Note

Carbon-11 Labeling of Fludiazepam[†]

Yoichi ARIYOSHI, Minoru MAEDA, Masaharu KOJIMA,
Makiko SUEHIRO* and Masaaki IIO**

Faculty of Pharmaceutical Sciences, Kyushu University
3-1-1, Maidashi, Higashi-ku, Fukuoka-shi 812

*Department of Nuclear Medicine and Radiological Sciences,
Tokyo Metropolitan Geriatric Hospital
35-2, Sakae-cho, Itabashi-ku, Tokyo 173

**National Nakano Chest Hospital
3-14-20, Egota, Nakano-ku, Tokyo 165

Received April 16, 1982

Key Words: carbon-11, fludiazepam, benzodiazepine receptors

1. Introduction

There is great interest in the development of positron-emitting radiotracers for mapping of brain specific receptors using positron emission computed tomography (PCT). Benzodiazepines are widely prescribed psychoactive drugs and specific binding sites which selectively recognize clinically and pharmacologically active benzodiazepines have been characterized in the mammalian central nervous system¹⁾. Recently, Comar, et al. have succeeded in the detection of the benzodiazepine brain receptors in a live baboon using ¹¹C labeled flunitrazepam²⁾.

Fludiazepam, 7-chloro-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one, is a new psychoactive drug which possesses marked anticonvulsant and taming effects in a smaller dose than the other related drugs reported previously, and is currently being evaluated in clinical use as a potent anti-anxiety agent³⁾. In order to evaluate the potential utility of fludiazepam as a radioligand for *in vivo* studies of benzodiazepine receptors, we planned to label fludiazepam with ¹¹C in the N-methyl group.

Desmethylation is a major process of fludiazepam metabolism in analogy with other benzodiazepines metabolism. Therefore, there is a great possibility that enzymatic degradation *in vivo* releases the radioactive isotope of ¹¹C-fludiazepam even during the earliest period after its administration when the molecule is labeled on the N-methyl group. It has been reported that the serum concentration of fludiazepam reaches a peak level at 2~3 h after oral administration in human, while that of its principal metabolite, 7-chloro-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (nor-fludiazepam), is very low during the first 4 h after administration⁴⁾. Thus ¹¹C-fludiazepam labeled on the N-methyl group appears to be a very attractive ligand for *in vivo* studies of benzodiazepine receptors due to its high pharmacological potency. The present paper deals with the preliminary description of the method for preparing ¹¹C-fludiazepam labeled on the N-methyl group.

2. Materials and Methods

2.1 Preparation of ¹¹C-methyl iodide

¹¹C-Methyl iodide was virtually prepared according to the method of Comar, et al.⁵⁾. Carbon-11 is produced by bombarding nitrogen under 4 atm. pressure in an aluminum target (*L*=20 cm, *V*=150 cm³) with 9 MeV protons using a Baby Cyclotron type 105 (made by

† フルジアゼパムの炭素-11標識。有吉洋一, 前田稔, 小嶋正治, 末広牧子*, 飯尾正明**: 九州大学薬学部放射性薬品化学教室, 812 福岡市東区馬出3-1-1 *東京都養育院 付属 病院, 173 東京都板橋区栄町35-2, **国立療養所中野病院, 165 東京都中野区江古田3-14-20。

Peak 1: acetone, 2: unidentified product, 3: nor-fludiazepam, 4: ^{11}C -fludiazepam, 5: 2-amino-5-chloro-2'-fluorobenzophenone, 6: ^{11}C -2-methyl-amino-5-chloro-2'-fluorobenzophenone

Fig. 1 High-pressure liquid chromatographic analysis of the reaction mixture following N-methylation of nor-fludiazepam.

the same as observed for the nonradioactive runs. In a purified ^{11}C -fludiazepam chromatogram, only one peak was observed by both u.v. and radioactivity detectors and it was identical in shape and position with those of authentic fludiazepam. The total preparation time is 50~60 min and the radiochemical yield is about 20% with respect to $^{11}\text{CH}_3\text{I}$ without correction for decay. A maximal 74 MBq (2 mCi) of ^{11}C -fludiazepam were obtained starting from 3.7 GBq (100 mCi) of $^{11}\text{CO}_2$ within 50~60 min.

The specific activity of the ^{11}C -fludiazepam at the completion of synthesis and column purification was in the range of 111~259 GBq (3~7 Ci)/mmol as determined by u.v. analysis, which indicates a high isotopic dilution. It is not sufficient specific activity to permit the mapping of benzodiazepine receptors *in vivo* using PCT, because the studies of most receptors

in vivo necessitates the synthesis of material with specific activity in the range of at least $37 \times 10^2 \sim 37 \times 10^3$ GBq ($10^2 \sim 10^3$ Ci)/mmol. Evidently the reason for the low specific activity obtained in the present study is that no special care was taken to avoid sources of contamination by stable carbon. However, the labeling procedure presented here is essentially applicable for the preparation of both chemically and radiochemically pure ^{11}C -fludiazepam, although the conversion of $^{11}\text{CO}_2$ into $^{11}\text{CH}_3\text{I}$ using the present technical procedure is unsatisfactory. Work is now progress to improve the specific activity of ^{11}C -fludiazepam and the technical handling of the preparation of $^{11}\text{CH}_3\text{I}$ for synthesizing large amount of high specific activity ^{11}C -fludiazepam.

Acknowledgment

The authors wish to thank Sumitomo Chemical Co. Ltd., Osaka, Japan for providing fludiazepam and nor-fludiazepam. This research was supported by grant from the Ministry of Health and Welfare, Japan.

References

- 1) J.F. Tallman, et al.: *Science*, **207**, 274 (1980)
- 2) D. Comar, et al.: *Nature* (London), **280**, 329 (1979); M. Maziere, et al.: *J. Radioanal. Chem.*, **56**, 229 (1980)
- 3) Y. Asami, et al.: *Arzneim.-Forsch. (Drug Res.)*, **24**, 1563 (1974)
- 4) M. Tanaka, et al.: *Psychopharmacology*, **58**, 217 (1978)
- 5) C. Marazano, et al.: *Int. J. Appl. Radiat. Isotopes*, **28**, 49 (1977)