

# Acute Challenge with Apomorphine and Levodopa in Parkinsonism

Paola Rossi<sup>a</sup> Carlo Colosimo<sup>b</sup> Elena Moro<sup>a</sup> Pietro Tonali<sup>a, c</sup>  
Alberto Albanese<sup>a, d</sup>

<sup>a</sup>Istituto di Neurologia, Università Cattolica del Sacro Cuore, Roma, <sup>b</sup>Clinica Neurologica I, Università 'La Sapienza', Roma, <sup>c</sup>Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italia; and <sup>d</sup>Service de Neurologie, Université de Lausanne, Lausanne, Suisse

## Key Words

Parkinson's disease · Multiple system atrophy · Progressive supranuclear palsy

## Abstract

**Background:** The diagnosis of different parkinsonian syndromes and the ability to predict long-term drug efficacy constitute important clinical issues. **Design:** Motor responses to the acute administration of levodopa and apomorphine were analyzed in a series of 134 parkinsonian patients, including 83 patients with a clinical diagnosis of idiopathic Parkinson's disease (PD), 28 patients with multiple-system atrophy (MSA), 6 with progressive supranuclear palsy, and 17 with an unclassified parkinsonian syndrome. **Methods:** The patients received oral levodopa/carbidopa (250/25 mg) and subcutaneous apomorphine (1.5, 3 and 4.5 mg). Clinical variations of the Unified Parkinson's Disease Rating Scale (UPDRS) motor score were evaluated 1 h following levodopa administration or 20 min following apomorphine. The motor improvement produced by each acute challenge was matched with the clinical diagnosis and with the response to chronic levodopa treatment. The diagnosis

was verified by repeated clinical assessments or by autopsy in 2 cases. A receiver operating characteristics curve was plotted comparing PD vs. non-PD, PD vs. MSA and chronic responders vs. nonresponders. Cutoff threshold improvement was defined as the value closest to the crossing point for 80% sensitivity and 80% specificity, corresponding to the best trade-off for a predictive evaluation. **Results:** 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%;  $p < 0.01$  with Student's *t* test). When PD patients were compared to non-PD patients, levodopa challenge had the best diagnostic accuracy with a threshold improvement of 16%. Apomorphine had the best diagnostic accuracy with a threshold improvement of 13.5% for 1.5 mg, 13% for 3 mg, and 16% for 4.5 mg. This meant that patients improving at least 16% in all tests had the highest probability of having PD. When PD patients were compared to 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, 15% for 3 mg, and 18% for 4.5 mg.

This meant that patients improving at least 18% in all tests had the highest probability of having PD rather than MSA. When patients who responded to chronic levodopa treatment were compared to 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 14% for 3 and 4.5 mg. This meant that patients improving at least 14.5% in all tests had the highest probability of responding to chronic treatment. **Conclusion:** A good agreement was found between acute challenges with levodopa/carbidopa and apomorphine, and the use of both improved the reliability of the test. Different threshold improvements after acute challenges would support a diagnosis of PD or the exclusion of MSA, and would have a predictive value for subsequent response to chronic levodopa therapy.

Copyright © 2000 S. Karger AG, Basel

## Introduction

While recognition of a parkinsonian syndrome may be immediate, the clinical diagnosis of idiopathic Parkinson's disease (PD) is difficult, due to the lack of a specific biological marker. Other parkinsonian syndromes present overlapping clinical features, and a high frequency of diagnostic errors has been reported in clinical pathological studies [1]. Response to antiparkinsonian medication is directly related to the diagnosis. It is accepted that lack or loss of response to levodopa is incompatible with a diagnosis of PD [1, 2]. It has also been established that multiple-system atrophy (MSA) non-PD patients may respond to levodopa for some time, before becoming unresponsive to chronic drug treatment [3, 4]. MSA patients with poor or no response to levodopa, who responded well to a dopamine agonist, have been recently reported [5]. This indicates that synaptic mechanisms involved in degenerative diseases are more complex and heterogeneous than previously thought.

Acute challenge with levodopa or apomorphine is a current practice in the clinical assessment of parkinsonian patients [6, 7], although its specific predictive value in relation to diagnosis and chronic response to oral medication has not been unequivocally assessed. Sustained response to levodopa has been observed in patients presenting 20–30% improvement following an acute challenge [8], but the exact predictive value of the direct agonist apomorphine and of the 'prodrug' levodopa has never

been specifically assessed. Therefore, it is not known whether their different mechanisms of action may allow for different uses in clinical practice.

## Patients and Methods

### *Drug Challenge*

One hundred and thirty-four parkinsonian patients (56 women, 78 men) were consecutively selected in the movement disorder clinic of the Gemelli Hospital to be evaluated for acute dopaminergic challenge in the period from 1992 to 1995. They all presented with akinesia and rigidity, often accompanied by other neurological symptoms. In order to prevent side effects, all patients received the peripheral dopamine antagonist domperidone (20 mg t.i.d.), starting at least 24 h before the assessment. All antiparkinsonian medication was withheld for at least 12 h according to published guidelines [9]. Patients were tested early in the 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 min between two subsequent doses or on separate days. The dosage was increased until either side effects occurred or the maximum dose was reached.

Motor responses were assessed at baseline and 60 min following the levodopa challenge or 20 min following each subcutaneous dose of apomorphine. The motor response was evaluated by clinical rating according to the Unified Parkinson's Disease Rating Scale (UPDRS) motor score (part III). The response was defined, for each challenge, as the percentage total of UPDRS motor score variation following each acute administration compared to baseline.

All patients received chronic treatment with levodopa. A patient was considered to respond to the chronic treatment when a sustained clinical improvement associated with levodopa-related motor fluctuations was observed.

### *Diagnosis*

Each patient received a provisional clinical diagnosis, which was updated in regular follow-up examinations at least twice a year. The most recent diagnosis or autopsy verification, if available, was considered in the retrospective evaluation (table 1). In most cases, the clinical diagnosis took into account the history of the patient's clinical response to dopaminergic drugs. However, this was not based on a formal evaluation with objective clinical scales. For the purposes of this study, the patients were classified as PD, MSA, progressive supranuclear palsy (PSP), or unclassified parkinsonian syndrome cases.

The clinical diagnosis of PD was based on the diagnostic workout proposed by the UK PD brain bank [10]. Brain imaging (MRI scans, in most cases, or CT scan) was performed at least once for every patient. The clinical diagnosis of MSA was made according to the commonly accepted definition of probable MSA [3]. The clinical diagnosis of PSP was made according to the consensus definition of probable (i.e., clinically definite) PSP [11]. Patients who did not meet any of the above-mentioned criteria were described as having an unclassified parkinsonian syndrome. Patients who did not match the criteria for a diagnosis of PD were classified as non-PD (a group including all MSA, PSP and unclassified cases).

The pathological diagnosis of PD, MSA or PSP was made according to commonly accepted criteria [12, 13].

**Table 1.** Patient demographics

|                                                             | PD              | Non-PD          | MSA             | PSP            | NC              |
|-------------------------------------------------------------|-----------------|-----------------|-----------------|----------------|-----------------|
| Number of patients (M/F)                                    | 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   |

NC = Unclassified parkinsonian syndrome.

### Predictive Value

Variations in the UPDRS motor score before and after an acute challenge were compared in the following combinations: PD vs. non-PD, PD vs. MSA, and chronic responders vs. nonresponders. To evaluate predictive accuracy, receiver operating characteristics (ROC) curves of the levodopa and apomorphine challenges were plotted. Sensitivity was defined as the ratio between the number of patients classified as PD, or as chronic responders, respectively, having a feature in the group and the total number of patients in the same group. Specificity was defined as the ratio between the number of patients not having a feature in the group classified as non-PD, as MA or as non-chronic responders, respectively, and the total number of patients in the same group [14].

For each test, sensitivity and specificity were computed with 5% intervals from 0 to 50% and with 1% intervals (0.5% in the case of apomorphine 1.5 mg) for the values encompassing 80% sensitivity and 80% specificity. The point closest to 80% sensitivity and 80% specificity was defined as the best trade-off threshold for UPDRS motor score improvement.

## Results

### Clinical Features

Based on clinical follow-up or on autopsy, 83 patients (61.9%) received a retrospective clinical diagnosis of PD, while 51 (38.1%) had a clinical diagnosis of a parkinsonian syndrome other than PD, i.e. non-PD. In the latter group, 28 (20.9%) had a clinical diagnosis of MSA and 6 (4.5%) had a clinical diagnosis of PSP. The remaining 17 patients had an unclassified parkinsonian syndrome. In 2 cases a pathological diagnosis was obtained. In one, pathology confirmed the clinical diagnosis of MSA; in the second case, which had been classified on clinical grounds as non-PD, postmortem revealed a typical PD picture, however, the presence of multiple lacunae in the basal ganglia resulted in this case being classified as a non-PD case.

Patient demographics, disease duration at the time of the acute challenge and duration of follow-up are reported in table 1. Based on chronic response to levodopa therapy,

78 PD patients were classified as chronic responders (the remaining being unclassified), while 22 non-PD patients were classified as chronic responders and 26 as non-chronic responders (3 patients remained unclassified). Overall, 100 patients (74.6%) benefited from chronic levodopa therapy, while 27 (20.1%) did not. Seventeen patients (13 PD, 2 MSA, 2 PSP) were drug-naïve at the time when they received the acute challenge.

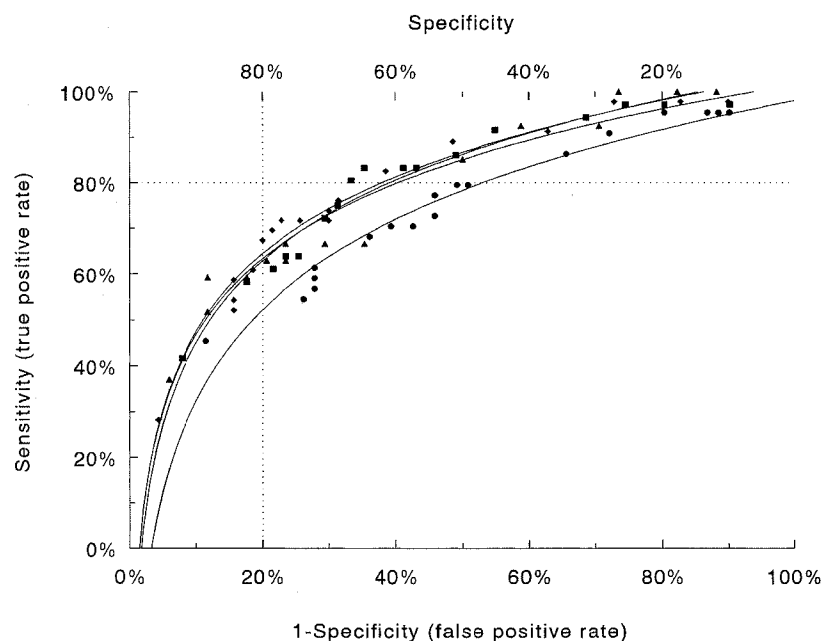
### Drug Challenge

The clinical effect of apomorphine was usually preceded by yawning, occurring approximately 15 min following an injection and lasting for less than 60 min. Adverse reactions to apomorphine included drowsiness, nausea, vomiting, hypotension, sweating; they prevented an increase in dosage in some patients. All the effects resolved within 30 min. The clinical efficacy of levodopa was detected approximately 30–50 min after oral administration. Levodopa was better tolerated than apomorphine, although nausea and vomiting occurred on occasion. For practical reasons, not every patient received all the possible combinations: oral levodopa/carbidopa was given to 70 PD and to 46 non-PD patients (24 MSA, 6 PSP, 16 unclassified); 1.5 mg apomorphine was administered to 61 PD and to 44 non-PD patients (25 MSA, 5 PSP, 14 unclassified); 3 mg apomorphine was administered to 51 PD and to 36 non-PD patients (21 MSA, 4 PSP, 11 unclassified); 4.5 mg apomorphine was administered to 34 PD and to 27 non-PD patients (15 MSA, 4 PSP, 8 unclassified).

Objective UPDRS motor score improvement was significantly higher in PD than in non-PD, MSA or PSP patients after acute challenges with either drug and any dosage ( $p < 0.001$  in each case; table 2).

When patients who received a diagnosis of PD were compared to non-PD patients, the levodopa diagnostic predictive value had a threshold improvement of 16%, yielding a sensitivity of 77.1% (54 of 70 PD were de-

**Fig. 1.** ROC curve displaying sensitivity and specificity for the prediction of a diagnosis of PD (as compared to a diagnosis of non-PD). Data plotted for the levodopa/carbidopa challenge are the closest to 80% sensitivity and 80% specificity. A beneficial response following acute administration of levodopa detects PD from non-PD patients, with sensitivity and specificity between 63.9 and 77.1%. ● = Apomorphine 1.5 mg; ■ = apomorphine 3 mg; ▲ = apomorphine 4.5 mg; ◆ = levodopa/carbidopa.



**Table 2.** Average percent 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). NC = Unclassified parkinsonian syndrome.

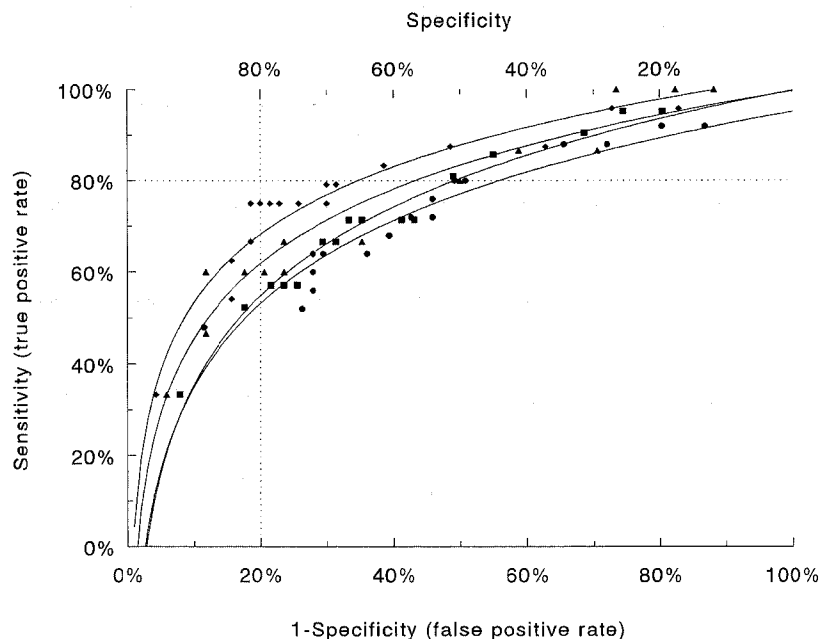
tected) and a specificity of 71.1% (33 of 46 non-PD were detected). Apomorphine 1.5 mg diagnostic predictivity had the best trade-off threshold with a 13.5% improvement (sensitivity 70.5%, 43 of 61 PD were detected; specificity 65.9%, 29 of 44 non-PD were detected). Apomorphine 3 mg diagnostic predictivity had the best trade-off threshold with a 13% improvement (sensitivity 76.5%, 39 of 51 PD were detected; specificity 63.9%, 23 of 36 non-PD were detected). Apomorphine 4.5 mg diagnostic predictivity had the best trade-off threshold with a 16% improvement (sensitivity 76.5%, 26 of 34 PD were de-

tected; specificity 66.7%, 18 of 27 non-PD were detected) (fig. 1).

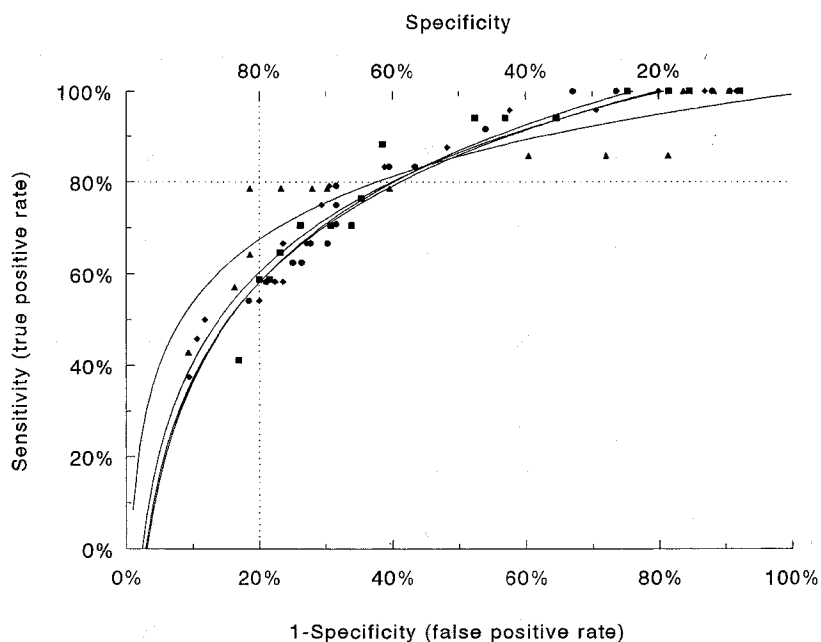
When patients who received a diagnosis of PD were compared to MSA patients, levodopa diagnostic predictive value had the best trade-off threshold with a 17% improvement (sensitivity 74.3%, 52 of 70 PD were detected; specificity 75%, 18 of 24 MSA were detected). Apomorphine 1.5 mg diagnostic predictivity had the best trade-off threshold with a 13% improvement (sensitivity 72.1%, 44 of 61 PD were detected; specificity 64%, 16 of 25 MSA were detected). Apomorphine 3 mg diagnostic predictivity had the best trade-off threshold with a 15% improvement (sensitivity 70.6%, 36 of 51 PD were detected; specificity 66.7%, 14 of 21 MSA were detected). Apomorphine 4.5 mg diagnostic predictivity had the best trade-off threshold with an 18% improvement (sensitivity 76.5%, 26 of 34 PD were detected; specificity 66.7%, 10 of 15 MSA were detected) (fig. 2).

When patients who responded to chronic levodopa treatment were compared to those who did not, levodopa provided the best predictive accuracy with a trade-off threshold of 14.5% improvement, yielding a sensitivity of 69.4% (59 of 85 chronic responders were detected) and a specificity of 79.4% (19 of 24 non-chronic responders were detected). Apomorphine 1.5 mg chronic response predictivity had a trade-off threshold of 13% improve-

**Fig. 2.** ROC curve displaying sensitivity and specificity for the prediction of a diagnosis of PD (as compared to a diagnosis of MSA). Data plotted for the levodopa/carbidopa challenge are the closest to 80% sensitivity and 80% specificity. A beneficial response following acute administration of levodopa detects PD from MSA patients, with sensitivity and specificity between 64 and 75%. ● = Apomorphine 1.5 mg; ■ = apomorphine 3 mg; ▲ = apomorphine 4.5 mg; ◆ = levodopa/carbidopa.



**Fig. 3.** ROC curve displaying sensitivity and specificity for the prediction of chronic response to levodopa. Data plotted for the apomorphine 1.5 mg challenge are the closest to 80% sensitivity and 80% specificity. A beneficial response following acute administration of levodopa detects chronic responders from nonresponders, with sensitivity and specificity between 64.6 and 79.4%. ● = Apomorphine 1.5 mg; ■ = apomorphine 3 mg; ▲ = apomorphine 4.5 mg; ◆ = levodopa/carbidopa.



ment (sensitivity 68.4%, 52 of 76 chronic responders were detected; specificity 79.2%, 12 of 17 non-chronic responders were detected). Apomorphine 3 mg had a threshold of 14% (sensitivity 64.6%, 42 of 65 chronic responders were detected; specificity 76.5%, 11 of 14 non-

chronic responders were detected). Apomorphine 4.5 mg had a threshold of 14% (sensitivity 72.1%, 31 of 43 chronic responders were detected; specificity 78.6%, 11 of 14 non-chronic responders were detected (fig. 3).

## Discussion

Motor response to acute drug challenge may provide useful clues for the prediction of response to chronic treatment and for the correct diagnosis of parkinsonian syndromes. This study calculates threshold values to be used in clinical practice and allows the following predictive assumptions to be made: a patient improving at least 14.5% in all tests has a high probability of having a chronic response to therapy. A parkinsonian patient improving at least 16% in all tests has a high probability of having PD. Finally, a parkinsonian patient improving at least 18% in all tests has a high chance of not having MSA. A limitation of this study is that at the time of the tests most patients had already been treated with antiparkinsonian medication, while 17 could be considered *de novo*. This bias reflects the fact that the Gemelli Hospital is a referral center and probably reduced the number of false-negative results in the acute challenges, which are expected in a greater proportion in *de novo* patients [15]. Consequently, the present data provide little predictive information for untreated, newly diagnosed patients.

In previous studies, acute responses to apomorphine and levodopa have been reported to predict the effect of chronic levodopa therapy in more than 90% of patients with advanced disease and in 67–85% of patients at the time of their first diagnosis [8, 16, 17]. In most previous studies the criteria for a positive response to acute challenge were established *a priori* [6, 17] and the patients were followed up for a relatively short period of time (a mean of 13 months in one study [17]). The same criticism also applies to a prospective study aimed at predicting chronic response to levodopa based on the *a priori* 20% cutoff UPDRS motor score improvement following an acute challenge with apomorphine [8]. If a too high cutoff value is defined, this greatly reduces the sensitivity of a test. Therefore, in the present retrospective evaluation, threshold values were measured considering the most convenient trade-off between sensitivity and specificity. In order to guarantee a reliable clinical diagnosis, the patients were followed-up for an average of 6.9 years from the onset of disease. The measured threshold values for diagnosis and for chronic response to levodopa were lower than the artificial values established *a priori*. This provides a possible explanation for the lower predictivity of acute challenge in the present series compared to earlier reports.

Parkinsonian syndromes are clinicopathological entities, for which a definite diagnosis can only be established by autopsy. In current practice a clinically definite diag-

nosis is based on the observation of a clinical picture matching established criteria, provided follow-up is of a length comparable to the average survival time in each category of patients. Average survival for MSA is 7.1 years, and for PSP it is 6.7 [3, 4], thus quite comparable to the average follow-up of 6.9 years in the present series.

The present report confirms, in a large series of patients, that apomorphine reliably predicts the chronic response to levodopa. This is surprising, as the two drugs differ quite significantly in their mechanism of action and central pharmacokinetics [7]. Apomorphine does not require metabolic conversion to a pharmacologically active metabolite, its activity depending on the integrity of striatal dopamine receptors. By contrast, levodopa, the natural precursor of dopamine, is a 'prodrug' whose action depends on dopa decarboxylase located in surviving dopaminergic neurons or in glial cells. Nonetheless, levodopa and apomorphine challenges provided similar results, in that their sensitivity was higher than their specificity, i.e. the 'true positive' values were correctly identified. Slightly better results were obtained with the levodopa challenge: 54 out of 70 PD patients were correctly identified. Responsiveness to levodopa is a requisite for the diagnosis of PD, while response to dopamine agonists is not. Very few cases of histologically proven PD have been reported not to respond to adequate doses of levodopa [18]. In addition, evidence has been recently collected that MSA patients who do not respond to levodopa may significantly improve following an acute challenge with apomorphine, and can also be treated chronically with a dopamine agonist [5]. Thus, although on average the acute challenge with levodopa or apomorphine yield similar results, there is evidence that in individual patients the use of both drugs may be of added benefit.

The predictive nature of acute challenges in relation to diagnosis or chronic response differed somewhat. Levodopa challenge had the most convenient trade-off for the diagnosis of PD (71.1% sensitivity, 71.7% specificity; fig. 1), while apomorphine (3 and 4.5 mg) challenge had the best trade-off for the prediction of a chronic response (fig. 3). This suggests that levodopa may more reliably predict a diagnosis of PD, while apomorphine may more specifically predict the chronic response, an observation further supporting the complementary role of the two drugs.

A significant proportion of MSA patients may present a transient response to levodopa in the initial disease stages [3]. These patients are more likely to be classified as PD on purely clinical grounds. The question arises as to whether acute challenge tests may reveal a poorer motor

response in such cases. Interestingly, when the response to an acute challenge with levodopa in MSA patients is compared to that of PD patients, specificity is higher than sensitivity (fig. 2). This indicates that a significant percentage of 'true negative' values are correctly detected by such comparison, as confirmed by the identification of 49 out of 70 PD patients. This observation supports the view that acute challenge tests may provide an aid for the differential diagnosis of parkinsonian syndromes.

The present study provided a direct comparison of the efficacy of apomorphine and levodopa. In a randomized double-blind study of the efficacy of apomorphine following an acute challenge, no improvement was observed with a placebo [19]. In the present study, no placebo was used because (a) the two drugs had different administration routes and (b) some typical side effects of apomor-

phine (e.g., yawning, mild nausea) could have easily allowed a patient or the doctor to identify this drug.

In conclusion, we propose that acute pharmacological challenges be considered supportive for the diagnosis of PD when acute improvement in the UPDRS motor score following levodopa and apomorphine challenges is higher than 18%. An improvement between 14.5 and 18% would predict response to chronic treatment, without having a diagnostic value.

## Acknowledgement

Pathological examination of the 2 deceased patients in this study was performed by Dr. S. Daniel at the UK Parkinson's Disease Society Brain Bank, London.

## References

- Hughes AJ, Ben-Shlomo Y, Daniel SE, Lees AJ: What features improve the accuracy of clinical diagnosis in Parkinson's disease? A clinicopathologic study. *Neurology* 1992;42:1142-1146.
- Rajput AH, Rozdilsky B, Rajput A, Ang L: Levodopa efficacy and pathological basis of Parkinson syndrome. *Clin Neuropharmacol* 1990;13:553-558.
- Quinn N: Multiple system atrophy; in Marsden CD, Fahn S (eds): *Movement Disorders 3*. London, Butterworth-Heinemann, 1994, pp 262-281.
- Albanese A, Colosimo C, Bentivoglio AR, Fenici R, Melillo G, Tonali P: Multiple system atrophy presenting as parkinsonism: Clinical features and diagnostic criteria. *J Neurol Neurosurg Psychiatry* 1995;59:144-151.
- Albanese A, Ghika J: Acute challenge with apomorphine predicts the response to dopamine agonists in multiple system atrophy. *Neurology* 1998;50:A366.
- Hughes AJ, Lees AJ, Stern GM: Apomorphine test to predict dopaminergic responsiveness in parkinsonian syndromes. *Lancet* 1990;336:32-34.
- Colosimo C, Merello M, Albanese A: Clinical usefulness of apomorphine in movement disorders. *Clin Neuropharmacol* 1994;17:243-259.
- Gasser T, Schwarz J, Arnold G, Trenkwalder C, Oertel WH: Apomorphine test for dopaminergic responsiveness in patients with previously untreated Parkinson's disease. *Arch Neurol* 1992;49:1131-1134.
- Langston JW, Widner H, Goetz CG, Brooks D, Fahn S, Freeman T, Watts R: Core assessment program for intracerebral transplantations (CAPIT). *Mov Disord* 1992;7:2-13.
- Gibb WR, Lees AJ: The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1988;51:745-752.
- Litvan I, Agid Y, Calne D, Campbell G, Dubois B, Duvoisin RC, Goetz CG, Golbe LI, Grafman J, Growdon JH, Hallett M, Jankovic J, Quinn NP, Tolosa E, Zee DS: Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): Report of the NINDS-SPSP international workshop. *Neurology* 1996;47:1-9.
- Daniel SE: The neuropathology and neurochemistry of multiple system atrophy; in Banister R, Mathias CJ (eds): *Autonomic Failure. A textbook of clinical disorders of the autonomic nervous system*. Oxford, Oxford University Press, 1992, pp 564-585.
- Forno LS: Neuropathology of Parkinson's disease. *J Neuropathol Exp Neurol* 1996;55:259-272.
- Metz CE: Basic Principles of ROC analysis. *Semin Nucl Med* 1978;8:283-289.
- Rybacki BA, Johnson CC, Gorell JM: Demographic differences in referral rates to neurologists of patients with suspected Parkinson's disease: Implications for case-control study design. *Neuroepidemiology* 1995;14:72-81.
- Hughes AJ, Lees AJ, Stern GM: Apomorphine in the diagnosis and treatment of parkinsonian tremor. *Clin Neuropharmacol* 1990;13:312-317.
- Hughes AJ, Lees AJ, Stern GM: Challenge tests to predict the dopaminergic response in untreated Parkinson's disease. *Neurology* 1991;41:1723-1725.
- Sage JI, Miller DC, Golbe LI, Walters A, Duvoisin RC: Clinically atypical expression of pathologically typical Lewy-body parkinsonism. *Clin Neuropharmacol* 1990;13:36-47.
- van Laar T, Jansen EN, Essink AW, Neef C, Oosterloo S, Roos RA: A double-blind study of the efficacy of apomorphine and its assessment in 'off'-periods in Parkinson's disease. *Clin Neurol Neurosurg* 1993;95:231-235.