Psychopharmacology (2001) 156:53–57
DOI 10.1007/s002130000679

ORIGINAL INVESTIGATION

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Higher occupancy of muscarinic receptors by olanzapine than risperidone in patients with schizophrenia

A [123I]-IDEX SPECT study

Received: 9 August 2000 / Accepted: 11 December 2000 / Published online: 8 May 2001
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Abstract *Rationale:* In vitro data have shown anticholinergic properties of the atypical antipsychotic drug olanzapine. Substantial occupancy of muscarinic receptors may be an explanation for the low incidence of extrapyramidal side effects induced by olanzapine. *Objectives:* To obtain an in vivo measurement of muscarinic receptor occupancy by olanzapine compared with risperidone in patients with schizophrenia stabilised on medication. *Methods:* Five patients with schizophrenia treated with olanzapine and five patients treated with risperidone were studied. Muscarinic receptor occupancy in the striatum and cortex was studied in vivo with SPECT using [123I]-IDEX as a radioligand. SPECT data were compared with those of six healthy subjects. *Results:* Patients stabilised on olanzapine showed significantly lower mean (±SD) striatal and cortical (1.50±0.21 and 1.51±0.22, respectively) muscarinic receptor binding ratios of [123I]-IDEX (reflecting higher levels of muscarinic receptor occupancy) than controls (3.91±0.61 and 3.65±0.70, respectively). Furthermore, [123I]-IDEX binding ratios in patients treated with risperidone were slightly lower than controls, reaching significance only in the striatum (2.99±0.27 versus 3.91±0.61, for risperidone and controls). *Conclusions:* The substantial occupancy of muscarinic receptors in the striatum and cortex by olanzapine may be an explanation for the low incidence and severity of extrapyramidal side effects of this antipsychotic drug. Furthermore, it may also explain the anticholinergic side effects of olanzapine.

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Keywords Muscarinic receptor · SPECT · [123I]-IDEX · Schizophrenia · Antipsychotic medication

Introduction

Antipsychotic medication is effective in decreasing psychotic symptoms of schizophrenia and in preventing psychotic relapse. However, antipsychotic medication, such as olanzapine or risperidone, also induces a variety of side effects. Moreover, side effects are a main reason to withdraw from medication after the acute psychotic phase. Furthermore, it has been shown that discontinuing treatment with antipsychotic drugs is the most important predictor of relapse (Robinson et al. 1999). Therefore, the aetiology of side effects of antipsychotic drugs is important to study.

High occupancy of dopamine D_2 receptors in the brain is thought to induce extrapyramidal symptoms. Recently, a Cochrane systematic review of 20 studies (Duggan et al. 2000) has shown a higher incidence and severity of extrapyramidal side effects in patients treated with risperidone than with olanzapine. Interestingly, positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies showed no difference in dopamine D_2 receptor occupancy between olanzapine and risperidone at therapeutic dosages (Dresel et al. 1999; Kapur et al. 1999; Lavalaye et al. 1999). This finding suggests that dopamine D_2 receptor occupancy may be necessary for inducing side effects, although this does not completely explain the pathophysiology of extrapyramidal side effects. However, neurotransmitter systems other than the dopaminergic system may also be involved in the occurrence of extrapyramidal side effects induced by antipsychotics.

In addition, in the Cochrane review (Duggan et al. 2000), anticholinergic symptoms such as dizziness and dry mouth were found to be more common in the olanzapine-treated group than in the risperidone group. This may be explained by a higher in vivo occupancy of muscarinic receptors by olanzapine than risperidone. This is supported by in vitro studies using rat striatum which

showed that olanzapine has a relatively high affinity for muscarinic receptors (K_i 26 nM), whereas risperidone has a low affinity (K_i >5000 nM; Schotte et al. 1996). Another in vitro study has shown that the affinity of olanzapine is relatively high for subtypes of the muscarinic receptor (K_i for the M_1, M_2, M_3 and M_4 receptors were 1.9 nM, 18 nM, 25 nM and 13 nM, respectively), comparable with clozapine. The receptor affinity of risperidone was low for these muscarinic receptor subtypes (inhibition of binding <50% at 10,000 nM concentration; Bymaster et al. 1996). A recent study also found a clear affinity of olanzapine for the muscarinic receptor (K_i ranging from 32 nM to 132 nM; Bymaster and Falcone 2000).

^{123}I-Dexetimide [(*S*)-(+)-3-phenyl-3-(4-piperidinyl)-2,6-piperidinedione ((*S*)-nordexetimide] ([^{123}I]-IDEX) is a high-affinity, non-selective muscarinic receptor antagonist which was developed and evaluated as a radioligand for imaging muscarinic receptors (Boundy et al. 1995) with SPECT (Müller-Gärtner et al. 1992). In order to determine whether higher in vivo occupancy of muscarinic receptors by olanzapine than risperidone account for higher occurrence of anticholinergic side effects in olanzapine-treated patients, the following study was designed. We used [^{123}I]-IDEX SPECT to determine the in vivo occupancy of the muscarinic receptor in patients with schizophrenia treated with olanzapine or risperidone. We hypothesised that the in vivo occupancy of muscarinic receptors by olanzapine is higher than the in vivo occupancy of muscarinic receptors by risperidone. In addition, we hypothesised that lower in vivo occupancy of muscarinic receptors is associated with lower anticholinergic side effects.

Materials and methods

Subjects

We studied ten young patients with schizophrenia according to DSM IV (for details see Table 1). All patients were admitted to the Adolescent Clinic of the Academic Medical Centre and were following a program for first episode schizophrenia. Five patients were treated with olanzapine, and five patients were treated with risperidone (Table 1). Patients were stabilised on a fixed dose for at least 4 weeks, and no concomitant medication was used, except for low-dose benzodiazepines that were withheld at the day of imaging. A group of six healthy subjects (Table 1) with no history of neurological or mental disorders was included to obtain control data. All patients and healthy controls gave their written informed consent to the research protocol, which was approved by the medical ethics committee of the Academic Medical Centre.

Clinical measurements

Psychotic symptoms were rated in all patients on the day of imaging by one of the investigators (J.L.). The structured clinical interview of the Positive and Negative Symptoms Scale of schizophrenia (PANSS; Kay et al. 1987) was used to rate psychotic symptoms. Akathisia was assessed with the Barnes akathisia rating scale (Barnes 1989). Cholinergic side effects were measured using the AMDP-5 rating scale (Association for Methodology and Documentation in Psychiatry 1981). The interviewer was blind to the results of SPECT imaging.

SPECT procedure

Subjects received potassium iodide orally to block thyroid uptake of free radioactive iodide the day before the injection and on the day of injection (total amount of approximately 230 mg). [^{123}I]-IDEX (specific activity of >200 MBq/nmol; radiochemical purity of >95%) was injected intravenously at an approximate dose of 185 MBq. ^{123}I labelling was performed by Amersham Cygne (Eindhoven, The Netherlands) with the precursor dexetimide obtained from Janssen Pharmaceuticals (Beerse, Belgium).

SPECT acquisition was performed at 8 h post-injection using a brain-dedicated camera (Strichman Medical Equipment Inc, Medfield, Mass.). This camera consisted of 12 individual crystals each equipped with a focussing collimator. The transaxial resolution was 7.6 mm full width at half maximum (FWHM) of a line source in air. Images were acquired in periods of 150 s from the orbitomeatal line to the vertex with an interslice distance of 5 mm. The energy window was set at 135–190 keV. Data acquisition took place in a 64×64 matrix. The measured concentration of radioactivity was expressed as Strichman Medical Units (SMUs; 1 SMU = 100 Bq/ml as specified by the Strichman Medical Equipment Inc).

Data analysis

[^{123}I]-IDEX binding was assessed in the total cortex, striatum, frontal, temporal and occipital cortices using a template with predefined regions of interest (ROIs) constructed according to a stereotactic atlas. ROIs were placed manually over two slices with the highest striatal and cortical [^{123}I]-IDEX binding and in a separate slice over the cerebellum.

At plateau (or pseudoequilibrium), it is assumed that striatal and cortical uptake represents total radioligand binding [(specific + non-specific binding) + free ligand]. Cerebellar activity provides a reference region for background activity (non-specific binding + free ligand). The cerebellum was used as a reference region for non-specific binding (Müller-Gärtner et al. 1992; Boundy et al. 1995) since the cerebellum is devoid of muscarinic receptors (Lin et al. 1986).

Occupancy of cortical and striatal muscarinic receptors by cold antipsychotic drugs decreases the amount of receptors available for specific binding to the radioligand, [^{123}I]-IDEX. The cortical/cerebellar ratio (or muscarinic binding index) is reduced in proportion to the degree of occupancy by the antipsychotic drugs. Thus, a high muscarinic binding implies low muscarinic receptor occupancy by the antipsychotic drug.

Statistical analysis

Differences between groups were analysed by analysis of variance (ANOVA) with a Tukey post-hoc test for multiple comparisons. A significance level of $P<0.05$ was considered significant. All statistical analyses were carried out with SPSS 9.0 for windows.

Table 1 Subject characteristics. Data are presented as mean (range)

	Controls (*n*=6)	Olanzapine (*n*=5)	Risperidone (*n*=5)
Age (years)	27.3 (22–36)	20.0 (18–22)	22.8 (19–27)
Sex (male/female)	4/2	4/1	5/0
Dose (mg)	–	15.0 (10–20)	4.0 (3–5)

Results

Patients treated with olanzapine exhibited [123I]-IDEX binding ratios that were, overall, significantly lower than in controls and than in patients treated with risperidone in all studied brain regions (Table 2; Fig. 1). Figure 2 shows a transversal [123I]-IDEX SPECT slice at the level of the striatum of a control subject, a patient treated with risperidone and a patient treated with olanzapine. As expected, total [123I]-IDEX binding in the cerebellum was low and not significantly different between groups (data not shown). Therefore, the cerebellum was considered as a region of non-specific binding, and all regions were divided by cerebellum values to obtain [123I]-IDEX binding ratios. Surprisingly, patients treated with risperidone had significantly lower [123I]-IDEX binding ratios in the striatum than controls (t=3.09, df=9, P<0. 05). The [123I]-IDEX binding ratios in the total, frontal, temporal and occipital cortices were lower in the risperidone group than in controls. However, these differences were not statistically significant (Table 2). Due to the small group size and small variation in medication dose, correlations between antipsychotic dose and [123I]-IDEX binding ratios were thought not to be reliable.

Side effects and psychotic symptoms

No correlations between side effects and [123I]-IDEX binding ratios were found. Akathisia was absent or questionable in all studied patients. Hypersalivation (mild) was scored in one patient with olanzapine and one with risperidone, dry mouth (mild) in one patient with olanzapine. In one patient on olanzapine and in one on risperidone, nausea (mild) was scored. In one patient on risperidone vomiting (mild) was reported. Altogether, two patients with olanzapine and one with risperidone reported mild gastrointestinal disturbances.

No correlation was found between psychotic symptoms and [123I]-IDEX binding ratios. Psychotic symptoms were absent to mild in all patients, mean total PANSS positive scores were 11.8 in the olanzapine group versus 14.6 in the risperidone group. Mean PANSS negative scores were 14.6 in the olanzapine group versus 16.6 in the risperidone group. Mean PANSS general psychopathology scores were 25.0 in the olanzapine group versus 35.4 in the risperidone group.

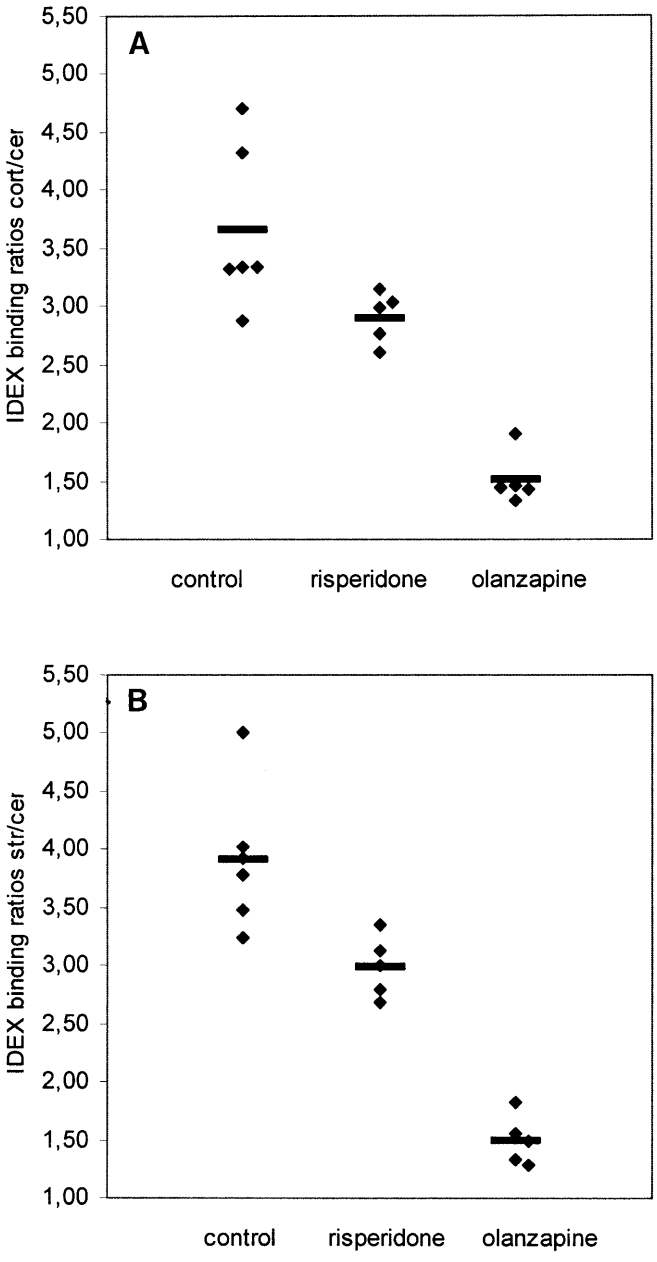

Fig. 1 [123I]-IDEX binding ratios of total cortex (**A**) and striatum (**B**) divided by cerebellum in controls and patients treated with risperidone or olanzapine

Table 2 [123I]-IDEX binding ratios in patients treated with olanzapine and risperidone and in controls. Data are binding ratios of region/cerebellum, presented as mean values (SD)

	Cortex	Striatum	Frontal	Temporal	Occipital
Controls	3.65 (0.70)	3.91 (0.61)	3.51 (1.18)	3.01 (0.30)	3.37 (0.79)
Olanzapine	1.51 (0.22)*	1.50 (0.21)*	1.49 (0.21)*	1.47 (0.13)*	1.34 (0.13)*
Risperidone	2.90 (0.21)**	2.99 (0.27)* **	2.80 (0.30)**	2.59 (0.37)**	2.73 (0.32)**

*Significantly different from controls, P<0.01
**Significantly different from olanzapine, P<0.001

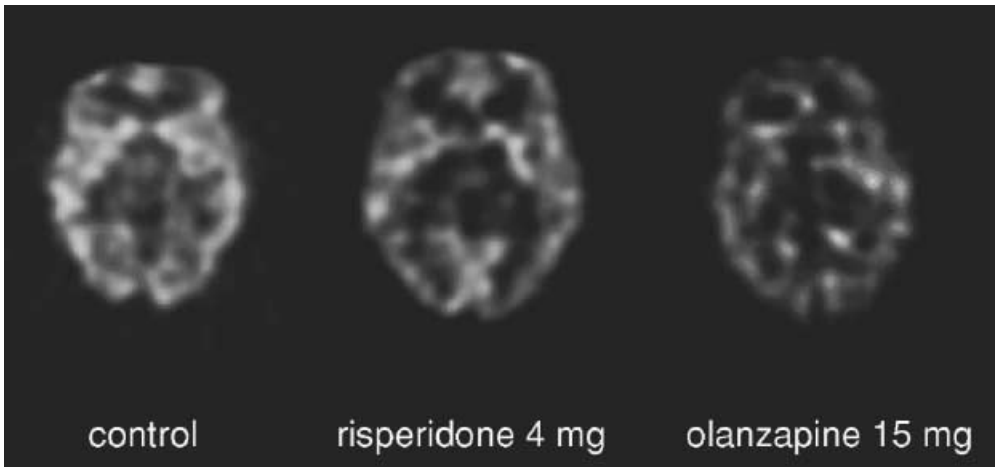

Fig. 2 [123I]-IDEX SPECT transversal slices at the level of the striatum of one patient treated with olanzapine 15 mg, one with risperidone 4 mg and a control subject. [123I]-IDEX binding in the striatum and cortex of the patient with olanzapine is lower than in the control, reflecting a substantial level of muscarinic receptor occupancy

Discussion

This study is the first in vivo comparison of the muscarinic receptor occupancy in patients with schizophrenia treated with the atypical antipsychotics olanzapine and risperidone. Olanzapine, in contrast to risperidone, was found to induce a substantial in vivo occupancy of muscarinic receptors in the brain. This finding is in line with in vitro studies (Schotte et al. 1996). A recent SPECT study also reported a significant occupancy of muscarinic receptors by olanzapine at doses of 5 mg and 20 mg, using [123I]-QNB as a radioligand (Raedler et al. 2000). Even at the low dose, there was a marked reduction of [123I]-QNB binding, suggesting that olanzapine is a potent antagonist of muscarinic receptors.

The presently observed very low [123I]-IDEX binding ratios in patients treated with olanzapine compared with controls suggests a high in vivo occupancy of muscarinic receptors by olanzapine. A high occupancy of these receptors would, however, likely induce cholinergic side effects. In contrast to this, and in agreement with the results of other studies, we did not find a high incidence of cholinergic side effects in our patient sample. Interestingly, a recent study using intact clonal cells in a physiological medium (Bymaster and Falcone 2000) showed that the affinity of olanzapine for the muscarinic receptor is not as high as shown previously (Bymaster et al. 1996; Schotte et al. 1996). Thus, both from a clinical point of view and from the results reported by Bymaster and Falcone (2000), it may be a reasonable suggestion that the occupancy of the muscarinic receptor by olanzapine is not very high. This suggestion, however, is not in line with our present data. However, one has to keep in mind that it is still not clear at which occupancy of the muscarinic receptor cholinergic side effects occur. Moreover, further imaging studies are needed to examine the exact relationship between in vitro affinity of muscarinic receptor and in vivo [123I]-IDEX binding ratios. Finally, since SPECT imaging cannot produce absolute quantitative measurements, we cannot exclude completely that our binding ratios overestimate muscarinic receptor occupancy. Nevertheless, our data at least suggest substantial occupancy of muscarinic receptor by olanzapine.

The higher occupancy of muscarinic receptors by olanzapine than risperidone might be an intriguing explanation for the lower incidence of extrapyramidal side effects by olanzapine than risperidone, even at high doses and high dopamine D_2 receptor occupancy. The anticholinergic property of olanzapine may be described as an intrinsic anticholinergic compound.

The finding of a significantly lower [123I]-IDEX binding in the striatum in patients with risperidone than in controls was unexpected, as in vitro studies showed that risperidone had a low affinity for muscarinic receptors in the striatum (Bymaster et al. 1996; Schotte et al. 1996). This slightly lower [123I]-IDEX binding in patients with risperidone could reflect low occupancy of muscarinic receptors. However, as expected, the occupancy of muscarinic receptors by risperidone was significantly lower than that by olanzapine.

Another explanation for the lower [123I]-IDEX binding is that muscarinic receptor density in patients with schizophrenia may be lower than in controls. This was also suggested in a recent SPECT study (Raedler et al. 2000) and was a finding of recent post-mortem studies (Crook et al. 1999, 2000). Therefore, schizophrenia per se may also explain the lower [123I]-IDEX binding in patients with risperidone than in healthy controls. The cholinergic aspects of schizophrenia are an interesting field, with studies suggesting an increased muscarinic cholinergic activity in schizophrenia, and the various anticholinergic aspects of antipsychotic drugs (Tandon 1999). For instance, an agonist effect of both clozapine and olanzapine on the muscarinic M_4 receptor has been described (Zeng et al. 1997), which may also be a relevant mechanism for the therapeutic efficacy and side effects of these antipsychotic drugs. Nevertheless, more work will be needed to achieve a complete understanding of the relationship between schizophrenia and muscarinic receptor binding availability, and the anticholinergic properties of antipsychotics.

A limitation of the present study is that patients treated with antipsychotics were compared with healthy vol-

unteers instead of with antipsychotic-free patients with schizophrenia. However, due to practical reasons, it was not feasible to include a large enough number of antipsychotic-free patients. Nevertheless, definite conclusions both on the occupancy of muscarinic receptors by antipsychotics and on possible differences in density of the muscarinic receptor between schizophrenic patients and controls can only be drawn after the inclusion of antipsychotic-naive patients. Future studies with a wide dosing range of antipsychotic medication and antipsychotic-free patients (to make a better estimation of occupancy of muscarinic receptors) should be performed to clarify the effect of the antipsychotic dose on the occupancy of the muscarinic receptor.

Patients with olanzapine or risperidone in our study experienced only mild anticholinergic and extrapyramidal side effects of medication. Therefore, it was not possible to determine a correlation between side effects and [^{123}I]-IDEX binding. It would be of interest to determine [^{123}I]-IDEX binding in patients with severe anticholinergic side effects to determine whether this is related to the degree of occupancy of muscarinic receptors. Moreover, psychotic effects might have an influence on either muscarinic receptor density or [^{123}I]-IDEX binding. Nevertheless, in this study we found no correlation between [^{123}I]-IDEX binding ratios and psychotic symptoms.

In conclusion, in this study we showed that the in vivo occupancy of muscarinic receptors is higher in olanzapine-treated patients than in risperidone-treated patients with schizophrenia. This finding might be an explanation for the lower incidence of extrapyramidal side effects by olanzapine than risperidone.

Acknowledgements This study was partly funded by grant no. 28-1241,2 from the Dutch Health and Development Council (ZON). We thank Amersham Cygne for their generous supply of the radioligand, Janssen Pharmaceuticals for donation of the precursor dexetimide and patients, staff and nurses, without whose efforts this study would not have been feasible.

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