

FOCUS ON PARKINSON'S DISEASE

ACUTE CHALLENGE WITH
APOMORPHINE AND LEVODOPA IN
PARKINSONISM

A. Albanese

HALLUCINATIONS, REM SLEEP,
AND PARKINSON'S DISEASE:
A MEDICAL HYPOTHESIS

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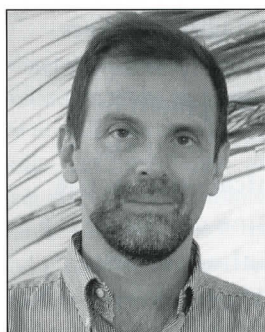
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ACUTE CHALLENGE WITH APOMORPHINE AND LEVODOPA IN PARKINSONISM

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Although the recognition of a parkinsonian syndrome may be immediate, the clinical diagnosis of idiopathic Parkinson's disease (PD) remains difficult, due to the lack of specific biological markers. Other parkinsonian syndromes may present with similar clinical features, and clinical diagnostic errors have been demonstrated in pathological series [1]. Ap-

proximately 75% of patients seen at movement disorder clinics exhibit the typical features of PD [2]; they may respond favorably to dopaminergic treatment and are likely to receive a clinical diagnosis of PD. Still, the diagnosis of PD is confirmed pathologically in only about 75% of these patients [1]. Response to antiparkinsonian medication is closely related to the diagnosis. PD always responds (often dramatically) to treatment with levodopa or dopamine agonists. Thus, a lack or loss of response to levodopa is considered incompatible with a diagnosis of PD [1, 3] and has been used as a criterion for the diagnosis of multiple-system atrophy (MSA) [4]. However, parkinsonian syndromes other than PD (e.g., drug-induced parkinsonism, MSA, autosomal recessive juvenile parkinsonism) may also improve significantly with dopaminergic drugs [3, 5-8].

Patients with MSA may respond to levodopa for some time before becoming unresponsive [7, 8]. In some of these patients, however, a sustained response to dopaminergic drugs can be retained throughout the course of the disease. Some MSA patients may respond to dopamine agonists, but not to levodopa. Table 1 shows an example of a

clinically definite MSA patient, who had a motor improvement greater than 50% following acute challenge with apomorphine, but not with levodopa. The acute test predicted that chronic treatment would be necessary, which was successfully achieved with pergolide 1 mg three times daily; chronic administration of levodopa was ineffective. In parkinsonian patients who do not improve following acute dopaminergic challenge, MSA is often suspected based on the assumption that nigrostriatal (as opposed to striatonigral) degeneration is accompanied by loss of dopaminergic response. Table 2 shows the results of the challenge tests in a patient with a cavernous angioma of the midbrain [9]. Initially, the secondary parkinsonism produced by this tumor was responsive to levodopa and to apomorphine; after a second hemorrhage

TABLE 1 - ACUTE CHALLENGE TESTS OF A CLINICALLY DEFINITE MSA PATIENT SHOWED IMPROVEMENT IN UPDRS MOTOR SCORE AFTER ACUTE CHALLENGE WITH APO-MORPHINE, BUT NOT LEVODOPA. CHRONIC RESPONSE TO LEVODOPA WAS UNSATISFACTORY; BASED ON THE ACUTE CHALLENGE, THE PATIENT WAS PUT UNDER CHRONIC TREATMENT WITH PERGOLIDE AND HAD A SIGNIFICANT IMPROVEMENT.

Acute challenge	Improvement
Levodopa/carbidopa 250/25 mg	- 7%
Apomorphine 1.5 mg	- 54%
Apomorphine 3 mg	- 65%
Apomorphine 4.5 mg	- 69%
Apomorphine 6 mg	- 69%

TABLE 2 – VARIATION IN UPDRS MOTOR SCORE IN RESPONSE TO ACUTE DRUG CHALLENGE IN A PATIENT WITH A CAVERNOUS ANGIOMA OF THE MIDBRAIN [9].

Drug	February 1994	November 1995
Levodopa/carbidopa 250/25 mg	43.2%	13.5%
Apomorphine 1.5 mg		14.6%
Apomorphine 3 mg	18.8%	16.8%
Apomorphine 4.5 mg		24.3%
Apomorphine 6 mg		24.3%

with enlargement of the lesion, the response to levodopa was lost, but the response to apomorphine was retained. Chronic treatment confirmed the response to drugs predicted by the acute challenge. These two examples highlight the type of clinical issues that can be addressed by acute dopaminergic challenge tests.

Challenge tests, designed to acutely stimulate central dopaminergic receptors, are commonly performed in clinical practice or in clinical research (such as surgical protocols, combined administration of drugs, studies on behavioral or dysautonomic changes) [10], and have been incorporated into guidelines for experimental studies on parkinsonian subjects [11, 12]. Acute challenge with levodopa or apomorphine is current practice in the clinical assessment of parkinsonian patients to confirm the diagnosis of levodopa-responsive PD and to predict the chronic response to oral medication [13, 14]. A sustained response to levodopa has been observed in patients who achieve 20-30% improvement following acute challenge with apomorphine [15], but the exact predictive value of the direct agonist apomorphine and of the "prodrug" levodopa is a matter of debate. It has also been postulated that the different mechanisms of action of apomorphine and levodopa may enable them to have different uses in clinical practice [16].

DRUGS

The available data are based mainly on the administration of levodopa or apomorphine.

Levodopa

Levodopa is administered orally; its efficacy depends mainly on the dose administered, on intestinal absorption and passage through the blood-brain barrier. The fraction absorbed varies depending on gastric motility and content, and on the galenic formulation administered. It has been suggested that the variability of the response to oral levodopa can be overcome by the administration of parenteral formulations, such as the soluble ester prodrugs of levodopa [17, 18].

Levodopa challenge is typically performed in the morning using a regular formulation, following withdrawal of all anti-parkinsonian medication and an overnight fast. Absorption can be hastened by administering a suspension of levodopa (e.g., dispersible co-beneldopa or crushed co-careldopa) in 100-150 ml of carbonated water. The dose of levodopa should be defined based on the purpose of the challenge; the observation of poor clinical improvement may mean that an insufficient dose of levodopa has been administered or absorbed.

In drug-naïve patients, the recommended dose is up to 250 mg (in association with peripheral decarboxylase inhibitors) in the morning and in the fasting state. In patients under chronic treatment, a levodopa dose that is higher than the usual morning dose may be administered to perform a supra-threshold challenge; such an increase in levodopa dose may compensate for other withdrawn antiparkinsonian drugs and overcome problems of absorption.

Although the use of levodopa for acute challenge has the advantage of using the natural precursor of dopamine, it also has some theoretical disadvantages compared with apomorphine: levodopa may prime dyskinesias, particularly in drug-naïve patients [19]; and, depending on the schedule, levodopa challenge may be time-consuming.

Apomorphine

Acute challenge with apomorphine has been introduced into clinical practice for a number of reasons: (1) clinical experience has shown that the potency of apomorphine is comparable with that of levodopa [13, 16, 20]; (2) subcutaneous administration minimizes the response variability; and (3) its short half-life enables repeat challenge to be undertaken and dose-response curves to be generated. A meta-analysis of the available data on dopaminergic testing has suggested that the negative predictive value of a chronic response to levodopa is almost identical to both the apomorphine test and the levodopa test [21]; however, in drug-naïve patients, levodopa has a better negative predictive value for a chronic response than apomorphine [15].

Apomorphine is usually administered subcutaneously in the abdomen, either as a single injection of 3 mg (or 50 µg/kg), or as repeated challenges with a starting dose of 1.5 mg (or 25 µg/kg) followed by stepwise increments of 1.5-3 mg, up to 9 mg, once every 30 minutes.

Compared with levodopa, apomorphine has the theoretical advantage in that it avoids priming dyskinesias, but it also has a number of disadvantages. First, it is less well tolerated, because side effects occur more often and are occasionally severe (mainly nausea, vomiting, or orthostatic hypotension) [22], and needle phobia or local pain may distress the patient. Second, the occurrence of symptoms that are easy to recognize (e.g., yawning or nausea) makes it less suitable than levodopa for a double-blind evaluation. And third, it must be given with

TABLE 3 – SERIES OF 134 CONSECUTIVE PARKINSONIAN PATIENTS EVALUATED BY ACUTE DOPAMINERGIC CHALLENGE TESTS [16].

	PD	non-PD	MSA	PSP	NC
Number of patients (male/female)	83 (51/32)	51 (27/24)	28 (13/15)	6 (2/4)	17 (12/5)
Age at disease onset (years $\pm$ SD)	56.4 $\pm$ 10.7	61.8 $\pm$ 10.7	58.3 $\pm$ 10.7	67.3 $\pm$ 6.4	63.3 $\pm$ 11.5
Disease duration at time of test (years $\pm$ SD)	4.8 $\pm$ 3.6	4.9 $\pm$ 3.7	4.7 $\pm$ 3.8	3.0 $\pm$ 2.5	5.6 $\pm$ 3.6
Disease duration at time of last evaluation (years $\pm$ SD)	7.1 $\pm$ 4.4	6.7 $\pm$ 4.1	6.5 $\pm$ 4.1	4.3 $\pm$ 4.0	7.8 $\pm$ 3.6

PSP = progressive supranuclear palsy; NC = unclassified parkinsonian syndrome.

the antiemetic domperidone and the two drugs are not universally available. In addition, the antiparkinsonian action of apomorphine is not mediated by dopamine and may be considered less suitable to predict a chronic response to levodopa.

ASSESSMENT

The clinical assessment should be performed by experienced personnel and videotaped for post-hoc verification; the intra- and interrater reliability should preferably be assessed in advance. These recommendations apply particularly to clinical research.

The outcome measures depend on the purpose of the challenge. The motor condition can be assessed by means of validated clinical scales (e.g., Unified Parkinson's Disease Rating Scale [UPDRS] motor score, tremor scales) [23, 24], by clinical measures (finger-tapping speed, walking time) [11], or by instrumental measurements (movement time, accelerometry, gait and posture analysis) [25]. Drug-related dyskinesias (such as "off"-period dystonia, diphasic or peak-dose dyskinesias) can be evaluated by appropriate clinical scales (Goetz's scale, AIMS, UPDRS part IV) [12, 26, 27]. Nonmotor effects (e.g., mood, sensory phenomena, autonomic function, sedation, neuropsychiatric phenomena) should be evaluated by appropriate clinical tools. Neurophysiological parameters (e.g., evoked potentials, intracerebral microrecordings) and functional neuroimaging may be employed for the purpose of specific assessments. The adverse effects must be monitored.

The time of the assessment varies depending on the goal of the challenge. The onset of motor effects occurs approximately 10 minutes after a subcutaneous injection of apomorphine and 30 minutes after oral levodopa. The motor effects last for up to 60 minutes after apomorphine and for several hours after levodopa [1, 3, 5]. The peak efficacy of subcutaneous apomorphine occurs after 15-25 minutes and that of levodopa after 45-90 minutes [14].

TABLE 4 – AVERAGE PERCENTAGE UPDRS MOTOR SCORE IMPROVEMENT IN PD, NON-PD, MSA, AND PSP PATIENTS.

Drug	PD	non-PD	MSA	PSP	NC
Apomorphine 1.5 mg	27.1%	10.5%	11.9%	12.4%	9.6%
Apomorphine 3.0 mg	27.7%	9.7%	14.3%	5.8%	7.6%
Apomorphine 4.5 mg	28.8%	11.8%	13.3%	6.9%	11.4%
Levodopa/carbidopa	29.8%	12.2%	12.8%	13.4%	13.1%

Comparison of PD cases to any other group was statistically significant ($p < 0.01$, in each case, with Student's *t*-test) [16].

PSP = progressive supranuclear palsy; NC = unclassified parkinsonian syndrome.

PREDICTIVE VALUE OF ACUTE CHALLENGE

In a recent study [16], a series of 134 consecutive parkinsonian patients (56 women, 78 men) with a parkinsonian syndrome were evaluated with acute challenge tests in the defined "off" condition [11]. Patients were tested in the early morning in a fasting state; they received a single standard oral dose of levodopa/carbidopa 250/25 mg on the first day and apomorphine on the following days. Apomorphine was given subcutaneously at a dose of 1.5, 3.0, or 4.5 mg, with a delay of at least 90 minutes between two subsequent doses or on separate days. Dosage was increased until either side effects occurred or the maximum dose was reached. Motor responses were assessed at baseline and 60 minutes after the levodopa challenge or 20 minutes after each subcutaneous dose of apomorphine. The motor response was evaluated by the UPDRS motor score.

Based on clinical follow-up or on autopsy, 83 patients (61.9%) received a retrospective clinical diagnosis of PD, and 51 patients (38.1%) had a clinical diagnosis of a parkinsonian syndrome other than PD. In the latter group, 28 patients (20.9%) had a clinical diagnosis of MSA; 6 patients (4.5%) had a clinical diagnosis of progressive supranuclear palsy. The

remaining 17 patients had an unclassified parkinsonian syndrome. Patients' demographics, disease duration at time of the acute challenge, and duration of follow-up are given in table 3. UPDRS motor score improvement was on average higher in PD than in non-PD patients (levodopa, 29.8% vs. 12.2%; apomorphine 1.5 mg, 27.1% vs. 10.5%; apomorphine 3 mg, 27.7% vs. 9.7%; apomorphine 4.5 mg, 28.8% vs. 11.8%; $p < 0.01$ by Student's *t*-test) (table 4).

When PD patients were compared with non-PD patients, levodopa challenge had the best diagnostic accuracy with an improvement of 16%. Apomorphine had the best diagnostic accuracy with a threshold improvement of 13.5% for 1.5 mg, of 13% for 3 mg, and of 16% for 4.5 mg. This meant that patients improving by at least 16% in all tests had the highest probability of having PD.

When PD patients were compared with MSA patients, levodopa acute challenge had the best diagnostic accuracy with a threshold improvement of 17%. Apomorphine had the best diagnostic accuracy with an improvement of 13% for 1.5 mg, of 15% for 3 mg, and of 18% for 4.5 mg. This meant that patients improving by at least 18% in all tests had the highest probability of having PD rather than MSA.

When patients who had a chronic response to levodopa were compared with those who did not, acute challenge with

levodopa had the best predictive accuracy with a threshold improvement of 14.5%. Apomorphine had the best predictive accuracy with an improvement of 13% for 1.5 mg, and of 14% for 3 and 4.5 mg. This meant that patients improving by at least 14.5% in all tests had the highest probability of responding to a chronic treatment.

SUMMARY

The study showed good agreement between acute challenges with levodopa and apomorphine, and the use of both improved the reliability of the test. Different threshold improvements after acute challenges support a diagnosis of PD or the exclusion of MSA, and have a predictive value for subsequent response to chronic levodopa therapy.

The data available do not enable a simple and universal rule for performing or interpreting acute dopaminergic challenge tests to be defined. A positive response to acute levodopa or to apomorphine can be used in clinical practice or in clinical studies as an additional inclusion criterion. This may increase the accuracy of identifying patients who will have a beneficial response to the chronic administration of levodopa and are therefore likely to have PD (the positive predictive value varies from 67% to 96%) [3, 10, 15, 28].

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EDITORIAL

In this issue of *Focus on Parkinson's Disease*, Prof. Albanese considers, in his original contribution, the value of the acute levodopa or apomorphine test in diagnosing Parkinson's disease. Clinical diagnosis of parkinsonism might be easy but, in the early stages of the disease, the exact differentiation between idiopathic Parkinson's disease and other forms of parkinsonism still remains difficult, because of the similarity of their main clinical symptoms. Despite the fact that parkinsonian syndromes are characterized by distinct neuropathological entities, there is still a lack of specific neurochemical, neurophysiological, and neuroimaging markers that can be used for in vivo diagnosis. However, early and precise diagnostic specification is important for the development of adequate therapeutic strategies and to predict the prognosis. In light of this, as an addition to well-defined clinical criteria, the performance of an acute levodopa or apomorphine challenge is a very useful diagnostic tool. In his article, the author provides a comprehensive overview of the technique and the predictive value of both tests.

In addition to the original contribution, this issue of *Focus on Parkinson's Disease* includes a number of extended abstracts that discuss actual problems in different clinical and preclinical fields of Parkinson's disease, two of which deal with the role of catechol-O-methyltransferase (COMT) inhibition and two others that deal with stereotactic surgery. As in previous issues, the reader will again find a number of carefully selected papers highlighting the latest developments in Parkinson's disease.

Prof. Dr. H. Baas, Editor