Possibility of quantification of cerebral blood flow using ^{123}I-Iomazenil as benzodiazepine receptor imaging agent

Shiro Tsuji, Hisashi Sumiya, Keiko Kinuya, Akihiro Ichikawa,
Ichiei Kuji, Teruhiko Takayama*, Mitsuhiko Nakamura**,
Itsuki Jibiki**, Kinichi Hisada, Nariyoshi Yamaguchi**

ABSTRACT

Brain perfusion indices(BPIs) with ^{123}I-Iomazenil, radioreceptor ligand of benzodiazepine receptor, were calculated using radionuclide angiography and graphical analysis. Sixteen patients with epilepsy and one of Pick's disease were examined with this tracer and with ^{99m}Tc-HMPAO, the tracer for estimating cerebral blood flow. BPIs of ^{123}I-Iomazenil were correlated with those of ^{99m}Tc-HMPAO. The regression line equation was Y = 0.459*X +5.58(X, HMPAO_BPI; Y, Iomazenil_BPI; n = 34, r = 0.578, p<0.001). Brain blood volume indices (BVIs) were also calculated significant correlation was obserbed between both tracers. This result shows that initial kinetics of both tracers are similar and it is possible to estimate brain perfusion with ^{123}I-Iomazenil. This method is useful for simultaneous evaluation of epileptic focus and cerebral blood flow level in the epileptic patient.

KEY WORDS

INTRODUCTION

It is not easy to detect epileptic focus of partial epilepsy even using electroencephalography, X-ray computed tomography or magnetic resonance imaging. Nuclear medicine methods, such as regional cerebral matabolism of glucose with ^{18}F-fluorodeoxy glucose by positron emission tomography or regional cerebral blood flow with ^{99m}Tc-hexamethylpropylene amine oxime (^{99m}Tc-HMPAO) by single photon emission computed tomography (SPECT)are applied to the diagnosis of epilepsy. But decrease of metabolic rate of glucose or that of cerebral blood flow is secondary change. More specific tracers are expected to be developed.

Disturbance of the inhibitory system associated with gamma-aminobutyric acid (GABA) in the epileptic focus is reported[1]. ^{123}I-Iomazenil is an antagonist of benzodiazepine (BZ) receptor that is coupling with GABA receptor (ionophore complex[2]). So reduction of binding of this tracer represents possibility of epileptic focus.

    Department of Nuclear Medicine, School of Medicine, Kanazawa University
 * Department of Radiological Technology, School of Allied Medical Professions, Kanazawa University
 ** Department of Neurology and Psychiatry, School of Medicine, Kanazawa University

Other than receptor density, the cerebral blood flow (CBF) measurement is important in epileptic patients. We examined possibility of estimating global CBF level using radionuclide angiography with ^{123}I-Iomazenil by comparing with ^{99m}Tc-HMPAO.

SUBJECTS
Seventeen patients (9 male, 8 female) aged 19-62 years (mean 36.2 years±S.D. 11.2 years) were examined. Sixteen had epilepsy, and one had Pick's disease.

METHODS
Theory:
The theoretical model of blood-brain exchange previously reported was employed in this study[3-5]. In the unidirectional transfer process, brain radioactivity as a function of time, B(t), was expressed as follows:

$$B(t) = K_u \bullet \int_0^t A(\tau)d\tau + V_n \bullet A(t) \qquad (1)$$

where $A(t)$ is the arterial activity as a function of measurement time(t), τ is time, K_u is the unidirectional influx rate, V_n is the initial distribution volume for the tracer. Dividing Equation (1) by $A(t)$ yields

$$\frac{B(t)}{A(t)} = K_u \bullet \frac{\int_0^t A(\tau)d\tau}{A(t)} + V_n \qquad (2)$$

The graphical approach by plotting $B(t)/A(t)$ versus $\int_0^t A(\tau)d\tau/A(t)$ from each group of data gives a unidirectional influx rate of K_u as a slope of a straight line and V_n as the ordinate intercept of this line[6]. Absolute values of mean CBF (mCBF) and brain blood volume index (BVI) were calculated from K_u and V_n. We evaluated and compared absolute values of both parameters with ^{123}I-Iomazenil and with ^{99m}Tc-HMPAO.

Data acquisition and analysis:
1) CBF study
Radionuclide angiography was performed by intravenous bolus injection of 740 MBq of ^{99m}Tc-HMPAO into the right brachial vein,

followed by SPECT. Data acquisition and analysis were performed using the same method described in the previous study[6]. BPI and BVI of each hemisphere were calculated by graphycal analysis of angiographic data.

2) BZ receptor study
Radionuclide angiography was performed by intravenous bolus injection of 167 MBq of ^{123}I-Iomazenil into the right brachial vein, followed by SPECT. Data acquisition and analysis were performed the same as ^{99m}Tc-HMPAO. As the angiographic images of ^{123}I-Iomazenil are low count rate and very noisy, each frame is multiplied by 10, then smoothed by nine point smoothing. BPI and BVI were also calculated.

3) Correlation of BPI and BVI
CBF study and receptor study were performed at the interval of 3-797 days (mean 148 days ± S.D.232 days). Correlation of BPI and BVI of each hemisphere of both tracers were calculated.

RESULTS
Correlation of BPIs of both tracers are shown in Fig 1. The regression line was $y = 0.459*x + 5.58$ (17 subjects, n=34, r=0.578, p<0.001)

Correlation of BVIs of both tracers are shown in Fig 2. The regression line was $y = 0.844*x + 1.63$ (17 subjects, n=34, r=0.678, p<0.001)

DISCUSSION
Brain perfusion index (BPI) of ^{99m}Tc-HMPAO highly correlates with mean cerebral blood flow calculated with ^{133}Xe inhalation method[6]. This index represents initial clearence of the tracer from blood to the brain tissue. In this study, significant correlation was observed between BPI of ^{123}I-Iomazenil and that of ^{99m}Tc-HMPAO. This result shows that possibility of ^{123}I-Iomazenil to estimate cerebral blood flow.
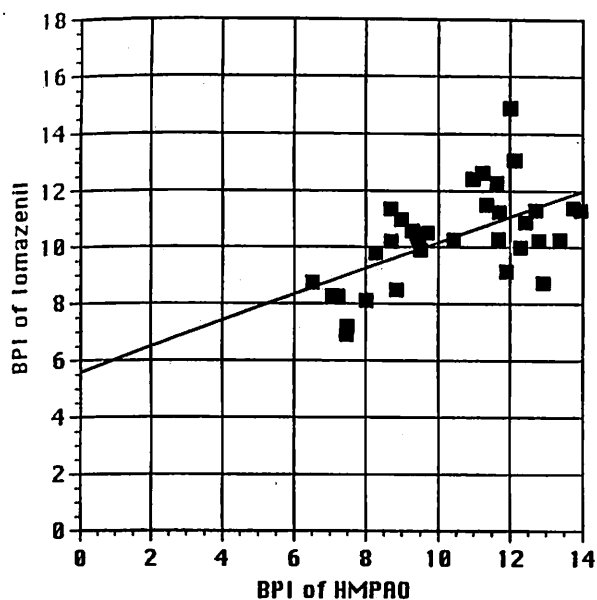
Brain blood volume indices(BVIs) of both

Fig.1　Correlation of BPI between HOPAO and Iomazenil

The regression line equation was y= 0.459* x+5.58(17 subjects, n=34, r=0.578, p<0.001)
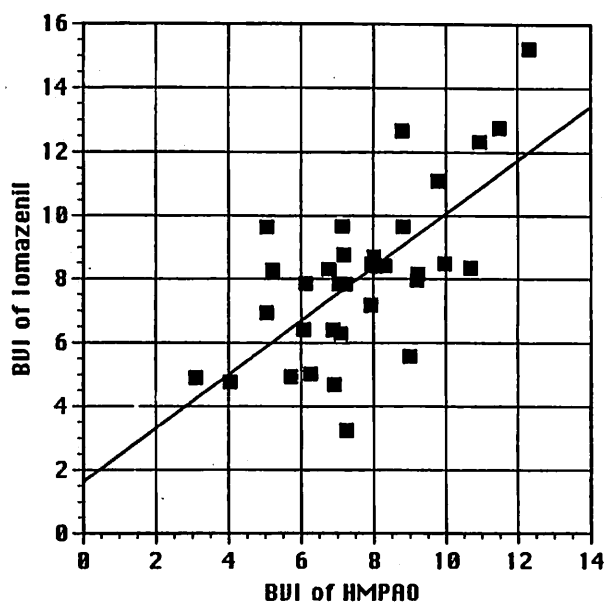

Fig.2　Correieation of BVI between HMPAO and Iomazenil

The regression line equation was y=0.844*x +1.63(17 subjects, n=34, r=0.678, p<0.001)

tracers were also correlated. From these two correlation, initial kinetics of both tracers in the brain are probably similar. Pharmacokinetic analysis of the tracer often calculates K_1 value, or initial uptake constant from blood to the brain. That is the product of flow and extraction fraction. Recent report ^{123}I-Iomazenil also calculates K_1 value[7]. So it is able to astimate cerebral blood flow with ^{123}I-Iomazenil theoretically. And we could evaluate cerebral blood flow using radionuclide angiography with ^{123}I-Iomazenil practically. This method is simple to perform and to analyze. It is useful to evaluate simultaneously cerebral blood flow and BZ receptor of human brain.

REFERENCES

1) Bartenstein, P.et al.: Benzodiazepine receptors and cerebral blood flow in partial epilepsy. Eur J Nucl Med. 18: 111-8, 1991.

2) Olsen, R.: The GABA postsynaptic membrane receptor-ionophore complex. Mol Cell Biochem. 39: 872-876, 1981.

3) Gjedde,A.: High- and low-affinity transport of D-glucose from blood to brain. J Neurochem. 36: 1463-1471, 1981.

4) Patlak, C.S. et al.: Graphical evaluation of blood-brain transfer constants from multiple-time uptake data. J Cereb Blood Flow Metabol. 3:1-7, 1983.

5) Patlak, C.S. et al.: Graphical evaluation of blood-to-brain transfer constans from multiple-time uptake data. Generalization. J Cereb Blood Flow Metabol. 5:584-590, 1985.

6) Matsuda, H. et al.: Quantitative approach to technetium-99m hexamethylpropylene amine oxime. Eur J Nucl Med. 19: 195-200, 1992.

7) Abi-Dargham, A. et al.: SPECT measurement of benzodiazepine receptors in human brain with iodine-123-Iomazenil: Kinetic and eqilibrium paradigms. J Nucl Med. 35:228-238, 1994.

ベンゾジアゼピンレセプターイメージング用剤である ^{123}I-Iomazenil を用いた脳血流定量の可能性

辻　　志郎, 隅屋　　寿,　絹谷　啓子, 市川　聡裕,

久慈　一英, 高山　輝彦,　中村　充彦, 地引　逸亀,

久田　欣一, 山口　成良

要　　旨

ベンゾジアゼピンレセプターリガンドである ^{123}I-Iomazenil を用いて RI アンジオグラフィを撮像し，グラフ解析法により脳血流指数を算出した。16例のてんかん患者と1例の Pick 病の患者を対象として，^{123}I-Iomazenil による脳血流指数(Y)と，脳血流用剤である ^{99m}Tc-HMPAO による脳血流指数(X)を比較した。両者は相関を示し，相関式は y＝0.459*X＋5.58(n＝34, r＝0.578, p ＜0.001)であった。同時に算出される脳血液量指数も両者で相関を示し，トレーサとしての初期動態が両者で類似であり，^{123}I-Iomazenil による脳血流の定量評価の可能性が示された。本法は非常に簡便でてんかん患者の焦点と脳血流レベルを同時に評価でき，有用と考えられた。