



Apomorphine Injections: Predictors of Initial Adverse Events

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ABSTRACT

Apomorphine injections effectively abort "off" episodes in Parkinson's disease; however, their use is limited by actual and perceived adverse events. Nausea and hypotension can be severe and necessitate medical supervision to monitor the initial injection. To our knowledge, no study has evaluated for predictors of who actually incurs these problems. We prospectively monitored for these and other adverse events in 28 PD patients receiving initial apomorphine injections in our clinic with sequential visual analogue scales for pre-specified AEs and by assessing orthostatic blood pressures at 10, 20, and 40 minutes post injection. Assessed historic variables included patient demographics, treatment histories (total dose, L-dopa equivalent to turn on, current or previous dopamine agonist use, etc.), previous AE to other PD treatments, and whether patients received the recommended three day dose of trimethobenzamide.

Results: Three days of trimethobenzamide, as recommended, was associated with more nausea than a single dose. No demographic or previous history of AE predicted nausea. Only younger age was associated with hypotension.

Conclusion: We do not feel three days of pretreatment with trimethobenzamide is justified. Previous histories of hypotension and nausea should not dissuade use of apomorphine if clinically justified.

INTRODUCTION

Apomorphine injections are currently used as rescue therapy to achieve an "on" state in fluctuation Parkinson's disease (PD). Studies have shown consistent and robust efficacy, but use has been limited by actual and perceived adverse events (AE).¹⁻³ Due to hypotension and to a lesser extent, nausea and other AEs, the initial injection is given by a health care professional. Tolerability varies markedly, as some patients have initial and persistent AE, some have initial AE that quickly resolve and others have no AE. Long term treatment emergent AEs are uncommon.¹⁻⁴ Furthermore, current protocol requires three days of oral trimethobenzamide prior to apomorphine injections to reduce nausea. Since there is considerable time, effort and cost employed to initiate therapy, predictions of who will tolerate apomorphine could be very particularly useful. However, to our knowledge no formal data assessing predictors of initial tolerability exist.

METHODS

All patients underwent initial apomorphine injections at the Baylor College of Medicine Parkinson's Disease Center and Movement Disorder Clinic. All patients started with 0.2 mg injections. Higher doses were subsequently used if patients did not achieve an "on" status. Supine and standing blood pressures (BP) and a nausea visual analogue scale were done at baseline and at 10, 20 and 40 minutes post injection. Orthostatic hypotension was defined by a drop in orthostatic BP (supine minus standing systolic BP) that was more than 10 points compared to the baseline orthostatic drop in standing SBP at any time after injections, or a subjective report of "light headed" that was not present before injections. We also specifically queried other known AEs including, dizziness, yawning, hallucinations, sedation, etc. Patient demographics, treatment histories (total dose, L-dopa equivalent to turn "on", current or previous dopamine agonist use, etc.), and previous AE to other PD treatments were obtained. Final apomorphine dose and reasons for discontinuation were obtained.

We strove to answer several questions in this report. Do patient demographics predict AEs to apomorphine? Do previous AEs, especially nausea and hypotension, predict AEs to apomorphine? Does the use of previous dopamine agonists mitigate apomorphine AEs? Does total or single dose of L-dopa equivalents predict the effective dose of apomorphine? Is a single dose of trimethobenzamide as effective as three days of treatment in preventing nausea? Are AEs, especially hypotension, dose dependent in subjects who required doses of greater than 2 mg?

RESULTS

Data sets were completed for 32 patients (20 male, age 60.2±10.3 years). The diagnosis was idiopathic PD (28), atypical parkinsonism (2), and restless legs syndrome (2). Analysis was performed on all 28 PD subjects, 18 male, ages 59.9±9.8, duration of PD 13.1±4.4 years. All had fluctuations, 23 had dyskinesia, and 21 had sudden offs. The mean duration to onset of first daily L-dopa dose was 44±17 minutes. "Off" UPDRS part III was 45.5±15.8, N=25. The mean daily L-dopa equivalent dose was 1228±1002 mg, and 8 had had some CNS surgery for PD. Eleven subjects (39%) were pre-treated with three days of trimethobenzamide as per recommended protocol. The rest took a single (N=15) or no dose (N=2) prior to apomorphine injections.

The most common other AEs were yawning (13), flushing (6), dyskinesia (5), drowsiness (5), headache (3) tachycardia (2), tachypnea (1), and hallucinations (1). After injections, any nausea (>0 at any time on nausea VAS) was reported by 15 subjects. This was not predicted by a previous history of nausea, any demographic or previous treatment. Interestingly, nausea was more common in subjects who took three days of trimethobenzamide.

Orthostatic hypotension was documented in 10 subjects, although only 5 of these reported subjective light headedness. One subject who reported OH did not have any drop in standing SBP compared to baseline but did have a marked increase in the delta between supine and standing SBP after injections that was masked by and increased supine SBP. OH correlated with younger age, p=0.01. Other demographics, use of three days trimethobenzamide, and a history of OH did not correlate with apomorphine induced OH.

Ten subjects required a second injection, mean dose 3.5 mg [range 0.3-0.4]. Compared to their 0.2 mg injection, AE were similar with the second higher dose injection.

The mean final dose at last visit (N=28) was 0.34 mg.±0.15 [range 0.16 - 0.8]. This did not significantly correlate with the latency to onset from L-dopa, the total daily L-dopa equivalent dose, or the L-dopa equivalent dose to turn "on", although the L-dopa dose had a non-significant correlation (Pearson = 0.49).

At last follow-up, only 10/28 continued on apomorphine injections. Reasons that contributed to discontinuation include adverse events (4) including hypotension (3) and nausea (1) that were all present with first injection, lack of efficacy (3), reduced fluctuations secondary to other medical or surgical care (3), cost (3), inconvenience despite good results (3), or no specific reason (2).

DISCUSSION

Apomorphine injects are an established treatment for PD. Their rapid onset and short duration make them most suitable for "rescue therapy". Continuous apomorphine infusions are also used as the mainstay of therapy in selected patients.^{5, 6} Our report found that previous nausea and hypotension with other treatments did not predict these two most problematic AE with apomorphine injections. Only younger age predicted hypotension, probably due to a more intact and reactive autonomic nervous system. Interesting three days of trimethobenzamide, did not prevent dopaminergic AEs, but actually correlated with greater nausea. This may be Type I error, or possibly is due to tolerance to the anti-nausea mechanisms (largely anti-histaminergic) of the drug after three days compared to a single dose.

The lack of correlation between dose of apomorphine injections required to achieve an "on" state and the dose of L-dopa dose to turn on, suggests that most variability in L-dopa dosing results from variance in L-dopa GI absorption and/or CNS bioavailability.

A large number of our patients eventually stopped apomorphine injects but, similar to previous reports⁴, this was not due to new onset AEs. Therefore tolerability is largely determined within a very short time of initiating therapy.

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