DISCUSSION

For the treatment of ROD, Tsukamoto et al. (*1,2*) reported on oral 1,25-dihydroxyvitamin D_3 pulse therapy. This therapy has been widely used to treat patients with ROD. In the field of nuclear medicine, a bone scan using ^{99m}Tc-labeled phosphate has been used to diagnose ROD. Typical scintigraphy findings relate to the biological parameters of calcium and phosphate metabolism. Scintigraphy assessment was done mainly by visual interpretation, which was thought sufficient to assess the degree and the extent of renal bone disease (*7*). Kida et al. (*8*) observed that semiquantitative analysis of whole-body bone scintigraphy was useful to assess the response to 1, 25-dihydroxyvitamin D_3 treatment in ROD. Technetium-99m-pyrophosphate bone scintigraphy was also used by Hodson et al. (*9*) to assess patients with ROD. Hodson et al. (*9*) reported that this scan did not provide any therapeutically useful information that could not be obtained by biochemical and radiological studies (*9*).

Our study clearly demonstrated that ^{99m}Tc(V)-DMSA was superior to ^{99m}Tc-HMDP in evaluating the vitamin D_3 pulse therapy in ROD. Technetium-99m(V)-DMSA has been used as a tumor-seeking agent and also used in patients with primary amyloidosis, although the exact uptake mechanism remains to be discovered. Distribution of ^{99m}Tc(V)-DMSA in the cardiovascular system and kidney were frequently seen, but visualization of bones was very rare. However, in this patient diffusely increased tracer uptake was observed in the whole skeleton, especially in the skull and mandible as also seen in the bone scintigram with ^{99m}Tc-HMDP. Markedly decreased tracer uptake was seen after vitamin D_3 pulse therapy, and, at the time of recurrence, gradually increased tracer uptake was noted again, which reflected clinical and laboratory findings. Our results indicate that a ^{99m}Tc(V)-DMSA whole-body scan is very sensitive in assessing the response of ROD to vitamin D_3 pulse therapy.

The mechanism of ^{99m}Tc(V)-DMSA accumulation has yet to be studied, but it has been shown that TcO_4^{3-} core exhibits characteristics comparable to those of PO_4^{3-} (*3,10,11*). The effects of pulse therapy are attained by direct action of 1,25-dihydroxyvitamin D_3 on the parathyroid gland and not by the resulting elevation of serum calcium levels (*1*).

CONCLUSION

Further studies are necessary to define the mechanism of ^{99m}Tc(V)-DMSA bone uptake, but it is very useful as a radiotracer for the diagnosis and follow-up in patients with ROD.

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Effect of Inhaled Surfactant on Pulmonary Deposition and Clearance of Technetium-99m-DTPA Radioaerosol

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To establish the effect of an aerosolized synthetic surfactant (Exosurf) on pulmonary ^{99m}Tc-diethylenetriamine pentaacetic acid (DTPA) aerosol deposition and clearance, radioaerosol studies were performed at varying times and under varying conditions after surfactant inhalation in canine lungs. **Methods:** Twenty-three dogs had a baseline ^{99m}Tc-DTPA study; 2 days later the study was repeated after inhalation of a 1.5-ml/kg dose of Exosurf aerosolized by an ultrasonic nebulizer. The clearance half-time ($T_{1/2}$) of ^{99m}Tc-DTPA from each lung was measured at different times (from 10 min to 3 hr) after Exosurf inhalation. For comparison, five animals had a ^{99m}Tc-DTPA study 10 min after inhalation of the same dose of saline as Exosurf. An additional five animals inhaled a ^{99m}Tc-DTPA–Exosurf mixture to investigate the distribution of Exosurf. **Results:** Technetium-99m-DTPA distributed uniformly without significant changes in penetration indexes before and after inhalation of Exosurf and the ^{99m}Tc-DTPA–Exosurf mixture. After Exosurf inhalation, ^{99m}Tc-DTPA clearance at 10 min ($T_{1/2}$; 35.6 ± 8.7 min; n = 6) and 40 min (29.4 ± 6.3 min; n = 4) was significantly prolonged compared with the matched baseline values (24.7 ± 6.4 min, $p < 0.0001$; and 21.7 ± 8.9 min, $p = 0.01$, respectively). However, later clearance times were not prolonged. By contrast, after saline inhalation, ^{99m}Tc-DTPA distributed inhomogeneously, and clearance times ($T_{1/2}$) were not altered from the matched baseline values. **Conclusion:** Aerosolized Exosurf distributes homogeneously in the lungs. Exosurf initially retards ^{99m}Tc-DTPA aerosol clearance, but ^{99m}Tc-DTPA transalveolar clearance returns to baseline rates within 1–2 hr. Technetium-99m-DTPA aerosol clearance measurements can be used to monitor the effect of inhaled Exosurf on pulmonary epithelial integrity.

Key Words: technetium-99-diethylenetriamine pentaacetic acid; surfactant; pulmonary aerosol scintigraphy; alveolar permeability

J Nucl Med 1998;39:543–547

Received Jan. 16, 1997; revision accepted Jun. 12, 1997.

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Alveolar surfactant, which forms a monomolecular film on the luminal surface of the alveoli, is essential for maintaining effective alveolar ventilation and is important for alveolar liquid balance and regulation of alveolar epithelial permeability to solutes (*1,2*). Surfactant dysfunction and deficiency are responsible for increases in epithelial permeability and resultant pulmonary edema in patients with adult respiratory distress syndrome (ARDS) and neonatal respiratory distress syndrome (NRDS) (*3–5*). In these patients, surfactant replacement therapy seems to help prevent or improve pulmonary epithelial or vascular injuries and edema (*6,7*). In the past, tracheal instillation of a surfactant has been used for therapy. However, this technique was not ideal because of complexities in patient manipulation, nonuniform distribution of surfactant in the lung and undesirable side effects attributable to a deposition of a large volume of the surfactant suspension fluid over a short period (*8,9*). Currently, aerosolized surfactant is proposed to solve these problems and is being evaluated in animal models and humans with various acute pulmonary injuries including ARDS and NRDS (*10–12*). Results from preliminary studies suggest that inhalation of aerosolized surfactant improves lung function and may be more efficacious than tracheal surfactant instillation.

To better understand changes in the alveolar epithelium that occur with aerosolized surfactant therapy, data on surfactant-induced changes in normal alveolar epithelial integrity are important. No studies of this type are yet available, but pulmonary clearance rates of aerosolized ^{99m}Tc-labeled diethylenetriamine pentaacetic acid (DTPA) provide a sensitive index to evaluate changes in alveolar epithelial permeability to small solutes. This study thus was designed to investigate the effects of aerosolized synthetic surfactant (Exosurf; Burroughs Wellcome Co, Research Triangle Park, NC) on ^{99m}Tc-DTPA aerosol deposition and clearance in canine lungs.

MATERIALS AND METHODS

Animal Models

Twenty-three mongrel dogs weighing 17.2–23.5 kg each (mean 19.8 ± 1.6 kg) were anesthetized with an intravenous administration of 30 mg/kg sodium pentobarbital. The animals were placed in the supine position, intubated using a cuffed endotracheal tube and connected to a volume-cycled piston ventilator (Harvard Instrument Co., Cambridge, MA). The respiratory rate was set at 15/min, with a tidal volume of 15 ml/kg (258–352 ml). Small supplementary doses of sodium pentobarbital (the total dose ranged from 3.0 to 6.8 mg/kg) were intermittently given during the course of the experiment as needed to maintain adequate levels of sedation.

Each of the 23 animals initially had a baseline ^{99m}Tc-DTPA aerosol clearance study. To assess the reproducibility of ^{99m}Tc-DTPA clearance rates, we repeated this study 2 days apart in each of eight of the 23 animals using exactly the same techniques. All of the 23 animals, including these eight animals, then had a ^{99m}Tc-DTPA clearance study after inhaling Exosurf. This study was performed 2 days after the baseline ^{99m}Tc-DTPA study in each animal (the above eight animals also had this study 2 days after the second baseline study). This post-Exosurf ^{99m}Tc-DTPA study was performed at different times (six animals at 10 min, four at 40 min, five at 1 hr, four at 2 hr and four at 3 hr) after the inhalation of an aerosolized suspension of Exosurf (1.5 ml/kg), which was composed of 85% dipalmityl-phosphatidyl-choline, 9% hexadecanol and 6% tyloxapol (*10–12*). A smaller amount of Exosurf than the standard dose for tracheal instillation (2.5–5.0 ml/kg) was administered in this study because other recent studies have shown that aerosolized surfactant is effective at lower doses than tracheally instillated surfactant (*7,8*). For comparison, five of the 23 animals later had a ^{99m}Tc-DTPA study 10 min after inhalating the same dose of aerosolized 0.9% saline solution as Exosurf. This saline inhalation study was performed 3 days after the Exosurf inhalation study. All 23 animals had a baseline chest radiograph and, for comparison, a repeat radiograph after completion of the experiment. These experiments were approved by the institutional animal care committee.

An ultrasonic nebulizer (Omron NE-U12, Tokyo, Japan) was used in these studies to deliver the Exosurf. This nebulizer consists of a 50-ml canister, which was warmed to 37°C operating temperature. This system can generate continuously a heterodisperse aerosol less than 2 μ in mean median aerodynamic diameter. The same dose of saline solution as Exosurf also was delivered using this system. Aerosolized Exosurf and saline were administered to the ventilated animals through the ventilated circuit. Because the aerosolization efficiency of this nebulizer system was changed depending on the fluid properties, such as a viscosity, it took approximately 80 min to complete aerosolization of the total dose of Exosurf (mean = 29.7 ± 2.4 ml for each dog) and approximately 20 min for saline. Technetium-99m-DTPA (740 MBq, 20 mCi) was aerosolized with 6 liters/min compressed air using a commercially available air jet nebulizer (Aerotech 1 aerosol unit, CA-1312, Bedford, MA) that generates submicronic polydisperse radioaerosols.

Scintigraphic Techniques

Intubated animals were positioned supine over a Picker 4/11 gamma camera (Picker, Bedford, OH) with a low-energy, all-purpose collimator. The camera was interfaced to a data storage and analysis computer system (Gamma-600, Macintosh PC). Technetium-99m-DTPA radioaerosol was delivered to the ventilated animals through the ventilation circuit under the same constant ventilation conditions as described earlier. The radioaerosol was administered until a count rate of more than 280/cps over lung fields was obtained (usually for 4–5 min). The clearance evaluation was started immediately after disconnecting the radioaerosol unit. Sequential posterior views of the lung images were obtained using a 64 × 64 matrix at 15-sec intervals for 30 min. To avoid changes in ^{99m}Tc-DTPA clearance in response to changes in the ventilation pattern (*13,14*), we continued the mechanical ventilation conditions just described throughout the collection of the clearance data. At the end of this time, a 100,000-count digital 128 × 128 radioaerosol images (posterior, both right and left posterior obliques and anterior) were acquired. To investigate the distribution of aerosolized Exosurf in the lungs, five of the 23 animals inhaled an aerosolized ^{99m}Tc-DTPA–Exosurf mixture. This was done 3 days after a post-Exosurf study in each dog. Approximately 10 min before the inhalation, 740 MBq (20 mCi) ^{99m}Tc-DTPA (volume < 1 ml) was added to 5 ml Exosurf in the ultrasonic nebulizer canister. The aerosolized mixture was delivered to the animals in the same way as in the ^{99m}Tc-DTPA aerosol study, and digital lung images were acquired as described earlier.

Data Analysis

To determine the borders of each lung, a 20% isocontour line of the maximum count in either lung field was traced by computer on the posterior lung images. Time–activity curves describing ^{99m}Tc-DTPA clearance from the lungs then were obtained from regions of interest (ROIs) that were placed over the peripheral one-third of each lung (Fig. 1). This was done to obtain as pure an alveolar ROI (i.e., alveoli only) as possible. After the correction for physical decay of ^{99m}Tc and for radioactivity in the upper chest wall (Fig. 1), the logarithmic regression line of the decreased radioactivity as a function of time was fit by the method of least squares to the experimental data from 1 to 30 min, and the clearance half-time

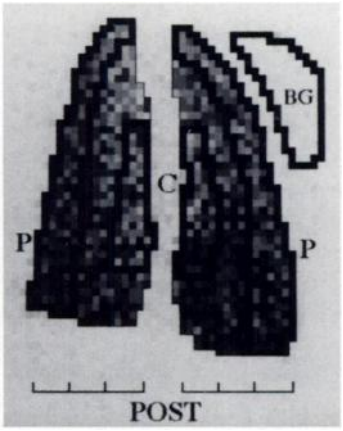

FIGURE 1. ROIs used to quantitate the ^{99m}Tc-DTPA radioaerosol study. P = peripheral ROI of each lung; C = central ROI corresponding to the inner third of the lung; BG = background area placed over the upper chest wall. The background correction formula is: Corrected mean counts/pixel in the ROIs = Original mean counts/pixel in the ROIs − the mean counts/pixel in the background area.

($T_{1/2}$) in minutes of the slope of the regression line was determined. The correlation coefficient for the fit always exceeded 0.900 (average 0.948 ± 0.025).

To quantify the distribution of ^{99m}Tc-DTPA aerosol in the lungs, the penetration index (PI), defined as the ratio of the mean activity per pixel of the peripheral one-third of the lung to that of the central one-third, was calculated for each initial 15-sec image (*15,16*). A central ROI was inscribed bilaterally in the perihilar region that covered approximately the central third of the lung, and counts in this region were compared with counts from the previously described ROI over the periphery of each lung.

Statistical Analysis

The $T_{1/2}$ and PI values are expressed as the mean ± s.d. All statistical analyses were performed using a paired t-test. Significance was set at the 0.05 level.

RESULTS

Technetium-99m-DTPA Aerosol Study

Technetium-99m-DTPA aerosol distributed uniformly throughout the lungs in all 23 animals before and after Exosurf inhalation, without significant changes in the PI (Fig. 2, Table 1). No central hyperdeposition of radioactivity was observed at the end of the endotracheal tube or in the central airways at the beginning or at the end of the scanning procedures. No significant changes were noted in the chest radiographs of any animals after Exosurf inhalation.

In the baseline ^{99m}Tc-DTPA study before Exosurf inhalation (n = 23), the mean $T_{1/2}$ of ^{99m}Tc-DTPA clearance was 26.7 ± 6.5 min. No significant difference was noted in $T_{1/2}$ between the right and left lungs (27.2 ± 6.3 min versus 26.3 ± 6.7 min, ns). The repeated baseline clearance half-times in the same eight animals demonstrated good reproducibility (27.3 ± 6.7 min versus 24.4 ± 7.3 min, ns). These results in the control dogs were consistent with those in a previous study (*17*).

The effects of Exosurf on the ^{99m}Tc-DTPA clearance times and PIs are summarized in Table 2. Technetium-99m-DTPA clearances ($T_{1/2}$) at 10 and 40 min after Exosurf inhalation were significantly prolonged compared with the matched baseline values. However, the clearances at 1 hr and beyond did not show any significant prolongation of ^{99m}Tc-DTPA clearance. As stated earlier, the PIs at these various data collection points remained similar.

After inhalation of the same dose of saline solution as

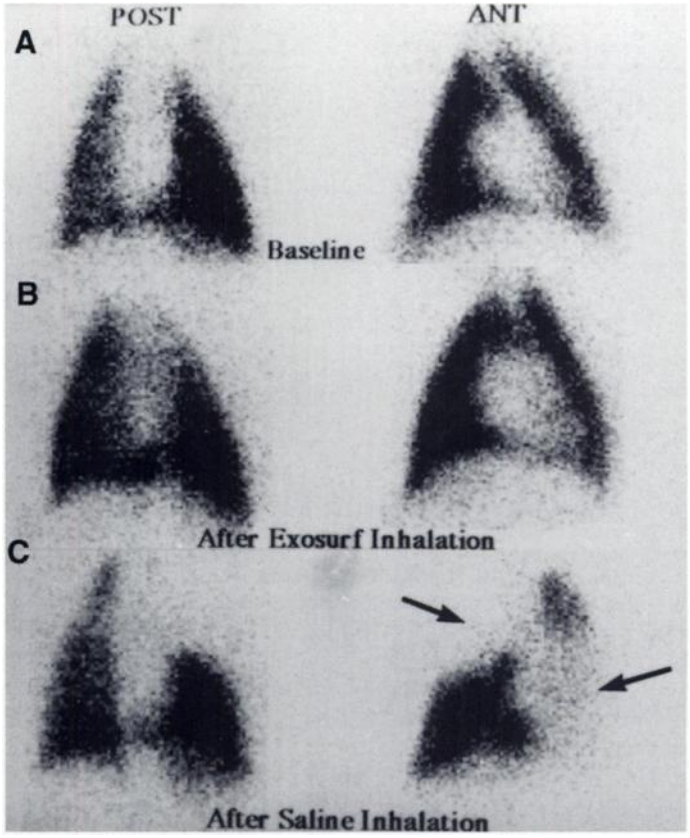

FIGURE 2. Technetium-99m-DTPA images acquired after three independent ^{99m}Tc-DTPA inhalations in the same animal. In (A) the baseline study and (B) after Exosurf inhalation, the radioaerosol distributes uniformly. After (C) saline inhalation it distributes heterogeneously with multiple deposition defects (arrows).

Exosurf, ^{99m}Tc-DTPA aerosol distributed inhomogeneously in five animals, with deposition defects, especially in the upper lobes (Fig. 2). The PIs were significantly lower than the matched baseline (Table 1). There also were marked variations in $T_{1/2}$ between the lungs in each animal (range 10.1–47.1 min). The overall ^{99m}Tc-DTPA clearance, however, was not significantly different from the matched baseline value (30.8 ± 9.8 min versus 26.7 ± 2.7 min, ns). Inhalation of an aerosolized ^{99m}Tc-DTPA–Exosurf mixture showed a homogeneous distribution in five animals, without a significant change in the PIs compared with the matched baseline value (Table 1).

DISCUSSION

This study clarified the time course of the effect of aerosolized surfactant (Exosurf) on ^{99m}Tc-DTPA deposition and clearance. The initial retardation of the clearance within 40 min after the administration provides evidence that inhaled Exosurf is temporarily a rate-limiting factor for the epithelial transfer of

TABLE 1
Penetration Index Before and After Inhalation of Exosurf, Saline and Technetium-99m-DTPA–Exosurf Mixture

Condition	Penetration index (%)		
	Baseline	After inhalation	p
Exosurf (n = 23)	105.4 ± 12.2	106.6 ± 16.3	ns
Saline (n = 5)	120.5 ± 13.2	99.2 ± 16.1	0.013
^{99m}Tc-DTPA–Exosurf mixture (n = 5)	112.9 ± 15.3	107.1 ± 11.8	ns

The data are expressed as mean ± s.d., n = 4–6 animals per group.

TABLE 2
Summary of Effects of Exosurf on Clearance Time ($T_{1/2}$) and Penetration Index of Technetium-99m-DTPA Aerosol

Time after Exosurf inhalation	Clearance time ($T_{1/2}$: min)			Penetration index (%)		
	Baseline	Exosurf	p	Baseline	Exosurf	p
10 min (n = 6)	24.7 ± 6.4	35.6 ± 8.7	<0.0001	106.0 ± 13.2	102.9 ± 12.5	ns
40 min (n = 4)	21.7 ± 8.9	29.4 ± 6.3	0.01	102.8 ± 11.5	108.7 ± 12.5	ns
1 hr (n = 5)	25.2 ± 7.3	21.3 ± 7.3	ns	103.1 ± 10.2	114.3 ± 30.7	ns
2 hr (n = 4)	29.8 ± 3.5	24.5 ± 6.1	<0.01	106.4 ± 9.1	102.9 ± 10.8	ns
3 hr (n = 4)	27.2 ± 4.4	22.6 ± 5.0	ns	109.8 ± 16.4	105.1 ± 8.3	ns

The data are expressed as mean ± s.d.; n = 4–6 animals per group.

^{99m}Tc-DTPA solute in the lungs. Several factors other than the altered epithelial permeability, such as changes in the deposition pattern of ^{99m}Tc-DTPA aerosol might have influenced the results (*15,18*). However, no significant differences were noted in ^{99m}Tc-DTPA aerosol distribution or PIs.

The suppression effect of excess surfactant on ^{99m}Tc-DTPA clearance has been demonstrated experimentally in rabbit lungs after tracheal instillation of natural surfactant (*19*). Several investigators also found that ^{99m}Tc-DTPA clearance was increased dramatically by lung lavage or detergent-mediated loss of surfactant activity and that these effects were reversed by tracheal instillation of natural surfactant (*18,20*). This characteristic suppression of ^{99m}Tc-DTPA clearance by surfactant may be explained by the fact that the excess alveolar surfactant would increase the thickness of the epithelial lining fluid, resulting in an increase of ^{99m}Tc-DTPA diffusion–path distance and an interruption of the paracellar route of ^{99m}Tc-DTPA solute absorption (*21*). The hydrophobic surfactant lining the alveolar membrane also would inhibit the adsorption and spread of a hydrophilic ^{99m}Tc-DTPA solute on the epithelial surface.

This study, however, revealed that the suppressive effect of inhaled Exosurf on ^{99m}Tc-DTPA clearance rate was short-lived, normalizing within 1–2 hr. This rapid loss of the suppression effect may result from the catabolism or elimination of some Exosurf from the physiological active pool during this period. Surfactant catabolic activity is significant in the epithelium (*1*), and surfactant is removed from the alveoli with a turnover half-time of 5–10 hr through the bronchial system, by alveolar macrophages and by movement from alveolar spaces into the blood or lymphatic system (*1*). Protein-free synthetic surfactant, including Exosurf, tends to be eliminated more rapidly from the alveoli than protein-containing surfactant (*22*). Mechanical ventilation also leads to elimination of surfactant from alveoli into the terminal airways (*1*).

The fact that the ^{99m}Tc-DTPA–Exosurf mixture distributed homogeneously without any significant changes in PIs from the baseline study (Fig. 2) suggests that inhaled Exosurf can reach uniformly to the terminal air spaces in approximately the same manner as ^{99m}Tc-DTPA aerosol (*13,17*). An aerosolized ^{99m}Tc-DTPA–Exosurf mixture is a reasonable method to evaluate the distribution of inhaled Exosurf because the predominant components of Exosurf are aerosolized similarly to ^{99m}Tc-DTPA when admixed with Exosurf, with preservation of the radiochemical purity of ^{99m}Tc-DTPA (*10*). This uniform distribution of Exosurf may be partially explained by the characteristic biophysical properties of surfactant showing rapid adsorption and spreading over a surface of the air–fluid interface in the airways and alveoli (*8,9*).

CONCLUSION

Therapy with an inhaled surfactant showing excellent lung delivery may be better than delivery by tracheal instillation in patients with diffuse lung disorders such as ARDS or NRDS (*7*), as recent preliminary studies have shown that aerosolized surfactant was more effective despite low quantities deposited than was the same dose of surfactant administered by tracheal instillation (*8,10–12*). Aerosolized Exosurf can temporarily retard ^{99m}Tc-DTPA clearance rate in the lungs with a single dose. This suggests that inhaled surfactant may contribute to the integrity of the epithelial barrier and help normalize transalveolar clearance of small solutes in these patients. A more prolonged suppression effect might be achieved by an increased dose or repetitive dosing because recent studies have demonstrated a dose-dependent efficiency to surfactant treatment (*6,8,11*). These findings and our data suggest that further characterization of the effects of synthetic surfactant on alveolar–epithelial integrity is warranted.

ACKNOWLEDGMENTS

We thank Peter D. Esser, PhD, and Ted Pozniakoff for their technical assistance and Dr. T. Wong for radiopharmaceutical preparation. We also thank Drs. Warrett and Scittschell of Burroughs Wellcome Co. (Greenville, NC) for providing Exosurf.

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Biological Dosimetry of Bone Marrow for Incorporated Yttrium-90

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The biological response of bone marrow to incorporated radionuclides depends on several factors such as absorbed dose, dose rate, proliferation and marrow reserve. The determination of the dose rate and absorbed dose to bone marrow from incorporated radionuclides is complex. This research used survival of granulocyte-macrophage colony-forming cells (GM-CFCs) as a biological dosimeter to determine experimentally the dose rate and dose to bone marrow after administration of ^{90}Y-citrate. **Methods:** The radiochemical ^{90}Y-citrate was administered intravenously to Swiss Webster mice. Biokinetics studies indicated that the injected ^{90}Y quickly localized in the femurs (0.8% ID/femur) and cleared with an effective half-time of 62 hr. Subsequently, GM-CFC survival was determined as a function of femur uptake and injected activity. Finally, to calibrate GM-CFC survival as a biological dosimeter, mice were irradiated with external ^{137}Cs gamma rays at dose rates that decreased exponentially with a half-time of 62 hr. **Results:** Femur uptake was linearly proportional to injected activity. The survival of GM-CFCs was exponentially dependent on both the initial ^{90}Y femur activity and the initial dose rate from external ^{137}Cs gamma rays with 5.1 kBq/femur and 1.9 cGy/hr, respectively, required to achieve 37% survival. Thus, ^{90}Y-citrate delivers a dose rate of 0.37 cGy/hr to the femoral marrow per kBq of femur activity and the dose rate decreased with an effective half-time of 62 hr. **Conclusion:** Survival of GM-CFCs can serve as a biological dosimeter to experimentally determine the dose rate kinetics in bone marrow.

Key Words: radionuclide therapy; biological dosimetry; bone marrow; dose rate

J Nucl Med 1998; 39:547–552

The goal of radionuclide therapies such as radioimmunotherapy is to deliver a sufficiently large dose to the tumor without unduly affecting the critical normal organs such as bone marrow. The biological response of the bone marrow encountered in such therapies is likely to depend on several variables, such as initial absorbed dose rate to the marrow, dose rate decrease half-time, the cumulative absorbed dose received by the marrow, repair and proliferative capacities of the marrow, and bone marrow reserve (*1–4*). No clear correlation has been observed between cumulated absorbed dose and biological response of the marrow. This is not surprising because it is unlikely that one can predict marrow response with a single variable when the response depends on a complex array of variables whose relationship to the response is poorly understood. The prediction of the biological response of bone marrow to radiation insults from incorporated radionuclides will ultimately rely heavily on both biological factors (e.g., prior exposure to chemotherapeutic agents, bone marrow reserve) and physical factors (e.g., temporal dependence of the dose rate, cumulated absorbed dose to the marrow) (*2–4*). Therefore, accurate dosimetric information is a prerequisite for understanding and predicting the marrow response.

The complications in bone marrow dosimetry arise primarily from difficulties in obtaining accurate quantitative biodistribution data. Early dose estimates for bone marrow after administration of therapeutic activities assumed that the blood activity concentration (readily measurable) was the same as the bone marrow activity concentration (*5*). However, Eary et al. (*6*) subsequently showed that in dogs, the concentrations of activity in the blood and bone marrow are not the same but differ by a factor of about 5. Consequently, other investigators have implemented a marrow-to-blood activity concentration ratio of 0.2:0.4 (*7,8*) in their bone marrow dose calculations. The adequacy of these assumptions and the theoretical models used to calculate marrow absorbed dose and dose rate kinetics have not been experimentally verified. Experimental verification of calculated absorbed doses to bone marrow with devices such as thermoluminescent dosimeters and MOSFET dosimeters are impractical for obvious reasons. Therefore, one must rely on biological dosimeters to obtain information on the absorbed dose rate profiles and cumulated absorbed doses to the marrow.

Several biological dosimeters have been used over the years

Received Dec. 23, 1996; revision accepted Apr. 25, 1997.
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