Systematic review of acute levodopa and apomorphine challenge tests in the diagnosis of idiopathic Parkinson's disease

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Authors' objectives
To perform a systematic review of studies examining the diagnostic accuracy of acute challenge tests with levodopa (LD) and/or apomorphine (APO) in parkinsonian syndromes, to assess their value in the diagnosis of idiopathic Parkinson's disease.

Searching
MEDLINE (from 1966 to September 1999) and the Cochrane Library (Issue 3, 1999) were searched using the terms 'Parkinson's disease' and its derivations 'multiple system atrophy' and 'progressive supranuclear palsy', cross-referenced with 'apomorphine' and 'levodopa'. The reference lists of the identified studies were reviewed for further studies. No attempts were made to identify unpublished studies. Studies of all languages were included in the review, and investigators were contacted for additional information where necessary.

Study selection
Study designs of evaluations included in the review
The authors do not state any inclusion criteria relating to the study design.

Specific interventions included in the review
Studies that reported the results of acute LD or APO challenges were included in the review. Most of the challenges were performed on admission as a day case, following pre-treatment with domperidone. The actual dosages were 275 mg of acute LD and between 0.7 and 10 mg of APO. The dosages for chronic LD, where stated, were less than 1,000 mg; the duration of treatment with chronic LD varied from 1 to 6 months.

Reference standard test against which the new test was compared
The authors do not state any inclusion criteria relating to the reference standard tests. The assessment methods included standard motor impairment rating scales, such as the unified Parkinson's disease rating scale motor component, Hoehn and Yahr scale, Webster scale and Columbia scale, along with timed tests such as repeated tapping, 3 to 20 m walk and tests of tremor and rigidity. The thresholds for a positive response to these tests varied considerably.

Participants included in the review
Patients with akinetic-rigid syndromes were included. In most studies, the patients had an established clinical diagnosis of idiopathic Parkinson's disease or another parkinsonian condition. In the remaining studies, the patients had received a diagnosis of idiopathic Parkinson's disease relatively recently.

Outcomes assessed in the review
The authors do not state any inclusion criteria relating to the outcomes.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

The authors abstracted standard descriptive statistics and diagnostic criteria from each report. These included: the year of publication, the number of patients with idiopathic Parkinson's disease or another parkinsonian condition, assessment methods, threshold for response, the number of tests for a positive result, follow-up for chronic LD, drug and dose.

Methods of synthesis
How were the studies combined?
Studies for particular challenge tests were compared by sensitivity and specificity analysis and logistic regression analysis. A conditional logistic regression analysis was used to compare those studies in which patients received both challenge tests, and their outcomes were then matched by patient. Confidence intervals (CIs) for sensitivities and specificities were obtained using the exact probability routines of the statistical package EGRET (Cytel Software Corporation). A meta-analysis for each challenge test was obtained by the variance weighting method for pooling proportions, and testing for homogeneity between the studies. Continuity corrections of adding 0.5 to frequencies were used, as some frequencies were zero. Logistic regression analysis was also used to test for significant variation in the diagnostic odds ratios of the studies. The meta-analyses were weighted for the number of patients in each study.

How were differences between studies investigated?
Heterogeneity of the methodology of the challenge studies and the sensitivities and specificities of the tests, was assessed.

Results of the review
Thirteen studies were included in the review. Nine studies (436 patients) were diagnostic case-control studies, where a group of patients thought to have had the disease for some time were compared with a second group thought to have non-parkinsonian conditions. The remaining four studies (209 patients) were diagnostic cohort studies of patients with newly-diagnosed idiopathic Parkinson's disease.

The sensitivity for the diagnosis of idiopathic Parkinson's disease with APO challenge was 0.86 (95% CI: 0.78, 0.94), compared with 0.75 (95% CI: 0.64, 0.85) for acute LD challenge and 0.91 (95% CI: 0.85, 0.99) for chronic LD therapy. The specificity for the diagnosis of idiopathic Parkinson's disease with APO challenge was 0.85 (95% CI: 0.74, 0.96), compared with 0.87 (95% CI: 0.77, 0.97) for acute LD challenge and 0.77 (95% CI: 0.61, 0.93) for chronic LD therapy. Neither heterogeneity tests in the meta-analysis, nor the logistic regression analysis comparing the diagnostic odds ratios of different studies, showed any signs of statistically-significant variation between the studies in terms of the sensitivities or specificities.

Authors' conclusions
The accuracy of the acute LD and APO challenge tests was similar to, but not superior to, that of chronic LD therapy in the diagnosis of idiopathic Parkinson's disease. As most patients will be given chronic dopaminergic therapy, these tests add nothing while causing significant adverse events and additional cost.

CRD commentary
The authors stated their review question clearly, although the inclusion criteria in relation to study design, reference standard and outcomes were not given. The search strategy was limited to two electronic databases and a review of the reference lists of identified studies, and there was no attempt to identify unpublished literature; relevant studies may therefore have been missed. The authors did not provide details of the review process, e.g. whether the study selection and data extraction processes were undertaken by more than one reviewer, and whether the reviewers were blinded to the source or results. Details of the studies were tabulated adequately, and the methods used to pool the studies were appropriate although poorly described. Heterogeneity was assessed and was found in relation to study methodology, but not in relation to the study results. The validity of the primary studies was not assessed.
The authors' conclusions should be interpreted with caution owing to the limitations highlighted.

**Implications of the review for practice and research**

Practice: The authors suggest that the diagnosis of idiopathic Parkinson's disease continues to rest on clinical features, the response to chronic dopaminergic therapy, and long-term clinical follow-up.

Research: The authors did not state any implications for further research.

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