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Spectral analysis applied to dynamic single photon emission computed tomography studies with N-isopropyl-p-(^{123}I)iodoamphetamine

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This study was performed to evaluate the usefulness of spectral analysis (SA) applied to dynamic single photon emission computed tomography studies with N-isopropyl-p-(^{123}I)iodoamphetamine (IMP). The unidirectional clearance of IMP from the blood to the brain tissue (K_1) obtained by SA (y (m*l*/g/min)) agreed well with that obtained from a two-compartment model using the nonlinear least-squares (NLSQ) method (x (m*l*/g/min)) ($y = 0.994x + 0.003$, r = 0.999, standard error of the estimate (SEE) = 0.005 m*l*/g/min). The rate constant for back diffusion of IMP from the brain tissue to the blood (k_2) obtained by SA (y (min^{-1})) also agreed well with that obtained by the NLSQ method (x (min^{-1})) ($y = 0.985x + 0.000$, r = 0.948, SEE = 0.001 min^{-1}). The brain vascular volume (V_0) obtained by SA (y (m*l*/g)) correlated well with that obtained by the NLSQ method (x (m*l*/g)) ($y = 1.138x + 0.000$, r = 0.867, SEE = 0.012 m*l*/g). These results indicate that SA is applicable and useful for quantification of the kinetic parameters of IMP in the human brain, and can be an alternative approach to compartment analysis.

Key words: spectral analysis, compartment analysis, dynamic SPECT studies, N-isopropyl-p-(^{123}I)iodoamphetamine

INTRODUCTION

N-ISOPROPYL-p-(^{123}I)IODOAMPHETAMINE (IMP) is a well known and widely used brain imaging agent. IMP has been synthesized and recommended for use as a tracer of cerebral perfusion.[1] More recently, Kuhl et al.[2] have used intravenously injected IMP with arterial blood sampling to demonstrate a local correlation between IMP and microsphere trapping in dog brain samples, and have extended this model to measurement of local cerebral blood flow (CBF) in humans by single photon emission computed tomography (SPECT).

Spectral analysis was introduced by Cunningham et al.[3] as a new technique for the analysis of dynamic positron emission tomography (PET) studies. This method provides a spectrum of the kinetic components which are involved in the regional uptake and partitioning of tracer from the blood to the tissue. This technique allows the unit impulse tissue response function to be derived with only an assumption of linear tracer kinetics. To our knowledge, however, there are no reports concerning its application to dynamic SPECT studies. The purpose of the present study was to apply spectral analysis to dynamic SPECT studies with IMP and evaluate its usefulness in comparison with compartment analysis.

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MATERIALS AND METHODS

Dynamic SPECT study

Dynamic SPECT studies were performed with the SPECT 2000H-40 (Hitachi Medical Corporation, Tokyo, Japan), a four-sided gamma camera arrangement equipped with a low-energy general-purpose collimator.[4] The head of the patient was positioned in the SPECT 2000H-40 scanner. Six millicuries (222 MBq) of IMP were injected into an antecubital vein; at the same time the scanner was started and arterial blood sampling was begun from a small catheter placed in the brachial artery. These arterial whole-blood samples were analyzed for the true tracer activity ($C_a(t)$) by using octanol extraction.[2,5] Scanning progressed for about one hour (20 scans) with a scan time duration of 160 sec. The transverse images were reconstructed by a

filtered back-projection method with a Shepp-Logan filter.[6] For attenuation correction, Chang's method[7] was used. The SPECT counts and arterial blood activity were corrected for decay and were mutually calibrated with a well-type scintillation counter (Abbott Lab. Auto-Logic).[5]

Regions of interest (ROIs) were selected in bilateral frontal, temporal, temporo-occipital, and occipital cortices on a slice through the basal ganglia in 13 patients with various brain diseases (6 patients with cerebral infarction, 3 patients with subarachnoid hemorrhage, 2 patients with cerebral hemorrhage, and 2 patients with transit ischemic attack), and a total of 104 ROIs were used in the analysis. When drawing ROIs, the diseased lesions were not specifically removed in the present study. The patients were 8 males and 5 females, and their ages ranged from 22 to 70 years (average of 55.8 years). Informed consent was obtained from each of the patients before entry into the study.

Spectral analysis

With spectral analysis,[3] the IMP activity in the brain tissue at a given time t ($C^s(t)$) was modeled as a convolution of the blood input function ($C_a(t)$) with a sum of k exponential terms as

$$C^s(t) = \sum_{i=0}^{k} \alpha_i \cdot \int_0^t C_a(t')e^{-\beta_i(t-t')}dt', \quad (1)$$

where α_i and β_i were assumed to be positive or zero. This constraint derived from an assumption of linear tracer kinetics. The upper limit, k, represented the maximum number of terms to be included in the model and was set to 1000 in this study. When using this model, the activity of IMP in the brain obtained by dynamic SPECT during the j-th scan (C_j^s) was calculated as

$$C_j^s = \frac{\int_{T_j}^{T_{j+1}} C^s(t)dt}{T_{j+1} - T_j}, \quad (2)$$

where T_j and T_{j+1} were the start and end time of the j-th scan, respectively. The α_i values were determined from C_j^s given by Eq. (2) and the brain activity of IMP measured by dynamic SPECT, by the non-negative least-squares method[8] for β_i ranging from 0 to 1 min^{-1} with an increment of 0.001 min^{-1}. When $C_a(t)$ was replaced by Dirac's delta function in Eq. (1), tissue unit impulse response function ($H^s(t)$) was given by

$$H^s(t) = \sum_{i=0}^{k} \alpha_i \cdot e^{-\beta_i t}. \quad (3)$$

Compartment analysis

We analyzed the kinetics of IMP in the human brain with a two-compartment model. With this model, the time-activity curve of IMP in the brain ($C^c(t)$) was given by[2]

$$C^c(t) = K_1 \cdot \int_0^t C_a(t')e^{-k_2(t-t')}dt', \quad (4)$$

where K_1 and k_2 represented the rate constants for the transport of IMP from the blood to the brain tissue and from the brain tissue to the blood, respectively. When we considered the effect of activity attributable to the vascular compartment, Eq. (4) became

$$C^c(t) = K_1 \cdot \int_0^t C_a(t')e^{-k_2(t-t')}dt' + V_0 \cdot C_a(t), \quad (5)$$

where V_0 was the brain vascular volume. As in Eq. (2), the activity of IMP in the brain obtained by dynamic SPECT during the j-th scan (C_j^c) was calculated as

$$C_j^c = \frac{\int_{T_j}^{T_{j+1}} C^c(t)dt}{T_{j+1} - T_j}. \quad (6)$$

The K_1, k_2 and V_0 values were estimated from the brain activity of IMP measured by dynamic SPECT and C_j^c given by Eq. (6), using the nonlinear least-squares method.[9]

Calculation of the K_1, k_2 and V_0 values by spectral analysis

From Eq. (3), the unidirectional clearance of IMP from the blood to the brain tissue (K_1) was given by the sum of the α values,[3] *i.e.*, $\sum_{i=0}^{k} \alpha_i$. When the effect of the tracer in the vasculature cannot be ignored, we should eliminate the highest frequency component (α_h) from this summation, to be discussed afterwards. In this case, α_h is defined as the α value at β_{max} which is the maximum value for β having a non-zero α value in the predefined range (0 to 1 min^{-1} in this study). The k_2 value was calculated from the β value having a non-zero α value except for β_{max}, while the V_0 value was calculated from α_h divided by β_{max}. In order to validate these values obtained by spectral analysis, we compared them with those obtained from the two-compartment model using the nonlinear least-squares method[9] as previously described.

Statistical analysis

Regression equations and correlation coefficients between the kinetic parameters obtained by spectral analysis and those obtained from compartment analysis by the nonlinear least-squares method were computed (Figs. 2–4). Standard errors of the estimate (SEEs) were also calculated.

RESULTS

Figure 1 shows a typical example of spectral analysis. Figure 1 (a) shows the time-activity curves of IMP in the arterial blood and brain tissue, which were used in spectral analysis. Figure 1 (b) is spectral analysis of tissue response, while Fig. 1 (c) is the corresponding tissue unit

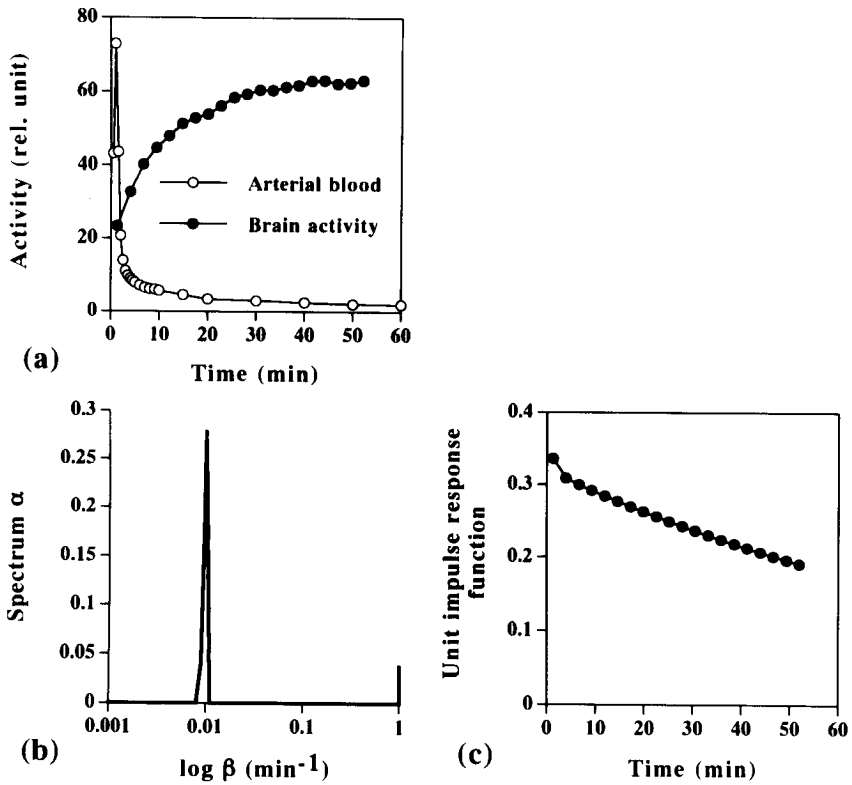

Fig. 1 Example of spectral analysis. Figure 1 (a) shows the time-activity curves of IMP in the arterial blood (○) and brain tissue (●). Figure 1 (b) is spectral analysis of tissue response, while Fig. 1 (c) is the corresponding tissue unit impulse response function.

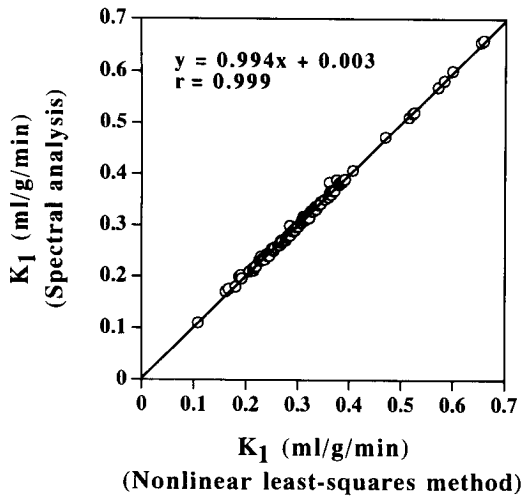

Fig. 2 Relationship between the K_1 values obtained using spectral analysis (y) and those obtained from compartment analysis using the nonlinear least-squares method (x). The solid line represents the regression line. The standard error of the estimate was 0.005 ml/g/min.

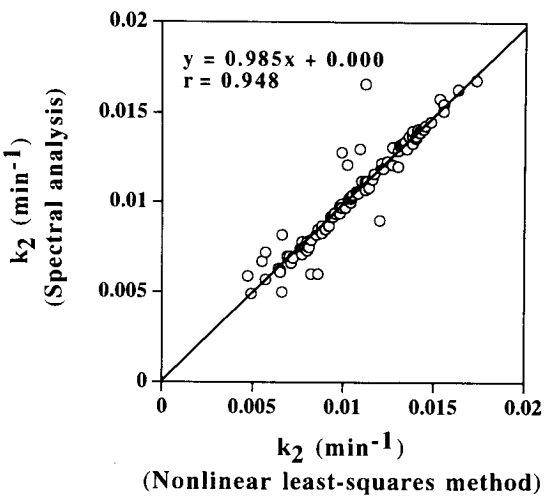

Fig. 3 Relationship between the k_2 values obtained using spectral analysis (y) and those obtained from compartment analysis using the nonlinear least-squares method (x). The solid line represents the regression line. The standard error of the estimate was 0.001 min^{-1}.

impulse response function.

Figure 2 shows the relationship between the K_1 values obtained by spectral analysis and those obtained by compartment analysis. The K_1 values obtained by spectral analysis (y (ml/g/min)) agreed well with those obtained by compartment analysis (x (ml/g/min)) ($r=0.999$, $p < 0.001$) with a regression equation of $y = 0.994x + 0.003$ and an SEE of 0.005 ml/g/min.

Figure 3 shows the relationship between the k_2 values obtained by spectral analysis and those obtained by com-

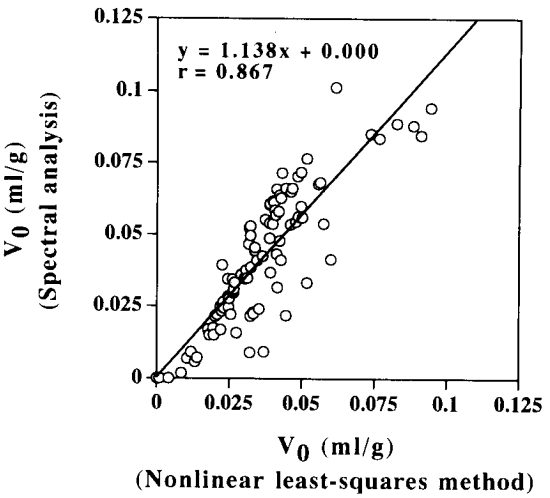

Fig. 4 Relationship between the V_0 values obtained using spectral analysis (y) and those obtained from compartment analysis using the nonlinear least-squares method (x). The solid line represents the regression line. The standard error of the estimate was 0.012 ml/g.

partment analysis. The k_2 values obtained by spectral analysis (y (min^{-1})) agreed well with those obtained by compartment analysis (x (min^{-1})) ($r = 0.948$, $p < 0.001$) with a regression equation of $y = 0.985x + 0.000$ and an SEE of 0.001 min^{-1}.

Figure 4 shows the relationship between the V_0 values obtained by spectral analysis and those obtained by compartment analysis. The V_0 values obtained by spectral analysis (y (ml/g)) correlated well with those obtained by compartment analysis (x (ml/g)) ($r = 0.867$, $p < 0.001$) with a regression equation of $y = 1.138x + 0.000$ and an SEE of 0.012 ml/g.

DISCUSSION

Spectral analysis has been applied to the analysis of dynamic PET studies in humans, where data consist of the time courses of the labels in tissue regions of interest and in arterial blood, following the administration of radiolabeled tracers.[3] This technique derives a simple spectrum of the kinetic components which relate the tissue's response to the blood activity curve. This technique facilitates the interpretation of dynamic PET data and simplifies comparisons between regions and between subjects.[3] With spectral analysis, the unit impulse tissue response function can be derived with only an assumption of linear tracer kinetics,[3] as previously described. For example, we do not need to assume the number of compartments in advance as in the conventional compartment analysis. Although the optimal number of compartments can be determined with the Akaike information criterion (AIC) or the Schwarz criterion (SC)[10] in the conventional compartment analysis, the fact that we do not need such *a priori* knowledge in spectral analysis appears to be preferable, but the major drawback of spectral analysis is that its application is limited to cases with linear tracer kinetics. This implies that this analysis cannot be applied to such a case when there is appreciable saturation of receptors for radiolabeled tracer. Our results demonstrated that spectral analysis is applicable and useful for kinetic analysis of IMP in the human brain.

When using a two-compartment model of IMP[5] with the activity attributable to the vascular compartment being taken into consideration, the activity in the brain tissue at time t is represented by Eq. (5). When $C_a(t)$ is replaced by Dirac's delta function ($\delta(t)$) in Eq. (5), Eq. (5) is reduced to

$$\tilde{C}^c(t) = K_1 \cdot e^{-k_2 t} + V_0 \cdot \delta(t). \quad (7)$$

This equation represents the case when a unit bolus was applied instantaneously at time t = 0, which corresponds to tissue unit impulse response. Theoretically, the tissue unit impulse response function obtained by spectral analysis (Fig. 1 (c)) can be represented by this equation when a two-compartment model is valid. As shown in Fig. 1 (b), there were two different frequency components in the spectrum obtained by spectral analysis. A high frequency component (corresponding to α_h) is located at the frequency coincident with the upper level of the predefined range of β (1 min^{-1} in this study) (corresponding to β_{max}). This frequency appears to be related to the rapid transit time of tracer in the vasculature within the ROI.[3] This is usually modeled as a constant volume term, a simple multiple of the measured blood activity (as V_0 in Eq. (5)). As previously mentioned, we calculated the vascular volume (V_0) by dividing α_h by β_{max} in spectral analysis. From Eq. (3), the value for the impulse response function attributable to the high frequency component (α_h) is given by $\alpha_h \cdot e^{-\beta_{max} t}$. On the other hand, when $\delta(t)$ in Eq. (7) is approximated with β_{max} as $\beta_{max} \cdot e^{-\beta_{max} t}$ ($\beta_{max} \gg 0$), the last term on the right-hand side of Eq. (7) becomes $V_0 \cdot \beta_{max} \cdot e^{-\beta_{max} t}$. Equating $V_0 \cdot \beta_{max} \cdot e^{-\beta_{max} t}$ to $\alpha_h \cdot e^{-\beta_{max} t}$ leads to the idea that α_h divided by β_{max} corresponds to V_0. As shown in Fig. 4, there was a good correlation between the V_0 values thus obtained by spectral analysis and those obtained by compartment analysis, supporting the above idea.

There are some reports concerning the physiological meaning of V_0.[11,12] Bol et al.[12] pointed out that there is a possibility that V_0 is overestimated due to dispersion of the tracer as shown in the Appendix, so that the V_0 values obtained in the present study might have been overestimated due to dispersion of IMP in the arterial blood.

The ROIs selected in the present study contain not only gray matter but also some white matter and/or diseased lesions. The kinetic behavior of IMP in these two regions should be different. We therefore expected that we could observe two low frequency components derived from these two regions except for α_h in the spectrum obtained by spectral analysis, but contrary to expectations, only

one low frequency component was observed as shown in Fig. 1 (b). This may be due to the fact that the contribution of white matter is much smaller than that of gray matter, or time and/or spatial resolution of the dynamic data used here is not enough for separating the contributions of these two regions. The reason is not yet clear. The low frequency component of the spectrum observed in Fig. 1 (b) is expected to be located at the frequency corresponding to the k_2 value. In order to validate this expectation, we compared this frequency with the k_2 value obtained by compartment analysis (Fig. 3). It should be noted that this frequency is indicated as the k_2 value obtained by spectral analysis in Fig. 3. As shown in Fig. 3, there was a good agreement between them, indicating that the above expectation is true.

As pointed out by Cunningham et al.,[3] the unidirectional clearance of the tracer from the blood to the tissue (denoted by K_1 in this study) is given by the sum of the α values. If the effect of the tracer in the vasculature is not negligible, we should eliminate the highest frequency component from the summation since the highest frequency component is related to the rapid transit time of the tracer in the vasculature as mentioned above. As shown in Fig. 2, there was excellent agreement between the K_1 values thus obtained by spectral analysis and those obtained by compartment analysis. K_1 is given by the product of CBF and the fraction of the tracer extracted by the brain tissue. Since the fraction of IMP extracted by the brain tissue is high,[13] K_1 appears to be nearly equal to CBF, so that these results suggest that spectral analysis allows us to quantify CBF with IMP in a simplified manner.

We previously investigated the validity of a microsphere model for the quantification of CBF with IMP in comparison with a two-compartment model.[5] As mentioned above, the kinetic parameters obtained from a two-compartment model by the nonlinear least-squares method generally agreed well with those obtained by spectral analysis. These findings appear to confirm the fact that the kinetics of IMP in the human brain can be described by a two-compartment model.

In conclusion, we demonstrated an application of spectral analysis to dynamic SPECT studies with IMP in the human brain. Our results indicated that spectral analysis is applicable and useful for quantification of the kinetic parameters of IMP in the human brain, and can be an alternative approach to compartment analysis.

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APPENDIX

When the following monoexponential function is used to take into account dispersion of the tracer in the arterial blood:[14]

$$d(t) = \frac{1}{\tau} \cdot e^{-t/\tau}, \qquad \text{(A.1)}$$

where τ is a time constant for dispersion, the relationship between the true cerebral input function ($C_{true}(t)$) and the measured arterial blood activity curve ($C_a(t)$) is given by

$$C_{true}(t) = \tau \cdot \frac{dC_a(t)}{dt} + C_a(t). \qquad \text{(A.2)}$$

When using a two-compartment model with the brain vascular volume (V_0) being taken as zero, the time-activity curve of the tracer in the brain tissue ($C^c(t)$) is given by

$$C^c(t) = K_1 \cdot \int_0^t C_{true}(t') e^{-k_2(t-t')} dt'. \qquad \text{(A.3)}$$

Substituting Eq. (A.2) into Eq. (A.3) yields

$$C^c(t) = K_1(1-k_2\tau) \cdot \int_0^t C_a(t') e^{-k_2(t-t')} dt' + K_1\tau \cdot C_a(t). \qquad \text{(A.4)}$$

Comparison between Eq. (A.4) and Eq. (5) suggests that K_1 is underestimated and V_0 is overestimated due to dispersion of the tracer.

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