Vol.45, Special n. : pp. 45-55, September 2002
ISSN 1516-8913 Printed in Brazil

BRAZILIAN ARCHIVES OF
BIOLOGY AND TECHNOLOGY

A N I N T E R N A T I O N A L J O U R N A L

Bone-seeking Therapeutic Radiopharmaceuticals

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ABSTRACT

Bone-seeking therapeutic radiopharmaceuticals are utilized on the basis of the radionuclide's particulate emissions (primarily low to intermediate beta emission). The requirements therefore are different from those of bone imaging agents that consist mainly of short-lived single photon emitters. Lately, the therapeutic bone seeking radiopharmaceuticals have attained increasing importance due to their potential role in alleviating pain from osseous metastases in cancer patients, for the treatment of joint pain resulting from inflamed synovium (radiosynoviorthesis, or radiosynovectomy), or from various other forms of arthritic disease. There is, however, a paucity of published data on the bio-pharmacokinetics of these agents when used following intravenous administration for bone pain palliation. This paper will briefly review and summarize the presently available chemical and biopharmacokinetic information on the various clinically approved as well as experimental bone-localizing therapeutic radiopharmaceuticals, and make projections on their clinical application for the treatment of primary/metastatic cancer in bone.

Key words: Therapeutic radiopharmaceuticals, Bone seekers, Pain palliation, Bio-pharmacokinetics, Radiosynovectomy

INTRODUCTION

Therapeutic radiopharmaceuticals are utilized on the basis of the therapeutic electron emissions of particular radionuclides, some of which may also emit imaging photon(s). The interest in application of radionuclides to therapy of bone malignancies, particularly for palliative relief of bone pain, is not new, but has recently undergone a renewal. It had its origin in the earliest days of the nuclear era but fell into relative obscurity for some time, until about a decade ago. Both strontium-89 and phosphorus-32 were investigated as early as the 1940's for the treatment of metastatic cancer to bone (Pecher, 1942; Friedell and Storaasli, 1950). The work of Firusian et al. (1976) suggested again that strontium-89 would be useful for relief of pain secondary to osseous metastases. Robinson and others further explored the utility of strontium-89 (Robinson, 1986; Quilty et al, 1994; Lewington et al., 1991; Robinson, 1987) resulting in the FDA approval for its routine application in 1993. This work has also stimulated clinical research in order to find other radionuclides, which may have improved physical properties that permit treatment with fewer side effects on the myeloproliferative

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cells in the bone marrow. This paper will compare the several agents that may be useful in treatment of bone malignancy and discuss possible ways in which they may be applied to provide increased benefits to patients. A short discussion of radiosynovectomy is also included.

The basis for the action of these therapeutic agents is their incorporation into bone mineral and their beta emission, which limits their range of action to the near neighborhood of their increased concentration in pathological areas such as metastases where the attempt at healing by the bone results in increased uptake. ^{117m}Tin is an exception in that its emission consists primarily of conversion electrons rather than beta particles. Table 1 lists the currently used isotopes (either approved or being investigated) for bone pain palliation and their nuclear and physical characteristics. These same radionuclides, in addition to a few others described in a later section, also have properties that make them useful for radiosynovectomy.

BONE PAIN PALLIATION

Desirable Radionuclide Characteristics

Half-life: The half-life of a radionuclide will determine the initial dose rate and therefore the total amount of radioactivity to be administered. What is an appropriate physical T½, is not well understood. A higher initial dose rate may result in more effective cell killing, but the therapeutic ratio of malignant cell destruction to normal cell recovery may be less. Too long a T½ creates obvious problems in environmental safety in case of spill or early death of the patient. A very short T½ is problematic so far as shipping and shelf life are concerned. It also requires a larger total of administered activity, which increases the radiation dose to personnel and family members and may require some hospitalization, thus increasing cost. On the other hand, repetitive doses may be given at shorter intervals making it possible to titrate dose to response.

Photon Emission: Accompanying photon emissions of the appropriate energy can be useful in monitoring the distribution of the radiopharmaceutical in the patient for assessing dosimetry, but are not essential. They also constitute a source of exposure to personnel and family, but this has not been a significant problem with the radionuclides investigated to date.

Electron Emission: Both strontium-89 and phosphorus-32, the earliest radionuclides used for this purpose, have highly energetic beta emissions. These penetrate deeply into the marrow cavity and may be the cause of increased myelotoxicity. More recent research has concentrated on radionuclides, which have much lower energy electron emissions and therefore, potentially reduced toxicity.

Other Factors: Ease of preparation, in-vitro and in-vivo stability, shelf life, and cost are other considerations. Radionuclides, which can be prepared in a reactor, are usually less costly. Ease of preparation and cost are dependent on the nuclear reactions and subsequent radiochemical processing required for manufacture.

Comparison of Radiopharmaceuticals

The relevant physical characteristics of the various radionuclides are given in Table 1. Strontium-89 chloride (Metastron) and Samarium-153 EDTMP (Quadramet) have been approved by the Food and Drug Administration within the last ten years. Phosphorus-32 as sodium phosphate was grandfathered as an approved drug when the FDA took over jurisdiction of radiopharmaceuticals from the Atomic Energy Commission many decades ago. Since P-32 is often used as a baseline for comparison, it will be discussed first. Rhenium-186 (which is approved in many non-U.S. countries), Re-188-HEDP, and Tin-117m Stannic DTPA are still under investigation in the U.S. Other newer radiolanthanide metals, such as Ho-166, and Lu-177, etc. are also undergoing investigation but will not be covered here since there is a paucity of definitive clinical and pharmacokinetic information in the literature on these agents.

Phosphorus-32: Phosphorus-32 as sodium phosphate (NaH_2PO_4), as mentioned earlier, was the earliest used agent for palliation of pain from osseous metastases. Originally it was believed that its effect was mainly from incorporation into the tumor itself. However, the tumor to non-tumor ratio is not very favorable and the relief of pain is primarily because of its uptake into bone mineral, not the tumor. In addition, uptake is higher in any rapidly dividing tissue such as bowel, but particularly so in the red marrow itself in addition to involved bone. Therefore, the bone to marrow ratio is low. Similar to Sr-89, P-32 has a highly energetic beta emission, and has no accompanying gamma photon making monitoring somewhat difficult. Results have been similar to Sr-89, but toxicity to the bone marrow has been severe at therapeutic level administrations. Phosphorus-32 has also been used in therapy of polycythemia vera and leukemia. Most of the information in patients in regard to localization and dosimetry has come from studies in such patients.

Table 1 - Physical and nuclear characteristics of bone-seeking therapeutic radionuclides[1].

	Maximum β^- energy (MeV)	**Average** β^- energy (MeV)	Average Range (mm)	$T_{½}$ (days)	γ **photon** (MeV)
Strontium-89	1.46	0.58	2.4	50.5	None
Phosphorus-32	1.71	0.70	3.0	14.3	None
Tin-117m	0.13[2] 0.15[2]	--- ---	0.22 0.29	14.0	0.159 (86%)
Erbium-169	0.34	0.11	0.30	9.3	None
Lutetium-177	0.50	0.14	0.35	6.7	0.208 (11%)
Rhenium-186	1.08	0.33	1.05	3.7	0.137 (9%)
Samarium-153	0.81	0.22	0.55	1.9	0.103 (29%)
Holmium-166	1.84	0.67	3.3	1.1	0.081 (6%)
Rhenium-188	2.12	0.64	3.8	0.71	0.155 (10%)

[1]Arranged in order of decreasing half-life
[2]Conversion electrons with discrete energies (and range).

Pharmacokinetics: The absence of any gamma-emitting isotope of phosphorus has made a study of its distribution and biokinetics in human beings extremely difficult. In a study in albino rats, Friedell and Storaasli (1950) showed that most of the intraperitoneally administered ^{32}P was taken up in the skeleton with lesser amounts in muscle, digestive tract, liver, skin and brain. There was no separation of skeleton into bone and red marrow. After two weeks, 46% of the administered activity had been excreted: 33% was in bone and 20% in the viscera and musculature. The authors determined that the biologic half-life for activity in the soft tissues was about 9 days and over 10 days for bone (bone and marrow ?).

The differential absorption ratio of radioactive phosphorus in patients with cancer of the breast, sarcoma of bone, and lymphoma, was studied by

Kennedy et al. (1941). This ratio was defined as the difference in concentration in the tissue examined compared to what the concentration would be if the ^{32}P were to be distributed evenly throughout the body. These ratios for breast cancer tissue ranged from 0.8 to 1.9 in 5 patients from 1 to 5 days after administration, whereas in normal breast tissue the ratio was 0.2 to 0.4. On the other hand, the ratio in osteogenic sarcoma was much higher, usually from 2.6 to as high as 8.3. Normal bone differential absorption ratios were mostly less than one. In some tumor specimens the ratio was less than one, attributable to the presence of necrosis in the specimens. It should be noted that 3 out of 5 patients had had considerable preoperative radiation some time prior to the surgery at which the specimens were obtained.

Strontium-89 chloride: Strontium-89 is a pure beta emitter. The maximum beta energy is high and penetration (average) in soft tissue is 2.4 mm. The long physical half-life means that low administered activity is given resulting in a rather low initial dose rate. In addition, it limits the possibility of repeat doses until much after the initial dosing. Nevertheless, it has proven effective (Lewington et al., 1991; Robinson et al., 1987; McEwan, 1994; Katin et al., 1993). Absence of an accompanying gamma photon makes it difficult, but not impossible, to monitor distribution. The energetic betas result in a low bone to marrow dose ratio but myelotoxicity has not been a major factor. While individual studies vary in results, the overall efficacy in terms of patients experiencing pain relief (complete + marked + moderate) appears to be in the range of 54% (McEwan, 1994) to 80% (Robinson et al., 1987).

Pharmacokinetics: Despite its approved status by the United States Food and Drug Administration (Metastron ®, Amersham Healthcare, Arlington Heights, IL), there is a paucity of data on the biokinetics of ^{89}Sr. Much of the early work on biodistribution was performed in order to better understand calcium metabolism and also to predict the effects of fallout from nuclear tests. Consequently, these studies were performed following oral administration. In addition, the lack of gamma photons has made it difficult to obtain data regarding information gleaned from imaging studies of whole body and specific organ distribution, although ^{85}Sr with a physical half-life of 65 days has been used as a gamma-emitting tracer. Furthermore, studies have been mostly in pathological situations, which makes each case unique unto itself. Cohn et al. (1963) compared the kinetics of ^{85}Sr as the chloride with ^{47}Ca chloride in a group of patients with various benign conditions. Significant differences between calcium and strontium were observed. Much more of the calcium was retained in the body and the renal clearance was lower. Over the period from 2 to 10 days after intravenous administration there was a total body loss of 5.54% per day of the strontium. This decreased to an average of 1.76% per day in the period 10 to 30 days after administration. Renal clearance was 8.22 liters/day in the period 5-10 days after administration and a total of 39.8% of strontium was excreted in the urine in the first 10 days. Fecal excretion during this same period was 13.0%. Strontium was excreted preferentially by the kidneys, in contrast to calcium. Consequently, whole body retention was less for strontium. There was a higher percentage of calcium retained in plasma and soft tissues. However, accretion rates into bone were similar for the two elements. Marshall (1972) described a model of strontium metabolism using a power function for whole body retention. The components of such a function were as follows: apposition-absorption rate = 2.4% per year; resorption rate of cancellous bone = 9.5% per year. A complication of assessing kinetics of ^{89}Sr is the long physical half-life. For radionuclides with a shorter half-life, the distribution in bone can be calculated as 50% on the surface of compact bone and 50% on the surface of trabecular bone. However, with the longer-lived radionuclides such as ^{89}Sr, the distribution must be considered on a volume rather than a surface basis. Therefore, the later time distribution is in a ratio of 4:1, compact to trabecular bone. Ten subjects were studied by Uchiyama et al. (1973) after intravenous

administration of ^{85}Sr. Six of these had a diagnosis of osteoporosis. Retention was determined by measuring urinary and fecal excretion over a period of 8 to 13 days. The retention curves were fitted by a sum of two exponential functions. The more rapid component (4.4-98.4%) varied with a T½ from 0.2 to 1.3 days. The T½ of slower component (50.5-92.5%) varied from 28.6-101.9 days. Breen et al. (1992) studied 5 males with prostate carcinoma with variable extent of disease. They measured whole body retention by means of urinary activity levels over a period of 6 days, and evaluated blood levels over a period of 7 days. Imaging was performed in 4 of the subjects using the far from ideal ^{85}Sr. Whole body images were obtained at intervals for up to 8 weeks. While actual numbers are not given in the report, there was a wide disparity in whole body retention after 4 days, ranging from about 50% to 92%. The fraction of administered activity in the plasma at 1 day and beyond showed much less variation. The renal plasma clearance rates varied from 8.3±3 liters per day to 12.8±1.7 liters per day. Although imaging indicated that there was some bowel excretion, it could not be quantified and did not enter into dose calculations. Concentration of strontium in bone lesions was from 2 to 25 times that in normal bone. The biological half times were also very variable. In normal bone they ranged from 20±4 to 137±27 days while in metastatic sites the range was from 20±1 to 104±14 days.

Samarium-153 EDTMP: This radiopharmaceutical has a short physical half-life of 1.9 days. This can be advantageous in that it is easier to administer repeated doses. However, it makes manufacturing and delivery a more difficult problem. The range of its beta particles is short (average 0.55 mm) resulting in good bone to marrow ratios ranging between 2-5.5. Myelotoxicity has been manageable at the approved dose schedule (1 mCi/kg), and efficacy is in a similar range as Sr-89 (Turner and Claringbold, 1991; Farhangi et al., 1992; Collins et al., 1993; Resche et al., 1997). At high levels of administered Sm-153, an increase in survival of patients with metastatic prostate cancer was demonstrated, but at the cost of severe myelotoxicity (Collins et al., 1993).

Pharmacokinetics: A series of chelates labeled with ^{153}Sm, an easily produced radionuclide, was studied by Goeckler et al. (1987) for the purpose of developing an agent with a relatively short physical half-life, beta emissions with a short range in tissue in order to reduce marrow dose, and a suitable gamma emission for monitoring distribution. The chelate, which gave the best distribution in rats, was ethylenediamine-tetramethylene phosphonate (EDTMP). It was found that 57.71±4.04% was deposited in the skeleton, while blood activity was 0.032±0.016% and liver was 0.252±0.038% of administered activity at 2 hours. The bone/blood ratio was 1833±1274 and bone/muscle ratio 1459±505. Urinary excretion was even more rapid than with 99mTc MDP with excretion complete by 2 hours. Bone uptake reached a maximum at 1 hour. Studies in human beings (Singh et al., 1989) showed nearly identical distribution of ^{153}Sm EDTMP and ^{99m}Tc MDP with very similar lesion to normal bone ratios. The percent administered activity remaining in whole blood was 5.17±1.05% at 2 hours and 2.09±0.52% at 4 hours. Cumulative urinary excretion was over 50% by 8 hours and remained unchanged thereafter. A somewhat larger series of patients was studied by Bayouth et al. (1994). The initial T½ of blood disappearance was 5.5±1.1 minutes and a slower component was 65.4±9.6 minutes. They found less than 1% of the injected activity remaining in blood at 5 hours. Skeletal uptake averaged 52.2±18.0%. The biological T½ for whole body retention (assumed to be in the skeleton) was determined to be 520 hours.

Rhenium-186 HEDP: The physical half-life of rhenium-186 is 3.7 days. This is long enough that shipment and shelf life are less of a problem than with samarium-153. It is short enough that repeated doses could be given over a relatively short period of time. However, the average beta energy is considerably higher than that of samarium-153, and consequently the range is

longer so that, at least theoretically, it is less sparing of the bone marrow. The dose ratio of bone to marrow is not particularly favorable and the compound is less stable than the other radiopharmaceuticals under discussion (Maxon et al., 1990; deKlerk et al., 1992).

Pharmacokinetics: Rhenium-186 has energetic beta emissions as well as a photon suitable for gamma imaging (Table 1). This combination suggested its usefulness for therapy in painful bony metastases. Methods for labeling the radionuclide to hydroxyethylidene diphosphonate (HEDP) were studied by Mathieu (1979) and Eisenhut (1982). The first studies in humans were reported by Maxon (1988). These studies were performed on patients with extensive bone involvement by malignancy. Therefore, the distribution is not exactly that which would be obtained in normal individuals and is extremely variable from one patient to another. Distribution was very similar to ^{99m}Tc MDP images performed on the same patients. Blood disappearance was rapid with 14% of administered activity remaining at 30 minutes. Cumulative renal excretion was 45% at 5 hours and 71% by 3 days. A more detailed study of pharmacokinetics was carried out by de Klerk et al. (1992) in 17 patients. The fraction of the cleared radioactivity averaged 0.69 with a standard deviation of 0.15. In 24 hours there was a total urinary excretion of 71±6%. Protein binding of ^{186}RE-HEDP in plasma was found to increase with time from 51±6% to 89±5%. Other pharmacokinetic values are shown in Table 2. These authors also utilized the bone scan index (BSI) of Blake (1988). There was, as expected, a good correlation of the BSI with the non-renal fraction of activity and with the volume of distribution.

Table 2 - Pharmacokinetics of rhenium-186 HEDP.

Parameter	Blood	Plasma	Plasma Water
Half-life (h)	40.1±5.0	41.0±6.0	29.5±6.4
Total clearance (m1/min)	40±13	28±9	145±38
Renal clearance (m1/min)	26±6	18±4	96±21
Non-renal clearance. (m1/min)	14±10	10±7	48±31
Distrib. Vol. (L/kg)		1.1±0.5	

Adapted from de Klerk et al. (1992): Values are mean± SD.

Tin-117m Stannic DTPA: At this time only limited clinical experience has been obtained with this compound (Atkins et al., 1993; Atkins et al. 1995; Krishnamurthy et al., 1997; Srivastava et al., 1998). Its physical characteristics are very favorable. The range of the electron emission (monoenergetic conversion electrons) is less than that of any of the other compounds so that the radiation absorbed dose to the marrow is considerably less, giving the best bone to marrow ratio (Table 3). The initial dose rate is higher than that obtained with strontium-89 and the half-life is ideal so far as shipment and shelf life are concerned. Its in-vitro and in-vivo stability are very high (Srivastava et al., 1994). An accompanying gamma photon is useful for monitoring. Results so far indicate a very low myelotoxicity (Table 4) and the efficacy is similar to the other compounds (Srivastava et al., 1998).

Table 3 - Dosimetry of bone agents*

	Radiation Dose, rad/mCi		
	Bone Surfaces	Red Marrow	Bone/Marrow Dose Ratio
Strontium-89Cl_2	63.0	40.7	1.6
Rhenium-186 HEDP	7.0	3.0	2.3
Samarium-153 EDTMP	15.4	2.8	5.5
Tin-117m Stannic DTPA	65.1	9.8	6.6

*Data from literature (Srivastava et al., 1998).

Pharmacokinetics: Tin-117m differs from the other therapeutic agents in that its primary emission is conversion electrons of discrete energies. These are also accompanied by an excellent gamma photon for monitoring distribution. The limited penetration of conversion electrons theoretically should reduce the absorbed dose to the red marrow. Studies in animals (Srivastava et al., 1985) demonstrated that the stannic form of Sn-DTPA behaved much differently from the stannous form. It was not rapidly excreted into the urine, as expected, but it is retained to a considerable extent in bone. Further studies (Oster et l., 1985) showed that its behavior mimicked that of ^{99m}TC MDP in certain pathological conditions. The biodistribution was studied in a group of patients with advanced metastatic disease from various primary malignancies.

Table 4 - Myelotoxicity Levels of Radiopharmaceuticals for Bone Pain Palliation (Srivastava et al., 1998).

	Dose Group		No of Patients with Grade $\geq$ 2 Toxicity	
Radiopharmaceutical	(mCi/Kg)	n	WBC	Platelets
Sr-89 Cl_2	0.154	67	25 (37%)	41 (61%)
	0.040	161	---------48 (31%)[2]---------	
Re-186-HEDP	0.500-1.143	12	2 (17%)	3 (25%)
Sm-153-EDTMP	1.00	20	3 (15%)	5 (25%)
	1.50	4	3 (75%)	1 (25%)
	3.00	4	4 (100%)	2 (50%)
Sn-117m DTPA	0.143	9	1 (11%)	0 (0%)
	0.179	5	0 (0%)	0 (0%)
	0.286	12	1 (8%)	0 (0%)

[1]Using NCI criteria.

[2]Only hematological toxicity@ grade $\geq$ 2 mentioned.

The disappearance rate from blood appeared to be considerably slower than other bone agents and urinary excretion slower. However, because of its rather long physical half-life relative to these biologic parameters, this is not a problem for radiation absorbed dose estimates. Once localized

in bone, the ^{117m}Sn appears to remain fixed with no or extremely slow release other than through physical decay (Atkins et al., 1993). Approximately 70% is taken up by bone, but this is highly variable and depends on the extent of disease. Imaging studies have shown no focus of uptake other than bone. The biologic parameters are shown in Table 5.

Table 5 - Pharmacokinetics of Sn-117m(4+)DTPA (Krishnamurthy et al., 1997).

Component	Plasma disappearance		Urinary excretion	
	T ½ (h)	%	T ½	%
1	5.4±2.1	81.8±3.7	38.6	29.8
2	102.6±15.3	18.2±3.7	796.7	70.2

THERAPY OF CANCER IN BONE

The compounds discussed above have been considered primarily as agents to provide pain palliation in far advanced metastases involving bone. The requirements for achieving this purpose are rather modest. It is not necessary to obtain much tumor regression and it is desirable to avoid significant toxicity. Therefore, for achieving pain palliation, it is not necessary to administer the highest doses possible.

However, there are hints that more than just pain palliation can be achieved in the appropriate clinical situation. Our data indicate that an earlier onset of response occurs with higher levels of administered tin-117m activity (Srivastava et al., 1998). The Trans-Canada Study performed with high doses of strontium-89 in patients with relatively early metastatic disease of the prostate demonstrated that, as an adjuvant to external beam treatment, the interval to new painful metastases could be significantly lengthened (Porter et al., 1993). In addition, others have demonstrated reversal of changes on the radionuclide bone imaging study with strontium-89 (Robinson et al., 1989). Radiographs following radionuclide therapy have shown healing of lytic metastases (Friedell and Storaasli, 1950; Fossa et al., 1992) thus demonstrating that tumor regression actually can occur. It has also been shown that treatment of earlier disease is more successful than the treatment of more advanced disease. Prolongation of survival has been reported using very high doses (2.5 mCi/kg) of samarium-153 EDTMP (Collins et al., 1993). This has been attained at the expense of increased morbidity as evidenced by greater increase in myelotoxicity.

On the basis of these findings it is reasonable to look at these agents in other situations. They may be very useful as adjuvant to external beam radiation therapy and chemotherapy. In primary bone malignancy the use of radionuclide therapy as an adjuvant to surgery may prevent the appearance of metastatic disease. Earlier application of these agents in a prophylactic mode appears warranted. Their ease of administration and relative lack of toxicity present a strong argument for this approach. If higher doses do prove to be advantageous, then that agent with the lowest toxicity should be considered as the most appropriate candidate. Tin-117m stannic DTPA appears to be the agent of choice if future studies (an extended Phase II/Phase III clinical trial is underway) continue to demonstrate reduced toxicity compared to the other agents, in particular strontium-89 and samarium-153. In summary, going beyond bone pain palliation, the use of these bone-seeking radiopharmaceuticals to actually treat the primary/metastatic cancer in bone is considered to be a very attractive prospect.

RADIATION SYNOVECTOMY

Radiation synovectomy is an attractive alternative to chemical or surgical synovectomy for the treatment of inflammatory synovial disease, including rheumatoid arthritis, as well as to some extent, osteoarthritis. The procedure entails a single injection of a beta-emitting radiopharmaceutical directly into the synovium to

control and ablate inflammation. The injected agents, typically colloids or larger aggregates, are assumed to be rapidly phagocytized by synoviocytes and then distributed within the synovium, primarily at the surface. The most common agents have been radiocolloids or macroaggregates employing high-energy beta emitters, Y-90, Au-198, Dy-165, and Re-186 (Deutsch et al., 1993). While these agents have shown good results, they are not widely used especially in the United States. All display some degree of leakage of the radionuclide from the joints leading to an increased radiation dose to normal organs. The size of these radiolabeled particles cannot be adequately controlled during formation, and it is assumed that small (<10 μm) particles leak from the synovium over time. However, a new type of particle, made from hydroxyapatite (HA), a natural constituent of bone, has become commercially available in various controlled sizes ranging from 1 - 80 μm. Research interest has thus focused recently on incorporating HA particles into new agents for radiation synovectomy. Initial studies in rabbits with antigen-induced arthritis (AIA) using Sm-153 labeled HA, showed minimal leakage of activity (0.09% over four days) from the treated joint compared to leakage rates obtained with other radiocolloid agents (5-45%). Results with Re-186-HA, however, showed 3.05% leakage over four days (Chinol et al., 1993).

The presumed heterogeneous distribution of radionuclide within the synovium has limited existing agents to only those labeled with high-energy beta emitters. It is presumed that the longer range of these particles is necessary to treat medium to large sized joints. However, low-energy beta emitters may be equally or more effective in reducing inflammation for small to medium joints since a much larger radiation dose could be delivered to the synovium without excessive irradiation of surrounding tissue. This could be analogous to the effectiveness of the short-range conversion electrons from Sn-117m for bone pain palliation, compared to the high-energy beta emitter Sr-89 (Srivastava, 1996; Srivastava and Dadachova, 2001). The only clinical examples to date for treating synovial inflammation using a low-energy beta emitter is the use of Er-169 (®$^{-}$ avg 111 keV) colloids to treat inflammation in the small finger joints (Deutsch et al., 1993). Based on various considerations, appropriate-size particles labeled with Sn-117m, Sm-153, and Er-169 would seem to be the agents of choice for radiation synovectomy.

RESUMO

Radiofármacos para terapia em nível ósseo são utilizados devido a emissão de radiação particular pelo radionuclídeo (primariamente beta de baixa e média). Portanto, as necessidades são diferentes daquelas usadas para imagem óssea que consiste principalmente de emissores de fótons de meia-vida curta. Ultimamente, a terapia do esqueleto com radiofármaco tem alcançado uma importância crescente devido ao papel em potencia de aliviar a dor de metástases ósseas em pacientes com câncer, para o tratamento de dor nas articulações devido a inflamação sinovial sinovite (radiosinovite ou radiosinovectomia), ou de várias outras formas de doenças articulares. Portanto, existe uma falta de publicações sobre a bio-farmacocinética desses agentes quando administrados intravenosamente como paliativo para dor óssea. Este artigo irá revisar rapidamente e resumir as informações sobre a química e a biofarmacocinética dos vários radiofármacos aprovados clinicamente e em experimentação disponíveis até o presente momento para terapêutica do esqueleto e fazer projeções para o tratamento clínico do câncer primário/metastático no osso.

ACKNOWLEDGEMENTS

This work was supported by the United States Department of Energy, Office of Health and Environmental Research, under Contract No. DE-AC02-98CH10886. The assistance of Ms. Amalia Ruggiero in the preparation of this manuscript is gratefully acknowledged.

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Received: July 18, 2002;
Revised: July 20, 2002;
Accepted: July 21, 2002.