SYNTHESIS OF ^{188}Re-HEDP AND ^{188}Re-OXABIPHORE COMPLEXES

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Introduction

Rhenium-188 ($E_{\beta-}$ = 2,12 MeV, E_γ = 155 keV, $T_{1/2}$ ≈17 h) is an attractive therapeutic radioisotope which is produced from decay of tungsten-188 parent ($T_{1/2}$ = 69,4 d) and thus conveniently is obtained from ^{188}W/^{188}Re generator system. Diphosphonates (^{188}Re-HEDP /1/, ^{186}Re-HEDP /2/, ^{188}Re-MDP /3/) and some aminomethylenephosphonates /4/ have been studied as agents for palliative treatment of pain associated with skeletal metastases.

The labeling studies of hydroxyethyledendiphosphonic acid (HEDP) and oxa-bis(ethylennitrilo)tetramethylenphophonic acid (oxabiphore or OBP) with ^{188}Re obtained from ^{188}W/^{188}Re generator using spectrophotometric and radiometric methods are reported.

Experimental

The ^{188}W/^{188}Re generator was prepared using the alumina column system with $^{188}WO_3$, produced by irradiation in Scientific Institute of Atomic Reactors (Dimitrovgrad, Russia). Rhenium-188 solution (7,4-37 MBk/ml) was obtained from the generator in a 0,9% NaCl solution.

To study the complex formation of the nonactive rhenium we mixed all components (ligand, reducing agent – $SnCl_2$, carrier – NH_4ReO_4, antioxidant – ascorbic acid) in a vial under argon and incubation of mixture at room temperature or on the boiling water bath. It was found that reduced rhenium formed with HEDP and OBP yellow complexes with maximum absorbance at wave length 430 nm and 435 nm respectively.

The radiochemical yield of complexes was determined by TLC on silica gel (Sorbfil, Russia) in acetone and electrophoresis on paper (0,02 M phosphate buffer, pH 7,5).

The dependence of the labeling yields upon the reaction conditions, such as concentrations of ligands, $SnCl_2$, ascorbic acid and carrier, pH, temperature of reaction was investigated.

Two series of experiments were carried out:

- the influence of reaction conditions on optical density of preparations at wave lengths of maximum absorbance (solutions didn't contain radioactive rhenium);
- dependence of the labeling yields of complexes upon the same reactions conditions using ^{188}Re from generator.

Results and discussion

^{188}Re - HEDP

The labeling yield depended on pH. It was found that the quantitative yields of complex were at pH < 6 (> 95%) and the yields decreased sharply at pH > 6.

The labeling yield of ^{188}Re-HEDP increased with increasing of $SnCl_2$ concentration ([HEDP] = 5-20 mg/ml; [$SnCl_2$] = 1-5 mg/ml) (Table 1). It was observed that at molar ratio Sn^{2+} : HEDP ≥ 1 the precipitate was formed. It was found that at $SnCl_2$ concentrations of 3,5-5 mg/ml the HEDP concentration of 20 mg/ml is effective in precipitation preventing.

The absence of carrier decreased the labeling yield to 75%. At concentration of carrier 0,01-0,03 mg Re/ml the yields were >95%.

The yield of complex didn't depend on concentration of ascorbic acid (1 – 3 mg/ml).

Table 1

The influence of component concentrations on complexation yield

Ligand	[Re], mg/ml	Labeling yield (%) upon $SnCl_2$ concentration (mg/ml)				
		1	2	3	4	5
HEDP, 20 mg/ml	0,04	84,0	95,0	96,4	98,5	99,0
	0,03					98,8
	0,02					98,8
	0,01					97,8

	0					75,8
OBP, 48 mg/ml	0,06 0	78,3 74,0	97,1 96,7	99,8 98,9	99,7 99.0	

A lyophilized kit was prepared under optimal conditions. The labeling yield of ^{188}Re-HEDP, prepared from the kit by adding of eluat from a generator was >97%.

The heating of reaction mixture influenced on the reaction rate (Table 2). Thus the maximum yields of complexes were obtained after 40 – 50 min incubation at room temperature, while the same yields (> 97%) were obtained after heating on the boiling water bath during 15-20 min. The complexes, obtained from a kit, was stable for at least 24 hours. The influence of the elute volume, which was added to a kit, was investigated. The complex yield were > 95% at eluate volume of 2-5 ml.

Table 2

Effect of temperature and time of reaction on labeling yield

Ligand	t°C	Labeling yield , %						
		0 min	10 min	20 min	30 min	40 min	50 min	60 min
HEDP	20	37,7	60,5	83,2	90,9	96,9	95,5	97.4
	100		98,8	98,9	99,5	98,4		95,1
OBP	20	66,7		98,5	99,4	99,5		99,5
	100		99,8	100	100			99,7

The biodistribution in normal rats showed that skeletal uptake of ^{188}Re-HEDP was ~22% with 57% excretion of activity at 3 h p.i. No significant uptake was seen in any other organ except bone.

^{188}Re-oxabiphore

It was found that the yield of ^{188}Re-OBP depended on pH. The maximum yield (> 95%) was obtained at pH less then 2 and then decreased sharply with increasing of pH. The effect of $SnCl_2$ concentration on the yield is presented in Table 1.

The addition of carrier didn't influence on complex yield, so as the addition of an ascorbic acid.

Now in Russia the kit for preparation of the Radiopharmaceuticals Technephor, ^{99m}Tc is produced. This kit consists of oxabiphor and $SnCl_2$ in concentrations less then it needed for ^{188}Re and it is stable for 1 year without antioxidant.

The lyophilized kit for preparation of ^{188}Re-OBP was produced under optimal conditions. The labeling yield of complex prepared from the kit by addition of eluat from a generator was found to be > 98% after incubation for 20 min at room temperature (Table 2). It was found that complex, obtained at pH 2, was stable up to pH≤ 6, and it decomposed at pH > 6. The complex, obtained from a kit, was stable at least for 24 hours.

References:

1. F.F.(Russ)Knapp, A.L.Beets et al. – Anticancer Research, 1997, ¹ 17, 1783-1796.
2. H.S.Bai, X.Y.Jin et al. – J.Radioanal. and Nucl. Chem., 1996, 206, ¹ 1á, 43-50.
3. K.Hashimoto, S.Bagiawati et al. – Appl. Radiat. Isot., 1996, 47, ¹ 2, 195-199.
4. K.Hashimoto. – The Second Japanese-Russian Seminar on Technetium, Shizuoka, Japan, 1999. Abstracts, p. 40-41.