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Bleomycin Clinical Pharmacology by Radioimmunoassay

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Summary. *Bleomycin pharmacokinetics were studied by radioimmunoassay in 11 patients who received 7–30 U intravenously (IV) and eight patients who received 4–30 U subcutaneously (SC). For patients who received IV bleomycin plasma disappearance was biphasic, with a mean initial half-life of 0.26 h and a terminal half-life of 2.3 h. Mean plasma drug clearance was 67.8 ml/min/m² and the volume of distribution was 13.2 l/m². Urinary excretion accounted for 63.9% of the drug in 24 h. After SC administration peak plasma levels occurred in 1.1 h, with a mean elimination half-life of 4.3 h. Mean plasma drug clearance was 60.5 ml/min/m² and the volume of distribution was 19.2 l/m². Bleomycin plasma clearance correlated well with serum creatinine ($r^2 = 0.72$).*

Bleomycin has a rapid plasma elimination and urinary excretion. Bleomycin bioavailability after SC administration appears comparable to that seen after IV administration as determined by the areas under the plasma disappearance curves. Prolonged plasma levels are seen after SC injection, suggesting this route of administration can produce plasma concentrations comparable to those attained with continuous IV infusions.

Introduction

Bleomycin, an antitumor antibiotic isolated from the fermentation products of *Streptomyces verticillus,* is used in the treatment of testicular, squamous head and neck, and lymphoid neoplasms. Despite the extensive clinical use of bleomycin, the optimum dose or schedule has not been determined. Only recently have clinical pharmacology studies been performed to determine a schedule of drug administration that would optimize bleomycin antitumor effects and diminish toxic side-effects.

In the past, bleomycin pharmacology studies were performed using microbiological assays [5, 7, 8]. Despite the lack of sensitivity and specificity and the long incubation periods required, these studies showed that the drug was predominantly excreted in the urine and had a rapid multiphasic disappearance from plasma. Animal tissue distribution studies using microbiological assays suggested the drug was more toxic in tissues where it accumulated and was not inactivated.

With the recent availability of a radioimmunoassay technique for concentration determinations, this system has been used to quantitate the drug in biological fluids [2]. The radioimmunoassay has proved to be more sensitive than the microbiologic assays at lower concentrations, while giving results similar to those obtained with the microbiological assay at higher drug concentrations [8]. We utilized the radioimmunoassay technique to study bleomycin pharmacokinetics in patients who received the drug as treatment for their metastatic neoplasms. The specific results reported here are the drug's plasma kinetics and urinary excretion after administration as a rapid IV injection and plasma pharmacokinetics after SC injection.

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Patients and Methods

Drug Administration and Sample Collection. Bleomycin pharmacokinetics were determined for 19 patients: 11 patients after IV and eight after SC drug injection. The patients' clinical characteristics are shown in Tables 1 and 2. Some patients were receiving other anticancer drugs, none of which was known to interfere with bleomycin determinations. All patients gave written informed consent prior to the study according to institutional policy. Bleomycin (Blenoxane) was dissolved in 50 ml 5% dextrose solution and administered IV over 5 min,

Table 1. Patients' characteristics (IV study)

Patient no.	Age (yrs)	Sex[a]	Diagnosis[a]	Treatment[a]	Bleomycin-dose (units)	Renal function, serum creatinine (mg/dl)
1	56	M	DHL	CHOP+B	15	0.8
2	31	F	DHL	CHOP+B	15	0.8
3	48	M	PDNL	CHOP+B	15	0.8
4	40	M	PDNL	CHOP+B	15	1.0
5	55	F	DHL	CHOP+B	15	0.8
6	31	M	DHL	CHOP+B	15	1.1
7	41	F	PDNL	CHOP+B	7	1.0
8	59	M	DHL	CHOP+B	8	1.2
9	65	F	SCHN	BMD	30	0.7
10	44	F	SCHN	BMD	30	1.3
11	65	M	SCHM	BMD	30	0.8

[a] M, male; F, female; DHL, diffuse histiocytic lymphoma; PDNL, poorly differentiated lymphocytic lymphoma, nodular type; SCHN, squamous cell carcinoma of head or neck; CHOP+B, cytoxan, adriamycin, vincristine, prednisone + bleomycin; BMD, bleomycin, methotrexate, *cis*-diamminedichloroplatinum (II)

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Table 2. Patients' characteristics (SC study)

Patient no.	Age (yrs)	Sex[a]	Diagnosis[a]	Treatment[a]	Bleomycin-dose (units)	Renal function, serum creatinine (mg/dl)
1	16	M	ALL	CHOP	5	1.8
2	30	M	DHL	CHOP+B	5	0.8
3	55	F	DHL	HOP+B	15	1.1
4	77	M	SCHN	BM	30	1.2
5	34	M	Lympho-epithelioma	BMD	30	0.8
6	52	F	Thyroid Ca[a]	BMD	30	0.7
7	75	M	Melanoma	B	4	1.2
8	62	M	SCHN	BMD	30	1.1

[a] M, male; F, female; ALL, acute lymphocytic leukemia; DHL, diffuse histiocytic lymphoma; SCHN, squamous cell carcinoma head or neck; CHOP, cytoxan, adriamycin, vincristine, prednisone; CHOP+B, CHOP + bleomycin; HOP, adriamycin, vincristine, prednisone; BM, bleomycin, methotrexate; BMD, BM+*cis*-diamminedichloroplatinum (II); B, bleomycin; Ca, carcinoma

Table 3. Bleomycin pharmacokinetics (IV study)[a]

	$t_{1/2}\alpha$ (hr)	$t_{1/2}\beta$ (hr)	Clearance (ml/min/m^2)	V_D (l/m^2)	Urinary excretion (cumulative % of dose 24 h)
All patients	0.26 ± 0.03	2.3 ± 0.6	67.8 ± 6.3	13.2 ± 0.9	63.9 ± 4.5
Patients with normal renal function who received 15 units ($n = 6$)	0.27 ± 0.04	2.0 ± 0.1	79.6 ± 6.1	13.8 ± 1.2	68.9 ± 5.9
Abnormal renal function ($n = 1$)	0.22	2.5	58.4	12.6	20.0

[a] Values are means ± SE

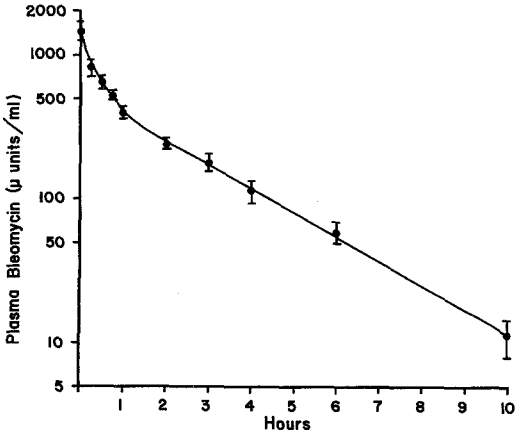

Fig. 1. Mean plasma bleomycin disappearance in six patients who received 15 units of bleomycin IV

dissolved in 2 ml 5% dextrose solution and administered IV over 5 min, or dissolved in 2 ml 5% dextrose solution and injected SC. Blood and urine were collected prior to drug administration and serially for 24 h after drug injection. Blood samples were put in tubes with heparin and centrifuged; the plasma was separated. The collected plasma and urine samples were frozen for later analysis.

Bleomycin Determinations and Calculations. Bleomycin was determined in plasma and urine by radioimmunoassay as previously reported [2, 9]. The plasma bleomycin concentrations were graphed over time on semilog paper. Best curve fit was determined by the least-squares fit, nonlinear regression analyses. The data were analyzed according to an open two-compartment model. Comparisons of mean pharmacokinetic parameters after IV and SC bleomycin administration were performed using the *t*-statistic of two means.

Results

The mean plasma pharmacokinetics of bleomycin after IV injection to 11 patients are shown in Table 3. The plasma disappearance appeared biphasic and the mean distribution half-life ($t_{1/2}\alpha$) was short (about 0.25 h) while the elimination half-life averaged about 2 h. A mean plasma disappearance curve for six patients who received 15 U is shown in Fig. 1, and their mean pharmacokinetic parameters are outlined in Table 3. Bleomycin was rapidly cleared from the plasma, as evidenced by high plasma clearance rates and short elimination half-lives. The drug's volume of distribution (V_D) was about 13–14 l/m^2. The rapid plasma disappearance was related to urinary excretion of the drug. Approximately 60%–70% of the drug was recovered from the urine within 24 h. One patient with minimal renal dysfunction excreted markedly less. Minimal renal disease did not markedly alter plasma pharmacokinetics. The area under the plasma concentration curve or C × t was related to dose. The mean C × t value was 1825.4 ± 223.7 (SE) μU-h/ml for two patients who received 15 U, 1193.7 ± 52.1 μU-h/ml for two patients who received 7–8 U, and 7329.2 ± 1352.0 μU-h/ml for the three patients who received 30 U.

The mean plasma pharmacokinetics for the eight patients who received bleomycin SC are shown in Table 4. Absorption from the SC site resulted in peak plasma levels in about 1 h, following which time plasma disappearance appeared to be monophasic. The mean elimination half-lives after SC drug administration were longer than after IV injection ($P < 0.001$). This difference was probably due to continued plasma absorption from the site of injection while elimination was occurring. No difference in plasma drug clearance was seen when SC and IV administration were compared ($P = 0.28$); however, the difference in the mean V_D was significantly greater ($P < 0.03$) after SC drug administration. The mean plasma concentration curve for four patients who received 30 U SC is shown in Fig. 2. Peak plasma concentrations were about 900 μU/ml after 30 U SC, while peak concentrations of 1,500 μU/ml were seen after only 15 U IV. These differences show that peak plasma concentrations after SC administration are about one-third those that would be seen after IV injection of a comparable dose. The mean area under the plasma disappearance curve (C × t) for the four patients who received 30 U SC was 5053.8 ± 802.7 (SE) μU-h/ml. This C × t value for 30 U bleomycin given SC is 2.8 times greater than the C × t for 15 U given IV. These data suggest that bleomycin C × t is

Table 4. Bleomycin plasma pharmacokinetics (SC Study)[a]

	Time to peak concentration (hr)	$t_{1/2}\beta$ (hr)	Clearance (ml/min/m^2)	V_D (l/m^2)
All patients ($n = 8$)	1.1 ± 0.2	4.3 ± 0.8	60.5 ± 0.85	19.2 ± 1.7
Patients with normal renal function who received 30 units ($n = 4$)	1.1 ± 0.2	4.2 ± 1.1	63.8 ± 10.2	20.5 ± 2.8
Abnormal renal function ($n = 1$)	0.9	7.9	46.5	17.2

[a] Values are means ± SE

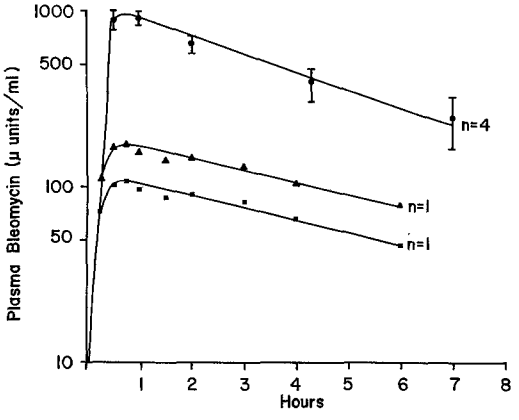

Fig. 2. Mean plasma bleomycin concentrations in four patients who received 30 units SC (●). Bleomycin plasma concentrations on day 1 (■) and day 2 (▲) in one patient who received four units of bleomycin SC every 6 h

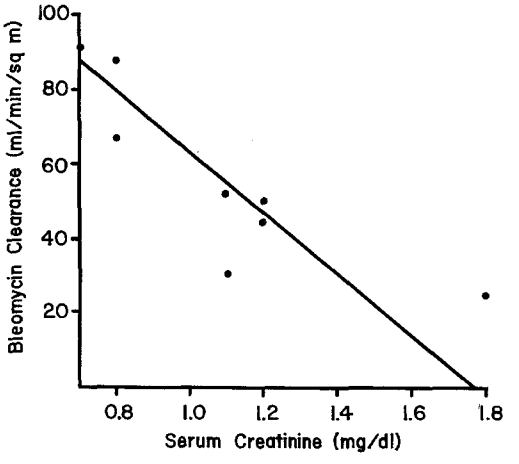

Fig. 3. Total bleomycin plasma clearance versus serum creatinine in eight patients who received the drug SC

comparable whether the drug is given by the IV or the SC route.

We also studied one patient who received 4 U bleomycin SC every 6 h for 4 days, and his plasma disappearance curves on day 1 and 2 are shown in Fig. 2. There did appear to be some plasma drug accumulation, as evidenced by the higher concentrations on the second day; however, the plasma disappearance appears quite similar on both days.

Although urine collections were not made after SC administration, bleomycin total plasma clearance could be correlated with serum creatinine concentrations (Fig. 3). As serum creatinine increased, plasma bleomycin clearance decreased ($r^2 = 0.42$). It appears from the urinary excretion data and plasma clearance correlation with serum creatinine that renal function is an important parameter determining bleomycin pharmacokinetics.

Discussion

The plasma disappearance of bleomycin after IV administration and after absorption from SC dosing appears similar. The peak plasma concentrations and area under the initial plasma decay curve are, however, greater after IV administration, while prolongation of lower plasma levels is seen after SC administration. Whether peak plasma concentrations or prolonged lower plasma drug levels are more important in determining toxicity or efficacy has not been determined. From our study it appears possible to obtain and keep plasma concentrations of 100 μU/ml by repeated SC injections of 4–6 U every 6 h. With 30 U/day by continuous IV infusion, after 35 h of infusion we noted a steady-state plasma level of ~ 146 μU/ml [6]. After the continuous infusion, the mean elimination half-life was 11.3 h and renal excretion accounted for about 63% of the administered dose. The continuous administration of bleomycin by the IV route or continued absorption from an SC injection site tended to prolong the elimination half-life of the drug. This suggests that the drug may be sequestered or bound to tissues in a peripheral compartment, where higher concentrations were achieved after a continuous IV infusion or multiple dosing.

Alberts and co-workers have also studied the pharmacology of bleomycin using our radioimmunoassay technique in patients treated by the IV, IPl, IP routes [1]. After IV administration, the $t_{1/2}$ was about 4.0 h, and although not different after IPl administration, it was prolonged after IP injection. The prolonged $t_{1/2}$ after IP injection was probably related to delayed absorption from the peritoneal site, analogously to the effect we saw after SC administration. Alberts determined that bleomycin absorption varied between 40% and 80%, depending on the route of administration.

The correlation of bleomycin pharmacokinetics with renal function has also been noted by Crooke et al., who utilized the radioimmunoassay system used in our study [3, 4]. They found the plasma elimination half-life was about 115 min and the volume of distribution was approximately 20 l. These data are similar to ours; however, they studied the pharmacokinetic correlation with renal function in detail and found little difference in pharmacokinetics when patients had creatinine clearances > 35 ml/min. However, when the creatinine clearance was < 25–35 ml/min the elimination half-life increased exponentially as the creatinine clearance decreased. The volume of distribution was not affected by changes in creatinine clearance in their study.

The results of our studies on the pharmacology of bleomycin after IV administration are similar to those reported by the groups of Alberts and Crook. Additionally, we have shown some pharmacokinetic differences after SC administration. The prolongation of plasma bleomycin concentrations after SC injection mimic plasma concentrations achieved during a continuous infusion of the drug. Therefore, SC

administration of bleomycin on an outpatient basis would produce a continuous plasma level of the drug. Repeated SC doses of bleomycin could be examined in bleomycin-sensitive tumors to see whether antitumor effects are enhanced; and repeated SC administration could also be studied in tumors relatively resistant to bleomycin to determine whether reproduction of a continuous plasma drug concentration is more effective than the routine bolus injection. It would be important to monitor patients' bleomycin plasma concentrations to insure that levels comparable to those achieved with effective regimens employing continuous infusion schedules are maintained.

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