

THE UNIVERSITY OF NEW MEXICO
COLLEGE OF PHARMACY
ALBUQUERQUE, NEW MEXICO

The University of New Mexico

Correspondence Continuing Education Courses
for
Nuclear Pharmacists and Nuclear Medicine Professionals

VOLUME II, NUMBER 1

*Radionuclide Therapy
of
Painful Osseous Metastases*

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Radionuclide Therapy of Painful Osseous Metastases

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The UNM Pharmacy Continuing Education Staff and the Editor would like to gratefully acknowledge Sharon I. Ramirez for her technical support and assistance in the production of this publication.

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Albuquerque, New Mexico

RADIONUCLIDE THERAPY OF PAINFUL OSSEOUS METASTASES

STATEMENT OF OBJECTIVES

This correspondence course is intended to increase the reader's knowledge of radiopharmaceuticals that are used in the treatment of pain associated with bone metastases from different types of cancer. A variety of aspects regarding the agents currently being used or tested are discussed.

Upon completion of this material, the reader should be able to:

1. List factors which cause bone pain.
2. Describe the steps by which metastasis occurs.
3. Describe how bone pain is evaluated.
4. List different pain relief indexes.
5. List different techniques that are used in controlling bone pain.
6. List the properties of an ideal radiopharmaceutical for bone pain therapy.
7. Define physical, biological, and effective half lives.
8. Define radiation absorbed dose.
9. Name all of the radiopharmaceuticals that are currently being used or tested for therapy of bone pain.
10. List the energies of the beta and/or gamma radiation associated with each radionuclide.
11. List the physical half lives of each radionuclide.
12. Draw the structure of each radiopharmaceutical described.
13. List the mechanism of localization of each radiopharmaceutical.
14. Describe the route of excretion of each drug.
15. List the absorbed radiation dose to all parts of the bone structure following administration of each drug.
16. List the side effects associated with each drug.
17. Describe the guidelines to follow for treatment of patients.
18. List the safety precautions suggested for each group of personnel involved with the patient's therapy.
19. Describe which drug is most effective for each type of disease discussed.

COURSE OUTLINE

INTRODUCTION

The concept of using radionuclides for therapy is certainly not a new one. As far back as the early to mid 1930s radioactive isotopes of iodine were being explored for use in the treatment of thyroid disease. The "magic bullet" theory of nuclear medicine was first applied to therapy doses and was based on the idea that one could inject a radioactive material that would go directly to a diseased organ and destroy the tumor or disease without harming other parts of the body. Unfortunately, researchers have never been able to develop a radiopharmaceutical drug that fits the magic bullet theory; all radioactive materials evaluated to date distribute to many parts of the body and do not concentrate just in one area.

Even though researchers realized flaws in the "magic bullet" theory, they continued to explore uses of radionuclides for therapeutic purposes. As early as 1941, Pecher (1) was using isotopes of calcium (Ca) and strontium (Sr) to treat bone cancers. Although Sr-89 was one of the first radionuclides used for treatment of bone disease, research began to focus on the use of ionic phosphorus (P-32) (2,3). Through the 1950s and 1960s some work using P-32 continued but only with limited success. During the mid to late 1970s a revival of Sr-89 was seen, only this time the concentration was not on curing bone disease but instead was on relieving the pain that is associated with bone metastasis of either breast or prostate cancers (4). In 1983, Robinson et al. (5) reported the results of data (collected over a period of six years) on treatment of pain associated with bone metastasis from primarily prostate or breast cancers. Recently, Robinson et al. (6) published information on nearly five hundred patients treated with Sr-89; pain relief was observed in nearly 80% of those receiving therapy.

Since neither P-32 nor Sr-89 have been found to be ideal nuclides for use in treatment of pain in all types of bone cancers, an effort to find new radionuclides was begun during the 1980s and continues yet today. Two separate groups (7,8) have reported results using compounds containing rhenium (Re-186) and samarium (Sm-153) for treatment of pain not only in patients with prostate and breast metastases but also in pain associated with osteogenic sarcoma.

Although it is recognized that agents based on the "magic bullet" theory will probably never be attainable, much work is currently being done and will continue to be done in the area of using radionuclides for therapy. In this CE lesson, aspects of the aforementioned radionuclides for treatment of bone pain from cancers will be discussed.

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MANAGEMENT OF BONE PAIN

Cause of Bone Pain

In order to understand how to treat a disease it is necessary to have a basic knowledge of what causes the disease and how it spreads. Since we are concerned with metastatic spread of cancer to bone tissue, we will concentrate on the pathway and the end cause of bone pain.

As outlined by Fidler (9), there are ten steps involved in the process of metastasis from the primary tumor site. Those steps are listed in Table 1. The process as shown is a complicated one and the tumor cells must survive each phase in order to metastasize to a new site.

Table 1. Process of Metastasis
1. Progressive growth of the primary tumor
2. Vascularization of the tumor
3. Invasions of the cellular walls
4. Detachment of cells or groups of cells
5. Embolization and transportation
6. Circulation survival
7. Arrest of cells in another organ
8. Extravasation into host organ
9. Invasion of host organs defense
10. New growth

After metastasis occurs and new growth is started, several things can contribute to the cause of bone pain (10). One form of pain is caused by an increase in pressure in the cells. Destruction of bone tissue by chemicals such as prostaglandins can also be a cause of pain. Once tissue in weight bearing joints has been destroyed, pain results from movement.

Evaluation of Bone Pain

One of the most difficult tasks when treating pain is to evaluate the results and determine how much, if any, relief the patient has received. There are various indexes used, including the Karnofsky index and others described by Nielsen et al. (11) Most methods use a variety of items to help evaluate the effectiveness of the treatment. Some of those items are listed in Table 2.

Since many patients do not always take medication properly or tend to forget some vital information, it is helpful to have patients use a log sheet system on which

they can write down all information as requested. Once this data is compiled, a reasonable evaluation of the effectiveness of treatment can be made.

Table 2. Pain Relief Indexes
1. Increase or decrease in pain medication
2. Change in type of medication (stronger or weaker)
3. Sleep patterns
4. Ability to move around on a daily basis (walk, cane, etc.)
5. Appetite

Current Control Techniques for Bone Pain

The spread of cancer from its primary site to the bone will almost always be fatal. For this reason, we can, at best, try to control pain and improve the patient's quality of life. There are several types of treatment available to the clinician.

The most commonly used techniques for the immediate treatment of pain are either surgery or radiation therapy. Surgery is primarily used in those cases of either fractured bones or areas that are considered to be impending fractures. Areas that are difficult to treat surgically, or are not in danger of immediate fracture, are usually treated with either spot or partial body radiation therapy.

Other therapies that are usually tried when the disease is first discovered are either hormonal therapy (estrogens or antiestrogens) or chemotherapy. The use of hormonal therapy drugs will normally give some relief over a period of time, but as they begin to fail, stronger chemotherapeutic drugs are necessary. Many times analgesic drugs such as morphine are used in conjunction with cytotoxic drugs.

The last category of drugs used for therapy of bone pain is, of course, radiopharmaceuticals. Radionuclides such as Sr-89, P-32, Re-186, and Sm-153 are currently being used or tested in the late stages of the disease. The literature (2,5,6,7) suggests that as high as 80% of the patients treated with radiopharmaceutical therapy do have moderate to 100% relief of pain from bone metastasis. Because of this, there is currently a great deal of interest in investigating the use of these radiopharmaceuticals in earlier stages of the disease in order to effect a curing process rather than a palliative one. Since these drugs are known to produce pain relief, they must, undoubtedly, be doing so by destroying some of the disease.

PROPERTIES OF AN IDEAL RADIOPHARMACEUTICAL FOR TREATMENT OF BONE PAIN

An ideal radiopharmaceutical for therapy of bone pain

would have the ability to not only symptomatically treat, but possibly cure, all types of bone cancer. Unfortunately no such drug exists. There are several specific properties to consider when designing or evaluating radiopharmaceuticals for therapy of bone pain.

Mechanism of Localization

Both the route of administration of a drug, as well as the specific mechanism by which a drug is extracted into an organ, affect final distribution of the drug within that organ. As with any drug, the distribution is also dependent upon blood supply to the organ system. Ideally a drug would be taken up 100% by the desired organ on the first pass. Since the metabolic rate of bone is very low compared to most organs, it is unreasonable to suggest that 100% first pass uptake will occur.

For practical purposes, an ideal radiopharmaceutical for localization in bone tissue would be one that is extracted quickly and is turned over or lost from bone cancer sites only very slowly, if at all. Any free, unbound drug should be rapidly excreted by way of urine. Rapid excretion insures that any amount of the agent that is not extracted by bone will clear the body, thus lowering radiation dose to unwanted areas.

One of the most important factors associated with localization of therapeutic bone agents is the site where the drug is deposited within the bone structure itself. In the best case, the radiopharmaceutical would be preferentially taken up by the hydroxyapatite crystal structure of the bone rather than being distributed throughout the entire tissue (which includes bone marrow). Agents residing in the crystal structure tend to have less effect on marrow production; thus, less effect on the platelet and white cell counts is observed.

Half-life

This section can be broken down into three different types of half-life. One must consider the physical, biological and effective half-lives in order to better understand the potential effectiveness of the radiopharmaceutical.

Physical. The physical half-life ($T_{1/2p}$) refers strictly to the decay of the radionuclide portion of the radiopharmaceutical. The $T_{1/2p}$ is a measurement of how long it takes for half of the nuclide to undergo nuclear transformation. Particulate-emitting radionuclides with short half-lives will, depending on the energy of the particulate radiation, typically deliver large amounts of radiation in short periods of time, which may be advantageous in certain cases.

Biological. The biological half-life ($T_{1/2b}$) is a function of the entire radiopharmaceutical and is not related to the $T_{1/2p}$ of the radionuclide. The $T_{1/2b}$ is a measurement of the time it takes for half of the drug to be eliminated from the desired organ system (or from the body). Ideally, the $T_{1/2b}$ in the organ system being treated would be long in order to ensure deposition of a

large dose of radiation to the desired area.

Effective. The effective half-life ($T_{1/2e}$) is directly dependent upon both the $T_{1/2p}$ and the $T_{1/2b}$ of the radiopharmaceutical. The $T_{1/2e}$ is defined according to the following equation:

$$T_{1/2e} = \frac{T_{1/2p} \times T_{1/2b}}{T_{1/2p} + T_{1/2b}}$$

By definition, the $T_{1/2e}$ is always shorter than either the $T_{1/2p}$ or the $T_{1/2b}$; as is evident from the above equation, the $T_{1/2e}$ is closely related to the shorter of either $T_{1/2p}$ or $T_{1/2b}$.

Radiation Absorbed Dose

Under ideal conditions, a radiopharmaceutical for therapy should deliver most of its radiation to the diseased site and very little to other areas of the body. There are several terms used for quantifying the amount of radiation received at a specific site; one of the more common is radiation absorbed dose. The radiation absorbed dose received by the diseased site is dependent upon many factors, some of which are discussed later in this lesson.

The effectiveness of the treatment is directly dependent upon the amount of radiation dose that is received by the diseased site. The highest dose will be delivered by those beta-emitting radiopharmaceuticals that remain in the site the longest and have a shorter $T_{1/2p}$. If a radiopharmaceutical (drug) is removed quickly from an organ, the radionuclide in that drug must decay quickly in order to deliver a significant radiation dose before the drug is biologically eliminated (i.e., one must compensate for a short $T_{1/2b}$ with a short $T_{1/2p}$).

Route of Excretion

The route and rate of excretion of any radiopharmaceutical are important because they can affect the localization of the agent as well as the absorbed dose delivered to any organ; these properties are especially important for therapeutic radionuclides. For drugs used in treatment of bone carcinomas it would be ideal to have most, if not all, of the excess drug excreted via the urinary tract. If the patient is properly hydrated, the excess radionuclide can be cleared at a reasonable rate, causing less of an unwanted radiation dose to other organ systems outside of bone tissue.

RADIOPHARMACEUTICALS CURRENTLY USED FOR THE TREATMENT OF BONE PAIN

Presently there are four radiopharmaceuticals that have been, or are being, used to treat bone pain caused from metastatic diseases. This section will examine aspects of each drug individually.

Strontium-89 Chloride (Sr-89 Chloride)

Structure and Chemistry. The element strontium is a member of the alkaline earth family, which includes beryllium (Be), magnesium (Mg), calcium (Ca), barium (Ba), and radium (Ra). The most unique thing about this group of nontransition metals is that, in solution, they all form salts in which the metal has a charge of +2. Since all of these elements are in the same family you would expect them to have similar chemical and biological properties. The closer the elements are to each other on the periodic chart, the more chemically and biologically alike they will be. Note that strontium is directly below calcium on the chart; thus we would expect the two elements to be chemically and biologically similar. The chemical form of Sr-89 as it is used in patients is the dichloride salt ($^{89}\text{SrCl}_2$). Strontium-89 remains ionized but is loosely associated with phosphates in the blood.

Mechanism of Localization. Strontium, like calcium, is carried to bone tissue where it undergoes ion exchange with the existing calcium to form $\text{Sr}_{10}(\text{PO}_4)_6(\text{OH})_2$ (strontium hydroxyapatite). Since the mechanism of localization is simple exchange with the calcium, the process is reversible in normal bone tissue. The turnover rate for Sr is faster than for Ca due to the size difference between the two ions. Since Sr is slightly larger than Ca, the Sr hydroxyapatite crystal structure is somewhat distorted, causing a preference for Ca. Differences in solubilities of Sr vs Ca compounds may also play a part in the rapid uptake and turnover of Sr by normal bone tissue. For unexplained reasons, Sr-89 tends to deposit in or near cancer sites in bone and will reside there longer than in normal tissue (15).

The localization of Sr-89 in hydroxyapatite crystal structure is advantageous since it can deliver a large radiation dose to the cortical bone without much radiation damage to the marrow. Because of rapid turnover by normal tissue and prolonged residence in tumor tissue, Sr-89 delivers relatively more of its radiation dose to the tumor site. Since Sr-89 is a pure beta emitter with an energy of 1.4 MeV, most of the radiation dose will be delivered very close to the deposit site in the bone.

Physical Properties. The characteristics of Sr-89, when compared to those of an ideal drug, are very favorable. Rapid uptake with rapid clearance from the body, except for areas of metastatic bone disease, along with its pure beta emission make Sr-89 a very good radionuclide for use as a drug in the treatment of bone metastasis. One of the major drawbacks to the use of Sr-89, however, is the fact that its $T_{1/2p}$ is 50 days. Because of its long $T_{1/2p}$, the radionuclide is effective only in those types of bone metastases in which the turnover rate for Sr is relatively slow, e.g., metastases from prostate cancer.

Rhenium-186 Hydroxyethylenediphosphonate (Re-186 HEDP)

Structure and Chemistry. The use of group VII B

transition elements (in the family of manganese) in nuclear medicine is certainly not new since technetium is also in this family. In fact, the chemistry of rhenium is very similar to that of technetium. Rhenium will form many different inorganic as well as organometallic complexes. Like technetium, rhenium will form cations with different charges. The most common oxidation states formed are the +7 and +4 states. Since there are many compounds of technetium being used, it would be expected that most, if not all, of the technetium radiopharmaceuticals could be duplicated using an isotope of rhenium.

Rhenium-186 (Re-186) is produced by a nuclear reactor using Re-185 as a stable target. Once the Re-186 is isolated as sodium perrhenate (NaReO_4) it is ready to be used for the preparation of Re-186 HEDP. Like technetium-99m (Tc-99m) radiopharmaceuticals, tin (stannous chloride) must be used as a reducing agent to form the Re-186 phosphate complex. The reaction of the perrhenate, $\text{Na}_2\text{H}_2\text{HEDP}$, SnCl_2 , and ascorbic or gentisic acid, takes place when heated in a boiling water bath for ten minutes. The reaction mixture is then loaded onto an anion chromatography cartridge using 10 ml of 0.003 M buffered ascorbic acid solution. The final product is washed from the cartridge using a solution of 0.3 M buffered ascorbic acid. The first milliliter of eluate is discarded and the Re-186 HEDP is eluted in the next three milliliters of solution. Radiochemical purity testing is performed using silica gel ITLC paper with saline and acetone as solvents, which is similar to the technique used for Tc-99m diphosphonates. Figure 1 shows the structure of HEDP. The final radiopharmaceutical may have tin involved in its structure although this has not yet been confirmed. The Re-186 is bound to the phosphonate compound through the oxygen groups (in the same manner as Tc-99m). With respect to purity, the final drug product should contain greater than 95% Re-186 HEDP.

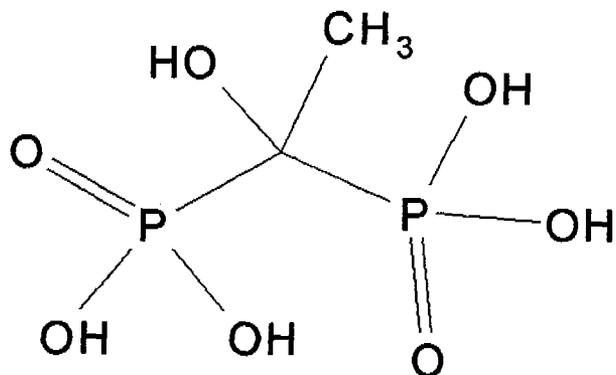


Fig. 1 Structure of HEDP

Mechanisms of Localization. The biodistribution and

method of localization for Re-186 HEDP are virtually the same as those for Tc-99m phosphonates. Localization occurs as chemisorption, resulting in a binding of the HEDP with the Ca ions in the hydroxyapatite molecule. As with other phosphates, there is increased deposition of the Re-186 HEDP in or next to metastatic sites in bone. As a means to minimize radiation absorbed dose to the kidneys and bladder, it is recommended that the patient be well hydrated.

Physical Properties. With a short $T_{1/2p}$ of 90 hours and a beta emission of 1.07 MeV, Re-186 is capable of delivering a fairly large radiation dose in a short time span. Rhenium-186 also emits a gamma ray at 187 keV (9%) which is adequate for imaging, thus allowing one to follow the biodistribution pattern using a gamma camera. One drawback to Re-186 HEDP is the fact that it does not clear rapidly from normal bone tissue. This characteristic of the drug results in a relatively high radiation dose to normal bone. A major advantage of Re-186 HEDP, on the other hand, is its ability to impart large doses of radiation in a short time, thus making it useful in treating bone cancers that have a high metabolic turnover rate such as osteogenic sarcomas.

Samarium-153 Ethylenediaminetetramethylene Phosphonic Acid (Sm-153 EDTMP).

Structure and Chemistry. Samarium (Sm) is one of the lanthanide series of elements which consist of several metals that are highly reactive. Samarium is known to be very reactive with oxygen and oxygen compounds, and will form extremely stable complexes with many oxygen compounds such as ethylenediaminetetraacetic acid (EDTA) or diethylenetriaminepentaacetic acid (DTPA) type molecules. One such molecule, ethylenediaminetetramethylene phosphonic acid (EDTMP), is shown in figure 2. According to the literature (16), Sm-153 will react with EDTMP on a 1:1 metal:ligand basis.

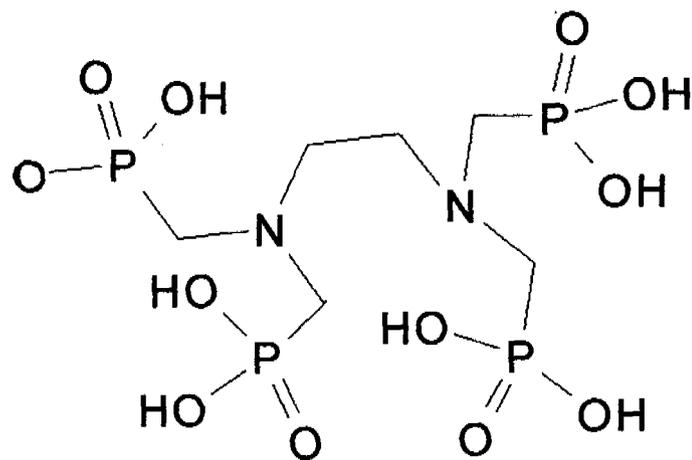


Figure 2: Structure of EDTMP

Samarium-153 is produced by a nuclear reactor from a target material of Sm-152 oxide ($^{152}\text{Sm}_2\text{O}_3$). The target after irradiation is soluble in 4M HCl. Once dissolved, the Sm-153 (as the oxide) is ready for use in complexation with EDTMP.

The radiopharmaceutical can be formed by direct addition of Sm-153 oxide in 0.1N HCl to Ca/Na EDTMP which has been sterilized and lyophilized. Once the complex is formed, it appears to be very stable. The radiopharmaceutical preparation is a single species, which requires no further purification.

Mechanism of Localization. The biological distribution and mechanism of localization are similar to those obtained with Tc-99m medronate (MDP) complexes. Based on the structure of the drug, one can predict that it will localize in hydroxyapatite crystals by binding to calcium ions. From animal biodistribution studies, it appears that a very high percent (above 50%) of the injected activity localizes in bone within two to three hours and most of the remaining drug is cleared within eight hours via the kidneys (17).

Physical Properties. The $T_{1/2p}$ of Sm-153 is 46.3 hours, so it is capable of delivering a large radiation dose to cortical bone over a short period of time. Unlike Sr-89 or Re-186, Sm-153 has three different beta particles (640, 710 and 810 keV). It is possible to follow the biodistribution of the radiopharmaceutical with a scintillation camera because of a gamma ray emission that occurs in 20% abundance at 103 keV.

As is the case with Re-186, a major advantage of using Sm-153 may be its shorter $T_{1/2p}$, which allows for treatment of bone cancers which are very metabolically-active. The advantage of Sm-153 EDTMP appears to be that even though it localizes in noncancerous skeletal tissue, the radiation dose to the bone marrow is minimal enough to cause no permanent major drop in production of blood cellular components. Since Sm-153 is produced in a nuclear reactor from an isotopic target, one possible disadvantage to this drug, like Re-186 and Sr-89, is that the specific activity can potentially be very low. [The effect of low specific activity is discussed in the section on "Side Effects . . ."]

Phosphorus-32 Sodium Phosphates

Structure and Chemistry. Element number 15, phosphorus (P), is a member of the group VA family. Even though elements such as nitrogen (N), arsenic (As), and others are members of this group, the chemistry of phosphorus is different than that of the others. Phosphorus forms mostly covalent bonds with other elements, unlike most of the other family members. Phosphorus also has the ability to bind to itself as well as to carbon, oxygen and several other elements. This unique ability contributes to making phosphorus a very important biological element. Most bodily functions depend on phosphorus, including DNA itself. Of particular interest is the fact that much of bone is

composed of hydroxyapatite (Ca,P and O).

In the clinical setting, the most widely used form of the phosphorus isotope, P-32, is as the sodium salt of orthophosphate (NaH_2PO_4). This compound is commercially available as a parenteral drug (as a mixture of monobasic and dibasic sodium phosphates). Phosphorus-32 is produced by a nuclear reactor using S-32 as a stable target. Once the P-32 has been formed, it is incorporated into a solution of sodium phosphate which is then prepared as a radiopharmaceutical.

Mechanism of Localization. Because of the incorporation of phosphorus into many biological systems, the biodistribution pattern and the mechanism of uptake of P-32 sodium phosphate into bone is not as simple as the other agents discussed. The amount of radioactivity in the bone changes with time; it takes up to three days for the P-32 to reach its maximum skeletal concentration. There is constant uptake in the hydroxyapatite crystal as well as constant turnover of P-32. The P-32 that is not in bone is concentrated in the spleen, liver, kidneys, and gastrointestinal (GI) tract (19). Any P-32 in the kidneys or GI tract is subject to reabsorption and recirculation. Since phosphorus is vital to red cell production, some of the P-32 ends up in the marrow of the bone, thus irradiating marrow cells much more than any of the previously-mentioned radiopharmaceuticals. The clearance of P-32 by the kidneys can be slow, plus much of the radionuclide is retained by the spleen and liver. These factors will greatly increase radiation dose to nonosseous sites and possibly cause unwanted damage to those tissues.

Physical Properties. Phosphorus-32 decays by beta emission with a maximum beta energy of 1.71 MeV; no gamma radiation is emitted. The $T_{1/2}$ for P-32 is 14.3 days which is between the shorter $T_{1/2}$ of Re-186 or Sm-153 and the longer lived Sr-89. In the case of P-32 it may be best that it has a longer $T_{1/2}$ since it stays in the biological system for several days or even weeks. A shorter $T_{1/2}$ for P-32 would result in large radiation doses to bone marrow and other tissues over a shorter period of time, thus potentially affecting the production of blood cellular components to a much greater extent. This topic is discussed in more detail later in this lesson. As it is, a major disadvantage in using P-32 as the orthophosphate is that it suppresses the marrow production to the point that many patients need one or more transfusions. Surprisingly, an advantage is that the P-32 can enter the metastatic site in bone by more than one mechanism. This allows for a large radiation dose to be delivered to metastatic sites over a longer period of time.

Although P-32 has been available for therapeutic use in bone metastasis for as long or longer than any of the other drugs mentioned, its use has never been widely accepted. Of all the radiopharmaceuticals being used today, it may be the least desirable.

RADIATION ABSORBED DOSE

Calculation Methods

The calculation of estimated radiation absorbed dose for any radiopharmaceutical is difficult at best. Since biodistribution patterns are often based on animal models, they are not always directly applicable to humans. With radionuclides that have imageable gamma rays it is easier to compare the images of animals with that of humans to make sure distributions are the same, or at least similar. With therapeutic radionuclides such as P-32 or Sr-89, which have no gamma emissions, it becomes very difficult to compare animal and human data. In the case of Sr-89, Sr-85 can be mixed with the Sr-89 and imaged to give a comparative scan. Phosphorus-32 data is almost solely based on animal data since it is extremely difficult to obtain any images using the 1% Bremsstrahlung that occurs.

Once data on the biodistribution is obtained, one can use this to estimate radiation absorbed dose using equations and information provided by the Medical Internal Radiation Dose (MIRD) Committee. The MIRD calculations are complex, but reasonably good estimates can be obtained from them. The calculation of radiation absorbed dose for any radionuclide uses the following equation:

$$D = \bar{A} S$$

where

D = radiation absorbed dose (rad)

\bar{A} = cumulated activity (uCi-hr)

S = absorbed dose per unit cumulated activity (rad/Uci-hr)

There are many factors that are taken into consideration by using this equation. Some of these factors are 1) the amount of radiation received by a target organ from nearby source organs that concentrate the radioactive material, 2) the type of radiation emitted during the decay of the radionuclide, and 3) the kinetics of the radiopharmaceutical. Actual calculations for each of the four drugs will not be shown; rather, discussion of the results obtained and their effects will follow.

Strontium-89 Chloride

The recommended amount of activity (dosage) that is given to the patient varies (6,14). All dosages used are based on the weight of the patient expressed in kilograms (kg). Recent studies (6,14,20) have compared the results using from 16 to 100 $\mu\text{Ci}/\text{kg}$. The population size of the studies has varied from 32 to nearly 500 patients. Estimated radiation doses to metastatic sites in osseous tissue range from 300 to over 1100 rads/mCi. The radiation dose can vary greatly depending on many factors, including tumor size and metabolic rate. The above-mentioned dose rates are considered to be

therapeutic and the results of almost all studies indeed show a response rate of about 80%.

Rhenium-186 HEDP

Due to the relatively short (90 hr) $T_{1/2}$ of Re-186, coupled with a high uptake in metastatic lesions of the bone, one might predict that the administration of this drug would result in a high radiation absorbed dose. The work of Maxon and coworkers (21) confirms this; these authors report estimated doses of 28 to 560 rads/mCi being delivered to metastatic sites. When compared to Sr-89 one can see a potential advantage to using Re-186 in patients with metabolically-active types of cancer because this dose is delivered over a short period of time (a few days).

Samarium-153 EDTMP

Most of the available information (22,23) on absorbed dose of Sm-153 is based on animal data. Since current MIRD estimates do not include values for Sm-153, it is difficult to compare data with other agents currently being investigated. A range of eight to 11 rads/mCi to metastatic bone lesions has consistently been reported. This value is considerably less than those for Re-186 or Sr-89. It would be reasonable to expect these values to be much higher considering the short (46 hr) half-life and high bone uptake of the drug. Since pain relief occurs in about 80% of patients treated, these estimated absorbed doses may be on the low side.

Phosphorus-32 Sodium Phosphate

The absorbed radiation dose to bone from use of P-32 sodium phosphate is very difficult to estimate because 1) P-32 is incorporated into many biochemicals that distribute throughout the body, and 2) phosphorus is rapidly turned over by the bone tissue. However, some rough estimates of the radiation absorbed dose have been proposed (18); reported absorbed doses to bone have ranged from 15 to 63 rads/mCi for P-32 orthophosphate. In fact, the dose probably varies considerably from patient to patient, depending on the extent of the disease. Actually, one would expect this to be true with all four of the therapeutic agents that have been discussed.

SIDE EFFECTS ASSOCIATED WITH RADIO-PHARMACEUTICALS USED FOR TREATMENT OF BONE PAIN

When using radiopharmaceuticals for diagnostic purposes, side effects are rarely encountered. However, as nuclear medicine moves more and more into the realm of therapy with radiopharmaceuticals, these phenomena must be routinely taken into consideration.

With most of the agents used for palliative bone therapy, the untoward effects are a direct result of radiation damage. There may be a possibility that very low specific activity drugs could induce a reaction which

is unrelated to the radioactive portion of the molecule. The most severe side effect for most agents is depression of platelet or white blood cell (WBC) production by the bone marrow. When using Sr-89 or P-32 it is well documented that the platelet count and the WBC count will be depressed with time. This depression usually occurs within a few weeks of the injection of the drug. Robinson and coworkers (24) have noted that with Sr-89, the platelet and WBC count will usually rebound within two to three months if no other types of therapy are being used on the patient. This is, however, not always the case with P-32. Depression of marrow production by P-32 leads to low platelet, WBC, and red blood cell (RBC) counts. In many instances the patient will need to be transfused one or more times within a few weeks of injection of P-32.

Radiation absorbed dose estimates to the bone marrow following administration of Sr-89 are in the range of four to five rads/mCi (12). This is considerably less than those estimates of 14-24 rads/mCi for P-32 (18). These differences in bone marrow dose may account for the fact that Sr-89 does not suppress marrow production to the point that transfusions are necessary.

The literature (21,22) indicates that both Re-186 and Sm-153 impart a radiation absorbed dose to the bone marrow on the order of two or less rads/mCi. Even though this is not much less than Sr-89, there has not been any reported prolonged depression of marrow when using either Re-186 or Sm-153. Two possible explanations for this may be that 1) the uptake of Re-186 and Sm-153 is more isolated to diseased areas of cortical bone, resulting in "patchy" absorbed doses to the marrow (doses not evenly distributed throughout the cortical bone) and 2) the energies of the beta emissions for Re-186 and Sm-153 are lower than those for Sr-89.

Although marrow suppression is the most serious side effect that must be considered, other side effects do occur. One side effect that is reported with the use of each of the four drugs mentioned is the onset of increased pain in the bone lesions within a few days after the administration of the drug. This is usually short lived (three to seven days) and is thought to be caused by swelling of the tumor tissue from the initial radiation damage. Because of the short $T_{1/2}$ of both Re-186 and Sm-153, it would be expected that this initial pain increase would be more severe with these two agents, as a large radiation dose is being delivered much quicker than with either Sr-89 or P-32. There is also the potential side effect of radiation damage to other organs that concentrate the radiopharmaceutical. This is minimal in most cases but could be expected to be more of a hazard with P-32 than the other drugs, because of its high uptake in the spleen and liver, combined with slow excretion over several days.

One interesting untoward effect that has been noted by Robinson's group (24) is the onset of calcium type flushes or groin flushes in some patients receiving Sr-89

chloride. This reaction appears to be directly related to the specific activity of the drugs. The flushing was noted in almost all patients who received more than 25 mg of "cold" (nonradioactive) strontium, due to very low specific activities of the manufacturer's previous formulation of the drug. This is not a problem today since specific activity is considerably higher than in the past.

TREATMENT GUIDELINES

The treatment of patients who have metastatic bone disease is dependent upon several factors. A guideline to treatment with Sr-89 has been outlined by Robinson et al.(6) These factors can basically be used for any of the radiopharmaceuticals that have been discussed.

Once it has been determined that a patient is a candidate for therapy, which is based on discussions with the patient as well as the results of a current bone scan, the most important factors to consider are related to hematology. These include the hematocrit, hemoglobin, WBC, and platelet levels. If a patient has a hemoglobin value of less than 10 gm% or if the WBC count and platelet counts are below 2,400 and 60,000 cells/mm³, respectively, it may not be advisable to treat a patient, particularly with P-32. However, even in some patients who have less than desirable values, it may be possible to administer the therapeutic agents, followed by transfusions, as required.

The current criteria for initiating treatment of patients with radiopharmaceuticals is usually failure of other forms of therapy. Many patients require the use of strong medications to relieve constant pain. Future studies may find that radiopharmaceutical drugs can be used at earlier stages of the disease in order to effect some curing aspects.

After treatment, it is very important that these patients are followed on a regular basis by a primary care physician. To begin with, hematology values and blood counts should be determined every other week, or more often as values/counts begin to fall. It is important that the patient understand that the pain may worsen the first few days due to swelling of the tumor sites from the radiation, but this should subside with time. It is also very important that the patient understand all the evaluation forms they are required to maintain for documentation of sleep habits, pain medication administration patterns, and mobility. Any new symptoms following the treatment, such as nausea or vomiting, are not likely to be caused by the radiopharmaceutical, but they should be reported immediately to the primary care physician.

Once all of the data (two to three months) has been collected, the patient should be consulted and the results evaluated. Based on published data, one should expect to observe moderate to complete pain relief in approximately 80% of treated patients, regardless of the

radiopharmaceutical used. Following initial therapy, the patient should be reevaluated to determine if retreatment is necessary.

PRECAUTIONS FOR HANDLING THERAPEUTIC RADIONUCLIDES

Precautions, as they pertain to use of therapeutic radionuclides, vary, depending on which population of people (healthcare employees, patients, general public) is being addressed and the physicochemical characteristics of the radionuclide in question. The use of radionuclides that emit only beta radiation vs radionuclides that emit both beta and gamma radiation will require that different sets of precautions be established for different sets of individuals involved.

Nuclear Pharmacy and Nuclear Medicine Personnel

When using pure beta emitting radionuclides such as Sr-89 or P-32, personnel handling the drug (nuclear pharmacists, nuclear medicine technologists, or nuclear medicine physicians) need to be more concerned with contamination than with external radiation from the nuclides. Since beta radiation does not travel far, even in air, it is easy to shield using plastic, such as lucite, rather than lead. Although lead can be used, one may be exposed to Bremsstrahlung radiation caused by interaction of the beta particles with the lead atoms. The primary concern with beta emitters is related to contamination of personnel. Both Sr-89 and P-32 can be absorbed through the skin rapidly, so gloves and long-sleeved jackets should be worn at all times when handling these radionuclides. Any contaminated articles such as tubing, syringes, needles, etc. should be disposed of according to your institution's regulations for handling radioactive therapy radionuclides. Any contaminated areas (floor, chair, benchtops, etc.) should be cleaned immediately with an appropriate decontamination material, and any waste handled carefully as stated above. If personnel do become externally contaminated with Sr-89, application of a solution of calcium versenate to the contaminated area will help complex the strontium, decrease its residence time on the body surface, and decrease the possibility of absorption of the radiopharmaceutical. If internal contamination of Sr-89 does occur, calcium disodium versenate can be injected to complex the radiopharmaceutical and facilitate its excretion. The use of P-32 presents a more difficult problem if internal contamination occurs, because it cannot be complexed and removed quickly from the body. Since long-lived beta emitting radionuclides yield very low external radiation doses, the handling of these radionuclides results in minimal external radiation exposure. On the other hand, if internal contamination occurs, the radiation exposure to a specific organ can be extensive if the radionuclide resides in the organ for a long period of time.

The use of short-lived radionuclides such as Re-186 or Sm-153 presents a different set of potential problems for personnel handling the radionuclides, thus requiring separate guidelines. Since these radionuclides emit gamma radiation as well as beta particles, it is advisable to use lead for storage. The radiation one might receive from Bremsstrahlung is very small compared to the direct radiation of the gamma rays. Disposal of Re-186 and Sm-153 is somewhat less of a problem, because they can more easily be detected and they have much shorter physical half-lives. Since neither Re-186 nor Sm-153 are volatile at room temperature, they can be stored with other radionuclides having similar physical half-lives and disposed of in the same manner. Because shorter-lived nuclides emit more radiation in a short period of time, one should handle these radionuclides with precautions similar to diagnostic gamma emitters. If internal contamination occurs, the radiation absorbed dose to the body can be decreased by forcing fluids.

Healthcare Personnel Not Employed in Nuclear Medicine

The radiation risks for healthcare personnel outside of nuclear medicine are very minimal. Personnel such as nurses that may be around patients who have had either P-32 or Sr-89 will not have to be concerned with radiation emissions from the body since these two radionuclides are pure beta emitters. However, any personnel who handles the patient's body fluids should wear gloves for the first five to seven days since P-32 and Sr-89 are excreted in the urine. The chances of any non-nuclear medicine personnel becoming contaminated internally are very small, but if they do, or have questions, they should contact an employee of nuclear medicine, radiation therapy, or radiation safety.

The use of either Re-186 or Sm-153 in patients will result in slightly more radiation exposure to personnel taking care of the patients. The reason for this increased exposure is due to the emission of gamma rays by both Re-186 and Sm-153. There is no reason for these patients to be treated any differently than patients who have received a diagnostic radionuclide, except that, again, gloves should be worn when handling urine for the first two to three days. Since these drugs are excreted in urine over a short period of time and they do also emit beta particles, internal contamination is possible. If internal contamination is suspected, someone in nuclear medicine, radiation therapy, or radiation safety should again be contacted.

Patient and Family Information

Advice to family members would be very similar to that for healthcare personnel not employed in nuclear medicine. If family members need to handle any urine, they, too, should wear gloves to avoid any possible internal contamination from any of the four radionuclides discussed. Patients themselves should wipe up any urine contamination on toilets and probably flush twice after

each use for the first few days after injection. Patients receiving either Re-186 or Sm-153 should avoid being physically close to children or pregnant women for the first three to five days after injection. Since Sr-89 and P-32 do not emit gamma radiation, there would not be the same concern for small children or pregnant women.

COMPARISON OF CURRENT AGENTS

As of February 1993, none of the four drugs are FDA approved for use in the treatment of pain in bone cancer. Although P-32 (sodium phosphate) is an FDA-approved drug, it is not indicated for palliation of bone pain since it really has never been adequately tested for this use. Of all the drugs discussed, P-32 is probably the least useful because of its kinetic properties.

Most of the data that is available today is on the use of Sr-89 chloride. At the time of this writing it is awaiting final FDA approval for use specifically as an agent for relief of pain associated with bone cancer. This would make Sr-89, available from Medi-Physics (a subsidiary of Amersham Healthcare), the only therapeutic radiopharmaceutical to be approved for such use. The drug is currently approved in England, Europe, and Canada and is being widely used. The use of Sr-89 will probably be primarily for males having bone metastasis from prostate cancer since it seems to be most effective in these patients.

The use of either Rhenium-186 HEDP or Samarium-153 EDTMP is very limited at this time. A major radiopharmaceutical manufacturer is currently producing and testing Re-186 HEDP; Sm-153 EDTMP has, to date, only been tested by the University of Missouri-Columbia group. Although only limited data is available, it does appear that both of these drugs may be useful in the treatment of osteogenic sarcomas.

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Questions

1. According to Fidler, there are _____ steps involved for a tumor to successfully metastasize.
 - a. 6
 - b. 3
 - c. 10
 - d. 7
2. An ideal radiopharmaceutical for use in bone pain relief would be taken up by the:
 - a. bone marrow
 - b. hydroxyapatite crystal structure
 - c. both a and b
 - d. neither a nor b
3. The preferred route of excretion of a bone therapy drug is:
 - a. 100% excretion by fecal material.
 - b. 100% excretion by perspiration.
 - c. 50% fecal excretion and 50% urine excretion.
 - d. 100% urinary excretion.
4. A beta-emitting radionuclide with a short physical half life ($T_{1/2p}$) will typically:
 - a. deliver a large radiation dose over a short time.
 - b. deliver a large radiation dose over a long time.
 - c. deliver a small radiation dose over a short time.

- d. deliver a small radiation dose over a long time.
5. The effective half life ($T_{1/2e}$) of an isotope is:
- equal to the $T_{1/2p}$.
 - longer than the $T_{1/2b}$.
 - longer than the $T_{1/2p}$.
 - shorter than either the $T_{1/2p}$ or $T_{1/2b}$.
6. Which of the following radionuclides used for therapy of bone pain emits a gamma ray?
- Sm-153
 - Sr-89
 - P-32
 - Tc-99
7. Strontium-89 in the form of a chloride salt will mimic which of the following within a biological system?
- sodium chloride
 - calcium chloride
 - manganese chloride
 - all of the above
8. The emission of a 1.4 MeV beta particle is characteristic of which radionuclide used for therapy of bone pain?
- Re-186
 - Sm-153
 - P-32
 - Sr-89
9. The two most common oxidation states of Re-186 are:
- +7 and +3.
 - +7 and +4.
 - +4 and +3.
 - +6 and +5.
10. A physical half life ($T_{1/2p}$) of 90 hours is characteristic of which radionuclide used for therapy of bone pain?
- Re-186
 - Sm-153
 - P-32
 - Sr-89
11. Sm-153 EDTMP has a biodistribution pattern similar to which of the following Tc-99m radiopharmaceuticals?
- Tc-99m mertiatide
 - Tc-99m disofenin
 - Tc-99m exametazime
 - Tc-99m medronate
12. Which radiopharmaceutical used in bone pain therapy has a structure similar to that of Tc-99m DTPA?
- Re-186 HEDP
 - Sm-153 EDTMP
 - Sr-89 chloride
 - P-32 sodium phosphates
13. A gamma emission of 103 keV is characteristic of which of the following radionuclides?
- Re-186
 - Sm-153
 - Sr-89
 - P-32
14. Which of the following radiopharmaceuticals may be useful in the treatment of high metabolic rate bone tumors?
- Re-186 HEDP and Sr-89 chloride
 - Sm-153 EDTMP and P-32 sodium phosphates
 - Re-186 HEDP and Sm-153 EDTMP
 - Sr-89 chloride and P-32 sodium phosphates
15. Besides concentrating in bone tissue, which of the following radiopharmaceuticals also concentrates in the liver, spleen, kidneys, and GI tract?
- Sr-89 chloride
 - P-32 sodium phosphates
 - Re-186 HEDP
 - Sm-153 EDTMP
16. Radiation absorbed dose estimates of 28 to 560 rads/mCi to bone tissue have been reported for which drug?
- Sm-153 EDTMP
 - Sr-89 chloride
 - P-32 sodium phosphates
 - Re-186 HEDP

17. Which of the following radiopharmaceuticals delivers the largest radiation dose to bone marrow?
- Re-186 HEDP
 - Sm-153 EDTMP
 - P-32 sodium phosphates
 - Sr-89 chloride
18. Which of the following side effects is most commonly seen when using bone therapy radiopharmaceuticals?
- marrow suppression
 - constipation
 - ventricular arrhythmias
 - all of the above
19. In order for a patient to be treated with any of the bone therapy agents, they should have which of the following?
- a hemoglobin value of greater than 10 gm%
 - a WBC count of greater than 2400 cells/mm³
 - a platelet count of greater than 60,000 cells/mm³
 - all of the above
20. One side effect associated with radiopharmaceuticals used for therapy of bone pain is increased pain in the area of the tumor within 2-4 days after injection of a therapeutic radiopharmaceutical. This is probably due to:
- lack of radiation to the tumor in early stages.
 - swelling of the tumor due to radiation damage.
 - something unrelated to the radiopharmaceutical.
 - lack of any pain medication.
21. Once administered to a patient, which of the following radionuclides would give off the least amount of external radiation to any healthcare worker?
- Re-186
 - Sm-153
 - P-32 sodium phosphate
 - Tc-99m
22. If you were to become contaminated with Sr-89, which agent might be used to complex the radionuclide?
- Radiac Wash
 - "cold" MDP
 - water
 - calcium versenate
23. Which of the following radiopharmaceuticals is FDA approved for use as a therapeutic agent for relief of bone pain?
- P-32 sodium phosphates
 - Re-186 HEDP
 - Sm-153 EDTMP
 - none of the above
24. The concept of using radionuclides for therapy has been around since:
- the 1930s.
 - the 1940s.
 - the 1950s.
 - the 1960s.
25. Which of the following radiopharmaceuticals may be best utilized for treatment of bone pain caused by metastases from prostate cancer?
- P-32 sodium phosphates
 - Sr-89 chloride
 - Tc-99m medronate
 - Re-186 HEDP

