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Therapeutic Experiences with an Abeorphine Derivative in Parkinson's Disease

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Apomorphine was the first dopaminergic substance to be applied in pharmacological trials of Parkinson's disease, even before the neostriatal dopaminergic deficit was known to be the neurobiochemical basis of Parkinson's syndrome (1,2).

In 1967, Cotzias et al. administered apomorphine in the treatment of parkinsonian syndrome, but the trial was complicated by emetic side-effects (3).

CI 201-678 is a abeorphine derivative with a pharmacological profile similar to that of apomorphine, but with a longer duration of action and oral efficacy. CI 201-678 has a stimulating D_1 and, to a lesser degree, D_2 receptor activity, as well as a presynaptic dopaminergic action. In animal models the substance demonstrates a three- to tenfold dopaminergic activity compared to bromocriptine. In contrast to apomorphine, CI 201-678 does not induce blood pressure fall because of its α-adrenergic stimulant properties. Emetic potency is markedly reduced in comparison to bromocriptine (4).

MATERIAL AND METHODS

In an open clinical trial, CI 201-678 was orally administered to 13 Parkinson's disease patients (10 male and 3 female) with a mean age of 59 (5 ± 8.0 years). Mean duration of disease was 8.0 ± 7.4 years. Eight patients showed predominant rigid-akinetic symptomatology, three showed a balanced degree of tremor, rigidity, and akinesia (5).

Twelve patients had been receiving levodopa therapy for a mean of 8.25 years at a latest mean levodopa dosage of 55.6 mg ± 427 mg/day. Six patients suffered from mild to moderate daily fluctuations (freezing, wearing-off, early morning akinesia, nocturnal akinesia, dyskinesias). CI 201-678 was increased slowly and administered in three to four divided daily dosages. Clinical ratings were performed on the third, seventh, and the thirtieth day of CI treatment, and in further monthly intervals. Motor symptoms were rated by means of the Webster Rating Scale and the stage of disease according to Hoehn and Yahr. Dyskinesias and daily fluctuations were assessed on a scale ranging from 0 to 4 (0, absent; 1, mild; 2, moderate; 3, marked; 4, severe). Routine laboratory tests, blood pressure measurement, and EKG were performed after 1 week and at further monthly intervals.

RESULTS

Nine patients were treated with CI 201-678 at an effective dosage, which had been gradually obtained after 4 to 7 weeks of treatment and optimized at 3 to 15 mg, mean 9.66 ± 3.85 mg/day given in three to four portions. In those patients duration of treatment with CI 201-678 ranged from 70 to 157 days, with a mean of 107 days. At the onset of the study eight of these nine patients were receiving levodopa therapy which could be gradually reduced during the increase of CI 201-678 dosage, altogether by a mean of 182.4 mg ± 160 mg of the daily levodopa dosage. The mean scores of clinical parameters before and with CI 201-678 treatment are listed in Table 1. Improvement was marked for posture, gait, and rigidity, as well as self-care. The Wilcoxon matched-pairs signed rank test of the assessed clinical parameters revealed a significant improvement of rigidity ($p = 0.042$) as well as the sum-score of the Webster scale ($p = 0.05$) although levodopa therapy was significantly reduced ($p = 0.012$).

One patient discontinued CI 201-678 treatment after 1 week without drug-related side-effects because of personal reasons. At the day of discontinuation the daily dosage of CI 201-678 was 0.3 mg. One patient suffered from protracted nausea after 14 days of treatment at 0.6 mg CI 201-678 daily, so that the daily dosage of CI could not be further increased. At that dosage no improvement was seen. Two patients were drug-related drop-outs. In one patient (56 years old, postencephalitic Parkinson's disease for 30 years, stage II), discontinuation of treatment was necessary after 1 week of treatment at 1 mg CI 201-678 daily because of tactile hallucina-

TABLE 1. *CI 201-678 in the treatment of Parkinson's disease*[a]

Webster scale	Before treatment	With treatment
Akinesia	1.88 ± 0.33	1.77 ± 0.83
Rigidity	1.77 ± 0.44	1.22 ± 0.66
Posture	1.00 ± 0.86	0.44 ± 0.72
Upper extremity swing	2.44 ± 1.42	2.11 ± 2.02
Gait	1.22 ± 0.83	0.77 ± 0.97
Tremor	0.55 ± 0.72	0.77 ± 0.83
Facies	1.33 ± 0.87	1.33 ± 0.71
Seborrhea	1.67 ± 1.73	1.67 ± 2.45
Speech	1.22 ± 0.44	0.89 ± 0.60
Self-care	1.00 ± 0.86	0.66 ± 1.00
Sum-score	12.89 ± 3.62	9.89 ± 4.78
Hoehn and Yahr scale		
Stage	2.2 ± 2.2	2.1 ± 0.92
Drug-induced dyskinesias	1.16 ± 2.47	1.27 ± 2.35
Daily fluctuations	2.88 ± 3.44	2.44 ± 3.08

[a]Patients with effective dosage; comparison of scores before and with CI 201-678 (9.66 ± 3.85 mg/day); duration of treatment, 107 ± 33 days; $N = 9$.

tions and insomnia. One parkinsonian patient (67 years old, idiopathic Parkinson's disease for 15 years, stage IV), suffering from silicosis with pulmonary hypertension, was withdrawn from CI 201-678 at 2 mg/day after 5 days of treatment because of trial fibrillations and ventricular extrasystoles, which disappeared spontaneously after discontinuation of treatment.

Side-effects were also seen in two patients with transient drug-induced dyskinesias, which disappeared with the reduction of the levodopa dosage. Four cases showed transient mild elevation of serum GOT (25–31 U/liter; normal range, 20 U/liter; normal range, 20 U/liter), but disappeared with continuation of CI 201-678 treatment.

SUMMARY

Marked improvement of the clinical state owing to CI 201-678 treatment was seen in six patients; no definite improvement was achieved in three patients. Daily fluctuations were improved in two patients. CI 201-678 demonstrated a good effect against rigidity, impairment of gait and posture, as well as impaired self-care, although daily levodopa dosage was concomitatly reduced. In two patients, CI 201-678 was discontinued because of side-effects, while one patient stopped treatment for reasons not related to the drug.

In contrast to apomorphine and other dopaminetic substances, the emetic side-effect of CI 201-678 is minimal (nausea in one patient), no arterial hypotension was not seen. It has to be mentioned that the two drug-related drop-outs were receiving CI 201-678 in a rapidly increasing dosage. It is likely that the side-effects would have been less pronounced if the dosage had been more slowly increased. However, the preliminary results indicate that CI 201-678 is a promising substance for the treatment of patients with predominant rigid-akinetic symptomatology, in combination with levodopa therapy or in the place of levodopa.

REFERENCES

1. Schwab, R. S., Amadori, L. V., and Lettoni, J. Y. (1951): Apomorphine in Parkinson's disease. *Trans. A. Neurol. Assoc.*, 76:251.
2. Struppler, A. (1953): Die Therapeutische Beeinflussbarkeit des Tremors. *Med. Mschr.*, 73:157–160.
3. Cotzias, G. C., Papavasilious, P. S., Tolosa, E. S., et al. (1976): Treatment of Parkinson's disease with apomorphines. Possible role of growth hormone. *N. Engl. J. Med.*, 294:567–572.
4. Jaton, A.-L. (1980): *Pharmalogical Data*, pp. 201–678. Sandoz, Basle.
5. Poewe, W., Gerstenbrand, F., and Ransmayr, G. (1983): Klinische Manifestationstypen des Parkinson-Syndroms. *Neuropsychiatr. Clin.* 2:223–227.