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Bleomycin Pharmacokinetics in Man

I. Intravenous Administration

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Summary. *Bleomycin plasma decay kinetics and urinary excretion were studied in nine patients after IV bolus injections of 13.7 to 19.9 U/M². Radio-immunoassay was used to measure bleomycin in plasma and urine samples. The resulting plasma concentration versus time data for each patient and the combined data obtained from all patients were fitted to a multiexponential equation using a nonlinear regression computer program. Pharmacokinetic parameters derived from the mean of all individual patient parameters and the composite of all plasma decay data were similar. Bleomycin initial and terminal plasma half-lives and volume of distribution for all plasma decay data from eight patients with normal serum creatinines were 24.4 ± 4.0 min, 237.5 ± 8.5 min, and 17.3 ± 1.5 L/M², respectively. Mean 24-h urinary excretion accounted for 44.8 ± 12.6% of the dose in seven patients who had normal serum creatinine values and complete urine collections. The total body clearance and renal clearance in these seven patients averaged 50.5 ± 4.1 ml/min/M² and 23.0 ± 1.9 ml/min/M², respectively. One patient with a serum creatinine of 1.5 mg% (normal 0.7 to 1.3 mg%) who was given 15.6 U/M² had a terminal plasma half-life of 624 min, a volume of distribution of 36.3 L/M², and 24-h urinary excretion of 11.6% of the dose. We conclude that bleomycin after intravenous bolus injection has a relatively short terminal phase plasma half-life and relatively large urinary elimination.*

Introduction

Bleomycin was isolated in 1966 by Umezawa (1966) from Streptomyces verticillus. The drug is a mixture of at least 13 different polypeptides (Fugii et al., 1973a and b), which have been designated A_{1-6}, A'_2, and B_{1-6}. Bleomycin has proven to be useful in the treatment of human lymphomas, testicular carcinoma, squamous-cell carcinoma of the head and neck, and carcinoma (Yagoda et al., 1972; Blum et al., 1972). Recently, it has also proven effective in the treatment of malignant pleural effusions and ascites (Paladine et al., 1976).

The total dose of bleomycin for an individual patient is limited to between 300 and 400 units because of the increasing risk of life-threatening pulmonary toxicity at higher doses (Yagoda et al., 1972; Blum et al., 1972). Bleomycin is used in several different dosage regimens and administered by various routes, including intravenous, intramuscular, subcutaneous, and intracavitary (i.e., intrapleural and intraperitoneal). Knowledge of the disposition kinetics of the drug in all of these settings and at varying doses may be essential for its optimal use. There has been one pharmacokinetic study of bleomycin administered at high intravenous doses (26–35 U/M²), where a microbiologic assay was employed (Ohnuma et al., 1974). Two other studies have been reported in which radioimmunoassay was used to examine bleomycin disposition after low-dose intravenous (about 7.5–10 U/M²), subcutaneous, and intrapleural administration (Paladine et al., 1976; Hall et al., 1977). The resulting data indicate rapid bleomycin clearance from plasma, with the predominant route of elimination being renal excretion (Ohnuma et al., 1974; Crooke et al., 1977a). Renal dysfunction and subcutaneous or intrapleural dosing appeared to cause prolongation of the terminal plasma half-life of bleomycin (Hall et al., 1977; Crooke et al., 1977a).

The present investigation is part of a larger ongoing study, which has examined the disposition kinetics of bleomycin in patients given intermediate intravenous doses of the drug (ca. 15 U/M²).

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Materials and Methods

Patients. Bleomycin disposition was examined in nine patients whose characteristics are summarized in Table 1. Informed consent was obtained from each patient prior to study. All patients had advanced disease at the time of their drug studies. Serum creatinine concentrations were in the normal range for eight of the nine patients. One patient (J. S.) had an elevated serum creatinine of 1.5 mg% (normal 0.7 to 1.3 mg%).

All patients received bleomycin as a part of the therapy for their cancer. None of the patients received other anticancer drugs within three weeks of the bleomycin pharmacokinetic studies. An attempt was made to stop all drugs at least three days prior to the bleomycin disposition studies; however, it was necessary to continue analgesic medication in four of the nine patients (Table 1).

Treatment. All patients were treated with intravenous bolus injections of a bleomycin dose of 13.7 to 19.9 (ave. 15.4) U/M^2 (Table 1).

Blood and Urine Sampling. Blood samples (10 ml) were obtained from a heparin lock and collected in tubes containing 100 IU of heparin. Blood samples were taken just prior to the start of therapy and at 5, 10, 15, 30, 45, and 60 min, and 2, 3, 4, 6, 8, and 24 h following drug administration. Fractional urine collections were taken for the first 8 h after drug injection and then at known intervals for up to 24 h. Urine samples were stored in sterile containers at 4° C.

Assay Procedure. Blood samples were centrifuged at 4° C (2,000 rpm for 10 min). The resulting plasma was frozen at −20° C. The bleomycin concentrations in plasma and urine were determined by the antiserum and radioimmunoassay technique developed by Broughton and Strong (1976).

Data Analysis. Bleomycin plasma concentration versus time data obtained from each patient and the combined data obtained from all patients were fitted to a multiexponential equation using a nonlinear regression computer program (Metzler, 1969). Preliminary parameter estimates were obtained with the aid of a recently published computer method (Sedman and Wagner, 1976). The equation used had the following form:

$$\ln C = \ln [Ae^{-\alpha t} + Be^{-\beta t}] \quad (1)$$

where C is the bleomycin plasma concentration, t is time after dosing, A and B are coefficients, α and β first-order disposition rate constants.

The plasma half-lives, $t^{\alpha}_{1/2}$ and $t^{\beta}_{1/2}$, were determined from the corresponding rate constants of the computer-fitted bleomycin plasma concentration versus time curve:

$$t^{\alpha}_{1/2} = \frac{0.693}{\alpha} \quad (2)$$

$$t^{\beta}_{1/2} = \frac{0.693}{\beta} \quad (3)$$

The total body clearance of bleomycin, Q_B, was calculated by dividing the intravenous (IV) dose of bleomycin by the area under the bleomycin plasma concentration versus time curve (CXT) from time zero to infinity. The calculation of total CXT and Q_B are given by Eqs. 4 and 5, respectively:

$$CXT = \frac{A}{\alpha} + \frac{B}{\beta} \quad (4)$$

$$Q_B = \frac{\text{IV dose}}{CXT}. \quad (5)$$

The renal clearance of bleomycin, Q_r, was determined by dividing the 24-h cumulative urinary excretion of bleomycin by the 0–24 h CXT.

The 0–24 h CXT was determined from the following equation:

$$CXT^{24}_0 = CXT - \frac{C_{24}}{\beta}. \quad (6)$$

where C_{24} is the bleomycin concentration 24 h after dosing.

The apparent volume of distribution of bleomycin, V_d, was determined from:

$$V_d = \frac{\text{IV dose}}{CXT \cdot \beta}. \quad (7)$$

Results

Bleomycin Radioimmunoassay. Bleomycin recovery studies performed in our laboratories showed 98.5 ± 2.5% mean recovery of 1–10 mU/ml from human plasma. The lower limit radioimmunoassay sensitivity was 10 μU/ml plasma.

Bleomycin Pharmacokinetics. The pharmacokinetic parameters of bleomycin obtained from nonlinear regres-

Table 1. Patient characteristics

Patient	Tumor Type	Sex	Age (years)	Weight (kg)	Height (cm)	BSA (M^2)	Serum creatinine (mg%)	IV Dose (U)	IV Dose (U/M^2)	Other drugs taken
S. H.	Head and neck	M	55	50.0	158	1.51	1.0	30	19.9	None
E. G.	Cervix	F	59	72.0	170	1.83	1.0	25	13.7	None
E. M.	Head and neck	F	64	54.3	170	1.67	0.9	25	15.0	None
H. H.	Cervix	F	61	58.6	159	1.60	1.2	24	15.0	Demerol
M. M.	Head and neck	F	61	92.8	158	1.86	0.9	30	16.1	Demerol
M. A.	Head and neck	M	56	99.4	171	2.05	1.0	30	14.6	Percodan
S. R.	Cervix	F	42	52.6	162	1.57	0.9	23	14.6	None
M. R.	Head and neck	M	84	60.0	163	1.65	1.1	24	14.5	None
J. S.	Ovary	F	61	57.5	141	1.41	1.5	22	15.6	Morphine

Table 2. Pharmacokinetic parameters of bleomycin after intravenous injection of 15 U/m²

Patient Dose	$t^{\alpha}_{1/2}$ min	$t^{\beta}_{1/2}$ min	CXT mU · min/ml	CXT[a]	V_d L/M²	Q_B ml/min/m²	24-h urinary excretion % dose	Q_r ml/min/m²
S. H. 30 U	31.7	270.7	377.9	252.5	20.5	52.6	29.1	15.5
E. G. 25 U	29.0	191.5	262.3	360.3	14.4	52.0	27.4	14.1
E. M. 25 U	32.3	182.6	302.2	397.2	13.0	49.5	49.2	24.3
H. H. 24 U	14.8	259.0	308.6	286.0	18.2	48.6	45.5	22.8
M. M. 30 U	21.2	226.5	226.0	223.1	23.3	71.4	—[b]	—[b]
M. A. 30 U	26.0	263.9	350.6	327.6	15.9	41.7	46.2	19.6
S. R. 23 U	15.5	275.2	295.9	265.1	19.7	49.5	61.5	31.3
M. R. 24 U	24.6	266.1	366.8	342.2	15.2	39.9	54.8	22.2
J. S. 22 U	73.9	623.9	386.7	143.0	36.3	40.3	11.6	5.82
Composite[c]	24.4 ± 4.0	237.5 ± 8.5	292.4 ± 23.9		17.3 ± 1.5	50.5 ± 4.1		23.0 ± 1.9
Mean[d]	24.4 ± 6.8	241.9 ± 37.0	299.5 ± 45.1	306.8 ± 59.6	17.5 ± 3.5	50.6 ± 9.6	44.8 ± 12.6	21.4 ± 5.8

[a] CXT normalized for $t^{\beta}_{1/2}$ = 4.0 h and bleomycin dose = 15 U/M²
[b] Incomplete urine collection
[c] Composite: pharmacokinetic parameters ± S.D. calculated from nonlinear regression fit of all plasma decay data (excluding patient J.S.)
[d] Mean: pharmacokinetic parameters ± S.D. calculated from mean of individual patient parameters (excluding patient J.S.)

sion fitting of the bleomycin plasma concentration versus time data are summarized in Table 2. The "mean" of the individual patient parameters and the "composite" results of the nonlinear regression fit of all plasma decay data (excluding patient J.S.) appear at the bottom of Table 2. There are no significant differences between these mean and composite pharmacokinetic parameters.

There were no statistically significant differences in the fitting of plasma decay data according to whether bi- or tri-exponential equations were used (Boxenbaum et al., 1974), and therefore the simplest equation was employed. Several of the estimated parameters have been expressed per square meter body surface area (BSA), since bleomycin doses are generally calculated on this basis. The values obtained for patient J. S. have not been included in the calculation of the parameter estimates in the combined data. This patient was known to have abnormal renal function and the terminal phase plasma half-life is significantly different than the corresponding value for other patients. No other important differences between the parameter estimates for the remaining patients were observed. Representative plots of the bleomycin plasma decay data for three patients (E. G.,

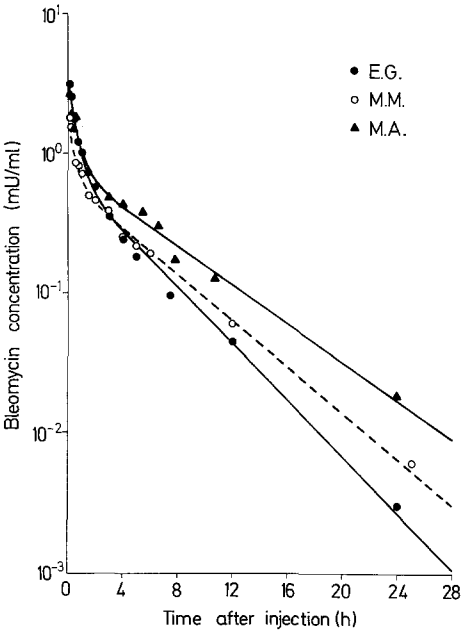

Fig. 1. Bleomycin plasma decay curves for 3 patients (E. G., M. M., M. A., Tables 1 and 2) after 13.7, 16.1, and 14.6 U/M² IV, respectively. Plasma concentration versus time data were fitted to a multiexponential equation using a nonlinear regression computer program

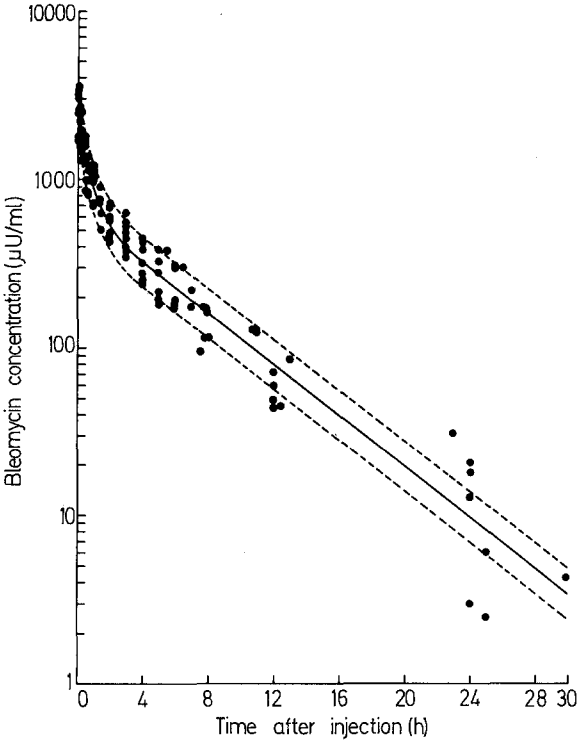

Fig. 2. Bleomycin plasma decay curve for 8 patients give 13.7–16.1 U/M² IV (excluding J. S., and including S. H. scaled to 15 U/M², Tables 1 and 2). The points represent individual plasma concentration measurements for all 8 patients. Upper and lower curves (---) represent one-standard-deviation error limits

M. M., and M. A., Tables 1 and 2) are shown in Figure 1. The plot of the composite bleomycin plasma concentration versus time data and the fitted curve are shown in Figure 2. The lines on either side of the bi-exponential fit give the standard deviation of the regression estimate for an individual observation. The standard deviation associated with the parameter estimates and the fitted curve were obtained by determining the corresponding propagated error (Deming, 1938).

Discussion

The clinically available bleomycin is a mixture of several closely related analogs (Blum et al., 1972). The A_2 and B_2 fractions make up at least 80% of bleomycin's total weight (Blum et al., 1972). The radioimmunoassay antibody used in this study was provided by Broughton and Strong (1976). Their radioimmunoassay appears to react 100% with bleomycin sulfate and bleomycin A_2, 75% with bleomycin B_2, 25% with bleomycin iso-A_2 and 12% with bleomycin A_5 (Strong et al., 1977). There is no cross-immunoreactivity with the bleomycin acid nucleus (Strong et al., 1977). On the basis of this specificity and its good correlation with existing microbiologic and DNA-breakage assays for the bleomycin sulfate mixture, the radioimmunoassay has been used by a number of investigators for the measurement of bleomycin concentrations in biologic fluids (Hall et al., 1977; Crooke et al., 1977a).

With the exception of the data from subject J. S., the values for the various bleomycin pharmacokinetic parameters are similar for all patients. The mean terminal elimination half-life of bleomycin was 4.03 ± 0.62 h. This value is about twice that reported by Hall et al. (1977), who used the same assay procedure but only half the dosage employed in the present study. The reason for this discrepancy between the two studies is not known, although it may be related to different degrees of renal function, radioimmunoassay techniques, clinical batches of drug, and/or dose ranges used in the two groups of patients. Only one patient (E. M., Table 1) had received prior nephrotoxic anticancer drug therapy. She had been treated with courses of methotrexate followed by cis-platinum (II) diaminodichloride before the bleomycin pharmacokinetic studies; however, her terminal phase bleomycin half-life was the shortest of all our study patients.

The limited sensitivity of the microbiological assay used by Ohnuma et al. (1974) necessitated their using large doses to examine the disposition of bleomycin. While their data did not yield estimates of the terminal elimination half-life, their results suggest relatively rapid distribution, which is consistent with the observations of Hall et al. (1977) and the results of the present study (see $t_{1/2}^{\alpha}$, Table 2).

Three previous investigations have provided estimates of the average renal excretion during 24 h after bleomycin dosing. These values ranged from 33% to 68% of the administered IV dose (Ohnuma et al., 1974; Hall et al., 1977; Fugita and Kimura, 1970). With the exception of one patient (J. S.), the 24-h urinary excretion values in this study ranged from 27% to 62%, with a mean of 44.8%. One patient (J. S.), who had moderately severe renal failure, excreted only 12% of the dose. This patient also had the longest elimination half-life (10.4 h). Hall et al. (1977) found a small increase in bleomycin half-life ($t_{1/2} = 2.5$ h) in one patient with poor renal function (creatinine clearance of 29 ml/min). In contrast, Crooke et al. (1977a) reported half-lives of 13 and 21 h in the same patient when creatinine clearances were 15.2 and 10.7 ml/min, respectively. More recently, Crooke et al. (1977b) have reported additional data which suggest that the elimination of bleomycin may be severely reduced in patients with renal insufficiency.

Since serum creatinine encompassed a small range of values in our patients, a useful correlation between serum creatinine and the terminal elimination rate constant or renal clearance of bleomycin cannot be provided. Such a correlation might be useful in adjusting

bleomycin doses in patients with renal insufficency; however, there is no available animal or human data showing that bleomycin toxicity is increased as a result of a prolonged elimination half-life, whatever the cause.

The mean volume of distribution (V_d) of bleomycin is 17.5 ± 3.5 L/M^2 or 0.46 ± 0.10 L/kg. The V_d of subject J. S. is about twice the value for all other patients. While we have no supporting data, this large volume may be a result of the impaired renal function in this patient. Further observations would have to be made to examine this possibility. Hall et al. (1977) report V_d values ranging from 14.6 to 36.4 L, with an average of 23.9 L. Using our average patient weight of 67.46 kg (excluding patient J. S.), the V_d is approximately 0.35 L/kg, a value statistically smaller ($P < 0.05$) than the one calculated in this study (i.e., 0.46 L/kg). While it is difficult to assign this apparent volume of distribution to a real physiological space, the value of V_d is similar in magnitude to total body water. If this is the case, then desired bleomycin plasma concentrations may be achieved more predictably among patients if dosing is based upon lean or ideal body weight.

In summary, we have shown that after intravenous bolus injection bleomycin has a short terminal phase plasma half-life and a relatively small volume of distribution, and that a substantial portion of the dose is renally excreted.

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