Iodine-123-IBF SPECT Evaluation of Extrapyramidal Diseases

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Iodine-123-IBF is a dopaminergic antagonist suitable for SPECT imaging of D2 receptors. Initial animal studies demonstrated that its affinity for D2 receptors is approximately four times that of the commonly used SPECT D2 ligand [^{123}I]IBZM. In this study we investigated whether this higher affinity would lead to an improved accuracy in differentiating between various extrapyramidal diseases. **Methods:** SPECT imaging was performed in 17 patients with idiopathic Parkinson's syndrome (IPS); 4 patients with progressive supranuclear palsy (PSP), 2 patients with multiple system atrophy (MSA) and 7 age-matched control subjects. SPECT imaging was performed 5, 60, 120 and 180 min following intravenous bolus injection of 150–250 MBq of [^{123}I]IBF. The ratio of ligand uptake in the basal ganglia and frontal cortex was determined as a measure of receptor status. **Results:** In PSP and MSA patients, the basal ganglia-to-frontal cortex ratio reached a plateau at 2 hr; in the control subjects and the IPS patients the ratio was steadily increasing. At 3 hr the basal ganglia-to-frontal cortex ratio was 2.66 ± 0.29 (control subjects), 3.01 ± 0.41 (IPS), 2.09 ± 0.22 (PSP) and 2.10 (MSA). In the IPS patients with predominantly one-sided symptoms, the striatum contralateral to symptoms showed a tendency towards relatively increased ligand uptake. Despite the higher affinity of IBF for the D2 receptor compared to IBZM, the separation of individual PSP and MSA patients from the control subjects was not as clear cut as reported for IBZM due to a relatively high variation in the control subjects. We hypothesize that the latter is due to imaging in nonequilibrium conditions. **Conclusion:** The data suggest that IBF-SPECT can help in discriminating extrapyramidal disease. The accuracy might be improved by an administration protocol that allows imaging in "true equilibrium" conditions, such as a bolus injection followed by a constant infusion.

Key Words: single-photon emission computed tomography; iodine-123-IBF; extrapyramidal diseases

J Nucl Med 1995; 36:1196–1200

Previous studies with [^{123}I]IBZM have demonstrated that SPECT imaging of D2 receptors may be useful in the differentiation between various extrapyramidal diseases (*1–4*) and could predict response to dopaminergic therapy (*5*). Other studies have shown the potential of the method to study direct and indirect effects of various drugs on central D2 receptors (*6,7*). Currently this agent, [^{123}I]IBF (5-iodo-7-N-((1-ethyl-2pyrrolidinyl)methyl)carbox-amido-2,3-dihydrobenzofuran), has become available for SPECT imaging of central dopaminergic receptors (*8*). Initial animal studies revealed that its affinity for D2 receptors was approximately four times higher than that of IBZM (*9*). It binds, however, not only to the D2 receptor but also to the D3 receptor with similar affinity (Kung, *personal communication*). In monkeys, most of the striatal binding could be blocked with haloperidol demonstrating relatively low unspecific binding (*10*).

The possibility of in vivo quantitative assessment of D2 receptor status using IBF SPECT and tracer kinetic modeling has recently been demonstrated (*11*). According to these data, [^{123}I]IBF seemed a promising agent for assessing D2 receptor status with SPECT in humans. The aim of this study was to evaluate the suitability of [^{123}I]IBF to discriminate different extrapyramidal diseases and compare the results to those of IBZM. For this purpose, we performed IBF-SPECT on normal control subjects and patients with idiopathic Parkinson's disease (IPD), progressive supranuclear palsy (PSP) and multiple system atrophy (MSA). D2 receptor status in these diseases has not only been assessed with IBZM-SPECT, but also with PET, the gold standard of in vivo receptor imaging. Studies with ^{11}C-raclopride and PET have demonstrated normal or increased D2 receptor density in IPD (*12–15*) and decreased receptor density in PSP (*15*) and MSA (*12*).

MATERIALS AND METHODS

Patients and Subjects

IBF-SPECT was performed on 23 patients and 7 age-matched control subjects. Seventeen patients (11 men, 6 women; mean age, 62 ± 14 yr; range, 48–85 yr) were diagnosed as having idiopathic Parkinson syndrome (IPS). The duration of disease was 5.5 ± 5 yr and the score on the Hoehn-Yahr scale was 2.06 ± 0.99 (mean ± s.d.). One patient displayed symmetric symptoms and 16 displayed predominantly one-sided symptoms. All patients had been on dopaminergic medication, mostly L-dopa. Four patients (3 men, 1 woman; age range 61–73 yr) had a diagnosis of PSP with a disease duration of 5.5 ± 1.5 yr and a score on the Hoehn-Yahr scale of 5.5 ± 1.0. One 49-yr-old man and one 69-yr-old woman were diagnosed as having MSA.

Received Jul. 7, 1994; revision accepted Oct. 18, 1994.

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The diagnosis in all patients was based on history, clinical symptoms and response to L-dopa therapy. In addition, all subjects with PSP had the typical signs of vertical up and down gaze palsy. When possible, the dopaminergic medication was stopped 24 hr prior to SPECT imaging. In 10 patients with IPD, L-dopa could not be discontinued for imaging.

The control subjects consisted of four healthy volunteers, one patient with a peripheral neuropathy, one patient with prostate cancer and two patients with newly diagnosed malignant melanoma. This yielded a total of seven age-matched control subjects (mean age 68 ± 5 yr; range 56–72 yr. Originally, another control subject (a 43-yr-old melanoma patient) was imaged. Since earlier studies with IBZM have shown a clear age-dependence of striatal D2 receptors (*3*) and this subject's age was out of the patients' range, he was not included in the final analysis. None of the control subjects had a history of extrapyramidal symptoms nor did clinical neurological examination reveal any signs of central nervous disorder. None of the cancer patients had received chemotherapy prior to the SPECT scan; the patient with prostate cancer had been treated with local radiation. None of the control subjects was on any medication with dopaminergic action.

Synthesis and Radiolabeling

Labeling of [^{123}I]IBF was performed as described previously (*16*). Briefly, 50 μl of ethanol was added to 50 μg of 5-tributylstannyl-7-N-[(1-ethyl-2-pyrrolidinyl)-methyl] carboxamido-2,3-dihydrobenzofuran. Iodine-123-NaI (in NaOH, pH = 11, volume varying from 110 to 600 μl) was acidified with 50 μl 1N HCl. Fifty microliters of 3% H_2O^2 was added and the reaction was allowed to proceed for 30 min, followed by 100 μl of $Na_2S_2O^5$ (8 mg/ml), after which the solution was neutralized with 1 ml of saturated $NaHCO^3$. The 3% H_2O^2 was prepared freshly by dilution of a 30% solution.

The resulting solution was transferred to a SEP-PAK C18 cartridge. The SEP-PAK cartridge was washed with 1 ml water followed by 3 ml water/ethanol (1/1) and the IBF eluted from the column with 15 ml ethanol into a rotavapor conical flask, containing 100 μl ascorbic acid solution (1 mg/ml). The ethanol was evaporated and the product dissolved in 5–10 ml physiological saline.

Quality control was performed by C18 reversed-phase HPLC with acetonitrile/0.5 m*M* dimethylglutaric acid (90/10 over PRP-1). The specific activity could not be measured because the UV signal was below the sensitivity of the UV detector and was thus estimated to be greater than 4000 Ci/mmole.

IBF-SPECT

SPECT imaging was performed 5–25 min (21 subjects), 50–70 min (29 subjects), 110–130 min (30 subjects) and 170–190 min (30 subjects) following intravenous injection of 150–250 MBq [^{123}I]IBF. Between scans subjects were allowed to leave the camera table. A laser alignment system was used for repositioning. Data were acquired on a triple-head camera (Picker Prism 3000, Bedford Heights, OH 120 projections, high-sensitivity, parallel-beam collimator, 64 × 64 matrix. Transverse slices with a thickness of 8 mm were reconstructed using filtered backprojection with only a ramp filter. Attenuation correction was performed using Chang's method with an attenuation factor 1.5 cm^2/g (*17*). For clearer definition of the cortex and the basal ganglia, the transverse slices were additionally filtered (Metz filter). On the slice with the highest concentration of IBF in the striatum, standardized anatomical regions of interest (ROIs) were placed over the left and right striatum and frontal cortex. These regions were then transferred to original slices (reconstructed with only a ramp filter) and the striatum-to-frontal cortex ratio was calculated.

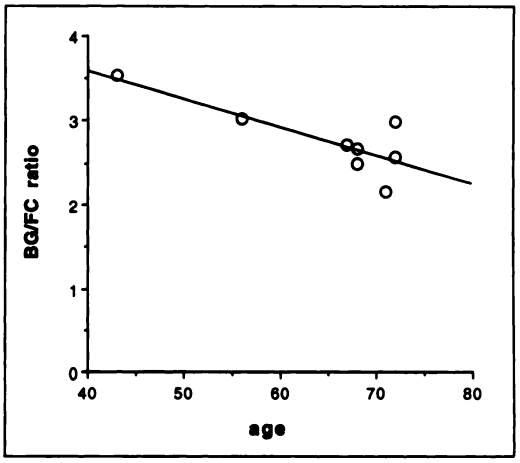

FIGURE 1. Age dependence of the basal ganglia-to-frontal cortex ratio in the normal control subjects. The plot includes the youngest control subject, which was excluded from the analysis because his age was outside the range of the patients. Linear regression yielded the correlation: basal ganglia-to-frontal cortex ratio = 0.033 * age + 4.91, r = 0.81.

Statistical Analysis

BG/FC ratios were expressed as mean ± s.d. Differences between the patient groups were evaluated with Student's t-test. Bonferroni correction for multiple t-tests was applied and values of $p < 0.05$ were considered significant.

RESULTS

Figure 1 demonstrates the declining basal ganglia-to-frontal cortex ratio with age in the control subjects. Figure 2 shows the basal ganglia-to-frontal cortex ratio (mean of left and right striatum) at the various imaging points for the different subject groups. In the control subjects and the patients with IPS, the ratio is constantly rising until 3 hr

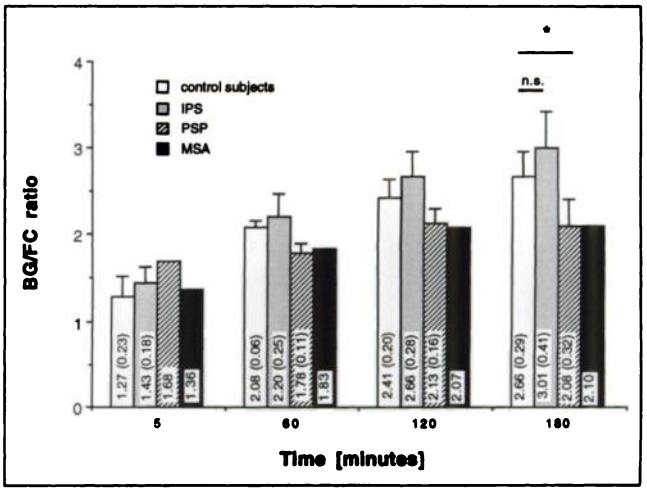

FIGURE 2. Basal ganglia-to-frontal cortex ratios at different timepoints for the patient groups and control subjects (mean of left and right striatum ± s.d.). n.s. = not significant. *$p < 0.05$.

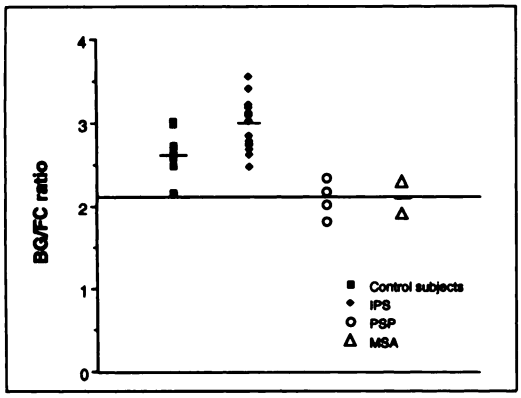

FIGURE 3. Basal ganglia-to-frontal cortex ratios at 3 hr for all patients and control subjects. The horizontal line is positioned 2 s.d. below the mean of the control subjects.

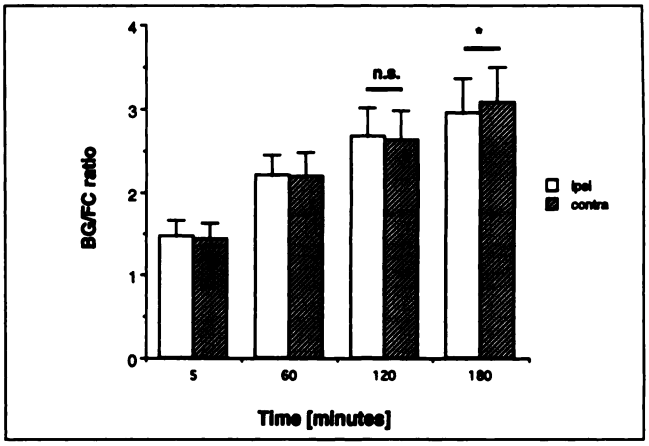

FIGURE 4. Basal ganglia-to-frontal cortex ratios in the IPS patients with predominantly one-sided symptoms (n = 16). Plotted are the ratios of the striatum contralateral and ipsilateral to symptoms (mean ± s.d.). n.s. = not significant. *p < 0.05.

postinjection. In the patients with PSP and MSA, a plateau in the ratio seems to be reached at approximately 2 hr. Compared to the control subjects, the ratio is reduced in the patients with PSP and MSA, reaching significance at 1 and 3 hr in the PSP patients. Due to the low patient number, no statistics were performed in the MSA group.

Figure 3 demonstrates the basal ganglia-to-frontal cortex ratios in all examined subjects. Clearly the lowest basal ganglia-to-frontal cortex ratio at 3 hr is reached in the patients with PSP and MSA. Two of the PSP and one of the MSA patients display a ratio more than 2 s.d. lower than the control subjects, the others fall between 1 and 2 s.d. below the ratio of the controls subjects. In the group with IPS, all subjects display a ratio in or above the range of the controls.

In the subgroup of patients with IPD and predominantly one-sided symptoms, the striatum contralateral to the symptoms displays a higher basal ganglia-to-frontal cortex ratio compared to the ipsilateral side, with the difference reaching significance at 3 hr ($p = 0.03$, paired t-test) (Fig. 4).

DISCUSSION

In comparison to [^{123}I]IBZM,[^{123}I]IBF displays a markedly higher basal ganglia-to-frontal cortex ratio (2.66 ± 11%) at 3 hr versus 1.55 ± 3%, at 2 hr (*1*) and 1.73 ± 5% (*3*). This result could be expected from the higher in vitro binding affinity (lower Kd). As shown in Figure 2, this ratio is probably still increasing after 3 hr in the normal control subjects and the patients with IPS, indicating that a state of "transient equilibrium" (explained below) between specific and nonspecific binding is not reached by that time.

Uptake ratios determined in the examined patient groups reflect the well known pattern established with IBZM and PET D2 ligands. In IPS there is a tendency for elevated striatal uptake compared to the control subjects and more pronounced in the striatum contralateral to symptoms. The asymmetry in striatal uptake ($p < 0.05$) in the 16 IPS patients with predominantly one-sided symptoms is in agreement with IBZM studies (*3*). This asymmetry is usually interpreted as D2 receptor up-regulation as response to decreased presynaptic dopamine.

In the PSP and MSA patients, our results are in good agreement with former studies (*2,3*), demonstrating a symmetrical reduction in ligand uptake in the basal ganglia. At 3 hr there is a 25% reduction in the PSP and MSA group compared to the normal control subjects. This reduction was highly significant in the PSP patients, but because of the low number of subjects, no statistics were obtained in the MSA group. For individual patients, the separation of the PSP and MSA patients from the normal control subjects was not as clear-cut as reported for IBZM (*1,3*). All six patients displayed a basal ganglia-to-frontal cortex ratio of at least 1 s.d. below the mean of the control subjects, but only three exceeded the reduced 2 s.d. which would allow a separation with >95% confidence (Fig. 3). In comparison to IBZM, this somewhat worse separation of the PSP and MSA groups from the control subjects can be partly explained by the higher variation in the control subjects [coefficient of variation = 11% in our data versus 3%–5% reported by Tatsch and Brücke for IBZM (1,3)]. One reason for this might be a true interindividual variation in striatal D2 receptors in the chosen control subjects. Another likely explanation is that at the time of imaging, receptor-bound ligand and unspecifically bound ligand are not in a state of "transient equilibrium."

General Comments on Receptor Imaging

Ideally, receptor imaging with SPECT is performed when all kinetic compartments (receptor-bound ligand, unspecific and free ligand in tissue and in plasma) are in a state of "true equilibrium," meaning that there is no net increase or decrease of ligand in neither compartment. This state can only be achieved by employing some kind of a prolonged infusion protocol. Under "true equilibrium" conditions, specifically bound ligand is directly proportional to receptor density. If one assumes that the ligand in the frontal cortex represents unspecific binding in the basal

ganglia, then the concentration of the receptor-bound ligand in the basal ganglia can be derived by simple subtraction. Normalizing specific binding to free ligand in plasma would directly yield the binding potential. This approach is clinically impractical because it requires the measurement of free tracer in plasma. The more easily obtainable basal ganglia-to-frontal cortex ratio will be a reasonable measure for receptor density if interindividual variation of unspecific binding is low. The infusion paradigm has been successfully applied to IBF studies in baboons (*6*) and other high-affinity receptor ligands such as [^{123}I]-iomazenil, a benzodiazepine receptor marker (*18*).

Following bolus injection, "true equilibrium" cannot be achieved. Depending on the clearance of ligand from plasma, however, the ratio of specific-to-nonspecific binding may reach a stable value. This state has been referred to as "transient equilibrium" (*19*), "pseudo-equilibrium" (*20*) or "quasi-equilibrium" (*21*). Under the "transient equilibrium," the basal ganglia-to-frontal cortex ratio is providing an overestimation of the receptor density, the degree of which increases with receptor density, affinity and the clearance rate of the ligand from plasma (*22*). Imaging under "transient equilibrium" conditions is therefore not ideal but may be clinically sufficient for receptor ligands with not very high affinity such as IBZM.

Our data and data from another study (*11*) indicate that with IBF a state of "transient equilibrium" is not reached at 3 hr following bolus injection. In this case, ligand uptake is further influenced by nonreceptor-related factors such as ligand delivery to the brain and the rate of disappearance in plasma, which may vary between individuals. Therefore, part of the observed variation of the striatum-to-frontal cortex ratio may be due to such nonreceptor-related variables. Considerable interindividual variability in the peripheral metabolism of IBF has been reported by Laruelle et al. (*11*).

There are methods to estimate the "true equilibrium" value for the basal ganglia-to-frontal cortex ratio following bolus injection. One proposed by Farde et al. makes use of the fact that "true equilibrium" between specific and nonspecific binding is mimicked for a short interval at the time of peak specific binding (*23*). A potential problem with this approach is the determination of the timepoint of peak specific binding, especially when the peak is flat and the data are noisy. The most complex method is tracer kinetic modeling which was applied to IBF-SPECT data by Laruelle et al. (*11*). The advantage of this approach is that it allows the calculation of more direct measures of receptor density, such as the binding potential. Both methods, however, require dynamic data acquisition which, for clinical purposes, is often impractical.

Some reduction of the nonreceptor-related variation in the basal ganglia-to-frontal cortex ratio might be achieved by imaging under "transient equilibrium" conditions at a later timepoint. SPECT imaging with ^{123}I is theoretically possible up to 24 hr or even later. From the available data with IBF, however, it is not clear whether a state of "transient equilibrium" in areas with high receptor densities can be achieved at all with a bolus injection. Furthermore, this approach would still suffer from the overestimation problem mentioned above. The constant infusion paradigm seems to be the most promising, clinically feasible approach to increase the accuracy of the presented method to separate various extrapyramidal diseases.

The above considerations illustrate the complexity of receptor imaging. High in vitro binding affinity per se does not render a ligand suitable for receptor imaging. Imaging and injection protocol must be carefully chosen depending on the in vivo kinetics of the ligand.

CONCLUSION

IBF-SPECT is suitable for imaging D2 receptors in various extrapyramidal diseases. Like IBZM, it has the potential to help the clinician in differentiating PSP and MSA from IPS which is essential with regard to dopaminergic therapy. Compared to IBZM, its basal ganglia-to-frontal cortex ratio is markedly higher, which, however, did not lead to more accurate discrimination between the examined extrapyramidal diseases. Further studies are needed to assess whether this accuracy can be increased by employing an infusion protocol that would allow imaging under "true equilibrium" and therefore minimize variation in striatal uptake not related to receptor density.

ACKNOWLEDGMENT

The authors thank the OPO-Stiftung in Zurich for financial support of this study.

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