THE INFLUENCE OF ANTIPSYCHOTICS ON NEUROLOGICAL SOFT SIGNS AND DYSKINESIA IN FIRST EPISODE PSYCHOSIS.

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Chapter 4

ABSTRACT

First episode psychosis patients on atypical antipsychotics had significantly less dyskinesia signs compared to patients on classical antipsychotics, but no differences regarding the total number of neurological soft signs (NSS). This suggests that antipsychotics do not influence NSS, but it associates atypical antipsychotics with less dyskinesia in the early stages of treatment.

INTRODUCTION

The influence of antipsychotics on neurological soft signs (NSS) in first episode psychosis is still subject to debate (Dazzan and Murray 2002). Particularly the relationship between dyskinesia, extra pyramidal signs (EPS) and NSS. The outcome of any study into the influence of antipsychotics on NSS will to a great extent be determined by the ability of the assessment of NSS to distinguish NSS from EPS and dyskinesia. In addition they should focus on categories of signs in order to enable the discovery of an association between medication and a particular category of NSS. Differences in NSS between patients on atypical and classical antipsychotics could give more insight in the background of evidence (Keefe et al., 1999) suggesting a different profile of atypical antipsychotics, not only regarding EPS and dyskinesia, but also regarding cognitive functions.

METHODS

We examined all admitted patients with a first psychotic episode with a comprehensive standardised neurological examination: the Cambridge Neurological Investigation (CNI) (Chen et al. 1995). The CNI includes EPS and dyskinesia signs. The dyskinesia category consists of nine signs and includes all simple, complex and dyskinetic abnormal involuntary movements in the face trunk and limbs. The EPS category includes increased tone in limbs, decreased associated movements in walking, shuffling gait, arm dropping, tremor and rigidity in the neck. After complete description of the study to the patients, written informed consent was obtained. Patients with a minimum of four weeks on stable medication with no prior medication history and with a diagnosis within the schizophrenia spectrum according to DSM IV were included in this study. Medication dosages were calculated in haloperidol equivalents (Leysen et al. 1998). We compared patients using classical antipsychotics to patients using atypical antipsychotics on ten categories of NSS. We used Mann-Whitney test to compare the groups and corrected for multiple comparison by means of the Bonferroni procedure.

42 patients used atypical antipsychotics (21 risperidone, 18 olanzapine, 1 sertindole, 2 quetiapine). The mean age was 26.3 years (SD 5.9); 67 percent were male; the mean antipsychotic dose in haloperidol equivalents was 4.8 mg (SD 2.0). The mean dose of olanzapine and risperidone in this study was 16.5 mg (SD 22.4) and 2.6 mg (SD 1.1) respectively. The mean duration of antipsychotic treatment was 14 weeks (SD 17.4). 20 patients used classical antipsychotics (4 haloperidol, 10 pimozide, 4 zuclopentixol, 1 flupentixol, 1 fluphenazine). The mean age was 29.2 years (SD 5.9); 70 percent were male; the mean dose in haloperidol equi-
Influence of antipsychotics

valents was 4.8 mg (SD 3.7). The mean duration of antipsychotic treatment was 22 weeks (SD 25.0). In the atypical antipsychotics group, 5 patients (12%) used co-medication (1 on anticholinergics, 3 on benzodiazepines, and 4 on a SSRI). In the classical antipsychotics group 2 patients (10%) used co-medication (1 on anticholinergics and a benzodiazepine, 1 on a tricyclic antidepressant). In the atypical antipsychotics group 21 patients suffered from schizophrenia, 9 patients from schizophreniform disorder, 8 patients from schizo-affective disorder, 1 patient from delusional disorder, 1 patient from brief psychotic disorder and 2 patients from psychosis NOS. In the classical antipsychotics group 11 patients suffered from schizophrenia; 2 patients suffered from schizophreniform disorder, 4 patients from schizo-affective disorder, 2 patient from brief psychotic disorder and 1 patient from psychosis NOS.

All raters received video instruction and 5 training sessions and were blind to any hypothesis. The interrater reliability across the three raters was assessed in a random sample of 40 cases. The intraclass correlations (ICC) were good; for dyskinesia 0.84, EPS 0.85 and for the total score 0.83. Sex, age and antipsychotics dosage in haloperidol equivalents did not significantly differ between groups.

RESULTS

Table 1 presents the data for NSS for both medication groups. We found significant differences between groups for dyskinesia but not for the overall NSS score.

**Table 1: Mean symptom score and test statistics on ten categories of NSS after correction for multiple comparisons.**

<table>
<thead>
<tr>
<th>Category of NSS</th>
<th>Atypical antipsychotics Mean score (range) (N= 42)</th>
<th>Classical antipsychotics Mean score (range) (N=20)</th>
<th>Mann-Whitney U-test (2-tailed) Z –score p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyskinesia</td>
<td>0.00 (0-0.0)</td>
<td>0.56 (0-5.0)</td>
<td>3.35 0.01*</td>
</tr>
<tr>
<td>Sensory Integration</td>
<td>2.92 (0-9.0)</td>
<td>1.65 (0-6.0)</td>
<td>2.04 NS</td>
</tr>
<tr>
<td>Hard signs</td>
<td>1.00 (0-8.0)</td>
<td>0.35 (0-4.0)</td>
<td>1.27 NS</td>
</tr>
<tr>
<td>Primitive Reflexes</td>
<td>0.00 (0-1.0)</td>
<td>0.10 (0-1.0)</td>
<td>0.45 NS</td>
</tr>
<tr>
<td>EPS</td>
<td>0.85 (0-7.5)</td>
<td>0.77 (0-4.5)</td>
<td>0.31 NS</td>
</tr>
<tr>
<td>Motor coordination</td>
<td>2.55 (0-12.0)</td>
<td>1.78 (0-7.0)</td>
<td>0.21 NS</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>1.54 (0-6.0)</td>
<td>1.68 (0-6.5)</td>
<td>0.12 NS</td>
</tr>
<tr>
<td>Suppression Failure</td>
<td>0.90 (0-5.0)</td>
<td>0.72 (0-3.0)</td>
<td>0.07 NS</td>
</tr>
<tr>
<td>Catatonia</td>
<td>0.37 (0-3.5)</td>
<td>0.21 (0-2.0)</td>
<td>0.05 NS</td>
</tr>
<tr>
<td>All signs</td>
<td>10.19 (0-33.0)</td>
<td>7.80 (0-22.0)</td>
<td>0.27 NS</td>
</tr>
</tbody>
</table>

* Significant p<0.05

We found a significant difference in the treatment duration between groups (Mann-Whitney Z= 2.5 p=0.014). Therefore we compared the two groups on the dyskinesia score by means of a univariate analysis of variance with the treatment duration as a co-variate. In the corrected model, the differences regarding dyskinesia remained significant (F=4.2, p= 0.02). To
investigate whether the CNI distinguished NSS from dyskinesia we calculated the correlations between the scores on the NSS categories. There was no correlation between dyskinesia and the total NSS score nor with any specific category of NSS.

**DISCUSSION**

Our study concurs with evidence that antipsychotics do not influence the number of NSS. Moreover it also suggests that atypical antipsychotics are associated with less dyskinesia, even after an average treatment period of 17 weeks and an average age of 27 years. This may indicate that differences in dyskinesia are apparent, shortly after the onset of treatment for a psychotic disorder.

In the absence of a baseline assessment, we cannot exclude the possibility that the groups differed in the severity of movement disorders at baseline. However the apparent low scores on dyskinesia suggests that any dyskinetic signs present were subtle and probably have not influenced treatment selection. Moreover, if there was a systematic effect of pre-existing movement disorder on choice of medication, it would be expected that the prescribing clinician would have selected an atypical antipsychotic for patients with pre-existing movement disorder. Other possible confounders (age, medication dose) did not differ significantly between groups. The influence of co-medication is limited because the majority of patients (89%) did not use co-medication and only one patient in each group used anticholinergics. Although the raters were not blind to the medication, the good interrater reliability reduces the likelihood of assessment bias. The ability of the CNI to distinguish between dyskinesia and NSS was confirmed by the absence of a correlation between the dyskinesia score and any of the specific NSS categories or total NSS score. The low scores on dyskinesia are likely to be related to the short duration of treatment and predominant male sex in our subjects. But above all by the limited sensitivity of the CNI to dyskinesia compared to assessments used in other studies.

Despite its limitations our study suggests a favourable effect of atypical antipsychotics on the level of dyskinesia compared to classical antipsychotics, shortly after the onset of treatment. This would be particularly interesting considering evidence regarding the association of dyskinesia with cognitive impairment in schizophrenia (Pantelis et al. 2001) and evidence that atypical antipsychotics improve cognitive function (Keefe et al. 1999). Therefore further research into the relationship between antipsychotics, dyskinesia and cognition seems warranted.

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REFERENCES


