Indium-111-Labeled White Blood Cells: Dosimetry in Children

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The distribution of [^{111}In]oxine-labeled leukocytes was studied by whole-body gamma camera imaging in nine pediatric patients. Images were obtained at ~24 hr after administration of the material. Organ distribution was estimated from stored data by manual region of interest assignment. Dosimetry estimates based on geometric mean and conjugate view absolute activity calculations showed close agreement in these patients. Leukocytes were distributed in liver, spleen and marrow. The mean percent uptakes ±s.d. were: spleen, 31.2 ± 18.3%; liver, 26.3 ± 10.8%; and marrow, 14.2 ± 5.7%. A significant portion (28.3 ± 9.9%) of administered white cell activity was found outside these organs in the remainder of the body. Mean organ absorbed doses (rad/mCi) were: spleen, 115.0 ± 84.8; liver, 13.9 ± 7.8; marrow, 7.6 ± 3.8; and total body 2.5 ± 1.0. The mean organ absorbed doses (rad/dose administered) were: spleen, 13.7 ± 10.6; liver, 1.48 ± 0.62; marrow, 0.79 ± 0.26; and total body, 0.28 ± 0.09.

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The indium-111 (^{111}In) oxine-labeled white blood cell (WBC) scan has been shown to be a useful procedure in the localization of occult or suspected inflammatory disease in a variety of clinical conditions and patients (*1–3*). The procedure has now been approved by the Food and Drug Administration for routine clinical use (*4*). In pediatric patients, the procedure has been used successfully and without reported adverse effect (*5,6*). Its use has not always been limited to life-threatening disease (*7*). Published dosimetry estimates have shown relatively high doses to the spleen and liver in adults (*8–10*). Dosimetry estimates in pediatric patients have thus far been extrapolations from adult data, rather than direct measurements (*5,6,11*). Doses have been postulated to be similar to those from gallium-67 (^{67}Ga) citrate scanning, a technique with lower expected sensitivity and specificity in many cases.

Concern regarding the radiation dose received by children from diagnostic doses of radionuclides is understandable. The greater potential life span of the child may allow a longer time for the manifestation of latent radiation effects, including malignancy. The smaller body size relative to the size of organs such as the liver and spleen results in a higher dose to non-target tissues. Furthermore, the use of "minimum" doses rather than calculated doses in very small children often results in far greater doses on a per kg basis than that administered to the adult.

It is the purpose of this work to calculate the radiation dose received by children who had undergone [^{111}In] WBC scans in our institution.

MATERIALS AND METHODS

Ten whole-body [^{111}In]WBC scans performed in nine pediatric patients, six females and three males ranging in age from 3 mo to 18 yr (mean 3.9 yr, median 2 yr), and in weight from 4.8 to 56 kg (mean 15.1 kg, median 11.6 kg) were selected for study. The clinical characteristics of each patient, including the patient's height, weight, diagnosis and administered dose of ^{111}In-labeled autologous white cells are summarized in Table 1. Each patient was referred because of suspected abscess or occult focus of infection. Three of these patients had biopsy proven cirrhosis. Hepatosplenomegaly without apparent cirrhosis was present in one patient. No patients with significant focal abnormalities on white cell scan were included in the series.

Autologous WBCs were used in each of these cases. The volume of blood for labeling was determined by the patient's size and peripheral WBC count, resulting in ~2 × 10^8 polymorphonuclear cells per 70 kg body weight.

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TABLE 1
Clinical Characteristics of Patients

Patient	Age	Sex	Wt kg	Diagnosis	Indication for scan	Dose μCi/kg	Comments
1	2 yr	M	11.9	Biliary atresia	Ascending cholangitis?	10.5	Cirrhosis, splenomegaly
2	11 mo	F	4.8	Cong. ht. disease	Sternal infection?	21.6	Osteomyelitis
3	15 mo	F	6.4	Cong. ht. disease	Sternal infection?	15.2	Candida, incision
4	2 yr	F	14.0	Wilm's tumor	Fever	9.5	
5a	1 yr	M	8.6	Biliary atresia	Ascending cholangitis?	6.4	Hepatosplenomegaly
5b	22 mo		11.3	Biliary atresia	Ascending cholangitis?	9.5	Hepatosplenomegaly
6	3 mo	F	5.0	Biliary atresia	Ascending cholangitis?	15.6	Hepatosplenomegaly
7	33 mo	F	12.3	Cong. ht. disease	Sternal infection?	8.7	
8	9 yr	M	21.1	Hb E/B thalassemia	Fever	7.7	Hepatosplenomegaly
9	18 yr	F	56.0	Renal transplant	Pyelonephritis?	7.6	

In vitro labeling of autologous leukocytes was performed according to a modification of the method of Thakur et al. (*1,3*). Briefly, the procedure was as follows:

1. Donor whole blood was collected aseptically into a heparinized syringe using a butterfly needle, 23 gauge or larger where possible.
2. Hydroxyethyl starch was added to the blood, which was then left at room temperature for an hour to allow red cell sedimentation.
3. The plasma-cell mixture was withdrawn using an 18 gauge spinal needle and centrifuged at 250 *g* for 5 min.
4. Supernatant plasma was withdrawn from the cell button.
5. Plasma was centrifuged at 1,000 *g* for 30 min to remove platelets from suspension.
6. The white cell button was suspended in saline prior to addition of (^{111}In)oxine, and incubated with the ^{111}In for 30 minutes.
7. Suspended white cells were re-centrifuged at 250 *g* for 5 min.
8. Supernatant ^{111}In was withdrawn from the white cell button.
9. White cells were resuspended in platelet-poor plasma for administration.

Labeling efficiencies were on the order of 90%. No labeled samples showed unusual red cell contamination. Doses of [^{111}In]oxine for labeling were estimated according to the following scheme: minimum dose 100 μCi for up to a 10 kg child's body weight, plus 10 μCi/kg for the next 10 kg of body weight, and an additional 5 μCi/kg for weight >20 kg. The maximum permissible dose was 500 μCi. Variations in administered dose resulted from differences in labeling yields and residual syringe activities. Administered doses were 55–427 μCi (mean 139 μCi) of ^{111}In-labeled white cells, with an average dose of 9.2 μCi/kg.

Images were obtained ~24 hr postadministration on a large field-of-view gamma camera equipped with a medium-energy collimator using whole-body anterior and posterior pass techniques or overlapping spot images. Dual energy peaks of 172 keV and 247 keV for ^{111}In were used with 20% windows. Imaging time and total counts were recorded for each image. Digital data was stored in a 128 × 128 word matrix for subsequent analysis. Regions of interest were assigned manually for the liver, spleen, marrow, and total body. Background corrections in counts per pixel were determined from multiple areas. If data for distal portions of the extremities was available in only a single projection, anterior and posterior counts were assumed to be equal.

Camera efficiency in counts per minute per μCi for [^{111}In] oxine was determined using filled flood phantoms containing ~500 μCi of [^{111}In] oxine in a volume of 1,845 ml.

Organ activities were estimated using the geometric mean and conjugate view absolute activity techniques (*8–16*). The percent organ uptakes were estimated by comparison to the total-body count rates in each individual patient using the geometric mean of the anterior and posterior count rates. The geometric mean (G) is defined as:

$$G = (A \times P)^{1/2} \quad (1)$$

where A and P are the anterior and posterior count rates, respectively. The G of each organ and of the total body were calculated. Total body G values were obtained according to Eq. (1), using whole-body anterior and posterior counts or, in cases with overlapping spot images, from summed counts in anterior and posterior body regions. The percent individual organ uptake was obtained by dividing the respective organ G value by the total-body G value multiplied by 100. Absolute organ activities A, in μCi, were then calculated by multiplying the various percent organ uptakes by the injected dose for

each patient. In addition, absolute organ activity A′ in μCi was estimated according to the formula:

$$A' = \frac{(A \times P)^{1/2}}{e^{-uT/2}} \times \frac{f}{C} \quad (2)$$

where u is the effective linear attenuation coefficient, T is the patient thickness in cm encompassing the organ or interest, f is a correction factor for the source attenuation and source thickness, and C is the system calibration factor in counts/μCi-min. The measured u value was 0.13 cm^{-1} using a water equivalent phantom. Due to the small organ sizes in this study, f was taken to be unity. Body thickness T was obtained from standard pediatric nomograms or measured from stored data where lateral views were available (*17*). In patients where both values were available, there was close correlation between measured and predicted body thickness.

For dosimetry calculations, distribution throughout the body was assumed to be instantaneous. The effective half-life was assumed to be the physical half-life for ^{111}In, i.e., 67.9 hr (*1,2*). The contribution of ^{114}In to the absorbed radiation dose was ignored. The dose to the target organ per unit administered activity can be expressed as:

$$D_{k \leftarrow h} = S_{k \leftarrow h} \tilde{A}_h, \quad (3)$$

where $D_{k \leftarrow h}$ denotes the absorbed dose in rads to target organ k, due to source organ h; $S_{k \leftarrow h}$ is the S-factor for organ h to organ k in rads per μCi-hr; and $\tilde{A}_h$ is the cumulated activity in organ h in μCi-hr (*18*). The individual S-factors for ^{111}In for newborns, 1, 5, 10, and 15 yr olds were provided by the Radiopharmaceutical Internal Dose Information Center, Oak Ridge, TN (*19*). The S-factors most closely corresponding to the patients' ages were used in the calculations.

The total dose to target organ (D_k) is given by:

$$D_k = {}_hD_{k \leftarrow h}, \quad (4)$$

where the source organs, h, are the spleen, liver, red marrow, and total body.

RESULTS

Activity at the injection site was not visualized in any patient. Therefore, no correction for extravasation was applied to the injected doses. The percentage of radionuclide uptake was calculated for spleen, liver, bone marrow, and rest of body. This distribution is given in Table 2. Based on these values, the mean ±s.d. absolute organ activities in μCi were: spleen, 40.4 ± 34.2; liver, 29.8 ± 8.8; and marrow, 14.5 ± 6.0. In comparison, the mean ±s.d. absolute organ activities in μCi obtained by Eq. (2) were: spleen, 39.8 ± 37.5; liver, 26.8 ± 10.8; marrow, 13.4 ± 7.0; and total body, 134.3 ± 101.8. There was no statistically significant difference between these two methods for activity estimation in any region using Student's t-test (*20*). Therefore, dosimetry estimates were obtained using Eqs. (3) and (4) with the absolute activity data based on the percent geometric mean data.

Estimates of absorbed radiation dose are presented in rad per mCi in Table 3. The mean ±s.d. organ absorbed doses were: spleen, 115.0 ± 84.8; liver, 13.9 ± 7.8; marrow, 7.6 ± 3.8; and total body, 2.5 ± 1.0 rad/mCi. Estimates of organ absorbed doses in rad per dose administered are presented in Table 4. The mean ±s.d. organ absorbed doses (rad/dose administered) were: spleen, 13.7 ± 10.6; liver, 1.48 ± 0.62; marrow, 0.79 ± 0.26; and total body, 0.28 ± 0.09.

TABLE 2
Percent Organ Uptake

Patient	Spleen	Liver	Marrow	Rest of body
1	72.1	10.4	6.5	11.0
2	27.2	30.8	13.7	28.3
3	18.9	35.3	12.9	32.9
4	21.3	26.8	13.5	38.4
5a	18.3	41.0	17.3	23.4
5b	18.9	36.1	9.0	36.0
6	29.1	9.9	21.4	39.6
7	17.6	31.7	24.4	26.3
8	55.1	23.1	8.1	13.7
9	33.3	18.1	14.8	33.8
Mean	31.2	26.3	14.2	28.3
± s.d.	18.3	10.8	5.7	9.9

DISCUSSION

The distribution of ^{111}In leukocytes in pediatric patients has not been previously reported. The distribution of labeled leukocytes in human adults has been presented in detail by other authors. Thakur et al. reported organ distributions based on whole-body scans obtained 22–28 hr after administration of the labeled cells. The organ uptakes of injected radioactivity were: spleen, 8–19%; liver, 12–37%; and marrow (lower spine only), 1–1.4% (*1*). The distribution found by Goodwin et al. was: spleen, 19%; liver, 19%; and rest of body, 62% (8). Their "rest of body" value was attributed primarily (85%) to marrow. Mean relative uptakes re-

TABLE 3
Dosimetry

Patient no.	Admin. dose (μCi)	Organ absorbed doses (rad/mCi)			Total body
		Spleen	Liver	Marrow	
1	125	338	7.8	5.4	3.2
2	104	129	19.0	9.4	3.1
3	97	90.2	21.4	9.0	3.0
4	133	101.5	16.9	9.5	3.0
5a	55	87.7	24.5	11.1	3.1
5b	107	90.5	22.0	7.0	3.1
6	78	138	7.7	13.7	3.0
7	107	47.9	10.9	7.5	1.6
8	162	97.8	5.9	2.1	1.2
9	427	29.7	2.6	1.5	0.6

TABLE 4
Dosimetry

Patient	Admin. dose (μCi)	Organ absorbed doses (rad/admin. dose) Spleen	Liver	Marrow	Total body
1	125	42.2	0.98	0.68	0.40
2	104	13.4	1.98	0.98	0.32
3	97	8.75	2.08	0.87	0.29
4	133	13.5	2.25	1.26	0.40
5a	55	4.82	1.35	0.61	0.17
5b	107	9.68	2.35	0.75	0.33
6	78	10.8	0.60	1.07	0.23
7	107	5.13	1.17	0.80	0.17
8	162	15.8	0.96	0.34	0.19
9	427	12.7	1.11	0.64	0.26

ported by Williams et al. were: blood, 34%; spleen, 25%; liver, 27%; lung, 8%; and bone, 6% (*9,10*). Fueger and Nicoletti have reported values of: spleen, 19%; liver, 21%, chest, 8%; marrow, 21%; and body background, 23% (*21*).

A variety of methods have been used to quantify in vivo distribution of radioactivity using gamma camera and computer techniques (*15,22–24*). It is necessary to correct the count rate of a region of interest for attenuation using a pair of anterior and posterior images. The relative merits and errors of each of the dual anterior-posterior techniques have been compared (*24*). The well-known geometric mean method for activity quantitation, used in this study, has been shown to be accurate to within 10–15% (*15,24,25*).

The nine patients (ten scans) included in this study do not represent a population of normal children but rather a group of clinically ill, febrile patients with suspected focal inflammatory disease. For ethical reasons, obtaining measurements in normal pediatric patients is not feasible. No correlation between patient age or size and percent organ uptake was demonstrable in this small number of patients.

Patients with obvious abscesses were excluded from the study. No patient in this series was subsequently shown to have an abscess, although one patient (Case 2) had a longstanding sternal wound infection not demonstrated on our images.

This relatively small population of patients also contained a disproportionately large number of patients with hematologic or biliary tract disease. There was a clinical suspicion of ascending cholangitis in the three patients with surgically treated biliary atresia. Relatively greater liver uptake was seen in only one of these patients on two scans (Case 5). Splenomegaly was not associated with high splenic uptake in all cases. However, in one patient with biliary atresia and advanced cirrhosis (Case 1) the spleen contained 72% of the total dose. In another patient with Thalassemia minor (Case 8), 55% of the dose was in the spleen.

The spleen also demonstrated the greatest variability in distribution of activity, ranging from 18 to 72% of the total activity. High splenic activity in our pediatric patients appeared to reflect the underlying disease states rather than higher lymphoid reactivity of that organ in children or differences in our technique. It is worthy to note that if the patient with advanced cirrhosis (Case 1) and the patient with Thalassemia minor (Case 8) are excluded, the spleens in the remaining eight scans contained 18 to 33% of the total activity. This is comparable to that previously reported in adults (*8,9,10,21*). Great variability was also found in our organ absorbed doses to the spleen, ranging from 30 to 338 rad/mCi. This reflects variability in activity distribution as well as the differences in the pediatric S factors. Differences in the pediatric S factors alone would result in a tenfold variation in splenic doses from newborn to age 15 yr, even if the biodistribution remained the same.

In one of our patients (Case 1), the splenic dose exceeded 40 rad per dose administered. Our mean splenic (critical organ) dose is 13.7 ± 10.7 rad per dose administered. If Cases 1 and 8 with high splenic uptake are excluded, the mean splenic dose of 9.8 ± 3.5 rad per dose administered is still higher than the predicted dose based on extrapolations from adult data (*5*). Beyond the effect of the pediatric S factors, it is unclear from this small number of patients whether most of the difference between pediatric and adult values is real or due to the variability in our data.

Although the greatest organ uptake was seen in the spleen, the difference between liver and spleen uptake was not statistically significant using Student's t test ($0.40 < p < 0.60$) in this small number of patients (*20*). Our mean hepatic uptake of 26.3 ± 10.8% is comparable to that reported in adults (*9,10,21*). The inclusion of patients with high splenic uptake (Cases 1 and 8) does not significantly alter the mean hepatic organ absorbed doses (1.6 ± 0.6 versus 1.5 ± 0.6 rad per dose administered).

Our estimates of marrow uptake are similar to those reported in adults by several authors including Thakur et al. and Williams et al. (*1,9,10*). However, others including Goodwin et al., have reported higher marrow doses using similar techniques (*8*). Although the organ absorbed doses to the marrow are much less than those to the spleen, the marrow doses may have greater biologic importance because of large numbers of undifferentiated hematopoietic cells.

Since active bone marrow is distributed over a larger portion of the skeleton in children than in adults, relatively greater marrow distribution might be expected in children. This was not the case in our study, where specific marrow regions of interest were used. The causes for this are unclear. Organ overlap led us to underestimate the marrow activity in ribs and in vertebrae near the liver and spleen. This alone should not

account for the relatively low marrow uptake (mean 14.2%) in our patients. Greater cell damage from the smaller needle sizes used in pediatric patients may account for part of this observed difference in distribution. In addition, all of the patients in this study had serious underlying chronic illness, which may have contributed to bone marrow suppression. The mean total WBC counts were 9.3×10^3 (range $4.2–15.6 \times 10^3$) cells per mm^3, with mean polymorphonuclear cell counts of 50.2%. This is lower than one might expect in pediatric patients with severe infection.

Marked granulocytosis was absent in these pediatric cases. Thus, relatively larger numbers of lymphocytes were present in the white cell mixture obtained by our technique. Using our estimates of 2×10^8 polymorphonuclear cells per 70 kg body weight, labeled WBCs contained an average of 323 μCi [^{111}In]oxine per 10^8 cells. Although granulocytes have been shown to be relatively radioresistant, significant lymphocyte damage has been postulated at these levels. As little as 20 μCi per 10^8 lymphocytes has been claimed to produce cell damage in animal models (*26*). Labeled lymphocytes in our cases may have undergone sufficient damage to impair their migration at 24 hr. Also, labeled mixed cells have been shown to have slower blood clearance than pure neutrophils (*1*). This may partly account for the relatively high soft-tissue and lower marrow activity levels observed in our cases.

When compared to adult values, higher organ absorbed doses in pediatric patients are expected because of differences in organ sizes and the resultant differences in pediatric S factors. In general, our mean percent organ uptakes for the liver and spleen differ little from those reported in adults. However, our results confirm the suspicion that the radiation dose to the spleen in pediatric patients may be quite high, particularly in cases of splenic hyperfunction or enlargement. Similarly, it is higher than reported doses from ^{67}Ga scans in children (*27*). Although our dosimetry measurements should not preclude performance of the scan, anticipation of high dose rates may modify test selection, administered doses or anticipated imaging times with limited doses.

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