

The use of Apomorphine in the older patient

Judging from the media reporting of Michael J Fox and Muhamed Ali, and more recently of Tom Isaacs on his historic walk around the coastline of Britain, one might think that PD mainly affected young males. However, without in any way detracting from the impact upon the lives of these brave young men, the mean age of onset of this disease is typically 60-65 years and problems of motor fluctuations do not commonly start to occur until more than five years have elapsed from diagnosis. Consequently, numerically the majority of complex problems will be found in patients in their seventh or eighth decade. In contrast to the younger patient who is more susceptible to the more dramatic motor fluctuations and dyskinesias, the older patient whilst certainly not immune to their occurrence, is more troubled by psychiatric sequelae, and particularly dementia¹. What then is the role of apomorphine in this patient group?

Apomorphine (APO-go[®]) is a dopaminergic agonist with a similar pharmacological profile of action to dopamine, exhibiting both D1 and D2 type effects. It has proven efficacy in the treatment of Parkinson's disease (PD) and is now widely used in the treatment of advanced Parkinson's disease. Previous articles in this ACNR series have demonstrated this and alluded to the theoretical and practical issues that arise. Currently, it has to be given by intermittent subcutaneous injection or by continuous infusion, which limits its use to cases of Parkinson's disease that are refractory to oral medication. Other dosage forms have been studied - and it can be administered by sublingual, intranasal, transdermal and rectal routes, but each has drawbacks, and we have the greatest experience with subcutaneous injection^{2,3}. We published a protocol for its use, and have audited the results of its use as a challenge, and in continued therapy⁴.

We have had more than a decade of experience with this dopamine agonist, and our experience confirms that apomorphine is a valuable drug. Our experience was similar to previously published series^{3,4}.

The demographic details of our patients are shown below.

Total tested n (m:f)	60 (39:21)
Mean Age at test (range - years)	67.5 (45-85)
Mean Age at Onset of PD (range - years)	57.8 (25-82)
Duration of PD (range - years)	9.4 (0.5-32)
Hoehn & Yahr (range)	4.2 (3-5)

Our protocol included pre-treatment with oral domperidone 30 mg thrice daily for a minimum of 48 hours, reducing in chronic use as tolerance develops. Most patients were admitted, partly due to logistics in this rural county, but also because we were using this drug in some quite disabled patients who would have found day-case testing difficult. This aspect remains under review.

We saw a relief of individual patient symptoms in between a third and 100%. We saw good responses in immobility and patients with severe "off" period symptoms including pain, painful dystonia, and control of dyskinesia in a number of patients with continued treatment. A beneficial response was most likely in patients with long duration of disease and younger age of onset, having had a good initial response to levodopa and those without cognitive impairment.

The mean age at test for the good responders was 65 which although 5 years younger than the non-responders did not achieve statistical significance. The age at onset is significantly different; those who responded well developed PD at 53 years whereas the non-responders had an age at onset of 68 years.

Similarly there was a highly significant difference between those who had had Parkinson's for well over 10 years who had a good response whereas those with a short duration of symptoms (3.2 years mean) had a poor



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PREDICTORS OF RESPONSE

Parameter Response:	Good	Partial	None	p
n	32	14	10	
Age at test mean (range) years	65.8 (47-74)	66.4 (45-83)	72.9 (47-86)	0.109
Age at onset mean (range) years	53.4 (25-82)	59.1 (36-78)	68.6 (41-83)	0.0075
Gender Male : Female	18 : 14	10 : 4	8 : 2	n.s
Duration of symptoms mean (range) years	12.2 (2-32)	7.4 (0.5-17)	3.2 (0.5-8)	0.0001
Good response to L-dopa	30	10	6	0.013
No response to L-dopa	2	4	4	0.013

The APO-go Pen



response mainly because of inclusion of cases of multi-system atrophy. There is also a strong correlation with the response to levodopa with those patients who had had a good response to also show a good response to apomorphine – and conversely those who had a poor response to levodopa correlated with a poor response to apomorphine. We noted that none of the 5 patients who had cognitive problems or hallucinations responded positively.

Side effects of test doses (n=60) included hypotension (9), dyskinesia (6), drowsiness (4), nausea/faint (2), and confusion (1). Side effects were generally reversible quite rapidly. Patients who had shown a good response to the challenge dose were subsequently offered apomorphine as treatment.

With continued usage and experience the frequency of problematic side effects was reduced. Persisting nausea occasionally occurs despite domperidone. Mild sedation in a few patients and occasional neuro-psychiatric complications have been seen.

These patients had been using apomorphine for an average duration of 4 years (range 1-6yrs). 21 have remained on bolus therapy with a typical average daily dose of about 9 mg (range 2-20 mg.), 8 of them went onto the syringe drivers with a typical daily dosage of 80 mg per day (range 40-120mg.) typically given over 12 hours.

Subsequently, five have died (3 syringe driver patients, 2 bolus apomorphine takers) showing the mortality in this group of patients. Six have discontinued (4 syringe driver patients, 2 bolus apomorphine takers) because of side effects and some of the bolus patients have decided to stop for various reasons. Two have had surgery, one of those has discontinued apomorphine, one continues with bolus doses.

In long term use, skin nodules and bruising are common side effects, the prevalence of which has been reduced by dilution of apomorphine with equal volumes of normal saline. Ultrasound was used to disperse subcutaneous nodules.

One particularly gratifying anecdote is of a widow who was able to stay at home rather than be admitted to a nursing home for about 4 years by use of apomorphine. Local district nurses supported her and although experiencing some visual hallucinations – typically of a black cat coinciding with the onset of relief of her PD symptoms – she welcomed these since her disease was so well relieved by this drug. Ultimately she died from an unrelated cause (a myocardial infarct).

Conclusions

Apomorphine has established its place in the treatment of patients with Parkinson's disease and some patients with parkinsonism as a valuable mode of treatment when patients have become refractory to oral drugs. It is useful in patients in whom there is diagnostic or therapeutic uncertainty, and for those patients who are considered unsuitable for neurosurgery.

Whilst the Parkinson's or movement disease clinic is desirable to support the use of this drug, the availability of a specialist nurse is essential. Older patients may need admission for testing, but provided they have shown a good response to oral levodopa and are not demented, they may benefit equally from this drug as do their younger counterparts, and its use can help even quite elderly patients to maintain their independence.

The APO-go Pump



References

1. Friedman A. *Old-onset Parkinson's disease compared with young-onset disease: clinical differences and similarities.* Acta Neurol Scand 1994 Apr;89(4):258-61
2. JR Playfer. *Drug therapy. Parkinson's Disease in the Older Patient.* Eds JR Playfer, JV Hindle. Arnold, London 2001; pp 298-9 ISBN 0 340 75914 3
3. Manson AJ, Turner K, Lees AJ. *Apomorphine monotherapy in the treatment of refractory motor complications of Parkinson's disease: Long-term follow-up study of 64 patients.* Mov Disord 2002 Nov;17(6):1235-41
4. DG MacMahon. *The Use of Apomorphine in Clinical Practice.* Advances in Neurology ed G. Stern 1999;80:529-33

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