Apomorphine in Parkinson's disease: an update

Apomorphine was first synthesised in 1869, and has been used in the treatment of Parkinson's disease for more than 50 years. It is a potent non-selective dopamine agonist. Current use is restricted to patients with advanced Parkinson's disease who have lengthy and unpredictable off periods. It has also been used as a diagnostic tool for Parkinsonian disorders. Many trials, albeit with small numbers of patients, have shown efficacy of subcutaneous apomorphine. Particular benefits are reductions in duration and frequency of off periods (comparable to that of levodopa), and reduction in daily levodopa requirements. NICE has provided guidance regarding apomorphine as a second-line agent, but states that it should not be used as a diagnostic test. Apomorphine is not widely used in the UK, yet specialist centres have acknowledged the potential of this drug. Further evidence is still needed from large clinical trials, therefore, its use will remain limited. However, apomorphine has its place in the treatment of Parkinson's disease and should be considered before invasive measures.

Dr T Matthew A Roy* Senior House Officer in General Medicine, Queens Hospital, Burton-on-Trent, UK.
Dr Bhaskar Mukherjee Consultant Stroke Physician, Queens Hospital, Burton-on-Trent, UK. ***email** roymatthew@hotmail.com

Parkinson's disease is a chronic neurodegenerative movement disorder that is characterised by loss of dopaminergic neurones within the substantia nigra. The symptoms of bradykinesia, tremor, and rigidity are caused by an imbalance between dopamine and acetylcholine, which current treatments try to stabilise.

Apomorphine was first synthesised in 1869 by Mathiessen and Wright[1] after heating morphine with hydrochloric acid. It was first noted to have anti-parkinsonian properties as early as 1951,[2] but little was known about its structure or mode of action. Schwab and co-workers[2] noted transient improvement in rigidity and tremor in patients with Parkinson's disease; but these clinical effects were negated because the drug was also very strongly emetogenic. Cotzias and colleagues[3] did the first double-blind study showing that the anti-parkinsonian effects of apomorphine were comparable to those of levodopa.

Since then apomorphine has been used in patients with advanced Parkinson's disease who have lengthy and unpredictable off periods. Although apomorphine has been used in Parkinson's disease for more than 50 years, it was first officially licensed in the UK in 1993, but since then little more has been clarified regarding its use. NICE guidelines issued in June 2006 suggest that apomorphine should be used as second-line adjuvant treatment in late Parkinson's disease and that it should not be used as a diagnostic test. Box 1 shows the key points of this article.

Box 1: Key points

- Apomorphine should be reserved for patients with advanced Parkinson's disease
- It can be used to reduce off time and to improve motor function
- Domperidone should be given before apomorphine to reduce nausea and vomiting
- Treatment can be given either by intermittent injection or by continous infusion

Pharmacology

Apomorphine is a short-acting non-ergoline alkaloid derivative of morphine. It, however, does not possess the narcotic properties and other opiate effects of its parent compound.[4] Its clinical effectiveness and use in Parkinson's disease is due to potent dopamine agonism, with particular affinity for D2 receptors and partial affinity for D1 and D3 receptors. It affects both pre-synaptic and post-synaptic terminals in the caudate nucleus and putamen,[4] and thus mimics endogenous activation of transmitters. Apomorphine has long-term efficacy despite progressive disease because of this mechanism.[5] It has also been shown to be a potent scavenger of free radicals, with neuroprotective properties in experiments.[6] However, we have no evidence that apomorphine is neuroprotective in human beings with Parkinson's disease.[7]

This molecule has a quite different structure from dopamine but does share an identical catecholaminergic moiety, which could explain their similar effects (figure 1). The plasma half-life of apomorphine is roughly 40 minutes with a range of 30–60 minutes,[8] but it has been documented to be as quick as 5·8 minutes.[9] 90% is bound to protein. Apomorphine also crosses the blood-brain barrier easily, with studies demonstrating its accumulation within cerebrospinal fluid.[10]

This drug is metabolised through several pathways,

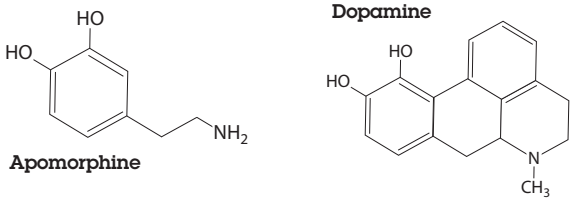

Figure:
Chemical structures of apomorphine and dopamine

namely oxidation, glucuronidation, sulphation, and by catechol-O-methyl-transferase. Only a very small proportion is excreted in the urine unchanged (0·3%)[11] suggesting that it has very limited renal clearance.

Routes of administration

Several routes of administration have been tried for apomorphine including intranasal, transdermal, sublingual, oral, rectal, intravenous, and subcutaneous. A number of these routes became favourable because apomorphine undergoes considerable first-pass hepatic metabolism. However, all routes have been linked with problems, except for subcutaneous dosing, which achieves clinical action in as quickly as 10 minutes, with effects lasting up to 2 hours. Apomorphine has wide interpatient variability and, therefore, particular care needs to be paid to the injection site, depth of injection, and even skin temperature, which can all affect absorption leading to variable accumulation of the drug within the body.[12]

Intranasal administration has also had interest, with small studies showing comparable efficacy to the subcutaneous route, to treat off phases.[13,14] Its use has been limited by substantial nasal irritation, but it has reached phase-3 development for Parkinson's disease in the UK (Britannia Pharmaceuticals, Redhill, UK).

Both intermittent and continuous use of apomorphine have been tested in patients with advanced Parkinson's disease. Both have shown efficacy in reducing off time, but continuous therapy is thought to more closely mimic normal physiology by providing continuous dopaminergic stimulation.

Clinical efficacy

Apomorphine undoubtedly has positive clinical effects in patients with advanced Parkinson's disease. The physiological mechanism is known and is plausible. Unfortunately, few clinical studies have been done, with very small numbers of patients involved. This restriction is understandable, given the type of patient needed for study.

Both open-label and randomised controlled trials show prompt and consistent relief of off episodes in patients already on maximum oral therapy. Unfortunately, little consistency was seen across all studies, particularly for doses, previous administration of other dopaminergic medications, and varying quantifications of motor function. However, we can still draw useful conclusions about time to onset, patient's response, and potential side-effects.

The APO202 trial by Dewey and colleagues[15] looked at apomorphine-naïve patients who were experiencing more than 2 hours a day of off time, despite optimum medical therapy. Patients were given either subcutaneous apomorphine (mean 5·8 mg and 2·5 injections a day) or placebo. Roughly 95% of off periods were successfully avoided in the treatment group compared with 23% on placebo ($p<0·001$) and addition of apomorphine resulted in a reduction in off time of 2 hours.

Subsequent studies were done, again with small numbers of patients; APO302 showed improvement in motor scores on the united Parkinson's disease rating scale[16] in patients already taking intermittent apomorphine.[17] This was a follow-on study of patients from APO301 to assess persistence of response. APO302 showed continued efficacy in patients, that tachyphylaxis does not develop, and that increasing doses empirically does not provide additional benefit. APO303 again looked at apomorphine naïve patients, just as in APO202. However, this time patients were titrated to the optimum dose and then followed-up for 6 months. The results again revealed significantly improved motor scores in the apomorphine group compared with placebo ($p<0·001$ at 20 and 40 minutes).[18]

Clinical indications and use

The only licensed subcutaneous apomorphine preparation available in the UK is APO-go (Britannia Pharmaceuticals, Redhill, UK). As mentioned previously, both intermittent injections and continuous infusions can be used, the indications for which are listed in box 2. Patients are selected on the basis of their symptoms, current treatment regimen, and probable response to treatment.

Apomorphine is a potent dopamine agonist and has strong emetogenic properties. Administration of domperidone 20 mg orally three times a day for three days is therefore required. Equally, 30 mg rectally four times a day can be used.[19] Generally, patients can be prescribed this in the community by their general practitioner and then be brought into hospital to receive their apomorphine. They can be gradually weaned off domperidone as tolerance to apomorphine improves.

Patients need to be in the off phase before administering apomorphine. This means that on some occasions, regular medications may need to be omitted. The patient's response to increasing doses, at intervals of 45 minutes to an hour, is then measured using the motor score. A patient is deemed non-responsive if they have not responded to a dose of

7 mg.[20] A positive response is a decrease in the motor score of more than 20% or at least a 20% improvement in either timed-hand or timed-walking tests.[20]

Once the clinician is happy that the patient is likely to gain symptomatic benefit from apomorphine, he or she must decide on the type of treatment (ie, intermittent or continuous). Both pre-filled multiple dose pens and drawn up syringes are available on the basis of patients' and carers' choice. Injection sites are rotated between thigh, abdomen, and any other site with adequate subcutaneous tissue.

An ambulatory syringe driver is also available. Patients tend to require a daytime infusion only, with doses usually about 50–100 mg a day.[18] The infusion is started at a rate of 1 mg/hour and is increased according to response. The maximum dose should be no more than 4 mg/hour.[20] Hospital admission is necessary for treatment initiation, and to assess patient's response and side-effects.

Unfortunately, apomorphine is associated with side-effects, notably nausea and vomiting, dyskinesias, neuropsychiatric complications, orthostatic hypotension, and haemolytic anaemia (in 0·1–1% of cases). Hence, patients taking apomorphine need to have a regular full blood count, reticulocyte count, and Coomb's test. Other potential complications related to administration exist, such as nodule formation, local infection, and discomfort.

Conclusion

The use of apomorphine will always be limited by selection of patients and lack of knowledge of its use. It is an extremely useful drug for treating patients with advanced Parkinson's disease who have lengthy off periods despite optimum oral treatment. Evidence is available, although trials have included small numbers of patients. Nevertheless, the results and clinical outcomes cannot be overlooked. Further research needs to be done; however, recruitment of patients will always be difficult. Although its use is limited, apomorphine has a role in the treatment of Parkinson's disease, particularly after other therapies fail. Hundreds of patients have benefited from this drug and it should always be considered in management of advanced Parkinson's disease.

We have no conflict of interest.

Box 2: Indications for use of apomorphine

Intermittent injection

Lengthy off periods in patients on maximum levodopa with less than 6 episodes a day

Continous infusion

Lengthy and more frequent off periods, in which benefit of oral medication is short (<6 hours a day)

Patients need many injections a day (6–8)

Patient has severe involuntary dyskinesias due to levodopa

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