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Applied Radiation and Isotopes 64 (2006) 462–469
Applied Radiation and Isotopes
www.elsevier.com/locate/apradiso

Preparation and preliminary biological evaluation of a ^{166}Ho labeled polyazamacrocycle for possible use as an intravascular brachytherapy (IVBT) agent

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Received 21 July 2005; received in revised form 25 October 2005; accepted 7 November 2005

Abstract

^{166}Ho can be considered as a potential radionuclide for intravascular brachytherapy (IVBT) using liquid-filled balloons owing to its suitable nuclear decay characteristics. The possibility of producing ^{166}Ho with adequate specific activity using moderate flux reactors and natural holmium target makes it an attractive alternative of ^{188}Re for developing IVBT agents. Keeping in mind the high thermodynamic stability of lanthanide complexes with polyazamacrocycles, ^{166}Ho complex of 1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetic acid (TETA) was prepared and studied for its suitability as a possible agent for IVBT. ^{166}Ho was produced with adequate specific activity and high radionuclidic purity by irradiating natural Ho_2O_3 powder. TETA was synthesized by a single step procedure using cyclam as the starting material. ^{166}Ho–TETA complex was prepared with excellent radiochemical purity and the complex was found to retain its stability for 7 days at room temperature. Biodistribution studies carried out in Wistar rats showed major renal clearance of the injected activity with almost no retention in any of the vital organ/tissue.

Keywords: IVBT; Balloon angioplasty; Restenosis; ^{166}Ho; TETA

1. Introduction

Percutaneous transluminal coronary angioplasty (PTCA), popularly known as balloon angioplasty, is the most established modality of treatment for patients suffering from atherosclerotic coronary artery disease (King, 1999; Joh et al., 2000). However, high rate of restenosis, the re-narrowing or blockage of a treated artery, is a major limiting factor in the long term effectiveness of the procedure (King, 1999; Kotzerke et al., 2000; Popma et al., 1991; Brad, 1996; Califf et al., 1991). Restenosis occurs within 6 months in 40–60% of the patients undergoing successful balloon angioplasty (Joh et al., 2000; Kotzerke et al., 2000; Califf et al., 1991; Dangas and Kuepper, 2002; Lin et al., 2000). Several studies have established that a suitable dose of ionizing radiation from beta/gamma emitting radionuclides delivered to the proliferating tissues at the arterial wall can effectively retard the onset of restenosis after coronary angioplasty (Kotzerke et al., 2000; Waksman, 1999; Teirstein et al., 1997; Verin et al., 1997). This methodology is known as intravascular brachytherapy (IVBT). Among the various modalities of delivering ionizing radiation dose, the most attractive is the use of radioactive liquid-filled balloon catheters containing short-lived high-energy β^- emitting radionuclide. This technique ensures the delivery of adequate ionizing radiation dose within a very short span of time in most uniform and homogeneous fashion (Weinberger and Knapp, 1999; Weinberger, 1998).

The primary requirement of a radiochemical agent to be used in liquid-filled balloon catheter for IVBT is that it should ensure delivery of significant radiation dose to the arterial wall upto a distance of ~4 mm with minimum dose to the tissues beyond 10 mm (Verin et al., 1997; Das et al., 2000a). A radionuclide with a moderate half-life of

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0969-8043/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.apradiso.2005.11.001

1–2 days and decaying by emission of β^- particle of maximum energy [$E_{\beta(max)}$] close to 2 MeV or higher would be preferred for this purpose (Weinberger and Knapp, 1999). The other important factor which requires consideration towards the choice of radionuclides is their ease of production with adequate radionuclidic purity as well as specific activity. Among the potential radionuclides for IVBT using radioactive liquid-filled balloons (Amols and Weinberger, 1999) (Table 1), ^{188}Re is the most preferred choice owing to its suitable decay characteristics and availability in a no-carrier-added form from a ^{188}W/^{188}Re generator installed at the hospital radiopharmacy that can be continuously used for a period of ~9 months (Weinberger and Knapp, 1999; Das et al., 2000a; Hsieh et al., 1999; Knapp et al., 1994; Knapp et al., 1997; Kamioki et al., 1994). However, the main constraint in setting up a ^{188}W/^{188}Re generator is the limited availability of ^{188}W, the parent radionuclide, since it requires a very high neutron flux ($>5\times10^{14}$ n cm^{-2} s^{-1}) as well as isotopically enriched $^{186}WO_3$ target to obtain reasonable quantities of ^{188}W with adequate specific activity (Knapp et al., 1994; Kamioki et al., 1994). There are only a couple of reactors across the world that can provide thermal neutron flux as high as $>5\times10^{14}$ n cm^{-2} s^{-1}. As a result, despite being the most efficacious radionuclide, limited availability is the major drawback in the use of ^{188}Re. In this context, ^{166}Ho can be considered as an ideal substitute for ^{188}Re owing to its favorable radionuclidic decay (Table 1) and chemical characteristics. The major advantage of ^{166}Ho over ^{188}Re is that it could be produced in adequate quantity and specific activity as well as with high radionuclidic purity by irradiating natural Ho target (^{165}Ho has 100% natural abundance and its thermal neutron capture cross-section is 66 barns) in reactors with medium thermal neutron flux (Chakraborty et al., 2001; Unni et al., 2002). In a typical IVBT procedure, approximately 3.7–5.5 GBq (100–150 mCi) of ^{166}Ho in 100–150 μL volume is recommended (Kotzerke et al., 2000). Therefore, the expected requirement of activity of the radionuclide for IVBT will be very large as the number of patients who will need this treatment is very high if the utility of the radioactive liquid-filled balloons for prevention of restenosis becomes an established practice. Hence, ^{166}Ho is a highly desirable and practical substitute for ^{188}Re in IVBT using radioactive liquid-filled balloons, particularly in places which do not have access to ^{188}Re.

Since the issue of the patient's safety in the event of an accidental balloon rupture is a major cause of concern, the radiochemical form in which the radionuclides are to be used in the liquid-filled balloons also require careful consideration (Weinberger and Knapp, 1999; Das et al., 2000a). As the activity required for IVBT using radioactive liquid-filled balloon is considerably large, in the event of an accidental balloon rupture a large amount of radioactivity will be released into the blood circulation and will result in unnecessary radiation dose to the vital organs/tissues (Das et al., 2000a; Hsieh et al., 1999; Oh et al., 1999). Hence, it is important that the radioactive species used for IVBT should exhibit rapid urinary excretion with minimum, preferably no uptake in any of the vital organs/tissues (Weinberger and Knapp, 1999; Das et al., 2000a; Hsieh et al., 1999; Das et al., 2000b). The choice of the chelating molecule for the radionuclide to be used in liquid-filled balloons is therefore guided by its ability to form metal–chelate complex with high in vivo stability as well as rapid clearance from the biological system (Weinberger and Knapp, 1999; Das et al., 2000a; Chakraborty et al., 2001; Das et al., 2000b; Knapp et al., 2001; Stoll et al., 2001). In case of any accidental release of the agent in blood circulation due to balloon rupture, the dissociation of the radiometal from the chelate could eventually be favored due to its very low concentration and the presence of a variety of competing chelators as well as metal ions in plasma (Volkert and Hoffman, 1999; Liu and Edwards, 2001). The loss of radiometal from the chelate could result in its accumulation in vital organs. Therefore, the chelating ligand chosen should form a thermodynamically stable as well as kinetically inert complex with the radiometal. A careful review of the literature has shown that lanthanide complexes with macrocyclic chelators demonstrate higher thermodynamic stability and kinetic inertness compared to their acyclic counterparts (Liu and Edwards, 2001; Cacheris et al., 1987; Clarke and Martell, 1991). Keeping this in mind, the polyazamacrocyclic chelator 1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetic acid (TETA) was chosen as the ligand to prepare a potential ^{166}Ho based IVBT agent. Herein, we report the preparation of ^{166}Ho–TETA complex and its preliminary biological evaluation in an animal model.

Table 1
Radionuclides proposed for intravascular brachytherapy using liquid-filled balloons

Radionuclide	Half-life (h)	E_β (max.) (MeV)	E_γ (keV)	Maximum soft tissue penetration (mm)	Production route
^{188}Re	17.0	2.12	155 (15%)	11.0	^{188}W/^{188}Re Generator
^{186}Re	90.6	1.07	137 (9%)	5.5	^{185}Re (n,γ)
^{90}Y	64.1	2.28	—	12.0	^{90}Sr/^{90}Y Generator
^{165}Dy	2.3	1.29	95 (4%)	7.5	^{164}Dy (n,γ)
^{166}Ho	26.8	1.85	81 (6%)	8.5	^{165}Ho (n,γ)