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Repeated rating improves value of diagnostic dopaminergic challenge tests in Parkinson's disease

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Summary. Clinicians use acute challenges with levodopa (LD) and/or apomorphine (A) for diagnostic dopaminergic response tests in Parkinson's disease (PD) patients. We consecutively compared the value of both drugs with performance of repeated ratings and adverse effect recording. Oral administration of 200 mg LD was superior to subcutaneous injection of 4 mg A in terms of tolerability and onset of temporary UPDRS motor score decline ([previously untreated PD patients] LD: 4.02 [mean] ± 2.45 [SD] {significant decrease: p = 1.42E-07} vs. A: 1.58 ± 3.38 {not significant decrease: p = 0.14}, p = 0.0009; [treated PD patients] LD: 7.71 ± 4.35 {significant decrease: p = 2.48E-06} vs. A: 5.19 ± 4.32 {significant decrease: p = 7.83E-05}, p = 0.07). We suggest diagnostic acute challenge test performance with LD as first- and A as second choice due to better tolerability and valuation in combination with repeated scoring procedures to improve sensitivity and specifity.

Keywords: Parkinson's disease, challenge tests, levodopa, apomorphine.

Introduction

Pathological studies pointed out, that the clinical diagnosis of Parkinson's disease (PD) is incorrect in around 25% of cases (Clarke and Davies, 2000). Therefore various partial expensive investigative methods, i.e. functional imaging techniques with various radiotracers, were suggested, but diagnostic accuracy did only improve to a certain extent (Clarke et al., 2000). Thus the simple, cheap challenge tests with levodopa or apomorphine are the most essential tools for many clinicians to test the response to dopaminergic stimulation, which is looked upon as one essential commonly accepted diagnostic feature of PD (Clarke et al., 2000). However the sensitivity and specifity of the acute challenge tests varies dependent on the application of levodopa or apomorphine, their use in "de-novo" or treated PD patients and the missing distinct superiority over initial chronic application of dopamimetic drugs

(Clarke et al., 2000). Nearly all studies report PD patients with a negative response to the various types of dopaminergic stimulation and they perform scoring after drug intake only once (Clarke et al., 2000). However gastrointestinal levodopa absorption and drug trespassing of the intact blood brain barrier individually differs in PD patients (Müller et al., 2000; Häussermann et al., 2001). Therefore this may influence rating results and onset of adverse events. Objectives of this study were to compare the motor response and the tolerability of an acute oral levodopa/benserazide application and a subcutaneous apomorphine injection, performed one after the other, in de-novo and treated PD patients.

Subjects and methods

Subjects

We enrolled 18 (I: female n = 6, male = 12) previously untreated (de-novo) and 14 (II: female n = 1, male = 13) treated non fluctuating idiopathic PD patients, taken off medication for at least 12 hours, into this study (Table 1). Treated PD patients were on a dopaminergic drug regimen, consisting of levodopa/benserazide (or carbidopa), one dopamine agonist and/or selegiline. We also administered to 11 other treated, non fluctuating PD patients, being off medication for at least 12 hours, (III: female n = 5, male = 6) oral placebo capsules and scored them under double-blind conditions within their participation in another trial with a similar design for evaluation of the response to placebo intake. All participants received breakfast after the challenge test. There were no significant differences between all three groups concerning age, Hoehn and Yahr Stage (HYS), Unified Parkinson's Disease Rating Scale (UPDRS) I-, UPDRS II- and Becks Depression Inventory (BDI) score at baseline, but UPDRS III score of patients of group III significantly differed from the other ones (results not shown) (Table 1, 3). All participants had idiopathic PD and responded to their following antiparkinsonian drug titration, respectively continuation.

Design

We scored hospitalized PD patients with the UPDRS, HYS and BDI before oral application of 250 mg levodopa/benserazide (Madopar®), respectively subcutaneous injection of 4 mg apomorphine. Our standardized test protocol eliminated putative influencing factors, i.e. sleep deficits, day time etc. All patients were pretreated with the peripherally acting dopamine receptor blocker domperidone (Motilium®) (40 mg t.i.d.) both the day before and 30 minutes before the dopaminergic drug administration in order to reduce

Table 1. Demographic data of groups of PD patients

Group		Age	HYS stage	UPDRS I	UPDRS II	BDI
I	mean ± SD	55.39 ± 10.38	2.28 ± 0.67	0.94 ± 1.11	7.00 ± 3.43	6.28 ± 3.80
	range	29–69	I–III	0–4	2–15	0–14
II	mean ± SD	61.14 ± 7.11	2.29 ± 0.73	1.50 ± 1.45	10.00 ± 4.00	7.21 ± 6.48
	range	47–72	I–III	0–5	1–15	0–18
III	mean ± SD	55.3 ± 13.5	2.2 ± 0.8	0.7 ± 0.8	8 ± 4.5	8 ± 4.6
	range	37–74	I–III	0–2	1–17	1–17

BDI Beck's Depression Inventory; *HYS* Hoehn and Yahr Scale; *SD* standard deviation; *UPDRS* Unified Parkinson's Disease Rating Scale, *I* mental behaviour, *II* activities of daily living, age is given in years

onset and/or intensity of side effects. We performed rating with the UPDRS III before (0 = baseline), 30, 60 and 90 minutes after drug application. We recorded the concomitant appearance of adverse events (items: nausea, dizziness, fatigue, yawning, numbness, orthostasis) and added them. Each item was only counted one time on each investigation day. Raters were blinded.

Statistics

We performed parametric tests due to normal data distribution. We calculated the mean change of UPDRS III-score at the various time points with the formula: [0 min] − ([30 min] + [60 min] + [90 min])/3 = mean change. We used ANCOVA with repeated measures design including UPDRS I-, II-, BDI-score, sex and age as covariates for comparisons of the computed mean UPDRS III response and the number of observed side effects between apomorphine- and levodopa application. We adjusted the p-value to 0.025. We analyzed the motor response to levodopa, respectively apomorphine, in the various groups of PD patients on each investigation day with ANCOVA with the same covariates in combination with Tukeys HSD-test for the post hoc analysis.

Ethics

Each subject gave written informed consent. The local ethical committee approved this study.

Results

UPDRS III rating

Levodopa administration significantly more reduced the UPDRS motor score than apomorphine injection (Table 2; line 2 and 7). There were distinct more deteriorations of the UPDRS motor score with apomorphine than with

Table 2. Comparison of the response to levodopa and apomorphine

Group		Levodopa/benserazide	Apomorphine	p	F
I	UPDRS change	4.02 ± 2.45; −0.67–8.33	1.58 ± 3.38; −3.33–7.33	0.0009	17.04
	mean side effects	0.61 ± 0.92; 0–2	1.79 ± 1.12; 0–3	0.008	9.75
	breaking off	0	4		
	total	54	44		
	negative response	4	14 [2]*		
II	UPDRS change	7.71 ± 4.35; 2.67–20.33	5.19 ± 4.32; −3.33–12	0.07	4.05
	mean side effects	0.29 ± 0.47; 0–1	1.46 ± 1.56; 0–4	0.025	6.51
	breaking off	0	2		
	total	42	36		
	negative response	1	4 [1]*		

Third and fourth column: all data are given as mean ± standard deviation; minimum–maximum; *I* de-novo PD patients; *II* treated PD patients, being off medication; *breaking off* number of PD patients, who stopped participation due to intolerability of the given drug, *F* F-value of ANCOVA; *p* p-value; *mean side effects* computed mean of items: nausea, dizziness, fatigue, yawning, numbness, orthostasis; significant results are bold; [ ]* total number of patients with negative response in all three rating procedures, *total* number of performed UPDRS III (items 18–31) ratings in each group, *UPDRS* Unified Parkinson's Disease Rating Scale

Table 3. Scored motor symptoms after levodopa, respectively apomorphine administration

Group		Baseline	30	60	90	F	ANCOVA p
I	LD/B	24.94 ± 12.05; 11–49	20 ± 11.44; 8–46	21.50 ± 11.76; 8–46	21.28 ± 11.32; 9–44	16.35	1.42E-07
	p*		0.0002	0.0003	0.0002		
	A	23.33 ± 9.76; 13–45	22.44 ± 9.78; 8–45	24.07 ± 9.71; 11–45	23.36 ± 9.16; 12–43	1.96	0.14
	p*		0.13	0.75	0.28		
II	LD/B	34.64 ± 12.71; 20–64	28.86 ± 14.05; 16–59	25.64 ± 10.01; 13–49	26.29 ± 9.84; 12–52	13.96	2.48E-06
	p*		0.003	0.0002	0.0002		
	A	31.36 ± 11.96; 17–63	25 ± 9.41; 17–51	24.67 ± 11.26; 13–54	27.75 ± 11.74; 11–60	9.97	7.83E-05
	p*		0.0005	0.0003	0.08		
III	placebo	15.36 ± 6.76; 6–26	15.14 ± 6.87; 6–26	15.14 ± 6.81; 6–26	15.09 ± 6.80; 6–26	1.08	0.37
	p*		0.53	0.53	0.38		

Baseline rating before drug administration; *30 (60, 90)* UPDRS III (items 18–31) scoring, which was performed 30 (60, 90) minutes after drug application; *column 3 to 6 (line 2, 4, 6, 8, 10)* UPDRS III (motor examination) scores are given as mean ± standard deviation; minimum–maximum; *I* de-novo PD patients; *II* treated PD patients, being off medication; *III* treated PD patients, who only received placebo; *F* F-value of ANCOVA; *ANCOVA p* p-value of the ANCOVA analysis; *p** p-value of the post hoc comparisons versus baseline; significant results are bold; *UPDRS* Unified Parkinson's Disease Rating Scale

levodopa, even three PD patients showed a negative response with an increase of the UPDRS motor score at all time points after the apomorphine injection (Table 2; line 6 and 12).

There was a significant reduction of UPDRS III scores after levodopa application (Table 3; line 2) but not after subcutaneous apomorphine injection in the previously untreated PD patients (Table 3; line 4). A significant decrease of UPDRS III scores occured after oral levodopa intake (Table 3; line 6) and after apomorphine administration in the treated PD patients (Table 3; line 8). We found no further significant comparisons in the post hoc analysis in both groups of patients.

Placebo treatment did not significantly alter UPDRS scores, six PD patients did not change at all in their UPDRS scores, four mildly deteriorated and one markedly improved (Table 3; line 10). No significant impact of covariates appeared in the whole ANCOVA analysis.

Adverse effects

Onset of side effects was significantly more pronounced with apomorphine than with levodopa (Table 2; line 3 and 8). Breaking off of the challenge test due to onset of side effects did not appear after levodopa administration. Two de-novo and two treated patients stopped repeated UPDRS rating after subcutaneous injection of apomorphine within the first 30 minutes, therefore they were not considered for the statistical evaluation. Further two de-novo PD patients did not continue after the first rating, their computed change between baseline and score after 30 minutes was included in the outcome calculation. The number of side effects of all these participants with a breaking off were not considered for the statistics. Placebo administration induced no adverse effects.

Discussion

Our results show, that challenge tests with 250 mg levodopa/benserazide are superior to 4 mg apomorphine in terms of tolerability and of motor response in particular in de-novo PD patients. Moreover the decline of the UPDRS motor score was not significant after apomorphine in the previously untreated PD patients. Subcutaneous injection of higher apomorphine dosages could hypothetically improve the diagnostic value. However, a challenge with 6 mg apomorphine and more will certainly be accompagnied by a further increased onset of side effects in particular in the de-novo PD patients according to our results on the tolerability.

The performed repeated rating procedure in our trial shows, that deteriorations of the motor score may occur followed by distinct improvements or vice versa with both compounds to a considerable extent and even under placebo to a lesser extent. We assume, that this contributed to the limited sensitivity and specifity of both types of acute dopaminergic challenge tests according to the literature (Clarke and Davies, 2000). The number of negative reponses was distinct higher in de-novo PD patients compared to the treated ones. Treated PD patients have a diminished dopamine autoreceptor function

and subsequently a dopaminergic treatment induced downregulation of the endogenous neuronal dopamine synthesis, which is regulated by the still working autoreceptor in de-novo PD patients (Skirboll et al., 1979; Ekesbo et al., 1999). However these presynaptic dopaminergic autoreceptors are at least six to ten times more sensitive to dopaminergic compounds, in particular apomorphine, compared to postsynaptic dopaminergic receptors (Skirboll et al., 1979; Ekesbo et al., 1999). Therefore we hypothesize, that application of the dopaminergic drugs at the given dosages initially induced a downregulation of the still existing presynaptic endogenous dopamine production in de-novo PD patients and correspondingly induced a deterioration of the UPDRS motor score.

Additional domperidone treatment did not prevent the significant distinct higher appearance of adverse events with the emetic apomorphine, which we used in more moderate dosages (Hughes et al., 1990; Steiger and Quinn, 1992) compared to trials with injection of up to 10 mg at the most (Rascol et al., 1990; D'Costa et al., 1991). However breaking off appeared only after apomorphine injection in particular in the de-novo PD patients. This supports the view, that long-term dopaminergic stimulation in treated PD patients induces tolerance to the known side effects of apomorphine (Montastruc et al., 1996).

Our study would be of more value with a repeated test procedure with application of various dosages of apomorphine, respectively levodopa/benserazide, consecutive drug plasma level monitoring, additional blinding of PD patients and a complementary comparison to chronic levodopa therapy with repeated UPDRS evaluation after the last dopaminergic drug intake.

In conclusion our study indicates that the described decreased sensitivity and specifity of dopaminergic challenge tests in the literature will improve with repeated scoring within a fixed time interval. We suggest diagnostic acute challenge test performance with levodopa as first- and with apomorphine as second choice due to better tolerability and valuation.

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