A review of intermittent subcutaneous apomorphine injections for the rescue management of motor fluctuations associated with advanced Parkinson's disease

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CRD summary
This review assessed the efficacy of intermittent subcutaneous apomorphine injections for the management of 'off' episodes in patients with Parkinson's disease. The authors concluded that apomorphine provides prompt and consistent rescue from 'off' episodes. The review has several methodological weaknesses and it is unclear whether the results of the included studies and the synthesis of them can be relied upon.

Authors' objectives
To review the clinical efficacy and tolerability, as well as the pharmacology, of intermittent subcutaneous apomorphine injections for the management of 'off' episodes (motor fluctuations due to the waning effect of dopaminergic drugs) in patients with Parkinson's disease (PD).

Searching
MEDLINE and International Pharmaceutical Abstracts were searched up to July 2005 for English-language papers. The Cochrane Database of Systematic Reviews was also searched. The reference lists of papers were checked and the U.S. manufacturer of apomorphine provided information.

Study selection
Study designs of evaluations included in the review
Inclusion criteria for the study design were not specified.

Specific interventions included in the review
Studies of intermittent subcutaneous injections of apomorphine were eligible for inclusion. Studies of continuous infusion and nonsubcutaneous administration were excluded. The daily dose, where reported, was 2 to 34.29 mg in the open-label studies and 3 to 14.5 mg in the double-blind studies. The dose per injection varied between studies. The mean duration of therapy ranged from one dose to 22 months in the open-label studies and from one dose to 2 months in the double-blind studies. All but one of the comparative studies were placebo-controlled.

Participants included in the review
Studies of patients with PD were eligible for inclusion. The baseline daily dose of levodopa received by patients in the included open-label studies was 635 to 1,430 mg. Further patient details were limited.

Outcomes assessed in the review
Inclusion criteria for the outcomes were not specified. The outcomes reported in the review were daily levodopa dose following the intervention, daily 'off' time (number of hours or proportion of waking day) and motor functioning based on a number of different scales.

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

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

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

**Methods of synthesis**

How were the studies combined?
Study details were tabulated and some individual studies were summarised in the text.

How were differences between studies investigated?
Open-label and double-blind studies were grouped separately.

**Results of the review**

Twenty-one studies were included: 8 double-blind trials (n=126), six of which were of a crossover design, and 13 uncontrolled open-label studies (n=202).

Following administration of apomorphine, the decrease in daily 'off' time from baseline ranged from 2.6 to 4 hours (6 studies) and 20.5% and 22% (2 studies) of the waking day in the open-label studies. Two studies reported that the difference was statistically significant, while six did not report a statistical comparison. The mean delay of onset ranged from 6 to 14 minutes (6 studies). The mean duration of effect ranged from 36 to 61.9 minutes (5 studies).

In the double-blind trials, all of the studies except one reported a statistically significant difference between apomorphine and placebo (8 studies) or levodopa (1 study) for motor functioning, with the improvement in favour of apomorphine. The mean delay of onset ranged from 8.1 to 22 minutes (3 studies). The mean duration of effect ranged from 56.6 to 96 minutes (2 studies).

Based on one study of 29 participants, which the authors stated provided the most extensive data on adverse events in apomorphine-naive patients, several adverse events were reported. The most common adverse events (30% or greater) were injection-site reaction, yawning, dyskinesias, drowsiness and nausea or vomiting.

**Authors' conclusions**

In patients with PD, apomorphine is effective at providing prompt and consistent rescue from 'off' episodes.

**CRD commentary**

Inclusion criteria were stated for the intervention and the participants of interest, but not for the outcomes or study design. Since only English language studies were included and only limited attempts were made to locate unpublished studies, relevant data might have been missed. The review methodology was poorly described and it was unclear whether appropriate measures had been taken to minimise error and bias. Study quality was not assessed and the impact of quality on the study findings was not discussed. Although the results of individual studies were tabulated, the authors did not systematically synthesis the results of all the studies in the narrative. Some individual studies were discussed, but it is unclear why these had specifically been selected for discussion. The reliability of the authors' conclusions is unclear given the poor reporting of the review process, the lack of a quality assessment, and the selective synthesis. In addition, the conclusions were based on a fairly small number of patients and the data available for some outcomes were limited.

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

Practice: The authors recommended close medical supervision and anti-emetic prophylaxis when initiating apomorphine therapy.

Research: The authors did not state any implications for further research.
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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.