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Pharmacokinetics of Bleomycin in Man

III. Bleomycin ^{57}Co Vs Bleomycin

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Summary. *Of all the bleomycin-containing radiopharmaceuticals, bleomycin ^{57}Co has proven the most useful whole-body tumor-imaging agent. We have studied its in vitro physicochemical properties and in vivo disposition in animals and man to optimize its use as a scanning agent. High-pressure liquid chromatographic analysis of the standard bleomycin ^{57}Co preparation (1 unit bleomycin plus 1 mCi chloride ^{57}Co showed it to contain 1% free chloride ^{57}Co. Dialysis experiments showed that bleomycin ^{57}Co does not dissociate as it diffuses through a dialysis membrane. In nine patients, bleomycin ^{57}Co had a $t_{1/2}^{\beta}$ of 3.4 h, a $t_{1/2}^{\gamma}$ of 45.8 h, a V_d of 12.1 liters/m^2 and a 24-h urinary excretion of 82.1% of the administered dose. In comparison, bleomycin, assayed by radioimmunoassay, had a terminal phase plasma $t_{1/2}$ of only 4.0 h, a similar V_d (17.3 liters/m^2), and a 24-h urinary excretion of only 44.8%. Bleomycin ^{57}Co tumor-to-plasma concentration ratios ranged from 14.1–23.8 at 1 day to 5.4 at 2 days after administration. Our finding that tumor imaging with bleomycin ^{57}Co is best achieved at 24 h is well explained by its almost complete urinary elimination in the first few hours after administration and the peak tumor-to-plasma ratio achieved at 24 h. One disadvantage of bleomycin ^{57}Co as a scanning agent is its very extended plasma $t_{1/2}$ In rabbits chloride ^{57}Co has the same prolonged plasma terminal elimination phase ($t_{1/2}^{\gamma}$) as our standard bleomycin ^{57}Co preparation, which contains chloride ^{57}Co as a 1% impurity. Removal of this impurity prior to scanning or use of cold cobalt chloride to help eliminate it from the plasma might result in a shortened bleomycin ^{57}Co plasma $t_{1/2}^{\gamma}$.*

Introduction

Bleomycin ^{57}Co is a useful whole-body tumor imaging agent in the evaluation of cancer [4, 6, 9–12]. It is one of a group of scanning agents formed by chelating the antitumor antibiotic bleomycin with a radionuclide label [5, 9]. Several investigators [3, 5, 18] have shown that bleomycin ^{57}Co has the highest tumor-to-nontumor tissue distribution ratios of all radiolabeled bleomycins. Furthermore, bleomycin ^{57}Co chelate may concentrate in tumor to a higher degree than free bleomycin [5]. Although there are published disposition data for bleomycin ^{57}Co in animals and man there has been no direct comparison between bleomycin and its ^{57}Co chelate in patients. We have studied the disposition of both bleomycin and bleomycin ^{57}Co in nine cancer patients in an attempt at a fuller understanding of the tumor-imaging properties of bleomycin ^{57}Co. Control studies were conducted in vitro and in animals to determine the stability of the chelate and the pharmacokinetics of bleomycin ^{57}Co so that effects of dissociation and/or metabolism could be determined.

Materials and Methods

Bleomycin ^{57}Co in Preparation and Tumor Imaging

Bleomycin ^{57}Co was prepared by diluting ^{57}Co in 0.5 *N* HCl to 0.1 *N* with normal saline, reconstituting bleomycin (Blenoxane, Bristol Laboratories, Syracuse, N.Y.) with normal saline, and combining ^{57}Co and bleomycin to achieve an activity of 1 mCi ^{57}Co per unit of bleomycin. The pH of the complex was adjusted to 6.0 with sodium acetate, and the volume was adjusted with normal saline to yield an activity of 1 mCi per milliliter. The final solution was filtered through a 0.22-μm sterile Millipore filter. Tests were performed to monitor sterility, apyrogenicity, and radiochemical and radionuclide purity.

Imaging studies were performed with the aid of a gamma camera with whole-body imaging table (Searle Radiographics Pho/Gamma IV) at 6 and 24 h after injection in all patients, and again at 48 h in 5 patients. Whole-body images and spot views of the anatomic areas of concern were obtained in all patients.

HPLC Analysis of Bleomycin ^{57}Co

The purity of bleomycin ^{57}Co was analyzed by high-pressure liquid chromatography (HPLC). Freshly prepared bleomycin ^{57}Co was di-

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rectly injected onto a reverse phase column (4 mm × 25 cm μC18, Bondapak, Waters Assoc., Milford, Mass.) and the inorganic ^{57}Co separated from the bleomycin ^{57}Co. The column was equilibrated with 10% acetonitrile in 0.01 *N* ammonium acetate (pH 4.5). Upon injection of the sample the solvent was programmed to 35% acetonitrile in 0.01 *N* ammonium acetate (pH 4.5). The flow rate was maintained at 2 ml per min and each 1-ml fraction was separately assayed for ^{57}Co content.

Dialysis of Bleomycin ^{57}Co

Back dialysis experiments were done to determine whether the ^{57}Co label remained in a chelated form as bleomycin ^{57}Co diffused through a dialysis membrane. Thirty 1-ml dialysis bags containing human plasma were placed into a 500-ml beaker containing 200 μCi bleomycin ^{57}Co plus 27 U bleomycin in phosphate-buffered saline (PBS) at 37° C. Twenty four hours later the dialysis bags were removed and placed in 500 ml fresh PBS. At 0, 0.5, 1, 2, 3, 5, 6, 8, 16 and 24 h, three dialysis bags were removed and their contents assayed for ^{57}Co by gamma counting and for bleomycin by radioimmunoassay (RIA).

Blood, Urine, and Tumor Sampling

Blood samples (10 ml) were obtained from patients through a heparin lock and collected in tubes containing 100 IU heparin. Blood samples were taken just prior to the start of bleomycin therapy and at 5, 10, 15, 30, 45, 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 varying intervals for at least 24 h. Urine samples were stored in sterile containers at 4° C. Tumor biopsies were obtained for diagnostic purposes in four head and neck cancer patients between 24 h and 6 days after radionuclide administration. The tissue samples were weighed and then assayed for ^{57}Co activity in a well scintillation counter.

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 means of the antiserum and radioimmunoassay (RIA) technique developed by Broughton and Strong [2]. Bleomycin was labeled for RIA with ^{125}Iodine; ^{57}Co and ^{125}I were counted simultaneously in a Hewlett Packard well scintillation counter with appropriate energy discrimination and correction for cross-talk between channels.

Plasma Disposition of Bleomycin ^{57}Co and Chloride ^{57}Co in Rabbits

Female New Zealand white rabbits (Blue Ribbon Rabbit Tree, Tucson, AZ) weighing 4 kg and maintained on normal laboratory rabbit chow were given 0.2 ml bleomycin ^{57}Co (200 μCi ^{57}Co) as IV bolus injections. Blood samples were collected from a heparinized, indwelling jugular catheter at 5, 15, 30, 60 min and 2, 4, 8, 12, 24, and 48 h after drug administration. The rabbits were kept in metabolic cages for collection of 24-h urine samples.

Patients and Treatment

Patient characteristics for the nine study patients are summarized in Table 1. Informed consent was obtained from each patient prior to study. All patients had advanced cancer and received bleomycin for therapeutic purposes. All patients but one (EL) received bleomycin and bleomycin ^{57}Co simultaneously by IV bolus injection. The bleomycin dose varied between 13.7 and 19.9 (mean 15.4) U/m^2 body surface area. All patients received 1 mCi bleomycin ^{57}Co.

None of the patients received other anticancer drugs within 3 weeks of the bleomycin pharmacokinetic studies. An attempt was made to stop all drugs at least 3 days prior to the bleomycin disposition studies; however, it was necessary to continue analgesic medication in four of the nine patients (Table 1).

Since bleomycin is eliminated mainly through the kidney, we studied patients with normal renal function. Serum creatinine concentrations were normal (0.7—1.3 mg%) for all nine patients.

Data Analysis

Bleomycin ^{57}Co concentration versus time data obtained from each patient and the composite data for all patients were fitted to a multiexponential equation, using NONLIN [7]. Preliminary parameter estimates were obtained from a recently published method CSTRIP [15]. Except for one patient (MR), the equation used was

$$\ln C = \ln (A_1 e^{-\alpha t} + A_2 e^{-\beta t} + A_3 e^{-\gamma t}) , \quad (1)$$

where C is the bleomycin ^{57}Co plasma concentration at time t after drug administration, A_{1-3} are coefficients, and α, β, and γ are first-order elimination rate constants. For patient MR a bi-exponential

Table 1. Characteristics of patients

Patient	Tumor type	Sex	Age (year)	Weight (kg)	Height (cm)	BSA (m^2)	Serum creatinine (mg-%)	Bleomycin IV dose (U)	Bleomycin IV dose (U/m^2)	Other drugs taken
SH	Head and neck	M	55	50.0	158	1.51	1.0	30	19.9	None
EG	Cervix	F	59	72.0	170	1.83	1.0	25	13.7	None
EM	Head and neck	F	64	54.3	170	1.67	0.9	25	15.0	None
HH	Cervix	F	61	58.6	159	1.60	1.2	24	15.0	Demerol
MM	Head and neck	F	61	92.8	158	1.86	0.9	30	16.1	Demerol
MA	Head and neck	M	56	99.4	171	2.05	1.0	30	14.6	Percodan
SR	Cervix	F	42	52.6	162	1.57	0.9	23	14.6	None
MR	Head and neck	M	84	60.0	163	1.65	1.1	24	14.5	None
EL	Ovary	F	63	63.1	157	1.62	1.0	—	—	None

equation was adequate to describe the concentration decay curves.

The plasma half-lives, $t^r_{1/2}$, were determined from the corresponding rate constants ($r = \alpha, \beta, \gamma$),

$$t^r_{1/2} = \frac{0.693}{r}. \quad (2)$$

The pharmacokinetic parameters associated with bleomycin ^{57}Co were calculated from only the α and β phases of the curve, since comparison between bleomycin ^{57}Co and cold bleomycin decay curves suggested (Fig. 6 and Discussion section) that the γ-phase of the bleomycin ^{57}Co curve was actually due to the existence of free ^{57}Co. The area under the curve (CXT) for bleomycin ^{57}Co was obtained from

$$CXT = \frac{A_1}{\alpha} + \frac{A_2}{\beta}. \quad (3)$$

The total body clearance Q_B and the apparent volume of distribution for bleomycin ^{57}Co were then evaluated from

$$Q_B = \frac{\text{total administered dose (TAD)}}{CXT}.$$

and

$$V_d = \frac{TAD}{CXT \cdot \beta}. \quad (5)$$

The renal clearance of bleomycin ^{57}Co, Q_r, was determined by dividing the 24-h cumulative urinary excretions of the drug by the 24-h CXT. The 24-h CXT was calculated from the following equation:

$$CXT_0^{24} = CXT - \frac{C_{24}}{\beta} \quad (6)$$

where C_{24} is the concentration of the drug at 24 h after injection.

The bleomycin ^{57}Co pharmacokinetics in rabbits were analyzed by the same methods described above. Equation 1 was used to fit data for all the rabbits (composite) and for each individual rabbit.

The disposition of chloride ^{57}Co in rabbits was also studied. Chloride ^{57}Co plasma decay curves were biphasic. The important pharmacokinetic parameters were calculated by the methods described above. Nonradioactive bleomycin disposition data analysis methods have been reported previously [1].

Results

HPLC Analysis of Purity of Bleomycin ^{57}Co

Chromatography of the fresh bleomycin ^{57}Co preparation showed that approximately 1% of it was free, inorganic cobalt (Fig. 1).

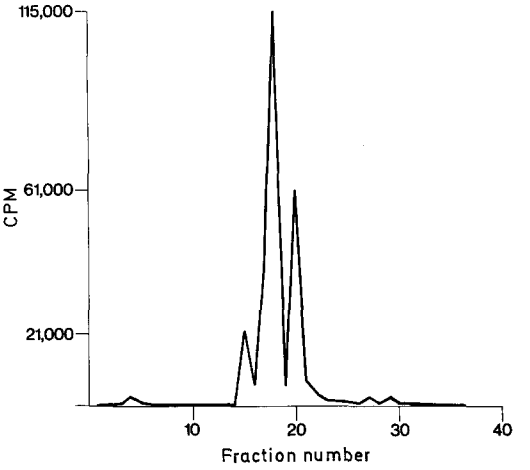

Fig. 1. HPLC fractionation of freshly prepared bleomycin ^{57}Co. The radiopharmaceutical was directly injected onto a reverse-phase μC18 Bondapak column. Inorganic cobalt (1% of the total cpm) appeared in fractions 4–6, whereas the bleomycin ^{57}Co chelate appeared in fractions 14–30

Dialysis Experiments

The rate of diffusion of bleomycin ^{57}Co from plasma through a dialysis membrane at 37° C was the same whether measured by radioimmunoassay or gamma counting (Fig. 2).

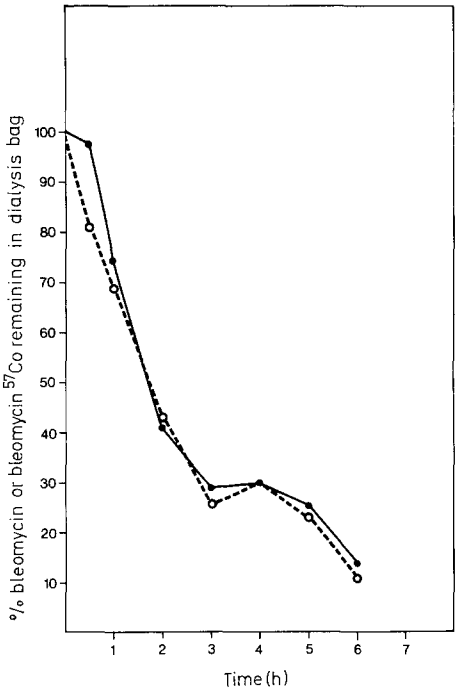

Fig. 2. Back dialysis of bleomycin ^{57}Co from human plasma. Dialysis bags containing human-plasma were placed into a dialyzate containing 200 μCi bleomycin ^{57}Co and 27 μ bleomycin. After 24 h the bags were placed into fresh PBS and plasma bleomycin ^{57}Co was assayed by RIA and ^{57}Co cpm at the indicated time intervals

Disposition of Bleomycin ^{57}Co and Chloride ^{57}CO in Rabbits

Pharmacokinetic parameters and urinary excretion data for bleomycin ^{57}Co and chloride ^{57}Co after IV administration in rabbits are summarized in Tables 2 and 3,

Table 2. Pharmacokinetic parameters of bleomycin ^{57}Co in rabbits

Rabbit	$t_{1/2}^{\beta}$ (h)	$t_{1/2}^{\gamma}$ (h)	V_d[a] (l/m^2)	Q_B[b] (ml/min/m^2)	72-h urinary excretion (% administered dose)
1	0.94	331.5	4.6	56.7	70.0
2	1.00	133.6	4.8	55.9	37.3
3	0.77	96.4	4.8	71.9	83.0
4	1.27	–[c]	6.1	55.1	92.4
5	0.94	65.9	4.3	52.8	50.0
Mean[d]	0.98 ± 0.18	156.8 ± 119.7	4.9 ± 0.68	58.4 ± 7.6	66.5 ± 22.8
Composite[e]	0.95 ± 0.13	86.9 ± 37.5	4.8 ± 1.7	58.7 ± 18.4	

[a] V_d, volume of distribution
[b] Q_B, whole-body clearance
[c] Half-life could not be determined
[d] Mean: Pharmacokinetic parameters ± SD calculated from mean of individual rabbit parameters
[e] Composite: Pharmacokinetic parameters ± SD calculated from nonlinear regression fit of all plasma decay data

Table 3. Pharmacokinetic parameters of chloride ^{57}Co in rabbits

Rabbit	$t_{1/2}^{\beta}$ (h)	V_d[a] (l/m^2)	Q_B[b] (ml/min/m^2)	24-h urinary excretion (%)
1	23.6	2.92	1.43	64.0 (16 h)
2	40.8	3.31	0.94	60.0
3	346.2	2.18	0.07	35.0
Mean[c]	136.9 ± 181.5	2.80 ± 0.57	0.81 ± 0.69	53.0 ± 15.7
Composite[d]	77.4 ± 97.8	3.02 ± 5.41	0.45 ± 0.57	

[a] V_d, volume of distribution
[b] Q_B, whole-body clearance rate
[c] Mean: Pharmacokinetic parameters ± SD calculated from mean of individual rabbit parameters
[d] Composite: Pharmacokinetic parameters ± SD calculated from nonlinear regression fit of all plasma decay data

respectively. The plots of the composite bleomycin ^{57}Co and chloride ^{57}Co plasma versus time data and their respective fitted curves are shown in Fig. 3. The relatively flat terminal slopes of these curves are similar, suggesting that free ^{57}Co accounts for the tail-end of both curves.

Disposition of Bleomycin and Bleomycin ^{57}Co in Humans

Pharmacokinetic parameters and urinary excretion data for bleomycin and bleomycin ^{57}Co after IV administration are summarized in Tables 4 and 5, respectively. The arithmetic means of the individual patient parameters and the composite results of the nonlinear regression fit of all plasma decay data appear at the bottom in Tables 4 and 5. In contrast to bleomycin's biexponential plasma decay, bleomycin ^{57}Co shows a triexponential decay. The terminal phase plasma half-life of 45.8 h for bleomycin ^{57}Co is significantly ($P < 0.05$) greater than that measured by radioimmunoassay for bleomycin, suggesting persistence of free ^{57}Co in the plasma. The 24-h urinary excretion for bleomycin ^{57}Co of 82% was almost twice that determined for bleomycin (i.e., 44.8%). Although the renal clearance rate (Qr) of 33.7 ± 10 ml/min/m^2 for bleomycin ^{57}Co was greater than the 23.0 ± 1.9 ml/min/m^2 for bleomycin, the two drugs had similar whole-body clearance rates.

Representative plots of the bleomycin and bleomycin ^{57}Co plasma decay data for two patients (EG and SH; Tables 1, 4, and 5) are shown in Figs. 4 and 5, respectively. The plots of the composite bleomycin and bleomycin ^{57}Co plasma concentration versus time data

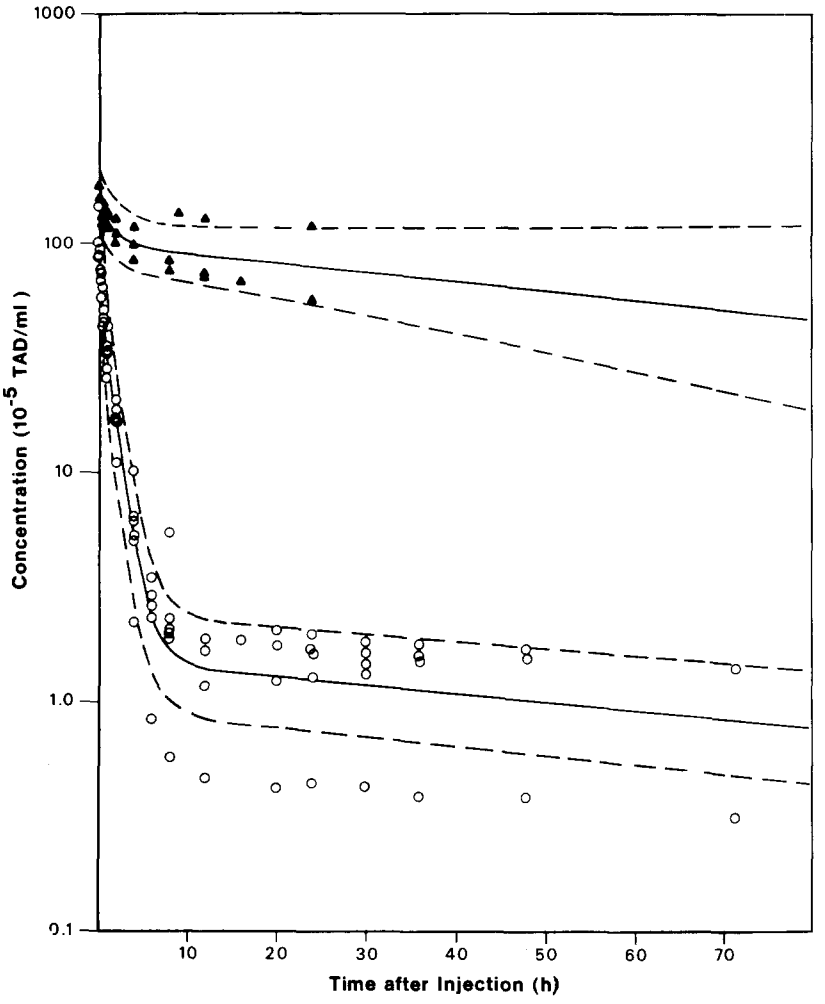

Fig. 3. Comparison of chloride ^{57}Co and bleomycin ^{57}Co plasma decay kinetics in rabbits. The medan and 1 standard deviation plots of the composite data are represented by solid and dashed lines, respectively

Table 4. Pharmacokinetic parameters of intravenous bleomycin in man

Patient (dose)	$t_{1/2}^{\beta}$ (h)	V_d[a] (l/m^2)	Q_B[b] (ml/min/m^2)	24-h urinary excretion (% dose)	Q_r[c] (ml/min/m^2)
SH (30 U)	4.5	20.5	52.6	29.1	15.5
EG (25 U)	3.2	14.4	52.0	27.4	14.1
EM (25 U)	3.0	13.0	49.5	49.2	24.3
HH (24 U)	4.3	18.2	48.6	45.5	22.8
MM (30 U)	3.8	23.3	71.4	—[d]	—[d]
MA (30 U)	4.4	15.9	41.7	46.2	19.6
SR (23 U)	4.6	19.7	49.5	61.5	31.3
MR (24 U)	4.4	15.2	39.9	54.8	22.2
Mean[e]	4.0 ± 0.6	17.5 ± 3.5	50.6 ± 9.6	44.8 ± 12.6	21.4 ± 5.8
Composite[f]	4.0 ± 0.1	17.3 ± 1.5	50.5 ± 4.1		23.0 ± 1.9

[a] V_d, volume of distribution
[b] Q_B, whole-body clearance rate
[c] Q_r, renal clearance rate
[d] Incomplete urine collections
[e] Mean: Pharmacokinetic parameters ± SD calculated from mean of individual patient parameters
[f] Composite: Pharmacokinetic parameters ± SD calculated from nonlinear regression fit of all plasma decay data

Table 5. Pharmacokinetic parameters of intravenous bleomycin ^{57}Co in man

Patient	$t^{\beta}_{1/2}$ (h)	$t^{\gamma}_{1/2}$ (h)	V_d[a] (l/m²)	Q_B[b] (ml/min/m²)	24-h urinary excretion (% TAD)	Q_r[c] (ml/min/m²)
SH	3.3	74.1	9.8	34.6	105.4	36.6
EG	3.6	657.1	15.5	49.5	66.8	33.3
EM	2.9	283.9	15.3	60.7	80.3	48.9
HH	3.7	15.9	8.8	27.7	72.8	20.3
MM	3.3	260.3	9.0	31.2	79.5	25.0
MA	4.3	128.7	11.0	29.5	93.4	28.1
SR	1.8	21.1	8.0	51.2	69.1	25.4
MR	5.5	–	20.3	43.0	73.3	32.8
EL	1.8	9.0	7.7	48.7	98.0	47.7
Mean[d]	3.4 ± 1.1	181.3 ± 220.4	11.7 ± 4.3	41.9 ± 11.1	82.1 ± 13.7	34.2 ± 9.5
Composite[e]	3.4 ± 0.6	45.8 ± 37.4	12.1 ± 3.6	40.8 ± 9.9		33.7 ± 10.0

[a] V_d, volume of distribution
[b] Q_B, whole-body clearance rate
[c] Q_r, renal clearance rate
[d] Mean: Pharmacokinetic parameters ± SD calculated from mean of individual patient parameters
[e] Composite: Pharmacokinetic parameters ± SD calculated from nonlinear regression fit of all plasma decay data

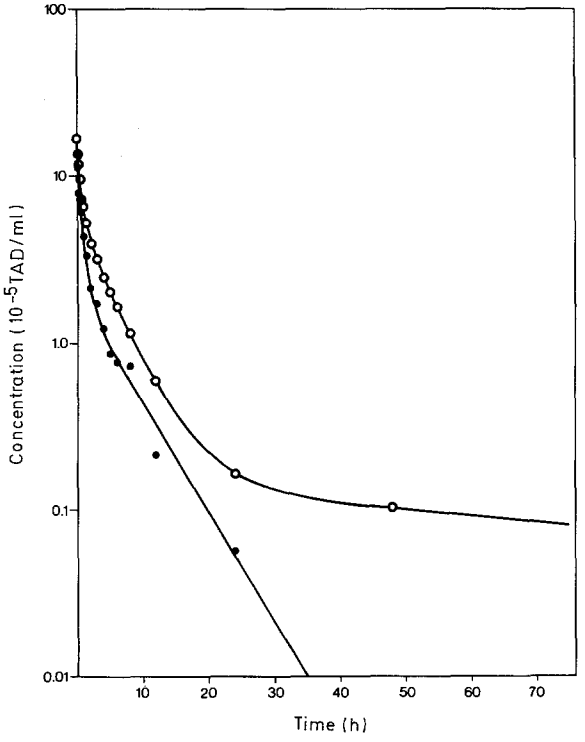

Fig. 4. Comparison of bleomycin and bleomycin ^{57}Co plasma decay curves for patient SH (Tables 1, 4 and 5). Bleomycin was measured by radioimmunoassay and bleomycin ^{57}Co by ^{57}Co radioactivity

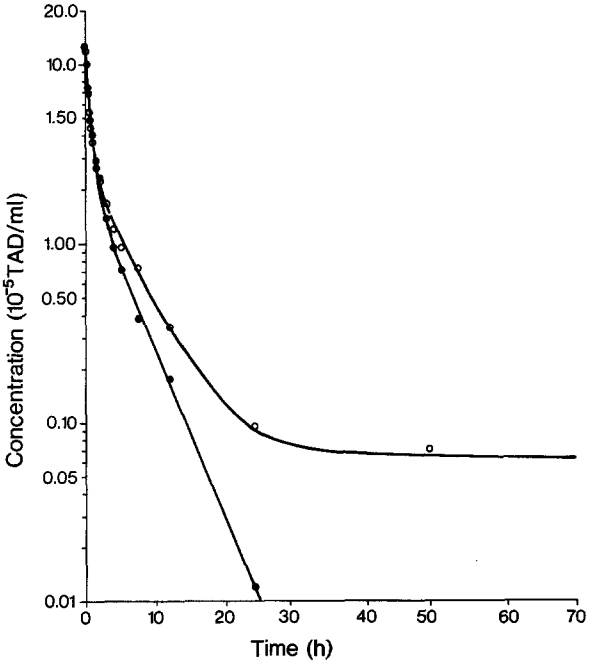

Fig. 5. Comparison of bleomycin (—●—) and bleomycin ^{57}Co (—○—) plasma decay curves for patient EG (Tables 1, 4, and 5). Bleomycin was measured by radioimmunoassay and bleomycin ^{57}Co by ^{57}Co radioactivity

and their respective fitted curves are shown in Fig. 6. The terminal plasma decay phase is relatively steep for bleomycin and flat for bleomycin ^{57}Co.

Tumor : Plasma Bleomycin ^{57}Co Ratios in Cancer Patients

Table 6 shows the bleomycin ^{57}Co tumor : plasma ratios for four patients with squamous-cell cancers of the head and neck. These ratios were highest at 24 h after radiopharmaceutical administration and fell to lower, but sustained levels between 2 and 6 days after.

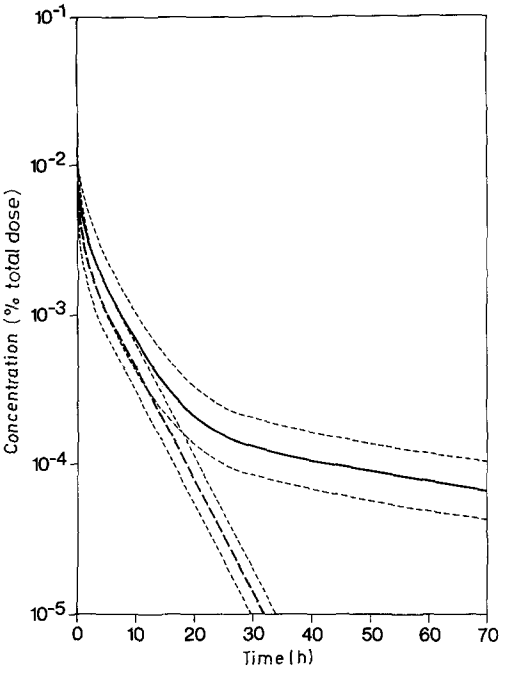

Fig. 6. Comparison of bleomycin and bleomycin ^{57}Co plasma decay curves for nine cancer patients. The median and 1 standard deviation plots of the composite data are represented by middle and associated outer curves, respectively

Table 6. Bleomycin ^{57}Co tumor: plasma ratios in patients with head and neck cancer

Patient	Tumor location	Days after drug administration	Ratio
SH	Nasal	1	23.8
MM	Floor of mouth	1	14.1
MA	Floor of mouth	2	5.4
ES[a]	Larynx	6	5.9
ES	Cervical lymph node	6	6.5

[a] No bleomycin ^{57}Co plasma or urine distribution data obtained

Tumor-Imaging Studies with Bleomycin ^{57}Co

The clearest tumor imaging with bleomycin ^{57}Co was seen in scans obtained 24 h after administration as against scans at 6 or 48 h [19]. Kidney, bladder, and generalized background activity was markedly higher at 6 than at 24 h after injection. Bleomycin ^{57}Co tumor rentention was greater at 24 h than at 48 h.

Discussion

Useful pharmacokinetic properties of a radiopharmaceutical tumor-scanning agent include high tumor-to-normal tissue uptake ratios, rapid plasma clearance, and almost complete urinary excretion. Our human disposition data on bleomycin ^{57}Co show relatively high tumor-to-plasma ratios, rapid plasma disappearance, and over 80% clearance from urine in the first 24 h. Although the terminal phase half-life (i.e., $t_{1/2}^{\gamma}$) was extremely long, the amount of ^{57}Co radiaoactivity present during this phase was very small (i.e., less than 2% of TAD).

Except for the terminal elimination phase of bleomycin ^{57}Co from human plasma, the plasma decay kinetics were not statistically different from those of bleomycin measured by radioimmunoassay (Tables 4 and 5). Our HPLC analysis of the freshly prepared bleomycin ^{57}Co, indicating that about 1% of it was unbound chloride ^{57}Co, provides confirmatory evidence for the hypothesis proposed by Robert et al. [13, 14] that free ^{57}Co could account for the very flat plasma γ phase of bleomycin ^{57}Co. The chloride ^{57}Co disposition data in rabbits show that this radionuclide has an extremely long β elimination phase from plasma. The slopes of the terminal elimination phases from plasma for bleomycin ^{57}Co and chloride ^{57}Co in the rabbit are not statistically different. We therefore conclude that the terminal persistence of ^{57}Co radioactivity in human plasma is mainly due to unbound chloride ^{57}Co present in the originally injected material.

The almost two-fold greater urinary elimination of bleomycin ^{57}Co than bleomycin by radioimmunoassay requires further explanation. Three possible mechanisms could obtain. First, there may be some metabolism of the bleomycin component of the radiopharmaceutical. The greater renal clearance rate but similar whole body clearance rate of bleomycin ^{57}Co compared to bleomycin suggests the possibility of bleomycin metabolism. Bleomycin-inactivating enzymes are present in various tissues [8, 17] and the radioimmunoassay mainly measures intact, native bleomycin [16]. Metabolism could account for decreased cold bleomycin activity but unchanged bleomycin ^{57}Co activity in the urine. However, it would be surprising if this bleomycin-inactivating en-

zyme activity could result in such large amounts of altered bleomycin after rapid IV injection and renal elimination. Second, although their initial clearance pathways appear similar, it is possible that bleomycin ^{57}Co binds less tightly than cold bleomycin to tissues, and is therefore eliminated into the urine more rapidly. Finally, ^{57}Co may dissociate from the bleomycin and be excreted into the urine. This last possibility is unlikely, in that investigators have shown in animals that almost all of the urinary ^{57}Co radioactivity represents intact bleomycin ^{57}Co [6, 12]. Furthermore, we have shown that bleomycin ^{57}Co does not dissociate as it diffuses through a dialysis membrane.

Our bleomycin ^{57}Co pharmacokinetic data help to explain its tumor-imaging characteristics. The rapid and almost complete urinary elimination accounts for the high bleomycin ^{57}Co activity seen in kidneys and bladder 6 h after injection and the decreased normal background activity observed in whole-body scans at 24 h. The higher bleomycin ^{57}Co tumor-to-plasma ratios at 24 h than at 2 and 6 days correlated well with the fact that the best tumor-imaging quality was found at 24 h.

Although bleomycin ^{57}Co has ideal tumor-imaging characteristics (i.e., rapid plasma clearance and almost complete urinary elimination), it has a few disadvantages. Besides having an extremely long half-life it has an extended γ phase plasma half-life. If this terminal elimination phase is due to chloride ^{57}Co bound to plasma proteins, then it might be beneficial to administer nonradioactive cobalt chloride before or along with the radionuclide. The excess cobalt chloride might therefore decrease chloride ^{57}Co protein binding and plasma half-life. In addition, careful removal of chloride ^{57}Co as an impurity of the initially injected bleomycin ^{57}Co might eliminate its markedly prolonged terminal γ plasma phase.

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