma and bile *versus* time. O, plasma; Δ, bile, Patient S, female, 16 mg MMC (10 mg/sq m), combination therapy (Adriamycin and 5-fluorouracil).

mined for 9 patients and varied from 2 to 15% of the administered dose. Chart 2 shows the cumulative urinary excretion curve for one patient in whom recovery of unchanged MMC was 10.3% in the first 6 hr. Pharmacokinetic evaluation of these data on urinary excretion, carried out according to standard methods (5), revealed a $t_{1/2}\beta$ of 35 min and a renal clearance of 1.7 liters/hr/sq m. These parameters could only be calculated from urine data in the limited number of cases in which urine sampling had been carried out frequently, *e.g.*, hourly over 8 hr.

In Chart 3, the course of MMC concentration in plasma and bile in one patient is depicted. Maximum level in the bile was reached about 2 hr after administration and amounted to 0.5 μg/ml. During the elimination phase, concentrations in bile were 5 to 8 times higher than in plasma. Biliary clearance and excretion could not be calculated because bile flow had not been measured.

Analysis of ascites fluid samples resulted in a concentration-time curve as shown in Chart 4. MMC penetrated rapidly into ascites fluid (rate constant, 0.044 min^{-1}), reached a maximum concentration of about 0.05 μg/ml after 1 hr, and was eliminated at about the same rate as from plasma. Comparison of the AUC for ascites fluid and plasma indicates a high degree of drug availability to the ascites fluid (about 40% of plasma exposure).

DISCUSSION

Studies on the clinical pharmacokinetics of MMC in man have been inadequate because of the insensitivity of the methods available (6, 10). In the present clinical study a sensitive and

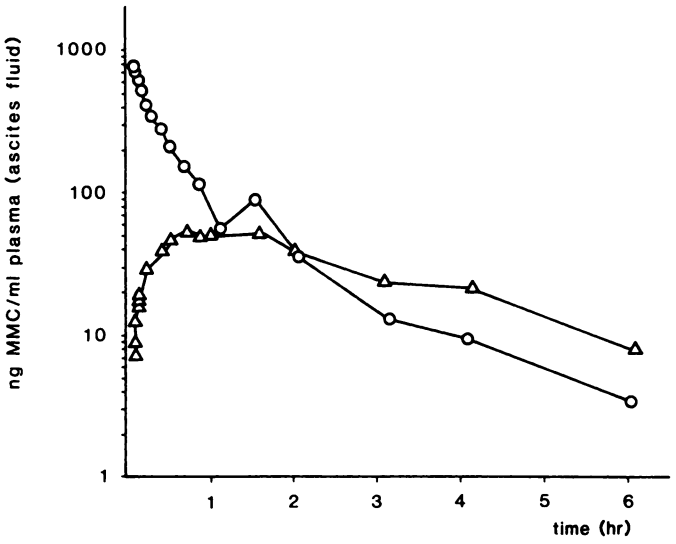

Chart 4. Semilogarithmic plot of MMC concentration in plasma and ascites fluid *versus* time. O, plasma; Δ, ascites fluid, Patient T, female, 18 mg MMC (12 mg/sq m), single-agent chemotherapy.

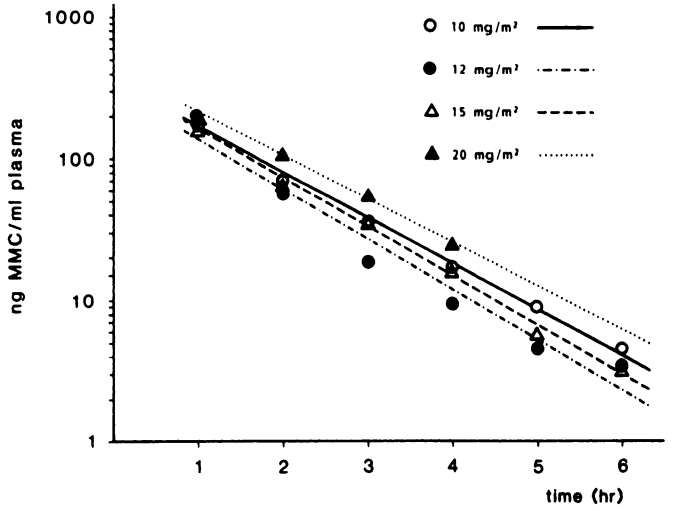

Chart 5. Fitted plasma elimination curves of MMC for various dose levels after i.v. push, single-agent chemotherapy. O, $n = 6$, $\beta = -0.0122$; ●, $n = 4$, $\beta = -0.0137$; Δ, $n = 5$, $\beta = -0.0135$; ▲, $n = 2$, $\beta = -0.0123$.

specific assay has been used to obtain pharmacokinetic data on MMC.

The assay is sensitive enough to determine MMC concentrations as low as 1 ng/ml sample and allows the drug to be detected in plasma during 4 to 8 hr following i.v. push injections. This corresponds to at least 6 times the $t_{½}\beta$, which is generally regarded as adequate for evaluation of the pharmacokinetic behavior of a drug. If the plasma levels should be measured over a shorter period of time, one of the disposition phases might be missed. On the basis of the data of Fujita (4), who measured plasma levels over only 2 hr, Reich proposed (10) a 2-compartment model for MMC. However, he did take into consideration that another phase might be present; if so, this would suggest the presence of a 3-compartment model. The present results confirm that a 2-compartment model is a good approach to adopt in describing the pharmacokinetic behavior of MMC in humans. The choice of this model was supported by the fact that the results of calculating the Cl_{tot} in a model-independent way (D/AUC) and in a model-dependent way ($V_C \cdot K_{10}$) were comparable in most cases. However, it should be pointed out that a triphasic decline in plasma concentration was observed in 2 patients, with the terminal phase in the concentration range below 10 ng/ml. Because this finding made only a small contribution to the total AUC, and consequently to the Cl_{tot}, parameters were calculated according to a 2-compartment model.

As the majority of the patients entered on the present study had received a short-term i.v. injection of MMC, this report deals *a priori* with that method of administration. The drug had been given either alone or in combination with other antineoplastic agents. The calculated parameters show a wide range, *e.g.*, $t_{½}\beta$ varies from 26 to 70 min, and V_B from 14 to 60 liters/sq m (Table 2). Because of these observations and the conclusions of Reich (10), we examined the possibility of nonlinear pharmacokinetics by looking at a dose-related trend for each parameter. Chart 5 shows the fitted elimination curves for i.v. push, single-agent chemotherapy at 4 dose levels. These plots were drawn from the median values determined at each time point. From this graph, it can be concluded that the rate of elimination at dose levels between 10 and 20 mg/sq m is not related to the dose. The same result was found in combination chemotherapy. Careful examination of all the other parameters also failed to show a dose-related trend. Another approach that could be used to investigate the possibility of nonlinearity was to plot the median value of the AUC *versus* dose (Chart 6). The data again show a linear relationship, both for single-agent chemotherapy and for combination regimens. A visual check on the plasma concentration-time curves to see if there are any indications that a zero-order process was taking place confirms our statement.

Thus, in patients receiving single-agent MMC up to 20 mg/sq m, or a combination including MMC up to 10 mg/sq m, the drug shows a linear pharmacokinetic behavior. Obviously, deviations from linearity, *e.g.*, the occurrence of saturation processes in the elimination, cannot be ruled out at higher dose levels.

In an initial attempt to attribute the wide range of the pharmacokinetic parameters to the clinical status of the patients, we failed to find any correlation. Clinical parameters which were considered included type of disease, sex, age, comedication, renal function (serum creatinine), hepatic function (serum bilirubin, serum glutamic-oxalacetic transaminase, serum glutamic-pyruvic transaminase, and alkaline phosphatase), and previous chemotherapy. In 3 patients, slight kidney and liver malfunction was shown not to have any significant influence on the phar-

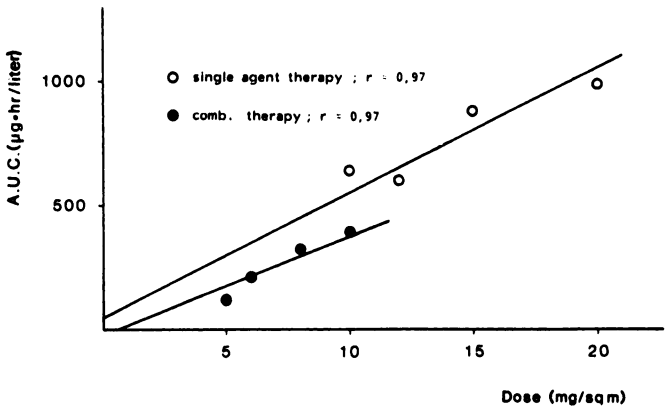

Chart 6. Schematic plot of the median AUC *versus* dose.

macokinetic parameters. Hematological toxicity (leukopenia and/or thrombopenia) did not appear to correlate with AUC or peak plasma concentration. Comparison of the calculated pharmacokinetic data for Groups A and B (Table 2) did reveal a difference. Group B showed a shorter $t_{½}\beta$ than did Group A. Table 2 shows that V_B is similar for the 2 groups, but that the Cl_{tot} of MMC is significantly larger ($p < 0.05$) in Group B than in Group A, which explains the shorter $t_{½}\beta$ in Group B. As the Cl_{tot} is calculated from the AUC, this finding is obviously reflected in a difference in the AUC (Chart 6).

In light of the linear kinetics, the data were recalculated at one dose level (10 mg/sq m) for each group, and the median values proved to be significantly different ($p < 0.05$). A possible explanation for this difference between Groups A and B might be a different ratio between unbound drug and drug bound to blood constituents within the 2 groups. Comparison of the AUC following i.a. and i.v. administration of identical dosages (Tables 2 and 3) does not support the data reported earlier (7), which indicated that hepatic extraction of MMC is 5 to 10%. However, this may be due to the limited number of patients examined after i.a. drug administration.

Calculation of pharmacokinetic parameters for the 24-hr i.v. infusions was impossible because the distribution phase was masked, due to a similarity in the rate of infusion and distribution. In addition, the number of plasma samples was insufficient to calculate reliable pharmacokinetic data. Regarding the 3-hr infusion, the infusion time was long enough to reach steady-state level. The Cl_{tot} appeared to be higher than it was after push injection. This effect was even more pronounced with 24-hr infusions, although the latter clearances could not be calculated precisely. The increased Cl_{tot} during long-term infusions results in lower plasma concentrations than expected on the basis of Cl_{tot} after push administration. The data calculated from the urine analyses in one patient are in good agreement with those obtained from plasma analyses, *e.g.*, $t_{½}\beta$ 35 and 37 min, respectively. Renal clearance was 1.7 liters/hr/sq m and Cl_{tot} was 17 liters/hr/sq m, indicating that renal excretion is not a major route of elimination for MMC. The rather low urinary recoveries support this conclusion. Elimination of MMC through the bile is shown by the data obtained from analyses of the bile samples in one patient (Chart 3). In view of this observation, the peaks observed frequently in the declining part of the plasma curves (Charts 1 and 4) are probably the result of enterohepatic recycling.

Penetration of MMC into ascites fluid has been shown, as well as a high degree of availability of MMC to ascites fluid. Since MMC is eliminated from ascites fluid at a rate similar to that from plasma, it can be concluded that ascites fluid does not behave like a separate compartment, but that it belongs to the peripheral compartment.

Our present data indicate that further studies should be done on the interaction of other antineoplastic agents with MMC. It is essential that dose-dependent kinetics should be properly evaluated at higher dose levels in order to prevent unexpected toxicity with high-dose treatment.

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REFERENCES

1. Crooke, S. T. Mitomycin C. *In:* H. M. Pinedo (ed.), Cancer Chemotherapy 1979, The EORTC Cancer Chemotherapy Annual, I, pp. 82–85. Amsterdam: Excerpta Medica, 1979.
2. Crooke, S. T. and Bradner, W. T. Mitomycin C: a review. Cancer Treat. Rev., *3:* 121–139, 1976.
3. den Hartigh, J., van Oort, W. J., Bocken, M. C. Y. M., and Pinedo, H. M. High performance liquid chromatographic determination of the antitumor agent mitomycin C in human blood plasma. Anal. Chim. Acta, *127:* 47–53, 1981.
4. Fujita, H. Comparative studies on the blood level, tissue distribution, excretion and inactivation of anticancer drugs. Jpn. J. Clin. Oncol., *12:* 151–162, 1971.
5. Gibaldi, M., and Perrier, D. Pharmacokinetics, Chap. 2, pp. 48–55. New York: Marcel Dekker, Inc., 1975.
6. Glaubiger, D., and Ramu, A. Antitumor antibiotics. *In:* B. A. Chabner (ed.), Pharmacologic Principles of Cancer Treatment, Chap. 19, pp. 402–415. Philadelphia: W. B. Saunders Co., 1982.
7. Gyves, J., Ensminger, W., VanHarken, D., Niederhuber, J., Knutsen, C., and Doan K. Improved regional selectivity of hepatic arterial mitomycin by starch microspheres. Proc. Am. Assoc. Cancer Res., *23:* 137, 1982.
8. Kennedy, K. A., Rockwell, S., and Sartorelli, A. C. Preferential activation of mitomycin C to cytotoxic metabolites by hypoxic tumor cells. Cancer Res., *40:* 2356–2360, 1980.
9. Nielson-Kudsk, F. Pharmacokinetic curve-fitting and parameter determination by nonlinear, least-squares regression analysis using a programmed minicalculator. Int. J. Bio-Med. Comput., *12:* 503–517, 1981.
10. Reich, S. D. Clinical pharmacology of mitomycin C. *In:* S. K. Carter and S. T. Crooke (eds.), Mitomycin C, Current Status and New Developments, Chap. 27, pp. 243–250. New York: Academic Press, Inc., 1979.
11. Schwarz, H. S., and Phillips, F. S. Pharmacology of mitomycin C. II. Renal excretion and metabolism by tissue homogenates. J. Pharmacol. Exp. Ther., *133:* 335–342, 1961.