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ORIGINAL PAPER

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Tc-99 HMPAO SPECT study of regional cerebral blood flow in olanzapine-treated schizophrenic patients*

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Abstract Dopamine D_2 blocking typical antipsychotic drugs are known to change the cerebral perfusion patterns of schizophrenic patients, especially in the frontal cortex and basal ganglia. In recent years atypical antipsychotics such as olanzapine, which have high serotonin 5-HT_{2A}/dopamine D_2 occupation ratios, have been shown to be more effective in the treatment of schizophrenia symptoms. The aim of this study was to evaluate the regional cerebral blood flow (rCBF) of the schizophrenic patients treated with olanzapine in a within-subject design. Twenty-four patients with schizophrenia participated as subjects in the study. Each subject was scanned in a medication-free state and after 6 weeks of 10 mg/day fixed dose olanzapine treatment. Despite the clinical improvement seen in the patients, repeated-measures analysis of variance showed that olanzapine produced no significant changes in cortical rCBF after the six-week treatment. This finding indicates that unlike typical antipsychotics olanzapine has no negative effect on cortical cerebral perfusion patterns of schizophrenic patients.

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Key words regional cerebral blood flow · schizophrenia · olanzapine · atypical antipsychotics

Introduction

Functional brain imaging methods are the best techniques to reveal patterns of cerebral perfusion abnormalities associated with specific clinical states and symptoms, neuropsychological deficits and responses to treatment. Most of this work indicates that patients with schizophrenia have decreased blood flow or reduced metabolic function, particularly in the frontal lobes and/or left hemisphere (Andreasen et al. 1992; Chen et al. 2000; Weinberger et al. 1988; Wolkin et al. 1985). There are also suggestions of abnormalities in various subcortical structures such as the hippocampus, parahippocampus, and globus pallidus in schizophrenia (Buchsbaum et al. 1982; Wolkin et al. 1985). Various functional imaging studies have examined the relationship between antipsychotic medication status and brain metabolism or blood flow in patients with schizophrenia (Bartlett et al. 1991; Buchsbaum et al. 1992; DeLisi et al. 1985; Holcomb et al. 1996; Miller et al. 1997). The most consistent findings with typical antipsychotics are that metabolism or blood flow are increased in the basal ganglia but decreased in the frontal cortex.

Most clinical trials support the idea that atypical antipsychotics have advantages in terms of greater efficacy for positive and negative symptoms, beneficial effects on cognitive functioning, and fewer extrapyramidal side effects. They have also fewer neuroendocrine side effects (Markianos et al. 2001). It is thought to be the ratio of serotonin 5-HT_{2A}/dopamine D_2 blockade that is responsible for their superior efficacy (Ichikawa and Meltzer 1999). However, it is also proposed that the fast dissociation of atypical antipsychotics from the dopamine D_2 receptor or their low level of dopamine D_2 receptor blockade makes atypical antipsychotics more efficacious than typical antipsychotics (Kapur and Seeman 2001; Xiberas et al. 2001).

The effects of atypical antipsychotics on brain metabolism or perfusion in schizophrenic patients have recently been explored, but the data are still preliminary and the overall picture is not yet clear (Honey et al. 2001; Miller et al. 2001; Nygan et al. 2002).

The objective of this SPECT study was to evaluate regional cerebral blood flow (rCBF) changes in schizophrenic patients who had responded unsatisfactorily to treatment with typical antipsychotics, had undergone a three week washout, and then had been treated for six weeks with olanzapine, an atypical antipsychotic.

Methods

Subjects

Twenty-four patients who fully met DSM-IV (American Psychiatric Association, 1994) criteria for schizophrenia were included as subjects in the study (Table 1). Eleven of them had paranoid and the others had undifferentiated subtype of schizophrenia. All patients had been followed for at least six months so that their diagnosis of schizophrenia could be confirmed. Brain computed tomographic scans performed on Shimadzu SCT 4800T (Japan), which were read by an experienced radiologist, revealed no morphological abnormality or cortical atrophy in the subjects. The inclusion criteria were the absence of organic brain disorder, alcohol or drug abuse, pregnancy, or any physical illness, as assessed on the basis of personal history, clinical examination, and laboratory data. All of the subjects were inpatients. None of the patients was antipsyhotic-naïve but none had received depot antipsychotic in the previous year. The average duration of treatment with typical antipsychotics was 52.76 ± 35.85 months (mean ± SD) and the average antipsychotic dose during the previous month before the recruitment was 445 ± 158 mg chlorpromazine equivalents per day. In each case the patients or their relatives wanted to change the ongoing treatment to olanzapine due to the side effects of typical antipsychotics (extrapyramidal symptoms, sexual dysfunction, mental dullness, galactorrhea, and irregular menses) or insufficient symptomatic response. None of the patients had tardive dyskinesia or was treatment refractory according to Kane's criteria (Kane et al. 1988). The patients underwent a three week drug washout period prior to a six week olanzapine treatment (10 mg/day fixed dose). Concomitant medication with lorazepam was allowed during the study except within 24 hours prior to a SPECT scan. Only four of our patients had lorazepam (mean 1.5 mg/day) in the week prior to the second scan.

Patients' symptoms were assessed on the day of the baseline SPECT scan with the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1988), the Clinical Global Impression scale (CGI; Guy 1976) and the Extrapyramidal Symptom Rating Scale (ESRS; Chouinard et al. 1980) to assess possible relationships between rCBF patterns and concurrent symptoms while they were drug-free. This assessment was repeated after six weeks of olanzapine treatment. The BPRS items related to suspiciousness, unusual thought content, grandiosity and hallucinatory behavior were taken as positive symptoms, while items associated with motor retardation, blunted affect, mannerism and posturing, and emotional withdrawal were considered negative symptoms (Overall and Gorham 1988). The ethics committee of our hospital approved of the study protocol, and the patients gave their written informed consent.

SPECT scanning procedure

All subjects were studied in the supine resting position with closed eyes in a silent and darkened room. No extreme anxiety was observed during the SPECT study. The SPECT scans were coded with random numbers and evaluated by two nuclear medicine specialists without having any knowledge of the clinical data. Their interrater reliability was 0.90.

Regional CBF images were obtained by SPECT using Tc-99m HMPAO (Ceretec, Amersham, International plc, UK) as a radiotracer prepared according to the manufacturer's instructions. The SPECT study was performed 20 minutes after the injection of 550 MBq of Tc-99m HMPAO with a 360° rotating single-head gamma camera system (Toshiba GCA 602 A/SA, Japan) equipped with a low-energy all-purpose collimator interfaced to a Toshiba computer system. Using the laser guide marks of the SPECT instrument, the patient's head was positioned so that the tomographic images were parallel to the orbitomeatal (OM) plane. Data were obtained in a 64X64 matrix through 360° rotation at 6° intervals for 30 s per arc interval. No zoom was used, and the corresponding pixel size was 5.5 mm. Image reconstruction was performed by filtered back-projection using a Butterworth filter (cut-off frequency = 0.25, power factor = 8). Slice thickness was 5.5 mm, and no attenuation or scatter correction was done. The images were reoriented to obtain transaxial slices parallel to the OM plane. Four transaxial slices were selected for analysis (approximately 22, 33, 66, and 77 mm above the OM plane; Gonul et al. in press). The slice levels were chosen based on the Matsui and Hirano atlas (Matsui and Hirano 1978). On the transaxial slices, hemisphere contours were drawn using a semiautomated technique to describe the limits of the whole brain cortex (W). Free irregular regions of interest (ROIs) consisting of cortical areas were drawn blindly by the same nuclear medicine specialist. A template containing all ROIs is shown in Fig. 1. Occipital ROIs in each hemisphere were combined

Table 1 The sociodemographic and clinical data of the patients

	Baseline		End point		Comparison	
	Mean	SD	Mean	SD	Z	p
Age	29.04	8.21	–	–	–	–
Gender (M/F)	12/12		–	–	–	–
Age of onset	23.39	6.37	–	–	–	–
Duration of illness (months)	92.86	55.63	–	–	–	–
No. hospitalizations	2.2	1.4	–	–	–	–
Height (cm)	1.65	8.56	–	–	–	–
Weight (kg)	64.8	6.39	67.1	5.8	3.29	0.001*
BPRS total	44.60	12.00	25.65	12.10	4.20	< 0.001*
BPRS positive**	14.34	4.34	7.60	3.75	4.11	< 0.001*
BPRS negative**	9.13	3.22	7.08	2.78	3.90	< 0.001*
CGI	4.56	0.50	3.60	0.58	3.60	< 0.001*
ESRS	12.6	1.5	12.3	0.8	0.7	0.46

* Significant (Wilcoxon signed ranks test); ** See text for the details

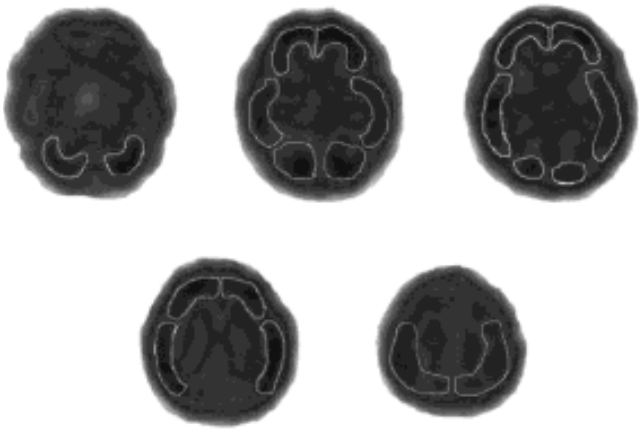

Fig. 1 SPECT region of interest template: transaxial view at five standard levels. Upper left slice: cerebellum. Upper middle slice: inferior frontal, inferior temporal, occipital cortical regions. Upper right slice: middle frontal, superior temporal, occipital cortical regions. Lower left slice: Superior frontal, inferior parietal cortical regions. Lower right slice: superior parietal cortex.

into one. The subcortical regions were omitted from analysis due to insufficient image quality.

The SPECT imaging data were evaluated by semiquantitative analysis. The whole brain ratio method was used to determine the index of the relative perfusion of each area in the form of a ratio (i. e., the index of relative perfusion was the ratio of average counts for each anatomical subdivision to the average counts of the whole brain).

Data analysis

A repeated-measures analysis of variance (ANOVA) was performed to compare SPECT data of the patients obtained while they were drug-free and after treatment with olanzapine. If the assumption of compound symmetry was not met, then Greenhouse-Geisser adjustment was used (Greenhouse and Geisser 1959). The statistical tests were corrected for multiple comparisons. Comparisons of the clinical variables of the patients were conducted with paired Wilcoxon signed rank tests. Spearman's rank correlations were used to study the relationship between the clinical ratings and the indices of the cerebral perfusion.

Results

The BPRS and CGI scores of our patients decreased significantly by the end of the six week olanzapine treatment compared to the drug-free baseline ($Z = 4.20$ $p < 0.001$ and $Z = 3.60$ $p < 0.001$ respectively; Table 1).

Table 2 shows the mean values and the standard deviations of the indices of perfusion relative to the whole brain in the listed cerebral regions before and after olanzapine treatment. Repeated-measures ANOVA revealed no significant effect of olanzapine treatment on rCBF in schizophrenic patients ($F = 3.23$, $df = 1,23$, $p = 0.085$). There was also no treatment by region interaction ($F = 2.07$, $df = 8, 184$, $p = 0.14$, Greenhouse-Geisser corrected).

Significant negative correlations were found between the left superior frontal cortical perfusion and BPRS negative symptom scores not only during the drug-free period but also after the treatment ($r = 0.64$ $p < 0.05$ and $r = 0.68$ $p < 0.05$, respectively).

Table 2 The rCBF values of the patients before and after the olanzapine treatment

Regions	rCBF ratios (ROI/Whole Brain)			
	Baseline		End-point	
	Mean	SD	Mean	SD
Superior frontal cortex				
Right	0.90	0.05	0.94	0.02
Left	0.88	0.07	0.94	0.05
Middle frontal cortex				
Right	0.89	0.07	0.94	0.02
Left	0.89	0.08	0.92	0.06
Inferior frontal cortex				
Right	0.91	0.04	0.93	0.06
Left	0.89	0.09	0.95	0.06
Superior Parietal cortex				
Right	0.94	0.05	0.96	0.08
Left	0.96	0.02	0.97	0.04
Inferior Parietal cortex				
Right	0.91	0.04	0.93	0.05
Left	0.93	0.05	0.98	0.06
Superior Temporal cortex				
Right	0.98	0.03	0.99	0.07
Left	0.99	0.05	1.01	0.06
Inferior Temporal cortex				
Right	0.98	0.03	0.99	0.05
Left	0.99	0.04	1.01	0.05
Occipital cortex				
Right	0.91	0.05	0.91	0.05
Left	0.94	0.06	0.93	0.06
Cerebellum				
Right	0.94	0.05	0.93	0.04
Left	0.95	0.05	0.94	0.04

Discussion

A substantial literature indicates that individuals with schizophrenia have a hyperdopaminergic state in limbic and other subcortical structures, but simultaneously manifest a hypodopaminergic state in the frontal cortex (Carlsson 1988; Moore et al. 1999). It is hypothesized that hypofrontality and negative symptoms may be related to the cortical hypodopaminergic state, and positive symptoms may be related to the subcortical hyperdopaminergic state (Weinberger et al. 1988). Typical antipsychotics like haloperidol, which have high affinities for dopamine D_2 receptors, successfully treat positive symptoms but may increase extrapyramidal side effects and negative symptoms. A decremental effect of typical antipsychotics on frontal metabolism by indirect mechanisms may contribute to the increased negative symptoms (Holcomb et al. 1996). On the other hand, the atypical antipsychotic drugs disinhibit dopamine transmission in the frontal cortex due to 5-HT1A receptor stimulation via 5-HT_{2A} (Kuroki et al. 1999; Ichikawa et al. 2001) and it has been suggested that this may lead to an improvement in negative symptoms (Hertel et al.

1996; Ichikawa and Meltzer 1999). Recently it has been shown that another atypical antipsychotic, amisulpiride, which has a high affinity only for dopamine D_2 and D_3 receptors, increases dopamine transmission at low doses in the frontal cortex (Scatton et al. 1997). It is thought that this effect is due to amisulpride's disinhibitory effect on the mesocortical dopaminergic bundle.

Negative symptoms and cognitive deficits seen in schizophrenia may reflect impaired prefrontal cortical function due to reduced dopaminergic activity in the mesocortical dopaminergic pathway. If this hypothesis is correct, one would expect that atypical antipsychotic medications might enhance or at least preserve the rCBF values especially in frontal regions, owing to their relative activating effect on dopamine release in frontal cortex.

Functional neuroimaging studies of atypical antipsychotics in schizophrenic patients so far have rendered somewhat conflicting results. Some authors have found that risperidone, another atypical antipsychotic, decreased the frontal rCBF/metabolism less than haloperidol, and that risperidone substitution for typical antipsychotics increased functional activity in the frontal cortex (Miller et al. 2001; Honey et al. 1999). Similarly, Vaiva et al. (2002) found that low dose (100 mg/day) amisulpride increased rCBF bilaterally in the frontal cortex, especially in dorso-lateral areas, after a four week treatment. However, Nygan et al. (2002) recently reported that a decrement of brain metabolism in the middle frontal cortex occurred even after the first dose of risperidone and still could be detected after six weeks of treatment.

The present study demonstrated that six weeks of fixed dose (10 mg/day) olanzapine treatment preserved the regional cortical perfusion pattern of schizophrenic patients even in the frontal cortex. One can speculate that olazapine's potent serotonin 5-HT_{2A} antagonism increases dopamine release in frontal regions, which nullifies the indirect effects of dopamine D_2 receptor blockade. This is also partially consistent with previous studies in which dopamine agonists have been shown to increase frontal rCBF and glucose metabolism (Kapur et al. 1994, Volkow et al. 1997). In the present study, as in previous studies (e. g., Tollefson and Sanger 1997), olanzapine was found to be effective in reducing negative symptoms of schizophrenia. Moreover, BPRS negative symptom scores were found to be negatively correlated with left superior frontal perfusion not only before the treatment but also after the treatment. This finding may be related to olanzapine's reported positive effect on frontal rCBF via blockade of serotonin 5-HT_{2A} receptors.

Although olanzapine and risperidone have similar serotonin 5-HT_{2A} receptor blockade ratios, risperidone causes a decrement of rCBF in the frontal cortex in most studies (Miller et al. 2001; Nygan et al. 2002). Moreover low doses of amisulpride without any effect on serotonin receptors has a positive effect on frontal rCBF. Thus, it is possible that other pharmacological properties of atypical antipsychotics (e. g., dopamine antagonism, antagonism of excitatory [glutamatergic] or inhibitory [GABAergic] circuitry) may influence blood flow (Moore et al. 1999). Atypical antipsychotics have different dopamine D_2 binding affinities. It has been shown that olanzapine and amisulpride have a lower potency for dopamine D_2 receptor compared to risperidone (Xiberas et al. 2001). One may speculate that the affinity to dopamine receptors might be one of the main modifiers of the rCBF in frontal cortex via direct and indirect mechanisms. Another explanation might involve olanzapine's ability to induce Fos protein (the protein product of immediate early gene c-fos) in the prefrontal cortex (Robertson and Fibiger 1996), an ability not shared by risperidone (Robertson et al. 1994).

A number of limitations of the present study should be mentioned. First and most important, the low resolution of our SPECT camera prevented assessment of the effects of olanzapine treatment on the basal ganglia. Second, the techniques we utilized give only a rough estimate of CBF. Although HMPAO uptake is roughly proportional to CBF, without blood sampling we were unable to convert tissue counts to measures of CBF, and thus do not have measures of absolute blood flow. We did not employ state-of-the-art techniques such as image overlay techniques combining anatomical and functional data. As the resolution of our single head gamma camera was relatively poor, it would have been misleading to apply high-resolution magnetic resonance anatomical localization to these functional images. Therefore, we were unable to determine precisely where the area of functional activity was localized in the brain. Third, we do not have a healthy control group with which to compare patients' data either before or after treatment. Finally, the olanzapine dosage used in this study might be lower than that used in recent clinical practice. However, during the planning of this study the results of clinical trials produced strong evidence that 10 mg/day of olanzapine was a therapeutic dose and adjustments in the dosages were not necessary for most patients (Nemeroff 1997).

In conclusion, our results showed that unlike typical antipsychotics, olanzapine has no negative effect on cortical perfusion patterns in schizophrenic patients. This finding might be the interpreted as olanzapine's preservation of the functional abilities of the cortical areas, especially frontal cortex. On the other hand, we still need better drugs to enhance the functional abilities of the frontal cortex of schizophrenic patients.

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