Dosimetric Evaluation of Copper-64 in Copper-67-2IT-BAT-Lym-1 for Radioimmunotherapy

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Copper-67 (^{67}Cu) is an attractive radionuclide for radioimmunotherapy because of its favorable physical and biologic characteristics. Current supplies of ^{67}Cu, however, contain as much as 60% of ^{64}Cu at the time of delivery. Scatter photons from ^{64}Cu enter the ^{67}Cu energy window, affecting image resolution and counting accuracy. The radiation dose to tissue is also altered. **Methods:** A line source and a small vial source of ^{67}Cu containing varying amounts of ^{64}Cu were used to evaluate the impact of ^{64}Cu on image resolution and activity quantitation, respectively. Identical pharmacokinetics for ^{67}Cu and ^{64}Cu was assumed, and the radiation dosimetry of ^{64}Cu was assessed using quantitative imaging data for ^{67}Cu because the amount of ^{64}Cu could be calculated for any time after ^{67}Cu production. MIRD formalism was used to estimate the therapeutic index, defined as the ratio of radiation dose to tumor divided by the radiation dose to bone marrow. **Results:** As the amount of ^{64}Cu increased, the full width at tenth maximum of the line spread function increased, although there was no significant change in full width at half maximum. The number of scatter counts from ^{64}Cu increased as the amount of ^{64}Cu or the size of the source region of interest increased. When ^{64}Cu was 25% of the total activity, less than 10% of the total ^{67}Cu photopeak counts detected with a scintillation camera were attributable to ^{64}Cu. Although the tumor radiation dose per unit of activity (cGy/GBq) from ^{67}Cu was five times greater than that from ^{64}Cu, the marrow dose (cGy/GBq) from ^{67}Cu was only three times greater than that from ^{64}Cu. Therefore, the therapeutic index was diminished by the presence of ^{64}Cu. When ^{64}Cu radioimpurity was less than 25% of the total activity, there was less than a 10% decrease in the therapeutic index. **Conclusion:** The shorter physical half-life of ^{64}Cu relative to that of ^{67}Cu and slower uptake and longer retention of antibody by tumor than by marrow result in a lower therapeutic index for ^{64}Cu. The 25% radioimpurity of ^{64}Cu causes less than 10% deviation in activity quantitation and diminution in the therapeutic index. The change in therapeutic index is predictable over time and can be used to determine the optimal time for radiopharmaceutical administration.

Key Words: radiation dosimetry; radioimmunotherapy; copper-67; copper-64

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Copper-67 is a promising radionuclide for radioimmunotherapy (RIT). It releases beta particles with mean energies and abundances of 121 keV (56%), 154 keV (23%) and 189 keV (20%) that are suitable for therapeutic purposes and photons with energies and abundances of 91 keV (7%), 93 keV (16%) and 184 keV (49%) that are suitable for imaging purposes (*1–4*). The relatively low-energy photon emissions reduce the radiation safety considerations associated with the more energetic photons from ^{131}I. Importantly, preclinical and clinical studies have confirmed that ^{67}Cu is retained in tumors in greater amounts and for a longer time than ^{131}I, thus delivering greater radiation doses to tumors (*5–8*).

Currently available, ^{67}Cu contains ^{64}Cu radioimpurity as a coproduct (*9*). Because the half-life of ^{64}Cu (12.7 hr) is much shorter than that of ^{67}Cu (61.9 hr), the ratio of ^{64}Cu to ^{67}Cu decreases after the end of bombardment (EOB). The average amount of ^{64}Cu as a percent of total activity in the supply at the time of delivery, typically 36–48 hr after EOB, is 43% (range 35%–61%).

In addition to photons (1346 keV [0.5%]), ^{64}Cu emits positrons that generate annihilation photons (511 keV [36%]) (*1*). These high-energy photons readily penetrate the septum of a gamma-camera collimator and can thus alter quantitation of the intended ^{67}Cu radiopharmaceutical. Copper-64 also affects radiation dosimetry. The present study investigates the impact of ^{64}Cu on quantitative imaging and radiation dosimetry for the ^{67}Cu-2IT-BAT-Lym-1 radiopharmaceutical. The radiopharmaceutical was prepared by conjugating the bifunctional chelate 6-[*p*-(bromoacetamido)benzyl]- 1,4,8,11- tetra-azacyclotetradecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid (BAT) to murine anti-lymphoma IgG_{2a} antibody (Lym-1) by 2-iminothiolane (2IT) (*10*).

MATERIALS AND METHODS

Quantitative Imaging

Images of conjugate views were acquired with a Siemens Bodyscan dual-head camera (Hoffman Estates, IL) equipped with a medium-energy collimator. The energy windows were centered on the primary photon emission energies of ^{67}Cu (93 and 184 keV) and were 20% in width. Images were obtained in a 128 × 128 word matrix and were terminated at either 2 million counts or 600 sec, whichever occurred first.

Effect of Copper-64 on Copper-67 Image Resolution. A line source made of fine plastic tubing (1-mm inner diameter) was used to measure the resolution of the camera system. Images of the line source containing different amounts of ^{64}Cu relative to ^{67}Cu were acquired using ^{67}Cu energy windows. Images were obtained for the line source at 10 cm from the detector in Lucite scatter medium (0.944 g/cc). The amount of ^{64}Cu in the line source varied from 50% to less than 0.2% of total activity. The full width half maximum (FWHM) and full width tenth maximum (FWTM) were determined for different amounts of ^{64}Cu.

Effect of Copper-64 on Source Counts for Copper-67 Imaging. A vial source (2.5 × 5.0 cm) of ^{67}Cu (9.83 MBq) containing ^{64}Cu (9.83 MBq) was used to assess the number of ^{64}Cu counts recorded in ^{67}Cu energy windows. Sequential images of the source 10 cm from the detector in air and in Lucite were acquired as the percentage of ^{64}Cu changed from 50% to less than 0.2% of total activity as a result of decay. Two regions of interest (ROIs) were selected to examine the effect of ROI size on quantitation of ^{67}Cu. One ROI was equal to the source size (2.5 × 5 cm), and the other was 10 times greater in area (8.0 × 15.8 cm).

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Radiation Dosimetry

In the present analysis, pharmacokinetic data from four patients were evaluated for 12 doses of ^{67}Cu-2IT-BAT-Lym-1 that ranged from 0.48 to 5.25 GBq (13–142 mCi). The maximum amount of ^{64}Cu at injection time was 20%, while the average was 12%. Methods for obtaining the pharmacokinetic data have been previously described (*6,11,12*) and validated in an abdominal phantom for ^{67}Cu (Shen S, et al., *unpublished data*). Briefly, planar images of conjugate views were acquired immediately, 4 hr and daily up to 10 days after administration of ^{67}Cu-2IT-BAT-Lym-1. The amount of activity in organs and tumors was determined using geometric mean or effective point source methods, depending on whether the source object could be identified on both conjugate views (*13*). Counting coincidence at high counting rates was corrected using a reference source in the field of view of the patient images (*14*). Images were accompanied by collection of blood samples. Cumulated activity in tissues was obtained by fitting pharmacokinetic data to either a monoexponential, biexponential or cubic spline function (*12*).

Because ^{64}Cu and ^{67}Cu radionuclides are chemically identical, biodistribution and metabolism of these two isotopes were assumed to be the same, and pharmacokinetic data for ^{64}Cu-2IT-BAT-Lym-1 were inferred from the pharmacokinetic data for ^{67}Cu-2IT-BAT-Lym-1.

Radiation doses to the organs and tumors were calculated using MIRD formalism (*15*), according to the following equation:

$$D_{total} = D_{self} + D_{RB}, \quad \text{Eq. 1}$$

where D_{total} is the total radiation dose to the target tumor or organ, D_{self} is the radiation dose to the target from activity in the target, and D_{RB} is the radiation dose to the target from activity in the rest of the body.

Radiation dose to tumors and bone marrow were of particular interest because this information relates to the therapeutic efficacy and dose-limiting toxicity of the radiopharmaceutical. Because the amount of radiolabeled Lym-1 in the tumor or bone marrow is small relative to that in the rest of the body, Equation 1 can be simplified to

$$D_{total} = D_{self,np} + D_{TB,p}, \quad \text{Eq. 2}$$

where $D_{self,np}$ is the dose of nonpenetrating radiation to the target from activity in the target, and $D_{TB,p}$ is the dose of penetrating radiation to the target from activity in total body. The S value for tumors from nonpenetrating radiation to self is simply total mean nonpenetrating energy emitted per transition divided by tumor mass (*1,15*). Uniform radionuclide distribution in the body was assumed for the calculation of $D_{TB,p}$ to tumors. The S values for penetrating ^{67}Cu or ^{64}Cu emissions were obtained by subtracting the S values for nonpenetrating emissions from that for penetrating and nonpenetrating emissions using MIRD data (*1,16*). The size of palpable tumors was determined using a caliper, and that of nonpalpable tumors was determined using computed tomographic or magnetic resonance images (*17*). To assess the relative radiation dose rates from ^{67}Cu and ^{64}Cu-2IT-BAT-Lym-1 to tumors, the dose rates were determined using the pharmacokinetics obtained for a 10-g tumor in a patient and the S value previously described.

The methods for calculating the $D_{self,np}$ and $D_{TB,p}$ to bone marrow have been described previously (*18*). The calculation of $D_{self,np}$ was based on the nonpenetrating ^{67}Cu or ^{64}Cu emissions in the blood, assuming that the specific activity of the blood in the marrow was 25% of that of circulating blood (*19,20*). A uniform distribution of radionuclide in the body was assumed for the calculation of $D_{TB,p}$ to the bone marrow, and the S values for penetrating emissions were obtained by subtracting the S values for nonpenetrating emissions from those for penetrating and nonpenetrating emissions using MIRD data (*1,16,18*). The dose equation for bone marrow is as follows:

$$D_{total} = 0.25\ \tilde{A}_{blood,ml}\Delta_{np} + \tilde{A}_{TB}S_{TB\rightarrow RM,p}, \quad \text{Eq. 3}$$

where D_{total} is the total radiation dose to the red marrow, $\tilde{A}_{blood,ml}$ is the cumulated activity in 1 ml blood, Δ_{np} is the mean energy emitted per nuclear transition for nonpenetrating radiations from ^{67}Cu or ^{64}Cu, $\tilde{A}_{TB}$ is the cumulated activity in the total body, and $S_{TB\rightarrow RM,p}$ is the S value for penetrating ^{67}Cu or ^{64}Cu emissions from body to red marrow.

TABLE 1
Characteristics of Line Spread Function with 10 cm of Lucite Scatter Medium Relative to the Percentage of Copper-64 as a Function of Total Activity

^{64}Cu (%)	FWHM (mm)	FWTM (mm)
50	14.3	36.6
45	14.3	33.1
30	14.2	30.1
22	14.2	27.8
2	14.2	23.2
<0.2	14.2	23.0

Therapeutic Index

The presence of ^{64}Cu in the ^{67}Cu radiopharmaceutical resulted in an additional radiation dose to the tumors and normal tissues. The advantage or disadvantage of ^{64}Cu was evaluated using the following therapeutic index:

$$\text{Therapeutic index} = \frac{\text{Radiation dose to tumor}}{\text{Radiation dose to marrow}}. \quad \text{Eq. 4}$$

The methods for calculating radiation dose to tumor and bone marrow are shown in Equations 2 and 3. Radiation dose to bone marrow was considered here because this is the dose-limiting organ for RIT. Here, MIRD formalism was used for radiation dose estimates; therefore, the therapeutic index does not take into account the microscopic dose nonuniformity in normal and tumor tissues.

The therapeutic index was calculated using the average radiation doses to the tumors and the marrow obtained for each of the 12 patients in this investigation, and these results were averaged.

RESULTS

Quantitative Imaging

Effect of Copper-64 on Copper-67 Image Resolution. The presence of ^{64}Cu, especially when greater than 25% of total activity, resulted in a deterioration of image quality, as reflected by the line spread function (Table 1). At 50% ^{64}Cu, the FWTM was 60% greater than when ^{64}Cu was less than 0.2%, although the FWHM was virtually unchanged.

Effect of Copper-64 on Source Counts for Copper-67 Imaging. Additional counts from ^{64}Cu in the source ROI were observed with and without scatter (Table 2). The contribution of ^{64}Cu counts was dependent on the amount of ^{64}Cu and the size of the source ROI. Absolute additional error to activity quantitation was significantly less for the ROI of actual size (7% at the 50% level of ^{64}Cu impurity) compared with 10 times the actual area (30% at the 50% level of ^{64}Cu).

At the greatest amount of ^{64}Cu (20%) given to our patients, the estimated degradation in FWTM was less than 20%, and the additional quantitative error in the large source ROI was less than 10% (Tables 1 and 2).

TABLE 2
Effect of Copper-64 Impurity on Counts in Copper-67 Photopeak Windows in Absence and Presence of Scattering Medium

^{64}Cu source* [MBq (% total activity)]	% Counts in source ROI†			
	ROI of source area		ROI 10 × source area	
	Air	Scatter	Air	Scatter
8.14 (50)	107	106	134	131
6.84 (45)	106	105	128	124
3.42 (30)	102	103	114	112
2.36 (22)	103	102	111	110
0.15 (2)	101	100	100	101
0.01(<0.2)	100	100	100	100

*Ten-milliliter source that initially contained 8.14 MBq ^{67}Cu and 8.14 MBq ^{64}Cu.

†Counts were normalized to the counts when ^{64}Cu was less than 0.2% of total activity.

Radiation Dosimetry

The average biologic clearance half-life was 11.5 ± 2.2 (n = 12) days for whole body, 0.18 ± 0.06 and −22.2 ± 11.1 (n = 12) days for fast and slow phases of blood, respectively, and 8.4 ± 4.2 (n = 53) days for tumors for copper-labeled 2IT-BAT-Lym-1. The radiation doses (cGy/GBq) to body, blood, tumors and bone marrow from ^{67}Cu were substantially greater than those from ^{64}Cu (Fig. 1), as were the peak dose rates to tumors (Fig. 2). The differences in radiation dose and dose rate reflected differences in emission energies and physical half-lives. For ^{67}Cu-2IT-BAT-Lym-1, the average radiation dose to the marrow was 4.1 ± 1.9 cGy/GBq (0.15 ± 0.07 rad/mCi) and 3.0 ± 0.9 cGy/GBq (0.11 ± 0.03 rad/mCi) from blood and whole body, respectively. For ^{64}Cu-2IT-BAT-Lym-1, the average marrow dose was 1.3 ± 0.7 cGy/GBq (0.049 ± 0.026 rad/mCi) from blood and 1.1 ± 0.3 cGy/GBq (0.04 ± 0.01 rad/mCi) from whole body. Using these values, the radiation dose to marrow resulting from 4.0 GBq of ^{67}Cu and 1.0 GBq of ^{64}Cu is equivalent to that from the administration of 4.3 GBq of pure ^{67}Cu.

Therapeutic Index

The mean therapeutic index was greater for ^{67}Cu-2IT-BAT-Lym-1 (22.7 ± 7.7) than for ^{64}Cu-2IT-BAT-Lym-1 (13.5 ± 4.6). Data for ^{67}Cu-2IT-BAT-Lym-1 indicated that the therapeutic index decreased linearly as the amount of ^{64}Cu increased (Fig. 3). The corresponding decreases in the therapeutic indices for the average and greatest amount of ^{64}Cu impurity (12% and 20%) in the patient doses were 4.9% and 8.1% from those of the pure ^{67}Cu pharmaceutical.

When the radiation doses from ^{67}Cu were compared with those from ^{64}Cu, the ^{67}Cu-to-^{64}Cu dose ratio was greatest for tumors (Fig. 4). The ^{67}Cu-to-^{64}Cu radiation dose ratio was 4.9 for tumors but 3.0 for marrow, accounting for the differences in the therapeutic indices of ^{67}Cu and ^{64}Cu.

DISCUSSION

Special attention to radioimpurities is required when new radioisotopes are introduced into clinical applications, such as RIT (*21–23*). The purpose of the present study has been to address this issue with respect to the presence of ^{64}Cu in ^{67}Cu-2IT-BAT-Lym-1. Quantitative imaging analyses, radiation dose estimates and therapeutic indices were used to evaluate the impact of ^{64}Cu on the therapeutic performance of ^{67}Cu-2IT-BAT-Lym-1.

Whereas pharmaceuticals containing long-lived radioimpurities are optimally administered as soon as received, the adverse effects of shorter-lived radioimpurities can be reduced by waiting for them to decay before administration. Because the half-life of ^{64}Cu is much shorter than that of ^{67}Cu, the contribution of ^{64}Cu to imaging and therapy diminishes with time so that, theoretically, one could allow ^{64}Cu to decay away. In practice, this may not be ideal because it increases the cost and reduces the specific activity of the ^{67}Cu radiopharmaceutical. Moreover, ^{64}Cu has been reported to be cytotoxic for tumor cells and less costly than ^{67}Cu (*24–26*). The impact of ^{64}Cu on a ^{67}Cu radiopharmaceutical is complex, and its effect on quantitative imaging and radiation dosimetry must be investigated to determine the optimal time to administer the radiopharmaceutical mixture to a patient.

Radiation dosimetry requires pharmacokinetic information for ^{67}Cu and ^{64}Cu that can be obtained by quantitative imaging. Annihilation photons, however, from ^{64}Cu penetrate the collimator septa and enter the ^{67}Cu photopeak windows by Compton scattering. The impact of ^{64}Cu on image resolution was significant for FWTM but not for FWHM when ^{64}Cu was greater than 20% of total activity (Table 1). This spreading effect, occurring mainly for FWTM, was also reflected in increased ^{64}Cu counts collected in a larger source ROI (Table 2). The ^{64}Cu counts collected in the true source ROI were similar for the source in air or scatter medium, suggesting that the scattered counts were mainly from ^{64}Cu counts penetrating the septum of the collimator. Septal penetration by high-energy photons can be reduced using a collimator with thicker septa (*27,28*). The scattered counts from ^{64}Cu can also be corrected using a restoration filter (*13,29*) or by scatter subtraction (*30,31*). Even without correction, the number of counts contributed from ^{64}Cu to the true source ROI was small (Table 2). For a larger source ROI (10 times the true area), the additional counting error was less than 10% when ^{64}Cu was less than 20%.

The therapeutic index, that is, the tumor dose relative to marrow dose, was 22.7 for ^{67}Cu-2IT-BAT-Lym-1 and 13.5 for ^{64}Cu-2IT-BAT-Lym-1 because the marrow dose (cGy/GBq) from ^{67}Cu was three times greater than that from ^{64}Cu, whereas, the tumor dose from ^{67}Cu was 4.9 times greater than that from ^{64}Cu. As a result, the therapeutic index decreased as the amount of ^{64}Cu increased (Fig. 3).

The therapeutic advantage of ^{67}Cu over ^{64}Cu in patients is

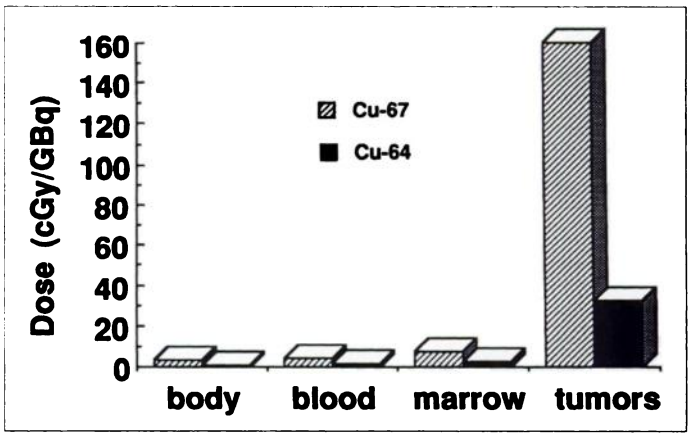

FIGURE 1. Mean radiation dose for body, blood, marrow and tumors (n = 12). The pharmacokinetics of ^{64}Cu-2IT-BAT-Lym-1 was assessed using quantitative imaging data for ^{67}Cu-2IT-BAT-Lym-1.

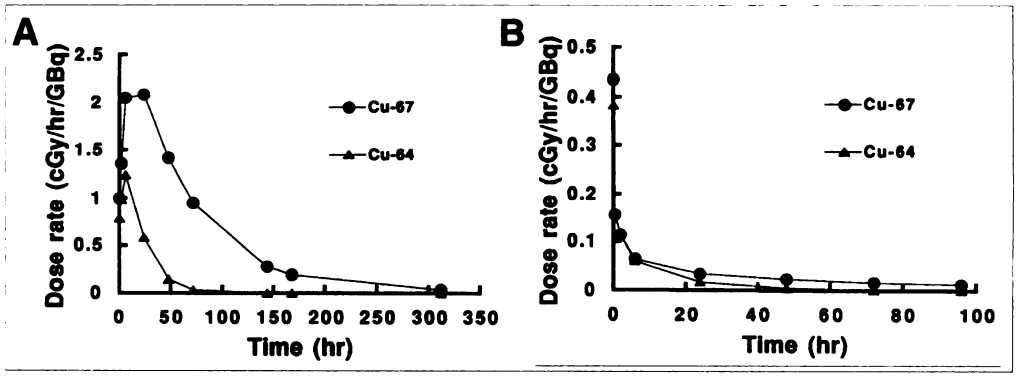

FIGURE 2. Relative radiation dose rates to (A) tumor and (B) marrow for ^{67}Cu-2IT-BAT-Lym-1 and ^{64}Cu-2IT-BAT-Lym-1. Copper-64 delivers lesser total radiation dose and dose rate to tumor (and marrow) despite the use of the same pharmacokinetics for ^{64}Cu-2IT-BAT-Lym-1 that were observed for ^{67}Cu-2IT-BAT-Lym-1 in this patient.

due to differences in their physical characteristics, tumor and marrow geometry and the pharmacokinetics of the radiopharmaceutical in these tissues. First, ^{67}Cu has greater nonpenetrating radiation and less penetrating radiation than ^{64}Cu (*1*), making the energy deposition of ^{67}Cu more favorable for small objects like tumor than ^{64}Cu. Second, the difference in uptake time for tissues affects the therapeutic index. Because of its vascularity, uptake of radiopharmaceutical by bone marrow is almost immediate (*6,7*). In contrast, tumors accumulate antibody over many hours. Copper-labeled Lym-1 required 24–72 hr to reach peak levels in the tumors. This pharmacokinetic difference, coupled with the shorter physical half-life of ^{64}Cu, results in less effective delivery of ^{64}Cu than ^{67}Cu to tumor (Fig. 2), in conformity with the results of detailed modeling (*32,33*). The resulting total radiation dose and dose rate advantage of ^{67}Cu over ^{64}Cu is not overcome by greater marrow radiation contributed by ^{67}Cu.

The results of the present work demonstrate a therapeutic advantage of ^{67}Cu over ^{64}Cu but do not imply that a longer-lived radionuclide is always better for RIT. The pharmacokinetic behavior of the antibody can be affected by the radioisotope (and radiochemistry), thereby influencing the therapeutic index. For example, although ^{67}Cu has a shorter half-life than ^{131}I, ^{67}Cu-2IT-BAT-Lym-1 delivers more radiation to tumor than ^{131}I-Lym-1 because ^{67}Cu is retained by tumor for a longer time (*6–8*). Similarly, retention by breast adenocarcinoma of ^{90}Y-Ch-L-6 is longer than that of ^{131}I-Ch-L-6, resulting in a better therapeutic index (*34*). The dosimetric advantage of ^{67}Cu over ^{64}Cu is consistent with the suggestion that longer-lived radionuclides are preferable (*32,33*) if the pharmacokinetics of the two radionuclides are similar, a circumstance that is almost certainly so for radioisotopes of the same element. However, this need not be true for radioisotopes of different elements because the effect of their physical half-lives is influenced by their biologic half-lives in tumor and bone marrow.

Apelgot et al. (*24*) and Anderson et al. (*25,26*) studied the relative lethal effects of ^{64}Cu and ^{67}Cu on mammalian cells human colon cancer cells in culture, respectively, and concluded that the intrinsic tumoricidal effectiveness of ^{64}Cu and ^{67}Cu per unit of radioactivity were roughly equal in this simple system. The differences in radiation dosimetry that we observed in patients reflect differences in the pharmacokinetics for tumor and bone marrow. The ^{67}Cu-to-^{64}Cu dose ratio is higher for tumor than for marrow because of slower uptake and longer retention of radiopharmaceutical by tumor than marrow; this accentuates the disadvantage of shorter-lived ^{64}Cu (Fig. 4).

CONCLUSION

Copper-67 has physical characteristics that are better than those of ^{64}Cu for RIT, but ^{64}Cu impurities that are less than 25% in ^{67}Cu supplies have minimal effect on the therapeutic index and on the accuracy of quantitative imaging and radiation dosimetry.

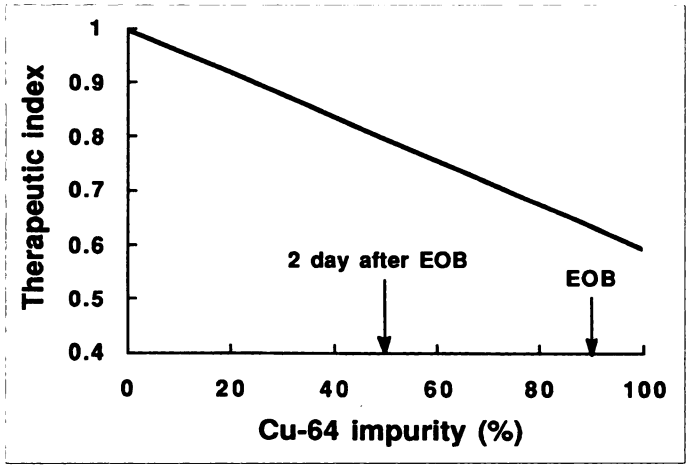

FIGURE 3. Therapeutic index (tumor radiation dose to marrow radiation dose) of various ^{64}Cu/total activity mixtures normalized to pure ^{67}Cu. Mean tumor and marrow radiation doses for ^{67}Cu-2IT-BAT-Lym-1 and ^{64}Cu-2IT-BAT-Lym-1 obtained from 12 patient studies were used to calculate the therapeutic index. The therapeutic index decreases as the amount of ^{64}Cu increases. The typical amount of ^{64}Cu in shipments is indicated at 2 days after the end of bombardment (EOB).

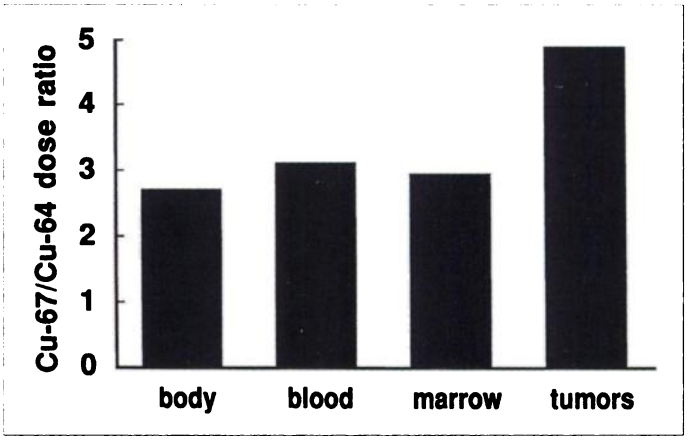

FIGURE 4. Comparison of radiation doses (cGy/GBq) from ^{67}Cu-2IT-BAT-Lym-1 and ^{64}Cu-2IT-BAT-Lym-1. The therapeutic advantage of ^{67}Cu over ^{64}Cu is evident because the dose ratio for tumor was higher than that for normal tissues.

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