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The Effect of Clozapine on Caudate Nucleus Volume in Schizophrenic Patients Previously Treated with Typical Antipsychotics

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Typical antipsychotics have been reported to enlarge the caudate nucleus in schizophrenic patients. The atypical antipsychotic, clozapine, is associated with a decrease in caudate size in patients previously treated with typical antipsychotics. The present study investigates whether a change in caudate volume after switching from treatment with typical antipsychotics to treatment with clozapine is related to improvement in symptoms or tardive dyskinesia (TD). Twenty-six schizophrenic patients participated in this open study. Caudate nucleus volume and TD were assessed before discontinuing typical antipsychotics and after 24 weeks of treatment with clozapine. After discontinuing typical antipsychotics, symptoms were assessed in a 3 days drug-free period and subsequently once a month. Treatment with clozapine resulted in a decrease in caudate volume, improvement in symptoms and amelioration of TD. However, no difference in caudate volume changes was found between responders and non-responders to clozapine and no correlations were found between caudate volume changes and reduction of TD. In conclusion, this study replicates earlier findings that clozapine decreases caudate volume in patients previously treated with typical antipsychotics and suggests that this effect is unrelated to treatment response or to amelioration of TD. ***[Neuropsychopharmacology 24:47–54, 2001]***

KEY WORDS: *Schizophrenia; Caudate nucleus; Clozapine; MRI*

Morphological changes in brain structures are extensively reported in schizophrenia (for reviews see McKenna 1987; Reynolds 1983; Buchsbaum 1990; McCarley et al. 1999; Westmoreland Corson et al. 1999a). Among them, enlargement of the caudate nucleus, as part of the basal ganglia, has been described several times (Jernigan et al. 1991; Mion et al. 1991; Breier et al. 1992; Swayze et al. 1992; Buchanan et al. 1993; Chakos et al. 1994, 1995; Hokama et al. 1995; Keshavan et al. 1995; Ohnuma et al. 1997). Since decreased thalamic, hippocampal and superior temporal gyral volume have been associated with specific symptoms in schizophrenia (Barta et al. 1990; Bogerts et al. 1990, 1993; Friston et al. 1992: Shenton et al. 1992; Flaum et al. 1995) and the caudate nucleus receives neuronal projections from these regions (for reviews see Alexander and Crutcher 1990; Graybiel 1990), one could speculate that caudate volume may be related to certain aspects of patient functioning in schizophrenia as well. Indeed, the basal ganglia are involved in higher cognitive functions (Schneider 1984; Phillips and Carr 1987; Alexander et al. 1990; for reviews see Chevalier and Deniau 1990; Goldman-Rakic and Selemon 1990).

In Huntington or Parkinson disease patients, pathological changes of the caudate have been related to cognitive and behavioral disturbances as well as movement disorders, particularly tardive dyskinesia (TD)

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(Denny Brown and Yanagisawa 1976; Selemon and Goldman Rakic 1990; Graybiel 1990, 1997), phenomena that are also observed in some never medicated schizophrenic patients (Cassady et al. 1998; McCreadie and Ohaeri 1994; Fenton et al. 1994; Caligiuri and Lohr 1994; Lidsky 1997; Kraepelin 1919; for review see Busatto and Kerwin 1997).

Several neuroanatomical and physiological studies (Francis 1979; Serby and Goodgold 1986; Braff and Geyer 1990; Jernigan et al. 1991; Mion et al. 1991; Swayze et al. 1992; Heckers et al. 1991; Heckers 1997; Keshavan et al. 1998; Westmoreland Corson et al. 1999b) support the hypothesis that the striatum, including the caudate nucleus, is involved in the pathophysiology of schizophrenia and/or TD. Assuming that an increase of basal ganglia volume in schizophrenia can be directly or indirectly attributed to the disease process, this finding has been interpreted as a consequence of a delay in programmed synaptic elimination (Feinberg 1982; Jernigan et al. 1991; Swayze et al. 1992) or as a compensatory response to a decreased input from anterior temporal lobe, frontal, mesolimbic, or thalamic regions (Swayze et al. 1992; Stevens 1992).

Interestingly, the changes in brain morphology may not be solely attributable to the disease process. Data are accumulating linking morphological abnormalities in schizophrenia with treatment with antipsychotic medication. Indeed, typical and atypical antipsychotics may produce different effects on brain morphology. For instance, typical antipsychotic use increases the size of the caudate nucleus (Chakos et al. 1994; Keshavan et al. 1994), whereas clozapine, following typical antipsychotic use, is associated with a decrease in the volume of the caudate nucleus (Chakos et al. 1995; Frazier et al. 1996; Westmoreland Corson et al. 1999a).

The effect of typical antipsychotics on caudate volume may be the result of a dopamine D1 and dopamine D2 receptor blockade which causes activation, regeneration, and hypertrophy of striatal synaptic and/or cellular elements and increase of bloodflow in the basal ganglia (Muller and Seeman 1977; Benes et al. 1983; Klintzova et al. 1989; Meshul and Casey 1989; Stevens 1992; Miller et al. 1997). The decrease in caudate size after switching to clozapine could then be the consequence of its weaker binding to D1 and D2 receptors as compared to typical antipsychotics (Hyttel et al. 1985).

Changes in brain morphology after antipsychotic treatment suggest that some neuroanatomical abnormalities in schizophrenia are dynamic or may be reversible rather than static or irreversible. One could speculate whether the effect of clozapine on caudate size following typical antipsychotic treatment is related to the well-documented clinical effect of clozapine or its beneficial effect on TD (Juul Povlsen et al. 1985; Casey 1989; Kane et al. 1988; Meltzer et al. 1989; Miller et al. 1994; Lindenmayer et al. 1994; Spivak et al. 1997). Therefore, the present study attempts to replicate earlier studies on morphological changes in caudate volume after switching from typical antipsychotics to clozapine in a larger sample ($n = 26$) and investigates whether these changes are related to improvement of symptoms and amelioration of TD.

METHODS

Subjects

Twenty-six patients, treated in the University Medical Center in Utrecht, participated in this open design study (twenty-nine patients were included; one patient dropped out because of leucopenia and two patients discontinued because they needed other psychotropic medication). Eighteen male and eight female subjects with a mean age of 35.23 years (SD 10.34) and a mean duration of illness of 159.5 months (SD 114.1) were included in the study. All but two were right-handed. Upon entry into the study, patients were evaluated using the Comprehensive Assessment for Symptoms and History (CASH)-interview (Andreasen et al. 1992) and met DSM IV criteria for schizophrenia: paranoid type ($n = 20$), disorganised type ($n = 2$), undifferentiated type ($n = 2$), and residual type ($n = 2$).

Patients with organic brain disorder, alcohol or drug abuse according to DSM IV criteria, serious medical illness, or having been on depot medication within two months prior to the study were excluded from participation. All subjects were previously treated with at least one typical antipsychotic for a minimum of four weeks [mean duration of treatment 109.6 months (SD 102.0), mean life time dose chlorpromazine equivalent 527.02 mg per day (SD 365.69)] (see Table 1). They all had failed to show adequate responses to treatment with typical antipsychotics [clinical global impression scale (CGI) > 4] or had severe extrapyramidal side effects or TD prior to entry into the study.

The study has been approved by the ethics committee of the University Hospital and written informed consent was obtained from all subjects.

Assessment

Psychopathology, duration of illness, number and duration of previous hospitalizations, and prior medication history were assessed using the CASH interview and the CGI. Patients were withdrawn from their antipsychotic medication over a period of 2–7 days and remained free of antipsychotic medication for three days. Clozapine was then started at 25 mg/day and increased gradually by 25–50 mg/day to a minimum of 200 mg/day and a maximum dose of 600 mg/day. During the drug-free period patients were hospitalized [mean duration of hospitalization 8.35 weeks (SD 5.63)] and after

Table 1. Use of Typical Antipsychotics in Individual Patients

Patient number	Age	Sex	Typical antipsychotic use in months	Doseyears[a]
1	20	M	1.5	0.63
2	34	M	32	8.13
3	45	M	99	23.51
4	46	M	276	115.00
5	43	M	10	4.17
6	29	M	1	0.42
7	35	F	145[b]	51.96
8	36	M	68	9.92
9	21	M	34	7.08
10	28	F	22	8.71
11	47	F	129	51.06
12	32	F	48	10.00
13	55	F	276	94.30
14	26	M	12	5.00
15	39	F	181	54.30
16	29	M	102[b]	12.75
17	43	M	192	48.80
18	31	M	96	75.00
19	47	M	336[b]	280.00
20	19	M	12[b]	2.50
21	26	M	6[b]	4.68
22	26	F	132	51.70
23	23	M	16	4.87
24	53	M	300[b]	468.75
25	41	F	142[b]	59.17
26	42	M	180	150.00

[a]1 doseyear = 1 year antipsychotic use of 100 mg chlorpromazine equivalent/day (for methods see Schultz et al. 1995).
[b]Depot medication in history.

adjustment to clozapine they were treated as outpatients.

Patients were treated for six months in an open design, the dose being adjusted for optimal clinical improvement [mean dose of clozapine 345.57 mg per day (SD 63.44)]. Compliance was assessed by clozapine plasma levels measured once a month. Benzodiazepines up to a maximum daily dose of 20 mg diazepam equivalents and chloralhydrate up to 1500 mg/day were allowed throughout the study. Four patients used a daily dose of 2.5–20 mg diazepam equivalents during the first 2–6 weeks of treatment with clozapine. No other psychotropic medications were allowed.

Before discontinuing typical antipsychotics (baseline) and after 24 weeks of treatment with clozapine, neuroanatomical variables were assessed using Magnetic Resonance Imaging (MRI), and TD was rated using the Simpson scale (Simpson et al. 1979). Psychopathology was rated on the last drug-free day, bi-weekly for the first eight weeks of clozapine use, and subsequently once a month using the Positive and Negative Symptom Scale (PANSS) (Kay et al. 1987) and the CGI. The PANSS interview was performed by two raters who independently scored the items and afterwards achieved consensus.

Magnetic Resonance Images (MRI)

MRI were obtained on a whole body 1.5 Tesla Philips Gyroscan NT, using a standard proton head coil operating at 64 MHz. For analysis of the caudate nucleus a T1-weighted scan with 1.2 mm contiguous coronal slices (TE = 4.6 ms; TR = 30 ms; flip angle 30°; FOV = 256/80%) of the whole head was used.

The MRI data were processed on a Unix 9000 series workstation. All scans were blinded with respect to medication use (typical antipsychotic or clozapine) and any identifying characteristics, including side (in 50% of the scans the left-right axis were exchanged). Images were put into Talairach frame and corrected for scanner nonuniformity. The caudate nucleus was measured manually. The head and body of the caudate nuclei were identified and delineated slice by slice in an anterior-posterior direction using ANALYZE™ (Mayo Clinic, Rochester, MN).

Segmentation started in the first slice the caudate nucleus was clearly visible. Its medial border was the lateral ventricle. Laterally, it was limited by the internal capsule, excluding the interconnecting gray matter striae between caudate and putamen visible in the internal capsule (the pontes grisei caudatolenticulares). Posteriorly, the last slice in which the caudate nucleus was segmented was the slice before the one in which the posterior commisure was clearly visible. Its inferior border was defined as follows: anterior, by the white matter connecting the rostrus corporis callosi and the capsula externa, as visible in the coronal view below the caudate nucleus. Then, from the first slice, where the putamen is clearly visible until the slice anterior to the slice in which the anterior commissure crosses the midline, the nucleus accumbens was separated from the caudate by a line from the most inferior point of the lateral ventricle to the most inferior point of the internal capsule (adapted from Chakos et al. 1994).

The reliability of the measurements was determined by the intraclass correlation coefficient (ICC) based on 10 brains. The interrater reliability was 0.98 for the left caudate nucleus and 0.97 for the right caudate nucleus.

Data Analysis

Analysis of the caudate nucleus size and total brain volume was performed using repeated measures analysis of variance (ANOVA) with the factors 'side' (right and left), 'treatment' (status during last week of treatment with typical antipsychotics versus status after 24 weeks of treatment with clozapine), and 'group' (responders and nonresponders). Patients were divided into responders (n = 13) and nonresponders (n = 13) based on

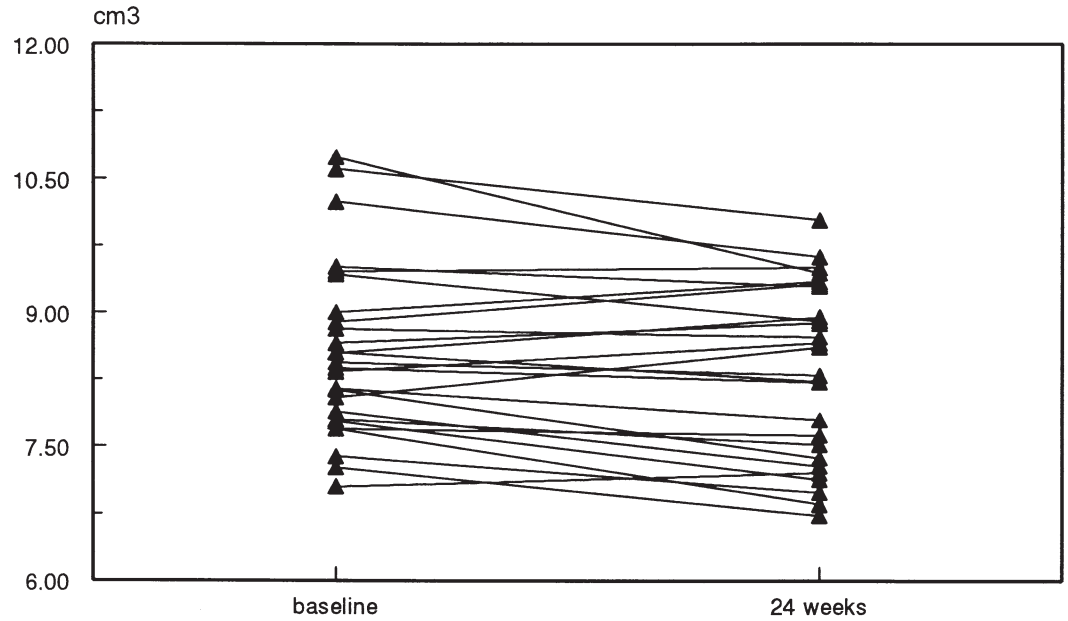

Figure 1. Individual changes in caudate nucleus volume after switching from typical antipsychotics (baseline) to clozapine (24 weeks).

a priori criteria of a total PANSS reduction of at least 20% from pre-clozapinetreatment scores.

ANOVA repeated measures analysis with the factor 'time' (seven levels; 0, 2, 4, 8, 12, 16, 20, and 24 weeks) was used to analyse treatment response as scored by the PANSS and CGI. A paired t-test was performed to analyse a change in the presence of TD. Pearson correlations were calculated to examine the relationship between caudate volume changes [Δcaudatus = (caudatus$_{24\ weeks}$ − caudatus$_{baseline}$)/caudatus$_{baseline}$ × 100%] following clozapine use and degree of psychiatric symptom improvement [ΔPANSS = (PANSS$_{24weeks}$ − PANSS$_{last\ drug\text{-}free\ day}$)/PANSS$_{last\ drug\text{-}free\ day}$ × 100%] and/or degree of TD amelioration [ΔTD = (TD$_{24\ weeks}$ − TD$_{baseline}$)/TD$_{baseline}$ × 100%.

RESULTS

Clozapine use was associated with a significant reduction in caudate volume (DF = 23; F = 5.3; $p < .05$; mean caudate volume at baseline: 8.49 ± 0.93 cm^3; after 24 weeks of clozapine treatment: 8.27 ± 0.97 cm^3). A treatment × side interaction was not observed (DF = 23; F = 0.16; $p = .7$). No differences in caudate volume were found between responders and nonresponders (treatment × group, DF = 23; F = 0.95; $p = .34$) (see Figure 1 for details on individual changes). No significant changes were found in total brain volume (DF = 22; F = 3.85; $p = .062$).

Patients significantly improved during treatment with clozapine as was demonstrated by lower scores on the PANSS and CGI over time (PANSS: DF = 8; F = 2.95; $p < .05$; CGI: DF = 8; F = 15; $p < .0001$) (see Figure 2). Likewise, the severity of TD was significantly reduced during clozapine treatment (t = 3.67; DF = 14; $p < .01$). However, no significant correlations were observed between caudate volume changes and improvement in total PANSS (r = 0.06; $p = .77$), positive symptoms (r = 0.26; $p = .22$), negative symptoms (r = −0.28; $p = .17$), CGI (r = 0.11; $p = .64$) or TD (r = −0.08; $p = .79$). Also, no significant correlations were found between caudate volume change and duration (r = 0.24; $p = .26$) or doses (r = −0.01; $p = .97$) of treatment with typical antipsychotics.

DISCUSSION

This study investigated whether a change in caudate volume, after switching from treatment with typical antipsychotics to clozapine, was related to improvement of symptoms and amelioration of TD in schizophrenia. Replacing typical antipsychotics with clozapine resulted in a significant decrease of caudate nucleus volume which was not significantly correlated with improvement of symptoms or amelioration of TD.

This open study replicated previous findings associating treatment with clozapine to caudate volume reduction (Chakos et al. 1995; Frazier et al. 1996; Westmoreland Corson et al. 1999a), symptom improvement (Juul

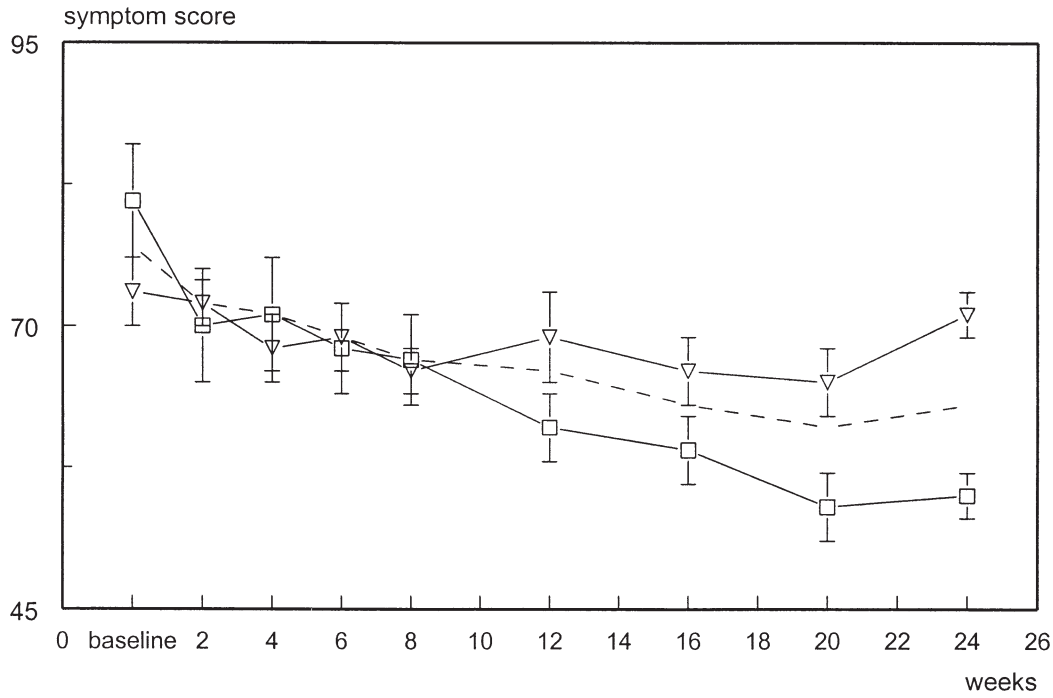

Figure 2. PANSS scores (± SD) during treatment with clozapine in all subjects (n = 26; —), responders (n = 13; □), and nonresponders (n = 13; ▽).

Povlsen et al. 1985; Meltzer et al. 1989; Miller et al. 1994; Lindenmayer et al. 1994; Kane et al. 1988), and TD amelioration (Casey 1989; Spivak et al. 1997). Whether the effect of clozapine on caudate nucleus volume is of clinical relevance was never investigated.

The basal ganglia play a part in higher cognitive functions (Schneider 1984; Phillips and Carr 1987; Alexander et al. 1990; for reviews see Chevalier and Deniau 1990; Goldman-Rakic and Selemon 1990). In previous studies, increased caudate volumes in schizophrenia were associated with poorer neuropsychological test performance on finger tapping and Hebb's Recurring Digits (Hokama et al. 1995) and cognitive impairment (Bilder et al. 1993). A trend was found for the caudate nucleus to be larger in schizophrenic patients with deficit symptoms (Buchanan et al. 1993). Mion et al. (1991) found significantly smaller volumes of caudate nuclei in schizophrenic patients with TD as compared to patients without TD and normal controls whereas in rats, increased striatal size was associated with high-vacuous chewing movement syndrome (Chakos et al. 1998). Since 'volume' is correlated with 'symptoms' one could speculate that 'volume-change' is correlated with 'symptom-change'. The fact that this study found no significant correlations between caudate volume change and clinical improvement suggests that volume changes in the caudate nucleus may rather be considered a non-specific trophic effect of antipsychotic treatment than a therapeutical effect. The effect of clozapine on caudate volume may then be explained by its pharmacological properties. Typical antipsychotics block D2 receptors that are highly concentrated in the striatum (Tune et al. 1993; Volkow et al. 1996; Kufferle et al. 1996) and chronic treatment with typical antipsychotics is reported to increase the dopamine D2 receptor density in this brain structure (Sedvall et al. 1995; Seeman 1987; Joyce et al. 1988).

Clozapine may exert its dopamine antagonistic effect predominantly through blockade of D3 and D4 receptors (for review see Kinon and Lieberman 1996). These receptors are only weakly expressed in basal ganglia but instead mainly found in the limbic system and cerebral cortex. It has been suggested that, since clozapine has a lower level of D2 antagonism in striatum, this could result in a downregulation of D2 receptors in these structures with subsequent dystrophic reduction of the striatal area (Lee et al. 1999).

It remains unclear whether the decrease in caudate volume is an effect of clozapine per se or it is related to prior treatment with typical neuroleptics. Two studies suggest that a reduction in caudate size through clozapine is probably due to the drug itself: clozapine was associated with a decrease of 4.5% in basal ganglia volume in four medication-naive schizophrenic patients (Gunduz et al. 1998) and a decrease of the striatum volume, without prior treatment with typical agents, in

rats (Lee et al. 1999). Unfortunately, extrapyramidal side effects were not assessed in this study which could be worth investigating in future research. Moreover, we investigated a treatment refractory sample of schizophrenic patients and thus results may be different in a more representative sample.

To conclude, this study replicates earlier findings that clozapine decreases the caudate volume in patients previously treated with typical antipsychotics and suggests that this effect is independent of treatment response.

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