KINETICS OF ^{111}In-BLEOMYCIN AND ^{111}In-CHLORIDES IN MICE

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Indium-111 as the chloride and chelated to bleomycin has been reported useful as a tumor-scanning agent. This is a report of the kinetics of these compounds compared in Yale-Swiss mice bearing a transplantable, in situ brain sarcoma. Indium-111-chloride, pH 1.5, gave a maximum tumor uptake of 18.5% dose per gram tumor, a maximum tumor-to-brain ratio of 17.0, and a maximum tumor-to-blood ratio of 4.4. Its renal blood clearance was a slow 0.0022 ml/min. Indium-111-bleomycin showed a maximum tumor uptake of 3.0% dose per gram tumor, a maximum tumor-to-brain ratio of 13.5, a maximum tumor-to-blood ratio of 6.8, and renal blood clearance of 0.254 ml/min. The labeling of bleomycin with ^{111}In results in a tracer with localizing properties in this tumor model which are quite different from those obtained with ^{111}In-chloride. Both ^{111}In as chloride or that labeled to bleomycin would appear to have significant potential as agents for imaging tumors.

Over the past several years a number of radiopharmaceuticals have been evaluated as possible diagnostic aids to tumor detection and as possible supplements to established methods of cancer diagnosis and staging. None has yet become generally accepted and all have been assigned more or less limited roles (*1,2*). The somewhat greater success of ^{67}Ga-citrate as a soft-tumor-scanning agent has revitalized interest in this area of research and the more recent availability of cyclotron-produced radionuclide ^{111}In has made studies possible with this radionuclide.

Indium-111 has been reported useful as a tumor-imaging agent, both in the chloride form (*3–5*) and complexed with the antibiotic bleomycin (*5–7*). We have compared the pharmacokinetics of ^{111}In-chloride, pH 1.5, ^{111}In-bleomycin, pH 6.5, and ^{111}In-chloride, pH 6.5, in Yale-Swiss mice bearing an in situ transplantable brain sarcoma as well as the kidney and liver kinetics and whole-body retention in normal mice.

MATERIALS AND METHODS

Radiopharmaceuticals. Indium-111-chloride was obtained from a commercial source (Diagnostic Isotopes, Inc., Upper Saddle River, N.J.) and diluted with 0.05 *N* hydrochloric acid to the desired assay (about 50 μCi/ml) and the pH carefully adjusted to 1.5 ± 0.2. No stabilizer was added.

The ^{111}In-bleomycin was commercially secured (Medi-Physics Corp., Emeryville, Calif.) and diluted with saline to the desired assay (about 50 μCi/ml). The pH was 6.5 ± 0.2.

As a control for free indium in the bleomycin preparation, an additional batch of ^{111}In-chloride was prepared and the final pH was adjusted to 6.5 ± 0.1. No stabilizer was added.

Mouse tumor and distribution studies. Yale-Swiss mice bearing a sarcoma-like, transplantable brain tumor originally induced by methylcholanthrene were used. The details of the technique of transplantation and experimentation have been described previously (*8–12*).

Renal clearance procedure. The procedure for determination of renal clearance in mice also has been described previously (*11–15*). No renal clearance determinations were possible with ^{111}In-chloride, pH 6.5, since it was almost entirely extracted by the liver.

Whole-body retention studies. Whole-body retention studies were performed up to 35 days. Six healthy 5-week-old mice were injected intravenously

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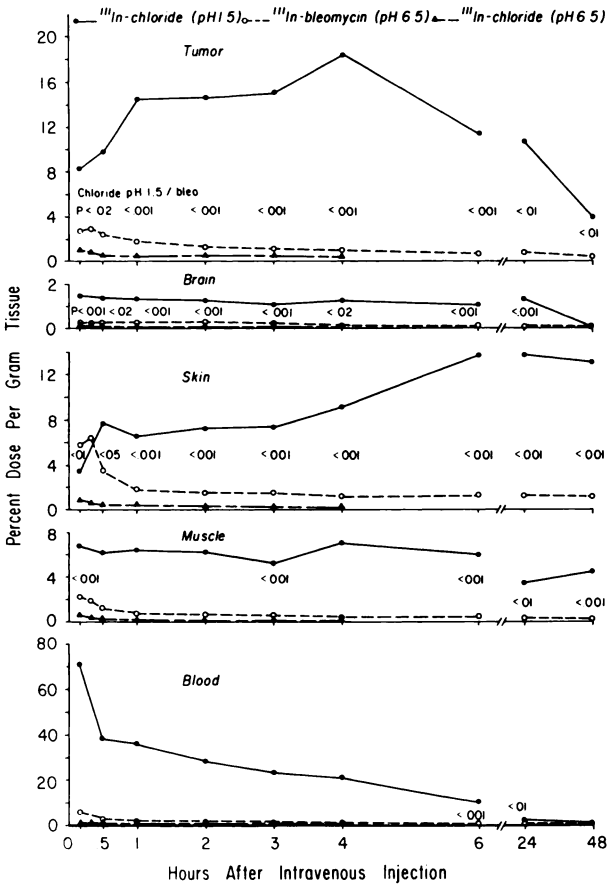

FIG. 1. Average percent dose per gram tissue of mouse tumor, brain, skin, muscle, and blood for varying time periods up to 48 hr after injection of ^{111}In-chloride, pH 1.5, ^{111}In-bleomycin, and ^{111}In-colloid, pH 6.5.

per body weight in grams with the radiopharmaceuticals using a Hamilton syringe with a 27-gage needle. Six vials containing identical amounts of radiopharmaceutical were prepared at the same time as standards. At the appropriate time the mice were induced to urinate, placed on a wire screen in a 5-liter beaker, and counted under fixed geometry in a whole-body counter. Immediately afterwards the standards were counted under identical conditions. The number of counts under the total peak in the energy spectrum was determined, corrected for background, and used to determine the radioactivity retained by the mouse whole body relative to the standard.

Evaluation of results. The average value of data obtained from at least six mice was used for each point. Student's t-test of significance was used to evaluate differences between groups of animals at level of significance arbitrarily chosen as $p < 0.05$. All renal clearances were standardized to a 1.73 m^2 surface area and compared with the clearance of inulin-^{14}C-carboxyl, whose clearance closely approximates that of inulin, the accepted standard for the measurement of glomerular filtration rate (GFR). This comparison permitted estimation of the amount of tubular reabsorption (TR) associated with the chloride, pH 1.5, and with the labeled bleomycin.

RESULTS

Tumor-tissue localization of radioactivity. The variations of mean percent dose per gram of tumor, brain, skin, muscle, and blood at 10, 20, and 30 min and 1, 2, 3, 4, 6, 24, and 48 hr are shown in Fig. 1. Indium-111-chloride was usually found in larger quantities than ^{111}In-bleomycin in all tissues studied. The ^{111}In-chloride at pH 6.5 showed minimal tissue uptake with the exception of the liver.

In Fig. 2, the tumor-to-brain, tumor-to-skin, tumor-to-muscle, and tumor-to-blood ratios at various time periods for the radiopharmaceuticals are presented. The tumor-to-tissue ratios of ^{111}In-chloride, pH 1.5, were generally equal to or superior to those of the ^{111}In-bleomycin after 30 min with the exception of the tumor-to-blood ratio at 48 hr.

Figure 3 gives the cumulative urinary excretion curves of the compounds after single intravenous injection. The injected ^{111}In-bleomycin was eliminated rapidly with about 78% being excreted after 2 hr. During this time period only 8% of the ^{111}In-chloride, pH 1.5, and essentially none of the ^{111}In-chloride, pH 6.5, was excreted.

From the data of Fig. 3 and from a blood disappearance curve from normal mice similar to that in Fig. 1, the renal blood and plasma clearance values were determined as described previously (*11–15*).

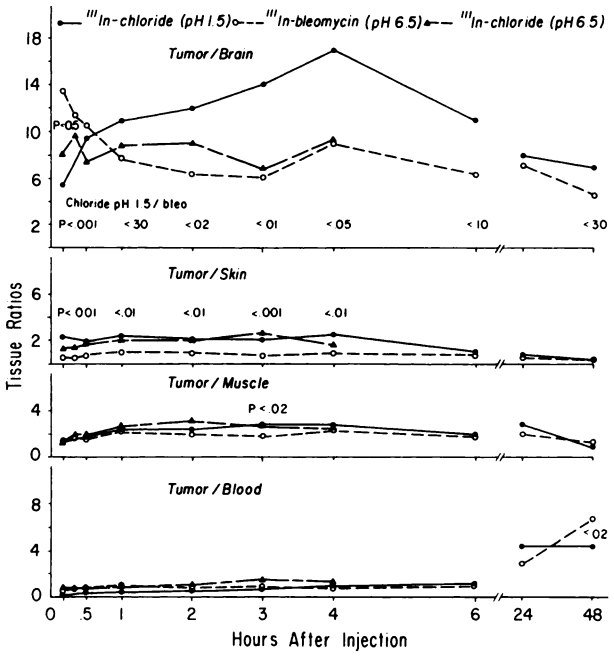

FIG. 2. Tumor-to-brain, tumor-to-skin, tumor-to-muscle, and tumor-to-blood tissue ratios in mice for varying time periods up to 48 hr after injection of ^{111}In-chloride, pH 1.5, ^{111}In-bleomycin, and ^{111}In-colloid, pH 6.5.

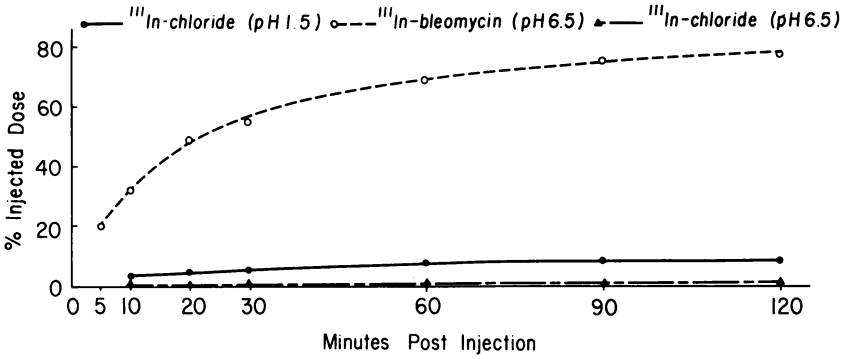

FIG. 3. Cumulative urinary excretion in mice after single intravenous injection in which percent injected dose is plotted against time for 2 hr after injection of ^{111}In-chloride, pH 1.5, ^{111}In-bleomycin, and ^{111}In-colloid, pH 6.5.

The kidney function indices calculated for these radiopharmaceuticals and compared with the clearance of ^{14}C-inulin are presented in Table 1. The labeled bleomycin was cleared the most rapidly.

Kidney–liver studies. Figure 4 shows the percent injected dose per single kidney and liver of the three compounds at the designated time intervals. The kidney retention of ^{111}In-chloride, pH 1.5, was consistently greater than that of the ^{111}In-bleomycin or ^{111}In-chloride, pH 6.5. As expected, the uptake by liver of the colloidal ^{111}In-chloride, pH 6.5, was greatest. Indium-111-bleomycin showed the least liver concentration.

Whole-body retention studies. Whole-body retention data for the radiopharmaceuticals are shown in Table 2. Indium-111-bleomycin was excreted most rapidly. Very little of ^{111}In-chloride, pH 6.5, was excreted, with over 72% of the injected dose retained after 23 days.

DISCUSSION

Comparison of the present results with those previously published. Three publications (*1,5,6*) present limited data on the simultaneous comparison in mice or rats of ^{111}In-bleomycin and ^{111}In-chloride. Other investigators have studied either the labeled chloride (*16,17*) or the labeled bleomycin (*6,7,18*) independently.

Most preparations of labeled indium chloride for blood-pool scanning have been gelatin-stabilized preparations at a pH range of 3–4 (*17,19,20*) or of 1.4–2.0 (*21,22*). The change of distribution of labeled indium chloride with changing pH has been emphasized (*19,21*). We found the distribution of ^{111}In-chloride, pH 3, in mice to be very inconsistent and unreproducible and we chose to use a formulation at pH 1.5 which gave consistent results without the addition of a stabilizer.

For colloidal indium used as a liver–spleen–marrow-imaging agent pH ranges have been reported varying from 3.5–7.8 (*17,20–24*). In order to serve as a control for free indium in ^{111}In-bleomycin, we chose to test ^{111}In-colloid at a pH of 6.5, the same pH as the ^{111}In-bleomycin.

The most definitive description of the pharmacodynamics of indium chloride and colloidal indium is that published by Castronovo, et al (*17*) who used the ^{114}In label. Although our kinetic data generally agree with theirs, there are some differences. In our mice, ^{111}In-chloride, pH 1.5, disappeared more slowly from the blood but, in agreement, the blood concentration had fallen to about 1%/gm or less by 48 hr. On a per-gram-tissue basis, more of our ^{111}In-chloride, pH 1.5, was found in the kidney and less in the liver. These and other data suggest that

TABLE 1. KIDNEY FUNCTION INDICES

		In mice		Extrapolated to a 1.73 m² S.A.			
	Urinary excretion (50%)	UV/B clearance (ml/min)	UV/P clearance (ml/min)	UV/B clearance (ml/min)	UV/P clearance (ml/min)	Ratio (UV/P) $\frac{C_X}{C_{IN}}$	TR (%)
^{14}C-inulin (control)	11 min	0.4910	0.2730	101.2	56.1	1.00	0.0
^{111}In-chloride (pH 1.5)	21 days	0.0022	0.0012	0.45	0.25	0.0045	—99.6
^{111}In-bleomycin (pH 6.5)	22 min	0.2535	0.1408	52.4	29.4	0.52	—48.0
^{111}In-chloride (pH 6.5)	51 days*	Not cleared					

* Extrapolated.

C_X is renal clearance of substance under investigation, C_{IN} is renal clearance of inulin (GFR), and TR, (tubular reabsorption) ratios of $C_{IN} - C_X \times 100$.

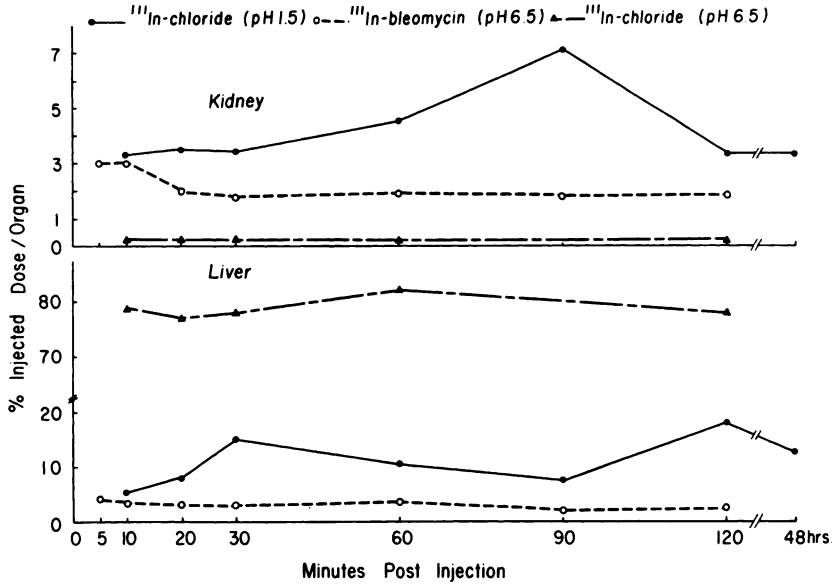

FIG. 4. Average percent injected dose per organ in mouse kidney and liver for varying time periods up to 48 hr after injection of ^{111}In-chloride, pH 1.5, ^{111}In-bleomycin, and ^{111}In-colloid, pH 6.5.

TABLE 2. WHOLE-BODY RETENTION STUDY IN MICE: PERCENTAGE OF INJECTED DOSE

	Time after single intravenous injection											
	1 hr	2 hr	4 hr	1 day	2 days	3 days	5 days	6 days	9 days	14 days	23 days	35 days
^{111}In-bleomycin (pH 6.5)	31.2	21.7	—	13.9	13.2	—	11.2	—	10.1	9.0	8.1	—
^{111}In-chloride (pH 1.5)	92.3	91.7	90.6	81.7	76.4	71.9	—	66.4	—	54.5	45.6	34.0
^{111}In-chloride (pH 6.5)	99.4	99.0	98.6	98.4	97.6	94.4	—	90.5	85.5	80.5	72.1	—

^{111}In-chloride may be more ionic at pH 1.5 than that at pH 3.0.

With minor variations, there is good agreement between our animal data and those reported by Robbins, et al (*5*) and by Thakur, et al (*6*).

There are several references reporting on the pharmacodynamics of ^{111}In-bleomycin in normal and tumor-bearing mice and rats (*1,5–7,18*). Again, there is generally acceptable agreement between our values and those reported by others.

Tumor studies. In this mouse-tumor biologic system, the brain-tumor uptake of ^{111}In-chloride, pH 1.5, was from 3 to 18 times greater than that of ^{111}In-bleomycin during the time intervals studied. It is the greatest brain-tumor uptake of any of the radiopharmaceuticals thus far studied. The affinity of this mouse-brain sarcoma for ^{111}In-chloride may be distinctive because other mouse and rat tumor systems have not shown this phenomenon with ^{111}In-citrate (*2*). As with ^{67}Ga-citrate, -lactate, and -chloride (*11*), ^{111}In-chloride also showed a high skin uptake which increased with time. Brain and muscle concentrations of all three labeled compounds remained quite constant.

Tumor-to-brain ratios for the chloride and bleomycin remained good through 48 hr, the chloride reaching a maximum at 4 hr and the bleomycin at 20 min. Tumor-to-skin and tumor-to-muscle ratios remained quite constant. The tumor-to-blood ratios for both compounds remained low through the first 6 hr but improved considerably at 24 and 48 hr. The bleomycin data are in agreement with the findings of Merrick, et al (*1*) who noted maximum tumor levels within 15 min of injection but best scans at 48–72 hr.

Kidney and liver studies. It has been proposed that, immediately on injection, ^{111}In-chloride binds firmly to transferrin in the blood stream, and slow renal clearance and translocation to the kidney, liver, spleen, and marrow takes place (*17*). Indium-111-bleomycin has been shown to be stable following 3 hr in vitro incubation with human serum albumin (*18*). However, it is enzymatically inactivated in vivo. The ^{111}In activity associated with the bleomycin becomes bound to transferrin as does the chloride within 4 to 6 hr (*6*). Another group of investigators has suggested that complete separation of the ^{111}In from the bleomycin has occurred by 48 hr (*5*).

Zeidler and coworkers (*25*) comment on the similarity of injected ^{111}In to iodinated albumin.

Two mechanisms have been suggested (*6*) to account for the deposition of the activity from the bleomycin in the liver and kidney: (A) ^{111}In may be released within the liver and kidney by enzymatic processes and remain there; (B) ^{111}In may be released from its transferrin complex in the blood stream or other organ and then be carried to the kidney and liver. The almost constant concentration of activity from the ^{111}In-bleomycin found in the kidney and liver during the first 2 hr after injection compared with the varying concentrations found from the injection of ^{111}In-chloride tends to favor the first proposed mechanism. In this respect, data generated from the administration of ^{111}In-bleomycin are somewhat similar to those found for ^{67}Ga-citrate and -lactate (*11*).

The renal blood and plasma clearance values for ^{111}In-chloride are the slowest of any radiopharmaceutical investigated in this biologic system thus far (*26*). The finding that the maximum mouse tumor uptake of ^{111}In-chloride is also the greatest of any radiopharmaceutical studied supports our previous findings with other nonspecific tracers that tumor uptake is usually inversely proportional to renal clearance (*11*).

Whole-body retention studies in mice suggest that ^{111}In activity separates from the bleomycin and then binds to plasma protein in a matter of hours. The amount of activity excreted between 24 hr and 23 days, divided by the amount retained at 24 hr, is almost the same for ^{111}In-bleomycin (42%) and ^{111}In-chloride (44%). This indicates approximately the same rate of excretion for both compounds after 24 hr. The similarity of tumor-to-tissue ratios at 24 and 48 hr for both ^{111}In-bleomycin and ^{111}In-chloride also would indicate separation of activity from the bleomycin and subsequent translocation to protein similar to ^{111}In-chloride.

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Dynamic Studies with ^{99m}Tc-HEDP in Normal Subjects and in Patients with Bone Tumors. Accepted 4/30/75.
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Design of a New Liquid Scintillation Vial (Letter to the Editor). Accepted 4/30/75.
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Scintigraphic Appearance of Bilateral Frontal Epidural Hematoma (Case Report). Accepted 4/30/75.
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Inconsistent Images of Thyroid Nodule Scintigrams Made with Iodine and Pertechnetate (Letter to the Editor). Accepted 4/30/75.
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Time-Dependent Image Quality Using ^{99m}Tc-Pyrophosphate. Accepted 5/1/75.
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