imperative to develop methods to control daughter nuclides, at least ^{212}Pb, in ^{224}Ra injectates.

This has been achieved by the new ^{224}Ra solutions described herein.

Summary

The present disclosure relates to radiopharmaceutical compositions comprising the mother nuclide ^{224}Ra, its daughter nuclide ^{212}Pb, and a complexing agent that complexes with the daughter nuclide. While ^{224}Ra targets the bone in its un-complexed form, an embodiment of the composition comprises the complexing agent EDTMP which complexes with ^{212}Pb and specifically targets it to the bone, thus avoiding and/or minimizing undesirable side effects and/or off-target effects due to ^{212}Pb. This is evident in a comparison of e.g. Fig. 3A and Fig. 3B. In another embodiment, the complexing agent is TCMC-labeled monoclonal antibody, e.g., trastuzumab (Herceptin) which enables specific targeting of ^{212}Pb to the blood. This is an unexpected feature very useful in a situation where, for example, there are circulating tumor cells in the blood. Thus, therapeutic efficacy above and beyond that available with ^{224}Ra can e.g. be achieved in a target-specific manner by specifically controlling ^{212}Pb targeting by the bone-seeking EDTMP and blood-circulating TCMC-labeled monoclonal antibody. Mice *in vivo* studies are presented in example 12, showing an improvement compared to the gold-standard treatment protocol.

An object of the present disclosure is to provide a radiopharmaceutical solution comprising ^{224}Ra and a complex capable of scavenging at least ^{212}Pb.

In one aspect of the present disclosure, there is provided a radiopharmaceutical solution comprising uncomplexed ^{224}Ra and complexes between a complexing agent and ^{212}Pb;

wherein said complexing agent is selected from the group consisting acyclic chelators, cyclic chelators, cryptands, crown ethers, porphyrins or cyclic or noncyclic polyphosphonates, DOTMP, EDTMP, bisphosphonate, pamidronate conjugated to DOTA, pamidronate conjugated to TCMC, TCMC, DOTA, p-SCN-Bn-DOTA, p-SCN-Bn-TCMC, antibody-conjugated-DOTA, and antibody-conjugated-TCMC.

In another aspect of the present disclosure, there is provided a radiopharmaceutical solution comprising ^{224}Ra, ^{212}Pb and a complexing agent selected from the group consisting of EDTMP, antibody-conjugated-DOTA, or antibody-conjugated-TCMC.

In one embodiment of the present disclosure, the complex comprises one or more compounds selected from the group consisting of acyclic chelators, cyclic chelators, cryptands, crown ethers, porphyrins or cyclic or noncyclic polyphosphonates, DOTMP, EDTMP, bisphosphonate, pamidronate conjugated to DOTA, pamidronate conjugated to TCMC, antibody-conjugated-DOTA, and antibody-conjugated-TCMC.

In another embodiment of the present disclosure, ^{212}Pb and/or ^{212}Bi is complexed by (bone-seeking) EDTMP.

In another embodiment of the present disclosure, the complexing agent is conjugated to a compound selected from the group consisting of a monoclonal, a polyclonal antibody, an antibody fragment, a synthetic protein, peptide, vitamin or vitamin derivative.

In another embodiment of the present disclosure, the complexing agent is the chelator TCMC conjugated to a compound selected from the group consisting of a monoclonal, a polyclonal antibody, am antibody fragment, a synthetic protein, peptide, vitamin or vitamin derivative.

One aspect of the present disclosure relates to a kit comprising a first vial comprising a radiopharmaceutical solution of the present disclosure, and a second vial comprising a neutralizing solution to adjust pH and/or isotonicity of the radiopharmaceutical solution prior to administration to a patient.

The present disclosure also relates to a kit comprising a first vial comprising a chelate labelled protein or peptide, a second vial comprising a ^{224}Ra solution.

In another aspect of the present disclosure, there is provided a kit comprising a first vial comprising a ^{224}Ra solution;
a second vial comprising a complexing agent selected from the group consisting of acyclic chelators, cyclic chelators, cryptands, crown ethers, porphyrins or cyclic or noncyclic polyphosphonates, DOTMP, EDTMP, bisphosphonate, pamidronate conjugated to DOTA, pamidronate conjugated to TCMC, antibody-conjugated-DOTA, and antibody-conjugated-TCMC, wherein the complexing agent is capable of complexing a daughter nuclide of ^{224}Ra, such as ^{212}Pb, and wherein the complexing agent does not complex ^{224}Ra in the pharmaceutical solution; and optionally, instructions for mixing the first vial and the second vial, thereby forming a pharmaceutical composition ready to be administered to a patient 1 minute to 12 hours after mixing.

A further aspect of the present disclosure also relates to a kit or a radiopharmaceutical solution of the present disclosure for use as a medicament.

Yet another aspect of the present disclosure relates to a radiopharmaceutical solution of the present disclosure for use in the treatment of skeletal disease.

In one embodiment of the present disclosure, the skeletal disease is selected from the group consisting of skeletal metastases from cancers to the breast, prostate, kidneys, lung, bone, or multiple myeloma, or non-cancerous diseases causing undesired calcification including ankylosing spondylitis.

In one aspect of the present disclosure, there is provided a method for providing a radiopharmaceutical solution according to the present disclosure, the method comprising
providing a first solution wherein the amount of ^{224}Ra and ^{212}Pb is in radioactive equilibrium;
providing a second solution comprising a complexing agent that is selected from the group consisting of acyclic chelators, cyclic chelators, cryptands, crown ethers, porphyrins or cyclic or noncyclic polyphosphonates, DOTMP, EDTMP, bisphosphonate, pamidronate conjugated to DOTA, pamidronate conjugated to TCMC, antibody-conjugated-DOTA, and antibody-conjugated-TCMC, wherein the complexing agent is capable of complexing a daughter nuclide of ^{224}Ra, such as ^{212}Pb, and wherein the complexing agent does not complex ^{224}Ra; and
mixing the first composition and the second composition, thereby providing a pharmaceutical composition according to the present disclosure.

The present disclosure also relates to a method of treatment of malignant or non-malignant disease by administration of a radiopharmaceutical solution of the present invention to an individual in need thereof.

The present disclosure also relates to a method for providing a ^{224}Ra solution comprising protein-complex or peptide-complex comprising mixing of chelate labeled protein, *e.g.*, a monoclonal antibody, or peptide with a solution comprising ^{224}Ra.

Brief description of the figures

Figure 1 shows the decay of ^{224}Ra and daughters.

Figure 2 shows the decay of ^{223}Ra and daughters.

Figure 3A shows the bio-distribution in nude mice of ^{224}Ra and progeny ^{212}Pb in a solution without chelator. Figure 3B shows bio-distribution in nude mice of ^{224}Ra solution containing EDTMP as chelator for progeny ^{212}Pb. Figure 3 C shows biodistribution in nude mice of ^{224}Ra solution containing TCMC-trastuzumab (Herceptin) as chelator for progeny ^{212}Pb.

Figure 4 shows main radiation properties from the ^{224}Ra series. [1]Average per ^{224}Ra transformation due to branching. Only X-rays or gammas above 1% effective abundance are accounted for. It adds up to a total effective energy of approximately 26.5 MeV of alpha of 0.7 MeV of beta per complete decay of ^{224}Ra and daughters.

Figure 5 shows ingrowth of ^{212}Pb from a pure 10 MBq ^{224}Ra source. Changes in activity level. Start activity 10 MBq pure 224-Ra.

Figure 6A shows thin layer chromatographic (TLC) profiles of ^{212}Pb in a solution of ^{224}Ra in equilibrium with progeny nuclides without and with complexing agents EDTMP and DOTMP.

Figure 6B shows thin layer chromatographic (TLC) profiles of ^{212}Pb in a solution of ^{224}Ra in equilibrium with progeny nuclides without and with complexing agents. Figure 6B shows TLC profiles for ^{212}Pb in the presence of antibody- TCMC or DOTA conjugates and antibody without chelator.

Claims

1. A radiopharmaceutical solution comprising uncomplexed ^{224}Ra and complexes between a complexing agent and ^{212}Pb;

wherein said complexing agent is selected from the group consisting acyclic chelators, cyclic chelators, cryptands, crown ethers, porphyrins or cyclic or noncyclic polyphosphonates, DOTMP, EDTMP, bisphosphonate, pamidronate conjugated to DOTA, pamidronate conjugated to TCMC, TCMC, DOTA, p-SCN-Bn-DOTA, p-SCN-Bn-TCMC, antibody-conjugated-DOTA, and antibody-conjugated-TCMC.

2. A radiopharmaceutical solution comprising ^{224}Ra, ^{212}Pb and a complexing agent selected from the group consisting of EDTMP, antibody-conjugated-DOTA, or antibody-conjugated-TCMC.

3. The radiopharmaceutical solution according to claim 1 or 2, wherein the complexing agent is capable of complexing at least ^{212}Pb.

4. The radiopharmaceutical solution according to any of the preceding claims, wherein the complexing agent is capable of complexing a daughter nuclide of ^{224}Ra, such as ^{212}Pb, in the pharmaceutical solution.

5. The radiopharmaceutical solution according to any of the preceding claims, wherein the complexing agent does not complex ^{224}Ra in the pharmaceutical solution.

6. The radiopharmaceutical solution according to any of the preceding claims, wherein the complexing agent is conjugated to a compound selected from the group consisting of a monoclonal antibody, a vitamin, a polyclonal antibody, an antibody fragment, a synthetic protein, and a peptide.

7. The radiopharmaceutical solution according to any of the preceding claims, wherein said complexing agent is selected from the group consisting of EDTMP, antibody-conjugated-DOTA, or antibody-conjugated-TCMC.

8. The radiopharmaceutical according to any of the preceding claims, wherein the radioactivity is 100 kBq to 100 MBq.

9. A kit comprising

- a first vial comprising a radiopharmaceutical solution according to any of the preceding claims, and

- a second vial comprising a neutralizing solution to adjust pH and/or isotonicity of the radiopharmaceutical solution prior to administration to a patient.

10. A kit comprising
    - a first vial comprising a ^{224}Ra solution;
    - a second vial comprising a complexing agent selected from the group consisting of acyclic chelators, cyclic chelators, cryptands, crown ethers, porphyrins or cyclic or noncyclic polyphosphonates, DOTMP, EDTMP, bisphosphonate, pamidronate conjugated to DOTA, pamidronate conjugated to TCMC, antibody-conjugated-DOTA, and antibody-conjugated-TCMC, wherein the complexing agent is capable of complexing a daughter nuclide of ^{224}Ra, such as ^{212}Pb, and wherein the complexing agent does not complex ^{224}Ra in the pharmaceutical solution; and
    - optionally, instructions for mixing the first vial and the second vial, thereby forming a pharmaceutical composition ready to be administered to a patient 1 minute to 12 hours after mixing.

11. The kit according to claims 9-10, or the radiopharmaceutical solution according to any of claims 1-8 for use as a medicament.

12. The radiopharmaceutical solution according to any of claims 1-8 for use in the treatment of skeletal disease.

13. The radiopharmaceutical solution for use according to claim 12, wherein the skeletal disease is selected from the group consisting of skeletal metastases from cancers to the breast, prostate, kidneys, lung, bone, or multiple myeloma, or non-cancerous diseases causing undesired calcification including ankylosing spondylitis.

14. The radiopharmaceutical solution for use according to any of claims 11-13, wherein the solution is to be administered at a dose in the range 50-150 kBq per kg of bodyweight, such as 50-100 kBq per kg of bodyweight.

15. A method for providing a radiopharmaceutical solution according to any of claims 1-8, the method comprising:

a) providing a first solution wherein the amount of ^{224}Ra and ^{212}Pb is in radioactive equilibrium;
b) providing a second solution comprising a complexing agent that is selected from the group consisting of acyclic chelators, cyclic chelators, cryptands, crown ethers, porphyrins or cyclic or noncyclic polyphosphonates, DOTMP, EDTMP, bisphosphonate, pamidronate conjugated to DOTA, pamidronate conjugated to TCMC, antibody-conjugated-DOTA, and antibody-conjugated-

TCMC, wherein the complexing agent is capable of complexing a daughter nuclide of ^{224}Ra, such as ^{212}Pb, and wherein the complexing agent does not complex ^{224}Ra; and

c) mixing the first composition and the second composition, thereby providing a pharmaceutical composition according to any of claim 1-8.