^{111}In-Oxine-Labeled Rabbit Platelets: In Vivo Distribution and Sites of Destruction

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We have studied the kinetics, biodistribution, and fate of autologous platelets labeled with ^{111}In-oxine in rabbits. The initial recovery was 75% and mean survival time was 2.8 days when the data were analyzed by the multiple-hit gamma function model. Using a modified geometric mean for correction of attenuation, there was good correlation between the values obtained by in vivo quantification and those obtained by postmortem measurements of the radioactivity in the liver and the spleen (i.e., $r = 0.854$ and 0.899, respectively, $n = 32$). Using this method, it was shown that after infusion, the ^{111}In-platelets rapidly accumulated in these two organs reaching 35% and 12% of the injected dose in the liver and spleen, respectively, by 1 day. Thereafter, there was little subsequent change. On the sixth day, when essentially all of the ^{111}In-platelets had cleared from the circulation, a total of 82% of the injected dose was deposited in the three major reticuloendothelial organs: liver (40%), spleen (14%), and bone marrow (28%). Our results suggest that in addition to liver and spleen, bone marrow played an important role in sequestering platelets in rabbits.

IN RECENT YEARS, ^{111}In-oxine has been increasingly used as a platelet label.[1-15] The combination of a high labeling efficiency and the physical characteristics that allow quantitative in vivo imaging makes ^{111}In-oxine a preferred platelet label over ^{51}Cr-sodium chromate. In vivo distribution studies of ^{111}In-labeled platelets in man[10,11,13-15] and dogs[12] have shown the liver and spleen to be major sites of platelet deposition. Yet, only 50%–75% of the injected dose could be accounted for in these organs. Since little or no ^{111}In is excreted in the urine or feces, it has been suggested that the remaining radioactivity is localized in the bone marrow,[10,11,14] but no direct measurement of platelet deposition in the bone marrow has been carried out.

In this study, the biodistribution and kinetics of ^{111}In-oxine-labeled platelets were studied in rabbits and compared with those of ^{51}Cr-labeled platelets. The distribution of the radiolabeled platelets in major organs, including bone marrow and bone, were determined at 6 days after infusion when the radiolabeled platelets were cleared from the circulation. In addition, we validated the method of external in vivo quantification of ^{111}In radioactivity in liver and spleen by comparison with results obtained at postmortem.

MATERIALS AND METHODS

Isolation and Labeling of Platelets

Platelets were labeled with ^{111}In-oxine in autologous plasma by a modification of the method described by Scheffel et al.[2] Briefly, ^{111}In Cl_3 (Medi-Physics, Emeryville, Calif.) was chelated with oxine (8-hydroxyquinoline). The complex was extracted with methylene chloride, evaporated to dryness, and dissolved in ethanol:normal saline (1:4), with a final volume of 400 μl.

Platelets were isolated from 42.5 ml of blood obtained by subxiphoid cardiac puncture using a 19-gauge needle and 50-ml plastic syringe containing 7.5 ml acid citrate dextrose (ACD NIH-A). All procedures used sterile plastic equipment and were done at room temperature. Platelet-rich plasma (PRP) was obtained by centrifugation at 220 *g* for 15 min. The red blood cells (RBC) were washed once, resuspended in 50 ml of sterile saline, and reinfused into the rabbit. The PRP was acidified to pH 6.5–6.7 with ACD NIH-A. After centrifugation at 1000 *g* for 10 min, the platelets were resuspended in 2 ml of platelet-poor plasma (PPP). For labeling with ^{111}In-oxine, platelets ($5–18 \times 10^9$) were incubated for 30 min with 100 μl of ^{111}In-oxine containing 10–15 μg oxine. For labeling with ^{51}Cr, $5–18 \times 10^9$ platelets were incubated for 1 hr with 10 μl of ^{51}Cr-sodium chromate (Squibb, East Brunswick, N.J.) containing 0.2–0.5 μg sodium chromate. The platelets were then washed with PPP, and any contaminating RBC, if present, were removed by centrifugation at 150 *g* for 5 min. Five milliliters of radiolabeled platelets in PPP were infused into the rabbit. The radioactivity infused was determined using a Mediac dose calibrator (Nuclear Chicago, Des Plaines, Ill.).

Platelet Survival Studies

Following the intravenous infusion of 30–350 μCi ^{111}In-platelets or 5–25 μCi ^{51}Cr-platelets into the marginal ear vein of the rabbit, heparinized blood samples (3 ml) were obtained at 10, 30, 60, 120 min postinfusion and daily thereafter for 6 days. Separate aliquots of 1 ml whole blood and 0.5 ml platelet-free plasma from each sample were prepared for counting. We have previously shown that essentially all the ^{111}In radioactivity in whole blood samples was associated with the platelets.[14] Aliquots of 50 μl of the radiolabeled platelet injectate in 2 ml water were used as standards. All samples and standards were counted to less than 3% statistical counting error in an Auto-Gamma system (Packard Instrument Co., Downers Grove, Illinois). The results were expressed as percentages of the injected dose in circulating platelets assuming a blood volume of

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4.25% of body weight.[2] All rabbits were female New Zealand whites (3.5–4.5 kg).

To estimate the mean platelet survival time (MPST), the data were subjected to computer analysis using linear, exponential, and multiple-hit survival curve models.[2,16,17]

^{111}In-Transferrin Studies

For the transferrin-bound ^{111}In studies, 5–7 ml rabbit serum was incubated with 100 μl of $^{111}InCl_3$ (Medi-Physics, Calif.) for 15–20 min at room temperature. A quantity of 50–100 μl of ^{111}In-transferrin was injected intravenously into a separate group of rabbits. At 6 days postinjection, the rabbits were sacrificed and multiple tissue samples were obtained and counted for radioactivity as described above.

External In Vivo Quantification Studies

A modification of the geometric mean computation for correction of photon attenuation was used for the ^{111}In-platelet studies. This method has previously been validated in phantom studies[18,19] and described elsewhere.[14,15] Briefly, the overall effective transmission factor (Tr) was determined before the ^{111}In-platelets were infused. The rabbits were placed in a horizontal restrainer[20] that can easily be rotated 360° in a horizontal plane. The chest and abdominal areas of the rabbits were positioned over a 38-inch diameter flood source containing 250–600 μCi ^{111}In. A static anterior image of 5–10 × 10^4 counts was obtained with a gamma camera (Pho/Gamma-HP, Searle, Des Plaines, Ill.) interfaced with a 250 keV fine resolution parallel-hole collimator and data processing system (150 DataSystem, Technicare, Solon, Ohio). The pulse-height analyzer was set to include the 247 keV photopeak with a 20% window. A second image was acquired of the flood source only. From images obtained after intravenous infusion of ^{111}In-platelets with the rabbit in the same position, the liver and spleen regions were outlined with a light pen. These regions were then used to obtain counts per region from both the transmission and flood images. *Tr* represents the ratio of counts transmitted through the organ region to the unfiltered flood counts of the same region.

The ^{111}In-platelets were infused with the rabbits positioned under the gamma camera. Anterior scintigraphic images were obtained immediately following the infusion. Ten-second images were obtained sequentially for 5 min. At 10 min, 2 hr, and daily thereafter for 6 days, anterior and posterior images of 3–5 × 10^4 count images of the liver/spleen region were acquired on each rabbit. To determine the sensitivity (S) of the imaging system in counts per μCi ^{111}In, a standard of ^{111}In was prepared and daily images of 3–5 × 10^4 counts of the ^{111}In standard were obtained. The percentage of the injected dose in the organ of interest was then calculated from the following equation:

$$\text{Percent injected dose} = 100\,[(C_a)(C_p)/Tr]^{1/2}\,(S^{-1})(P^{-1}),$$

where C_a and C_p are counts per organ from anterior and posterior images, respectively, and P is the amount (μCi) of ^{111}In-platelets injected.

Biodistribution Studies

Following the last blood sampling and any imaging procedure done on the sixth day of the study, the rabbits were sacrificed by an overdose of pentobarbital. Multiple tissue samples of liver, spleen, lungs, kidneys, muscle, and tibia bone and bone marrow were obtained. The radioactivity was determined by counting all samples with standards in the same manner as described for the blood samples. The radioactivity was expressed as percentages of the injected dose per organ using the following assumptions: skeletal muscle mass is 43% of total body weight (TBW); skeletal mass is 10% of TBW; and bone marrow volume is 2.2% of TBW.[21–23]

Statistical Methods

All data are expressed as mean and the standard error of the mean (SEM). Differences between means were tested for statistical significance by the t test with p values of the differences given.[24,25]

RESULTS

Platelet Survival Studies

Labeling efficiencies of >90% were routinely obtained with ^{111}In-oxine as compared to 2%–3% for ^{51}Cr. The results of the platelet survival studies are given in Table 1. No significant difference in mean platelet survival time of ^{111}In-labeled and ^{51}Cr-labeled platelets was seen, regardless of which model of survival curve analysis was used. However, initial recoveries of ^{111}In-platelets were higher than those of ^{51}Cr-platelets. These results are similar to those reported previously.[2]

External In Vivo Quantification Studies

The accuracy of this method was assessed by comparison with the values obtained from postmortem samples of the same organs on the sixth day after injection. Figure 1 shows the correlation between the in vivo and sacrifice values in liver and spleen. There was good agreement between the two methods: the correlation coefficients were 0.854, $p<0.001$ for liver and 0.889, $p < 0.001$ for spleen; and the ratios of in vivo to sacrifice values were approximately 1.05 and 1.10, respectively.

The temporal distribution of ^{111}In-platelets in liver and spleen was also followed by external in vivo quantification immediately after injection. As seen in Fig. 2, ^{111}In radioactivity in the liver increased to about 25% of the injected dose by 4 min, reaching 35% by day 1, with no significant changes over the following 5

Table 1. Mean Platelet Survival Time (Days) of ^{111}In- and ^{51}Cr-Labeled Platelets

	Linear		Exponential		Multiple-hit		Percent Recovery*	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
^{111}In-Platelets (n = 14)	4.87	0.06	1.19	0.04	2.86	0.19	75.48	2.06
^{51}Cr-Platelets (n = 5)	4.97	0.06	1.37	0.13	2.55	0.34	60.79	3.43
p	>0.2		>0.05		>0.4		<0.005	

*Percent recovery as estimated from the multiple-hit survival curve model.

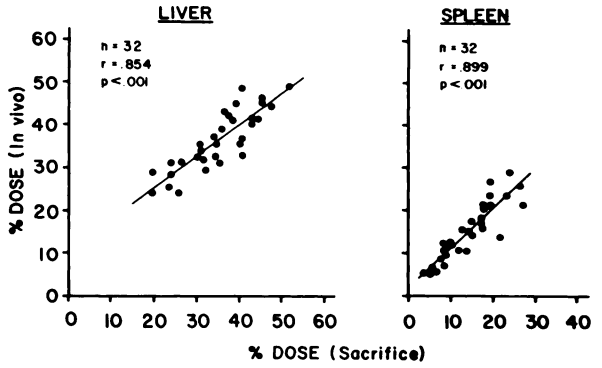

Fig. 1. Correlation between the in vivo quantification and the postmortem determinations of ^{111}In-platelet radioactivity at 6 days postinfusion for the liver and spleen.

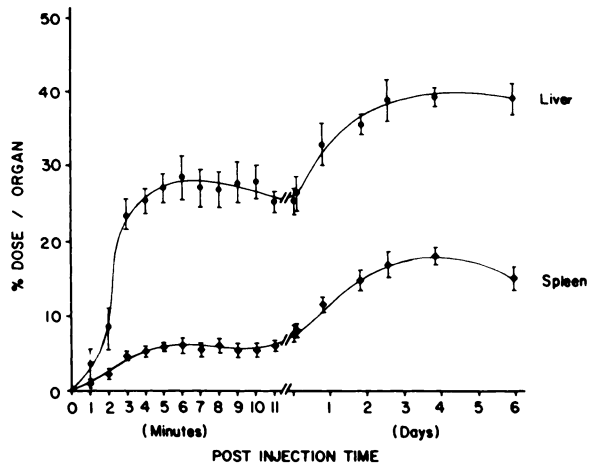

Fig. 2. Temporal distribution of ^{111}In-platelets in rabbit liver and spleen. Values plotted are mean ± 1 SEM for 9 rabbits.

days. The ^{111}In-platelets accumulated in the spleen reached 5% by 3 min, increasing to 14% by the second day with little subsequent change.

Biodistribution Studies

The results of the postmortem biodistribution studies are summarized in Table 2. Ninety-five percent of total injected dose of ^{111}In-platelets was accounted for in the major organs measured, while only 75% of the ^{51}Cr-platelets was recovered. ^{111}In-platelets had similar distributions to those of ^{51}Cr-platelets, except for the liver (mean = 40.00%, SEM = 1.52% versus mean = 22.76%, SEM = 2.08%, respectively, $p<0.001$). The reason for this discrepancy is not clear.

The skeleton had 3.9% and 4.3% of ^{111}In and ^{51}Cr radioactivity, respectively. The bone marrow received a significant portion of the radiolabeled platelets regardless of the label used (28% for ^{111}In-platelets and 26% for ^{51}Cr-platelets). When ^{111}In-transferrin was infused, only 8% was found in the bone marrow and 5% in the bone.

It has been shown that there is an inverse relationship between the deposition of red cells in the spleen and bone marrow.[26] As shown in Fig. 3, a similar inverse relationship was also observed for radiolabeled platelets.

DISCUSSION

With the introduction of ^{111} In-oxine as a platelet label,[1] it has become possible to accurately quantify the temporal and spatial distribution of platelets in vivo. Using whole body surface counting, Heyns and coworkers[10] are able to estimate the deposition of ^{111}In-platelets in the liver and spleen in man expressed as percentages of the total body dose. However, in canine studies, these quantitative measurements were found to be subject to error when compared to the postmortem measurements, e.g., overestimating the radioactivity of the spleen, while underestimating that of the liver.[12]

We have previously described a mathematical approach to in vivo quantification using anterior, posterior, and transmission images. Using this system of

Table 2. Biodistribution in Rabbits at 6 Days After Infusion

	Percent Injected Dose*							
	(n = 19)		(n = 5)		(n = 4)			
	Mean	SEM	Mean	SEM	Mean	SEM	p†	p‡
Liver	40.00	1.52	22.76	2.08	14.47	0.93	<0.001	<0.001
Spleen	14.25	0.80	13.37	2.33	0.46	0.15	>0.5	<0.001
Bone marrow	27.53	2.15	26.37	5.13	7.88	1.52	>0.5	<0.001
Bone	3.91	0.32	4.30	0.26	5.12	0.68	>0.5	>0.05
Muscle	3.82	0.31	4.51	0.64	10.12	1.52	>0.2	>0.2
Blood	2.53	0.20	1.71	0.30	1.87	0.39	>0.05	>0.1
Kidneys	2.17	0.14	0.96	0.09	4.46	0.48	<0.001	<0.001
Lung	0.98	0.61	0.28	0.14	0.55	0.12	>0.5	>0.5
Total	95.31	2.71	74.33	3.03	44.92	2.08	<0.005	<0.001

*Bone marrow: 2.2% of body weight (BW); bone mass: 10% of BW; muscle mass: 43% of BW; blood volume: 4.25% of BW.

†p Value between means of ^{111}In-platelets and ^{51}Cr-platelets.

‡p Value between means of ^{111}In-platelets and ^{111}In-transferrin.

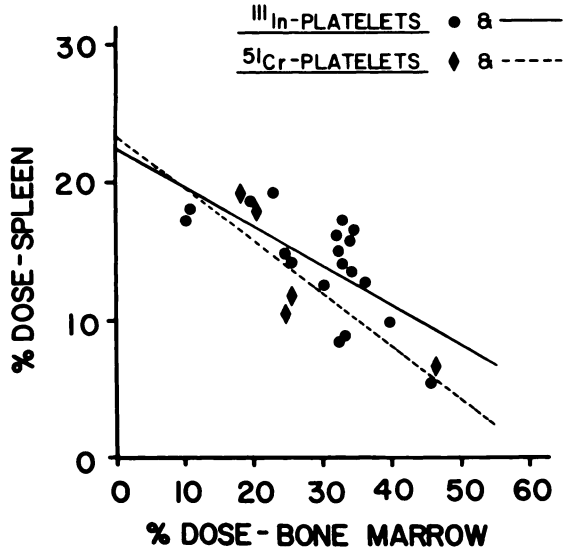

Fig. 3. Correlation of bone marrow sequestration to spleen sequestration of ^{111}In-platelets and ^{51}Cr-platelets. Curves were obtained by least-squares method of linear regression.

image acquisition, potential errors involving counting geometry, scatter, and photon attenuation are minimized. The outlining of the regions of interest need not be exact, since small errors will have a negligible effect on the measurement of total counts within the outlined region. We have chosen liver and spleen as the organ regions for quantification; however, any region with well defined limits in the images may be used. Another potential source of error in this method is associated with the organ thickness. Thomas[27] suggested that since the radioactivity present in the organ region is not a point source, a correction factor for organ thickness is necessary. However, we have found that when this correction factor was calculated for ^{111}In, no error was associated with organ thicknesses up to 2 cm and less than 7% error for thicknesses up to 10 cm. This result, combined with the fact that exact organ thicknesses are unknown in in vivo studies, has lead us to omit this factor from our calculations. Thus, a slight over-estimation of absolute radioactivity results in organs greater than 2 cm in thickness. A similar assessment has been reported by Links et al.[28] for the measurement of absolute left ventricular volumes using ^{99}Tc-red blood cells.

In this study, we have further validated this method using the rabbit model. There was good correlation between the values obtained by in vivo quantification and those obtained by postmortem measurements of the radioactivities in both the liver and the spleen. Using this method, it was shown that after infusion, ^{111}In-platelets rapidly accumulated in these two organs and that the radioactivity in these organs did not change substantially thereafter (Fig. 2). We postulate that the initial deposition of ^{111}In-platelets in the liver and spleen was in part due to pooling, while at later days, it was due to sequestration of platelets by the macrophage system in these organs.

In earlier studies using surface scanning of ^{51}Cr-platelets, only liver and spleen were seen as areas of platelet sequestration or pooling. Yet these organs represented only 50%–75% of the total injected dose.[10,11,13-15] The rest of the radioactivity was assumed, by some, to be diffusely distributed.[29] The improved imaging qualities of the ^{111}In label have been instrumental in providing the means by which any additional sites of platelet deposition could be identified. Indeed, several groups have reported visualization of ^{111}In-radioactivity in human subjects in areas corresponding to bone marrow.[10,14,30]

In this study, we have determined the radioactivity in the bone marrow on the sixth day after infusion of ^{111}In-labeled or ^{51}Cr-labeled platelets when they were cleared from the circulation. We assumed that the radioactivities in the bone marrow were due to sequestration of radiolabeled platelets for the following reasons: First, similar results were obtained when two different platelet radiolabels were used (28% for ^{111}In-platelets and 26% for ^{51}Cr-platelets). Second, in studies using ^{51}Cr-red cells, ^{51}Cr that had eluted from the cells was found in the urine and there was no evidence of any significant transfer of free ^{51}Cr to bone marrow.[31] Elution of ^{111}In from platelets is minimal.[3,10,11,15] Even if some elution did occur, the free ^{111}In would most probably bind to plasma transferrin. When we injected transferrin-bound ^{111}In into a separate group of rabbits, less than 8% of the total dose was found in the bone marrow at 6 days postinjection and 55% was excreted.

In rabbits, 55%–90% of ^{51}Cr-red cells are also found to be sequestered in the bone marrow.[31] Based on the observation of erythrophagocytosis by marrow macrophages, Travassoli[32,33] suggests that this mechanism is responsible for the sequestration of senescent red cells in rabbits. There is an inverse relationship between the deposition of red cells in the spleen and bone marrow.[26] In this study, we have also observed a similar inverse relationship for radiolabeled platelets. Thus, in rabbits, liver, spleen, and bone marrow are the major sites of platelet sequestration accounting for 82% of the total injected^{111} In-platelets.

There may be species differences in the role of bone marrow in the sequestration of platelets. Aster[34] has shown that in rats, bone marrow sequestered only 2.7% of the injected ^{51}Cr-platelets. No direct measurement in humans has been carried out. However, in view of the visualization of ^{111}In radioactivity in areas corresponding to the bone marrow distribution in man,[10,14,30] bone marrow may also play an important role in the sequestration of platelets in man.

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