RADIOIODINATION AND PHARMACOKINETICS OF BIVALENT ANALOG OF PRACTOLOL AS MYOCARDIAL IMAGING AGENT*

Cao Guoxian (曹国宪), Li Weiyi (李卫一), Zhang Rongjun (张荣军)
and Yu Huixin (俞惠新)
(Jiangsu Institute of Nuclear Medicine, State Key Laboratory of Nuclear Medicine, Wuxi 214063)

ABSTRACT

Solid phase exchange radioiodination method was used to label the compound. Pharmacokinetics was studied in rats and the data were dealt with by computer. The results indicate that the compound would be a potential myocardial imaging agent.

Keywords Bivalent analog of practolol, Radioiodination, Pharmacokinetics, Myocardial imaging agent, ^{125}I

1 INTRODUCTION

It is a hot subject in the nuclear medicine that radioiodinated ligands with high selectivity to receptors in vivo are used as receptor-site-directed imaging agents, such as dopamine receptor ligands which were used as imagings of the brain. In the past decade, a number of radioiodinated analogs of the β-adrenoceptor antagonists have been prepared and evaluated as myocardial imaging agents for visualizing the heart in vivo[1], but their receptor affinities were too low to be useful receptor imaging agents. Therefore, enhancement of receptor affinity while retaining cardioselectivity has been a major problem in the development of receptor-site-directed myocardial imaging agents.

According to Kizuka[1], one method to solve the problem is to employ bivalent ligand based on the structure of practolol. These bivalent ligands consisted of two pharmacophores of practolol (p) and one spanner group (x). The bivalent ligand (p-x-p) would enhance receptor affinity relative to the monovalent ligand (p) when the spanner group was long enough to permit simultaneous binding of the pharmacophore to two or more receptors.

Recently, we prepared a bivalent ligand of practolol (BAP)[2], as a myocardial imaging agent. In this paper, its radioiodination and pharmacokinetics are reported for the first time.

2 MATERIALS AND METHODS

2.1 Synthesis of BAP

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BAP was prepared according to Fig.1[1,2].

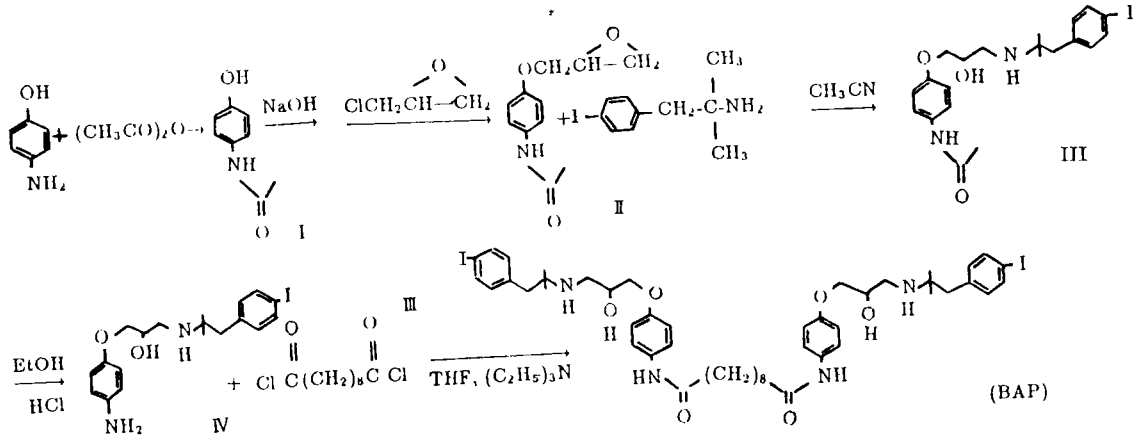

Fig.1 Synthesis of BAP

2.2 Radioiodination of BAP

BAP was radioiodinated according to the solid phase isotopic exchange method of Manger *et al*[3]. The reaction mixture consisting of 1 mg BAP (0.96 μg, in acetone), 4 mg ammonium sulfate (7.6 μmol, in distilled water) and carrier-free $Na^{125}I$ (74 MBq) in a vial was dried under nitrogen at 90~ 100°C, and the dry reaction mixture was maintained at 120~ 130°C for 15 min. After being removed nitrogen, the mixture was heated at 150~ 160°C for 1 h. Being cooled to room temperature, the ^{125}I-BAP was extracted with $CHCl_3$ after adding 0.5 ml of 0.1 mol/L NaOH. The $CHCl_3$ layer was washed with 1 mol/L sodium metabisulfite solution and distilled water and purified by medium pressure liquid chromatography using a LoBar prepacked silica gel column.

2.3 Pharmacokinetics of BAP

The pharmacokinetics of ^{125}I-BAP was evaluated in 180±20 g Sprague-Dawley rats. Aliquots of 0.2 ml of ^{125}I-BAP (0.3 MBq) were injected to rats via the tail vein. Of groups of four rats each, 20 μl blood samples were drawn at 3, 5, 15, 30, 60, 120, 240, 480, 720 min after injection and counted by γ-counter.

3 RESULTS AND DISCUSSION

It is unsuitable to use routine labelling methods such as the chloramine-T to label this compound because of its molecular structure. Therefore, the solid phase isotopic exchange method is selected to label BAP. Solid phase exchange between carrier-free radioiodide and unactivated aryl iodide in the presence of ammonium sulfate is a mild, simple technique for the production of radiolabeled iodo-aromatic compounds of high specific activity. By the method, ^{125}I-BAP can be obtained with the specific activity of 25 MBq/mg (26 MBq/μmol) and the radiochemical purity of 93%. It can be stable for 20 d without obvious deiodination stored at −18°C.

These data were dealt with by computer program and they conformed to the two-compartment model of pharmacokinetics. The results are listed in Table 1.

Table 1

Pharmacokinetics of ^{125}I-BAP in rats

Time /min	3	5	15	30	60	120	240	480	720
Found*	1.02±0.11	0.96±0.10	0.71±0.09	0.51±0.06	0.29±0.04	0.20±0.03	0.12±0.03	0.07±0.02	0.05±0.01
Calculated*	1.019	0.960	0.724	0.498	0.291	0.184	0.134	0.078	0.046
Equation	$C=0.8873\exp(-0.03798t)+0.2291\exp(-0.002238t)$								
Parameters	$V_1=89.57$ ml, $V_2=265.76$ ml, $V_d=355.32$ ml,								
	$K_{12}=0.02177\ min^{-1}$, $K_{21}=0.009574\ min^{-1}$, $K_e=0.008878\ min^{-1}$, $CL=0.7952\ ml\cdot min^{-1}$								
	AUC=125.76% injected dose·min·ml^{-1}, $t_{1/2\alpha}=18.25$ min, $t_{1/2\beta}=309.66$ min								

*Unit is fraction of injected dose per ml blood ×100±SD×100

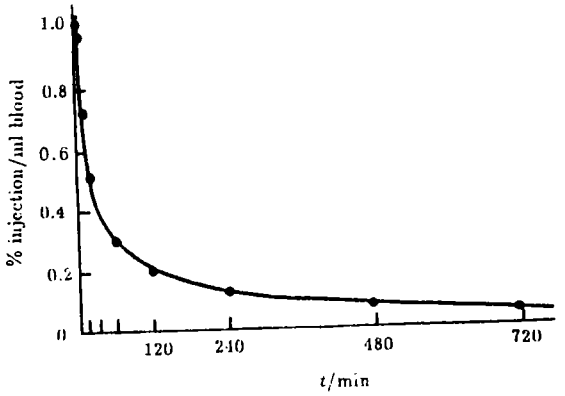

Fig.2 The curve of radioactivity of ^{125}I-BAP in rat's blood vs time

Fig.2 showed the curve of radioactivity of ^{125}I-BAP vs time. BAP exhibited enhanced receptor affinity to β-adrenoceptors in rat heart (unpublished data) because it had two functional groups to bind to receptors. This resulted in the slow washing-out rate from the heart compared with that of monovalent ligands. Although blood clearance of BAP was somewhat slow ($t_{1/2\beta}$ = 309.66 min, possibly due to higher serum protein binding), its heart-to-blood ratio steadily increased during the 240 min after injection. The fact that V_d was 355.32 ml indicated that BAP was a medium lipophilic compound and was suitable to be a myocardial imaging agent. The small value of K_{12} demonstrated that the rate of BAP from the central compartment (consisted of blood and organs which have plentiful volume of blood flow such as heart) to the peripheral compartment (the other tissues) was slow, because there are less β-adrenoceptors in these tissues than that in the heart.

This work showed that BAP may be a potential myocardial imaging agent. If BAP was labeled with ^{123}I, it would be an useful imaging agent in clinical diagnosis.

REFERENCES

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