Samarium-153-Particulate Hydroxyapatite Radiation Synovectomy: Biodistribution Data for Chronic Knee Synovitis

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Biodistribution data for the radiation synovectomy agent samarium-153-particulate hydroxyapatite (^{153}Sm-PHYP) are reported. **Methods:** Mean extra-articular activity accumulation calculated from serial whole-body scans in 13 patients treated for chronic knee synovitis was 0.74% of injected activity (range 0%–3%). **Results:** In four patients (31%), activity was noted in the lung (mean 0.68% of injected activity). In six patients (46%), 0.29% of injected activity accumulated in the regional lymph nodes and in three patients (23%), 0.62% of injected dose accumulated in the liver. Absorbed dose estimates were lung: 14 mGy, regional lymph nodes; 50 mGy, liver; 4 mGy. SPECT demonstrated good distribution of ^{153}Sm-PHYP throughout the anterior knee compartments, although distribution to the posterior compartment was variable. **Conclusion:** Distribution is dependent on adequate knee flexion immediately following injection and may be influenced by the size range of labeled particles. Favorable biodistribution data suggest that ^{153}Sm-PHYP is a potentially useful radiation synovectomy agent.

Key Words: samarium-153-particulate hydroxyapatite; knee synovitis

J Nucl Med 1995; 36:51–57

Since the work of Ansell in the early 1960s (*1*), radiation synovectomy has been successfully employed in the treatment of synovitis in rheumatoid arthritis (RA) and other inflammatory arthropathies. Clinical results with colloidal yttrium-90 (^{90}Y) preparations, for example, are comparable with those obtained with open and arthroscopic synovectomy (*2*). However, widespread adoption of the technique has been impeded by concerns about activity leakage from the injected joint and subsequent exposure of healthy tissue to radiation.

Data from studies with colloidal ^{90}Y suggest that up to 45% of activity escapes from the injected joint (*3*). Studies using dysprosium-165-ferric hydroxide macroaggregates (^{165}Dy-FHMA) have demonstrated that the use of a particulate radiopharmaceutical can be associated with low levels of extra-articular activity accumulation (*4*). An ideal particulate agent designed to result in little or no leakage of activity from the injected joint would have the following characteristics: high-affinity binding to a relevant beta-emitter both in vitro and in vivo, uniform distribution throughout the joint cavity following injection and uptake into the synovium without initiating an inflammatory response. Additionally, the biological half-life within the joint should not be less than the physical half-life of the bound radionuclide and ultimately the particle should be biodegradable within the synovium. The biodistribution characteristics of different particulate radiopharmaceuticals have been the focus of a number of studies (*5–8*) and particle size has been proposed as an important determinant of activity leakage from an injected joint (*5*). Low levels of activity leakage from rabbit joints injected with samarium-153 (^{153}Sm) and rhenium-186 (^{186}Re)-labeled particulate hydroxyapatite (PHYP) have recently been demonstrated (*9*). Importantly, PHYP (Fig. 1) is easily and efficiently labeled by these radionuclides. Samarium-153 has a half-life of 46.3 hr, maximum beta-energy of 0.81 MeV and an average soft-tissue penetration of 0.8 mm. There is also a spectrum of gamma decay including a 20% abundant 130-keV photon.

In a clinic-based feasibility study, we have assessed both the intra-articular distribution of ^{153}Sm-PHYP and the extra-articular activity accumulation in patients treated for chronic knee synovitis.

MATERIALS AND METHODS

Patients

Patients with chronic inflammatory synovitis were enrolled if judged to require an intra-articular corticosteroid injection by their rheumatologist. Patients with significant cartilage loss indicated by <2-mm joint space in either medial or lateral compartments on weight-bearing antero-posterior knee radiographs were excluded. Radiographs of patients with RA were graded (*10*). Pregnant or breast feeding females and patients younger than 18 yr were excluded. Written informed consent was obtained from patients and ethical approval was granted by the University College London Medical School, Clinical Investigations Panel.

Methods

Either a medial or lateral injection approach was used. The skin and subcutaneous tissues were anesthetized with 1% lignocaine.

Received Mar. 25, 1994; revision accepted Jun. 28, 1994.
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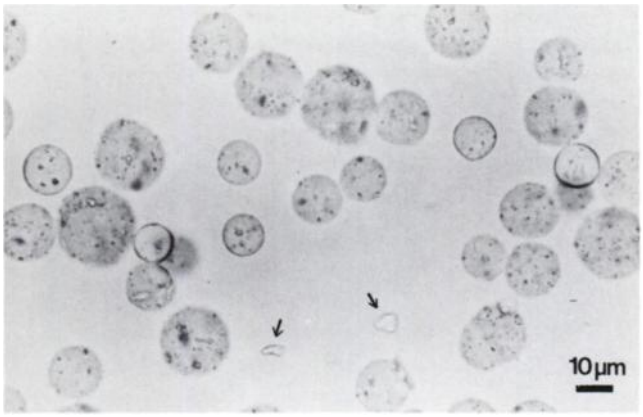

FIGURE 1. Hydroxyapatite particles (magnification × 50). Particle fragments are also seen (arrowed).

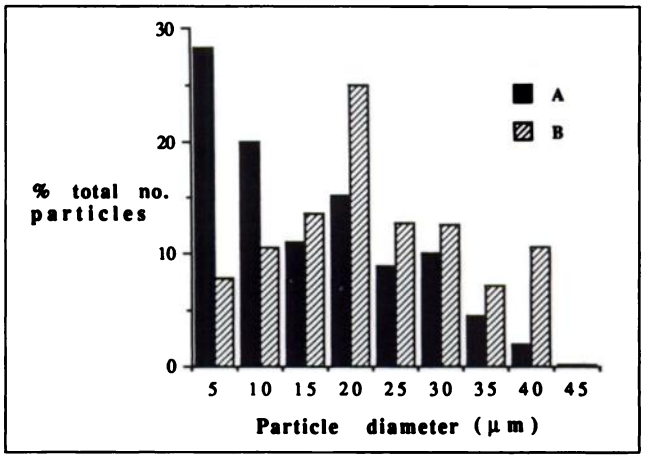

FIGURE 2. Hydroxyapatite particle diameter range. (A) Normal sample (mean 16 μm). (B) Suspension aspirated sample (mean 22 μm).

Any synovial fluid (SF) was aspirated through a 21-gauge needle and after disconnecting the syringe, ^{153}Sm-PHYP in 2 ml of normal saline was injected through the needle and flushed through with 40 mg of triamcinolone hexacetonide. A total volume of 4 ml was injected. The activity remaining in the injection apparatus was later measured. Immediately after injection, the knee was passively flexed to augment intra-articular distribution (Shortkroff S, *personal communication*) and the range of flexion recorded. A Robert-Jones orthopedic bandage was applied to serve as a semi-rigid splint. The patient remained nonweight-bearing for 4 hr with the leg supported. This was chosen as the maximum reasonable period of time over which to keep an arthritic patient immobile in a chair. In all patients, urine was collected over the 4 hr and blood drawn hourly for activity analysis. A further 24-hr urine collection was analyzed in six patients. Patients were allowed home 4 hr postinjection, advised to rest but allowed to resume their normal activities the following day.

Preparation of ^{153}Sm-PHYP

Hydroxyapatite particles (Ceramed Corp., Lakewood, CO) were labeled with 15 mCi (555 MBq) of ^{153}Sm (University of Missouri Research Reactor, St. Louis, MO) following methods previously published (*9*). However, for alternate treatments a procedure was undertaken aimed at excluding the smallest particles. Prior to labeling, particles were suspended in 2 ml of saline, the suspension agitated and allowed to settle for 30 sec. Particles remaining in suspension were removed by aspiration (21-gauge needle). The sediment was then labeled, resuspended and prepared for injection. The difference in particle size range produced by this procedure was studied using light microscopy: slides were prepared from both a normal PHYP sediment and a sediment produced following the procedure above. Using an eyepiece graticule, the diameter of each particle in 100 consecutive fields from each sample (magnification × 50) was recorded. The lowest particle diameter scored in either sample was 5 μm and the range was 5–45 μm. Some particles <5 μm were noted (PHYP fragments) but not scored (Fig. 1). The average particle diameter and size range in both samples are recorded in Figure 2.

Urine and Blood Activity Analysis

The total volume of urine collected was recorded. A 20-ml aliquot was analyzed by single-channel pulse-height analysis using a sodium iodide crystal scintillation counter. The photopeak was set at 103 keV with a 20% window. The counts were corrected for background and decay corrected to the time of injection. Total urine activity was then calculated by comparing the counts to those obtained from a ^{153}Sm standard of known activity. Blood (5 ml) was collected in EDTA vacutainers and an aliquot of 2 ml analyzed as above. Total ^{153}Sm blood-pool activity was estimated by assuming blood volume to be 7% total body weight.

Extra-articular Activity Analysis

Anterior and posterior whole-body scans were acquired immediately following injection, 4, 24, 72 and 168 hr (7 days) later on an IGE single-headed gamma camera (XCT or Starcam) with a low-energy, high-resolution (LEHR) collimator. Images were obtained using a 20% window centered at 106 keV (i.e., a 3% offset) with a 128 × 512 matrix over a field of view of 0.4 × 2 m. All scans on each patient were performed with the same camera. Background counts were obtained from "dummy" whole-body acquisitions (without patients) just prior to treatment. A geometric mean of the counts detected in anterior and posterior views from the whole-body, knee region of interest (ROI) and any focal activity was calculated from each pair of scans. Counts from the different ROIs (interpreted to represent organ localization of activity, e.g., liver, lung) were adjusted by attenuation correction factors to account for variable attenuation by the different organs. These factors were derived from the attenuation of the 103-keV ^{153}Sm photons measured on corresponding regions of a 75-kg healthy male volunteer (Table 1). All correction factors were adjusted relative to the attenuation correction factor for the knee joint, taken to be 1. From the quantitative estimate of relative activity distribution and the record of injected activity (IA), the activity in the whole body, remaining in the knee and in various organs was calculated. These results formed the basis for dosimetry estimates.

TABLE 1
Relative Attenuation

Region	Factor
Knee	1.00
Liver	1.45
Lung	0.80
Whole body	1.00

TABLE 2
Clinical Data of Patients Treated with ^{153}Sm-PHYP

Patient no.	Sex/Age	Diagnosis* /Duration (yr)	Previous joint injections†	Radiological knee grade‡	Knee effusion (ml)
1	F/48	RA/16	CS 6	3	—
2	F/63	RA/7	CS 3	2	—
3	M/35	PsA/12	CS 8	—	80
4	F/54	RA/5	CS 10+	2	30
5	M/62	RA/35	CS 8/SI 1	2	30
6	F/25	RA/20	CS 8	1	20
7	F/60	RA/28	CS 1	3	—
8	M/26	PsA/8	CS 1	—	—
9	F/76	RA/7	CS 10+	2	20
10	M/27	PsA/10	CS 3/SI 1	—	50
11	M/29	SARA/5	CS 3	—	60
12	M/39	SARA/25	CS 20+	—	50
13	F/24	RA/12	CS 3	2	—

*RA = rheumatoid arthritis; PsA = psoriatic arthritis; and SARA = sexually acquired reactive arthritis.
†CS = corticosteroid. SI = saline irrigation.
‡Steinbrocher radiological grades (*10*) (RA patients only).

Extra-articular Dosimetry

Whole-body and nontarget organ dosimetry estimates have been made utilizing time-activity curves constructed from the whole-body scan data. Estimates were based on data from the four patients in whom the maximum extra-articular activity occurred. All beta energies were assumed to be absorbed within the organ in which the activity was detected. We have overestimated the gamma absorbed dose by assuming generous dimensions for the cross-sectional area of the target organ and by assuming all gamma energy passing through this area is absorbed within the organ. Possible beta energy absorbtion by nonsynovial peri-articular tissues as a result of activity within the joint has not been included in the calculations. Estimates of absorbed energy by synovium and peri-articular tissues following intra-articular injection of various beta-emitting radiopharmaceuticals have recently been presented in a paper which discusses the difficulties inherent in absorbed dose calculations of joint tissues in radiation synovectomy (*11*).

Intra-articular Distribution Analysis

Serial anterior and lateral static knee scans were performed in the week following treatment (IGE XCT/Starcam, LEHR collimator, 3-min acquisition on a 256 × 256 matrix). Also, in the week following injection, SPECT knee images were acquired using an IGE Optima twin-headed camera fitted with a LEHR collimator on a 128 × 128 matrix. Most patients were scanned 7 days following treatment. Each image was acquired for 10 sec per view and 128 views over 360° were obtained. Patients' legs were immobilized by straps and saline bags serving as soft-tissue equivalent were packed between the knees. Images were reconstructed using a Butterworth filter with a cut-off frequency of 0.55 cm^{-1} and a power factor of 10. Activity distribution in the suprapatellar pouch, anterolateral and anteromedial compartments and four areas of the posterior knee compartment was subjectively scored (good = 2, patchy = 1, poor = 0). Activity distribution indices were calculated for each joint compartment by dividing the sum of distribution scores (for n patients) by the maximum possible sum of distribution scores (2n).

RESULTS

Clinical Details

The clinical details of the 13 patients studied are summarized in Table 2. Most patients had numerous previous intra-articular corticosteroid injections. Invariably, the most recent injection resulted in a limited period of symptomatic relief.

Injected Activity

PHYP was labeled (>99% efficiency) with on average 16 mCi (590 MBq) of ^{153}Sm (range 14.5–16.7 mCi). Mean injected activity was 10 mCi (366 MBq; 62% of mean prepared activity). The range varied (4–14 mCi) depending on particle retention in the injection apparatus. There was no difference in the activity retained between the two groups injected with different PHYP preparations.

Extra-articular Activity Distribution

Low levels of activity were present in urine over the initial 24 hr following treatment and traces of activity were detected in blood at all sampling times (Table 3).

The maximum extra-articular activity accumulation was calculated from whole-body scan data. The mean was 0.7% IA (range 0%–3%, n = 13) over 7 days, however, specific organ accumulation of activity was evident in only 6/13 (46%) patients whereas in 7/13 (54%), no extra-articular localization of activity was detected by the whole-body scans. Lung activity was detected in four patients (mean 0.68% IA), appearing immediately following injection in two patients and detected initially 24 hr after treatment in the other two. Two of these patients had received the PHYP preparation with a greater mean particle size. Regional lymph node activity uptake occurred in six patients (mean 0.29% IA) though was not detectable until 24 hr after treatment. Liver uptake was noted in three patients (mean

TABLE 3
Urine and Blood* Activity Analysis

Sample	Mean %IA†	Range
Urine 0–4 hr (n = 13)	0.003	10^{-7}–0.01
Urine 4–24 hr (n = 6)	0.007	10^{-4}–0.02
Blood +1 hr (n = 6)	0.001	0–0.004
Blood +2 hr (n = 6)	0.003	0–0.12
Blood +3 hr (n = 6)	0.002	0–0.12
Blood +4 hr (n = 5)	0.004	0–0.14

*Activity calculated in total blood volume at the indicated time following joint injection.
†Injected activity.

0.62% IA). Patterns of organ activity uptake are shown in Table 4 and a comparison of the mean activity accumulation in various organs shown in Figure 3. Absorbed dose estimates are shown in Table 5. Overall, there was no difference in extra-articular activity accumulation in patients treated with different PHYP preparations or injected from different approaches. No relationship between the level or pattern of extra-articular activity distribution with any particular clinical characteristic was evident.

TABLE 4
Activity Localization in Different Organs of Six Patients Postinjection

Patient no.	Organ	Time following joint injection: Immediate	4 hr	24 hr	72 hr	168 hr
1	lung	+	+	+	+	+
	liver	–	–	–	–	–
	lymph nodes	–	–	+	+	+
7	lung	–	–	–	+	+
	liver	–	–	+	+	+
	lymph nodes	–	–	+	+	+
9	lung	+	+	+	+	+
	liver	–	–	+	+	+
	lymph nodes	–	–	+	+	+
10	lung	–	–	–	–	–
	liver	–	–	–	+	+
	lymph nodes	–	–	–	+	+
12	lung	–	–	+	+	+
	liver	–	–	–	–	–
	lymph nodes	–	–	+	+	+
13	lung	–	–	–	–	–
	liver	–	–	–	–	–
	lymph nodes	–	–	+	+	+

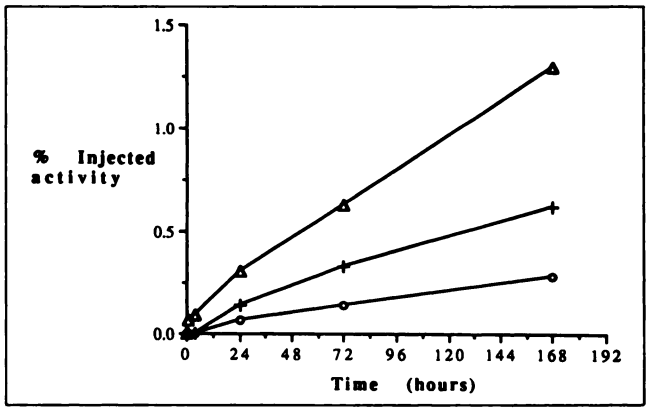

FIGURE 3. Extra-articular accumulation of activity in 6/13 patients with organ localization of activity. Mean % injected activity accumulating in the lung (Δ) n = 4, regional lymph nodes (o) n = 6 and liver (+) n = 3.

Intra-articular Distribution

Distribution of intra-articular ^{153}Sm-PHYP to different knee compartments analyzed from tomographic datasets is summarized in Table 6. Suprapatellar activity distribution indices were maximal irrespective of injection approach, PHYP size range or joint flexion ability. In each compartment, a lower activity distribution index was seen in patients unable to flex the knee more than 110° (immediately postinjection) compared to those with a good range of flexion. Higher indices of distribution were associated with an absence of effusion prior to injection, a lateral injection approach and patients injected with the full size range of PHYP (smaller mean particle diameter). These trends were maintained when the data from patients with poor knee flexion were excluded and the remainder reanalyzed. Count profile analysis of both planar and serial tomographic dataset slices suggested that no major shift in activity distribution occurred after 4–24 hr (Fig. 4).

DISCUSSION

The data suggest that very low levels of ^{153}Sm accumulate outside the knee following intra-articular injection of

TABLE 5
Extra-articular Absorbed Dose Estimates*

Organ/Region	Absorbed dose (mGy)
Lung	14
Regional lymph nodes	50
Liver	4
Whole body	0.9

*Estimates based on the data from the four patients with the maximum extra-articular activity accumulation.

TABLE 6
Intra-articular Activity Distribution Indices* of Different Knee Compartments in Patients Treated with ^{153}Sm-PHYP

Patient groups	Knee compartment						
		Antero-inferior		Posterior			
	SPP	Medial	Lateral	Sup/Med	Sup/Lat	Inf/Med	Inf/Lat
All patients (n = 13)	1	0.77	0.77	0.62	0.65	0.62	0.69
Injection approach							
Medial (n = 10)	1	0.75	0.75	0.55	0.60	0.60	0.65
Lateral (n = 3)	1	0.83	0.83	0.83	0.83	0.67	0.83
PHYP size range							
Full (n = 7)	1	0.93	0.71	0.71	0.79	0.71	0.71
Adjusted (n = 6)	1	0.58	0.83	0.50	0.50	0.50	0.67
Effusion							
+ (n = 8)	1	0.75	0.63	0.50	0.56	0.56	0.63
− (n = 5)	1	0.80	1	0.80	0.80	0.70	0.80
Knee flexion range							
≤110 (n = 4)	1	0.63	0.50	0.38	0.25	0.38	0.25
>110 (n = 9)	1	0.83	0.89	0.72	0.83	0.72	0.89

*Indices calculated from the sum of distribution scores of n patients (good = 2, patchy = 1, poor = 0) divided by maximum possible sum of scores for those patients (2n). Maximum activity distribution index in any compartment = 1.
SPP = suprapatellar pouch.

^{153}Sm-PHYP. The absence of focal extra-articular activity in some patients and the blood or urine activity indicate that it is possible to attain very high levels of activity retention within the knee joint. These findings are important as potential damage to extra-articular tissues and the possibility of mutagenesis are major theoretical disadvantages of radiation synovectomy. Previous studies undertaken with colloidal ^{90}Y suggest that either a period of bed-rest or rigid splinting with a plaster-of-Paris cylinder (*12*) reduces both activity loss from the injected knee joint and the level of peripheral lymphocyte chromosome damage. Clinical practice largely reflects this finding and patients are often admitted to the hospital for 24–48 hr following knee radiation synovectomy with a colloidal preparation. Experience from the use of ^{165}Dy-FHMA also suggests postinjection ambulation may affect activity leakage from the joint and may increase the regional lymph node absorbed dose sixfold in some patients (*13*). Therefore, the finding of low or negligible levels of extra-articular activity in patients allowed to ambulate 4 hr after intra-articular ^{153}Sm-PHYP injection is encouraging and indicates that out-patient treatment will unlikely increase the risk of extra-articular spread of activity.

The appearance of activity in the lung occurred in a minority of patients but suggests that under certain conditions, particle-bound activity may escape from the knee. Immediate accumulation in the lung (seen in two patients) implies passage of ^{153}Sm-PHYP into the blood (presumably as a result of traumatization of synovial vessels during the procedure) with trapping in the pulmonary capillaries. There was no obvious association between accumulation of activity in the lung (n = 4) and mean injected particle size; two patients received the PHYP preparation with the larger mean particle size.

As capillary diameter is of the order of 5 μm, most of any PHYP carried through the venous system would be expected to be arrested in the pulmonary vasculature. However, fragments of PHYP (Fig. 1) may carry activity through the pulmonary capillary network. The fate of this particle bound activity is uncertain. There were no short-term symptomatic sequelae as a result of this small amount of lung exposure.

Perhaps not surprisingly, a small amount of liver activity accumulated in patients who had prior or concomitant extra-articular organ activity uptake. As the amounts were small, it was difficult to interpret from time-activity curves from which site the activity principally originated. However, it would seem reasonable to assume that this activity was largely particle bound as free ^{153}Sm is likely to be either excreted by the kidneys or bound to bone (*9*).

The low levels of activity detected in urine collected immediately postinjection may either originate from unbound injected ^{153}Sm-citrate or in vivo particle-dissociated ^{153}Sm. The pattern of activity residency (allowing for accumulation and decay) in lung and lymph tissue suggests against significant removal of activity from each tissue, which might be expected if extensive dissociation of ^{153}Sm from PHYP was occurring. Also ^{153}Sm-PHYP has been shown to remain tightly bound in vivo (*9*). Therefore, it would seem more likely that the urine activity is the result

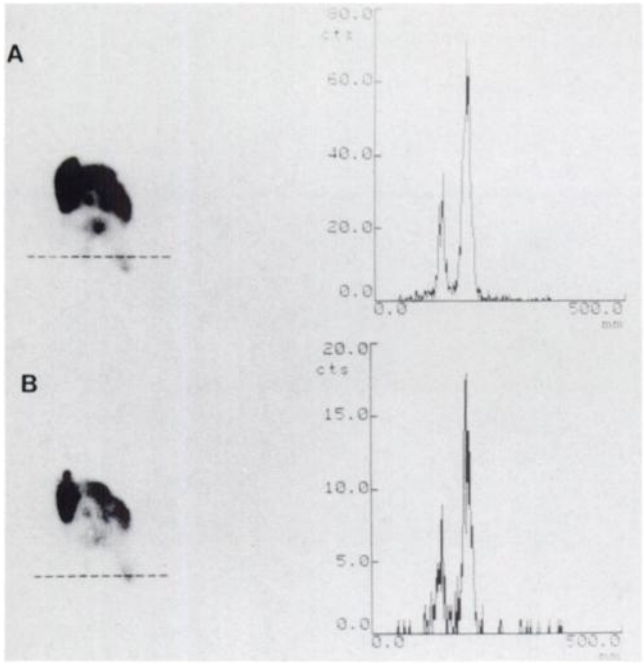

FIGURE 4. Count profile across the medial and lateral knee compartments 24 (A) and 48 (B) hr following intra-articular injection with ^{153}Sm-PHYP. The profile curves (cts/pixel) from coronal slice SPECT images shown on the right suggest similar patterns of activity distribution.

of excretion of a small amount of free ^{153}Sm. This hypothesis has not been fully tested by activity analysis of delayed urine collections, which, putatively would not contain significant activity, but if correct would further enhance the reputation of PHYP as a particulate vehicle capable of extremely stable ^{153}Sm binding in vivo.

Regional lymph node exposure invariably occurs following radiation synovectomy, although it is significantly greater with colloidal than with particulate preparations. For example, the absorbed dose of regional lymphoid tissue from some colloidal ^{90}Y preparations can be over 100 Gy (10,000 rad) (*14*), but with the particulate preparation, ^{165}Dy-FHMA was only 166 mGy (16.6 rad) (*13*). The theoretical risk of hematological malignancy following radiation synovectomy has been brought sharply into focus by the report of leukemia in a patient previously treated with colloidal ^{198}Au (*15*). Previous studies using this radiopharmaceutical have shown up to 48% of injected activity leaks to draining lymph nodes from the treated joint resulting in an absorbed dose of up to 150 Gy (15,000 rad) (*16*). These values are considerably higher than those derived from studies with particulate agents including our data using ^{153}Sm-PHYP, but the case report clearly illustrates the importance of considering carefully the use of radiopharmaceuticals associated with a higher lymph tissue dose in younger patients.

The effective dose equivalent (excluding dose to intra-articular tissues) calculated from these data was 3.8 mSv (380 mrem). This unwanted exposure is comparable with that received from a ^{99m}Tc-diphosphonate bone scan (3.7–6 mSv) (*17*).

SPECT images provide a useful guide to activity distribution within the knee but have been interpreted with caution for a number of reasons. In most patients intra-articular distribution was analyzed from 7-day post-treatment images. However, in some patients, scans were only obtainable 4 or 24 hr postinjection. In some patients where serial images were available for comparison, the distribution of activity in the 4-hr and 24-hr scans was significantly different. The changes, subjectively interpreted from serial tomographic datasets analyzed by activity-profile curves, were consistent with an improvement in intra-articular distribution, i.e., more extensive distribution. Information solely derived from the earlier scans is therefore likely to be an underestimate of the eventual extent of intra-articular distribution. Serial image analysis suggested that there was no gross change in activity distribution after 24 hr. The development of this argument is that images obtained 4–24 hr or more after injection represent synovial localization of activity, whereas the earlier images are acquired when a proportion of activity remains in the synovial fluid prior to synovial uptake and has the ability to re-distribute through the cavity. The precise time for which the ^{153}Sm-PHYP remains in the SF is not known.

Notwithstanding, distribution indices are high for most joint compartments. The implication from the finding that patients with poor knee flexion have worse distribution, is that these patients may have a poor clinical response. These patients did not necessarily all have advanced disease. Synovial thickness, residual fluid in the joint and the presence of a popliteal cyst were all found to influence knee flexion. The smaller differences in distribution indices seen in the presence of an effusion and in patients treated by different injection approaches and with different PHYP preparations may not be significant. However, there may be physical effects exerted by intra-articular structures which influence particle dispersion through the SF and therefore affect the access of PHYP to the whole synovial surface. Synovial bulk, local variations in surface contour or the presence of a synovial plica or shelf may impede the distribution into or throughout a particular compartment. Other physical factors which may be important include local pressure, the presence of cellular and extracellular tissue debris within the SF (e.g., fibrin) and the viscosity of the fluid itself. Many of these factors are likely to interfere with the distribution of larger particles more than that of smaller ones. As even distribution of ^{153}Sm-PHYP (or any particulate synovectomy agent) over the whole synovial surface is desirable, the relative importance of these intra-articular physical effects warrants further study.

SUMMARY

This study has shown that knee radiation synovectomy with ^{153}Sm-PHYP is easily undertaken as an out-patient procedure and is associated with very low extra-articular

activity accumulation. The incidental extra-articular doses are likely to be predominantly determined by factors which influence uptake of activity into synovial blood vessels at the time of the procedure. The degree of synovial vascularity and local tissue trauma from the injection may be important in this respect. Radiation doses of nonarticular structures are significantly smaller than with colloidal synovectomy agents and comparable to levels estimated from the use of ^{165}Dy-FHMA. Careful injection techniques are needed to maximize injected activity. Intra-articular distribution of ^{153}Sm-PHYP is dependent on a good range of knee flexion following injection but the agent is potentially able to reach all knee compartments. Biodistribution data suggest that ^{153}Sm-PHYP is a promising radiation synovectomy agent and further clinical studies are warranted.

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