

HOW TO DO IT

apomorphine for Parkinson's disease



Andrew Lees and Kirsten Turner

Reta Lila Weston Institute for Neurological Studies, UCL, Windeyer Medical Institute, 46 Cleveland St, London, UK; E-mail: a.lees@ion.ucl.ac.uk

Practical Neurology, 2, 280–286

Apomorphine was first used to treat behavioural vices in domesticated farm animals in the nineteenth century and is still used in veterinary medicine. It has had a chequered history in medical therapeutics, being successfully recommended as an emetic, a sedative, a treatment for narcotic and alcohol dependence and most recently for sexual dysfunction and impotence. It was first proposed as a treatment for movement disorders 150 years ago, but this indication was not pursued until the 1950s when Schwab in Boston confirmed its potential (Schwab *et al.* 1951). Following his demonstration that large doses of dopa improved Parkinson's disease, George Cotzias looked for other dopamine analogues that might have complementary effects and carried out a series of scrupulous and fascinating experiments with apomorphine (Cotzias *et al.* 1970). These indicated that the effects of the drug, when administered by subcutaneous

ease

injection, were potent but short-lived, and that vomiting and postural hypotension were common adverse events. The need for parenteral administration, the brevity of action and the unwanted adverse effects limited its clinical usefulness but its potential role as an investigative tool in clinical neuropharmacology, and the possibility that it may have antidyskinetic as well as anti-Parkinsonian properties, were unfortunately not pursued. The advent of orally-active dopamine receptor agonists led to a further waning of interest in apomorphine, although it remained the prototype dopamine agonist in preclinical research. The concept of continuous tonic dopaminergic stimulation as a strategy for minimizing the long-term L-dopa syndrome renewed interest in apomorphine, and it is now recognised as a useful if under-utilised option for refractory motor fluctuations in late stage Parkinson's disease.

THE USE OF APOMORPHINE AS AN INVESTIGATIVE TOOL

A subcutaneous (s.c.) apomorphine challenge is useful in assessing the amplitude of motor response in patients on dopaminergic therapy and in determining the pattern and distribution of dyskinesias in the long term L-dopa syndrome. It is also helpful in the assessment of a patient's suitability for long-term s.c. apomorphine therapy.

Thirty-six hours prior to the apomorphine challenge, the peripheral dopamine receptor antagonist domperidone (30 mg orally every 8 h) is started. This should begin before the patient comes to hospital. No oral anti-Parkinsonian medication should be given for a minimum of

4–6 h prior to the challenge. Patients may eat a normal breakfast. Motor function is assessed at baseline, then 1.5 mg apomorphine s.c. is administered and the patient's motor response is observed for up to 30 min. The improvement in motor function is frequently preceded by a bout of yawning, beginning 10–20 min after the injection. If there is no response or equivocal effects, a subsequent dose of 3 mg is given. The dose is increased incrementally every 30 min (i.e. 1.5 mg to 3 mg to 5 mg to 7 mg) until a response is seen. If at 7 mg no response is observed, then the patient is considered a non-responder. If a mild response is noted at 7 mg, then a final maximum dose of 10 mg can be administered to try to clarify the effect.

Motor function is quantified using the Unified Parkinson's Disease Rating Scale (UPDRS) at baseline and then 20–30 min after each sequential dose of apomorphine. The time it takes the patient to rise from a chair with arms folded and then walk 12 m is also used as an additional measure of response. A challenge is judged to be positive if there is an improvement in UPDRS score of 15–20%, or a 25% increase in the walking time. Computerised tapping tests such as the BRAIN test are other options for assessment. The apomorphine challenge may be used in outpatient clinics or day hospitals in patients on long-term Parkinson's therapy where one wishes to get an idea of the amplitude of dopamine response and the profile of dyskinesias. A single 3 mg injection is the ideal single challenge dose, because at least 70% of patients will respond maximally to this dose.

The therapeutic success of apomorphine therapy depends on concordance between

patient and doctor and subsequent regular outpatient follow-up and telephone back-up support by a Parkinson's nurse specialist. District nursing teams need to receive training from the Parkinson's nurse specialist or from a representative from Britannia Pharmaceuticals before anyone using apomorphine is discharged home from hospital.

Apomorphine is a colourless aqueous solution. There are two ampoules available, a 20 mL preparation containing a 2 mL solution with 20 mg of apomorphine, and a 5 mL ampoule containing 50 mg of apomorphine. There is also a pre-filled penject device containing 30 mg of apomorphine and the dose is set according to the individual needs of a user via the Apo-go penject (see Fig. 1). Doses of apomorphine range from a few milligrams daily by intermittent injection to 456 mg administered by mini-pump over a 24 h period.

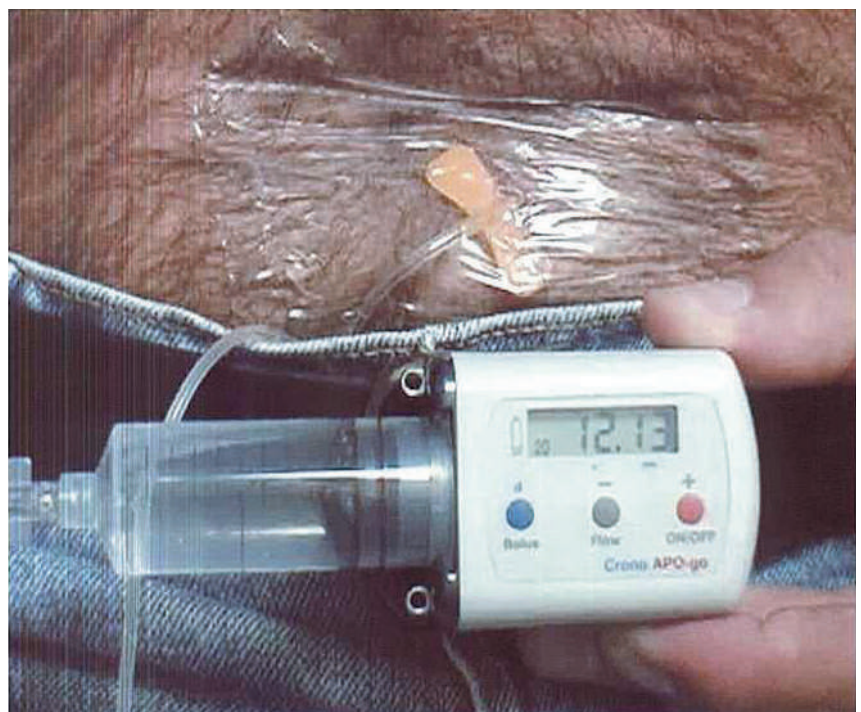
TREATMENT STRATEGIES

Intermittent subcutaneous injections

Intermittent subcutaneous injections are used as a rescue strategy for disabling refractory 'off' periods, in patients already receiving optimum oral anti-Parkinsonian therapy. The timing of each injection is crucial if an impending 'off' period is to be averted and patients should be instructed to recognise and respond promptly to the earliest, and often extremely brief, premonitory signs of impending immobility. In addition to restoring functional independence, apomorphine is valuable in relieving dystonias and other disabling 'off' period symptoms including bowel



(a)



(b)

Figure 1 (a) The APO-go penject for intermittent treatment and (b) the crono-Apo Go pump for continuous administration of apomorphine.

and bladder problems, swallowing difficulties and pain.

Patients should be taught how to draw up and administer the apomorphine by a Parkinson's disease nurse specialist prior to discharge from hospital. Drawn up unused syringes should be discarded within 24 h and disposed of in a 'sharps container'. The dose of each injection should be determined on the basis of the apomorphine challenge test and modified depending on the subsequent long-term response. A maximum of six injections a day is recommended.

Injections are administered into the lower abdominal wall (below the umbilicus), the upper outer aspects of the thighs or the arms and shoulders (see Fig. 2). Injection sites should be rotated to avoid pain and reduce nodule formation. Apomorphine is available as a pre-filled multiple dose pen device, which removes the

apomorphine should
always be offered prior to
functional neurosurgery
and again in patients who
remain handicapped after
deep cerebral stimulation
or pallidotomy

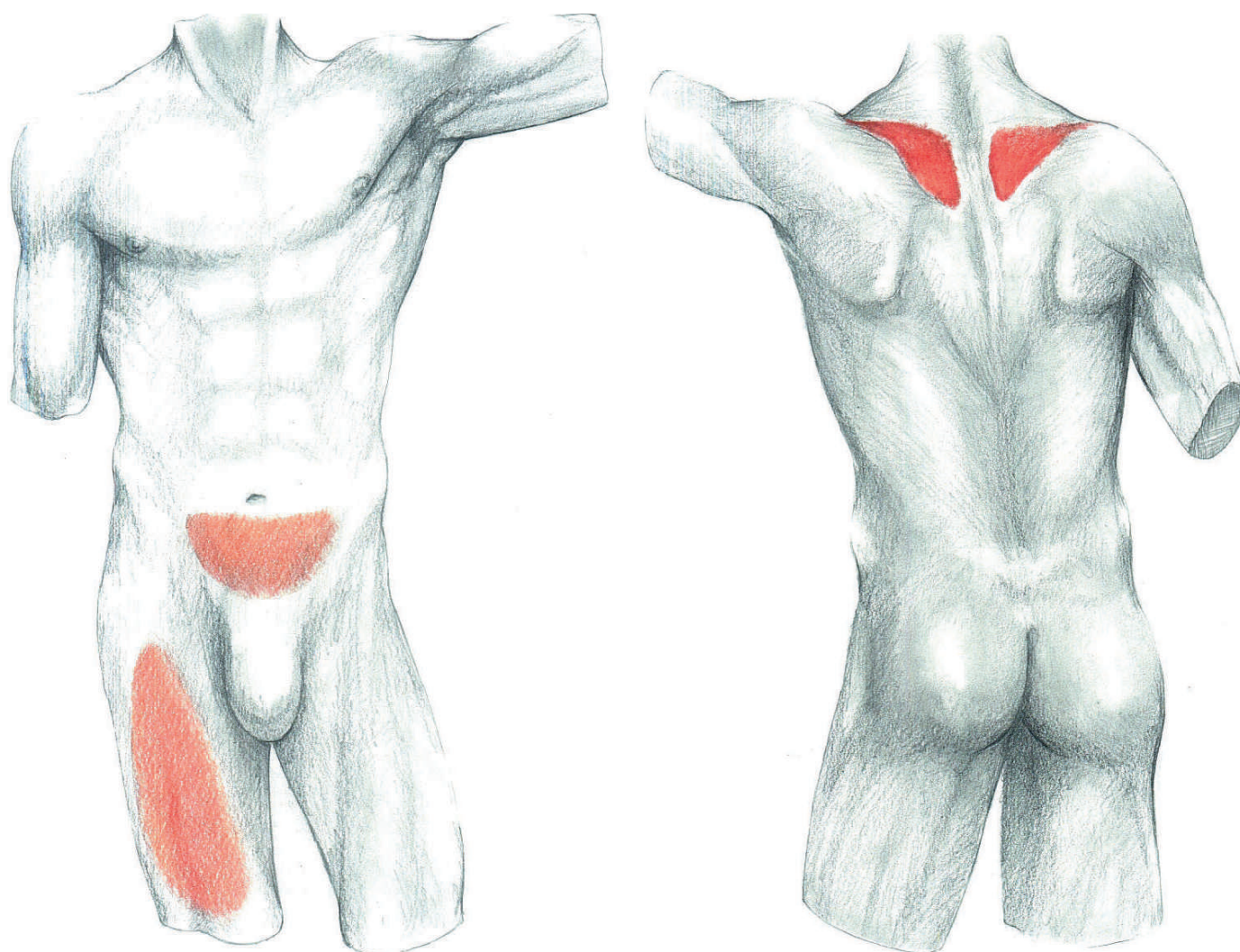


Figure 2 Injection sites for apomorphine indicated in red.

need to prepare syringes. It has an expiry time of 48 h once the first needle has been attached and the seal broken on the cartridge. This device is more socially acceptable, as members of the public often associate insulin syringes with drug abuse. A few patients have found the plunger difficult to manipulate, so in these cases an insulin syringe may be preferable.

Continuous subcutaneous infusion of apomorphine

Continuous waking day subcutaneous apomorphine infusions are recommended for all patients with refractory motor fluctuations (on–off effects) that cannot be managed by oral medication, or less than six intermittent subcutaneous injections of apomorphine. Patients with disabling interdose dyskinesias or ‘off’ period disability for more than 30% of the day are ideal candidates. The treatment should always be offered prior to functional neurosurgery and again in patients who remain handicapped after deep cerebral stimulation or pallidotomy. Temporary perioperative apomorphine therapy in patients with Parkinson’s disease having major abdominal surgery has also proved useful.

Patients should be fully informed about the potential benefits of apomorphine and the technical demands prior to initiation of therapy. Concordance is essential to ensure success. Information is available including an educational video and booklet but the most effective way to encourage patients and their families to try the treatment is a series of frank but encouraging discussions with the physician and nurse specialist.

Apomorphine pump therapy is best started in hospital. After the initial challenge, subcutaneous continuous apomorphine is started. Initially a very low dose is given (on average 2 mg per hour), the dose is then increased on a daily basis using the patient’s initial challenge and the patient’s response as a guide to the speed of increase. Patients, their family and carers should be taught how to draw up and administer the apomorphine and informed that when spilt on clothes, plastic surfaces or any material it can indelibly stain olive-green. A mention that this warning has been given should be recorded in the patient’s notes together with a detailed account of the teaching programme that the patient and their carer have received. Patients should also be informed that panniculitis (itchy nodules) are common at the injection sites and daytime sleepiness may occur. Auto-immune

haemolytic anaemia is a rare complication but routine blood checks should be carried out at 3-monthly intervals. (full blood count, reticulocyte count and Coombs test)

A 3 year follow-up of 64 patients on apomorphine therapy at the Middlesex Hospital showed that 25% of patients managed their apomorphine independently, 50% with the help of their carer and only 25% required outside help from district nurses.

The Crono APO-go syringe driver (Cane-Milan) has been specifically designed for the purpose of delivering apomorphine. It is small and may easily be hidden in a pocket or under a shirt. (Fig. 1b). Easy adjustments of the dose rate may be made in small (0.22 mg) increments and it can be used with a 20 mL syringe. This means that most patients can receive a full day treatment without needing to change the syringe. This pump has a time display that allows the patient to know exactly how long the infusion will run for. A spacer is provided so that the pump can also be adapted to fit a 10 mL syringe if this is preferred. Care should be taken when setting the flow rate of the pump that the correct syringe size is indicated on the display.

A 50% dilution of the apomorphine with 0.9% normal saline is preferable as this significantly reduces nodule formation. With stronger solutions ulceration of the skin and severe nodule formation occurs more commonly. Before an APO-go pump is used it is recommended that the Department of Medical Bioengineering at the hospital double-check the efficient working of the pump, particularly the reliability of the flow-rate.

The Parkinson’s disease nurse specialist provides the essential teaching that is required for both patients and their carers. What may seem a simple instruction to health professionals is often quite daunting to the patient and carer and a calm unhurried patient approach is the secret of success. A 24-hour help line for patients and health professionals is provided by Britannia Pharmaceuticals in the UK (+44 1737 773 741).

Before discharge from hospital the patient’s GP should be notified and appropriate contact made with both the district nursing service and the community Parkinson’s disease nurse specialist. An outpatient appointment for 1–2 weeks after discharge should be fixed prior to discharge. Patients may need reductions to oral anti-Parkinsonian medications and increases to the apomorphine therapy in between

out-patient visits. District nurses may need to be taught how to use the Apo-go pump and have a clear understanding of the indication for using apomorphine therapy prior to the patient being discharged from hospital. Advising the patients regarding difficult titration of oral medications, and identifying potential adverse effects early, are important roles for the Parkinson's disease nurse specialist.

In patients with severe dyskinesias, despite a 6 week trial of amantidine 100–300 mg a day, every attempt should be made to completely tail off L-dopa during the period of infusion

Most patients require between 50 and 200 mg per day of apomorphine by subcutaneous administration. The pump should be started on waking and continued until the patient goes to bed. Some patients need and benefit from round-the-clock administration. A normal life is encouraged but the pump has to be removed during swimming. It is usually possible to markedly-reduce oral medication. This needs to be done gradually, starting with adjuvant medication such as selegiline, anticholinergics, COMT inhibitors and the orally-active dopamine agonists and then finally reducing the L-dopa dose. In patients with severe dyskinesias, despite a 6 week trial of amantidine 100–300 mg a day, every attempt should be made to completely tail off (at a rate of around 50 mg/day/week) L-dopa during the period of infusion. This is usually possible in about 50% of patients and leads to a remarkable reduction in involuntary movements comparable to that seen with surgical approaches.

Abdominal wall nodules seem to be idiosyncratic in their occurrence and can be minimised by scrupulous aseptic technique of needle insertion, the use of very thin needles such as Polyfin infusion set (Applied Medical Technologies,

Cambridge, UK), 42' tubing (106.7 cm) with 27 g needle. The Baxter autosyringe infusion set (Applied Medical Technologies) 42' tubing (106.7 cm) with 27 g needle is ideal. Weekly abdominal wall ultrasound therapy and the use of silicone gel patches can help reduce the build up of nodule formation. Rotation of the needle site around the abdominal wall and outer thighs is advised and the trapezii muscles may be used if nodule build-up occurs. It is important to avoid siting the needle close to an existing nodule as this may lead to sequestration of apomorphine, erratic or negligible absorption with diminished benefit and increased panniculitis. Daytime somnolence may be helped by methylphenidate or modafinil in very severe cases but is rarely a major problem. Domperidone can usually be discontinued after the first 2–3 months of treatment with the pump but may need to continue for patients using intermittent injections. Psychotoxicity rarely occurs and drug withdrawal or introduction of one of the newer antipsychotic drugs like quetaipine or clozapine in low doses may be temporarily required (Hanagasi & Emre 2002). However, apomorphine is no more likely to induce these problems than oral agonist therapy and the drug is even reported to have anti-psychotic properties.

CONCLUSION

Studies over the last decade have confirmed that apomorphine is efficacious in treating refractory on-off oscillations in Parkinson's disease when all other medical strategies have failed, and the drug is now licensed in many European countries and Canada. It is more potent than any currently-available orally-active dopamine agonist and has identical quantitative and qualitative effects on the cardinal symptoms of Parkinson's disease to L-dopa. Not all patients and their families are willing to accept the demands of continuous pump therapy but many are still being deprived of a life-saving treatment because of scepticism or inertia by neurologists, and strictures relating to cost imposed by Health Authorities. The cost of apomorphine with a daily dose range of 20–100 mg/day is about £3–11 000 per annum. Patients with young-onset Parkinson's disease are particularly suited to apomorphine pump therapy but elderly non-demented patients may also derive worthwhile improvement. Those who have a poor response to L-dopa will not benefit. An oral L-dopa challenge is preferable to an apomorphine challenge in assessing dopaminergic responsiveness in a *de*

novo patient, or in a patient on therapy where non-responsiveness is suspected.

USEFUL ADDRESSES

Britannia Pharmaceuticals Ltd
41–51 Brighton Road
Redhill, Surrey RH1 6YS
Apo help line 01737-773-741

Polyfin infusion sets, Mini Med Technologies, 42' tubing (106.7 cm) with 27 g needle, Ref. No. MMT-133 and Baxter Autosyringe infusion set, 42' tubing (106.7 cm) with 72 g needle, Ref. No. M8451, available from:

Applied Medical Technologies
4-5 Orwell Thurlong
Cowley Road
Cambridge
UK
CB4 3WY

SIMS–Graseby Medical Flo Safer infusion set, 100 cm with 25 g needle, Ref. No. 0105–0029, available from:

SIMS–Graseby Medical Ltd.
Colonial Way
Watford
Hertfordshire
UK
WD2 4LG

Transparent Dressing, Tagerderm, prescribable (in UK) on FP10, available from:

3M Health Care Ltd
2M House
Morley Street
Loughborough
Leicestershire
UK
LE11 1EP

Silicone Gel Sheets, Nagosil Topical Gel Sheets, 100mmx 100 mm, available from:

Nagor Ltd
PO Box 21
Douglas
Isle of Man
British Isles

REFERENCES

- Cotzias GC, Papavasiliou PS, Fehling C *et al.* (1970) Similarities between neurologic effects of L-dopa and apomorphine. *New England Journal of Medicine*, **282**, 31–33.
- Hanagasi HA & Emre M (2002) Management of the neuropsychiatric and cognitive symptoms in Parkinson's Disease. *Practical Neurology*, **2**, 94–102.
- Schwab R, Amador L, Lettvin J (1951) Apomorphine in Parkinson's disease. *Transactions of the American Neurological Association*, **76**, 251–253.

RECOMMENDED FURTHER READING

- Colzi A, Turner K & Lees AJ (1998) Continuous subcutaneous waking day apomorphine in the long term treatment of levodopa induced interdose dyskinesias in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, **64**, 573–6.
- Poewe W & Wenning GK (2000) Apomorphine: an underutilized therapy for Parkinson's disease. *Movement Disorders*, **15**, 789–794.
- Dewey RB, Hutton JT, Le Witt PA, Factor SA (2001) A randomized double-blind placebo-controlled trial for subcutaneously injected apomorphine for parkinsonian off-state events. *Archives of Neurology*, **58**, 1385–1392.
- Kanofsky P, Kubova D, Bares M *et al.* (2002) Levodopa-induced dyskinesias and continuous subcutaneous infusions of apomorphine: results of a two year prospective follow-up. *Movement Disorders*, **17**, 188–91.
- Manson A, Turner K, Lees AJ (2002) Apomorphine in the treatment of refractory motor fluctuations of Parkinson's Disease – a 3-year follow-up study. *Movement Disorders* (in press).

