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Holmium-166 labeled DTPA Bisamide Derivatives for Radiation Brachytherapy using Balloon Catheters

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1. Introduction

Coronary angioplasty is performed by inserting a percutaneous transluminal coronary angioplasty (PTCA) balloon catheter into a stenosed coronary artery. The opening process is achieved by a simple repeated inflation of the balloon, which applies pressure to the artery walls. However, a re-closure rate of 50% results from this treatment.

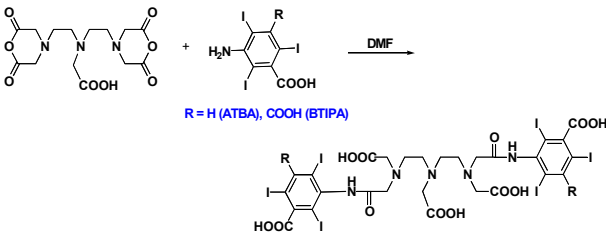
The radioactive liquid balloon is proposed as one of the most effective methods for the prevention of restenosis after the angioplasty procedure. Filling the dilatation catheter balloon with radioactive solutions has the advantage of providing accurate source positioning and uniform dose delivery to the vessel walls.

Since a coronary angioplasty using a liquid radiation source is performed with an angiography, use of a CT contrast agent is a good alternative not only to see if the balloon has close contact with the blood vessel wall for the delivery of a sufficient radiation dose to the stenotic artery, but also to realize an early detection of a leakage in the worse case scenario of a balloon's rupture.

Therefore, we developed ^{166}Ho based radiopharmaceuticals for IVRT possessing with the character of a CT contrast. We synthesized DTPA bisamide derivatives containing iodine in the compound. To estimate the feasibility of the minimal risk in the event of balloon rupture, the pharmacological behavior was evaluated using animal models.

2. Methods and Results

2-1. Synthesis of DTPA bisamide derivatives



Scheme 1. Scheme for synthesis ; DTPA-ATBA, DTPA-BTIPA

The DTPA bisamide derivatives, DTPA-ATBA (3-amino-2,4,6-triiodobenzoic acid) and DTPA-BTIPA(3-amino-2,4,6-triiodoisophthalic acid) were prepared by the reaction of DTPA dianhydride freshly prepared *in situ*.

2-2. Preparation of ^{166}Ho-DTPA-comlexes

A lyophilized vial containing 20 mg of DTPA-derivatives was prepared. To each kit, 1 ml of ^{166}Ho solution with 370 MBq was added. Each reaction mixture was incubated with a gentle stirring for 15 min at room temperature. The radiolabelling yield was determined by an ITLC scanner when ITLC-SG and 75% MeOH were used. The ITLC pattern of ^{166}Ho and that of ^{166}Ho-DTPA-complexes were found at the origin and at the solvent front, respectively. High radiochemical stability (>98%) was maintained over a period of 6 hours at room temperature.

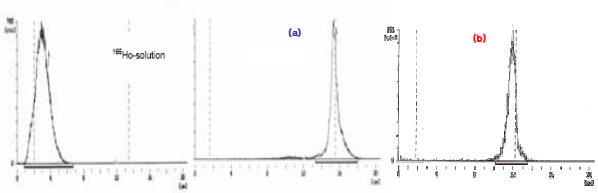
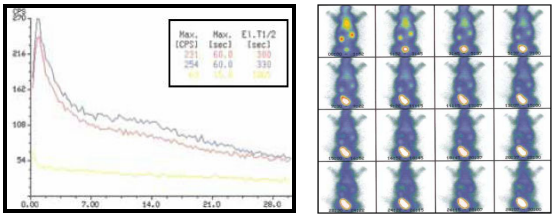


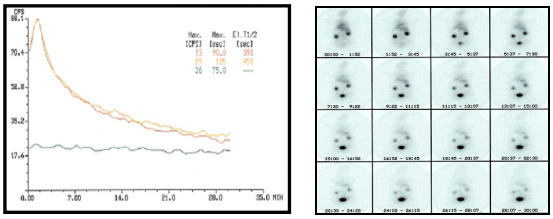
Fig 1. The ITLC pattern of the ^{166}Ho, ^{166}Ho-(DTPA-ATBA) (a) and ^{166}Ho-(DTPA-BTIPA)(b)

2-3. Animal experiments

To examine the *in vivo* retention of ^{166}Ho-DTPA-complexes, male New Zealand white rabbits were used. Each rabbit was injected with the ^{166}Ho-DTPA-complex via the left ear vein with 111 MBq/0.5 ml (3.0 mCi/0.5 ml). To confirm the dynamic kinetics of the ^{166}Ho-complex, whole-body dynamic images and time-radioactivity curves of the kidneys for 30 min using a gamma camera were obtained. The serial static image scans of the rabbit administered with the ^{166}Ho-complex revealed that none of the tissues except for the urinary system had radioactivity concentrations.



(a)



(b)

Fig 2. The time-radioactivity curve of the kidneys and the images of rabbit after an intravenous administration of ^{166}Ho-(DTPA-ATBA)(a) and ^{166}Ho-(DTPA-BTIPA)(b)

3. Conclusion

The prepared ^{166}Ho-DTPA-complexes revealed a rapid renal clearance, adequate *in vivo* stability and a low uptake in the vital organs which is important in case of an accidental release of the radiopharmaceutical inside the body due to the rupture of the balloon.

^{166}Ho-DTPA-complexes with the characteristics of a CT contrast have advantages in the visualization of both the position and the shape of a balloon. It enables us to see whether or not there is a formation of a void volume of the liquid inside the balloon, as well as to detect radiation leakage on a real-time basis during radiation angioplasty.

In conclusion, ^{166}Ho-DTPA-complexes are a potential radiation source for vascular brachytherapy having the characteristic of a CT contrast agent. Also, the ligand, DTPA derivatives, can be applicable for the preparation of the ^{188}Re–complex as a radiation source for the prevention of in-stent restenosis.

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