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Parkinsonism by Haloperidol and Piribedil

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Abstract. Three groups of schizophrenic patients were treated with haloperidol, with a low dose of piribedil (a dopamine agonist), and with a combination of the two treatments, respectively. After a few days, all 7 patients treated with the drug combination showed marked rigidity and akinesia, while patients treated with haloperidol alone (4) and piribedil alone (4) showed either mild or no symptoms of parkinsonism. The drug combination induced mainly an akinetic-hypertonic syndrome, while tremors were absent or mild. The results suggest that low doses of the DA-agonist potentiate the extrapyramidal side effects of haloperidol by acting on self-inhibitory DA receptors, thereby blocking the compensatory increase in dopaminergic firing elicited by the neuroleptic agent.

Key words: Piribedil – Haloperidol – Parkinsonism – Self-inhibitory dopamine receptors.

Piribedil (ET 495), a dopamine-(DA-)receptor agonist, at high doses ameliorates the cardinal features of Parkinson's disease (Chase et al., 1974) and exacerbates manic and schizophrenic symptoms (Angrist et al., 1975), probably by stimulating postsynaptic DA receptors (Miller et al., 1974). On the other hand, piribedil, at low doses, has some antimanic properties (Post et al., 1976) that conceivably consist in a preferential action on a special kind of DA receptor that inhibits dopaminergic nerve activity and DA synthesis (self-inhibitory DA receptor, presynaptic DA receptors, and/or autoreceptors) (Carlsson et al., 1975; Bunney et al., 1975).

Since such neuroleptics as haloperidol are thought to exert their antipsychotic effect by preferentially blocking postsynaptic DA receptors (Corrodi et al., 1967), we considered that a combined treatment with haloperidol and low doses of piribedil might result in greater antipsychotic activity. Thus we carried out a clinical trial with such a drug combination on schizophrenic patients. Although this combined treatment somewhat ameliorated psychic conditions, the unexpected occurrence of early and marked parkinsonian symptoms obliged us to interrupt our experimental design. We report here on this study.

Materials and Methods

Fifteen schizophrenic patients (6 male, 9 female) aged from 16 to 36 were studied in our Institute of Nervous and Mental Diseases. They were divided into the following diagnostic subgroups: paranoid (6), hebephrenic (5), and schizo-affective (4).

All patients suffered from an acute episode of the disease and were kept free of drugs for at least one week before the investigation began. The patients were randomly divided into three groups that received piribedil (60 mg daily in 3 divided oral doses), haloperidol (3 mg daily in 3 divided oral doses), or the combination of the two drugs, respectively.

Two physicians, making independent and blind assessments, evaluated extrapyramidal signs every day before the morning treatment. Their scores were based on simple evaluation from 0 (absent) to 3 (marked) for each of the three major symptoms of parkinsonism, tremor, rigidity, and akinesia. Piribedil tablets (Trivastan-Servier, 20 mg) and haloperidol tablets (Serenase-Lusofarmaco, 1 mg) were administered at 8 a.m., 12 a.m., and 6 p.m.

The experiment was stopped when marked extrapyramidal side effects became evident, at this point the therapy was discontinued.

Statistical evaluations were made with Student's t-test.

Results

As indicated in Table 1 only two of the patients treated with haloperidol alone showed mild symptoms of rigidity and tremor (M. G. and T. F.), and none of the patients treated with piribedil alone had extrapyramidal signs up to the seventh day. On the other hand, after a few days all patients under the drug combination presented severe symptoms of parkinsonism. Three out of the seven subjects presented such high scores of rigidity and akinesia that we stopped treatment on the third day. Similar degrees of disability occurred in

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Table 1. Parkinsonism induced by the combination of low doses of piribedil and haloperidol in schizophrenic patients

Patient	Sex	Treatment (mg daily)	Days of treatment	Disability scores[a]			Other effects
				Rigidity	Akinesia	Tremor	
P. F.	F	haloperidol (3)	7	0	0	0	–
M. G.	F	haloperidol (3)	7	1	0	1	Pallor
T. F.	M	haloperidol (3)	7	1	0	1	Pallor
C. M.	M	haloperidol (3)	7	0	0	0	–
S. L.	F	piribedil (60)	7	0	0	0	–
M. E.	F	piribedil (60)	7	0	0	0	–
R. G.	M	piribedil (60)	7	0	0	0	–
G. M.	M	piribedil (60)	7	0	0	0	–
B. A. M.	F	haloperidol (3) + piribedil (60)	3	3	3	1	sweating
S. A.	F	haloperidol (3) + piribedil (60)	4	3	3	1	hypersalivation and pallor
M. A.	F	haloperidol (3) + piribedil (60)	4	3	3	0	dysphoria
C. A.	F	haloperidol (3) + piribedil (60)	7	1	1	0	pallor
A. G. A.	F	haloperidol (3) + piribedil (60)	7	1	0	0	–
V. F.	M	haloperidol (3) + piribedil (60)	3	3	2	0	pallor and sweating
P. P.	M	haloperidol (3) + piribedil (60)	3	3	3	0	hypersalivation

[a] Disability scores were evaluated as follows: 0 = absent, 1 = mild, 2 = moderate, 3 = marked

patients S. A. and M. A. on the fourth day of treatment, while C. A. and A. G. A. showed mild symptoms of rigidity and akinesia on the second day; the disability remained unchanged until the seventh day. Since tremor was absent or only mild in all the patients of this group, akinetic-hypertonic syndrome appears to be the proper definition of the effect elicited by this drug combination. Almost all patients in this group variably complained of such other side effects as sweating, hypersalivation, pallor, and dysphoria. The mean disability scores for rigidity or akinesia in this group were significantly different from the values of the other groups ($P = 0.001$), while the statistical evaluation for tremor among the groups did not reveal any significant differences.

Discussion

Our results indicate that low doses of piribedil can markedly potentiate haloperidol-induced parkinsonism in schizophrenic patients. These data agree with recent observations in rats, which reveal that appropriate doses of apomorphine can potentiate haloperidol-induced catalepsy (Fadda et al., 1975). One possible interpretation of these findings is based on the existence in the CNS of a special kind of DA receptor, the stimulation of which results in an inhibition of DA synthesis and of electrical activity of DA neurons (Aghajanian et al., 1977). These receptors might be a means by which these neurons control their own activity (firing, DA synthesis, and release) via the DA released by the nerve endings or by dendrites in the substantia nigra (Iversen, 1977). There is convincing evidence that both piribedil and apomorphine can, at low doses, selectively stimulate these receptors in animal and man (Carlsson, 1975; Post et al., 1976; Corsini et al., 1977). Thus, low doses of piribedil may counteract the compensatory increase in firing rate and DA synthesis of DA neurons secondary to haloperidol's blockade of postsynaptic DA receptors in the striatum. This could result in a more effective blockade of dopaminergic activity and a higher degree of rigidity and akinesia.

Although the present study did not lead to any conclusion on the antipsychotic efficacy of the combination of low doses of piribedil and haloperidol, because of the early and marked extrapyramidal symptoms, a more accurate dosage of these drugs in a different experimental design might provide useful information on the therapeutic activity of this combination in psychotic states.

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