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New design of N-isopropyl-p-[^{123}I]iodoamphetamine (^{123}I-IMP) lung imaging in the patient with lung cancer

Eiko TANAKA,* Michiaki MISHIMA,* Kenzo KAWAKAMI,* Naoki SAKAI,* Naoharu SUGIURA,* Takashi TANIGUCHI,** Motoharu OHI,* Harumi ITOH*** and Kenshi KUNO*

*Department of Clinical Physiology, Chest Disease Research Institute, Kyoto University
**Department of Neurobiology, Kyoto Pharmaceutical University
***Department of Radiology, Faculty of Medicine, Kyoto University

N-isopropyl-p-[^{123}I]iodoamphetamine (^{123}I-IMP) was injected intravenously into primary non small cell lung carcinoma patients (n = 17). The average pixel count ratios of the cancerous area to the whole lung was measured in the initial and delayed images. In the initial image, this ratio was less than 1.0 for the entire group of patients, and was thought to reflect decreased blood flow in the cancerous tissues. The rate of counts within a ROI in the delayed image to counts in the same ROI in the initial image was also calculated and called the remain rate. The remain rate (delayed count/initial count) was significantly higher in the cancerous area than in the whole lung (0.65 ± 0.30, median 0.62, 0.38 ± 0.05, median 0.38, $p < 0.01$). This observation was thought to be due to a relative decrease in the blood flow and the accumulation of IMP, which forms pools within the alveolar spaces of the cancerous areas. The image prepared with the remain rate revealed a hot image in the cancerous regions, even when this was not apparent in the delayed image. The remain rate image may therefore be useful in the identification of cancerous areas in lung tissue if it is used in comparison with the initial image.

Key words: N-isopropyl-p-[^{123}I]iodoamphetamine (^{123}I-IMP), lung cancer, IMP lung imaging, IMP receptor

INTRODUCTION

N-isopropyl-p-[^{123}I]iodoamphetamine (^{123}I-IMP) is a brain imaging agent which has been reported to accumulate substantially in the lungs during its first pass through the pulmonary circulation.[1,2] Many studies have confirmed that lung images generated with IMP show different patterns with various pulmonary diseases, such as cancer and tuberculosis. IMP accumulates much less in cancerous tissue than in normal lung tissue.[3-5]

We report that there was no difference between normal and cancerous tissues in the amount of IMP receptors and suggest that decreased blood flow may play an important role in the poor accumulation of IMP in cancerous tissue.[6] In the present study, we compared the delayed (after 4 h) image with the first pass image (initial 30 sec), and estimated the usefulness of IMP in the diagnosis of lung cancer.

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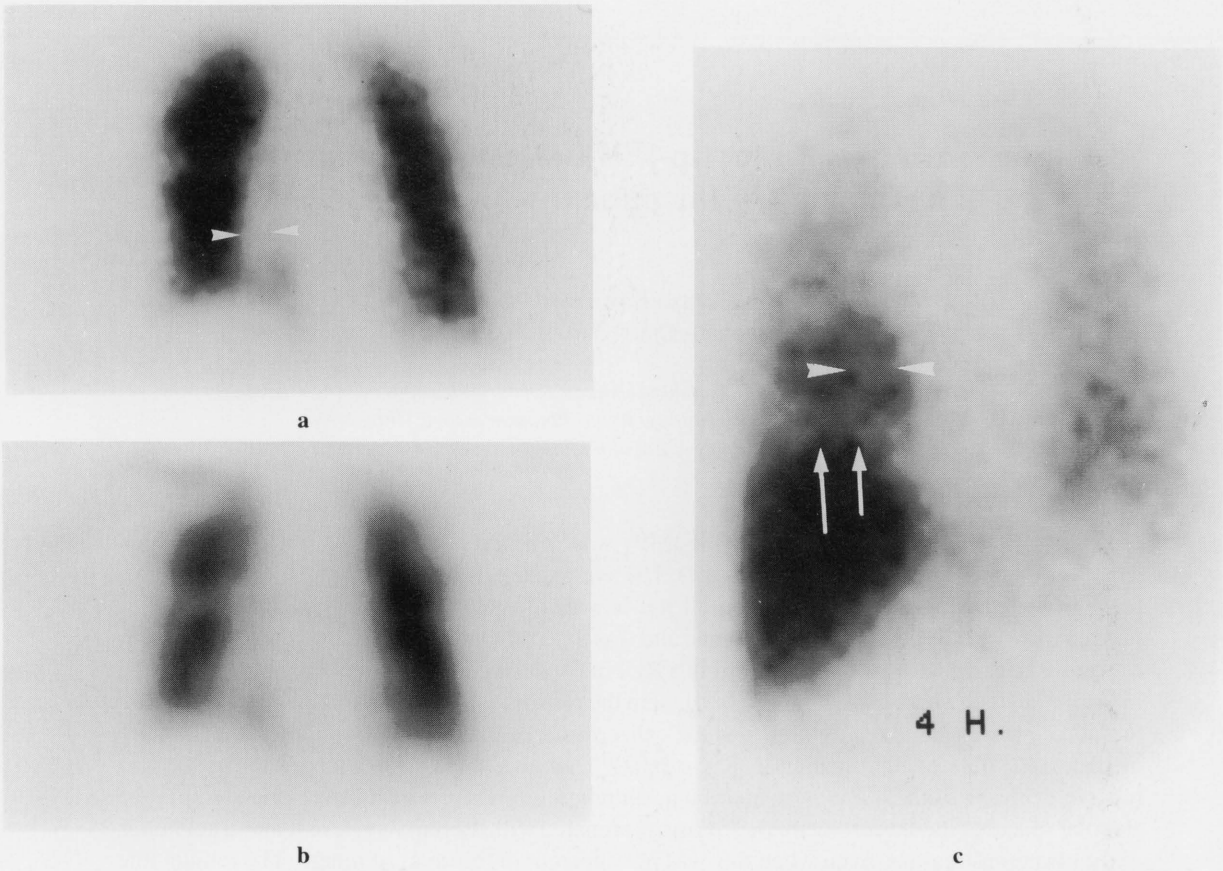
For reprint contact: Eiko Tanaka, M.D., Department of Clinical Physiology, Chest Disease Research Institute, Kyoto University, 53-Shogoin Kawahara-cho, Sakyo-ku, Kyoto 606, JAPAN.

MATERIALS AND METHODS

The subjects consisted of 17 patients (age range: 44–79 years; 6 males and 11 females) with primary, non small cell lung cancer (cell types: 10 adenocarcinomas, 6 squamous cell carcinomas, 1 large cell carcinoma, size range: 1.0 cm × 1.0 cm–2.0 cm × 1.5 cm, 6, 2.0 cm × 2.0 cm–3.0 cm × 3.0 cm, 10, 3.0 cm × 6.5 cm, 1). Thirty seconds after a bolus injection of ^{123}I-IMP (111 MBq) in 5 m*l* of saline via the cubital vein, with the patient supine, sequential images were obtained for two minutes (first pass or initial image) in a 64 × 64 matrix with a time resolution of 1 sec per frame. Four hours later, the static image (delayed image) was obtained over 2 min with a gamma camera with a median energy diverging parallel collimator (G.E. Co.). The energy window was centered on the 159 KeV energy emission of ^{123}I with a 20% width. The median



a

b

c

Fig. 1 Example of ^{123}I-IMP accumulation in a patient with a non-small cell lung carcinoma in the right lower lobe. (a) Initial ^{123}I-IMP lung image, showing low accumulation in the cancerous area (arrow heads). (b) The ^{99m}Tc-MAA lung perfusion image is similar to the initial image. (c) Four hour (delayed) ^{123}I-IMP lung image, showing low accumulation in the cancerous area (arrow heads) but high IMP accumulation in the surrounding area and at the lung–liver border (arrows). However, accumulation is higher than in the initial image.

counts obtained were 1155 ± 34 per unit pixel. Data acquisition and processing were performed with a Maxistar (G.E. Co.). The initial sequential images (30 frames) were integrated, and a single image (initial image) was reconstructed and compared with the ^{99m}Tc-MAA lung perfusion scintigram. In the delayed image, the counts were corrected for the decay constant of ^{123}I ($T1/2 = 13.2$ hours) in order to match with the initial one.

Regions of interest (ROIs) were drawn around the tumor itself, and the whole lung, in both the initial and delayed images. The ratio of the average pixel counts within the cancerous region to the counts within the whole lung was then calculated. The rate of counts within a ROI in the delayed image to counts in the same ROI in the initial image was also calculated and called the remain rate (RR). The tumor adjacent to the liver was omitted, because the influence of the high density hepatic tissue in the delayed image obscured the increase in the RR of the tumor. The RR image (remain rate image) was then made. Data were presented as means ± SD and as median values. Statistical procedures were carried out by means of non-parametric tests.

RESULTS

In Figure 1, typical examples of initial and delayed images are shown. The accumulation of IMP in the initial image was decreased in the cancerous area and the image was similar to that obtained by ^{99m}Tc-MAA lung perfusion. In the delayed image, however, increased accumulation of IMP was noted in the cancerous area and decreased accumulation occurred in the normal area.

In Figure 2, the ratios of average pixel counts within the cancerous region to those within the whole lung are shown. The ratios for the initial image were less than 1.0 in all subjects, whereas the ratios were significantly increased for the delayed image (0.63 ± 0.18, median 0.70, vs. 0.96 ± 0.16, median 0.95, $p < 0.01$).

In Figure 3, the remain rates (RR: average pixel count in delayed image/average pixel count in initial image) are shown. The RRs in cancerous regions were significantly higher than those in the whole lung (0.65 ± 0.30, median 0.62, vs. 0.38 ± 0.05, median 0.38, $p < 0.01$).

Two examples of the image constructed by the RR are shown in Figure 4, where a hot lesion was clearly noted in

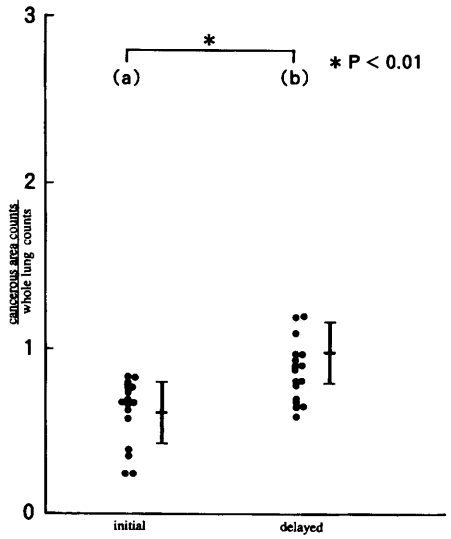


Fig. 2 Ratio of counts for the cancerous area to the whole lung, in the initial (a) and delayed images (b).

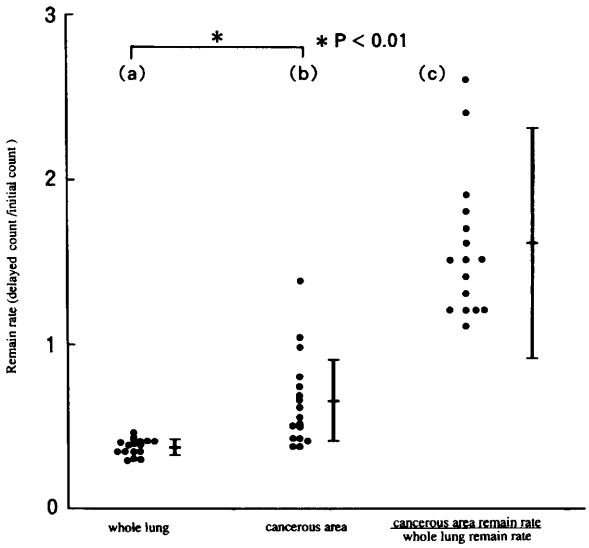


Fig. 3 Remain rate (RR: average pixel count in delayed image/ average pixel count in initial image) for the whole lung (a) and the cancerous area (b), and the ratio of these two values (c).

the cancerous region.

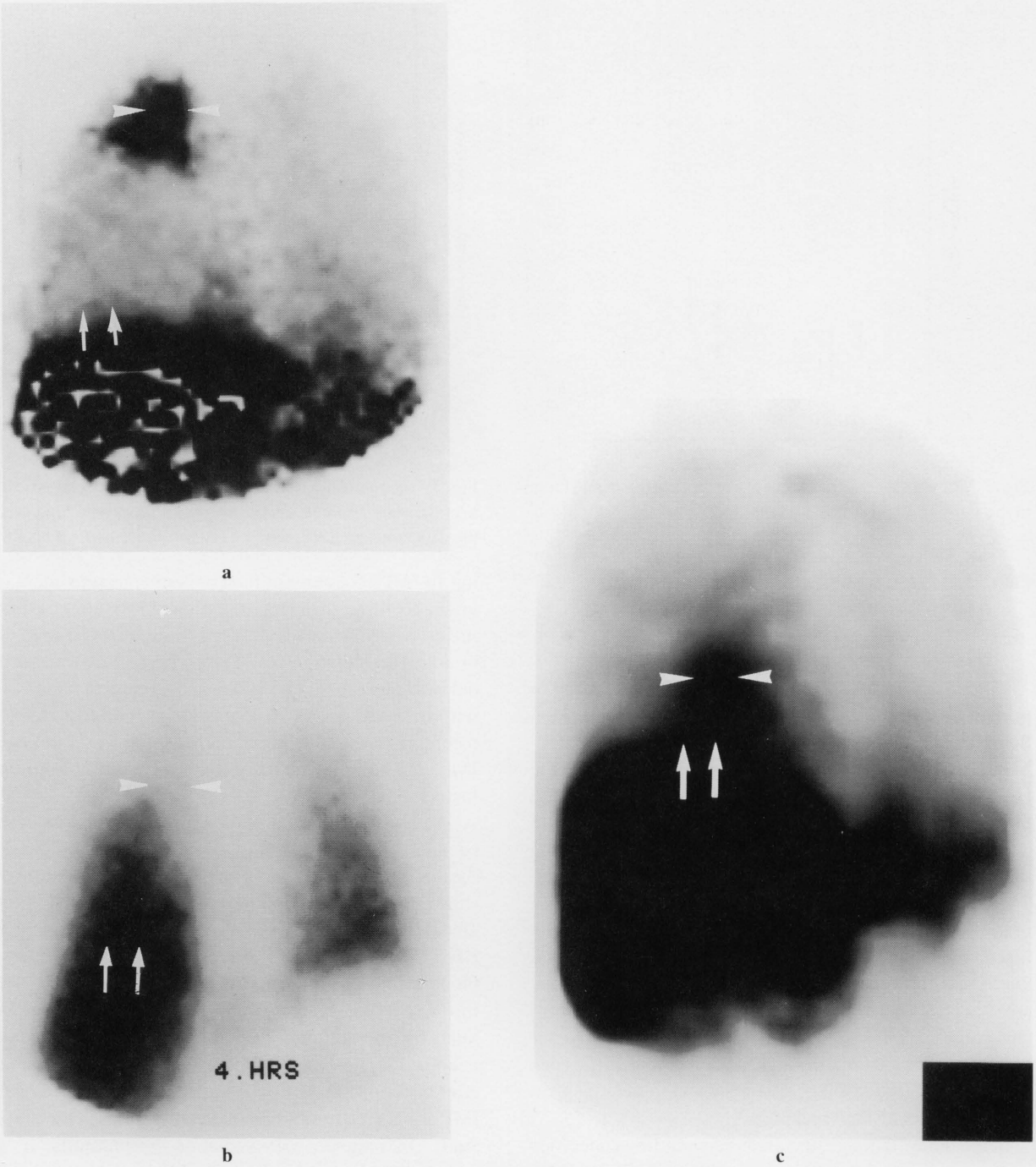
DISCUSSION

The initial image of IMP distribution was considered to primarily reflect the distribution of pulmonary blood flow, because this image was similar to that of the ^{99m}Tc-MAA lung perfusion scintigram. In the initial image, the ratio of counts within cancerous regions to those within the whole lung, was less than 1.0. This suggests that a decrease in blood flow might be important in explaining the poor accumulation of IMP in the cancerous tissues. This is further supported by Rahimian's report that 96% of the IMP injected intravenously was captured during the first pass,[7] and by the report of Suga et al. that IMP injected via the cubital vein did not accumulate within cancerous areas in lung cancer patients with a well developed bronchial artery.[8] This hypothesis is also supported by our previous report indicating that there was no difference between normal and cancerous tissues in human lungs in the expression of IMP receptors.[6]

In the delayed image, the areas surrounding cancerous lesions were noted to have a high accumulation of IMP, similar to that observed in pneumonia, and atelectasis with/without pleural effusions, which may be caused secondarily by cancer.[4,5,8,9] This may therefore cause the enlargement of the hot area in the delayed image. Furthermore, the images used in the present study were two dimensional, and therefore the results may be influenced by the surrounding areas to some extent. To enhance the utility of the IMP lung image, the rate of the count in the delayed image to the count in the initial image was calculated and called the remain rate (RR). An image was then made with the RR. In the two cases in which the RR was more than 1.0, it is possible that the amount of binding to IMP receptors in the cancerous lesions increased gradually through the recirculation of IMP after the initial image was taken. This delayed filling effect due to continuous recirculation of IMP has been shown to further delay clearance.[8,9] The relative decrease in blood flow within the cancerous tissue may delay binding to the IMP receptors of the cancer and increase the washout time of IMP. The RR may be increased as a result of both these factors.

The passage of IMP effluent into the alveolar space may be another important factor which increases the RR. Analysis of broncho-alveolar-lavage (BAL) fluid has shown that a large amount of IMP is transported into the alveolar space and is absorbed by the alveolar cells.[10] The BAL fluid counts were much higher than the systemic blood counts. An increase in IMP grain density was noted in the alveolar space of both normal and irradiated rat lungs by microautoradiography, 24 hours after the intravenous injection of ^{125}I-IMP, but no changes were noted after injection.[11] These observations may explain why low IMP counts remained even in healthy lungs in the present study. In patients with radiation pneumonitis, it was reported that both BAL fluid and BAL cells showed radioactivity four hours after IMP intravenous injection. It has been suggested that IMP and its metabolites are transported through the capillary-alveolar barrier.[12] In patients with lung cancer, it has also been inferred that the amount of IMP passing through the capillary-alveolar barrier increases because of the destruction of the barrier by the cancer.[11] This may cause the pooling of IMP within the alveolar spaces adjacent to the cancer tissues, leading to the accumulation of IMP around the tumor as noted in the delayed image.

The metabolism of IMP is also an important consideration. It has been reported that 96% of IMP injected



a

b

c

Fig. 4 Example of an image constructed using the RR (a), the delayed image (b), and the RR image of Figure 1 (c).

intravenously is captured by the lung during the first pass.[7] IMP is then dealkylated into p-iodoamphetamine (PIA) by the mixed function oxidase (MFO) which is abundant in lung tissue. Both IMP and PIA are released into the plasma, where PIA is converted to the end product, p-iodohyppuric acid, via p-iodophenyl acetone and p-iodobenzoic acid. About 20% of the iodo compound in the body is reported to be excreted into the urine each day. It is important to note that only IMP and PIA are detected in the lung tissue, even 24 hours after injection, and that these two compounds behave in essentially the same way.[13,14] This fact suggests that the activity or amount of MFO in cancerous tissue has no influence on the RR of iodo compounds, even if significantly more or less MFO is present, but impairment of the mechanism for releasing IMP and PIA into plasma may play a role in the increase in the RR in cancerous tissue.

Images of lungs with atelectasis or pneumonia have

been reported to show a cold region in the initial image and then a hot region in the delayed image, whereas cancerous lesions show a cold region in both the initial and delayed images.[4,5,7,8] Thus the differential diagnosis of atelectasis or pneumonia versus cancerous lesions in lung tissue, may be possible with the delayed image, but a high accumulation of IMP was noted in the delayed image of two patients with lung cancer in the present study. In such cases, discrimination between atelectasis or pneumonia versus cancer may be impossible. In the remain rate image, a hot image was revealed even if the delayed image did not reveal hot in the surrounding area.

In conclusion, the distribution of blood flow may determine the pattern of the initial image, whereas a comparative decrease in blood flow and the pooling of IMP in the alveolar space as a result of the destruction of the capillary-alveolar barrier may play an important role in the increase in the RR within cancerous tissue. Increased RR within cancerous areas may therefore reflect not only the presence of a tumor, but also the extent of local damage caused by the tumor. This unique capability of IMP imaging differentiates it from other morphological diagnostic tools such as X-ray CT. Moreover, a comparison of initial and RR images may reveal conspicuously cancerous areas in lung tissue.

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REFERENCES

1. Winchell HS, Baldwin RM, Lin TH. Development of I-123-labeled amines for brain studies, *J Nucl Med* 21: 940–946, 1980.
2. Winchell HS, Horst WD, Braun L, et al. N-isopropyl-p[^{123}I]iodoamphetamine: Single-pass brain uptake and washout; binding to brain synaptsomes; and localization in dog and monkey brain. *J Nucl Med* 21: 947–952, 1980.
3. Van Zandwijk N, Zwijnenburg A, Hoefnagel CA, et al. N-isopropyl-p[^{123}I]iodoamphetamine, a new agent for lung imaging studies. *Thorax* 41: 801–803, 1986.
4. Nakajo M, Uchiyama N, Hiraki Y, et al. Increased accumulation of iodine-123-IMP in the pulmonary inflammatory lesion surrounding a lung cancer. *Ann Nucl Med* 2: 49–53, 1988.
5. Nakajo M, Uchiyama N, Shinohara J, et al. Differentiation of bronchogenic carcinoma from secondary changes, obstructive pneumonitis and/or collapse by I-123 IMP lung imaging. *Ann Nucl Med* 4: 1–13, 1990.
6. Tanaka E, Mishima M, Kuno K, et al. N-isopropyl-p-iodoamphetamine receptors in normal and cancerous tissue of the human lung. *Eur J Nucl Med* 20: 293–296, 1993.
7. Rahimian J, Glass EC, Touya JJ, et al. Measurement of metabolic extraction of tracers in the lung using a multiple indicator dilution technique. *J Nucl Med* 25: 31–37, 1984.
8. Suga K, Matsumoto T, Nakanishi T, et al. Clinical Study on the Mechanism of Abnormal Accumulation in Lung Scanning with N-isopropyl-p-iodoamphetamine (^{123}I-IMP). *KAKU IGAKU (Jpn J Nucl Med)* 25: 625–631, 1988.
9. Nakajo M, Shimada J, Shimozono M, et al. Serial Lung Imaging with ^{123}I-IMP in Localized Pulmonary Lesions. *KAKU IGAKU (Jpn J Nucl Med)* 25: 441–450, 1988.
10. Ikeda H, Mariko M, Komatsu M, et al. Prolonged lung retention of ^{123}I-IMP in pulmonary disease. *Eur J Nucl Med* 15: 646–648, 1989.
11. Kosuda S, Kawahara S, Ishibashi A, et al. Experimental Study on N-isopropyl-p-iodoamphetamine Lung Uptake. *KAKU IGAKU (Jpn J Nucl Med)* 27: 149–153, 1990.
12. Kosuda S, Kawahara S, Tamura K, et al. Evaluation of Lung Uptake of ^{123}I-IMP by Bronchoalveolar lavage. *Nippon Act Radiol* 49: 484–486, 1989.
13. Moretti JL, Holman BL, Delmon L, et al. Effect of antidepressant and narcoleptic drugs on N-isopropyl-p-iodoamphetamine biodistribution in animals. *J Nucl Med* 28: 354–359, 1987.
14. Baldwin RM, Wu J. *In Vivo* Chemistry of IMP. *J Nucl Med* 29: 122–124, 1988.