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[54] **BONE SEEKING TECHNETIUM 99M STANNOUS PHOSPHATE COMPLEX**

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[52] **U.S. Cl.**..... **424/1,** 252/301.1 R, 423/249

[51] **Int. Cl.**..... **A61k 27/04**

[58] **Field of Search** 423/2, 249; 424/1

[56] **References Cited**

OTHER PUBLICATIONS

Subramanian et al., Radiology, Vol. 99, pp. 192–196, April 1971.

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[57] **ABSTRACT**

A metabolizable radioactive technetium-99m-stannous-ring phosphate complex in which at least 15 to 20% by weight, and preferably 40 to 100%, of the phosphate moiety is a ring or cyclic phosphate of molecular weight less than 300 and in which no more than 5 to 15% or 20% by weight of such phosphate moiety is a linear polyphosphate of molecular weight greater than pyrophosphate, a method of making the same, a method of using the same by in vivo intravenous administration to a mammal of the sterile-non-pyrogenic complex followed by radioassay scanning or imaging the skeletal structure, and a kit made up of a stannous-phosphate complex in which at least 15 to 20% and preferably 40 to 99% of the phosphate moiety is the aforesaid ring or cyclic phosphate and in which no more than 5 to 15% or 20% by weight of such phosphate moiety is a linear polyphosphate of molecular weight greater than pyrophosphate.

10 Claims, No Drawings

BONE SEEKING TECHNETIUM 99M STANNOUS PHOSPHATE COMPLEX

BACKGROUND OF THE INVENTION

It has been known for some time that phosphates, including long chain linear polyphosphates, when introduced into the blood stream of mammals will selectively seek out and collect in the bone or skeletal structure. Pro. Soc. Exp. Biol Med. Volume 100, pages 53–55 (1959); Journal of Labelled Compounds, April–June 1970, Vol. VI, No. 2, pages 166–173; Journal of Nuclear Medicine, Vol. 11, No. 6, pages 380–381, 1970; Journal of Nuclear Medicine, Vol. 1, No. 1, January 1960, pages 1–13. In these cases a phosphorous atom or atoms of the phosphate are radioactive, i.e., ^{32}P.

It has also been known for some time that technetium-99m (^{99m}Tc) is a preferred radionuclide for radioactively scanning organs because of its short half life and because it radiates gamma rays which can be easily measured, compared, for example, to beta rays. See Radiology, Vol. 99, April 1971, pages 192–196.

It has also been known for some time to use divalent stannous tin (SN^{++}) in the form of stannous chloride, or divalent iron (Fe^{++}) or reduced zirconium to bind radioactive ^{99m}Tc to carriers, such as chelating agents, red blood cells, albumin and other proteins, which selectively seek out certain organs of the body, in order to carry the ^{99m}Tc with them to such organs of the body where it is concentrated, whereby such organ can be radioactively scanned or imaged for diagnostic or other purposes, e.g. radioactive treatment of a pathological condition. See Journal of Nuclear Medicine, Vol. 11, No. 12, 1970, page 761; Journal of Nuclear Medicine, Vol. 12, No. 1, 1971, pages 22–24; Journal of Nuclear Medicine, Vol. 13, No. 2, 1972, pages 180–181; Journal of Nuclear Medicine, Vol. 12, No. 5, May 1971, pages 204–211; Radiology, Vol. 102, January 1972, pages 185–196; Journal of Nuclear Medicine, Vol. 13, No. 1, 1972, pages 58–65.

Also, it has been suggested to label a stannous compound with ^{99m}Tc for radioactively imaging bone marrow, Journal of Nuclear Medicine, Vol. 11, 1970, pages 365–366.

It has also been known for some time that the stannous ion Sn^{++} forms soluble complexes with long chain polyphosphates, Journal Inorganic Nuc. Chem., Vol. 28, 1966, pages 493–502.

It has been suggested to employ the aforesaid ^{99m}Tc for radioactively scanning the skeletal bone structure of mammals by complexing or binding it to tripolyphosphate carrier by use of the aforesaid stannous ion as a binding agent in order for such phosphate to selectively carry the ^{99m}Tc to, and concentrate it in, the skeletal bone structure upon in vivo intravenous administration for subsequent radioactive scanning or imaging the skeletal structure. Radiology, Vol. 99, April 1971, pages 192–196. The use of ^{99m}Tc in this manner in alleged to have certain advantages over the use of strontium, e.g. ^{85}Sr, as the radioactive label which has been used for radioactive bone scanning in the past. These advantages are those which are inherent in ^{99m}Tc, i.e. short half life and lower energy gamma rays. However, the bone uptake (the percent of the total dosage which becomes concentrated in the skeletal structure within a certain time after in vivo intravenous administration) of such ^{99m}Tc by the other organs of the body (the higher these ratios the better), i.e. radioactive contrast, are not nearly as high as with radioactive strontium.

STATEMENT OF THE INVENTION

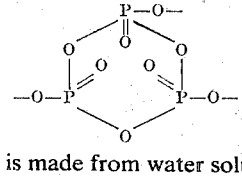
It has been discovered that if, in the aforesaid ^{99m}Tc-stannous-phosphate complex the phosphate moiety comprises a cyclic or ring (meta) phosphate of formula $P_nO_{3n}^{-n}$, preferably having a molecular weight of less than 300, rather than a polyphosphate, which is a linear straight or branched chain phosphate having the general formula $P_nO_{3n+1}^{(-n+2)}$, bone uptake of the ^{99m}Tc and the ratios of bone uptake to uptake of ^{99m}Tc by other organs, i.e. the liver, blood, kidneys and gastrointestinal system (G.I.) are substantially increased. It has also been discovered that optimum results are achieved if at least 15 to 25% by weight, preferably at least 30 to 40% (between 80 and 90 to 100% is more preferred), of such phosphate moiety is made up of such ring phosphate and if such phosphate moiety contains no more than about 15 to 20% or 25%, preferably no more than 5 to 10% and more preferably no more than 5% (less than 5% is the most preferred), by weight of such polyphosphate of molecular weight greater than that of pyrophosphate.

The term "phosphate moiety" as used herein refers to the phosphorus and oxygen atoms only of the phosphate.

The presence of polyphosphates of formula $P_nO_{3n+1}^{(-n+2)}$ and molecular weight greater than 300, more particularly greater than that of pyrophosphate, seems to reduce bone take-up and the aforesaid ratios, as compared to complexes without such higher molecular weight polyphosphates. However, as aforesaid, some of such higher molecular weight polyphosphates can be tolerated, preferably not more than about 15 to 20% or 25%, more preferably no more than 5 to 10% and still more preferably not more than 5% (less than 5% is the most preferred), by weight of the total phosphate moiety.

The rest of the phosphate moiety of the complex, where the ring phosphate does not constitute 100% of the phosphate moiety, is preferably ortho (PO_4^{-3}) and pyrophosphate (phosphate moiety molecular weight of less than 300) and more preferably pyrophosphate only.

A highly preferred ring phosphate is trimetaphosphate ($P_3O_9^{-3}$-molecular weight of 237) of the formula:



The complex is made from water soluble alkali metal (preferably sodium) or ammonium salt or acid salt of the ring phosphate, e.g. sodium trimetaphosphate.

Preferably the sodium trimetaphosphate is admixed with a stannous salt, e.g. $SnCl_2$ (the stannous salts of other acids which are pharmaceutically acceptable, i.e., safely intravenously administered, can be used) to form the stannous-trimetaphosphate complex, the pH of which is adjusted to 3–8, preferably 5–8, by a pharmaceutically acceptable base, such as NaOH or Na_2CO_3 or $NaHCO_3$, followed by admixing with the stannous-trimetaphosphate complex, an aqueous saline solution of radioactive sodium pertechnetate (^{99m}Tc) to form the ^{99m}Tc-stannous-trimetaphosphate complex at

the time it is desired to intravenously administer the ^{99m}Tc complex. The stannous-trimetaphosphate complex may be sealed in a sterile non-pyrogenic container or vial as a solution or a dry lyophilized solid and shipped as a kit with the freshly generated sterile and nonpyrogenic ^{99m}Tc being added aseptically at the situs just prior to use.

DETAILED DESCRIPTION OF INVENTION (INCLUDING EXAMPLES)

The following compositions were prepared:

TABLE 1

Sample No.	Description
1	A commercial sodium polyphosphate sold by FMC Corporation under the trade name FMC Glass H (average chain length of 21 and average M.W. about 2100).
1-1	A first high molecular weight fraction of the FMC Glass H of Sample 1 obtained by fractionating an aqueous solution of Sample 1 with acetone according to the technique described in Van Wazer, Phosphorous And Its Compounds, Interscience Publishers, Inc. 1961 (pages 744–747) to precipitate out of the aqueous solution of the FMC Glass H, as an oil, the highest molecular weight fraction of polyphosphates (composition given in TABLE 2).
1-2	A second acetone fraction of FMC Glass H achieved by adding more acetone to precipitate out of the remaining supernatant of 1–1, as an oil, the next higher molecular weight polyphosphates (composition given in TABLE 2). The acetone decreases the solubility of the polyphosphates in the water; the higher the molecular weight of the polyphosphate the less soluble it is so that the highest molecular weights are forced out of solution first.
1-3	A third acetone fraction of FMC Glass H containing the next higher molecular weight polyphosphates is precipitated out of the remaining supernatant solution of 1–2, as an oil, upon addition of further amounts of acetone (composition given in TABLE 2).
1-4	A fourth acetone fraction of FMC Glass H containing the next higher molecular weight polyphosphates (composition given in TABLE 2) is precipitated out of the supernatant solution of 1–3, as an oil, by adding more acetone.
1-5	A fifth acetone fraction of the FMC Glass H (containing the next higher molecular weight polyphosphates) (composition given in TABLE 2) is precipitated out of the remaining supernatant solution of 1–4, as an oil, by adding more acetone.
1-6	A sixth acetone fraction of FMC Glass H (composition given in TABLE 2) is precipitated out of the remaining supernatant solution of 1–5, as a solid precipitate of the next higher molecular weight polyphosphates by adding more acetone.
1-7	A seventh acetone fraction of FMC Glass H (composition given in TABLE 2) is precipitated out of the remaining supernatant solution of 1–6, as a solid precipitate of the next higher molecular weight polyphosphate by adding more acetone.
1-8	The residue fraction in the supernatant liquid left after removal of the 1–7 fraction (composition given in TABLE 2) is recovered by evaporating off the supernatant liquid.
2	An acetone end fraction of sample 1 after 90% by weight had been previously fractionated off and leaving by removal of such end fraction 3% by weight in the supernatant (composition given in TABLE 2).
4	A mixture of 86% sodium trimetaphosphate ($Na_3P_3O_9$), 3% sodium orthophosphate (Na_3PO_4) (molecular weight of phosphate moiety-95) and 10% sodium pyrophos ($Na_4P_2O_7$) (linear polyphosphate—molecular weight of phosphate moiety-174) obtained by acetone fractionation of sodium trimetaphosphate obtained from Monsanto. Sodium trimetaphosphate as aforesaid, is one of a plurality of cyclic phosphates having the general formula $P_nO_{3n}^{-n}$. Sodium orthophosphate is a phosphate monomer. Sodium pyrophosphate is a dipolyphosphate.
5	An acetone end fraction of a food grade polyphosphate sold by FMC under the name FMC FG (composition given in TABLE 2).
6	A commercial cyclic trimetaphosphate sold by Stauffer Chemical, (composition given in TABLE 2)
7	Sodium orthophosphate.
8	Sodium pyrophosphate.
9	Sodium tripolyphosphate.
10	Sodium tetrapolyphosphate—$Na_6P_4O_{13}$—a polyphosphate—phosphate moiety having a M.W. of 348. It, together with the pyrophosphate and tripolyphosphate, fall in the class of linear chain polyphosphates having the general formula $P_nO_{3n+1}^{-(n+2)}$.

An aqueous solution of each of the phosphate composition samples 1 through 10 (40 mg. phosphate/1 ml. solution) were made with distilled water in which the dissolved oxygen content was reduced in a conventional manner by bubbling through such water gaseous nitrogen for a period of 2 hours. The water and phosphates were mixed to form the solutions in a nitrogen atmosphere and in a nitrogen flushed container. The reason for this is to reduce oxidation of the divalent Sn^{++} to be subsequently admixed with each solution sample. However, it is not essential (but highly preferred) to use nitrogen-treated water or a nitrogen atmosphere or a nitrogen-flushed container. Other known pharmaceutically acceptable conditions, which will inhibit oxidation of the Sn^{++} upon subsequent mixing thereof with the phosphate solution, can be used, including the use of conventional pharmaceutically acceptable reducing agents and anti-oxidants in the products used.

Each of these solutions, samples 1 through 10, in an amount equal to 100 ml. was mixed with 0.16g of solid $SnCl_2.2H_2O$ under a nitrogen atmosphere. The $SnCl_2.2H_2O$ was made by adding to 84.5 mg. of metallic tin, sufficient concentrated HCl with mixing until all the tin has dissolved followed by removing excess acid and water by lyophilization (this operation also being carried out in a vacuum or in a nitrogen atmosphere and in a nitrogen flushed container to prevent oxidation of stannous to stannic). Antioxidants, which can be administered intravenously, may also be used. A stannous (SN^{++}) -phosphate complex or mixture of some kind was formed in each case, the phosphate moiety of each sample corresponding to the phosphate moieties of the phosphates set forth in TABLE 2. Thus, in the case of sample 1–7, 60% of the phosphate moiety was trimetaphosphate whereas in sample 1, 96.5% of the phosphate moiety constitutes long chain linear polyphosphates of 5 or more phosphorous atoms.

Sufficient aqueous solution of 3N NaOH (sodium carbonate or bicarbonate can also be used), in the case of all samples except 8, and 3N HCl, in the case of sample 8, is then added to each sample to give a pH of 6.0 to achieve a pH suitable for subsequent intravenous in vivo administration into the body of a mammal, in this case adult mice. The pH adjustment is preferably done under a nitrogen atmosphere also.

After thorough mixing, the solutions are sterilized by passing them through a Millipore biological filter of 0.22 micron pore size under a nitrogen atmosphere. Thereafter milliliter portions of each of the sterile solutions are poured into individual sterile and nonpyrogenic storage glass vials under aseptic conditions and the vials are aseptically sealed so that the interior and contents of each sealed vial is sterile and nonpyrogenic and under a nitrogen atmosphere.

In the case of each sample, vials are lyophilized by conventional freeze drying equipment under aseptic

conditions to remove water. This provides a solid stannous-phosphate complex which aids in shipping and which is more stable than the complex in solution.

Each vial contains 1.35 mg. $SnCl_2$ and 40 mg. of the phosphate.

The vials can be sealed and stored until needed subsequently to form the technetium-99m-stannous-phosphate complex at the use situs.

To prepare the technetium-99m complex, 3 to 7 (5) ml. of fresh sodium pertechnetate, removed as a sterile non-pyrogenic eluate from a sterile NEN ^{99m}Tc Generator (any other source of pharmaceutically acceptable ^{99m}Tc can be used, including ^{99m}Tc generators manufactured by others than NEN), in a 0.9% saline solution is aseptically added to each vial containing the sterile and non-pyrogenic stannous-phosphate complex and the vial is swirled until a solution is obtained. In each case a technetium-99m-stannous-phosphate complex or mixture of some kind is formed in aqueous solution (9 mg. per ml. solution when 5 mil of pertechnetate are used), the phosphate moiety of which corresponds to the phosphate moieties of the phosphate compounds of each sample set forth in TABLE 2.

Aseptic techniques and sterile, non-pyrogenic ingredients and containers were used at all steps, such procedures being standard to those skilled in the art.

Each of the technetium-99m-stannous-phosphate complex-containing solutions is aseptically intravenously injected in vivo into a vein in the tail of adult mice (average weight 0.040 kgs) in an amount equal to between 1 and 3 mCi and a volume of 0.12 ml (8 mg. of phosphate per ml solution in samples 1 through 10).

Three hours after intravenous administration, some of the mice to which each sample was administered were sacrificed and the various organs of their bodies (skeletal, liver, G.I., blood, kidneys) were counted by conventional gamma ray counting techniques to determine uptake of ^{99m}Tc by each organ and thereby determine contrast of bone uptake as compared to uptake by other organs. As aforesaid, it is not only important to have a high bone uptake (based on total technetium-99m dosage) but it is also important that the ratio of uptake by the bone to uptake by the other organs be high.

The results are set forth in TABLE 2 below, in which the uptakes (the bone uptake figures represent the average bone uptake for the skeletal system) are in terms of percent of the total technetium-99m activity injected (corrected for radioactive decay) which has collected in the various organs indicated 3 hours after in vivo intravenous injection, in which the ratio amounts are computed from the uptake amounts, in which "Percent Having Phosphate Moiety M.W. Less than 300" refers to weight percent of the phosphate moiety based on the total phosphate moiety of the sample identified in the first horizontal column, in which the percents referred to under Phosphate Composition are weight percents of the whole phosphate moiety of the sample (as aforesaid, phosphate moiety as used herein is limited to that part of the compound or complex made up of phosphate phosphorus and oxygen atoms), in which Ortho P1 refers to the phosphate moiety of sodium orthophosphate, Pyro P2 refers to the phosphate moiety of sodium pyrophosphate, Tripoly P3 refers to the phosphate moiety of sodium tripolyphosphate, Tetrapoly P4 refers to the phosphate moiety of sodium tetrapolyphosphate, Trimeta R3 refers to the phosphate moiety of sodium trimetaphosphate, Tetrameta R4 refers to the phosphate moiety of sodium tetrametaphosphate, both trimeta and tetrametaphosphates falling within the class of cyclic or ring phosphates having the formula $P_3O_{3n}^{-n}$, in which "Pentapoly And Longer Linear Chains" refers to the phosphate moiety of soidum pentapolyphosphate and longer linear (linear as used herein includes straight and branched linear phosphate chains) polyphosphates of formula $P_nO_{3n+1}^{-(n+2)}$, in which "Average M.W." refers to the average molecular weight of the phosphate moiety of the sample and in which "Fraction In Raw Stock" with reference to samples 1–1, 1–2, 1–3, 1–4, 1–6, 1–7 and 1–8 refers to the normalized percent by weight of each of these samples in sample 1, which is the raw stock which is fractionated.

Conventional gamma counting techniques for measuring technetium 99m take-up in the organs are conventional gamma ray-excitable scintillation counters for radioassaying multiple samples of the organs of the sacrificed mice.

Also, conventional scanning by radioactive imaging using a gamma ray-excited scintillation or gamma camera and a dual crystal rectilinear scanner was used in vivo. In vivo scintiphotos of the total body using the Anger camera were obtained as well as rectilinear total body scans.

The figures given in TABLE 2 are average figures achieved by the aforesaid conventional counting techniques, each sample having been intravenously administered to mice followed by radioactive counting.

Following intravenous administration, the technetium 99m-stannous-ring phosphate complexes of the invention are rapidly cleared from the blood by deposition in bone and excretion into urine. Thus, the technetium-99m-stannous-ring phosphate complexes are metabolizable. The deposition of the ^{99m}Tc-stannous-ring phosphate complexes of the invention appears to be primarily a function of the bone blood flow as well as being related to the efficiency of the bone in extracting the complex from the blood which perfuses the bones.

It was observed that the deposition of the ^{99m}Tc in the skeleton is bilaterally symmetrical with increased accumulations being present in the axial skeleton as compared to the appendicular skeleton. There is also increased deposition in the distal aspect of long bones.

Localized areas of abnormal accumulation of the radio-pharmaceutical may be seen in primary malignancies of the bone, metastatic malignancies of the bone, acute or chronic osteomyelitis, arthritides, recent fractures, areas of ectopic calcification, Paget's disease, regional migratory osteoporosis, areas of aseptic necrosis and in general any pathological situation involving bone in which there is increased osteogenic activity or localized increased osseous blood perfusion.

The acute toxicity level in mice ($LD_{50/30}$) for Sample No. 2 has been determined to be 150 mg/Kg body weight and for Sample No. 6 it is 800 mg/Kg and for Sample No. 8 it is 70 mg/Kg. Subacute toxicity studies in mice of Sample 2 have shown no signs of toxicity after 15 daily injections at dose levels as high as 63 mg/Kg body weight/day. A similar subacute study in dogs indicates no signs of toxicity at a dose level of 3.6 mg/Kg body weight/day.

TABLE 2

Phosphate sample	1 FMC	1-1	1-2	1-3	1-4	1-6	1-7	1-8	2	4	5	6	7	8	9	10
Uptake:																
Blood	1.7	4.0	4.2	4.6	2.9	3.4	1.3	1.3	1.6	1.3	0.65	1.0	4.5	1.2	1.8	3.3
Liver	23	2.7	2.7	2.8	2.2	6.8	0.9	2.0	1.3	1.3	0.52	0.85	5.9	7.5	1.3	4.7
G.I	4.9	8.5	5.5	7.5	4.2	4.8	1.8	1.5	2.2	1.9	0.75	1.9	1.8	1.7	2.2	4.0
Kidneys	3.6	3.7	3.1	3.2	1.7	2.6	0.9	0.9	1.1	1.5	0.88	0.82	1.1	1.3	1.5	3.1
Avg. bones	17	35	31	32	31	35	45	65	53	70	70	57	20	56	45	29
Ratios:																
Bone/blood	5	4	4	4	5	5	18	29	17	30	58	32	2	34	13	5
Bone/liver	0.5	7	6	7	8	3	29	19	24	32	78	38	2	5	20	3
Bone/G.I	5	6	8	7	11	11	37	63	36	55	140	55	17	49	31	11
Bone/kidneys	1	1	1	1	3	2	9	12	8	9	13	12	3	9	5	1
Percent having phosphate moiety M.W. less than 300	15	3	3	5	13	17	90	100	55	99	98	98	100	100	100	10
Phosphate composition:																
Ortho P^1 (percent)	3	1.0	1	2	5	5	10	50	5	3	15	4.0	100	0	0	0
Pyro P^2 (percent)	2	0.5	0.5	1	2	1	15	10	10	10	5.0	8.0	0	100	0	0
Tripoly P^3 (percent)	2	0.5	0.5	1	2	1	5	----	0	0	0	0	0	0	100	0
Tetra Poly P^4 (percent)	2	0.5	0.5	1	3	10	5	----	1	0	1.0	0	0	0	0	90
Trimeta R^3 (percent) cyclic	8	0.5	0.5	1	4	10	60	40	40	86	78	86	0	0	0	10
Cyclic tetra meta R^4 (percent)	4	0.5	0.5	1	4	50	5	----	40	----	0	0	0	0	0	0
Penta poly P^5 and longer linear chains	79.0	96.5	96.5	93	80	23	0	0	5	----	2	1	0	0	0	0
Average M.W	2,100	3,900	2,700	1,800	1,200	----										
Fraction in raw stock	100	3.5	61	916.2	7.5	5.0	6.1	0.7	----							

It was found that samples 4 and 6 were only one-fourth as toxic to mice as sample 2 and one-eighth as toxic to mice as sample 1.

The complexes of the invention have been used successfully as a skeletal imaging or scanning agent to visualize areas of altered blood flow to the bone and altered osteogenic activity, including suspected bone lesions not shown on X-ray, bone survey performed as part of the work-up in patients with known or suspected malignancy, to follow the response of metastatic or primary bone lesions to radiation therapy, metabolic bone disease, to diagnose arthritis and osteomyelitis, and to diagnose and determine healing rate of bone fractures.

The technetium-99m (^{99m}Tc) labeling reactions involved in preparing the ^{99m}Tc stannous-phosphate complexes of the invention depend on maintaining the tin in the reduced or stannous (Sn^{+2}) state. Oxidants present in the pertechnetate supply may adversely affect quality.

The radioactive dosage of the ^{99m}Tc complex of the invention may vary from 1 to 25 mCi (millicuries) but preferably is from 10 to 15 mCi. The dosage in terms of the ^{99m}Tc complex may vary over a wide range, i.e. from 0.001 to 30 mg per kilogram body weight of mammal.

The concentration of ring phosphate moiety in the final solution is preferably between 1 and 40, more preferably between 2 and 20 mgs per ml of solution.

An advantage of a complex containing a relatively large amount of ring phosphate is that the ring phosphate, in addition to providing excellent up-take and bone-to-other-organ ratios, has a low toxicity. Where the phosphate moiety contains phosphate other than ring phosphate it is advantageous for such other phosphate to be pyrophosphate because of its high bone uptake.

Scanning may be commenced as early as one hour after intravenous administration and may be as long after injection as clinically useful amounts of ^{99m}Tc remain in the organ.

Another manner of making the complex of the invention is to weigh 4 mg. of $SnCl_2.2H_2O$ and 100 mg of sodium trimetaphosphate into a flask (the flask is sterile and non-pyrogenic and is flushed with nitrogen before weighing and is kept under nitrogen during this step and for the next step). Add, under aseptic conditions, 12 ml of sterile, non-pyrogenic sodium pertechnetate in 0.9% saline solution. Shake the mixture until a solution is obtained followed by intravenous injection (preferably the pH of the mixture is aseptically adjusted to pH 4–8 before intravenous injection).

Also, the sterile stannous chloride can first be aseptically mixed with the sterile ^{99m}Tc saline solution to form a ^{99m}Tc-stannous complex, followed by adding the sterile sodium ring phosphate under aseptic conditions to form the ^{99m}Tc-stannous-ring phosphate, adjusting the pH to 4–8, followed by intravenous injection.

It can be seen from TABLE 2 that the ^{99m}Tc-stannous-phosphate complexes, the phosphate moiety of which is cyclic (in the form of a ring) and has a molecular weight of less than 300, e.g. samples 1–7, 1–8, 2, 4, 5 and 6, provide surprising and markedly higher bone uptake of ^{99m}Tc and higher ratios of bone uptake to other organs, as compared to those complexes, the phosphate moiety of which is in the form of linear long chains of molecular weight above that of pyrophosphate, e.g. samples 1, 1–1, 1–2, 1–3, 1–4, 1–6, 9 and 10.

In accordance with the invention, the ring phosphate moiety of the ^{99m}Tc-stannous-phosphate complex should be at least 15 or 20%, preferably at least 30 to 40%, more preferably more than 50 or 60% and most preferably 80 to 90% or more, by weight of the total phosphate moiety of the complex.

Trimetaphosphate is a highly preferred ring phosphate.

Although the stannous (Sn^{++}) ion is by far preferred, the divalent ferrous (Fe^{++}) ion in the form of ferrous ascorbate, and reduced zirconium can also be used but without as good results. All these metals can exist in a plurality of redox states.

The phosphate may be added to the solid $SnCl_2$ as an aqueous solution, or it may be added to a solution of the $SnCl_2$ to form the Sn^{++}-phosphate complex followed by adding the ^{99m}Tc solution.

Very little Sn^{++} need be used to form the complex of the invention, e.g. less than 7 to 10% of the phosphate based on molecular weights.

The weight ratio of Sn^{++} ion to the ring phosphate moiety may vary over a wide range, i.e. from 10^{-3} to 0.50, preferably 0.01 to 0.4. The maximum ratio of dictated by the amount beyond solubility of the Sn^{++}. The minimum amount required that amount necessary to bind a sufficient amount of ^{99m}Tc to the ring phosphate to achieve good bone uptake and contrast. This can be determined by routine experiment.

The pH of the stannous-phosphate complex should be between 3 and 8.

The water used for making the complexes of the invention is distilled and is at an elevated termperature of 200°F during removal of dissolved oxygen and reduction of oxidants by bubbling the nitrogen gas therethrough.

The maximum amount of ^{99m}Tc is that beyond the capacity of the Sn^{++}-ring phosphate complex to bind the ^{99m}Tc. This can be determined by routine thin layer radiochromatography to determine the percent of free or unbound ^{99m}Tc in the complex. The minimum amount is dictated by that amount below which there is an insufficient amount to give good scanning of bone uptake and contrast, which also can be determined by routine experiment. Generally, the amount of ^{99m}Tc added to the Sn^{++}-ring phosphate complex should be sufficient to achieve the counting rate desired by the doctor or laboratory personnel for the volume to be injected; ordinarily, as aforesaid, the activity dosage varies from 5 to 25 millicuries.

Although sodium ring (meta) phosphates are preferred, any alkali metal, such as potassium and lithium, or ammonium can be used as the cation so long as it is pharmaceutically acceptable so that it can be safely administered intravenously. Also, the acid pyrophosphates of such cations can be used.

Although in the examples give above saline water was used as the vehicle, any other vehicle which is pharmaceutically acceptable for intravenous administration can be used.

It is not intended that the invention be limited to any theory which may have been given above or to the specific examples set forth above but only by the claims appended hereto and their equivalents.

We claim:

1. A metabolizable radioactive bone seeking composition for in vivo concentrating ^{99m}Tc in the skeletal structure of mammals comprising a technetium-99m-stannous-phosphate complex, at least 15 to 20% by weight of the phosphate moiety of which is a ring phosphate having the formula $P_nO_{3n}^{-n}$ and a molecular weight of less than 300, said phosphate moiety containing no more than 25% by weight of linear polyphosphates of formulation $P_nO_{3+1}^{116\ (n+2)}$ having a molecular weight greater than that of pyrophosphate.

2. A bone seeking composition according to claim **1**, said phosphate moiety being substantially free from said linear polyphosphates.

3. A metabolizable radioactive bone seeking composition according to claim **1**, at least 30 to 40% by weight of said phosphate moiety being said ring phosphate.

4. A metabolizable, radioactive bone seeking composition according to claim **3**, said phosphate moiety also including pyrophosphate, and at least the major portion of any remaining phosphate moiety being ortho phosphate.

5. A composition according to claim **1**, where n is equal to 3.

6. A composition according to claim **1**, more than 50% by weight of said phosphate moiety being said ring phosphate.

7. A composition according to claim **3**, said phosphate moiety comprising a mixture of said ring phosphate, a pyrophosphate and an orthophosphate and wherein n is 3.

8. A composition according to claim **3** wherein n is 3.

9. A composition according to claim **8**, substantially the remaining phosphate moiety comprising one or more phosphates having the formula $(P_nO_{3n+1})^{-(n+2)}$ where n is less than 3.

10. A composition according to claim **8**, substantially the remaining phosphate moiety being one or more phosphates of formula $(P_nO_{3n+1})^{-(n+2)}$ of which not more than 20% by weight has an n value greater than 2.

* * * * *

UNITED STATES PATENT OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 3,852,414

DATED : December 3, 1974

INVENTOR(S) : Norman Adler, Leopoldo Lazaro Camin

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

First page, the second inventor's name is Camin

Column 2, lines 12 and 29, the formula should read $P_nO_{3n+1}^{-(n+2)}$

The same formula should be corrected in the claims, Column 10 line 6.

Signed and sealed this 6th day of May 1975.

(SEAL)
Attest:

RUTH C. MASON
Attesting Officer

C. MARSHALL DANN
Commissioner of Patents and Trademarks

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