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Acute Challenge with Apomorphine in Huntington's Disease: A Double-Blind Study

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Summary: Apomorphine (1.5 or 3 mg) or placebo was acutely administered to choreic patients affected by Huntington's disease in a double-blind fashion. The patients were evaluated before the administration, and at 15-min intervals for 2 h afterward, by means of a rating scale for Huntington's disease. As compared to baseline, the total score improved by 38.54% after 1.5 mg and by 30.41% after 3 mg; no variations were observed after placebo. Several items of the scale improved after the administration of 1.5 mg. An average 35.25% improvement was observed in items measuring the intensity of chorea (at rest, with arms outstretched, during conversation, and voluntary movements of the limbs); in addition, motor impersistence (as measured by tongue protrusion) and the capability to suppress associated movements (as measured by head movements during saccades) improved by an average of 31.46 and 61%, respectively. Some items of the scale improved after the administration of 3 mg. Items measuring the intensity of chorea improved by an average 30.41%; in addition, the extent of vertical gaze improved by 63.77%. These data indicate that apomorphine brings about a transient symptomatic improvement of chorea and of other associated clinical features in Huntington's disease. The time course observed for the antichoreic activity is only partially consistent with the antiparkinsonian action of apomorphine. **Key Words:** Apomorphine—Chorea—Dopamine—Huntington's disease.

The recent discovery of the Huntington's disease (HD) gene (1) is expected to foster the development of a specific therapy for this disabling condition. So far, only a few symptomatic therapies are available in the clinic. Neuroleptic drugs are used to reduce chorea and to control behavioral abnormalities. This approach is often poorly effective and has the drawback of aggravating parkinsonian features, characteristic of advanced HD (2). In addition, some dopamine receptor agonists have been occasionally used (also in association with neuroleptics) as a symptomatic therapy for chorea in HD (3–6). The rationale for this combined approach

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is that dopamine receptor agonists, including apomorphine, are thought to stimulate the dopaminergic autoreceptor, thus inhibiting the activity of midbrain dopaminergic neurons.

Apomorphine is a potent dopamine receptor agonist that is currently used to treat Parkinson's disease and other movement disorders (7). The pharmacological profile of apomorphine is characterized by a short latency and short duration of clinical effects and by a peculiar profile of activity on dopaminergic receptors. Apomorphine has a high affinity for D_4 receptors, intermediate affinity for D_2 and D_3 receptors, and a low affinity for D_5 and D_1 receptors (8). Thus, at variance with other dopaminergic drugs, apomorphine is active either on D_1-like or on D_2-like dopaminergic receptors.

This study was undertaken to evaluate whether apomorphine may have a symptomatic effect on chorea and on other clinical features in HD when it is administered at doses that are effective on parkinsonian symptoms.

PATIENTS AND METHODS

Nine patients (four men and five women; mean age, 42.33 ± 4.07 years; range, 29 to 61 years) affected by HD were studied. They had a definite diagnosis, based on the finding of clinical features of hyperkinetic HD and of at least one other family member with typical HD (9). All patients had computed tomography (CT) or magnetic resonance imaging (MR) scans showing atrophy of the caudate. Patients with the following features were not included in the study: (a) younger than 20 years, (b) lack of ability to cooperate, (c) severe associated diseases, (d) drug abuse, and (e) acute psychosis. Seven patients (two men and five women) had had previous treatment with neuroleptics at low doses, and two were drug naive. The nature and purpose of the investigation were explained to each patient and to their next of kin; informed consent was obtained from both.

Neuroleptic drugs were discontinued for at least 3 months before the study; none of the patients had parkinsonian features. Domperidone (20 mg t.i.d.) was started 3 days before the first testing session. Apomorphine hydrochloride, dissolved in saline solution (1 mg/ml), or saline solution alone was given subcutaneously in a double-blind design. The injections were performed by a physician who did not communicate with the assessor. Two different doses of apomorphine (1.5 mg and 3 mg) or 3 ml of placebo was administered in random order at the same time in the morning on 3 consecutive days. Neurological features were assessed in each patient just before the injection and every 15 min afterward for 2 h. The neurological evaluations were all performed by a single assessor, who had been trained on the scale for more than a year in the outpatient clinic, and consistently rescored the same videotape series after a 3-month interval. The motor performance of each patient was assessed by means of a clinical rating scale for HD derived from that of David et al. (10). The following items were evaluated: (a) *Eye movements:* either the extent or the smoothness of lateral or of vertical gaze, and speed and smoothness of saccades; (b) *Motor suppression:* blink suppression and head rotation during saccades; (c) *Motor impersistence:* gaze holding for 10 s, tongue protrusion for 20 s, eye closure for 20 s; (d) *Chorea:* at rest, with arms

outstretched at 90°, during conversation, during fine motor tasks (e.g., buttoning or folding a sheet); and (e) *Global features:* ability to walk on a flat surface (width of base, straightness of gait) and posture while standing (degree of trunk extension).

Statistical analysis was performed using Wilcoxon's nonparametric test, by comparing the mean baseline score and the mean best score recorded after each treatment, for each item and for the total score. In addition, the mean baseline score was compared to the mean score recorded at any 15-min epoch. The least significance level was $p < 0.05$.

RESULTS

All patients showed a typical clinical picture of HD: they all had chorea and a family history of autosomal dominant transmission. Chorea had been present for 4.44 ± 0.88 years (mean ± SEM). Eight patients received two different doses of apomorphine (1.5 mg and 3 mg) and placebo (saline solution) in random order; patient 5 received only 1.5 mg of apomorphine and placebo, because of severe orthostatic hypotension after that dose of apomorphine.

The latency of action of apomorphine was measured by the occurrence of yawning. Repeated yawning was observed in all patients treated with apomorphine 8.87 ± 1.96 min after an injection of 1.5 mg and 8.71 ± 2.19 min after an injection of 3 mg. It was also observed in four patients (44%) treated with placebo 31.25 ± 11.25 min after the injection of saline solution.

The maximal improvement of the total score occurred at different times in each patient. The comparison of the baseline total score with the total score at the time of peak effect after placebo did not show variations. The same comparison in patients who received apomorphine revealed a 38.54% reduction of the total score after an injection of 1.5 mg ($p < 0.01$) and a 30.41% reduction after 3 mg ($p < 0.05$) (Table 1). On average, the peak effect occurred 50.00 ± 2.50 min after the administration of 1.5 mg of apomorphine and 50.62 ± 9.37 min after 3 mg.

As compared to baseline, no significant variations in the individual items of the scale were found after placebo. After an injection of 1.5 mg of apomorphine, an improvement was observed in the items related to eye movements, motor suppression, motor impersistence, and chorea (Table 2). After an injection of 3 mg, an improvement was observed in the items related to eye movements and chorea (Table 3).

The time course of variations was measured for the items that differed from

TABLE 1. *Baseline total score compared to the best total score after apomorphine or placebo (mean ± SEM; number of observations is nine for placebo and 1.5 mg, eight for 3 mg)*

Apomorphine (mg)	Baseline score	Best score	Time of best score	Improvement (%)	Significance level
0	17.72 ± 1.50	15.22 ± 1.66	—	—	NS
1.5	17.72 ± 1.43	10.89 ± 1.34	50.00 ± 2.50	38.54	$p < 0.01$
3	15.62 ± 1.51	10.87 ± 1.15	50.62 ± 9.37	30.41	$p < 0.05$

TABLE 2. *Baseline score compared to the best score recorded after 1.5 mg apomorphine (mean ± SEM, n = 9)*

Item	Baseline score	Best score	Improvement (%)	Significance level
Eye movements				
Extent of lateral gaze	0.28 ± 0.15	0.11 ± 0.11		NS
Smoothness of lateral gaze	0.33 ± 0.14	0.11 ± 0.11		NS
Extent of vertical gaze	0.39 ± 0.18	0.11 ± 0.11		NS
Smoothness of vertical gaze	0.67 ± 0.19	0.33 ± 0.14	55.75	$p < 0.05$
Smoothness of saccades	1.05 ± 0.21	0.61 ± 0.23	41.90	$p < 0.05$
Speediness of saccades	0.94 ± 0.23	0.72 ± 0.21		NS
Motor suppression				
Head movement during saccades	1.00 ± 1.17	0.39 ± 0.16	61.00	$p < 0.05$
Blink suppression during saccades	0.89 ± 0.26	0.50 ± 0.23		NS
Motor impersistence				
Gaze holding	0.33 ± 0.17	0.11 ± 0.11		NS
Tongue protrusion	0.89 ± 0.07	0.61 ± 0.07	31.46	$p < 0.05$
Eye closure	0.61 ± 0.07	0.22 ± 0.09		NS
Chorea				
Chorea at rest	1.78 ± 0.19	0.89 ± 0.14	50.00	$p < 0.01$
Chorea with outstretched arms	1.89 ± 0.14	1.33 ± 0.12	29.62	$p < 0.05$
Chorea during conversation	2.50 ± 0.25	1.72 ± 0.26	31.20	$p < 0.05$
Chorea during voluntary movement	2.22 ± 0.20	1.55 ± 0.21	30.18	$p < 0.05$
Global features				
Walking	1.44 ± 0.24	0.55 ± 0.23	61.80	$p < 0.05$
Posture	0.61 ± 0.23	0.39 ± 0.14		NS

NS, not significant.

baseline. It was observed that most variations from baseline occurred from 30 to 60 min after the administration of 1.5 mg or of 3 mg of apomorphine. After a dose of 3 mg, significant variations from baseline occurred only for chorea and for the total score (Table 4); after a dose of 1.5 mg, a higher number of items varied significantly from baseline (Table 5). No significant time course variations occurred after placebo.

Side effects were observed in six patients after the administration of apomorphine. After a dose of 1.5 mg, five patients suffered from mild nausea, appearing 8.00 ± 2.00 min after the treatment and lasting for 31.67 ± 10.14 min; three patients had drowsiness, appearing 6.20 ± 1.62 min after the injection and lasting

TABLE 3. *Baseline score compared to the best score recorded after 3 mg apomorphine (mean ± SEM, n = 9)*

Item	Baseline score	Best score	Improvement (%)	Significance level
Eye movements				
Extent of vertical gaze	0.69 ± 0.16	0.25 ± 0.13	63.77	$p < 0.05$
Chorea				
Chorea at rest	1.69 ± 0.23	1.00 ± 0.23	40.83	$p < 0.05$
Chorea with outstretched arms	1.88 ± 0.21	1.44 ± 0.20	23.40	$p < 0.05$
Chorea during conversation	2.44 ± 0.26	1.69 ± 0.25	30.74	$p < 0.05$
Chorea during voluntary movement	2.31 ± 0.25	1.69 ± 0.19	26.84	$p < 0.05$

Only items presenting significant variations are shown; for a complete list of items, see Table 2.

TABLE 4. *Time course of significantly different variations after apomorphine 1.5 mg (mean ± SEM; number of observations is shown in parentheses)*

Item	Baseline score		Score at time shown	Improvement (%)	Significance level
Smoothness of saccades	1.05 ± 0.21 (9)	t_{60}	0.61 ± 0.23 (9)	41.90	$p < 0.05$
Head movement during saccades	1.00 ± 0.17 (9)	t_{45}	0.44 ± 0.15 (9)	56.00	$p < 0.05$
	1.00 ± 0.17 (9)	t_{60}	0.44 ± 0.17 (9)	56.00	$p < 0.05$
Tongue protrusion	0.89 ± 0.07 (9)	t_{45}	0.61 ± 0.07 (9)	31.46	$p < 0.05$
Chorea at rest	1.69 ± 0.19 (8)	t_{30}	1.06 ± 0.15 (8)	37.27	$p < 0.05$
	1.78 ± 0.19 (9)	t_{45}	0.94 ± 0.13 (9)	47.19	$p < 0.01$
	1.78 ± 0.19 (9)	t_{60}	1.17 ± 0.14 (9)	34.26	$p < 0.05$
Chorea with arms outstretched	1.89 ± 0.14 (9)	t_{45}	1.44 ± 0.15 (9)	23.80	$p < 0.05$
Chorea during conversation	2.43 ± 0.27 (8)	t_{30}	1.69 ± 0.21 (8)	30.45	$p < 0.05$
	2.50 ± 0.25 (9)	t_{45}	1.72 ± 0.26 (9)	31.20	$p < 0.05$
	2.50 ± 0.25 (9)	t_{60}	1.89 ± 0.22 (9)	24.40	$p < 0.05$
	2.50 ± 0.25 (9)	t_{75}	2.11 ± 0.25 (9)	15.60	$p < 0.05$
Chorea during voluntary movement	2.25 ± 0.23 (8)	t_{30}	1.81 ± 0.23 (8)	19.56	$p < 0.05$
	2.22 ± 0.20 (9)	t_{45}	1.61 ± 0.20 (9)	27.47	$p < 0.05$
	2.22 ± 0.20 (9)	t_{60}	1.61 ± 0.18 (9)	27.47	$p < 0.05$
	2.22 ± 0.20 (9)	t_{75}	1.89 ± 0.61	14.86	$p < 0.05$
Walking	1.44 ± 0.27 (8)	t_{30}	0.69 ± 0.31 (8)	52.08	$p < 0.05$
	1.44 ± 0.24 (9)	t_{45}	0.89 ± 0.27 (9)	38.19	$p < 0.05$
	1.44 ± 0.24 (9)	t_{60}	0.94 ± 0.27 (9)	34.72	$p < 0.05$
Total score	16.75 ± 1.90 (6)	t_{15}	15.59 ± 1.96 (6)	6.93	$p < 0.05$
	17.63 ± 1.62 (8)	t_{30}	13.00 ± 1.48 (8)	26.26	$p < 0.05$
	17.72 ± 1.43 (9)	t_{45}	11.50 ± 1.35 (9)	35.10	$p < 0.01$
	17.72 ± 1.43 (9)	t_{60}	12.17 ± 1.59 (9)	31.32	$p < 0.05$

for 55.00 ± 17.56 min; one patient had hypotension, and two vomited. After a dose of 3 mg, five patients had severe nausea, appearing 8.60 ± 1.86 min after the treatment and lasting for 33.75 ± 8.26 min; five patients had drowsiness, appearing 8.00 ± 3.00 min after the injection and lasting for 52.50 ± 7.50 min (Table 5). Some evaluations were not performed because of the inability of patients to comply with the task when side effects occurred. The number of missing evaluations was reckoned as a global measure of the incidence of side effects after each dose.

TABLE 5. *Time course of significantly different variations after apomorphine 3 mg (mean ± SEM; number of observations is shown in parentheses)*

Item	Baseline score		Score at time shown	Improvement (%)	Significance level
Chorea at rest	1.69 ± 0.23 (8)	t_{60}	1.13 ± 0.23 (8)	33.14	$p < 0.05$
Chorea with arms outstretched	1.88 ± 0.21 (8)	t_{60}	1.43 ± 0.20 (8)	23.94	$p < 0.05$
Chorea during conversation	2.44 ± 0.26 (8)	t_{45}	1.67 ± 0.33 (6)	31.56	$p < 0.05$
	2.44 ± 0.26 (8)	t_{60}	1.88 ± 0.25 (8)	22.95	$p < 0.05$
	2.44 ± 0.26 (8)	t_{75}	2.06 ± 0.22 (8)	15.57	$p < 0.05$
Total score	16.90 ± 2.30 (5)	t_{30}	14.60 ± 2.34 (5)	13.61	$p < 0.05$
	16.33 ± 1.96 (6)	t_{45}	12.84 ± 1.95 (8)	21.37	$p < 0.05$
	15.62 ± 1.50 (8)	t_{60}	12.13 ± 1.50 (8)	22.34	$p < 0.05$
	15.62 ± 1.50 (8)	t_{75}	13.50 ± 1.61 (8)	13.57	$p < 0.05$
	15.62 ± 1.50 (8)	t_{90}	14.75 ± 1.82 (8)	5.57	$p < 0.05$

All evaluations were performed after placebo; four assessments (three at t_{15} and one at t_{30}) were not performed after 1.5 mg; nine assessments (four at t_{15}, three at t_{30}, and two at t_{45}) were not performed after 3 mg (not considering patient 5). Patient 5 had severe hypotension after the administration of 1.5 mg; therefore, she did not receive the 3-mg dose.

DISCUSSION

Our study indicates that apomorphine, when injected subcutaneously, is able to induce a transient improvement of motor performance in HD patients. The total score had a maximal improvement of 38.54% at 50 min after the administration of 1.5 mg ($p < 0.01$), of 30.40% at 50.62 min after the administration of 3 mg ($p < 0.05$), and no improvement after placebo. The analysis of individual items of the rating scale showed that improvement occurred in some specific items after 1.5 mg, but not after 3 mg. The improvement after 1.5 mg was observed not only for the items measuring the intensity of chorea (chorea at rest, with arms outstretched, during conversation, and voluntary movements of the limbs; 35.25% on average) but also for those related to motor impersistence (tongue protrusion and eye closure; 65.74% on average) and those evaluating the capability of suppressing associated movements (head movements during saccades; 61% on average). This symptomatic improvement occurred from 30 to 60 min after the administration of 1.5 mg of apomorphine (i.e., for a longer time of action than that of apomorphine in Parkinson's disease; 11). This is also confirmed by the observation that the total score improved from 45 to 75 min after the administration of 1.5 mg.

This study also shows that the administration of 3 mg of apomorphine was efficacious only for chorea and on the total score. Our observation is in keeping with earlier data showing that some dopamine agonists may be beneficial at low doses but not at high doses in HD chorea. Chronic administration of bromocriptine was shown to reduce chorea at a daily dose of 10 mg but not at higher doses (5). Chronic low doses of terguride (1 mg daily) were also effective in reducing chorea in patients affected by HD (6). These earlier observations were interpreted as caused by an effect of dopamine receptor agonists on presynaptic but not on postsynaptic dopaminergic receptors; this effect could reduce the activity of midbrain dopaminergic neurons. However, the doses of apomorphine used in our experiments were presumably all postsynaptic, because they are commonly em-

TABLE 6. *Percentage incidence of side effects after the administration of 1.5 mg and 3 mg of apomorphine (the number of cases is shown in parentheses)*

Side effect	1.5 mg	3 mg
Nausea	55.55 (5)	62.50 (5)
Drowsiness	44.44 (3)	50.00 (5)
Hypotension[a]	11.11 (1)	0
Vomiting	22.22 (2)	0

[a] Patient 5, who had severe hypotension after the administration of 1.5 mg of apomorphine, was not treated with 3 mg.

ployed to test the response to dopaminergic therapy in Parkinson's disease (7). In addition, the average improvement of chorea after the lower and the higher doses of apomorphine was of comparable magnitude (35.25% as compared to 30.41%), and its time course was similar (e.g., compare Table 4 with Table 5). In keeping with this is the demonstration that postsynaptic doses of lisuride (150 μg daily) are acutely effective on HD chorea (12). Furthermore, it may well be that the number of the available assessments after 3 mg of apomorphine was insufficient to reach statistical significance in some items. Because of the higher incidence of side effects after the 3-mg dose, nine evaluations were missing (as compared to four after 1.5 mg). The missing information was clustered from t_{15} through t_{45} (i.e., coincidentally with the time of best scores).

Sedation may exert a nonspecific beneficial effect on chorea. However, it is unlikely that it may improve motor impersistence or the capability to suppress associated movements with a time course similar to that observed for the improvement of chorea. This suggests that the overall clinical efficacy has a weak relationship with drug-induced sedation. In keeping with this are some observations suggesting that the antichoreic efficacy of apomorphine and that of lisuride are independent of the sedative effects of these drugs (3,12,13).

The time course of the clinical effects observed in this study is not completely consistent with the known pharmacokinetics of apomorphine in Parkinson's disease, because the improvement of parkinsonian features occurs on average 11 min after a suprathreshold dose of apomorphine and lasts for 42 min (11). However, the latency of yawning and that of side effects were similar to what is observed in parkinsonian patients treated with apomorphine. Why antiparkinsonian drugs should have antichoreic activity is not completely clear. This feature is not shared by levodopa, known to produce a dose-dependent symptomatic increase of chorea in HD (14), but is shared by most dopamine receptor agonists, including apomorphine. Based on the acute response to apomorphine, HD patients may be treated chronically with dopamine receptor drugs per os, at doses tailored to obtain a long-lasting symptomatic benefit.

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