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Consensus Statement on the Role of Acute Dopaminergic Challenge in Parkinson's Disease

Alberto Albanese, MD,[1]* Ubaldo Bonuccelli, MD,[2] Christine Brefel, MD,[3] K. Ray Chaudhuri, MD, FRCP,[4] Carlo Colosimo, MD,[5] Tobias Eichhorn, MD,[6] Eldad Melamed, MD,[7] Pierre Pollak, MD,[8] Teus Van Laar, MD, PhD,[9] and Mario Zappia, MD[10]

[1]*Istituto di Neurologia, Università Cattolica, and Istituto Nazionale Neurologico, Milano, Italy*
[2]*Clinica Neurologica, Università di Pisa, Pisa, Italy*
[3]*Laboratoire de Pharmacologie Médical et Clinique, INSERM U455, Toulouse, France*
[4]*Department of Neurology, King's College Hospital, London, United Kingdom*
[5]*Dipartimento di Scienze Neurologiche, Università La Sapienza, Roma, Italy*
[6]*Klinik für Neurologie, Zentrum für Nervenheilkunde, Philipps-Universität Marburg, Germany*
[7]*Department of Neurology, Beilinson Medical Centre, Sackler Medical School, Tel-Aviv, Israel*
[8]*Service de Neurologie, Université J. Fourier, Grenoble, France*
[9]*Department of Neurology, Leiden University Medical Centre, Leiden, The Netherlands*
[10]*Clinica Neurologica, Università di Catanzaro, Catanzaro, Italy*

Abstract: Available evidence on the practice of acute pharmacological challenge tests in parkinsonian patients was reviewed by a committee of experts, which achieved a general consensus. The published data deal mainly with the acute administration of levodopa and apomorphine in Parkinson's disease. Such challenge may serve different purposes, e.g., research, diagnosis, or tailoring of treatment. Unique protocols describing the clinical setting and practice parameters are not available. The present paper describes the scientific background and supplies practical guidelines, whenever possible, to perform and evaluate acute challenge tests in parkinsonian syndromes. With the appropriate indication and setting, acute challenge tests are useful in diagnosis and therapy of Parkinson's disease and related disorders. © 2001 Movement Disorder Society.

Key Words: apomorphine; levodopa; diagnosis; Parkinson disease; treatment

Approximately 75% of patients seen at Movement Disorders clinics exhibit the typical features of Parkinson's disease (PD);[1] they may respond favorably to dopaminergic treatment and are likely to receive a clinical diagnosis of PD. However, the diagnosis of PD is confirmed pathologically in only about 75% of these patients.[2] PD always responds (sometimes even dramatically) to treatment with levodopa or dopamine agonists. However, parkinsonian syndromes other than PD (e.g., drug-induced parkinsonism, multiple system atrophy, autosomal recessive juvenile parkinsonism) may also improve significantly with dopaminergic drugs.[3–5] Acute 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), and have been incorporated into guidelines for experimental studies on parkinsonian subjects.[6,7]

An acute dopaminergic challenge allows a rapid enhancement of brain dopaminergic transmission. According to the drug used, presynaptic, synaptic or postsynaptic mechanisms may be involved. The action of levodopa involves the presynaptic as well as the postsynaptic level,[8] while dopamine agonists, such as apomorphine, mainly act on postsynaptic dopaminergic receptors.[9] An acute challenge can be applied to different clinical issues: (1) the prediction of a chronic response to levodopa or to dopamine agonists,[10–15] (2) the support of a clinical diagnosis of PD based on the assumption that levodopa

*Correspondence to: Alberto Albanese, Istituto Nazionale Neurologico, Via G. Celoria, 11, I-20133 Milano, Italy.
E-mail: alberto.albanese@rm.unicatt.it
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responsiveness is a necessary feature,[3,15,16] (3) the direct assessment of response in parkinsonian patients (latency, magnitude and duration of response, characterization of dyskinesias).[17–20]

SETTING

Inpatients or outpatients may receive an acute dopaminergic challenge, either for clinical or for research purposes. Some general operational criteria for acute dopaminergic challenge will be outlined hereafter, but no unique guideline can be set for all the previously mentioned testing conditions.

The acute challenge is usually performed in the *off* state, which has to be defined according to the goals of the challenge. Naturally occurring *off* (that is, not produced by experimental drug withdrawal) allows the evaluation of the effect of a challenge on motor phenomena, such as early morning dystonia, afternoon *off* periods, etc. A practically defined *off* condition[6] allows the evaluation of the short-duration dopaminergic response in most occasions. More than 12 hours of withdrawal may be necessary for drugs having longer half-lives; as a rule, it is suggested that withdrawal for an anti-parkinsonian drug before an acute challenge should last from three to five times its elimination half-life, but no longer than the patient is able to tolerate. A prolonged wash out, until the achievement of absolute baseline condition, may be necessary for studies in which the abolition of the long-duration response is required.[18,21] Drug holiday, with its inherent discomfort and risks to the patient, will commonly last for 1 or 2 weeks in such cases.

Occasionally, the acute dopaminergic challenge can be performed in a motor state different from the *off* state, such as a partial *on* state, to evaluate diphasic dyskinesias,[22,23] or a typical *on* state, to evaluate additional *on* phenomena, peak dose dyskinesias, etc.[24]

DRUGS

The available evidence is mainly based on the administration of levodopa or apomorphine.

Levodopa

Levodopa is administered orally; its efficacy depends mainly on the dose administered, on intestinal absorption, and the delivery through the blood-brain barrier. The fraction absorbed varies, depending on gastric motility and content, and on the galenic formulation administered. There are suggestions 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.[25,26]

Levodopa challenge is typically performed in the morning using a regular formulation, following withdrawal of all anti-parkinsonian medication and overnight fast (Table 1). Absorption can be hastened by administering a suspension of levodopa (e.g., dispersible Madopar® or crushed Sinemet®) 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-naive 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 higher than the usual morning dose may be administered to perform a supra-threshold challenge; such an increase of levodopa dose may compensate for other withdrawn anti-parkinsonian drugs and overcome problems of absorption.

The use of levodopa for an acute challenge has the advantage of using the natural precursor of dopamine but also some theoretical disadvantage compared to apomorphine: (1) levodopa may prime dyskinesias, particularly in drug-naive patients;[27] (2) depending on the schedule, levodopa challenge may be time-consuming.

Apomorphine

Acute challenge with apomorphine has been introduced into clinical practice because: (1) clinical experience has shown that the potency of apomorphine is comparable to that of levodopa,[10,15,28] (2) subcutaneous administration minimizes the response variability, and (3) its short half-life allows the repetition of a challenge and to generate dose-response curves. A meta-analysis of the available data on dopaminergic testing has suggested that the negative predictive value for a chronic response to levodopa is almost identical with both the apomorphine

TABLE 1. *Dosage and timing for single dose-response test.*

	Levodopa	Apomorphine
Dosage	125–250 mg of a regular formulation (plus peripheral decarboxylase inhibitor)	1.5–9 mg (or 25–150 μg/kg)
Route	Oral	Subcutaneous
Modality	Single dose	Stepwise increments once every 30 minutes
Setting	In the morning following withdrawal of all anti-parkinsonian medication and overnight fast	

test and the levodopa test;[29] however, in drug-naive patients, levodopa has a better negative predictive value for chronic response than apomorphine.[30]

Apomorphine is usually administered subcutaneously in the abdomen, based on one of the following paradigms: (1) a single injection of 3 mg (or 50 μg/kg); (2) 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 (Table 1).

Compared to levodopa, apomorphine has the theoretical advantage of avoiding the priming of dyskinesias, but it has the following disadvantages: (1) it is less tolerated, because side effects occur more often and are occasionally severe (mainly nausea, vomiting, or orthostatic hypotension),[31] and needlephobia or local pain may distress the patient; (2) the occurrence of symptoms that are easy to recognize (e.g., yawning or nausea) makes it less suitable than levodopa for double-blind evaluation; (3) it must be given with the anti-emetic domperidone and the two drugs are not universally available. In addition, the anti-parkinsonian action of apomorphine is not mediated by dopamine and may be considered less suitable to predict a chronic response to levodopa.

Other Drugs

The coadministration of domperidone is often necessary, in order to prevent unwanted peripheral dopaminergic effects, such as nausea, emesis, or hypotension. The addition of domperidone is mandatory in drug-naive patients first receiving levodopa and in those given an apomorphine challenge. It is recommended that a dose of 20 mg three times a day of domperidone is started at least 2 days before the challenge; one dose is administered 1 hour before the apomorphine injection. Higher daily doses, up to 100 mg, can be used for a short time, if required.

Other antiparkinsonian drugs have been used or proposed for an acute challenge. These include biperiden,[32,33] amantadine,[6] piribedil,[34] bromocriptine,[35] intravenous lisuride,[36] and ester prodrugs of levodopa.[37] Placebo (usually an inert tablet given orally or saline solution administered parenterally) may be given to patients receiving single- or double-blind evaluations, particularly for experimental studies.

ASSESSMENT

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

The outcome measures depend on the purpose of the challenge (Table 2). The motor condition can be assessed by means of validated clinical scales (e.g., UPDRS part III, tremor scales, etc.),[38,39] by clinical measures (finger tapping speed, walking time),[6] or by instrumental measurements (movement time, accelerometry, gait and posture analysis).[32] 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).[7,17,40] 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, etc.) and functional neuroimaging may be employed for the purpose of specific assessments. The adverse effects must be monitored.

TABLE 2. *Purposes and limitations of single dose-response tests*

Purposes
Prediction of chronic response to levodopa
Determination of dopaminergic response as diagnostic criterion for PD
Evaluation of fluctuating dose-response pattern as guide to management
Quantification of the motor response in research (drug trial, surgical treatment trial, long-term follow-up study)
Limitations
Domperidone required to prevent nausea with apomorphine and with levodopa in some levodopa naive patients
Single dose response may not reveal the full range of motor fluctuations in an indivdiual patient
Occasional drug-naive patients will not respond to a single dose challenge, but will eventually prove to be responsive to chronic levodopa treatment
A strong long duration response can occasionally mask the response to single test doses during the early phase of pharmacological treatment of PD

PD, Parkinson's disease.

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 up to 60 minutes after apomorphine and for several hours after levodopa.[2–4] The peak efficacy of subcutaneous apomorphine is at 15–25 minutes, that of levodopa is at 45–90 minutes.[9]

Significance of the Motor Assessment

Based on the available evidence, the following consensus is reached on the motor effects of oral levodopa or subcutaneous apomorphine following an acute challenge. The response magnitude to an acute challenge increases as nigrostriatal degeneration progresses;[41] consequently, a positive response may be defined differently at differ-

ent disease stages. In drug-naive patients, a positive response is defined as an improvement in motor scores of at least 20% compared to baseline.[30] In treated patients, a positive response should be defined in advance according to the purpose of the acute challenge.

A positive response to acute levodopa or to apomorphine can be used 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%).[3,10,11,30]

There is no satisfactory definition of a positive chronic response to levodopa; a minimum threshold of 30% motor improvement, compared to baseline, has been considered to be clinically relevant.[42] A chronic response to levodopa cannot be excluded unless a dose of at least 800 mg daily of standard levodopa preparations is given t.i.d. or four times a day for a period of 3 months. Exceptionally, a higher daily dosage (up to 1,200 mg) or a longer observation time (up to 6 months) may be required to detect a chronic response. The appearance of the long-duration response to levodopa[18] may be considered as a positive response to chronic treatment. A satisfactory long-duration response is defined as the improvement in parkinsonian disability, measured in the morning before the first levodopa dose intake, of at least 50% of the maximal improvement observed for the short-duration response to an acute challenge with levodopa.[21] The latency, magnitude, and duration of the long-duration response may be evaluated.[43]

In fluctuating patients, acute challenge tests allow the characterization of the short-duration response. They can also be used to detect the clinical features accompanying a response to a single dose of medication. An acute challenge does not always reflect the complete range of motor fluctuations that a patient experiences in daily life, such as severe rebound off-state, or severe end of day dyskinesias.

Different motor symptoms may display a different response threshold to a dopaminergic challenge. Higher doses are commonly required to observe improvement of severe tremor, freezing of gait, or of handwriting rather than limb rigidity or akinesia. Dose-response curves based on continuous infusions of apomorphine for some hours may permit measurement of such different thresholds.[44] Occasionally, excessive dopaminergic activation may paradoxically worsen parkinsonian symptoms, which are otherwise improved by medication at standard doses (e.g., dysarthria, freezing of gait, or tremor).

Acute challenge tests can be applied to clinical research protocols (such as surgical protocols, the combined administration of drugs, or studies of behavioral or dysautonomic changes). There is a consensus that the patients who respond to levodopa would normally respond to dopamine agonists.

Lack of motor improvement following an acute challenge demands caution on certain occasions: (1) lack of a positive response in a drug-naive patient or in a patient at the beginning of treatment does not always exclude a positive chronic response.[10,11,30] The false negative rate in drug-naive patients for dopaminergic challenge tests predicting a response to chronic levodopa may be as high as 40%; therefore, acute challenge with dopaminergic drugs is not considered a routine clinical practice in such patients; (2) following a negative response to apomorphine, an additional levodopa challenge may be warranted, because it has been occasionally reported that patients who do not respond to apomorphine may respond to levodopa;[11,30] (3) following a negative response to an initial dose of levodopa, the challenge should be repeated by successive stepwise increases of at least 25%.[45] It may be necessary to measure plasma levels of levodopa in order to assess successful absorption and its rate; (4) in non-fluctuating PD patients, who have an unclear response to chronic dopaminergic treatment, the short-duration response to an acute challenge may be masked by the long-duration response to the chronic treatment.[20]

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