

Apomorphine treatment: A neurologist's perspective

This article is the second in our series looking at the use of apomorphine. In our first article (Vol 2, issue 5) we had the specialist nurses' perspective. In this article, Drs Steiger and Tyne comment on use of apomorphine by neurologists.

The long-term pharmacological management of patients with Parkinson's disease on dopaminergic therapy is associated with motor fluctuations, unpredictable 'off' periods and dyskinesia¹. These can be difficult to manage despite manipulation of levodopa preparations, oral dopamine agonists, COMT inhibitors and amantadine. 'Off' periods may be unpredictable, not only causing reduced mobility, but patients suffer other distressing 'off' symptoms such as painful dystonia, depression, anxiety and fatigue^{2,3,4}. An effective reliable method of relieving such 'off' periods is the use of apomorphine.

Apomorphine was first tried in patients with Parkinson's disease in 1951⁵, but it was noted to be potentially emetic. The development of an effective peripheral dopamine receptor antagonist, that did not cross the blood brain barrier (domperidone), led Stern and Lees to review and develop the role of apomorphine in Parkinson's disease⁶.

Apomorphine is a selective and potent dopamine agonist at D1 and D2 receptors. Given by subcutaneous injection it can rapidly reverse the time spent 'off'⁶. Apomorphine is given by intermittent subcutaneous injection as required, or by subcutaneous infusion over several hours per day.

Indications

One of the major uses of apomorphine is in patients who, despite optimal oral therapy, experience sudden disabling 'off' periods. When given by intermittent subcutaneous injection the latency to onset is 10-12 minutes, with duration of effect of 20-60 minutes. For those patients experiencing frequent 'off' periods, particularly if the 'offs' are unpredictable, then apomorphine by subcutaneous infusion can be effective. Furthermore, as shown by Colzi apomorphine may reduce dyskinesias⁷. The mechanism in part relates to a reduction in oral levodopa dosage with apomorphine and also to a more physiological constant dopaminergic stimulation.

To use apomorphine either patient and/or carer (spouse) must be able to administer the subcutaneous injection. The patient and/or carer need to clearly understand when the drug should be given.

Restrictions in the use of apomorphine are relatively few, for example age or a history of confusion should not necessarily prevent patients receiving apomorphine, since it appears to have a lower incidence of neuropsychiatric side effects compared to other dopamine agonists⁸.

How to start apomorphine

The patient attends the day ward after commencing domperidone 20mg tds for 48 hours prior to their first dose. This reduces side effects, particularly nausea. Patients are requested to abstain from anti parkinsonian medication from the night before, so they are in a practically defined 'off' state. Subcutaneous apomorphine is given in increasing amounts to find the threshold dose needed to relieve the 'off' period. The average dose is 3mg, but can vary from 2mg to 8mg. Patients, and if possible their carer, are taught how to draw up, and administer the injections. Arrangements may be made for District Nurse support to assist in drawing up a supply of apomorphine for injection, which can be stored in the fridge.

Those requiring apomorphine by infusion are taught either as an outpatient, or in the patient's own home, with the District nurse and/or GP present to allow for their training with the infusion device. The dose is increased over the next few weeks, depending on symptoms. Oral dopaminergic medication may subsequently be reduced. The pump device also allows for bolus dosing during the infusion period if required. Patient's requirements vary, but dosage of up to 180mg, over 12 to 24 hours can be given if necessary.

Concomitant medication

Apomorphine can be used along with oral dopamine agonists. Once established on an infusion, oral agonists, as well as levodopa, may be slowly reduced if necessary.

Follow up

We recommend a close liaison between patient, Nurse Practitioner and Primary Care. Particularly after initiating apomorphine therapy, to overcome any potential problems that the patient may experience.

The majority of patient's prescriptions of apomorphine are from Primary Care.

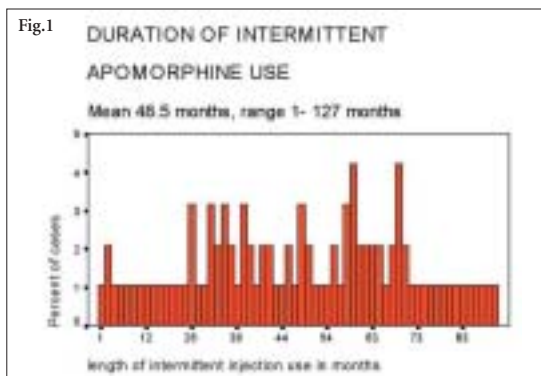
Long term effects and benefits

Apomorphine is well tolerated, especially with domperidone cover. The majority of patients eventually stop domperidone with no increase in side effects. Confusion, hallucinations, postural hypotension, nausea, and sedation are all uncommon and haemolytic anaemia is very rare. The two most common problems may be an increase in dyskinesia on commencement; this may require a reduction in oral medication. Skin nodules can be reduced by rotating sites of injections, and ensuring that there is at least a 1:1 ratio of normal saline to apomorphine in the

Dr Malcolm J. Steiger MD FRCP is a Consultant Neurologist at the Walton Centre for Neurology and Neurosurgery, Liverpool, having trained in Neurology at the National Hospital, London. He has a particular interest in Parkinson's disease.

The Movement Disorder service at Walton offers care and management of patients with all stages of PD, including a large apomorphine programme and stereotactic surgery to suitable patients.

Dr Hilary Tyne is a Research Registrar in Neurology at the Walton Centre. Her main research interest is Parkinson's disease.



- KEY MESSAGES ABOUT APOMORPHINE**
1. It is NOT addictive.
 2. It is NOT a respiratory depressant.
 3. It CAN be levodopa sparing when given by infusion, and
 4. May reduce dyskinesia (Colzi *et al*).
 5. May rapidly reverse rare 'off' period phenomena such as: pain, dystonia, restless legs.
 6. Relatively low risk of neuropsychiatric side effects as compared to other dopamine agonists.
 7. Is particularly useful in the post operative state, when oral medication may not be absorbed.
 8. The pre-filled variable dose injector pen (APO-go Pen) is easy to use, especially in patients without a spouse or full-time carer. However it is expensive compared to the use of a simple insulin-type syringe.
 9. It will not prevent the next dose of levodopa working.

infusion. Painful nodules respond well to massage and ultrasound therapy.

We have been using apomorphine in Parkinson's disease for 10 years; Figure 1 shows the duration of treatment for our patients on intermittent injections. Patients can be treated with apomorphine for many years without loss of efficacy.

Infusion pumps can be obtained on loan from Britannia Pharmaceuticals. The cost of apomorphine usage includes the infusion lines, needles, syringes for intermittent injections and apomorphine.

Conclusions

For many Parkinson's disease patients the usage of apomorphine has been extremely valuable in maintaining quality of independent life. The cost of apomorphine should be placed into perspective, in that it often allows patients to be independent and remain in their own home. The reliable rapid relief of distressing 'off' periods is an advantage of the subcutaneous injection. Subcutaneous infusion is usually well tolerated by patients, helping to reduce fluctuations and dyskinesias in the long-term. Apomorphine remains underused at pre-

sent in our view. The success in the individual patient requires liaison and support from all those involved in the patient's care is needed, particularly the Parkinson's disease nurse specialist.

References

1. Poewe WH, Wenning GK. *The natural history of Parkinson's disease.* Ann Neurol 1998;449(suppl 1):S1-9
2. Cantello R, Gilli M, Riccio A, Bergamasco B. *Mood changes associated with "end of dose" deterioration in Parkinson's disease: a controlled study.* J Neurol Neurosurg Psychiatry 1986;49:1182-1190
3. Quinn NP, Lang AE, Koller WC, Marsden CD. *Painful Parkinson's disease.* Lancet 1986;I:1366-1369
4. Witjas T, Kaphan E, Azulay JP *et al.* *Nonmotor fluctuations in Parkinson's disease: frequent and disabling.* Neurology 2002 ;59:408-413
5. Schwab RS, Amador LV, Lettvin JY. *Apomorphine in Parkinson's disease.* Trans Am Neurol Ass 1951;76:251-253
6. Stribe CMH, Lees AJ, Kempster PA, Stern GM. *Subcutaneous apomorphine in Parkinsonian on-off oscillations.* Lancet 1988; I: 403-406
7. Colzi A, Turner K, Lees AJ. *Continuous subcutaneous waking day apomorphine in the long term treatment of levodopa induced inter-dose dyskinesias in Parkinson's disease.* J Neurol Neurosurg Psychiatry 1998; 64: 573-577
8. Ellis C, Lemmens G, Parkes JD, *et al.* *Use of Apomorphine in Parkinsonian patients with Neuropsychiatric complications to oral treatment.* Parkinsonism and Related disorders 1997;2: 103-107

"We would like to thank Britannia Pharmaceuticals for sponsoring this article".

Correspondence to:
Dr MJ Steiger, Walton Centre for Neurology & Neurosurgery, Lower Lane, Fazakerley, Liverpool L9 7LJ

www.advancedmedicalequipment.com www.neuro.com

advanced MEDICAL equipment ltd

The new home in the UK & Ireland for: **NEUROSCAN**
A COMPUTER/CO COMPANY

En España contactar a Intelimed Ibérica al:
(34) 651087457

For more information please contact
Advanced Medical Equipment Ltd,
42 Pelham Court, Bishopric
Horsham, West Sussex, RH12 1TP, UK
Tel: +44(0) 1403 260156
Fax: +44(0) 1403 260175
e-mail: admin@advancedmedicalequipment.com
web: www.advancedmedicalequipment.com