Eur Arch Psychiatr Neurol Sci (1985) 235:60–64

European Archives of Psychiatry and Neurological Sciences

Treatment of Drug-induced Exogenous Psychosis in Parkinsonism with Clozapine and Fluperlapine

E. Scholz and J. Dichgans

Neurologische Universitätsklinik, Liebermeisterstrasse 18–20, D-7400 Tübingen, Federal Republic of Germany

Summary. A total of 13 patients with drug-induced psychosis in Parkinson's disease were treated with two non-classical neuroleptics—clozapine and fluperlapine. Patients mainly complained about severe hallucinatory symptoms and different degrees of paranoid delusions. Complete relief was observed in 8 patients, moderate improvement in 3 and no effects in 2. Parkinsonian disability did not increase under neuroleptic medication with clozapine and fluperlapine, but could be ameliorated by additional L-dopa or bromocriptine medication. The non-classical neuroleptics employed are dopamine D2 blocking agents with a preferential binding to mesolimbic, mesocortical and hippocampal D2 receptors and no substantial binding to striatal dopamine receptors. Restricted use of these two neuroleptics is necessitated because of the danger of agranulocytosis.

Key words: Drug-induced psychosis – Parkinson's disease – Clozapine – Fluperlapine – Mesolimbic system – Hippocampus

Introduction

In recent years mental disorders in Parkinsons's disease have become a topic of increasing interest. Problems are the development of global dementia including forgetfulness and organic confusional states and psychotic disorders such as depression and paranoid-hallucinatory psychosis which are a side effect of treatment. Initially called "Dopa psychosis" [5] these paranoid-hallucinatory symptoms were later observed in all kinds of drug treatment in Parkinson's disease, so that we would prefer to use neutral terms such as exogenous or drug-induced psychosis. Treated with L-dopa, 19% of Birkmayer's Parkinson patients developed a "Dopa psychosis" [8]. Higher rates ranging up to 30% were observed under treatment with dopamine agonists such as bromocriptine, lisuride or pergolide [21, 22, 26] so that these drugs were judged contra-indicated in patients with a history of psychosis since they tend to cause more psychiatric disturbances than L-dopa [10].

Although L-tryptophan in high doses of up to 3 g/day was considered a useful drug in early studies on psychosis [6, 13], a later double blind study showed that with doses of up to 6 g/day these positive results could not be confirmed [4]. As medication is generally accepted as the cause of the observed psychotic side effects, drug reduction or drug cessation are the main therapeutic recommendations given in the literature [23], often leading to increased motor disabilities.

Offprint requests to: E. Scholz at the above address

The classical neuroleptics ameliorate psychosis but worsen akinesia and rigidity. Reports on treatment using non-classical neuroleptics such as clozapine or its successor fluperlapine have not been published to our knowledge. Since no extrapyramidal side effects have been reported in schizophrenic patients under treatment with these drugs [2, 11, 19], a therapeutic trial seemed promising in patients with parkinsonism.

Patients

Clozapine Group. Patients data are listed in Table 1. All four of them showed a moderate disability [17], one patient was 54 years old, and the other three ranged in age from 67–80 years when treated for psychotic complaints. The duration of Parkinson's disease was rather longer with a mean of 10.2 years. All patients had been taking L-dopa plus benzerazide for between 1 and 7 years (mean 5.0; standard deviation $s = 2.8$ years), and two had received concomitant therapy with bromocriptine. Hallucinatory psychosis started 7 days after the introduction of bromocriptine in one of them, so that psychosis could be related to this newly given medication. In the other three patients no change of drug regimen immediately preceeded the manifestation of psychosis. All patients complained about progressive forgetfulness but only one patient, aged 80 years, showed stronger signs of developing dementia with loss of orientation in time and space.

Visual hallucinations occurred in three of them, while paranoid delusions dominated in two, and developed later in the course of the disease in a third.

Patient No. 3 can be taken as a typical example. An early combination therapy of 125 mg L-dopa plus benzerazide and 20 mg bromocriptine were given daily for 1 year before visual hallucinations started. The patient described how incomplete or damaged people evolved out of objects of his familiar surroundings. Later on whole scenes of people surrounding him, who never spoke a word, appeared and became quite familiar. Although he could voluntarily overcome these delusions in the beginning, he later felt more and more threatened and finally haunted by these hallucinations. Psychotic episodes reappeared several times for 2 to 3 weeks, vanished without treatment in the beginning, but finally became so frightening that treatment had to be started. Haloperidol at a low dose (3×1 mg/day) cleared his mind but led to a considerably increasing akinesia. L-Tryptophan (3×1 g/day) in a later episode had no measurable effect. Clozapine was started with 25 mg in the evening and then increased to 50 mg which cleared his mind within 6 days with no further parkinsonian

Table 1. Clozapine treatment group

No.	Init.	Age (years)	Duration of disease (years)	Stage (Hoehn and Yahr)	Daily medication L-dopa + benzerazide (mg) bromocriptine (mg)	Clozapine (mg)	Efficacy
1	BA	67	10	III	500 20	25	++
2	ZG	54	14	III	600	100	++
3	SE	71	8	III	125 20	50	++
4	LJ	80	9	III	500	25	++
	$\bar{x}$ = 68.0 s = 10.8	10.2 s = 2.6				$\bar{x}$ = 493.7, s = 92	$\bar{x}$ = 61.5, s = 19

Table 2. Fluperlapine treatment group

No.	Init.	Age (years)	Duration of disease (years)	Stage (Hoehn and Yahr)	Daily medication L-dopa + benzerazide (mg) bromocriptine (mg)	Fluperlapine (mg)	Efficacy
1	FG	66	5	III	500 7.5 + Amantadine	40	++
2	MG	66	0.5	III	375	50	+
3	BG	78	3	III	375 + Biperiden	30	+
4	RM	75	5	IV	500–0	35	++
5	FE	74	2	V	312.5 + Amantadine + Biperiden	75	–
6	SK	64	12	IV	750 30 + Amantadine	20	++
7	CF	70	17	V	625 5	50	+
8	GH	78	6	III	750 5	50	–
9	SK	76	12	III	500 + Trihexyphenidyl	50	++
	$\bar{x}$ = 71.6 s = 5.6	6.8 s = 4.9			520.8 s = 159.3	40 s = 21.6	

symptoms. One of the other patients in the group exhibited marked paranoid delusions with predominantly sexual topics, being tortured by the idea of having raped his own daughter.

Fluperlapine Group. Patients data are listed in Table 2. The patients disabilities ranged from moderate to severe, and six of the nine patients were older than 70 years. The duration from the start of the disease to the beginning of psychotic symptoms ranged from 6 months to 15 years. The mean duration of disease (6.8; s = 4.9 years) was shorter than in the clozapine group (statistical analysis could not be performed because both groups were small and quite different in number). In addition to L-dopa four patients received bromocriptine, which was continued under fluperlapine treatment or newly instituted. Amantadine or anticholinergics, however, were withdrawn since they were judged ineffective in late stages of the disease and were considered a possible source of additional mental deterioration sometimes leading to dementia in anticholinergics.

Although we started the study with non-demented patients only, we later included four patients with varying degrees of clinical signs of dementia such as disorientation in time and space, also exhibiting additional signs of hallucinations, agitation, sleep disturbances and paranoid delusions.

One patient had received L-tryptophan (3 × 1 g/day) at an early stage of psychosis, with moderate effects, which could not be repeated later. Two patients showed no response to the same regimen.

Both, the clozapine and the fluperlapine group are comparable concerning mean age and pre-treatment doses of L-dopa and bromocriptine (see Tables 1 and 2). EEG recordings were done in all patients. Only 2 of them—1 in each group—

showed a normal EEG with predominance of alpha-activity, the remaining 11 showed abnormalities with predominant theta-activity in 10 and theta-delta in 1, 2 showed a temporal theta focus.

A CT scan was done in 11 of the 13 patients, 1 in each group was considered normal, 2 showed signs of a mild cortical atrophy, 7 moderate global atrophy, 3 subcortical vascular damage and defects in the basal ganglia and 3 focal cortical—probably vascular—damage.

Results of Treatment

Clozapine Group. Four patients were treated with a mean dosage of 61.5 mg (range 25–100). The drug was usually started with an evening dose of 25 mg. Medication of L-dopa plus benzerazide (Madopar) and bromocriptine was not changed. Two patients showed a prompt resolution of psychotic symptoms within 2 days under 25 and 100 mg of clozapine respectively. The other two responded to the therapy within 6 and 13 days respectively. Patient No. 2 (Table 1) who started with 100 mg of clozapine, showed considerable sedation, so that the dosage had to be reduced to 50 mg/day. In patient No. 4, who was started with 25 mg, the dosage had to be increased up to 100 mg until a sufficient therapeutic effect could be observed. Patient 2 was transiently treated with thioridazine at a low dose (3 × 25 mg) and developed remarkable akinesia, which rapidly vanished after being treated again with clozapine. In patient No. 3 psychotic symptoms vanished under a medication of low dose haloperidol (3 × 1 mg/day over a 2-week interval) but remarkable akinesia developed.

The symptoms of Parkinson's disease were unchanged in all four patients while treated with clozapine.

Fluperlapine Group. The mean dosage of fluperlapine was 40 mg (range 20–75), starting with an evening dose of 10 mg in the demented patients and 25 mg in the non-demented. All patients showed good hypnotic effects with resolution of the often observed sleep disturbances from the first night on. Only one patient initially showed a marked day-time sedation, that resolved within 2 days without changing the drug specimen of 50 mg.

Four patients showed a prompt cessation of psychotic symptoms under 35 to 50 mg of fluperlapine within 3 to 4 days. Three patients had a moderate reduction under a medication of 30 to 50 mg, two patients did not respond to therapy within 2 weeks at a dosage of 50 mg and 75 mg respectively.

Patients with only moderate effects were those showing marked signs of dementia with disorientation in time and space. After intermittent withdrawal of medication in two of them hallucinations returned within 1 day. After reinstitution of therapy they responded as before.

Parkinsonian symptoms (see Fig. 2) remained unchanged in two patients who retained their former L-dopa and bromocriptine medication. One patient had had a complete withdrawal of L-dopa before treatment in hospital because of her paranoic symptoms without amelioration of her complaints. She developed marked akinesia with frequent falls requiring hospitalization. After reinstitution of L-dopa combined with fluperlapine, she rapidly regained complete mobility and lost her paranoid fears completely. In four additional patients the drug regimen had to be readjusted because of a reduced effect, leading to increased doses of L-dopa or an additional

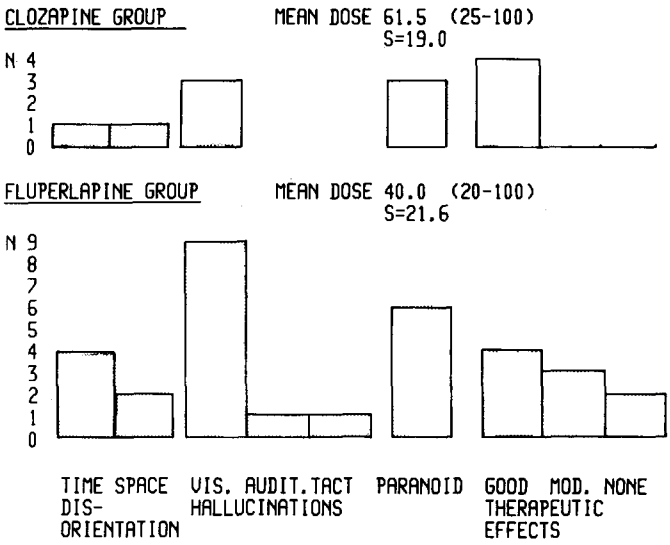

Fig. 1. Psychotic symptoms in parkinsonian patients

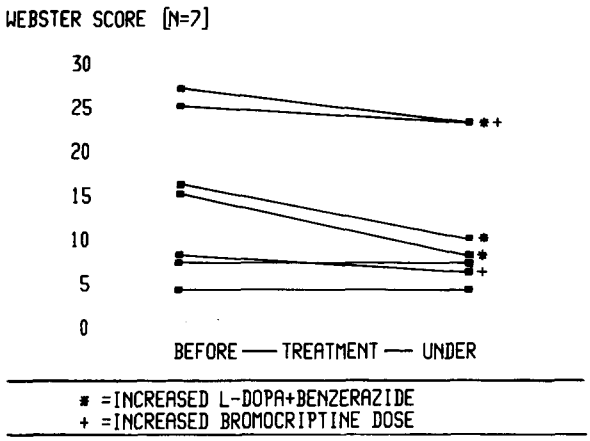

Fig. 2. Parkinsonian symptoms under treatment with fluperlapine

Table 3. Parkinson patients with psychotic episodes

	Clozapine	Fluperlapine
Treatment group	$n = 1$ Female = 1 Male = 3	$n = 9$ Female = 2 Male = 7
Mean age	68.0 years s = 10.8 (54–80)	71.6 years s = 5.6 (64–78)
Parkinson stage (Hoehn and Yahr)	III = 4	III = 5 IV = 2 V = 2
Mean duration of disease	10.2 years s = 2.6 (8–14)	6.8 years s = 4.9 (0.5–15)
Mean duration of Dopa medication	5.0 years s = 2.8 (1–7 years)	2.8 years s = 2.8 (6 weeks–6 years)

administration of bromocriptine. Thereafter parkinsonian disability ameliorated under concomitant fluperlapine therapy.

As a side effect of fluperlapine, three patients initially developed marked dystonia of the trunk. In contrast to the other patients those three showed signs of a focal cortical damage in the insular region in CT scanning, twice contralaterally to the side of trunk dystonia and once ipsilaterally. Without changing the drug regimen this dystonia vanished within a few days.

Patients showing no effects from neuroleptic therapy could probably have been successfully treated with higher doses of fluperlapine, since the dosage used was considerably below the mean dosage of 400 mg/day used in schizophrenic patients [29]. Those patients belonged to the non-demented parkinsonian patients, but since they were treated in the early exploratory phase with this regimen, we did not try doses larger than 75 mg.

Discussion

Together with fluctuations in motor disability drug-induced psychosis is one of the most difficult problems in the therapy of advanced stages of Parkinson's disease [20, 24, 25, 27].

Psychotic phenomena are provoked under all kinds of antiparkinsonian drugs such as anticholinergics, amantadine or dopaminergic medication. In particular changes in drug regimen with increased doses of L-dopa or newly instituted dopamine agonists are possible causes of psychotic episodes, but even under a stable medication—as in most of our patients—symptoms may develop [15]. The hallucinatory states observed in most of our patients, very closely resemble those evoked by acute ingestion of other agents affecting biogenic amines [15]. Psychosis usually started with hypnagogic hallucinations in the dark—often stopped by switching on the light, superimposed at least in the beginning on a clear sensorium, featuring mainly human creatures often of a fantasy nature. While patients could control these phenomena in the beginning, in later stages of the disease increased hallucinations and delusions were combined with paranoid fears and anxiety, so that therapy became mandatory.

L-Tryptophan as described in the literature showed only limited effects in one patient in an early stage of the disease [6, 13] but no effects in three others [4]. Marked akinetic effects of haloperidol had been expected, but not the same effects of a low dose of thioridazine that is said to have only limited extrapyramidal side effects [11] and has therefore been recommended for therapy of psychotic episodes in parkinsonian patients [23].

The missing cataleptic side effects in patients treated for schizophrenia has been the reason for classifying dibenzapine neuroleptics like clozapine or fluperlapine as "non-classical neuroleptics" [2, 11, 14, 19, 29]. These so called non-classical neuroleptics did not show additive extrapyramidal side effects in our treated patients. Different sites of action of L-dopa or dopaminergic agents are discussed as a cause of psychotic hallucinatory and paranoid symptoms in parkinsonian patients under long-term treatment. Those are mainly the mesolimbic system [7] including so-called mesocortical frontal (neocortical) areas. Dopa may also stimulate the recently investigated dopaminergic neurons of the hippocampus-amygdala complex [9], and the adjacent medial aspects of the temporal lobes, the entorhinal, perirhinal periamygdaloid cortices forming the parahippocampal gyrus and uncus. Electrical stimulation of those sites [16] or spontaneous focal ictal activity [28] produces complex formed predominantly visual hallucinations sometimes complete scenes or dream-like images [16]; a description rather similar to the observed hallucinations in our psychotic patients.

Drugs like clozapine or fluperlapine are reported to act as dopamine D2 receptor antagonists [12]. But unlike classical neuroleptics they predomiantly block hippocampal binding sites with only weak effects on striatal dopamine receptors [9]. Only higher doses of some non-classical neuroleptics such as sulpiride, tiapride or thioridazine cause a partial blocking of striatal dopamine receptors [9]. The latter may account for the observed deterioration in one of our patients treated with thioridazine. Fluperlapine supposedly binds less to dopamine receptors than clozapine in striatum, nucleus accumbens or cortex, but leads to higher increases of HVA concentrations [12], thus indicating a higher dopamine turn-over. This increased dopaminergic activity might be the cause of the observed acute dystonic reaction in three of our fluperlapine patients.

The dose of clozapine or fluperlapine needed for control of drug-induced hallucinatory psychosis was considerably lower than mean dosages applied in schizophrenic patients where clozapine is usually started with 50–100 mg and increased up to 800 mg [1] and fluperlapine was given with a mean dosage of 400 mg [29].

The main problem in treatment with clozapine and fluperlapine is drug-induced agranulocytosis [3, 18]. Alarming reports of eight lethal outcomes in Finland led to restricted use of clozapine, although the overall incidence of agranulocytosis in other populations was as high as the risk in phenothiazine neuroleptics [1]. Fluperlapine induced reversible agranulocytosis in two cases in early clinical treatment studies. As a result the drug has been withdrawn from clinical trials.

Since there is no other similarly effective treatment for drug-induced psychosis as a late complication of Parkinson's disease we would recommend treatment with clozapine under the condition that severe akinesia or severe response fluctuations occur if L-dopa treatment is withdrawn or reduced or if dopa agonist treatment is terminated. Clinical treatment with clozapine necessitates blood counts prior to medication and weekly thereafter for 3 to 4 months, special attention paid to infections and exclusion of patients with a previous history of drug-related blood dyscrasias.

Acknowledgements. Fluperlapine used in the study was supplied by Sandoz, Basle. We wish to thank Mrs. C. Portzehl for typing the manuscript.

References

1. Ackenheil M, Hippius H (1977) Clozapine. In: Usdin E, Forrest I (ed) Psychotherapeutic drugs, vol 2, part 2. Marcel Dekker Inc, New York Basel, pp 923–956
2. Andén NE, Stuck G (1973) Effect of clozapine on the turn-over of dopamine in the corpus striatum and in the limbic system. J Pharm Pharmacol 25:346–348
3. Andermann B, Griffith RW (1977) Clozapine-induced agranulocytosis: A situation report up to August 1976. Eur J Clin Pharmacol 11:199–201
4. Beasley BL, Nutt JG, Davenport RW, Chase TN (1980) Treatment with Tryptophan of levodopa-associated psychiatric disturbances. Arch Neurol 37:155–156

5. Birkmayer W (1966) Experimentelle Befunde und neue Aspekte bei extrapyramidalen Erkrankungen. Wien Z Nervenheilkunde 23:128–139
6. Birkmayer W, Neumayer E (1972) Die Behandlung der Dopa-Psychosen mit L-Tryptophan. Nervenarzt 43:76–78
7. Birkmayer W, Riederer P, Rausch WD (1979) Neuropharmacological principles and problems of combined L-Dopa treatment in Parkinson's disease. Adv Neurol 24:499–510
8. Birkmayer W, Riederer P (1980) Die Parkinson-Krankheit. Biochemie, Klinik, Therapie. Springer, Wien, New York
9. Bischoff S, Delini-Stula A, Maitre L (1985) Blockade der Dopamin-Rezeptoren im Hippokampus als Indikator antipsychotischer Wirksamkeit: Korrelationen zwischen neurochemischen und psychopharmakologischen Wirkungen von Neuroleptika. In: Pflug B, Foerster K, Straube E (Hrsg) Perspektiven der Schizophrenie-Forschung. Gustav Fischer, Stuttgart New York, S 87–103
10. Calne DB (1983) Ergot derivates and extrapyramidal disease. In: Calne DB, Horowski R, McDonald RJ, Wuttke W (eds) Lisuride and other dopamine agonists. Raven Press, New York, pp 357–361
11. Carlsson A (1978) Antipsychotic drugs, neurotransmitters, and schizophrenia. Am J Psychiatry 135:164–173
12. Eichenberger E (1984) Pharmacology of Fluperlapine compared with Clozapine. Arzneim Forsch / Drug Res 34:110–113
13. Gehlen W, Müller J (1974) Zur Therapie der Dopa-Psychosen mit L-Tryptophan. Dtsch Med Wochenschr 99:457–463
14. Gerlach J, Koppelhus P, Helweg E, Monrad A (1974) Clozapine and Haloperidol in a single-blind cross-over trial: therapeutic and biochemical aspects in the treatment of schizophrenia. Acta Psychiatr Scand 50:410–424
15. Goetz CG, Tanner CM, Klawans HL (1982) Pharmacology of hallucinations induced by long-term drug therapy. Am J Psychiatry 139:494–497
16. Halgren E (1982) Mental phenomena induced by stimulation in the limbic system. Human Neurobiol 1:251–260
17. Hoehn MM, Yahr MD (1967) Parkinsonism: onset, progression, and mortality. Neurology 17:427–442
18. Idänpään-Heikkilä J, Alhava E, Olkinnora M, Palva IP (1977) Agranulocytosis during treatment with Clozapine. Eur J Clin Pharmacol 11:193–198
19. Korsgaard S, Noring U, Gerlach J (1984) Fluperlapine in tardive dyskinesia and parkinsonism. Psychopharmacology 84:76–79
20. Lesser RP, Fahn S, Snider SR, Cote LJ, Isgreen WP, Barrett RE (1979) Analysis of the clinical problems in parkinsonism and the complications of long-term levodopa therapy. Neurology 29: 1253–1260
21. Lieberman A, Kupersmith M, Neophytides A (1980) Bromocriptine in Parkinson's disease: report on 106 patients treated up to 5 years. In: Calne DB, Goldstein M, Lieberman A, Thorner M (eds) Ergot compounds and brain function: Neuroendocrine and neuropsychiatric aspects. Raven Press, New York, pp 245–253
22. Lieberman A, Goldstein M, Leibowitz M, Neophytides A, Kupersmith M, Pact V, Kleinberg D (1981) Treatment of advanced Parkinson's disease with pergolide. Neurology 31:675–682
23. Marsden CD, Fahn S (1981) Problems in Parkinson's disease. In: Marsden CD, Fahn S (eds) Movement disorders. Butterworth Scientific, London, pp 1–7
24. Moskovitz C, More H, Klawans H (1978) Levodopa induced psychosis: a kindling phenomenon. Am J Psychiatry 135:218–226
25. Schneider E, Fischer PA, Jacobi P, Grotz A (1984) Exogene Psychosen beim Parkinsonsyndrom. Häufigkeit und Entstehungsbedingungen. Fortschr Neurol Psychiatr 52:207–214
26. Stern Y, Mayeux R, Ilson J, Fahn S, Cote L (1984) Pergolide therapy for Parkinson's disease: Neurobehavioural changes. Neurology 34:201–204
27. Sweet RD, McDowell FH, Feigenson JS, Loranger AW, Goodell H (1976) Mental symptoms in Parkinson's disease during chronic treatment with leveodopa. Neurology 26:305–310
28. Wieser HG (1983) Electroclinical features of the psychomotor seizure. Gustav Fischer, Butterworth, Stuttgart New York
29. Woggon B, Heinrich K, Küfferle B, Müller-Oerlinghausen B, Pöldinger W, Rüther E, Schied HW (1984) Results of a multicenter AMDP study with Fluperlapine in schizophrenic patients. Arzneim Forsch / Drug Res 34:122–124

Received May 10, 1985