^{111}In-BLEOMYCIN KINETICS IN MICE BEARING TRANSPLANTABLE TUMORS OF LUNG, SKIN, AND BONE

Philip J. Robbins, Edward B. Silberstein, and Donald L. Fortman

Nuclear Medicine Laboratory, Bureau of Radiological Health, and Radioisotope Laboratory, University of Cincinnati Medical Center, Cincinnati, Ohio

Stable and chemically pure ^{111}In-bleomycin for injection can be prepared easily from carrier-free ^{111}InCl, and an aqueous solution of bleomycin by mixing the two at pH 1.5, adjusting the pH to 6.5–7, and autoclaving. This radiopharmaceutical shows definite tumor affinity within an hour after injection as would be predicted from its efficacy as a chemotherapeutic agent, but optimum ^{111}In tumor-to-blood ratios in three transplantable mouse tumors are not reached for 2 days. At 48 hr postinjection, it is not known if ^{111}In is still chelated to bleomycin.

Bleomycin has proven useful as an antitumor agent. It is comprised of a group of 13 polypeptides isolated from a strain of Streptomyces verticillus (*1*). The ^{57}Co chelate of bleomycin has been used as a tumor-scanning agent by Nouel, et al (*2*). While ^{57}Co has a very favorable energy (122 keV) for the commonly available imaging devices, its very long physical half-life (270 days) imposes a necessary limitation on its use, i.e., the urine from patients who receive the agent must be collected and processed to remove the radiocontaminant (*3*).

To avoid this limitation, we surveyed the chart of the nuclides for a gamma emitter whose chemical properties would be suitable for chelation with bleomycin and whose physical properties were also suitable for use with radionuclide imaging devices. Some of the amino acids contained in bleomycin contain the appropriate configuration and charge for chelation. These have been identified after hydrolysis of this antibiotic (*4*). Renault, et al (*5*) have tagged bleomycin with ^{57}Co, ^{64}Cu, ^{65}Zn, and ^{203}Hg. Of these, only ^{57}Co proved useful, but its half-life appeared disadvantageous to us as noted above. Indium-111 was selected because it has a short half-life (67 hr), gamma-ray energies of 179 and 247 keV, and no beta emission. It is available commercially in a radioisotopically pure form.

In this paper we describe the preparation of ^{111}In-bleomycin, some of its physical and chemical properties, and its distribution in tumor-bearing mice compared with $^{111}InCl_3$ in the same mice.

MATERIALS AND METHODS

Preparation of ^{111}In-bleomycin. Carrier-free $^{111}InCl_3$* was purchased in the sterile, pyrogen-free form.

1. Five milligrams of bleomycin powder† were dissolved in 3 ml of Water for Injection, U.S.P. The pH was adjusted to 1.5 with approximately 0.5 ml 0.5 *N* HCl.
2. Approximately 1 ml (100 Ci) $^{111}InCl_3$, supplied at pH 1.5, was mixed with the bleomycin solution.
3. The solution was adjusted to pH 6.5–7 with approximately 0.6 ml 0.5 *N* NaOH.
4. The solution was passed through a 0.45-micron Millipore filter or sterilized by autoclaving at 121°C, 15 psi for 15 min.

The radiochemical purity and tagging yield were determined using instant thin-layer chromatography (ITLC)‡ with 10% ammonium acetate:methanol (1:1) as solvent. The $^{111}InCl_3$, adjusted to pH 7, had an R_f value of 0–0.08 and the ^{111}In-labeled bleomycin an R_f value of 0.49–1.0.

Thermal stability. The thermal stability of the

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For reprints contact: Philip J. Robbins, FDA, BRH, Nuclear Medicine Laboratory, Cincinnati General Hospital, Cincinnati, Ohio 45229.

* Diagnostics Isotopes Inc., Upper Saddle River, New Jersey.

† Bristol Laboratories, Division of Bristol-Meyers, Syracuse, New York.

‡ Type SG, Gelman Instrument Co., Ann Arbor, Michigan.

^{111}In-bleomycin was determined by incubating the preparation for 48 hr at room temperature and at 37°C, and by autoclaving for 30 min at 121°C, 15 psi. Instant thin-layer chromatography of the radiopharmaceutical at 1, 24, and 48 hr after preparation and before and after autoclaving was done to show the amount of free indium formed.

Chemical stability. The stability of ^{111}In-bleomycin was challenged in vitro by incubating the ^{111}In-bleomycin with various metal ions found in vivo as suggested by Thakur, et al (*6*). Excesses of Ca^{2+} and Cu^{2+} ($CaCl_2$ and $CuSO_4$ equivalent to 100 mg of the cation) were incubated with ^{111}In-bleomycin at room temperature for 48 hr. Samples withdrawn at 1, 24, and 48 hr after start of incubation were chromatographed using the ITLC system described above to indicate the amount of free indium formed.

Distribution studies in mice. Mice (AKR strain) bearing Ridgeway osteogenic sarcoma and C57B1/6 mice bearing Lewis lung tumor and B-16 melanoma, implanted subcutaneously 1–2 weeks before the tissue distribution studies, were kindly supplied by the Southern Research Institute of Birmingham, Alabama. Bleomycin has been shown to inhibit tumor growth in mice bearing B-16 melanoma and Lewis lung tumors (*7*).

Groups of mice were injected intraperitoneally with 10–80 μCi of $^{111}InCl_3$ and ^{111}In-bleomycin containing 0.2 mg bleomycin per injection. Each mouse received 0.2 ml of the ^{111}In-bleomycin solution. The mice were sacrificed by acute trauma to the head at 1, 6, 24, and 48 hr after injection. Samples of heart blood were withdrawn immediately. Samples of the tumor, skin, fat, muscle, lung, kidneys, liver, spleen, lower and upper intestine, and heart were removed from the mice and weighed in tared counting tubes containing 2 ml saline. The ^{111}In activity in each sample was counted in a well scintillation counter set on integral mode to count the activity from 30 keV photons and above. The counting rates were corrected for background and for decay of ^{111}In to the time of injection. Standards were prepared in triplicate by transferring 0.2-ml doses of ^{111}In-bleomycin to volumetric flasks and dilution to an activity level approximately equal to the sample. A 2-ml aliquot of each standard was counted in the well counter. The counting rates were corrected in the same manner as the samples. The data are expressed as percent dose per gram tissue.

RESULTS

The yield of ^{111}In-bleomycin was 90–99% determined by ITLC. Figure 1 is a histogram representing the chromatography of ^{111}In-bleomycin and $^{111}InCl_3$.

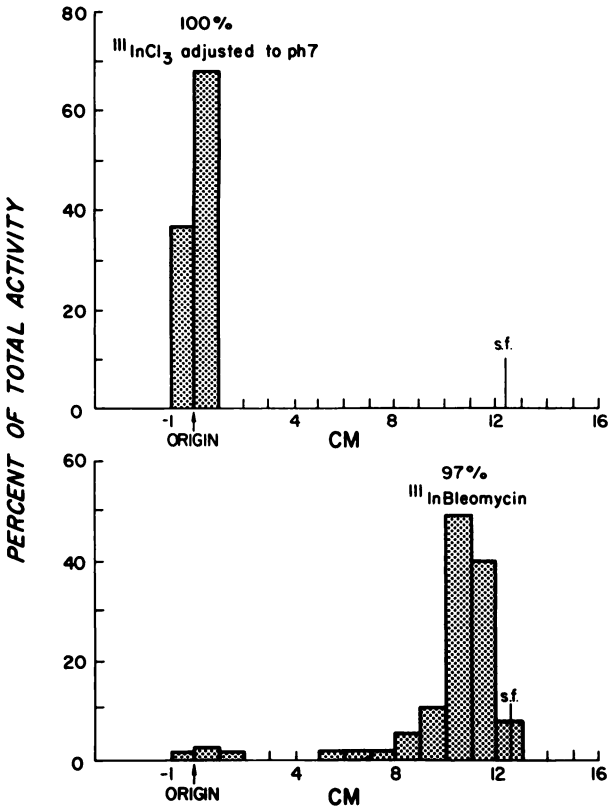

FIG. 1. Chromatograms of $^{111}InCl_3$ adjusted to pH 7 (upper) and ^{111}In-bleomycin at pH 7 (lower). The chromatograms were developed by ascending method on ITLC type SG media. Solvent system was 10% ammonium acetate:methanol (1:1).

TABLE 1. DEPENDENCE OF TAGGING YIELD ON THE QUANTITY OF BLEOMYCIN USED

Quantity of bleomycin (mg/5 ml)	Yield* ^{111}In-bleomycin (%)
30	95
15	95
5	91
1.5	31
0.5	4
0.15	6

* Yield determined by ITLC 10% ammonium acetate: methanol (1:1).

Forty to 60% of the activity remained on 0.22 and 0.45-micron Millipore filters when filtration was used to sterilize the product.

As seen in Table 1, the yield of ^{111}In-bleomycin decreased with decreasing quantities of bleomycin used in the procedure described under "Materials and Methods".

The thermal stability of ^{111}In-bleomycin was excellent. Samples incubated at room temperature and at 37°C for 48 hr were chromatographed using the ITLC system and showed no change during that

TABLE 2. DISTRIBUTION OF $^{111}InCl_3$ IN C57B1/6 MICE BEARING LEWIS LUNG TUMORS (PERCENT DOSE/GM TISSUE ± ERROR)*

Organ	Time after injection			
	1 hr	6 hr†	24 hr	48 hr
Tumor	11.80 ± 0.16	13.26	18.97 ± 3.56	16.00 ± 2.52
Skin	3.94 ± 0.45	4.85	4.09 ± 0.20	2.84 ± 0.16
Fat	27.58 ± 8.52	18.18	11.83 ± 1.67	13.13 ± 11.42
Muscle	11.48 ± 8.69	—	6.08 ± 0.27	2.81 ± 0.02
Lung	17.64 ± 7.56	18.45	7.22 ± 2.53	4.97 ± 0.03
Kidneys	82.85 ± 23.35	213.04	81.43 ± 61.81	84.97 ± 19.40
Liver	13.75 ± 1.35	23.60	11.39‡	9.18 ± 6.85
Spleen	11.60 ± 2.30	20.73	11.97 ± 3.86	18.20 ± 2.03
Blood	36.21 ± 0.51	11.05	4.27 ± 1.30	1.62 ± 0.03
Heart	9.68 ± 0.76	6.09	2.96 ± 0.28	4.50 ± 0.69

* Two mice per group; average value ± one-half the range of the individual values.
† Single mouse sacrificed at 6 hr; individual values.
‡ Liver from one mouse only; individual values.

TABLE 3. DISTRIBUTION OF ^{111}In-BLEOMYCIN IN C57B1/6 MICE BEARING LEWIS LUNG TUMORS (PERCENT DOSE/GM TISSUE ± ERROR)*

Organ	Time after injection			
	1 hr	6 hr†	24 hr	48 hr
Tumor	6.59 ± 0.81	2.49	2.70 ± 0.03	3.66 ± 0.25
Skin	7.55 ± 2.13	2.83	1.62 ± 0.29	1.30 ± 0.05
Fat	4.58 ± 2.04	1.19	1.71 ± 0.42	1.14 ± 0.09
Muscle	6.34 ± 2.52	3.48	0.91 ± 0.14	0.64 ± 0.07
Lung	7.98 ± 1.54	2.44	2.19 ± 0.36	1.12 ± 0.10
Kidneys	28.35 ± 9.69	15.96	16.90 ± 3.77	18.37 ± 1.73
Liver	4.57 ± 1.31	3.43	2.59 ± 0.09	2.96 ± 0.12
Spleen	3.60 ± 0.79	2.05	3.12 ± 0.66	2.04 ± 0.32
Blood	10.53 ± 3.90	2.72	1.06 ± 0.09	0.41 ± 0.05
Heart	5.93 ± 2.49	1.15	1.03 ± 0.03	0.51 ± 0.05

* Two mice per group; average value ± one-half the range of the individual values.
† Single mouse sacrificed at 6 hr; individual values.

time. One to 2% free indium was present in both samples throughout the 48-hr incubation. Autoclaving an ^{111}In-bleomycin preparation showed no change in the amount of free indium present. The presence of 1.5% free indium on the ITLC before and after autoclaving indicates that the preparation may be sterilized by this technique.

In the presence of Ca^{2+} in vitro, ^{111}In-bleomycin was stable when sampled during the 48 hr-incubation. In the presence of Cu^{2+}, the ^{111}In-bleomycin label was destroyed in 1 hr. The ITLC of the latter sample withdrawn at 1 hr after start of incubation showed 94% of the activity in the R_f 0–0.08 region.

The results of the tissue distribution studies in mice are given in Tables 2–5. Table 2 presents results from the study of $^{111}InCl_3$ in C57B1/6 mice with Lewis lung tumors; while Tables 3–5 show the results from ^{111}In-bleomycin injected into C57B1/6 mice bearing Lewis lung tumors, C57B1/6 mice bearing B-16 melanoma, and AKR mice bearing Ridgeway osteogenic sarcoma, respectively. Table 6 gives a comparison of ratios of tumor to blood, lung, skin, kidney, liver, muscle, and fat in the C57B1/6 mice bearing Lewis lung tumors for both ^{111}In-bleomycin and $^{111}InCl_3$. Tables 7 and 8 provide similar data for ^{111}In-bleomycin only for C57B1/6 mice bearing B-16 melanoma and AKR mice bearing Ridgeway osteogenic sarcoma.

It is apparent that the $^{111}InCl_3$ tumor concentration is considerably greater than that of ^{111}In-bleomycin but is cleared more slowly from the blood. By 48 hr postinjection the tumor-to-blood ratios exceed 9 with both agents (Table 6). In fact, the ratios of tumor to kidney, liver, lung, and muscle are remarkably similar by 48 hr.

DISCUSSION

The cumulative human therapeutic dose of bleomycin has been limited to 3 mg/kg, and with a single dose of 0.1 mg/kg some febrile responses

TABLE 4. DISTRIBUTION OF ^{111}In-BLEOMYCIN IN C57B1/6 MICE BEARING B-16 MELANOMA (PERCENT DOSE/GM TISSUE ±1 S.D.)*

Organ	Time after injection			
	1 hr	6 hr	24 hr	48 hr
Tumor	7.28 ± 1.61	4.28 ± 1.05	4.19 ± 1.05	3.48 ± 0.95
Skin	6.06 ± 0.94	2.72 ± 0.21	1.67 ± 0.65	1.42 ± 0.73
Fat	2.26 ± 0.45	1.28 ± 0.20	1.26 ± 0.68	1.48 ± 0.80
Muscle	6.56 ± 4.09	1.29 ± 0.73	0.54 ± 0.22	0.61 ± 0.25
Lung	8.06 ± 2.42	2.75 ± 0.33	1.16 ± 0.50	1.40 ± 0.38
Kidneys	27.30 ± 3.14	19.73 ± 4.89	16.51 ± 4.90	17.44 ± 1.08
Liver	4.42 ± 0.66	2.47 ± 0.44	3.12 ± 1.13	4.29 ± 1.12
Spleen	3.55 ± 1.16	1.69 ± 0.20	2.09 ± 1.14	2.07 ± 0.53
Blood	5.85 ± 0.79	2.99 ± 0.54	0.72 ± 0.30	0.33 ± 0.18
Heart	2.48 ± 0.33	1.00 ± 0.19	0.49 ± 0.18	0.45 ± 0.05

* Three mice in each group; average value ±1 s.d.

TABLE 5. DISTRIBUTION OF ^{111}In-BLEOMYCIN IN AKR MICE BEARING RIDGEWAY OSTEOSARCOMA (PERCENT DOSE/GM TISSUE ±1 S.D.)*

Organ	Time after injection			
	1 hr	6 hr	24 hr	48 hr
Tumor	4.93 ± 3.23	2.88 ± 1.15	2.15 ± 0.01†	1.61 ± 0.43
Skin	4.56 ± 1.87	2.26 ± 0.28	1.29 ± 0.41	1.64 ± 0.36
Fat	2.14 ± 1.50	1.00 ± 0.15	0.73 ± 0.25	1.22 ± 0.13
Muscle	3.93 ± 2.06	1.14 ± 0.31	0.74 ± 0.23	0.81 ± 0.07
Lung	3.79 ± 1.43	2.32 ± 0.87	1.24 ± 1.00	0.84 ± 0.32
Kidneys	12.05 ± 7.31	9.59 ± 4.11	7.88 ± 0.71	8.91 ± 2.09
Liver	1.99 ± 0.49	1.55 ± 0.23	1.62 ± 0.85	5.70 ± 6.23
Spleen	1.61 ± 0.54	1.17 ± 0.23	1.32 ± 0.66	1.71 ± 0.37
Blood	4.00 ± 0.63	3.35 ± 0.56	0.84 ± 0.54	0.38 ± 0.14
Heart	1.65 ± 0.41	0.95 ± 0.16	0.46 ± 0.25	0.44 ± 0.03

* Three mice in each group; average value ±1 s.d.
† Tumors from 2 mice; average value ± one-half the range of the individual values.

have been noted (*8*). The diagnostic dose, therefore, should be as low as practicable. In our labeling procedure, a 5-mg quantity was the smallest amount of bleomycin that would give a yield better than 90%. Therefore, this quantity has been used throughout our study. The preparation contains 1 mg/ml. At this concentration an average patient given a nominal 1-ml volume would receive 0.014 mg/kg. This is well below the level mentioned above which has produced febrile responses in patients. The decreasing yield with decreasing quantity of bleomycin employed is an indication of the capacity of bleomycin to complex trivalent cations as discussed by Renault (*5,9*).

Millipore filtration of ^{111}In-bleomycin would be the most convenient method of sterilizing the preparation. However, since 0.45 and 0.22-micron filters reduce the quantity of ^{111}In-bleomycin obtained, sterilization by autoclaving is the method preferred. The thermal stability at autoclave temperature and pressure permits the autoclave method to be used. The material that is filtered from the ^{111}In-bleomycin solution is some of the tagged polypeptide. The material on the filter could not be insoluble indium hydroxide since a strong chelate is formed with bleomycin. Thin-layer chromatography confirmed the high tagging yield (90–99%).

The thermal stability at room temperature indicates that this radiopharmaceutical can be prepared several hours in advance of its use. The stability at body temperature (37°C) indicates the suitability of ^{111}In-bleomycin for use in the human.

The exchange of Cu^{2+} with the ^{111}In-bleomycin that occurred in the in vitro experiment suggests possible dissociation of the ^{111}In-bleomycin chelate when this metal is encountered in vivo. This is not unexpected since it is known that Cu^{2+} forms more stable chelates than In^{3+} with bleomycin (*9*).

The similarity of the tumor-to-kidney, liver, lung, and muscle ratios at 48 hr for $^{111}InCl_3$ and ^{111}In-bleomycin (Table 6) suggests dissociation of the bleomycin label. Thakur, et al have shown that the ^{111}In of ^{111}In-bleomycin is found on transferrin within 4 hr postinjection in man (*6*), which suggests

TABLE 6. TUMOR:ORGAN RATIOS FOR $^{111}InCl_3$ AND ^{111}In-BLEOMYCIN IN C57B1/6 MICE BEARING LEWIS LUNG TUMORS

	Time after injection							
	1 hr		6 hr		24 hr		48 hr	
Ratio	In*	BLM†	In*	BLM†	In*	BLM†	In*	BLM†
Tumor:Blood	0.33	0.62	1.20	0.92	4.44	2.55	9.87	9.04
Tumor:Lung	0.67	0.83	0.72	1.02	2.63	1.23	3.22	3.27
Tumor:Skin	2.99	0.37	2.74	0.88	4.64	1.67	5.64	2.58
Tumor:Kidney	0.14	0.23	0.06	0.16	0.23	0.16	0.19	0.20
Tumor:Liver	0.86	1.44	0.56	0.73	1.67	1.04	1.74	1.24
Tumor:Muscle	1.03	1.04	—	1.00	3.12	2.97	5.70	5.72
Tumor:Fat	0.43	1.44	0.73	2.09	1.60	1.58	1.22	3.21

* In = $^{111}InCl_3$.
† BLM = ^{111}In-bleomycin.

TABLE 7. TUMOR:ORGAN RATIOS FOR ^{111}In-BLEOMYCIN IN C57B1/6 MICE BEARING B-16 MELANOMA

	Time after injection			
Ratio	1 hr	6 hr	24 hr	48 hr
Tumor:Blood	1.24	1.43	5.82	10.55
Tumor:Lung	0.90	1.56	3.61	2.49
Tumor:Skin	1.05	1.57	2.51	2.45
Tumor:Kidney	0.27	0.22	0.25	0.20
Tumor:Liver	1.65	1.73	1.34	0.81
Tumor:Muscle	1.11	3.32	7.76	5.70
Tumor:Fat	3.22	3.26	3.33	2.35

TABLE 8. TUMOR:ORGAN RATIOS FOR ^{111}In-BLEOMYCIN IN AKR MICE BEARING RIDGEWAY OSTEOSARCOMA

	Time after injection			
Ratio	1 hr	6 hr	24 hr	48 hr
Tumor:Blood	1.23	0.86	2.56	4.24
Tumor:Lung	1.30	1.24	1.73	1.92
Tumor:Skin	1.08	1.27	1.66	0.98
Tumor:Kidney	0.41	0.30	0.27	0.18
Tumor:Liver	2.47	1.86	1.33	0.28
Tumor:Muscle	1.25	2.53	2.91	1.99
Tumor:Fat	2.30	2.88	2.94	1.32

competition by transferrin for the ^{111}In label and/or exchange of serum cations for the chelated indium. Studies using ^{14}C-labeled bleomycin compared with ^{111}In-bleomycin to resolve these two suggestions are contemplated. The absolute uptake of activity by the tumor (Tables 2 and 3) and the tumor-to-organ ratios (Table 6) for $^{111}InCl_3$ and ^{111}In-bleomycin suggest that $^{111}InCl_3$ is a superior scanning agent to ^{111}In-bleomycin.

In agreement with the original studies of Umezawa on unlabeled bleomycin in mice bearing Ehrlich carcinoma (*10*), we find tumor concentration at a maximum 1 hr postinjection. But, at variance with his data, Tables 3–5 indicate concentrations of ^{111}In-bleomycin in many tissues at 1 hr at a level close to that of the tumors we studied. We find persistently high kidney activity at 48 hr while the renal concentration of Umezawa's unlabeled preparation fell to levels lower than those found in tumor within 5 hr. Apparently ^{111}In-bleomycin as a chelate is metabolized differently from the material studied by Umezawa.

The highest ratios of tumor to blood in this study clearly occur at 48 hr for the three tumors studied (Tables 6–8) but the ratios of tumor to liver, skin, kidney, muscle, and fat are higher at 24 hr for the Ridgeway osteosarcoma. The data suggest optimum scanning time at 24–48 hr. We studied no animals beyond 48 hr.

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