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Pharmacokinetics of mitomycin C in non-oat cell carcinoma of the lung

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Summary. *The disposition kinetics of the cancer chemotherapeutic agent mitomycin C have been studied in six male patients receiving mitomycin C in combination with cisplatin and vinblastine for non-oat cell carcinoma of the lung. Following rapid IV administration of mitomycin C (10 mg/m^2), serum concentration-time course data were biexponential, with biologic half-lives of 46.2 ± 12.1 min (mean ± SD). Pharmacokinetic analysis of data by the CSTRIP and NONLIN digital computer programs generated parameters which suggested extensive distribution (V_{area} = 656.8 ± 169.8 ml · kg^{-1}, mean ± SD) and, as reported for other alkylating agents, rapid elimination (total body clearance = 10.3 ± 3.2 ml · kg^{-1} · min^{-1}, mean ± SD). Interpatient variations in pharmacokinetic parameters were relatively small, suggesting that close monitoring of mitomycin C therapy might be unnecessary in patients with normal renal and hepatic function.*

Introduction

Mitomycin C (MMC), a chemotherapeutic agent derived from *Streptomyces cyespitosus,* has demonstrated activity against a variety of human malignancies. The introduction of MMC in 1958 [27] was followed by initial clinical trials in Japan with reported response rates as high as 37% [7]. However, the results of early trials in the United States were relatively poor [6, 10]. In later years, revision of dosage regimens and closer hematologic supervision appeared to improve response rates and reduce toxicities [9, 22]. As a single agent MMC has produced response rates of up to 30%, although serious hematopoietic toxicities have been reported [24, 28]. Among the successful drug combinations involving MMC are those used for non-small cell lung cancer. Using MMC, methotrexate, cisplatin, and vinblastine for the treatment of non-small cell lung cancer, Niell et al. reported a response rate of > 54%, with only occasional unacceptable toxicities [15]. Very few reports even mention MMC pharmacokinetics in animals or humans, largely because of a long-existing lack of suitable analytical methodology for MMC in biologic fluids. An early study by Fujita [8] presented several serum MMC concentration-time course curves in humans, although the description of the biological assay was incomplete, discussion of the patient characteristics was inadequate, and no pharmacokinetic analysis of the data was included. While recent advances in analytical methodology [1, 4, 5, 12, 21, 23] have simplified such studies, only van Hazel and Kovach have reported MMC pharmacokinetics in humans [25], presenting data from two patients receiving MMC only and one patient receiving MMC in combination with doxorubicin and cisplatin.

Due to recently reported activity in lung cancer chemotherapy [2, 14, 17], MMC was incorporated into several protocols for the treatment of non-small cell lung cancer at the Veterans Administration Medical Center in Memphis, TN. One such protocol involves MMC, cisplatin, and vinblastine for the treatment of non-oat cell carcinoma of the lung. The present report describes the pharmacokinetics of MMC in this protocol.

Materials and methods

Six male patients with histologically confirmed non-resectable but evaluable squamous cell adenocarcinoma or large cell lung cancer were used for the study. All patients were diagnosed and staged at the Veterans Administration Medical Center in Memphis, TN between January 1982 and January 1983. All patients were ambulatory with a performance status of at least 50% [11]. Other prerequisites for inclusion in the study were: negative history of another tumor, no previous chemotherapy, normal blood counts, normal renal function (C_{rCl} > 60 ml/min), and normal serum alkaline phosphatase, SGOT, and SGPT. Prior to therapy all patients underwent standard staging procedures according to the T, N, M classification [3] after chest X-rays, bronchoscopy, liver, brain, or bone scans, and blood chemistries. When indicated, patients underwent mediastinoscopy, mediastinotomy, or thoracotomy. Computerized axial tomography of the head, thorax, or abdomen were occasionally needed to define tumor extent. On day 1 of therapy each patient received a drug combination consisting of MMC (10 mg/m^2), vinblastine (5 mg/m^2), and cisplatin (80 mg/m^2). MMC and vinblastine were administered as single rapid IV injections. Cisplatin was administered as two 4-h infusions [40 mg/m^2 in 1,000 ml (5% dextrose, 0.45% saline with 12.5 gm mannitol)]. This drug combination was repeated every 28 days.

Blood samples (5 ml) were obtained from a peripheral arm vein of each patient using a heparin well and a 10-ml nonheparinized glass tube. A sample was obtained 10 min prior to MMC administration and serial samples were obtained over a 3-h postadministration period. Serum was separated by centrifugation and stored at −80° C until assay.

Serum MMC concentrations were determined using a recently reported high-performance liquid chromatography

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Table 1. Coefficients (C_i) and exponents (λ_i) of biexponential equations[a] which best describe serum MMC concentration-time course data from each patient

	Patient					
	1	2	3	4	5	6
Dose ($mg \cdot kg^{-1}$)	0.25	0.25	0.31	0.15	0.21	0.18
C_1 ($\mu g \cdot l^{-1}$)	242.4 (28.7)	130.9 (22.5)	243.2 (77.7)	160.4 (11.6)	344.6 (61.0)	164.0 (33.2)
λ_1 (min^{-1})	0.019 (0.002)	0.011 (0.001)	0.024 (0.01)	0.013 (0.001)	0.014 (0.003)	0.015 (0.003)
C_2 ($\mu g \cdot l^{-1}$)	987.7 (363.2)	722.6 (22.1)	6,058.5 (5,677.5)	930.1 (89.4)	2,830.9 (183.6)	472.2 (44.7)
λ_2 (min^{-1})	0.146 (0.031)	0.045 (0.001)	0.473 (0.204)	0.212 (0.022)	0.179 (0.016)	0.126 (0.023)

[a] $C = C_1e^{-\lambda_1 t} + C_2e^{-\lambda_2 t}$ Figures in parentheses give SD of computer fit in each case

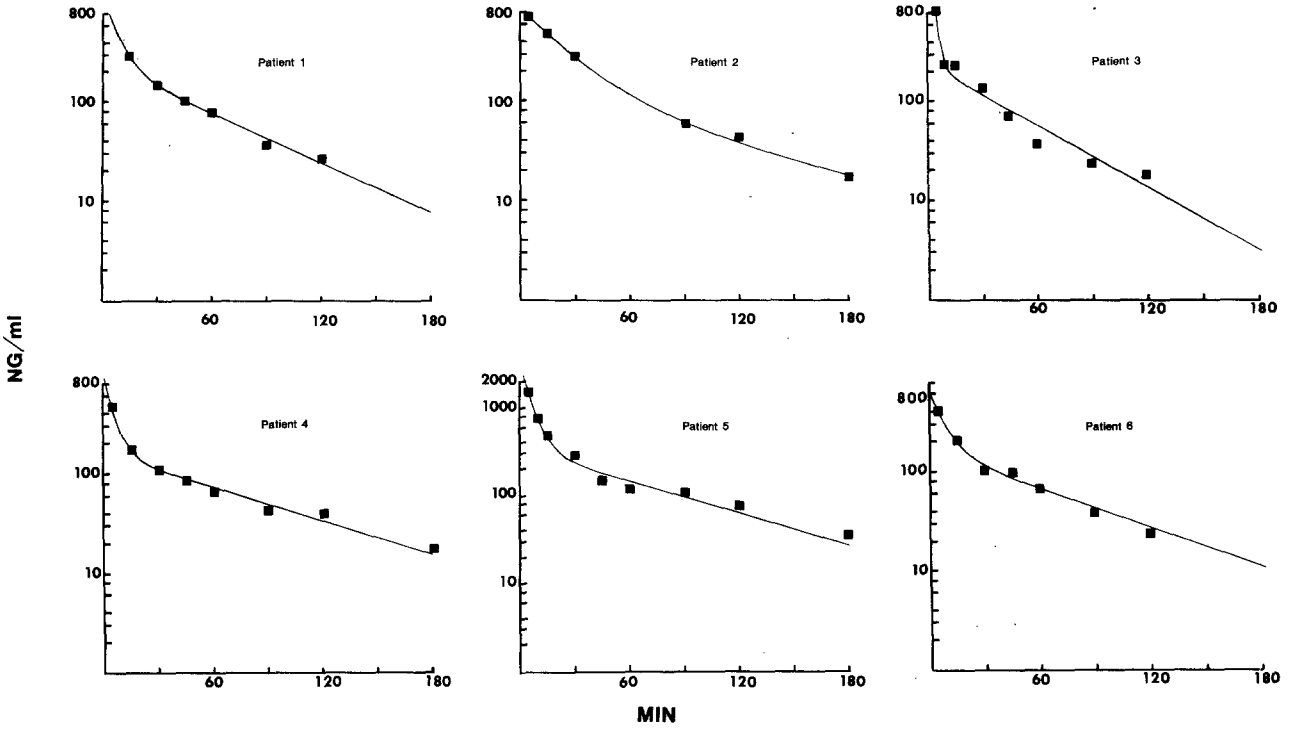

Fig. 1. Individual serum mitomycin C concentration-time course data compared with theoretical curves. Curves were simulated using computer-calculated coefficients and exponents presented in Table 1

Table 2. MMC pharmacokinetic parameters calculated for each patient using coefficients and exponents presented in Table 1

	Patient							
	1	2	3	4	5	6	$\bar{X}$ (S_X)	CV
AUC ($\mu g \cdot l^{-1} \cdot min^{-1}$)	19,578.8	28,004.9	22,815.4	16,472.5	40,239.9	14,435.2	23,591.1 (9,464.4)	40
V_1 ($ml \cdot kg^{-1}$)	203	293	49	138	66	283	172.0 (105.3)	61
V_{area} ($ml \cdot kg^{-1}$)	674	800	563	700	371	833	656.8 (169.8)	26
Cl ($ml \cdot kg^{-1} \cdot min^{-1}$)	12.8	8.8	13.5	9.1	5.2	12.5	10.3 (3.2)	31
$t_{1/2}$ (min)	36.5	63.0	28.9	53.3	49.5	46.2	46.2 (12.1)	26

$\bar{X}$ = Mean S_X = Standard deviation

CV = Coefficient of variation = $\frac{S_X}{\bar{X}} \times 100\%$

method [1]. The instrumentation consisted of a U6K injector, a model 6000A solvent delivery system, a μ-Bondapak C-18 column, and a model 440 UV detector (365 nm) (Waters Associates, Milford, MA). The mobile phase (methanol/water, 35/65) was passed through the column at 1.0 ml/min. Analytical samples were supplied by Bristol Laboratories, Syracuse, NY. All solvents were HPLC grade and all reagents were analytical grade. Prior to HPLC analysis, MMC was separated from serum using a reversed-phase sample preparation cartridge (SEP PAK, Waters Associates, Milford, MA). Calibration standards in methanol, simulating the selected serum MMC concentration range, were added to 15-ml silanized conical tubes. Methanol was evaporated to dryness under nitrogen, 1 ml normal human serum was added, and each tube was vortexed for 45 s. To each 1-ml calibration sample and each 1-ml patient sample was added 1 ml phosphate buffer (0.1 *M*, pH 8.5). After vortex mixing for 45 s the mixture was twice passed through a sample preparation cartridge which had been pretreated with 10 ml methanol followed by 10 ml posphate buffer (0.1 *M*, pH 8.5). The cartridge was then vaccum-dried and MMC was eluted with 2 ml methanol. Methanol was evaporated to dryness under nitrogen and the residue reconstituted in water prior to injection. Extraction recovery over a concentration range of 10–100 ng/ml was 81.6% ± 3.7% (mean ± SD) with a between-day precision of 4.5% (n = 5). The within-day precision at 50 ng/ml was 5.6% (n = 10). UV detection at 365 nm was sensitive to serum concentrations of 10 ng/ml.

Serum MMC concentration-time course data were analyzed by digital computer using standard pharmacokinetic programs. Following analysis by CSTRIP [20] suitable polyexponential equations were selected. Data from each patient were fitted to a selected equation by NONLIN, a nonlinear least-squares fitting program [13], and pharmacokinetic parameters were calculated from computer-generated coefficients and exponents as described by Wagner [26].

Results

Serum MMC concentration-time course data are presented in Fig. 1. CSTRIP analysis revealed that each set of data fitted to a biexponential equation [$C = C_1e^{-\lambda 1t} + C_2e^{-\lambda 2t}$] produced a relatively small sum of squares for the deviation of theoretical and experimental data. An adequate fit of experimental data to this equation was further evidenced by small standard deviations of computer-generated coefficients (C_1) and exponents (λ_i) relative to their means (Table 1). Moreover, visual inspection of Fig. 1 suggested that theoretical curves properly represent experimental data. A slight deviation from fit was observed in the data from patient 3, whose C_2 and λ_2 values revealed standard deviations which were somewhat larger than those of other patients, although smaller than their respective means. Scatter in the time course data of patient 3 (Fig. 1) could account for this.

Discussion

Although enterohepatic recycling of MMC has not been reported, secondary peaks in serum concentration time course curves tend to suggest that this process occurs (Fig. 1). While there was very minimal scatter due to such peaks, each curve was clearly biexponential, with a relatively short biologic half-life (Table 2). MMC serum concentration-time course curves approached linearity within 45 min of administration, with most concentrations below assay sensitivity (10 ng/ml) after 180 min. Ratios of V_{area}/V_1 (Table 2) suggest that during the linear phase a large portion of existing drug is in peripheral fluids and tissues. Interpatient variation in overall volumes of distribution (V_{area}) was relatively small (CV = 26%, Table 2). V_{area} values from patients 3 and 5 were significantly smaller than those from other patients because of small central compartment volumes (V_1). While it initially appeared that an improper data fit might account for unusually small V_1 values, refitting patient 3 and patient 5 data to a triexponential system did not significantly alter the results. Smaller V_1 values might suggest fewer fluids and tissues in rapid equilibrium with serum although there was no apparent clinical reason for this.

MMC is removed from the body largely by nonrenal routes with only a small fraction cleared by renal excretion of parent drug [19]. While hepatic clearance has been reported in rats [18] and some evidence has suggested metabolism at multiple tissue sites [19], the major mechanism of MMC clearance has not been clearly established. As hepatic and renal functions in each patient were within normal limits, interpatient variation in total body clearances was understandably moderate (CV = 31%, Table 2).

Biologic half-lives from the present study were similar to those calculated by Reich [16] using the data of Fujita [8], and by van Hazel and Kovach [25]. Interpatient variation in half-lives was not excessive (CV = 26%, Table 2).

The present group of patients was selected from acombination chemotherapy protocol, and all had normal hepatic and renal function. The findings presented here reveal no excessive interpatient variation. The present findings and their consistency with previous reports [16, 25] tend to suggest that close monitoring of MMC might be unnecessary in patients with normal renal and hepatic function. However, future studies should investigate the effects of hepatic and renal dysfunction as well as that of other drug combinations on MMC disposition. A partial response was observed in patients 1, 2, 3, and 5 after two courses of chemotherapy. Patients 4 and 6 failed to respond. Previously reported in vitro data do not permit extrapolation of the present findings to minimum inhibitory concentrations of MMC, although future studies should consider this. Further work in the future should attempt to correlate serum MMC and metabolite concentrations with therapeutic and toxic effects.

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