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SYMPOSIUM

Extrapyramidal Symptoms during Long-Term Treatment with Antipsychotics

Special Focus on Clozapine and D_1 and D_2 Dopamine Antagonists

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In schizophrenic patients in maintenance treatment, clozapine, compared to classic neuroleptics, induces relatively few extrapyramidal syndromes (EPS), especially less akathisia and tremor and usually no dystonia or rigidity. In patients with dyskinetic movements (acute or tardive) induced by other neuroleptics, clozapine may reduce or even remove dyskinesia or permit it to disappear. It cannot, however, be excluded that clozapine can induce dyskinesia in extremely rare cases, but it seems more likely that this is due to previous treatment with classic neuroleptics. The earlier clozapine is started, the less chance of development of dyskinesia.

The low level of EPS with clozapine may be linked to the special receptor-binding profile of this drug: during treatment with therapeutic doses of clozapine, the level of D_2 receptor blockade is too low (40% to 50% occupancy by positron emission tomography) to induce EPS, and the D_1 receptor blockade (also 40% to 50% occupancy) has a lower EPS potential than D_2 blockade. This binding profile may at the same time contribute to the special antipsychotic properties of clozapine. Other receptor affinities may contribute to the beneficial effect of clozapine in EPS and schizophrenia. ***[Neuropsychopharmacology 14:35S–39S, 1996]***

KEY WORDS: *Clozapine; Dopamine receptors; EPS; Parkinsonism; Tardive dyskinesia*

Neuroleptic-induced extrapyramidal syndromes (EPS) can be divided into four main categories: akathisia, dystonia, dyskinesia, and parkinsonism. These are the classic EPS, which can be related to neuroleptic treatment and seen during and/or following treatment. These syndromes may also occur spontaneously, independent of neuroleptic treatment, due to high age and/or disease. The syndromes are all well known and thoroughly described in the literature (for reviews, see Casey 1991; Barnes and Edwards 1993), and several rating scales are available for their evaluation (Kane et al. 1992; Gerlach et al. 1993).

Extrapyramidal syndromes can be distressing and disabling and are a major cause of poor compliance with treatment, which in turn has implications for relapse, hospitalization, and morbidity. They cause suffering for both patients and relatives and limit possibilities for development and activities. At times they may counteract the therapeutic effect of neuroleptics and deter social integration. Finally, EPS entail the risk of becoming irreversible and thereby a concrete expression of neuroleptics' ability to produce permanent brain damage.

With this background it is important to try to understand the pathophysiologic mechanisms underlying these EPS and to limit their development as far as possible.

Clozapine[1] causes fewer EPS than traditional neuro-

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[1]Clozapine is available under the trade names Clozaril and Leponex.

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leptics. Whereas EPS may be seen in at least 75% of patients treated with traditional neuroleptics, they have been found to be relatively rare in clozapine-treated patients (about 5%) (Casey 1989; Fitton and Heel 1990). However, the prevalence is still not clear, and especially the EPS profile during long-term maintenance treatment with clozapine has been insufficiently evaluated.

The purpose of this study is to briefly discuss: (1) EPS in chronic schizophrenic patients during long-term antipsychotic treatment with clozapine versus traditional neuroleptics, and (2) based on studies in nonhuman primates, the possibility of reducing the risk of EPS by means of D_1 antagonists and combined D_1 and D_2 receptor antagonists.

EPS DURING MAINTENANCE TREATMENT WITH CLOZAPINE VERSUS TRADITIONAL NEUROLEPTICS

In a retrospective-prospective study (Peacock et al. 1996), 100 chronic schizophrenic patients on clozapine and 100 patients on classic neuroleptics (flupenthixol, perphenazine, and zuclopenthixol, the three most frequently used classic neuroleptics in Denmark) were examined for EPS and other side-effects (only the EPS data are discussed here). The indications for using clozapine were: therapeutic resistance 47 patients; EPS vulnerability 11; both 42.

The two groups had received their present neuroleptic for similar periods of time: clozapine patients for a median of 5 years (range 0.3 to 19) and control patients for 5 years (0.3 to 24). However, the clozapine patients had previously received traditional neuroleptics for 9 years (0.5 to 31). The total length of neuroleptic treatment was similar for the two groups.

The median daily dose of clozapine was 400 mg (100 to 1200) versus 9 mg (flupenthixol), 24 mg (perphenazine), and 20 mg (zuclopenthixol) for the control group (corresponding to haloperidol 8 to 10 mg). Concomitant medication included benzodiazepines (clozapine patients 33% versus controls 26%), anticholinergics (6% versus 63%) and antidepressants (16% versus 3%).

The EPS were evaluated blind (by means of a video) with the St. Hans Rating Scale for extrapyramidal syndromes (Gerlach et al. 1993).

Clozapine treated patients showed less parkinsonian signs than control patients. A total of 33 out of 100 clozapine-treated patients (33%) showed some signs of parkinsonism as compared to 61% of the control group (in spite of anticholinergics in 63% of the control patients). In both cases, bradykinesia was the predominant feature, as is common in neuroleptic-treated patients. In the case of clozapine, however, it can be discussed whether the bradykinesia/slow movements are due to a true parkinsonism, as the patients often are hypotonic and do not otherwise show typical parkinsonian features. Tremor was seen in 3% of clozapine-treated patients versus 11% of control patients, and rigidity in 0% versus 19%.

No acute dystonia was seen in any of the groups, but 13 of the control patients reported recent dystonic symptoms versus 0 in the clozapine-treated group. Furthermore, 10 control patients displayed splaying of one or more fingers in fixed positions (probably a localized, mild form of dystonia) compared to one in the clozapine group. Only one case of dystonia-dyskinesia has been reported in the literature (Thomas et al. 1993).

Fourteen percent of the clozapine treated patients and 40% of the controls had subjective akathisia ($p < .001$), whereas 7% of clozapine treated patients and 29% of the controls were found to have objective akathisia ($p < .001$).

As can be seen from Figure 1, 33 patients had dyskinesia before clozapine (evaluated from the charts). This number decreased to 15 patients during the median 5-year clozapine treatment period (evaluated blind from video). The corresponding figures for the control group were 19 and 16, an apparently lower reduction ($p < .07$).

Fourteen clozapine-treated patients whose charts did not contain information about previous dyskinesia showed dyskinesia at the time of evaluation versus 41 in the control group ($p < .001$). In these cases, the present drug may have induced the syndrome, but the syndrome may also have been present in a latent form at the start of the treatment or not mentioned in the charts. Under all circumstances, these observations suggest that clozapine permits dyskinesia to disappear to a higher degree than classic neuroleptics, and it especially induces fewer new cases.

In conclusion, this study strongly indicates that clozapine has a lower potential to induce both acute and tardive EPS.

D_1 AND D_2 RECEPTOR MECHANISMS IN THE DEVELOPMENT OF EPS

Studies from different nonhuman primate centers indicate that, although D_1 antagonists can produce EPS, these are more benign than those induced by D_2 antagonists. The following observations from studies in Cebus monkeys must be emphasized:

1. D_1 antagonists produce dystonia when given in low single doses to animals pretreated with D_2 antagonists (Kistrup and Gerlach 1987; Peacock et al. 1990) and when given in high single doses to drug-naive animals (Casey 1992).
2. However, tolerance to dystonia is seen during prolonged treatment, implying that no dystonia is seen

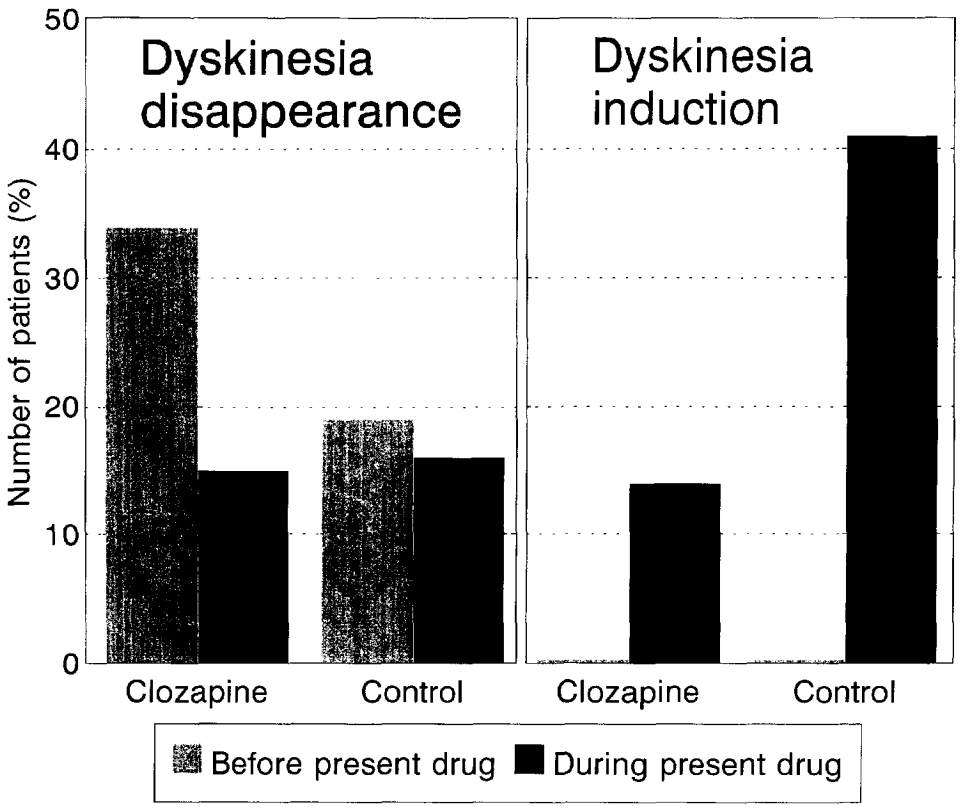

Figure 1. Dyskinesia disappearance and potential induction during long-term treatment (median 5 years) with clozapine ($N = 100$) versus classic neuroleptics ($N = 100$). The clozapine patients had previously been treated with classical neuroleptics for median 9 years. Difference with respect to disappearance: $p < .07$; with respect to potential induction: $p < .001$.

when the same dystonia-inducing dose is continued daily for a few days (Coffin et al. 1989; Lublin et al. 1993; Casey in press) or when gradually increasing doses are given to drug-naive (Gerlach and Hansen 1993) or to D_2-sensitized monkeys (Lublin et al. 1993).

3. Only mild acute dyskinesia and apparently no tardive dyskinesia are seen during and after long-term administration of D_1 antagonists in high and low doses to both drug-naive and drug-sensitized monkeys (Gerlach and Hansen 1993; Lublin et al. 1994a).
4. Bradykinesia (parkinsonism) can be induced during treatment with D_1 and D_2 antagonists (Gerlach and Hansen 1993; Lublin et al. 1994a), but some tolerance may develop with low to moderate doses of D_1 antagonists (Casey 1995).
5. D_1 antagonists counteract amphetamine-induced increased arousal and social isolation (Ellenbroek et al. 1989; Lublin et al. 1994b).
6. D_1 agonists, however, elicit two interesting syndromes: (1) an atypical grooming syndrome consisting of a stereotyped, purposeless behavior where the animal plucks its fur continually in a single spot on its body (e.g., on the hand) without interesting itself in the environment (may be a model of autism and other negative symptoms in schizophrenia); and (2) oral dyskinesia, that is, repetitive chewing movements and/or tongue protrusions, very similar to and a potential model of tardive dyskinesia (Peacock et al. 1990; Lublin et al. 1992; Gerlach and Hansen 1993).

All in all, these observations indicate that chronic treatment with D_1 antagonists, in humans and nonhuman primates, may induce tolerance, especially to dystonia, but also, to a degree, to dyskinesia and maybe bradykinesia. Furthermore, diverse pharmacological tests, predictive of antipsychotic efficacy, in both rodents and nonhuman primates, indicate that D_1 antagonists possess an antipsychotic effect. Furthermore, the results from the Cebus monkeys (points 5 and 6) indicate an especially beneficial effect on introvertedness and autism.

D_1 ANTAGONISTS IN TREATMENT OF SCHIZOPHRENIA

With this background, D_1 receptor antagonists are an interesting group of new potential antipsychotics. The question is whether they will have a sufficient antipsychotic effect on the positive symptoms in schizophrenia,

on hallucinations, paranoid ideas, and thought disorders. Studies with SCH 39166 have not been encouraging in this regard. Thus, three open studies (Beaupaire et al. 1995; Den Boer et al. 1995; Karlsson et al. 1995) have not been able to prove any beneficial effect on positive symptoms in schizophrenic patients, not even the usual placebo effect, of SCH 39166 in doses up to 600 mg/day (which should result in an almost total blockade of D_1 receptors in the brain). A significant decrease in negative symptoms was found in one of these studies (Den Boer et al. 1995). In an open study in a few patients with another D_1 antagonist, NNC 01-0687, in doses up to 100 mg TID for 5 weeks, mild beneficial effects were found in both positive and negative symptoms (Karle et al. 1995), especially in regards to thought disturbances and hallucinations.

Only very few side-effects were seen in these studies. Slight sedation or akathisia were found in a few cases. No dystonia or dyskinesia, but mild bradykinesia, were seen in single cases. There was no prolactin increase; on the contrary, one study found decreased prolactin levels (Karlsson et al. 1995).

Although not proven, these negative findings with D_1 antagonists on positive symptoms of schizophrenia may be explained by the same tolerance seen with EPS in the nonhuman primates (see preceding section). However, more clinical studies are needed to clarify the therapeutic potential of D_1 antagonists. Will it be possible to use the potential activating effect in the treatment of the deficit syndrome, depression, and dysphoria related to schizophrenia? Can D_1 antagonists be positive adjuncts to D_2 antagonist therapy or lead to the use of a lesser D_2 receptor blockade (and fewer EPS)? Do we need a particular relationship between the D2 and the D_1 receptor blockade, as has been suggested in the case of D_2 and 5-HT_2 receptor blockade (Meltzer 1991)? Clues may be found in clozapine's dopamine receptor affinities. On the other hand, clozapine has so many other biochemical effects that it is not possible to make any definite conclusions about the impact of D_1–D_2 receptor antagonism on this preparation's unique therapeutic characteristics. Other interesting therapeutic potentials of D_1 antagonists are the treatment of involuntary movements, such as tardive dyskinesia and L-Dopa–induced dyskinesias in Parkinson patients.

CONCLUSION

Long-term experience with clozapine has shown that the agent has an EPS profile that is distinct in many ways from that of classic neuroleptics. It can produce parkinsonianlike bradykinesia and mild akathisia, but no rigidity and rarely tremor. Clozapine may allow tardive dyskinesia to diminish or disappear. The beneficial effect of clozapine in EPS may relate to the low level of both D_1 and D_2 receptor occupancy (40% to 50%). On the other hand, it is not possible to draw conclusions about clozapine's unique antipsychotic effect, as D_1 antagonists, given alone, have not elicited any significant antipsychotic effect. Clozapine's binding to other known and unknown receptors may provide the explanation.

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