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Bleomycin Pharmacokinetics in Man

II. Intracavitary Administration

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Summary. *Disposition of bleomycin was studied in plasma and urine (14 patients) and ascites fluid (2 patients) after intraperitoneal (IP) and intrapleural (IPl) administration, by radioimmunoassay. Peak plasma bleomycin concentrations after 60 U/m² in 12 patients ranged between 0.4 and 5.0 mU/ml. For those patients with creatinine clearances greater than 50 ml/min the composite terminal phase bleomycin plasma half-lives (± SD) for three 'IPl' and six 'IP' patients were 3.4 ± 0.3 and 5.3 ± 0.4 h, respectively. The composite IP plasma half-life was significantly longer than the IPl hal-life ($P < 0.001$) and previously reported IV half-life ($t_{1/2} = 4.0 \pm 0.6$ h) ($P < 0.01$). In patients with normal renal function, bleomycin excretion during the first 24 h was in most cases lower following intracavitary (IC) than following IV administration (21.7% ± 8.6% vs. 44.8% ± 12.6%, respectively) ($P < 0.005$). Comparison of bleomycin plasma concentration time products normalized for dose and half-life for IV and IC administration allowed an estimate that about 45% of the IC bleomycin dosage is absorbed into the systemic circulation. When calculating the total systemic exposure to bleomycin for a patient we suggest using the sum of the IV dose and one-half of the IC dose.*

Introduction

Intracavitary bleomycin administration can induce complete remission of malignant pleural and peritoneal effusions [9]. It has been especially effective in the treatment of effusions associated with lung, breast, and ovarian carcinoma [9]. Intracavitary bleomycin toxicity is manifested mainly by fever. In the studies of Paladine et al., there was no evidence for pulmonary toxicity, but the maximum total bleomycin dosage was only 240 U (range 30–240 U) [9].

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An increasing incidence of life-threatening pulmonary toxicity has limited total bleomycin dosage to approximately 400 U/m² BSA [3]. All bleomycin dosages with potential systemic absorption should be included in this total. Only limited published data are available concerning the systemic absorption of bleomycin following IC administration. We have studied bleomycin pharmacokinetics after IV [2] and IC administration to quantitate systemic absorption resulting from IP and IPl administration.

Material and Methods

Patients. Bleomycin disposition was examined in 15 patients whose characteristics are summarized in Table I. All patients had advanced cancer at the time of study. The serum creatinine was normal in 14 of 15 patients receiving IC therapy at normal therapeutic doses. Patient PE (Tables 1 and 2) had a serum creatinine of 2.9 mg/100 ml. In all but one patient (KD, Table 1) there was cytologic confirmation of cancer in the pleural and peritoneal effusions.

None of the patients received other anticancer drugs within three weeks of the bleomycin pharmacokinetic studies. An attempt was made to stop all routine-type drugs at least three days prior to the bleomycin disposition studies; however, it was necessary to continue narcotic administration in 6 of the 15 patients receiving IC therapy.

Treatment. All patients given IC bleomycin received approximately 60 U/m², except one patient (PE, Table 1) who received only 15 U/m². Bleomycin in doses of 30–110 U (Table 1) was diluted in 100 ml normal saline and injected in bolus form into the thoracic or peritoneal cavity after maximal evacuation of effusion fluid. The only exception was patient VP (Table 1 and 2), in whom peritoneal fluid was not removed prior to bleomycin instillation.

Biological Fluid Sampling. Blood samples (10 ml) were obtained from a heparin lock and collected in tubes containing 100 IU heparin. Samples were taken just before the start of therapy and in most cases at 5, 10, 15, 30, 45, and 60 min and 2, 3, 4, 6, 8, and 24 h after 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 and stored in sterile containers at −20° C.

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Table 1. Characteristics of patients receiving intracavitary bleomycin

Patient	Tumor type	Sex	Age (years)	BSA (m^2)	Creatinine clearance (ml/min)	Bleomycin dose (U/m^2)	Administration route[a]
VO	Ovary	F	21	1.38	85.8[b]	54.3	IP
EL	Ovary	F	63	1.63	56.0[b]	61.3	IP
JP	Endometrial	F	64	1.60	107.6	60.0	IP
PE	Hepatoma	M	50	2.00	0.7	15.0	IP
AS	Hepatoma	M	79	1.60	23.4	60.0	IP
MC	Ovary	F	55	2.00	53.0	60.0	IP
RD	Pancreas	M	47	1.60	53.3[b]	75.0	IP
EP	Ovary	F	50	1.75	74.0[b]	60.0	IP
VP	Ovary	F	77	1.67	34.4[b]	60.5	IP
DO	Ovary	F	29	1.80	128.4[b]	59.0	IP
TW	Ovary	F	73	1.50	50.0	53.0	IP
DB	Ovary	F	44	1.62	90.1[b]	55.6	IPl
GP	Ovary	F	56	1.53	123.1[b]	60.8	IPl
KD	Lung	M	57	1.52	17.8	59.2	IPl
CJ	Breast	F	54	1.80	94.9[b]	61.1	IPl

[a] IP: Intraperitoneal; IPl: Intrapleural
[b] Creatinine clearance estimated from serum creatinine, lean body weight and age [7]

Table 2. Pharmacokinetic parameters of bleomycin after intraperitoneal administration

Patient	$T^{\beta}_{1/2}$ (h)	C × T[a] (mU · min/ml)	Normalized C × T[b]	24-h urinary excretion (% dose)	Response to therapy[c]
EL	8.8	2395	272	[d]	Uncontrolled
PE[e]	8.2	4127	2013	[d]	Uncontrolled
JP	5.2	340	65	11.3	Uncontrolled
AS[e]	16.0	1045	65	16.6	Uncontrolled
MC	6.1	1029	169	[d]	Uncontrolled
EP	2.1	487	232	21.9	Controlled
VP[e]	30.7	937	31	6.7	Uncontrolled
DO	3.2	519	162	32.5	Uncontrolled
TW	7.6	653	86	18.3	Uncontrolled
Mean[f]	5.5 ± 2.6	904 ± 767	135 ± 87	23.5 ± 9.5[h]	
Composite[g]	5.3 ± 0.4	–	–	–	

[a] C × T: concentration · time product of bleomycin in plasma
[b] C × T normalized for $t_{1/2}$ = 4.0 h and bleomycin dose = 15 U/m^2
[c] Controlled: disappearance of malignant effusion for > 30 days; Uncontrolled: no change or incomplete disappearance of dffusion
[d] Incomplete 24-h urine collections
[e] The plasma $T^{\beta}_{1/2}$ and C × T[a] values for patients PE, AS, and VP were not included in the calculation of the mean or composite $t_{1/2}$ or C × T[a] but the normalized C × T[b]s of patients AS and VP were used in the calculation of the mean normalized C × T[b]
[f] Mean: pharmacokinetic parameters ± SD calculated from mean of individual patient parameters
[g] Composite: pharmacokinetic parameters ± SD calculated from nonlinear regression fit of plasma decay data
[h] Urinary excretion data include 33.6% for the 24-h bleomycin excretion of patient VO, Table 1

Assay Procedure. Blood samples were centrifuged at 2,000 *g* for 10 min and the plasma was separated and frozen at −20° C. The bleomycin concentrations in plasma and urine were determined by means of the antiserum and radioimmunoassay technique developed by Broughton and Strong [5].

Data Analysis. Bleomycin plasma concentration-versus-time data obtained from each patient were fitted by computer to a multiexponential equation according to a nonlinear regression program NONLIN [8]. Preliminary parameter estimates were obtained by means of a recently published computer method [10]. The equations used for IP and IPl instillation have the following forms:

$$C = A_1 e^{-\beta t}, \tag{1}$$

$$C = A_2(e^{-\beta t} - e^{-k_a t}), \tag{2}$$

or

$$C = A_3 e^{-\alpha t} + A_4 e^{-\beta t} - (A_3 + A_4)e^{-k_a t} \tag{3}$$

depending on the shape of the curve, where C is the bleomycin plasma concentration at time t after the injection, A_i are coefficients, α, β, and k_a are the apparent first-order rate constants for disposition (α and β) and absorption (k_a).

The plasma decay half-life, $t_{1/2}$, was determined from the terminal slope of the computer-fitted plasma concentration-versus-time curve:

$$t_{1/2} = \frac{\ln 2}{\beta}. \tag{4}$$

The area under the plasma concentration-versus-time curve (C×T) was calculated by using the trapezoidal rule from time zero to the last time point plus the integral of the appropriate equation from the last time point to infinity. To allow comparison of the IC and the IV data (results of a previous report) [2], all C×Ts were normalized to a $t_{1/2} = 4$ h and a dose of 15 U/m². A two-tailed Student's *t*-test [4] was then used to compare the normalized C×Ts for different routes of administration.

The composite curves for IP and IPl injections were obtained by dividing each patient's plasma concentrations by the corresponding C×T and fitting patients' data to Eq. 2. A two-tailed *t*-test [4] was used to compare the half-lives for different routes of administration. Bleomycin systemic availability following IC administration was calculated from the ratio of the IP to IV and IPl to IV average of normalized C×Ts and 24-h urinary excretion.

Results

Bleomycin Pharmacokinetics After Intracavitary Administration. The pharmacokinetic parameters of bleomycin obtained from a nonlinear regression fit of the plasma concentration-versus-time data for nine patients receiving IP and for four patients receiving IPl doses are summarized in Tables 2 and 3, respectively. In two patients (VO and RD, Table 1) plasma decay data were not obtained. Representative plasma concentration-versus-time curves are shown in Figs. 1–3. The plots of the 'composite' bleomycin plasma concentration-versus-time data and their respective fitted curves for IP and IPl administration are shown in Figs. 4 and 5, respectively. Peak bleomycin concentrations after approximately 60 U/m² in 12 patients (excluding PE, who received 15 U/m² IP) varied between 0.4 and 5.0 mU/ml. For those with normal renal function (i.e., creatinine clearances greater than 50 ml/min) the composite terminal phase bleomycin plasma half-lives (± SD) for three 'IPl' and six 'IP' patients were 3.4 ± 0.3 and 5.3 ± 0.4 h, respectively. The composite IP plasma half-life was significantly longer than the IPl ($P < 0.001$) and the previously reported IV $t_{1/2}$ (4.0 ± 0.6 h) $P < 0.01$) [2]. In

Table 3. Pharmacokinetic parameters of bleomycin after intrapleural administration

Patient	$T^{\beta}_{1/2}$ (h)	C × T[a] (mU · min/ml)	Normalized C × T[b]	24-h urinary excretion (% dose)	Response to therapy[c]
DB	2.9	1035	357	13.9	Controlled
GP	3.5	287	82	[d]	Uncontrolled
KD[e]	9.3	507	55	4.0	Uncontrolled
CJ	4.5	322	72	20.6	Uncontrolled
Mean[f]	3.6 ± 0.8	548 ± 422	142 ± 144	17.3 ± 4.7	
Composite[g]	3.4 ± 0.3	–	–	–	

[a] C × T: concentration · time product of bleomycin in plasma
[b] C × T normalized for $T^{\beta}_{1/2} = 4.0$ h and bleomycin dose = 15 U/m²
[c] Controlled: disappearance of malignant effusion for > 30 days; Uncontrolled: no change or incomplete disappearance of effusion
[d] Incomplete 24-h urine collection
[e] The $t^{\beta}_{1/2}$ and C × T[a] values for patient KD were not included in the calculation of the mean or composire $T^{\beta}_{1/2}$ or mean C × T[a]
[f] Mean: pharmacokinetic parameters ± SD calculated from mean of individual patient parameters
[g] Composite: pharmacokinetic parameters ± SD calculated from nonlinear regression fit of plasma decay data

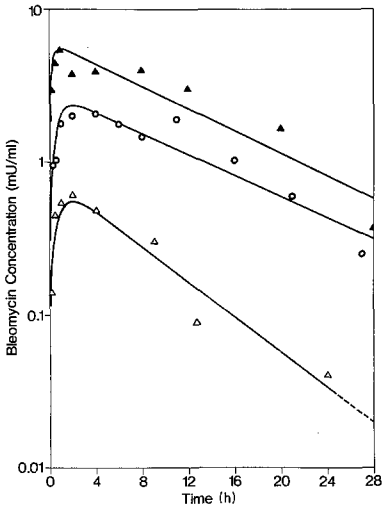

Fig. 1. Bleomycin plasma decay curves for two patients receiving approximately 60 U/m² (△ and ○) and one patient (PE: ▲) receiving 15 U/m², IP. The solid line is the best fit to the data points

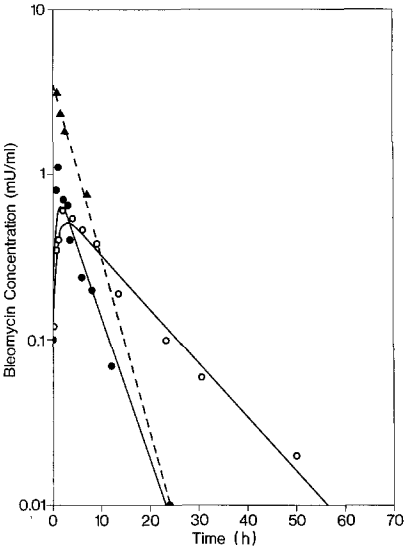

Fig. 3. Bleomycin plasma decay curves for three patients (●: GP; ○: KD; ▲: DB) receiving approximately 60 U/m² IPl. The lines are the best fit to the data points

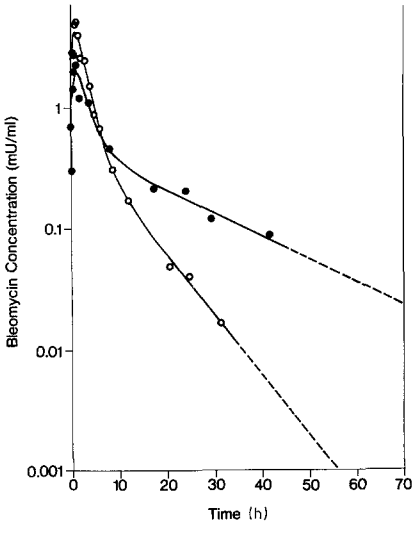

Fig. 2. Bleomycin plasma decay curves for two patients (○: MC; ●: AS) each receiving 60 U/m² IP. The solid line is the best fit to the data points

patients with normal renal function for whom urine collections were complete, bleomycin excretion during the first 24 h was significantly lower following IC than following IV administration (21.7% ± 8.6% vs. 44.8% ± 12.6%, respectively) ($P < 0.005$) [2].

For those patients with normal renal function (i.e., creatinine clearance ≥ 50 ml/min), the mean plasma C × T (concentration time product normalized for $t_{1/2}$ = 4 h and bleomycin dose = 15 U/m²) of 135 ± 87 mU · min/ml for IP patients was similar to that of 142 ± 144 mU · min/ml for IPl patients, and significantly lower ($P < 0.001$) than that for the IV patients (307 ± 60) [2]. Although patient PE (Tables 1 and 2, Fig. 1) received only 15 U/m² bleomycin IP, as against the approximately 60 U/m² given the other 14 IC patients, his corrected C×T was almost 10 times that calculated for the high-dose patients. There is no definitive explanation for this observation.

Because of the abnormal renal function seen in patients PE, AS, and VP, their bleomycin plasma $t^{\beta}_{1/2}$ and C × T values (Tables 1 and 2) were not included in the calculation of the mean or composite $t^{\beta}_{1/2}$ or C × T in Table 2. Another reason for excluding VP's data was the fact that she was the only patient whose effusion was not evacuated before bleomycin administration. The normalized bleomycin plasma C×T for patient PE was not used in the calculation of the mean normalized C×T in Table 2. His normalized C×T value was 7–8 times that calculated for all the other patients in the study. Finally, because of KD's low creatinine clearance of 17.8 ml/min and markedly reduced urinary bleomycin excretion, his plasma $t^{\beta}_{1/2}$ and C × T values were omitted from the calculation of mean or composite bleomycin $t^{\beta}_{1/2}$ and mean C × T (Table 3).

Patients RD and VP had serial measurements of bleomycin concentrations in their ascites fluid after IP drug administration. In VP the plasma terminal phase half-life was approximately 30 h. At comparable time points bleomycin ascites fluid concentrations were about tenfold greater than those measured in plasma. The ascites fluid concentrations of bleomycin from patient RD (Table 1) was 67.5 mU/ml at 15 min, 19.8 mU/ml at 75 min, 18 mU/ml at 180 min, and below the assay sensitivity at 24 h after 60 U/m².

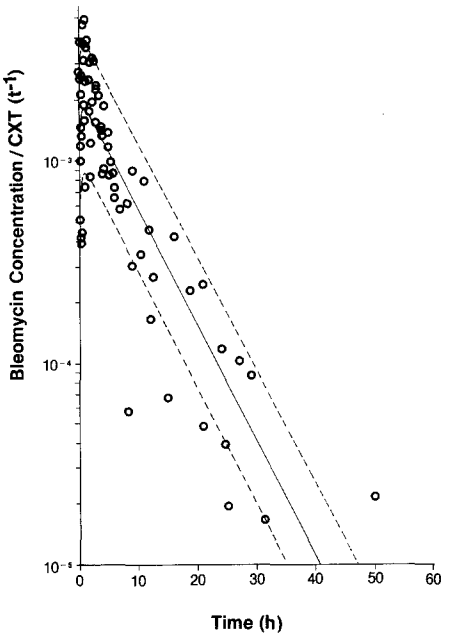

Fig. 4. Bleomycin plasma decay curve for six patients given 53.0–61.3 U/m² IP (excluding patients PE, AS, and VP, Tables 1 and 2). The points represent individual plasma concentration measurements normalized by C×T values (See Methods) for all six patients. The solid line is the best fit to the data points, while the upper and lower curves (– – –) represent one-standard-deviation error limits

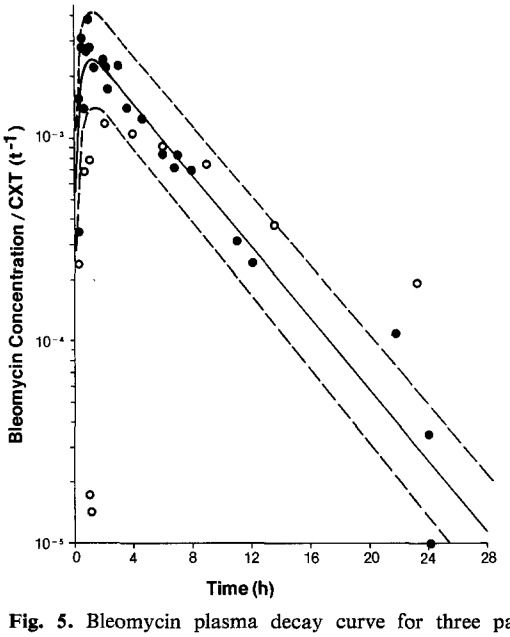

Fig. 5. Bleomycin plasma decay curve for three patients given 55.6–61.1 U/m² IPl (excluding patient KD (○), Tables 1 and 3). The points (●) represent individual plasma concentration measurements divided by C×T values (See Methods) for all three patients. The solid line is the best fit to the data points, while the upper and lower curves (– – –) represent one-standard-deviation error limits

In three of 15 patients (VO, EP, DB) receiving IC bleomycin the malignant effusion ceased for more than 30 days. There appeared to be no obvious relationship between clinical response and length of bleomycin plasma half-life or size of C×T.

Discussion

Intracavitary bleomycin has proven an effective therapy for malignant effusions associated with carcinomas of the breast, lung, and ovary. Limited pharmacokinetic data are available on the disposition of bleomycin after IC administration. Paladine et al. used a microbiologic assay to show that only about 5% of the IP bleomycin was still in the intrapleural space 24 h after instillation [9]; 10%–52% of the IPl dose was recovered in the urine during the first 16 h in six of their patients. There have been no reports other than our own preliminary results [1] of bleomycin disposition kinetics following IP administration.

The degree of systemic bleomycin absorption after IC administration can be estimated by comparing bleomycin plasma C×T values for IV and IC administration. If it is assumed that the pharmacokinetics of bleomycin are linear with dose, then it becomes possible to compare IV and IC plasma C×T values (Table 4). We have normalized the plasma C×Ts of our IV and IC patients for a bleomycin dose of 15 U/m² and a terminal phase half-life of 4 h. The 'normalized' mean C×Ts of the IP and IPl patients were approximately 45% of the previously reported IV patients (Table 4) [2]. These data suggest that only about 45% of the IC bleomycin dosage is absorbed into the systemic circulation. The mean urinary bleomycin excretion of 21.7% ± 8.6% for seven IC patients with normal renal function who had complete 24-h urine collections was 49% of that observed

Table 4. Systematic availability of bleomycin after intracavitary administration[a]

Comparison	Plasma C × T ratio	Urinary excretion ratio[e]
IP[b] : IV[c]	0.44	0.52
IPl[d] : IV	0.46	0.39
IP + IPl : IV	0.45	0.49

[a] Bleomycin data normalized to 15 U/m² dosage and a half-life of 4 h
[b] IP: bleomycin intraperitoneal data from Table 2
[c] IV: bleomycin intravenous data from Reference [2]
[d] IPl: bleomycin intrapleural data from Table 3
[e] Ratio of intracavitary to intravenous bleomycin 24-h urinary excretions

following equivalent IV dosing, and again suggests decreased, but substantial bleomycin systemic absorption. When calculating total bleomycin dosage for a given patient, it is essential to take all routes of drug administration into consideration. As about 45% of the IC bleomycin dosage may be absorbed into the systemic circulation, we suggest using one-half the IC dosage when calculating total 'systemic' bleomycin dosage.

The approximately 45% systemic absorption of IC bleomycin suggests the persistence of high drug concentrations in the peritoneal or pleural spaces. The phenomenon of this incomplete systemic absorption and complete disappearance from ascites in one of our patients (RD, Table 1) and from pleural fluid in one of the patients of Paladine et al. [9] within 24 h suggests significant bleomycin uptake into tumor and/or normal tissues.

The bleomycin plasma half-life after IP administration was significantly longer than that recorded with the IPl ($P < 0.001$) and IV ($P < 0.01$) routes. This may be due to an incomplete evacuation of peritoneal fluid prior to bleomycin instillation. The work of Dedrick et al. [6] suggests that the absorption rate of a drug from the intraperitoneal space into the systemic circulation is dependent on the volume of peritoneal fluid. As the peritoneal fluid volume increases the drug absorption rate is likely to decrease. Patient VP's terminal phase plasma $t_{1/2}$ of 30 h which was about five times the composite $t^{\beta}_{1/2}$ (Table 2), was perhaps caused by her unusually large volume of unevacuated peritoneal fluid.

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