Use of apomorphine in Parkinson's disease

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Apomorphine is a dopamine agonist administered subcutaneously as intermittent injections or in a continuous infusion. It is useful in managing advanced Parkinson's disease, and provides an alternative to neurosurgical procedures. This review summarizes indications and practical guidelines for its use.

A number of pharmaceutical and surgical therapies are now available for the management of Parkinson's disease. Although levodopa combined with a peripheral decarboxylase inhibitor remains the cornerstone of treatment, its long-term use is associated with complications including fluctuations in the motor response and drug-induced dyskinesias which are responsible for considerable disability. Alternative therapeutic options include direct-acting dopamine agonists, inhibitors of catechol-O-methyl transferase (COMT) and monoamine oxidase (MAO), and amantadine, as well as stereotactic surgical lesions or chronic electrical stimulation of the thalamus, pallidum or subthalamic nucleus.

Apomorphine is a potent dopamine agonist that was first reported to successfully reverse symptoms of Parkinson's disease nearly 50 years ago (Schwab et al, 1951). It has proven to be beneficial in the management of advanced Parkinson's disease, yet it remains underused. This article reviews the development of apomorphine therapy and outlines its role as a diagnostic tool for assessing dopaminergic responsiveness, and in the management of advanced Parkinson's disease, particularly the complications of long-term levodopa therapy. Both intermittent and continuously administered apomorphine will be reviewed and possible side-effects described.

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HISTORICAL BACKGROUND

Apomorphine was first discovered in 1869. Since then it has been used variously to curb behavioural vices in domestic animals, and in clinical medicine as an emetic, expectorant, sedative, aphrodisiac, antipsychotic, anticonvulsant and in the management of narcotic and alcoholic dependence (Lees, 1993). Although originally derived from morphine, apomorphine is quite distinct pharmacologically and its therapeutic use is not associated with respiratory depression or rapid tolerance necessitating progressive dose increases.

The use of apomorphine in Parkinson's disease was suggested as early as 1884, following beneficial effects observed in Sydenham's chorea. It was not until 1951, however, that a clear improvement in parkinsonian tremor and rigidity following the subcutaneous injection of apomorphine was first reported (Schwab et al, 1951). This was still more than a decade before it was recognized that apomorphine acted upon dopamine receptors or that nigrostriatal dopamine deficiency occurred in Parkinson's disease. Orally administered apomorphine was found to be well tolerated and efficacious when doses were slowly increased, but dose-dependant reversible elevations of blood urea and creatinine observed at the high doses necessary in view of extensive first pass metabolism precluded further assessment of this route (Cotzias et al, 1976).

Confirmation of apomorphine's beneficial effects followed, but the need for parenteral administration, frequent adverse reactions including vomiting, postural hypotension and sedation, and the successful introduction of oral levodopa limited its use. The finding that concomitant oral administration of domperidone, a peripheral dopamine receptor antagonist, reduced apomorphine-induced nausea, drowsiness and hypotension was important in extending its use (Corsini et al, 1979).

A further significant observation was that apomorphine could reliably reverse refractory levodopa-induced 'off' period motor disability, indicating that striatal postsynaptic dopamine receptors remain responsive to stimulation dur-

ing levodopa-induced motor fluctuations (Hardie et al, 1984). The development of more practical drug delivery systems and strategies to minimize side-effects has led to subcutaneously administered apomorphine becoming a practical and often highly effective agent in managing levodopa-induced complications in advanced Parkinson's disease.

PHARMACOLOGY

Apomorphine is structurally similar to dopamine and is a potent agonist at both D1- and D2-type dopamine receptors. This is in contrast to available oral dopamine agonists which act predominantly on the D2 receptors. The rapid onset (usually 5–10 minutes) and short duration (usually 40–90 minutes) of clinical effects following subcutaneously administered apomorphine reflect its pharmacokinetic properties (Gancher et al, 1989). High liposolubility results in rapid equilibration between blood and brain compartments, and the short half-life is explained by rapid hepatic degradation. Bioavailability is close to 100% by the subcutaneous route which is more convenient in clinical use than intravenous administration (Gancher et al, 1989).

The quality of the motor response to apomorphine and levodopa are indistinguishable (Kempster et al, 1990). Furthermore, the motor response to both apomorphine and levodopa is largely 'all or nothing', although there is considerable inter-subject variability in the threshold dose. Supra-threshold doses prolong the duration of action and may increase the incidence and severity of side-effects, including dyskinesias. Although some experimental evidence suggests that repeated administration of apomorphine may lead to tolerance, such an effect appears to be relevant only at doses around the motor threshold (Hughes et al, 1991). Significant dose increases have not been required during long-term clinical use of either intermittent and continuously administered apomorphine, including a few patients requiring continuous 24-hourly administration (Hughes et al, 1993; Pietz et al, 1998).

USE OF APOMORPHINE AS A DIAGNOSTIC TOOL

A therapeutic challenge with subcutaneous apomorphine is indicated to determine or confirm dopaminergic responsiveness, and to establish dose requirements in patients before commencing long-term apomorphine therapy. Patients are pretreated with domperidone for 2–5 days before the assessment to minimize peripheral dopaminergic side-effects and the authors have found a dose of 30 mg three times daily is often necessary. Other antiparkinsonian medication should be withheld for at least 8 hours, usually overnight. Following baseline assessment of motor function, increasing doses of apomorphine (1.5, 3, 5, then 7 mg) are administered via subcutaneous injection into the abdominal wall. These are given at 30-minute intervals until patients experience motor improvement or significant side-effects.

Criteria vary but we consider the challenge positive if there is at least a 20% improvement in two or more of the following: reduction in the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn et al, 1987; Gasser et al, 1992), improvement in timed hand tapping, or improvement in timed walking. Less improvement on two or more of these measurements is considered equivocal.

An apomorphine challenge may be used to improve diagnostic accuracy in parkinsonian syndromes, to predict response to oral levodopa and to assess whether patients on long-term levodopa therapy are optimally treated. The clinical diagnosis of Parkinson's disease is supported by a favourable response to levodopa therapy, whereas a failure to respond makes a diagnosis of Parkinson's disease extremely unlikely. The apomorphine test provides a quick and reliable indicator of dopaminergic responsiveness that correlates well with results from oral levodopa challenges (Hughes, 1999). The latter may be preferred in previously untreated patients as it is usually associated with fewer adverse reactions which can cloud interpretation, and may better predict the response to long-term levodopa therapy in this population.

Apomorphine challenges are particularly useful in assessing patients whose response to levodopa has become uncertain. Such ambiguity can result from the development of dopamine-resistant clinical features, the use of subtherapeutic levodopa doses, an early unsustained levodopa response in parkinsonian syndromes other than Parkinson's disease, or from uncertainty in assessment of the motor effect because of neuropsychiatric complications. The response to apomorphine in these situations may influence the decision whether to discontinue medication or change doses.

False negative responses can occur as a result of adverse reactions interfering with the response, or minimal pretreatment disability in early disease such that a significant improvement cannot be detected on test parameters. A trial of 3 months of 200 mg levodopa plus a peripheral decarboxylase inhibitor three times daily should be performed in these situations to confirm lack of dopaminergic responsiveness.

CLINICAL USE

Rescue therapy

Intermittent subcutaneous injections of apomorphine are indicated for patients with Parkinson's disease who have developed motor fluctuations resistant to oral antiparkinsonian therapy and characterized by good quality 'on' periods but disabling 'off' periods. Those with sudden or unpredictable 'off' periods often notice the greatest benefit.

The ability of patients or their carers to clearly recognize 'off' and 'on' periods and to carry out subcutaneous injections during or just before 'off' periods is important. Patients unlikely to benefit are those who have not responded or have experienced intolerable adverse reactions during levodopa therapy or dopaminergic challenges and those with poor quality 'on' periods. Adequate patient education is essential in ensuring the success of apomorphine treatment and the support of a Parkinson's disease nurse specialist, where available, is invaluable.

The threshold dose determined during the apomorphine challenge is usually doubled to determine the therapeutic dose, typically between 1 and 5 mg. Injections can be given using insulin-type syringes usually drawn up in advance for a 24-hour period. Pre-filled multiple dose pen injectors are available and although more expensive, these devices are often more convenient and easier to use (*Figure 1*). Injections are usually given into the lower abdominal wall but the thighs and upper arms can also be used. Patients are instructed to inject at the onset or ideally during anticipation of an 'off' period.

Subcutaneous injections of apomorphine have been shown to be useful in the termination of specific 'off' period disabilities. Improvement has been reported in distressing off-period dystonia and pain, belching, anismus, functional bladder outlet obstruction, and erectile dysfunction (Lees, 1993).

Figure 1. Pre-filled multiple dose pen injection system (Britaject pen, Britannia Pharmaceuticals, Redhill, UK).

Continuous infusions

Continuous subcutaneous infusions are generally reserved for patients requiring very frequent intermittent injections during the day for complex motor fluctuations. We have started to initiate apomorphine therapy as a continuous infusion in view of thepotential benefits of this route of administration in reducing dyskinesias as well as motor fluctuations (Colzi et al, 1998). Suitable patients whose disability renders them unable to self-inject while 'off' are also candidates for continuous infusion. Apomorphine infusions may also be useful in correcting levodopa withdrawal or neuroleptic malignant syndrome, and following major surgery where oral administration of antiparkinsonian drugs is impossible.

Infusions, using portable syringe drivers (*Figure 2*), are commenced at a rate of 1 mg/hour and increased according to the individual's response. Typically, infusions are administered throughout the waking day and stopped overnight, although some patients with prominent nocturnal symptoms run the infusion overnight. Continuous 24-hourly infusions increase cutaneous side-effects and are seldom necessary.

EFFICACY

A number of groups now have demonstrated a reduction of at least 50% in the time spent 'off' per day after commencing intermittent or continuous subcutaneous apomorphine, with efficacy maintained for up to 5 years (Frankel et al, 1990; Hughes et al, 1993; Poewe et al, 1993; Pietz et al, 1998). The majority of patients are able to gradually cease or substantially reduce their oral levodopa and other parkinsonian medications over a few months after commencing continuous waking-day apomorphine infusions (Colzi et al, 1998). Those who achieve continuous waking-day apomorphine monotherapy may still require a dose of levodopa or oral dopamine agonist overnight and/or in the morning while the infusion is not running.

Figure 2. Typical syringe driver (M16A, SIMS Graseby, Watford, UK) for continuous subcutaneous infusion.

Changing to continuous waking-day apomorphine monotherapy has been shown to further reduce the time spent 'off' and substantially reduce levodopa-induced dyskinesias which remain a major therapeutic challenge in advanced Parkinson's disease (Colzi et al, 1998; Manson et al, 1998) (*Figure 3*). These benefits are similar to those obtained from stereotactic lesions or deep brain stimulation in the internal globus pallidus or subthalamic nucleus (Obeso et al, 1997). Levodopa-resistant features such as postural instability, gait and speech disturbance increase with advancing disease and may limit the overall benefit of all dopaminergic drug therapy, including apomorphine, and of functional neurosurgery.

OTHER ROUTES OF ADMINISTRATION

The limitations of the subcutaneous route have prompted investigation of other routes of administration. Sublingual, rectal and nasal administration of apomorphine have all been shown to be effective but limited particularly by local mucosal reactions (van Laar et al, 1995; Dewey et al, 1998; Ondo et al, 1999). Novel preparations of the drug being developed for these routes of administration may provide useful alternatives. Continuous intravenous infusion via an implanted long-term central venous catheter is currently being investigated for patients with major skin-related problems.

ADVERSE REACTIONS

Dopaminergic side-effects

Stimulation of dopamine receptors outside the central nervous system are responsible for a number of adverse events associated with all dopamine agonist drugs, although they are often more prominent with subcutaneous apomorphine as a result of the potency and rapid onset of dopamine receptor stimulation. Nausea, vomiting and arterial hypotension occur commonly, but can be reduced in most patients by coadministration of domperidone. Tachyphylaxis to these effects occurs, particularly those on continuous infusion in whom domperidone treatment can usually be withdrawn within a few months (Colzi et al, 1998; Pietz et al, 1998). Less common cardiovascular effects include peripheral oedema (rarely), and both bradycardia and tachycardia indicating that significant arrhythmia should be excluded on electrocardiogram before commencing treatment.

Adverse effects may also occur as a result of stimulation of dopamine receptors in the central nervous system. Neuropsychiatric side-effects, principally hallucinations, occur in up to 44% of patients on long-term therapy (Frankel et al, 1990; Hughes et al, 1993; Poewe et al, 1993; Pietz et al, 1998). However, this incidence may be less than with equivalent doses of oral dopamine agonists, and a reduction in neuropsychiatric toxicity has been reported in patients switched from oral therapy to apomorphine (Ray-Chaudhuri et al, 1991). Occasional patients using apomorphine or other dopaminergic therapy develop hypomania, hypersexuality and other behavioural disturbances, which can be associated with a tendency to abuse their medication. Dose-related sedation may be problematic in patients on continuous apomorphine. Yawning and occasionally penile erections may occur as acute centrally-mediated effects.

Although dyskinesias may occur with apomorphine, a reduction of concomitant oral therapy in patients receiving continuous apomorphine may actually decrease dyskinesias (Colzi et al, 1998). In contrast to the more typical peak-dose dyskinesias, biphasic dyskinesias occur at the beginning and end of a levodopa dose effect, are associated with intermediate levels of dopaminergic stimulation, and can be exacerbated by continuous apomorphine therapy.

Cutaneous complications

Subcutaneous nodules often develop acutely after commencing infusions of apomorphine and occur in all patients on long-term infusions (Frankel et al, 1990; Hughes et al, 1993; Poewe et al, 1993; Colzi et al, 1998; Pietz et al, 1998). They occur infrequently in patients using only intermittent injections. Histologically, the nodules are characterized by a panniculitis with prominent eosinophils, suggesting a hypersensitivity reaction (Acland et al, 1998).

Dilution of the apomorphine solution with equal parts of 0.9% sodium chloride, rotation of injection sites, massage, low frequency ultrasound

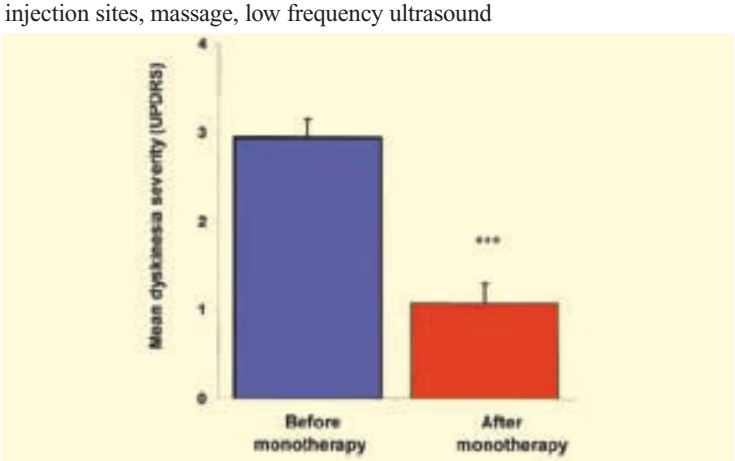

*Figure 3. Mean drug-induced dyskinesias severity (Unified Parkinson's Disease Rating Scale (UPDRS) score) for 22 patients with Parkinson's disease and motor fluctuations before and on average 2.6 years after switching to continuous waking-day apomorphine monotherapy. *** P<0.001 by Mann–Whitney test. From Manson et al (1998).*

and application of silicone patches can minimize nodule formation. Uncommonly, nodules can ulcerate, bleed, or become infected or painful. Increasing nodularity in long-term users may affect drug absorption, resulting in a loss of efficacy and necessitating frequent needle resiting.

Haematological reactions

Mild eosinophilia may occur after starting apomorphine but often resolves with continued treatment. Coombs' direct antibody test is occasionally positive, and haemolytic anaemia has been reported in a few patients treated with apomorphine (Hughes et al, 1993; Colzi et al, 1998; Pietz et al, 1998). Haemoglobin, reticulocyte count and Coombs' test should be checked in all patients before starting therapy and periodically during apomorphine treatment.

CONCLUSIONS

Subcutaneously administered apomorphine can provides substantial improvements in the disability of patients with advanced Parkinson's disease complicated by motor fluctuations. Intermittent injections are useful for on-off fluctions, particularly when sudden. Continuous infusions are beneficial for complex fluctuations and, if oral dopaminergic drug therapy can gradually be reduced, drug-induced dyskinesias can decrease substantially. Apomorphine therapy should be considered in all patients before stereotactic neurosurgical intervention in view of the operative risks. Subcutaneous nodule formation and neuropsychiatric toxicity are the major limitations of long-term therapy. HM

KEY POINTS

- Apomorphine can be distinguished from available oral dopamine agonists by its rapid onset and short duration of action, and the need for subcutaneous administration.
- Concomitant use of the peripheral dopamine receptor antagonist domperidone counteracts unwanted side-effects, principally nausea and vomiting.
- Subcutaneous injections of apomorphine can be used to rapidly test for dopaminergic responsiveness in parkinsonian syndromes where there is diagnostic uncertainty, or when the response to levodopa has become unclear.
- Intermittent subcutaneous injections of apomorphine are useful in rapidly and reliably rescuing patients from refractory 'on-off' motor fluctuations.
- Continuous subcutaneous infusions of apomorphine by minipump are beneficial in reducing 'off' periods by at least 50% in patients with frequent motor fluctuations not responding to oral medication.
- Apomorphine monotherapy as a waking-day infusions can provide a similar reduction in both 'off' time and drug-induced dyskinesias as lesions or deep brain stimulation of the internal globus pallidus or subthalamic nucleus but with less morbidity. Apomorphine should therefore be considered in the management of patients with advanced Parkinson's disease before neurosurgical procedures.

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