
Radiopharmaceuticals for Radiation Synovectomy: Evaluation of Two Yttrium-90 Particulate Agents

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Radiation synovectomy, a noninvasive therapeutic alternative to surgical synovectomy, has not gained widespread acceptance in the United States because of the lack of a suitable radiopharmaceutical. Two new radioactive particles, [⁹⁰Y]Ca oxalate and [⁹⁰Y]ferric hydroxide macroaggregates (FHMA), were developed in our laboratory and evaluated for size, stability, and joint leakage. More than 90% of the [⁹⁰Y]Ca oxalate particles were in the optimal size range of 1–10 μm, and the unbound activity in serum and synovial fluid was 3.7% to 5.0%. Following injection in rabbit knees, leakage of [⁹⁰Y]Ca oxalate was 5 ± 2%, with localization primarily in the bone and virtually no uptake by the lymph nodes or liver. Yttrium-90 FHMA particles were larger (95% > 10 μm), and at least on a microscopic level, appeared to distribute homogeneously over the articular surface. Leakage of [⁹⁰Y]FHMA was initially less but eventually slightly exceeded that of [⁹⁰Y]Ca oxalate. Nevertheless, both radiopharmaceuticals can provide a satisfactory therapeutic dose to the knee with less than half the leakage and a marked reduction in absorbed dose to nontarget tissues compared to previously tested agents. Ease of preparation, physical characteristics of the ⁹⁰Y beta ray, and apparent lack of substantial leakage from the joint make these agents extremely attractive for clinical evaluation in rheumatoid arthritis patients who are unresponsive to medical therapy.

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Approximately 2% of adults in the United States have rheumatoid arthritis by current diagnostic criteria (1). The major cause of pain, as well as physical and economic disability, in these patients is destruction of diarthroidal or synovial joints; 87% of the patients will ultimately have involvement of the metacarpophalangeal joints, and 56% will have involvement of the knee joint (2). Untreated, chronic synovial inflammation is not only accompanied by perpetual pain and loss of motion, but leads to pannus formation and to eventual destruction of the articular cartilage.

In severe cases of chronic rheumatoid arthritis where medical therapy has been unsuccessful (3,4), surgical removal of the inflamed joint lining (surgical synovectomy) has been shown to provide symptomatic relief lasting from 2 to 5 yr (5–9). Although surgical synovectomy can temporarily arrest the disease process and

provide significant symptomatic relief, the recesses and crevices of joints make it technically very difficult, if not impossible, to excise all of the inflamed synovium, thus leading to eventual regrowth of diseased synovium and recurrence of symptoms. Additionally, at the time of recurrence, the presence of extensive fibrosis and scar tissue from the previous surgical synovectomy essentially precludes a second surgical intervention.

Chemical synovectomy, using osmic acid, alkylating agents such as thiotepa and nitrogen mustard, or antiproliferative agents such as methotrexate, has achieved limited acceptance because of concerns regarding systemic toxicity and local injury to articular cartilage (10, 11). Similar concerns have been expressed with repetitive intraarticular injection of corticosteroids (12).

Another treatment, radiation synovectomy, has been used extensively in Europe as an alternative to surgical synovectomy. First reported in 1952 (13), this procedure consists of the intraarticular injection of a radionuclide in colloidal or particulate form to ablate the inflamed synovium. The radiocolloids most frequently used have been those of yttrium-90 (⁹⁰Y) and gold-198

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(¹⁹⁸Au), whereas erbium-169 (¹⁶⁹Er), rhenium-186 (¹⁸⁶Re), and phosphorous-32 (³²P) radiocolloids have been used less often (14–20).

In contrast to gold and rhenium, which have significant drawbacks, the physical decay characteristics of ⁹⁰Y (a pure beta-emitter, 2.3 meV maximum energy, 2.7-day half-life and maximum tissue penetration of nearly 1 cm with ~80% of the energy deposited in the first 4–5 mm) make it a nearly ideal radionuclide for intraarticular radiation synovectomy of large joints (knees). Since the early 1970s, ⁹⁰Y has been used in Europe in the silicate, citrate, ferric hydroxide, and resin forms (21–23), and its use as the colloidal silicate is still widespread (24,25). The particle size of ⁹⁰Y in this latter form ranges from 10 nm to 100 nm, which allows for homogeneous distribution over the synovium and uniform radiation exposure. However, the relatively small size of the colloidal suspension is associated with moderate leakage from the joint. Attempts to quantify the amount of leakage have given values of 5–10% at 24 hr after administration, and between 15 and 25% at 5 days (23). Even with an optimistic assumption of 5–10% leakage, the radiation absorbed dose from 5 mCi of ⁹⁰Y would be between 250 and 500 rad to the liver and 5,000 to 10,000 rad to 10-g regional lymph nodes (26). Such estimates of radiation exposure have raised the level of concern and dampened enthusiasm for radiation synovectomy in many U.S. medical centers.

The problem of radioactive leakage from the inflamed joint can be diminished in three ways. First, leakage can be reduced by using radioactive particles of a proper size. An investigation aimed at determining the ideal particle size for minimal leakage with concomitant uniform coating and radiation exposure indicated that particles in the 2–5 μm range would possess the most desirable characteristics (27). Second, immobilization of the treated joint has been shown to reduce particle leakage in the first 48 hr after administration (28). Third, choosing a radioisotope with a short half-life minimizes the cumulative radiation dose to nontarget tissue because a greater fraction of the radioactive decay occurs prior to leakage from the joint.

This latter parameter led to the use of dysprosium-165 -ferric hydroxide macroaggregates ([¹⁶⁵Dy]FHMA) in the United States (29,30). Although ¹⁶⁵Dy has several attractive attributes (2.3-hr half-life, nearly pure beta-emitter and ease of preparation into 1–5 μm macroaggregates), the technique has not met with widespread acceptance because the extremely short half-life requires that the medical center be located within a short distance from a high-flux nuclear reactor.

Since ⁹⁰Y is presently considered the radionuclide of choice for therapeutic applications and is in clinical trials attached to monoclonal antibodies (31,32), it appeared to us that the preparation of a properly sized

particle labeled with ⁹⁰Y would lead to minimal leakage from the joint and thus alleviate all of the difficulties found in the production of [¹⁶⁵Dy]FHMA, while maintaining the desired radiation ablation of the inflamed synovium. To this end, we have prepared and tested in animals a new radioactive particle, [⁹⁰Y]Ca oxalate, and a second potential therapeutic agent, [⁹⁰Y]FHMA, prepared in a manner similar to that described for [¹⁶⁵Dy]FHMA (33).

MATERIALS AND METHODS

Radionuclide Production

The ⁹⁰Y activity was obtained from a 25-mCi ⁹⁰Sr/⁹⁰Y generator (34), which was eluted with 0.003 M EDTA (pH = 4.6). The ⁹⁰Y was liberated from the ethylenediaminetetraacetic acid (EDTA) chelate prior to the preparation of the particles in a standardized remote system (35) using a 1:1 mixture of concentrated H₂SO₄:HNO₃. Next, the ⁹⁰Y activity was taken up in 0.5 ml of 0.05 M sodium acetate (pH = 6.0). The amount of ⁹⁰Sr breakthrough was accurately determined for each elution of the generator using a published method (36) in which an anion exchange resin retains most of the ⁹⁰Y, while allowing the ⁹⁰Sr to be eluted for counting. Briefly, 1 ml of the eluate was evaporated to dryness on a planchette and then counted at a fixed geometry with an end-window GM counter with and without a 220-mg/cm² aluminum absorber along with a standard containing 0.01 μCi of ⁹⁰Sr-⁹⁰Y, also mounted on a planchette.

Phantom Studies

Counting and imaging were performed on a Picker Dyna Camera equipped with interchangeable collimators. In order to establish the best collimator and the best window settings capable of detecting small amounts of ⁹⁰Y and in order to maximize the signal-to-noise ratio, we assembled a phantom consisting of a Plexiglas tube, 50 cm long and 8 cm wide, filled with water, and having a hollow plastic sphere (100 ml in volume) attached at one end, while a human torso phantom containing internal organs such as the liver, heart, kidneys, and bladder was positioned at the other end. The plastic ball, which simulates the knee joint, was filled with water containing 1 mCi of ⁹⁰Y activity, and the best counting statistics were obtained using a pinhole collimator located 3 cm above the source with the following settings: energy range: 77–120 (keV); window: 50%. A pinhole collimator was selected for its ability to minimize counts from scattered radiation.

In order to determine the minimum amount of ⁹⁰Y that could be detected externally in the lymph nodes or liver due to leakage from the joint, a sensitivity study was carried out by placing 5 mCi of ⁹⁰Y into the 100-ml sphere and varying percentages of that amount (0.5%, 1%, 2%, 5%, 10%, 20%) in the liver compartment. Background counts, counts over the knee phantom, and counts over the liver, with and without shielding of the knee joint, were recorded.

Particle Preparation

Yttrium-90 calcium oxalate. One to two millicuries of ⁹⁰Y activity in the acetate form was transferred from the quartz vial, where the EDTA chelate had been destroyed, to a test

tube containing 0.5 ml of 0.1 M CaCl₂ (pH = 6.5). One milliliter of 0.1 M sodium oxalate (pH = 6.8) was then added to the test tube while shaking, and a white precipitate was formed. Three milliliters of 2% gelatin was added to stabilize the size of the particles, and the test tube was then maintained, with intermittent shaking, for 1 hr at 37°C. Next, the particulate suspension was centrifuged at 2,000 rpm for 3 min to remove microparticles ("fines") as well as excess oxalate. The supernatant was removed and counted in a calibrated radioisotope assay chamber. The amount of radioactivity found in the discarded supernatant was expressed as a percentage of the initial activity. The precipitate was then resuspended a second time in 2 ml of 1% gelatin, shaken for 1 min by means of a vortex mixer, and ultrasonicated for 15 sec. The suspension was again centrifuged at 2,000 rpm for 3 min and the supernatant removed and counted, as described above. Finally, the particles were resuspended for injection in 0.6 ml of 1% gelatin by shaking in a vortex mixer.

⁹⁰Y-ferric hydroxide macroaggregates. This material, precipitated with the desired amount of ⁹⁰Y activity in the acetate form, was prepared according to a method described by Hnatowich et al. (33). For the injection, the particles were resuspended in 0.6 ml of 1% gelatin by shaking in a vortex mixer.

In Vitro Sizing and Stability Studies

Preliminary estimates of the particle size were accomplished with an optical microscope and a hemocytometer using 40 X magnification. The particles were suspended in 1% gelatin and placed on the hemocytometer; size distribution was then estimated relative to the 50 μm × 50 μm squares. A more accurate estimate of the particle size, particularly for particles in the 0.1–1.0 μm range, was obtained by selective Nucleopore filtration according to the method of Davis et al. (37), with the particles suspended in saline.

The in vitro stability studies were carried out in 2 ml each of normal saline solution, human serum, and human synovial fluid diluted 1:1 with saline (to reduce viscosity). Approximately 1 mg of the particles was placed in a 10-ml vial, and 2 ml of each medium was added. The vials were stoppered and placed on a rocking platform for gentle agitation, then immersed in a water bath incubator maintained at 37°C. At various times, the tubes were removed and 2 ml of saline was added; the tubes were then shaken and centrifuged at 5,000 rpm for 5 min. Three aliquots of 1 ml each were removed from each test tube with a volumetric pipette and placed in three different 10-ml vials so that the geometry was the same in all the samples. The vials were then counted in a NaI (TI) well counter.

In Vivo Studies

New Zealand White rabbits (3–5 kg) were placed in metabolic cages. For each procedure, the animals were anesthetized with a single intramuscular injection of a mixture of ketamine (35 mg/kg) and xylazine (5 mg/kg). All radioactive preparations were injected through the patellar ligament in a volume ranging from 0.4 ml to 0.5 ml to avoid the possibility of leakage resulting from increased intraarticular pressure. The injections were performed under x-ray fluoroscopy to ensure correct placement of the needle inside the articular cavity.

Counts and images were taken immediately after injection and for many days thereafter by placing the anesthetized animals under the pinhole collimator in such a way that the

knee joint, bent at a 30° angle, fit into the external ring of the collimator. A radioactive standard, prepared by placing 0.1 ml of the injected agent into a 1-ml syringe, was centered over the opening, taped to the external ring of the collimator, and counted each time the knee was counted to allow correction for radioactive decay. Background counts were also taken at each counting interval. As another means of measuring possible joint leakage, blood samples were taken from the ear vein, and urine and feces were collected on a daily basis. At the conclusion of the in vivo counting studies, the biodistribution of the radioactivity was determined. The liver, heart, spleen, lungs, kidneys, right and left inguinal lymph nodes, and specimens from bone (ribs and femur) and bone marrow were removed. After being weighed, samples were counted in a NaI(Tl) well counter, along with a standard of the injected preparation.

RESULTS

In Vitro Studies

The labeling efficiency for the preparation of the [⁹⁰Y]Ca oxalate particles ranged from 85 to 95%. The [⁹⁰Y]Ca oxalate particles observed under the optical microscope appeared as individual spheres, with more than 90% smaller than 10 μm. Because of the macroaggregate nature of the [⁹⁰Y]FHMA, sizing was more difficult, but most of the particles appeared >10 μm in size. The optical determination of particle size was confirmed by a more quantitative technique, selective filtration. With this method, the [⁹⁰Y]Ca oxalate particles showed the following size distribution: 1% <0.4 μm, 2% <0.8 μm, 38% between 0.8 and 3.0 μm, 55% between 3 and 10 μm, and 4% greater than 10 μm. The [⁹⁰Y]FHMA aggregates gave the following analysis: 2% <1 μm, 3% between 1 and 10 μm, and 95% > 10 μm.

The stability of both particle systems was studied in serum, synovial fluid, and isotonic saline over an 11-day period. The saline values were always lower than the serum and synovial fluid values, which were essentially equal. For the [⁹⁰Y]FHMA particles, the unbound activity in saline ranged from 0.2 to 0.5% over the 11-day period, whereas the values in serum and synovial fluid ranged from 0.5 to 1.5%. The ⁹⁰Y-Ca oxalate particles gave somewhat higher unbound values, with saline results ranging from 2.3 to 3.5% and serum and synovial fluid values ranging from 3.7 to 5.0%.

In Vivo Studies

Gamma camera detection of radioactivity in possible sites of accumulation such as the inguinal lymph nodes, liver, and osseous structures after injection of ~2 mCi of ⁹⁰Y in the rabbit knee failed to show statistically significant counts above background. This observation was corroborated in the phantom studies where 1% of the 5 mCi of ⁹⁰Y contained in the knee was the detectable limit in the liver. Since both the in vivo and in vitro phantom measurements showed that the exter-

nal counting by gamma camera lacked the sensitivity to measure leakage values $< 50 \mu\text{Ci}$, leakage could only be measured by repetitive knee counting.

Using the bremsstrahlung settings, it was possible to obtain good images of the ^{90}Y activity distribution within the articular cavity. As can be seen in Figures 1 and 2, both agents appear to distribute uniformly on a macroscopic level over the articular surface. The radioactivity found by gamma camera counting in the injected knees is shown in Table 1. It can be seen that for the $[^{90}\text{Y}]\text{Ca}$ oxalate particles the average leakage was $<3\%$ of the injected dose at 3 days postinjection (^{90}Y half-life = 2.7 days) and $<5\%$ at 7 days postinjection. For the $[^{90}\text{Y}]\text{FHMA}$, the observed leakage rates were very similar to those of the oxalate particle system, with a cumulative leakage over 7 days averaging 3.3% of the injected dose. Both sets of leakage data show excellent agreement with the in vitro stability data in serum and synovial fluid. The biodistribution of ^{90}Y radioactivity that leaked to sites other than the knee is shown in Table 2. The results are expressed as the percentage of the injected dose per total organ, based on the organ weights reported by Kozma et al. (38), and also assuming that the bone structures and bone marrow constitute 10% and 4% of whole-body weight, respectively.

For urine, the percentage of dose shown is per volume of urine collected during the period specified. It can be seen that for each radiopharmaceutical $\sim 1\%$ of the injected activity was excreted in the urine at 24 hr, with an additional 0.5 to 1.0% excreted in the next

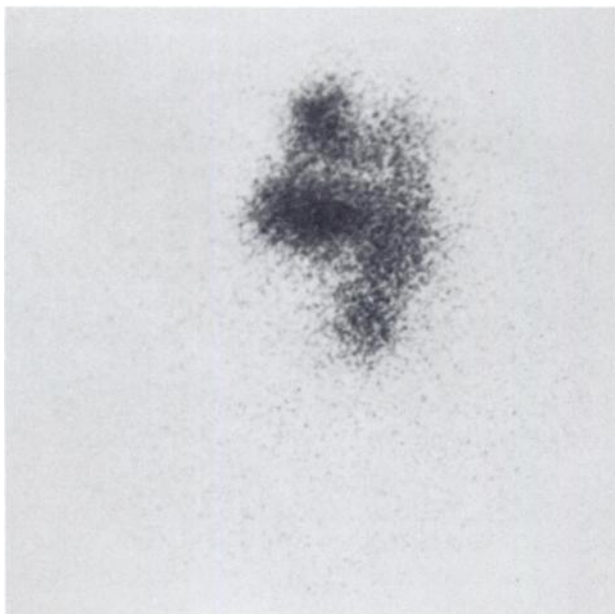


FIGURE 1
Gamma camera image of the rabbit knee using bremsstrahlung radiation 48 hr after injection of 1.2 mCi of $[^{90}\text{Y}]\text{Ca}$ oxalate. Picture represents collection of 47k counts in 600 sec.

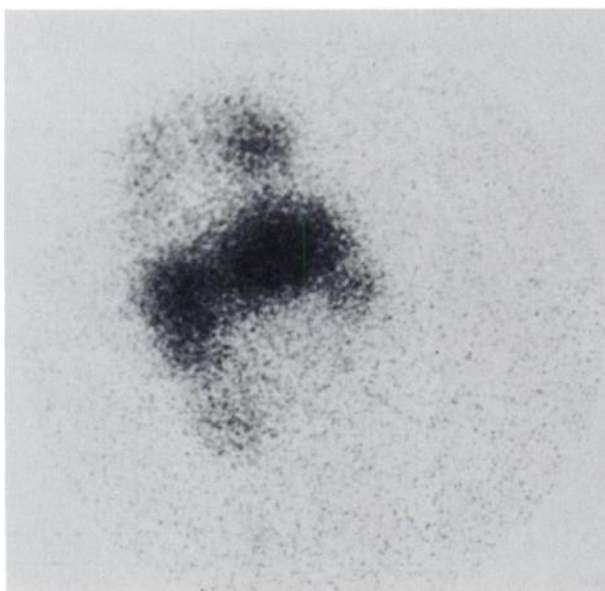


FIGURE 2
Gamma camera image of the rabbit knee using bremsstrahlung radiation 24 hr after injection of 1 mCi of $[^{90}\text{Y}]\text{FHMA}$. Picture represents collection of 51k counts in 600 sec.

24 hr and undetectable amounts thereafter. Values in blood were one order of magnitude lower than those found in urine. The amount of radioactivity found in the lymph nodes for either agent was always less than 0.01% of the injected dose for all time points checked. Very low levels of radioactivity were found in the liver and in all other organs sampled, with the exception of bone, which is clearly the major site of accumulation in both sets of data, with $\sim 5\%$ of the injected dose (equal to $>90\%$ of the total leakage measured) at 3 days or 9 days postinjection. Yttrium-90 Ca oxalate and $[^{90}\text{Y}]\text{FHMA}$ showed similar values for cumulative leakage, with between 2% and 3% found at 48 hr postinjection, and subsequent levels of $\sim 5\text{--}7\%$ found at all other time points. It should be noted that these studies were performed on normal joints. Therefore, the results cannot be compared directly with those obtained by other research teams using inflamed joints.

DISCUSSION

The nuclear medicine community long ago realized the potential importance of beta-emitting radiopharmaceuticals for the treatment of rheumatoid arthritis. The technique, known as radiation synovectomy, has evolved as an alternative to surgical synovectomy in patients who have been refractory to medical management. Although the modality has been used extensively in Europe for the past 25 years to treat rheumatoid arthritis in the knee joint, it has generated only modest research or clinical interest in the United States to date.

TABLE 1
Percentage of Administered ⁹⁰Y Activity Remaining in Rabbit Knees by Gamma Camera Bremsstrahlung Counting

Radiopharmaceutical	Time after administration (in days)				
	1 (n = 7) [*]	2 (n = 7)	3 (n = 2)	6 (n = 2)	7 (n = 3)
[⁹⁰ Y]Ca oxalate	100.0 ± 0.1	97.9 ± 1.8	97.9 ± 3.0	97.0 ± 0.5	96.5 ± 0.3
[⁹⁰ Y]FHMA	99.2 ± 2.1	99.0 ± 2.1	100.0 ± 0	97.8 ± 0.6	98.1 ± 1.9

^{*} Number of knees evaluated.

Clinical trials conducted by Sledge and Zuckerman (30, 39) using [¹⁶⁵Dy]FHMA for radiation synovectomy of the knee comprise virtually the entire U.S. patient experience. Although the results compared quite favorably to those of surgical synovectomy, the technique has not achieved widespread adoption because of the shortcomings of the radionuclide ¹⁶⁵Dy.

The superior physical decay characteristics of ⁹⁰Y compared to ¹⁶⁵Dy make it an obvious choice for radiation synovectomy of the knee, with the concomitant absolute requirement that leakage be restricted to <5% of the administered dose. The radiopharmaceutical used primarily in the European experience, [⁹⁰Y]silicate, unfortunately does not meet this last requirement,

TABLE 2
Biodistribution of ⁹⁰Y Radioactivity After Injection of Two ⁹⁰Y-Labeled Radiopharmaceuticals in the Knees of Normal Rabbits

Organs	[⁹⁰ Y]Ca oxalate Time after injection (in days)					[⁹⁰ Y]FHMA Time after injection (in days)				
	1	2 (n = 1)	3 (n = 1)	7 (n = 2)	9 (n = 1)	1	2 (n = 1)	3 (n = 1)	7 (n = 2)	9 (n = 1)
Right lymph nodes	— [†]	<0.001	0.001	0.008 ±0.02	0.002	—	<0.001	<0.001	0.001 ±0.005	0.002
Left lymph nodes	—	<0.001	0.001	0.008 ±0.02	0.002	—	<0.001	<0.001	0.001 ±0.004	0.001
Blood [§]	0.101 ±0.0004	0.037 ±0.0003	ND [‡]	ND	ND	0.07 ±0.0004	0.04 ±0.0003	0.04	ND	ND
Kidney	—	0.108	0.03	0.108 ±0.008	0.06	—	0.03	0.138	0.136 ±0.007	0.016
Liver	—	0.253	0.05	0.202 ±0.001	ND	—	0.074	0.317	0.362 ±0.000	0.318
Heart	—	0.005	0.003	ND	ND	—	ND	0.001	ND	ND
Spleen	—	0.002	<0.001	0.004 ±0.001	<0.001	—	ND	0.003	0.004 ±0.0004	ND
Lung	—	ND	0.02	0.04 ±0.001	ND	—	ND	0.02	0.124 ±0.0004	ND
Bone	—	0.429	4.31	4.34 ±0.0001	4.69	—	0.19	3.35	4.89 ±0.004	7.14
Bone marrow	—	ND	—	0.114	—	—	ND	—	0.01	—
Urine [§]	1.138 ±0.113	0.822 ±0.08	ND	ND	ND	0.933 ±0.013	0.625 ±0.121	ND	ND	ND
Feces	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Total activity measured	1.239	1.658	4.416	4.824	4.755	1.003	0.96	3.87	5.528	7.48
Cumulative leakage		2.86	6.78	6.90			1.92	5.48	7.18	

^{*} Expressed as % of injected dose per total organ.

[†] No data.

[‡] None detected (n = 1).

[§] n = 5.

with reports showing leakage varying from 5% to 25%. For this reason, it has never been used in clinical trials in this country. Thus, the challenge remains to prepare a particulate agent of the proper size such that leakage will remain <5% of the administered dose, with homogeneous deposition on the inflamed synovium, thus yielding a uniform radiation exposure and complete ablation of the diseased tissue. Another major advantage of ^{90}Y is that it can be obtained from a radionuclide generator that can supply high-purity ^{90}Y on a weekly basis for a period of more than 1 yr.

The question of ideal particle size for radiation synovectomy remains a matter of some debate. It has been shown that the larger the particle, the less leakage from the joint (27). The consensus is that a particle size of 5–10 μm minimizes leakage while still allowing homogeneous deposition on the synovial surface. It can be seen from our results that the calcium oxalate gives an activity size distribution where >90% of the activity is on particles between 1 and 10 μm in diameter, whereas the [^{90}Y]FHMA has a distribution where >95% of the activity is on particles >10 μm . Thus, while the in vitro stability data favored the FHMA particles over the oxalate, the particle size distribution would favor the oxalate over the FHMA.

When performing intraarticular injections in patients, it is relatively easy to be assured that the needle is, in fact, within the articular cavity. With animal models, however, it is not possible to have such a high degree of confidence, and for this reason we chose to perform all intraarticular injections under fluoroscopic guidance. In our initial studies the particles were suspended after centrifugation in the standard intravascular radiographic contrast agent Reno M-60 (E.R. Squibb & Sons, Inc., Princeton, NJ) prior to injection in the knee. Figures 3 and 4 show the placement of the needle traversing the patella ligament and ending in the intra-articular space. Figure 5 shows a typical lateral projection of the knee following removal of the needle after administration of 0.5 ml of particles suspended in Reno M-60. The presence of small amounts of EDTA as a stabilizer in the Reno M-60 caused removal of the ^{90}Y from the particles and precluded its use in the studies reported here.

Following intraarticular administration of ^{90}Y -labeled particulates, radioactivity may leave the knee joint by three routes. First, the particles may escape from the joint space intact, most commonly by way of the lymphatic system after phagocytosis by macrophages; the venous system following phagocytosis or endocytosis; or mechanical leakage into the interstitium. A second method of escape would involve breakdown of the particles within the joint space and liberation of the cationic species of the metal, in this particular instance Y^{3+} . Free to diffuse through the joint capsule, the cation would be picked up by the venous

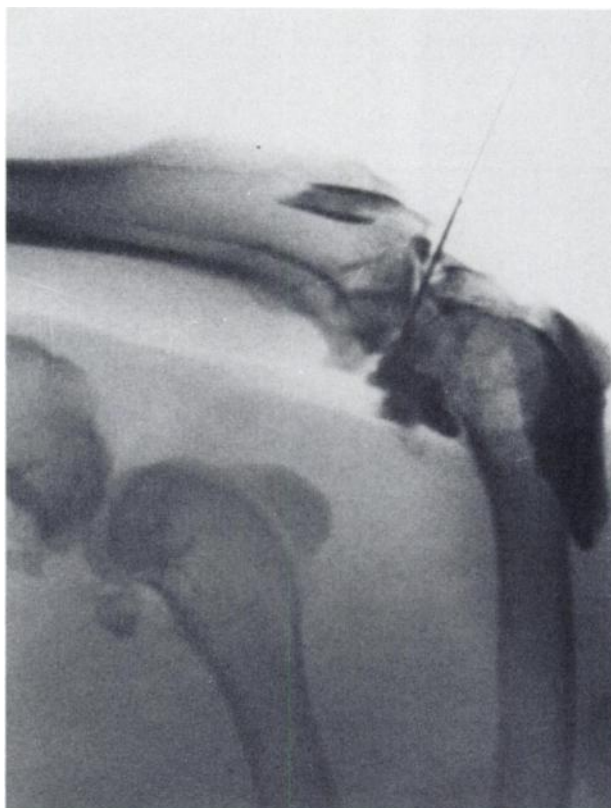


FIGURE 3
Lateral projection of the rabbit knee during injection of [^{90}Y]Ca oxalate particles suspended in Reno M-60.

drainage of the knee, and thus would give a biodistribution similar to that obtained by the i.v. injection of ionic yttrium. Finally, the breakdown to ionic yttrium could be followed by binding of the yttrium cation to either to large biologic macromolecules, such as albumin or transferrin, or small chelates, such as were already indicated in the case of EDTA in the Reno M-60.

In each of the situations described above, a particular biodistribution would be seen. In the case of leakage of the intact particles, the localization would occur in either the regional lymph nodes or the reticuloendothelial system. In the second case, the free cation would behave as ionically administered yttrium, which is known to be a bone-seeking element with little other tissue specificity. In the final case of binding to biologically active species, the yttrium either would be found in the vascular system, if bound to large macromolecules, or be excreted rapidly in the urine, if bound to small species in chelated form.

As shown in Table 2, the absence of any activity within the regional lymph nodes or those organs containing reticuloendothelial cells is clear evidence that the particles do not escape from the joint space intact. The lack of any significant amount of radioactivity in the blood also indicates that there is an insignificant

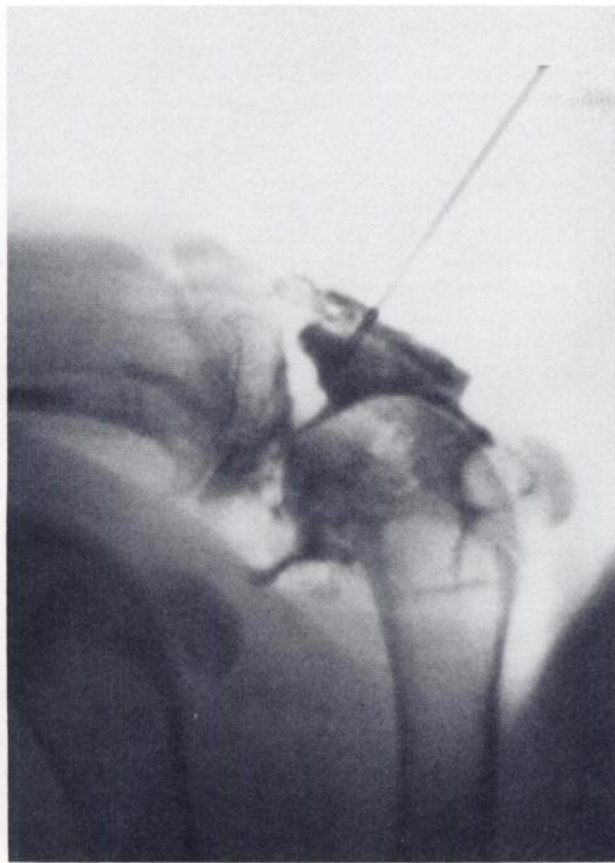


FIGURE 4
Lateral projection of the rabbit knee during injection of [⁹⁰Y]FHMA particles suspended in Reno M-60.

amount of binding of cationic yttrium to biologic macromolecules. Thus, the only plausible explanation for the ~5% leakage of radioactivity from the joint must be that cationic yttrium is produced, taken up in the venous supply, and delivered throughout the body to localize in those organs where it has a known affinity.

Thus, the bones and urine should be, and in fact are, the two biologic compartments where radioactivity is found in any significant amount. Excretion of ⁹⁰Y activity in the urine occurs mostly during the first 48 hr and is insignificant thereafter, accounting for 1% to 2% of the initially administered dose. Bone localization accounts for ~4% to 5% of the administered activity and for ~65% of total leakage.

As can be seen in Table 2, 98% of the activity found in whole bone resides within the osseous component, and 2% within the marrow. This has an extremely important prognostic implication for future patient trials. If the biodistribution results found in this animal study can be extrapolated to the patient situation, it would mean that 5 mCi of ⁹⁰Y administered intra-articularly would deliver 10,000 rad to the diseased synovium, while only imparting a few (up to perhaps 10 rad) to other organs, compared to the hundreds to



FIGURE 5
Lateral projection of the rabbit knee following removal of the needle. Note the absence of contrast agent outside the joint space, signifying satisfactory intraarticular administration.

thousands of rad delivered to liver and regional lymph nodes from the leakage with [⁹⁰Y]silicate.

CONCLUSION

In summary, rheumatoid arthritis and nonrheumatoid inflammatory synovitis are common diseases for which an affective medical therapy is not at hand. Radiation synovectomy with ⁹⁰Y silicate has been shown to be efficacious with respect to ablation of the inflamed synovium, but its safety has been questioned in light of the leakage problem and radiation exposure to nontarget organs. Radiation synovectomy with [¹⁶⁵Dy]FHMA has been shown to be both safe and effective, but lacks widespread clinical utility as a result of the very short physical half-life of the radionuclide. Both agents studied here, and in particular the [⁹⁰Y]Ca oxalate, overcome most of the previously encountered problems relating to leakage and homogeneity of deposition related to particle size. We are planning limited clinical trials to assess both the safety and efficacy of these two promising ⁹⁰Y-labeled radiopharmaceuticals.

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