Dysprosium-165 Ferric Hydroxide Macroaggregates for Radiation Synovectomy

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Radiation synovectomy of the knee has been performed previously with colloidal-sized particles containing long-lived radionuclides such as yttrium-90 and gold-198. Although the majority of patients respond well, a significant problem has been the leakage of radioactive material from the knee. We have improved the procedure by using (a) larger particles to minimize leakage and (b) a radionuclide with a shorter physical half-life, so that only leakage occurring soon after administration contributes to radiation exposure. The particles are ferric hydroxide macroaggregates with a size range of 0.5–5 μm, labeled by coprecipitation with dysposium-165. This radioisotope is a short-lived ($T_{1/2}$ = 139 min) beta emitter, which may be produced at high specific activity by reactor irradiation of natural dysprosium.

We have studied the particles in both normal and arthritic rabbits. The leakage following injection of the macroaggregates into the knee has been found to be lower than that for gold colloid in the same animal model. At 24 hr, the accumulation is about 0.3% of dose in the liver, the major site of uptake, about 0.1% in the kidneys, and considerably less in other tissues. Because of the low leakage rates and the use of a short-lived radionuclide, it may be estimated that a patient's whole-body exposure due to therapy of a knee with this technique will be about 0.4 rads to the whole body and about 2 rads to the liver.

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Radiation synovectomy, in which the beta-emitting radioactivity in some particulate form is injected into the synovial sac, offers an attractive alternative to surgical synovectomy in the treatment of rheumatoid arthritis, since the method is noninvasive and the radiation may reach 100% of the synovium. Most of the previous work in radiation synovectomy has been applied to the knee and has used gold-198 or yttrium-90 attached to colloidal particles in the size range of 10–60 nm (*1–3*). All of these studies have shown a degree of clinical improvement in the majority of patients treated (*4,5*).

The drawback common to all clinical applications of radiation synovectomy is that significant leakage of radioactive material from the injected joint occurs, with subsequent accumulation in certain organs of the body (*6,7*). Leakage is estimated to be approximately 15–25% at 5 days with Y-90 (*8*) and as high as 60% with Au-198 (*9*). The radiation exposure received by the regional lymph nodes has been calculated to be as high as 15,000 rads for Au-198 and 4,500 rads with Y-90 (*7*).

We have reduced leakage of radioactivity by using particles that are much larger (in the micron range) than the colloidal-sized particles used previously, and

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by using a beta-emitting radionuclide with a short physical half-life. We wish to report here on the radiochemical and animal tracer studies; a more detailed report on in vivo testing will appear elsewhere (*10*).

Radionuclides. Both Y-90 and Au-198 have been used frequently for radiation synovectomy (*1–3*), and recent studies have mentioned the use of erbium-169 and rhenium-186 (*11,12*). Table 1 lists the physical half-life, maximum beta energy, major gammas, if any, emitted in the decay and the soft-tissue beta range for these four radionuclides along with that for dysprosium-165.

The importance of nuclear properties such as beta energy and half-life is not well established. Obviously radionuclides with prominent gamma emissions, such as Au-198, are unattractive for this application. Concerning tissue range, all that may be stated at present is that Y-90, Re-186, and Au-198 have been proven clinically effective (*1–3*), although the energetic beta particles from Y-90 may be capable of penetrating cartilage and bone (*13*). The effect of half-life is likewise unknown; the relative effectiveness of acute radiation exposure (short half-life) as opposed to chronic exposure (long half-life) has yet to be determined.

Among the short-lived radionuclides suitable for this purpose, perhaps the most attractive is dysprosium-165. This nuclide has a 139-min half-life, a 1.3 MeV maximum beta energy, and little accompanying gamma emission. Dysprosium-165 can be obtained at high specific activity by the irradiation of natural dysprosium in a nuclear reactor via the $^{164}Dy(n,\gamma)^{165}Dy$ reaction. This nuclide has been used previously for the treatment of brain tumors (*14*).

Ferric hydroxide macroaggregates. The particle system that has received attention in this study is ferric hydroxide macroaggregates (FHMA) coprecipitated with dysprosium hydroxide. When coprecipitated with Tc-99m or In-113m, FHMA has been used for lung imaging (*15*); as such, the majority of the particles have been in the micron size range. The attractiveness of this particle type is that it is biodegradable, the preparation time is only a few minutes, and any label that may be prepared in a suitably insoluble chemical form may be incorporated. Furthermore, the macroaggregates are capable of incorporating the weight of dysprosium necessary for therapy; although the Dy-165 is of high specific activity, it is not carrier free, appreciable amounts of stable dysprosium being present along with the radioactive Dy-165. It is for this reason that particles such as preformed and presized albumin microspheres were not considered, since there the label is on the surface and as such the weight of particles required to carry the therapeutic dose would be excessively large.

TABLE 1. PHYSICAL PROPERTIES OF SEVERAL BETA-EMITTING RADIONUCLIDES

Nuclide	Half-life	Radiation	Energy (MeV)*	Beta soft-tissue range (cm) (21)
Y-90	2.7 d	beta	2.3 (max)	1.11
Dy-165	139 min	beta	1.3 (max)	0.57
		gamma	0.09 (4%)	
Er-169	9.4 d	beta	0.34 (max)	0.09
Re-186	3.7 d	beta	1.07 ((max)	0.45
		gamma	0.14 (9%)	
Au-198	2.7 d	beta	0.95 (max)	0.39
		gamma	0.41 (96%)	

* Taken from Ref. (16). Percentage of abundance of gamma photons is given in parentheses; only photons greater than 2% abundant are listed.

METHODS

Radionuclides. Spectrographically standardized dysprosium oxide was irradiated to produce Dy-165. A multichannel gamma ray spectrometer with Ge(Li) detector was used to establish the radionuclide purity of Dy-165 and to measure the activity produced. The absolute detection efficiency of the spectrometer for 362 keV photons was determined using gamma ray standards. By correcting for the 1.1% abundance of the 362 keV gamma photon in the decay of Dy-165 (*16*), the activity of the irradiated solution was determined. The solution was then used to calibrate an ion-chamber dose calibrator. The dose calibrator was thereafter used to provide a rapid determination of the activity produced in each irradiation.

The tracer studies required a long-lived radionuclide. Dysprosium-159 ($T_{1/2}$ = 144 days) has been used in this study, but it is expensive and available only at low specific activity. Alternatively, since dysprosium is a rare-earth element and the chemical behavior of these elements is similar, radioisotopes of other rare-earth elements may be used as tracers. The majority of tracer studies were conducted with gadolinium-153 ($T_{1/2}$ = 242 days).

Dysprosium-159 was obtained by irradiating 20.8% enriched Dy-158 in a high-flux reactor. Gadolinium-153 and Au-198 colloid for injection were purchased commercially.

Ferric hydroxide macroaggregates. This material precipitated with tracer activity or with therapeutic doses of Dy-165 was prepared according to a method similar to that of Davis et al. (*15*), except that

colloidal-sized particles ("fines") were removed as described below.

The following solutions were prepared: 2 mg/ml Fe^{2+} (as $FeSO_4$); a dilute polyvinylpyrrolidone (PVP) solution containing 7.5 mg/ml; and a concentrated PVP solution containing 16 mg/ml at pH 9.5. The dilute PVP solution and a 0.1 *M* NaOH solution were sterilized by autoclaving. The remaining solutions were sterilized by membrane filtration. All solutions were stored in sterile vials at room temperature; the concentrated PVP solution was discarded when its pH value fell below 9.0.

Preparation procedure. Sterile saline, 4.7 ml, was added to a 16- × 100-mm vacutainer. The $FeSO_4$ solution (0.5 ml) was then added to the vacutainer followed by the radioactive solution. In the case of Dy-165, the activity consisted of 0.35 ml of the irradiated solution (0.85 mg/ml of Dy_2O_3 in 0.01 *M* HNO_3), whereas for the tracer studies, the radioactive solution consisted of a similar volume of dilute HNO_3 or HCl solution containing the desired tracer.

The vacutainer was agitated by hand for 1 min and 2.0 ml of the 0.1 *M* NaOH solution was added as rapidly as possible. The vacutainer was agitated for an additional minute and 1 ml of the dilute PVP solution was added. The vacutainer was again agitated, this time for 15 sec, and then centrifuged for 3 min at 1,700 RPM. Using an 18 gauge 3½-in. needle and a 10-cc syringe, the supernate was removed and the precipitate resuspended in 6 ml of the concentrated PVP solution. The vial was placed in an ultrasonic bath for 10 sec and then centrifuged for 3 min at 1,000 RPM. The supernate containing the fines was removed with an 18 gauge needle and the precipitate resuspended for injection in 0.65 ml of sterile saline. The final volume was 0.8 ml and the labeling efficiency averaged 70%. The total procedure required about 20 min.

In vitro studies. The particles were prepared to contain tracer activity and sufficient stable dysprosium carrier (where necessary) to approximate the specific activity of Dy-165 in the therapy trials. About 1 mg of the particles was added to a 10-ml vial, and 3 ml of either normal saline or a solution of human synovial fluid diluted 1:1 with saline (to reduce viscosity) were added. The vials were stoppered and placed on a rocking platform for gentle agitation. At various times, the tubes were removed and centrifuged so that the top 1.5 ml of the solution could be removed with a needle and syringe. The solution was passed through a 0.45-μm membrane filter directly into a counting vial and counted, along with a standard, in a NaI(Tl) well counter.

In vivo studies. An antigen-induced arthritis model in New Zealand white rabbits was used (*17*). These animals exhibit a condition very similar to rheumatoid arthritis of the knee for a period of at least 30 wk. The synovium becomes inflamed and hypertrophic and develops a pannus that leads to cartilage destruction.

As in the case of the in vitro studies, the particles administered to rabbits for in vivo studies contained the long-lived tracers Dy-159 or Gd-153, along with dysprosium carrier. Particles containing 300–500 μCi/mg of either Dy-159 or Gd-153 were prepared and suspended in saline to a concentration of 1.25 mg/ml. Each animal received about 100 μCi of activity. To avoid the possibility of leakage due to increased articular pressure, the volume injected was always 0.4 ml or less.

Because of the high mortality rate among the arthritic rabbits, and the length development time (2–3 mo), in vivo tracer studies were first performed with normal rabbits. In both cases, preparations were injected into the right knee and, following sacrifice at 5 or 24 hr, the right and left inguinal lymph glands, right kidney, and right hepatic lobe were removed. Samples of urine and blood—and, in the case of the 24-hr rabbits, a collection of feces—were taken. After weighing, samples were counted in a NaI(Tl) well counter along with a standard of the injected preparation. The results have been expressed for the lymph nodes and right kidney as percentage of injected dose per total organ; for the liver and blood as percentage of injected dose per gram and milliliter, respectively; and for urine as the percentage of dose per 5 ml of urine. Where necessary, the results were decay-corrected.

Several normal rabbits were also injected with Au-198 colloid so that labeled FHMA could be compared with an agent previously employed for radiation synovectomy. In addition, leakage from FHMA preparations containing fines was determined in normal rabbits and, compared with that for FHMA particles, free of fines.

RESULTS

Dysprosium-165. An 8-hr irradiation of 0.8 ml of the Dy_2O_3 solution in a neutron flux of 4×10^{12} n/cm²-sec produced 125 mCi of Dy-165 (specific activity 210 mCi/mg). Several solutions were counted periodically with a Ge(Li) detector and multichannel analyzer over a 2-day period; the activity was seen to decay with a single half-life of 139.9 min as expected for Dy-165. The only radioimpurity detected by gamma ray analysis was Na-24, which was present at 10^{-10}% of the Dy-165 activity at the end of irradiation.

In vitro studies. The importance of resuspension

with concentrated PVP solution in the FHMA preparation was demonstrated by determining the activity of the precipitate during preparation. Following the initial coprecipitation of ferric hydroxide, an average of 99% of the activity was incorporated into the precipitate. Following resuspension in concentrated PVP solution, ultrasonication, and centrifugation, an average of only 70% of the activity was in the precipitate, with 30% remaining in suspension. A second resuspension, ultrasonication, and centrifugation did not appreciably reduce the activity in the precipitate.

The size of FHMA in a typical preparation was determined by selective filtration according to the method of Davis et al. (*18*). About 2% of the activity was in particles less than 0.4 μm in size, 5% was in particles greater than 5 μm in size and 93% was in particles in the range of 0.5–5 μm.

Based on three measurements, the in vitro washout of activity from labeled FHMA particles into normal saline was found to be 0.16% at 5 hr and 0.08% at 24 hr. The results with 1:1 human synovial fluid conducted at 37°C were similar.

The effect of radiation damage to FHMA on in vitro washout was investigated. One milligram of FHMA containing 5 μCi of Dy-159 and 30 mCi of Dy-165 was agitated for 4 hr in normal saline. The leakage, determined several days later after the Dy-165 had decayed, was found to have been 0.4% at 4 hr.

In vivo tracer studies. The results obtained in the rabbit tracer studies are presented in Table 2. Normal rabbits were studied with Gd-153 and Dy-159 labeled FHMA and with Au-198 colloid. Arthritic rabbits were administered Gd-153 FHMA.

A comparison of the results with Gd-153 FHMA, with and without fines, obtained at 5 hr in normal rabbits, shows that when fines are not removed, a significantly greater ($p < 0.02$) accumulation of activity occurs in all extra-articular tissues sampled, except the lymph nodes. A difference in the two preparations is no longer apparent at 24 hr.

In normal rabbits differences were observed in the leakage of Gd-153 from FHMA in which fines were removed, compared with Au-198 colloid. At 5 hr the kidney and left inguinal lymph node accumulation is similar, but the accumulation in the blood, the right lymph node, and the liver are lower in animals administered FHMA ($p < 0.05$). At 24 hr, the blood concentrations are still an order of magnitude lower with FHMA as compared with Au-198 colloid.

These data show that, of the tissues sampled, the liver is the major site of accumulation, receiving about 0.1% of the injected dose at 5 hr and about 0.3% at 24 hr. The kidney is the next highest, with about 0.05% and 0.1% at 5 and 24 hr, respectively. Very little accumulation was found in the lymph nodes.

DISCUSSION

In addition to macroaggregates, we have investigated human serum albumin microspheres, in which the label is incorporated within the particles during preparation. Microspheres are attractive since their size and biodegradability may be varied through changes in the preparation procedure (*19*). The leakage with these particles, however, was not found to be substantially lower than with FHMA, and because of the ease with which the latter particles can be prepared, the macroaggregates were adopted for subsequent study.

Since macroaggregates exhibit a broad size distribution, resuspension with concentrated PVP solution was included to remove the smallest (possibly colloidal) fraction. The observation that, unlike the first resuspension, virtually all the activity remains in the precipitate following a second resuspension indicates that the colloidal fraction may be removed by this procedure and, of equal importance, the large particles do not break down to reform colloidal-sized particles.

The dilute PVP solution was used in the preparation to help suspend the colloidal-sized particles which would otherwise spin down with the larger particles.

The in vivo tracer studies show that leakage of Dy-165 radioactivity, following administration of labeled FHMA in rabbits, is lower than that observed with Au-198 colloid, an agent that has seen considerable use in radiation synovectomy. Sledge et al. (*10*) have measured the leakage of radioactivity in rabbits following administration of labeled FHMA by imaging the intact animal with a gamma camera, and have shown that approximately 1% of the activity leaves the knee in 24 hr. This result is in good agreement with the values obtained in our work by postmortem sampling. Using a dual-isotope technique, these authors have also shown in preliminary studies that the synovium may be effectively ablated with Dy-165, and that the leakage from the knee is not significantly increased following the destruction of the synovium. The observation that removing the fine particles in the FHMA preparation significantly reduced leakage occurring soon after administration (Table 2) suggests that a reason for the low leakage may be the use of large (0.5–5 μm) particles.

Patient radiation exposure may be expected to be lower than that currently associated with radiation synovectomy of the knee, not only because of the

TABLE 2. BIODISTRIBUTIONS FOLLOWING INTRA-ARTICULAR ADMINISTRATION (PERCENTAGE OF INJECTED DOSE × 10^{-3})

	Animals	R. Lymph*	L. Lymph*	Blood†	R. Kidney*	Liver‡	Urine¶	Feces*
5 hr								
Au-198 colloid	4 normal	(1–59)	(0.0–0.2)	(101–131)	(9–14)	(1.1–6.0)		
		26	0.1	120	12	3.1	—	—
Gd-153 FHMA with		(0.2–1.5)	(0.0–2.3)	(33–177)	(77–328)	(1.4–3.7)		
fines	4 normal	1.0	1.0	110	210	2.5	—	—
Gd-153 FHMA fines		(0.0–3.3)	(0.0–0.6)	(4–49)	(5–83)	(0.2–1.3)	(0.8–9.7)	
removed	7 normal	1.0	0.3	17	27	0.7	3.0	—
Gd-153 FHMA fines		(0.0–1.1)	(0.5–1.0)	(12–62)	(32–82)	(0.5–3.4)	(0.5–6.5)	
removed	5 arthritic	1.0	0.7	33	58	1.3	3.0	—
Dy-159 FHMA fines		(0.2–0.7)	(0.0–0.5)	(18–43)	(41–104)	(0.0–9.2)	(1.4–6.6)	
removed	3 normal	0.3	0.2	23	49	0.2	3.0	—
24 hr								
Au-198 colloid	3 normal	(0.9–4.0)	(0.4–0.9)	(204–283)	(29–55)	(3.2–6.6)		(1–41)
		3.0	0.6	230	43	5.9	—	15
Gd-153 FHMA with		0.9–2.6)	(0.7–1.5)	(27–132)	(142–259)	(3.3–7.2)		(23–69)
fines	3 normal	2.0	1.0	83	190	5.3	—	43
Gd-153 FHMA fines		(0.7–12)	(0.4–9.6)	(4–77)	(21–326)	(1.7–6.3)	(1–151)	(0.5–20)
removed	5 normal	3.0	3.0	34	140	3.7	44	8.0
Gd-153 FHMA fines		(0.1–1.6)	(0.3–2.1)	(8–132)	(37–189)	(0.7–5.1)	(1–34)	(1.4–28)
removed	6 arthritic	1.0	1.0	49	120	2.7	15	7.0
Dy-159 FHMA fines		(0.1–1.0)	(0.0–0.7)	(6–55)	(30–170)	(0.6–4.9)	(1.8–5.3)	(0.0–1.8)
removed	4 normal	0.4	0.3	22	63	0.9	4.0	0.4

Range in parenthesis.
* per total organ.
† per ml.
‡ per gram.
¶ per 5 ml.

reduced leakage but also because of the short half-life of Dy-165. Assuming that 5 mCi of Y-90 is required for effective synovectomy, by correcting for half-life and average beta energy, it may be estimated that about 270 mCi of Dy-165 will be required. Since Dy-165 emits several low-abundance gammas, the whole-body exposure will be due to gamma radiation in addition to bremsstrahlung. Finally, exposure will result from the leakage of radioactivity from the knee. The whole-body exposure due to the first two sources is estimated by the method of absorbed fractions (*20*) as less than 0.02 rads due to bremsstrahlung and 0.4 rads due to accompanying gammas. The cumulative exposure due to the leakage of 1% of the activity during the life of Dy-165 will add an additional whole-body exposure of 3 mrads if the activity is uniformly distributed. The in vivo tracer study shows that as much as 0.3% of the administered dose may accumulate in the liver in 24 hr. With this figure, the exposure to the liver is estimated to be 2 rads.

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