RADIOCHEMISTRY AND RADIOPHARMACEUTICALS

A New Formulation of Tc-99m Minimicroaggregated Albumin for Marrow Imaging: Comparison with Other Colloids, In-111 and Fe-59

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The biodistributions of five Tc-99m colloids were compared with the 24-hr distributions of Fe-59 and In-111 in dogs by direct radioassay 1 hr after intravenous injection. One formulation of Tc-99m minimicroaggregated albumin (particle size 30–100 nm), produced the highest marrow concentration, approximately six times that of Tc-99m sulfur colloid, with similar blood and liver concentrations and a lower splenic uptake. Nevertheless, the best colloid marrow uptake was lower than the 24-hr value for In-111 and much lower than that for Fe-59. The marrow concentration of minimicroaggregated albumin was also higher than that of sulfur colloid in rats at 30 min after injection. The principal disadvantage of Tc-99m antimony sulfide colloid was its slow blood clearance. Clinical evaluation of Tc-99m minimicroaggregated albumin for marrow imaging appears warranted, although its hepatic activity will obscure overlying and immediately adjacent marrow.

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Soon after the production of Tc-99m sulfur colloid (S) from hydrogen sulfide (*1*), a similar but larger-particle colloid, prepared by heating and acid reduction of thiosulfate (*2*), became the most popular agent for hepatosplenic imaging. However, images of the functioning bone marrow were relatively poor because of its low colloid concentration. No significant improvement was achieved in trials of other Tc-99m colloids, including antimony sulfide (SbS) colloid (*3*), stannous oxide colloid (*4*), microaggregated albumin (*5*), and small albumin microspheres (*6*). Soluble Tc-99m stannous phytate (*7*), by becoming colloidal in vivo, localized well in the marrow of rabbits but not in other species. With attempts to improve its marrow localization by autoclaving, the hydrolyzed labeled products localized in the skeleton rather than the marrow (*8*).

Indium-111 is also used for marrow imaging. This radionuclide, injected at an acidic pH, labels transferrin in vivo and concentrates in the marrow by 24 hr (*9*). Its marrow localization in patients with some hematological abnormalities, however, is markedly different from that of Fe-52 or Tc-99m S colloid (*10*) and the marrow radiation dose from this agent is high (3.8 rads/mCi) (*11*).

Many years ago microaggregated albumin was prepared by heat denaturation and was labeled with I-131 for experimental studies of the reticuloendothelial system (*12,13*); later it was labeled with Tc-99m (*5*). A commercial kit of microaggregated albumin for Tc-99m labeling is now available (M-NEN).* In a recent comparative imaging study of several Tc-99m colloids (*14*), minimicroaggregated albumin (MM-NEN)* showed the best marrow concentration, followed by SbS colloid, stannous phytate, and S colloid. The present study was undertaken to optimize the formulation of minimicroaggregated albumin for marrow imaging and to compare its marrow concentration with that of other colloids, Fe-59, and In-111 in the rat and dog.

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MATERIALS AND METHODS

Fe-59 citrate,† In-111 chloride,‡ Tc-99m S colloid,‖ and Tc-99m microaggregated albumin (M-NEN)* were obtained commercially. An experimental commercial preparation of Tc-99m minimicroaggregated albumin (MM-NEN)* was also obtained. Several other formulations of Tc-99m minimicroaggregated albumin were prepared, varying albumin, stannous ion and electrolyte concentrations, stabilizer, surfactant, pH, and heating time and temperature. A preliminary evaluation of the biodistribution of these colloids was obtained by (a) direct radioassay of the tissues 30 min after intravenous injection in rats and (b) posterior camera images of the dog abdomen 15 min and 1 hr after 5 mCi of the Tc-99m colloids were given intravenously. Each of the ten colloids was tested in three dogs and the same three animals were used for all preparations. The 500-Kcount images were acquired in a 64 × 64 matrix on a PDP 11/34 computer. Areas of interest were flagged over the liver, body background, and lumbar spine. Count ratios for marrow to liver and liver to background were determined after normalizing all counts to 50 matrix elements.

The preparation of minimicroaggregated albumin (MMAA) that achieved the best marrow localization was selected for further evaluation. It was prepared from an aqueous solution of 1 mg/ml human serum albumin§ and 2 mg/ml of Poloxamer 210 (F-88),¶ to which 0.4 mg/ml stannous chloride ($SnCl_2 \cdot 2\ H_2O$ in 0.2 *N* HCl) was added. The pH was adjusted to ~7 with disodium phosphate, resulting in a clear solution. This was heated in a water bath at 70 °C, with continuous stirring, for 30 min. The colloid formed was then cooled to room temperature and filtered through a 0.22-μ membrane filter. Normal human serum albumin was added to a level of 10 mg/ml to serve as stabilizer, and 1-ml aliquots in serum vials were lyophilized in a freeze dryer. Labeling was obtained by adding 20–75 mCi of pertechnetate (Tc-99m) eluant to each vial.

Instant paper chromatography and ITLC were used for quality control: Whatman paper 31, ethanol-acetone for free pertechnetate, and silica-gel ITLC-SG in saline for water-soluble albumin activity. More than 97% of the radioactivity remained at the origin in both systems, indicating excellent binding. Particle sizing of this colloid and MM-NEN was determined by passing aliquots of labeled colloid through Nuclepore membrane filters of various pore sizes.

Commercial Tc-99m SbS colloid proved unsatisfactory for marrow imaging because of a sizable fraction of unbound activity, so we prepared this colloid locally according to the method of Martindale et al. (*15*), except that PVP-40 was used instead of PVP-44. 1.5 ml of pertechnetate (Tc-99m) were added to an equal volume of preformed colloid in a 10-ml serum vial followed by 0.2 ml of 1.0 *M* HCl. This mixture was autoclaved at 128 °C for 15 min, cooled, and pH adjusted to ~6.3 using a phosphate buffer ($Na_2HPO_4 \cdot 7\ H_2O$, 93 mg/ml; $NaH_2PO_4 \cdot H_2O$, 5.4 mg/ml). In the biodistribution experiments to be described below, the labeling efficiency of all colloids was greater than 97%.

Blood clearance and tissue-to-organ radioassays were carried out in 25 mongrel dogs of either sex with a mean weight of 19.6 kg (range 14.2–27 kg). Five dogs were used for each of five Tc-99m colloids: sulfur colloid (S), antimony sulfide colloid (SbS), microaggregated albumin (M-NEN), minimicroaggregated albumin (MM-NEN), and minimicroaggregated albumin prepared as described above (MMAA). In all animals, 20 μCi of Fe-59 citrate were administered intravenously, to serve as an internal standard of marrow uptake, and the first five dogs also received 200 μCi of In-111 chloride at pH 2 intravenously. On the following day, the dogs were anesthetized with 30 mg/kg of sodium pentobarbital intravenously. Two intracaths were inserted into subcutaneous veins, one for blood sampling and the other for administrating the radioactivity. Twenty-three hours after the Fe-59 citrate injection, each animal received 2.5 mCi of one of the Tc-99m colloids, and heparinized blood samples were withdrawn at 3, 5, 10, 30, and 60 min.

Immediately thereafter the animal was killed with 10 ml of euthanasia solution intravenously. The liver, spleen, lungs, kidneys, thyroid, and bladder with urine were removed in toto and weighed: a minimum of three weighed samples were obtained from each of these organs, and from a section of the gastrocnemius muscle, for well counting in comparison with a standard of the administered activity. Samples of cortex and medulla of the right kidney were obtained separately, weighed, and counted. Three urine samples were taken after noting the total volume in the bladder. In preliminary experiments, marked variation in activity was found between multiple liver samples. Consequently, the entire liver was homogenized after weighing and three samples of the homogenate were taken for counting. Cores of red marrow were obtained with a quarter-inch orthopedic crown drill from the upper neck of the left femur and right humerus, then weighed and counted. The sternum, left humerus, and left fibula were stripped of all overlying soft tissue, weighed, placed in plastic containers, fragmented, and counted with a two-inch probe scintillation detector with flat-field collimator at a distance of 23 cm; these were compared with a standard of the injected activity in the same geometry. Dual- and triple-peak gamma spectrometry was used to separate Fe-59, In-111, and Tc-99m activities, using appropriate crosstalk correction factors. Data were expressed as the percent of administered activity in the whole organ. It was assumed that the skeletal muscle was 54.45% of the body weight and the skeleton 8.71% of body weight (*16*). The canine blood volume varied from 7.2 to 10.2% of the body weight in

various literature sources (*17*); a "middle" figure of 8% of the body weight was arbitrarily selected to calculate the activity in the total blood volume.

Three methods were used to calculate the total activity in the "functioning" bone marrow. The first two were based on a previous complete study by Greenberg et al. (*18*) of the distribution of Tc-99m S colloid in all parts of the skeleton in five normal mongrel dogs. They found that 6.075% of the total skeletal reticuloendothelial activity was contained in one humerus, and 2.73% in the sternum. In the first method we multiplied the percent administered activity in the sternum by 100/2.73, and in the second method the percent administered activity in one humerus was multiplied by 100/6.075. In the third method, the total red marrow activity was calculated from the percent administered activity in the core samples obtained from the humeral and femoral marrow, assuming that the proportional mass of red marrow is the same as in a standard 70 kg man (*19*)—i.e., 2.14% of the body weight. This arbitrary estimate of canine marrow mass is similar to published measurements. In two young adult dogs the marrow volumes were 2.4 and 1.9% of body weight (*20*) and from data on 25 dogs (*21*) a mean marrow volume of 1.9% of the body weight was calculated.

Various ways of expressing the marrow concentration data for the five colloidal preparations were evaluated by analysis of variance (*22*). Multiple comparisons of colloid pairs were made by Tukey's "honestly significant difference" procedure (*22*).

Similar radioassay measurements were performed in Sprague-Dawley rats with a mean weight of 367 g (range 307–540 g). Four of the five colloids were studied (omitting M-NEN) for comparison with Tc-99m albumin.* Three animals were used for each substance. Four to six microcuries of Tc-99m agent in 0.2 ml were administered through a femoral vein, and the animal killed at 30 min. The values were expressed as percent administered activity per whole organ. Marrow to blood and marrow to muscle concentration ratios were also calculated, based on the percent administered activity per one percent body weight of tissue. The mass of skeletal muscle was assumed to be 45.5% of body weight (*23*). For animals of this size, the blood volume was estimated at 5.5% of the body weight, based on the work of Keene (*24*). The total marrow content was calculated from the activity in one stripped femur, assuming that this presented 9.5% of the total marrow (*24*), with negligible activity localized in bone.

RESULTS

Mean blood clearances of the five Tc-99m colloids during the first hour after injection appear in Fig. 1. S colloid had the fastest clearance, followed closely by MMAA. The SbS colloid had the slowest clearance and

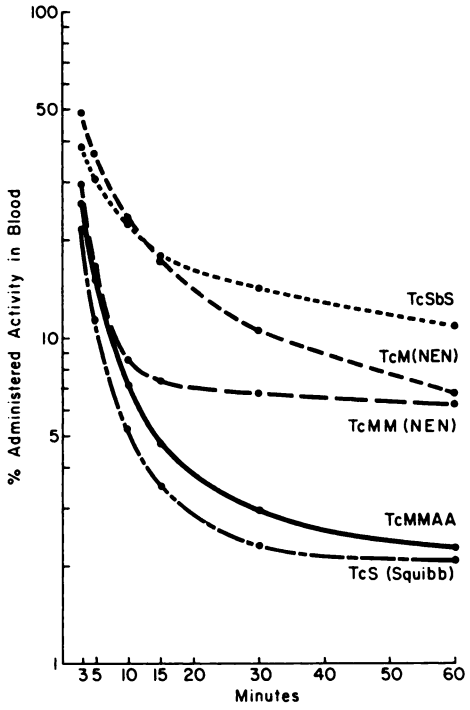

FIG. 1. Blood clearances of five different Tc-99m colloids in dog.

M-NEN, an agent designed primarily for hepatosplenic imaging, had the second slowest. The minimicroaggregated albumin preparation (MM-NEN) initially cleared rapidly but slowed markedly after the first 10 min.

The organ distributions in the dog for the five Tc-99m colloids at 1 hr, and In-111 and Fe-59 at 24 hr, are compared in Table 1. The three methods for calculating the percent administered activity in the marrow are in reasonable agreement for each agent, with the exception of Method 3 for In-111. The marrow content is highest for radioiron, followed by radioindium. S colloid had the lowest marrow concentration, MMAA the highest marrow concentration of any of the colloids, and MM-NEN the second highest. In the first two methods, it was assumed that all of the radioactive colloid content of the sternum or humerus was contained in the marrow and that the activity in the skeletal tissue was negligible. This skeletal activity was calculated indirectly by radioassay of the stripped and weighed fibula, assuming that the canine skeleton was 8.71% of the body weight (*16*). A previous study of Greenberg et al. (*18*) showed that the fibula contained no functioning marrow. Using this indirect method, we found the total skeletal content of Tc-99m MMAA to be 1% or less. Hence, the error produced by neglecting the skeletal content of radioactivity in comparing the colloid marrow concentrations appeared small.

Several marrow concentration ratios for each of the five Tc-99m colloids are listed in Table 2. In every instance, the MMAA colloid had the best ratio. The results of analysis of variance of the marrow content of the

TABLE 1. ONE-HOUR BIODISTRIBUTION OF Tc-99m COLLOIDS. Cf 24 HR FOR In-111 AND Fe-59 IN DOGS. % ADMINISTERED ACTIVITY/ORGAN: MEAN VALUES (STANDARD DEVIATIONS)

	S	SbS	M-NEN	MM-NEN	MMAA	In-111	Fe-59
No. of animals	5	5	5	5	5	5	25
Blood	2.09 (0.828)	10.8 (7.18)	6.16 (2.10)	6.77 (0.970)	2.27 (0.231)	10.9 (4.19)	2.80 (0.752)
Liver	81.4 (10.9)	66.1 (9.89)	71.8 (6.05)	81.7 (6.01)	82.8 (5.68)	15.3 (3.19)	9.96 (5.48)
Spleen	16.1 (8.25)	13.0 (5.28)	11.6 (6.33)	4.17 (2.22)	1.97 (0.803)	2.79 (1.93)	15.55 (9.72)
2 Lungs	2.34 (1.63)	1.75 (0.879)	2.08 (0.910)	1.03 (0.520)	0.744 (0.233)	3.06 (0.881)	0.855 (0.365)
2 Kidneys	0.411 (0.0717)	0.512 (0.206)	1.16 (0.316)	1.87 (0.195)	1.26 (0.309)	2.20 (0.236)	2.78 (1.15)
cortex	0.389 (0.0673)	0.430 (0.173)	0.979 (0.330)	1.70 (0.178)	1.04 (0.276)	2.06 (0.236)	2.73 (1.14)
medulla	0.0110 (0.00335)	0.0410 (0.0172)	0.0908 (0.0130)	0.0856 (0.0222)	0.111 (0.0330)	0.0679 (0.0139)	0.0234 (0.0178)
Urine	0.0929 (0.0543)	0.499 (0.280)	0.934 (0.590)	0.636 (0.369)	1.16 (0.426)	0.183 (0.242)	0.008 (0.02)
Muscle	1.07 (0.496)	5.64 (4.93)	4.43 (1.61)	2.73 (0.902)	1.56 (0.283)	14.6 (4.95)	11.2 (6.33)
Thyroid	0.00307 (0.00161)	0.00240 (0.0004)	0.0771 (0.0443)	0.0129 (0.0255)	0.00153 (0.0005)	0.00535 (0.00172)	0.0122 (0.0152)
Sternum	0.0456 (0.0303)	0.0511 (0.0241)	0.0830 (0.267)	0.180 (0.0676)	0.313 (0.0939)	0.440 (0.112)	1.04 (0.333)
Lt humerus	0.0845 (0.0154)	0.1483 (0.0980)	0.147 (0.0719)	0.266 (0.0612)	0.501 (0.158)	0.912 (0.574)	1.94 (0.758)
Marrow method 1	1.67 (1.11)	1.872 (0.882)	3.04 (0.978)	6.59 (2.48)	11.5 (3.44)	16.1 (4.10)	36.1 (12.2)
method 2	1.39 (0.253)	2.44 (1.61)	2.42 (1.18)	4.38 (1.01)	8.25 (2.60)	15.0 (9.45)	31.9 (12.4)
method 3	1.43 (0.691)	2.44 (1.07)	2.34 (0.853)	7.21 (3.94)	8.28 (3.74)	7.48 (3.59)	35.8 (18.1)

Tc-99m colloids using six different methods of evaluation are listed in Table 3. The differences between S, SbS, and M-NEN colloids were not significant ($P > 0.05$) and MM-NEN was better than S colloid in only two of six criteria. However, the MMAA colloid was significantly better than all other colloids in at least four of the six criteria.

The liver concentration was lower for Fe-59 and In-111 than for any of the colloids. Among the colloids, the SbS had a relatively low liver concentration and relatively high uptake in muscle. The liver concentration of MMAA colloid was similar to that of S colloid but the splenic content was much lower. The lungs, kidneys, and urine had relatively low concentrations for all agents tested. For all colloids, from 84 to 95% of the renal activity was contained in the cortex. The extremely low thyroid activity indicated an absence of free pertechnetate in vivo.

The results of the biodistribution study in rats of four of the Tc-99m colloids, compared with Tc-99m albumin, are summarized in Table 4. These animals were killed at 30 min because this time interval, for a 370-g animal, is biologically equivalent to about 1.4 hr in a 20-kg dog and about 3 hr in a 70-kg man (*25*). The calculated marrow concentrations for the SbS, MM-NEN, and MMAA colloids were higher than that of the S colloid.

TABLE 2. MARROW CONCENTRATION RATIOS OF Tc-99m COLLOIDS IN THE DOG. MEAN VALUES FROM FIVE ANIMALS EACH (STANDARD DEVIATIONS)

	Colloid	S	SbS	M-NEN	MM-NEN	MMAA
	humeral marrow	0.0785	0.102	0.131	0.260	0.325
		(0.0445)	(0.121)	(0.156)	(0.171)	(0.140)
Colloid / Fe ratios						
	femoral marrow	0.0693	0.0947	0.120	0.185	0.339
		(0.0393)	(0.100)	(0.127)	(0.129)	(0.174)
Humeral marrow / blood ratios						
		4.59	0.710	1.36	3.28	13.90
		(2.30)	(0.342)	(0.329)	(2.32)	(7.11)
Humeral marrow / muscle ratios						
		59.4	14.3	12.9	62.1	131.6
		(35.3)	(9.05)	(3.94)	(50.8)	(37.6)

The marrow concentration ratio for SbS/S was 2.7, compared with a figure of 2.4 from Martindale et al. (*15*) in the same species. Unfortunately, however, the blood level of the SbS colloid is much higher than that of the other colloids. The MM-NEN and MMAA colloids had better marrow-to-blood and marrow-to-muscle concentration ratios than either S or SbS colloids.

Nuclepore membrane filtration of different batches of MMAA indicated that the particle size distribution was highly reproducible. One hundred percent of the colloidal particles passed through a 0.2-μ filter, 87% through 0.1 μ, and 85% through 0.05 μ. Moreover, the biodistribution of different batches of this labeled colloid in the rat was highly reproducible. Eighty-three percent of the particles of MM-NEN colloid were between 0.03 and 0.2 μ. According to the manufacturers, 95% of the particles of M-NEN colloid range between 0.2 and 2 μ. For S colloid prepared from hydrogen sulfide, 80% of the particles are less than 0.45 μ (*26*). For most commercial S colloids prepared by acid thiosulfate reduction, 82%

TABLE 3. P VALUES* FOR ANALYSIS OF VARIANCE OF MARROW CONTENT OF Tc-99m COLLOIDS IN THE DOG (MULTIPLE COMPARISONS OF COLLOID PAIRS BY TUKEY'S PROCEDURE)

Colloid	A S	B SbS	C M-NEN	D MM-NEN	E MMAA		
Source of variation	% Admin. activity marrow (method 1)	% Admin. activity marrow (method 2)	Colloid/Fe ratios humeral marrow	Colloid/Fe ratios femoral marrow	Humeral marrow/blood ratios	Humeral marrow/muscle ratios
Between all groups	$\ll$0.001	$\ll$0.001	<0.05	<0.05	<0.001	<0.001
E—A	<0.01	<0.01	=0.05	<0.05	<0.01	<0.01
E—B	<0.01	<0.01	NS	<0.05	<0.01	<0.01
E—C	<0.01	<0.01	NS	NS	<0.01	<0.05
E—D	<0.01	<0.01	NS	NS	<0.01	<0.05
D—A	<0.01	=0.01	NS	NS	NS	NS
D—B	=0.01	NS	NS	NS	NS	NS
D—C	NS†	NS	NS	NS	NS	NS
C—A	NS	NS	NS	NS	NS	NS
C—B	NS	NS	NS	NS	NS	NS
B—A	NS	NS	NS	NS	NS	NS

* Probability of random variation.
† NS = not significant (P >0.05).

TABLE 4. THIRTY-MINUTE BIODISTRIBUTION OF Tc-99m COLLOIDS OF Tc-99m ALBUMIN IN RATS. % ADMINISTERED ACTIVITY PER ORGAN: MEAN VALUES FROM THREE ANIMALS

	S	SbS	MM-NEN	MMAA	Alb
Blood	5.89	13.9	7.78	1.92	42.7
Liver	72.5	60.4	70.4	81.0	11.4
Spleen	5.98	7.85	3.39	2.43	0.96
2 Lungs	1.05	0.58	0.24	0.10	1.36
2 Kidneys	3.02	0.73	2.41	1.90	6.72
Bladder and urine	2.51	1.29	0.89	1.79	6.36
GI tract and contents	0.030	1.72	2.74	1.16	5.91
Muscle	3.75	2.76	2.26	0.96	6.73
Marrow	1.55	4.24	5.99	5.18	3.79
* Marrow/blood	0.441	0.387	0.844	2.45	0.095
* Marrow/ Muscle	6.03	17.84	37.4	54.7	5.02

* Based on % dose/1% BW of tissue.

of the particles range between 0.1 and 3 μ, 78% between 0.1 and 1 μ, and 60% between 0.1 and 0.4 μ (*27*). SbS colloid has the smallest particles, ranging from only 1 to 13 nm by electron micrography (*15*).

DISCUSSION

Many factors influence the rate of blood clearance and distribution of colloids, including particle size and number, the presence of stabilizers, surface-active agents, competing colloids, opsonins, the chemical nature of the colloid surface, and the distribution of surface charge and electrophoretic mobility (*26,28,29*). In addition, blood clearance in experimental animals is hastened under anesthesia, probably due to increased liver blood flow (*28*). From studies of radioactive colloids of Au, Y, Zr, Nb, and La (*30*), smaller particles are cleared from the blood more slowly than larger ones. With chromic phosphate (P-32) colloids (*28*), liver activity decreases with smaller particles but a striking increase in marrow activity occurs only in rabbits. Colloidal blood clearance follows first-order kinetics up to 10^{13} particles/kg, and the rate is limited by the blood flow to the major reticuloendothelial organs; increasing the number of particles beyond this limit slows the clearance rate (*31*). Coating of particles with opsonins is essential for clearance by the RE cells. Opsonin has been identified (*32*) as an α-2 surface-binding glycoprotein (plasma fibronectin, α-2-cryoglobulin, cold insoluble globulin or CIg) with a molecular weight of 450,000 and a normal human serum level of 0.3–0.4 mg/ml. With a large number of colloidal particles injected, this protein is rapidly exhausted and plasma clearance is delayed.

From the available biological data on Tc-99m S colloid, the Task Group of the MIRD Committee (*33*) concluded that in a normal adult 85% of the administered activity localized in the liver, 7% in the spleen, 5% in the marrow, and 3% in the rest of the body. In comparing new agents for marrow imaging with this colloid, direct marrow radioassays in humans are not feasible; data must be obtained either from external measurements or by extrapolation of animal data. Unfortunately, there are marked species differences in marrow localization. The rabbit is probably not suitable for this assessment, since unlike other species, active marrow is distributed throughout the entire skeleton (*34*). Although its cortical bone blood flow is similar to that of other species (about 0.01 ml/min/g), the marrow flow is 25 times greater than cortical bone blood flow (*35*), compared with only eight times greater in the dog (*36*). The uptake of chromic phosphate(P-32) colloid was much higher in the rabbit than in other species (*28*). The rat also is not an ideal model for marrow agents because the marrow mass is relatively small and decreases with age from 1.2 to 0.4% body weight (*34*), compared with a more constant level of about 2% for man and several other species.

In mice, Atkins et al. (*26*) found that Tc-99m S colloid prepared from hydrogen sulfide had an uptake of about 8% in the marrow. With the injection of relatively huge doses of colloidal particles or gelatin stabilizer, the uptake was increased to 13% with a concomitant decrease in liver activity. However, S colloid prepared by thiosulfate acid reduction had a marrow uptake of only 5–6%. In rats and mice, Davis et al. (*27*) also observed an increased marrow uptake of smaller-particle (<0.1 μ) S colloid compared with other commercial colloids, but marrow visualization was not noticeably improved in clinical images.

In the dog only 0.84% of administered activity was recovered in the marrow with colloidal Au-198 (10–27 nm), calculated from the data of Zilversmit et al. (*37*). In one dog, 2.8% of injected activity was found in the skeleton (*18*) using S colloid prepared from hydrogen sulfide gas, compared with our value of about 1.5% for commercial S colloid. Greenberg et al. (*18*) observed that the fractional distribution of S colloid skeletal activity in different parts of the skeleton was surprisingly similar to the distribution of ferrous (Fe-59) citrate injected 24 hr previously. Taketa et al. (*38*) repeated this observation in young adult rhesus monkeys. In this study, 83% of the S colloid localized in the liver, 3.6% in the spleen, and 5.4% in the marrow compared with the Fe-59 values of 10%, 0.6%, and 57%, respectively. These workers noted marked but parallel differences from previous reports in marrow concentrations of Fe-59 and S colloid in different species. Comparing these values in the monkey with the present dog data, we find the liver

concentrations of Fe and S colloid similar in the two species but the marrow content in the dog considerably lower. In canine marrow, only about 0.5% of all cells are RE cells (*39*). As expected, the relatively large contractile spleen in the dog contained more activity than in other species.

In the baboon, Heyman et al. (*14*) estimated the marrow content of different Tc-99m colloids using camera-and-computer techniques. With MM-NEN colloid, marrow uptake was improved by a factor of 3 compared with S colloid and with SbS or M-NEN colloids, by a factor of 2. In the current dog study, this factor was 4 for MM-NEN, 1.5 for SbS, and 1.7 for M-NEN colloid. With the new formulation of MMAA, marrow uptake was increased by a factor of 6 compared with S colloid. Although the marrow uptake of four Tc-99m colloids in the rat was quantitatively different from the values obtained in the dog, the marrow concentrations of the two minimicroaggregated albumin preparations were again higher than those of sulfur colloid, without the high blood levels associated with SbS colloid.

The current study shows that the MMAA colloid reaches a higher marrow concentration than other preparations in the dog and rat, with relatively low activity in blood and skeletal muscle. In a clinical crossover study of 15 patients (*40*), improved marrow imaging was obtained with MM-NEN compared with S colloid. With the new formulation, the high activity in the liver and spleen will remain a problem in obscuring the adjacent and underlying marrow in camera images. Nevertheless, clinical trials of this agent appear warranted. Assuming no biological excretion and instant uptake of 80% of the administered activity to the liver, 2% to the spleen, 15% to the marrow, and 3% to the rest of the body, the marrow radiation dose in "standard man" would be 0.055 rads/mCi, using the published "S" factors (*41*).

FOOTNOTES

* New England Nuclear, North Billerica, MA.
† Mallinckrodt, St.Louis, MO.
‡ Medi-Physics, Emeryville, CA.
‖ Tesuloid, Squibb, New Brunswick, NJ.
§ Cutter Laboratories, Berkeley, CA.
¶ Wyandotte Chemical, Wyandotte, MI.

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