National PBM Drug Monograph

Apomorphine (Apokyn®)

July 2004

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Executive Summary:

FDA-approved Indication: Apomorphine is a direct-acting dopamine agonist with strong D_1 and D_2 dopamine receptor stimulating properties. Apomorphine is approved for the treatment of acute, intermittent hypomobility, "off" episodes (end-of-dose wearing off and unpredictable "on/off" episodes), associated with advanced Parkinson's Disease.

Dosing: Apomorphine is indicated for subcutaneous administration. Patients must be titrated to an effective dose of apomorphine. The agent is a potent emetogenic agent and patients must be pre-treated with an antiemetic prior to use. The current recommendation is to begin therapy three days prior to the initial use of apomorphine with trimethobenzamide 300 mg, by mouth, three times daily. The regimen should continue during the first two months of therapy and be altered as needed. Currently, the manufacturer is proposing a third party distribution system.

Safety: In the North American efficacy trials of apomorphine, 107 patients were exposed to therapy. The commonly reported adverse events included nausea, vomiting, hallucinations, dyskinesias and yawning. Hypotension and syncope are common adverse effects and must be considered in the titration of the agent. Apomorphine must not be given with $5HT_3$ antiemetic agents as profound hypotension has been reported. Other possible adverse effects include nodule development at the injection site,

Efficacy: Recently, key trials have been conducted in North America that led to the approval of apomorphine in the US. The National Institute of Health Study (NIH) involved patients with a range of disability and concomitant medications. All patients demonstrated a response to apomorphine with some difference being found in the durations of effect among the subgroups. There have been several multicenter, randomized, double blind trials of apomorphine, which were pivotal in the approval of the agent. These trials have demonstrated the efficacy of apomorphine in the decrease of hypomobility episodes associated with PD. The use of apomorphine has also been shown to enable a decrease in levodopa dose that can help lessen the occurrence of dyskinesias. Hypotension appears to be the most serious adverse effect and patients require monitoring during the titration phase of the agent.

Conclusion: Apomorphine occupies a unique niche in the therapy of Parkinson's Disease. It provides a rapid onset of effect that is efficacious in the control of "off"episodes. It can also be beneficial in the control of pain, dystonia and gastrointestinal motility problems of PD. Although it is a highly emetogenic agent, this can be controlled with pretreatment and does not usually limit drug use

Recommendation: Given the unique nature of this agent and its place in therapy, apomorphine should be added to the National Formulary restricted to neurology for use in the FDA approved indication. This would also require the addition of the antiemetic agent trimethobenzamide with the same restrictions.

Introduction

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating apomorphine for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics [1-4]

Apomorphine is a direct-acting dopamine agonist with strong D_1 and D_2 dopamine receptor stimulating properties. The precise mechanism of action is unknown but is thought to be the result of post-synaptic D_2 receptor stimulation in the caudate nucleus and putamen. The agent is highly lipophilic in nature, allowing for rapid diffusion across the blood-brain barrier after injection. This results in an onset of effect within 10 minutes of injection. Apomorphine has a short plasma half-life, however clinical effects may last from 60-90 minutes.

Apomorphine displays a significant degree of interpatient variability in its pharmacokinetic profile. Studies of both intravenous and subcutaneous injection routes found this variation was not attributable to body weight, age, gender, duration of Parkinson's Disease or levodopa dose/duration alone. The average T_{max} occurs within 10-20 minutes with a range of 5-45 minutes in a number of studies. The exact method of metabolism is unknown. Hypothesized routes include sulfation, N-demethylation, glucuronidation and oxidation. The drug appears to undergo renal excretion as patients with renal impairment display increased plasma concentrations.

FDA Approved Indication(s) and Off-label Uses [5]

Apomorphine is approved for the treatment of acute, intermittent hypomobility, "off" episodes (end-of-dose wearing off and unpredictable "on/off" episodes), associated with advanced Parkinson's Disease. This agent was approved on April 21, 2004 with an approval rating of 1P, V.

Current VA National Formulary Status

The VA National Formulary includes other dopamine agonists such as bromocriptine, pergolide and pramipexole. However, apomorphine is the only parenteral agent available to treat acute episodes of hypomobility.

Dosage and Administration [1-5]

Apomorphine is indicated for subcutaneous administration. The agent is a potent emetogenic agent and patients must be pre-treated with an antiemetic prior to use. The current recommendation is to begin therapy three days prior to the initial use of apomorphine with trimethobenzamide 300 mg, by mouth, three times daily. The regimen should continue during the first two months of therapy and be altered as needed.

The dose of apomorphine must be titrated based on tolerance and response. Patients should be initiated on therapy with a dose of 0.2 ml (2 mg). An initial test dose of 0.2ml (2mg) should be given during an off episode and in a location where the patient's blood pressure can be monitored. Both supine and standing blood pressure should be monitored pre dose and at 20, 40 and 60 minutes post dose. If the patient develops no hypotension and demonstrates a clinical response (improvement in hypomobility) they may be continued on the 0.2 ml dose. In patients who tolerated the 0.2 ml dose but showed no response a dose of 0.4 ml may be tried with the next "off" episode. This should not occur earlier than 2 hours after the first test dose. Blood pressure should be monitored in the same manner as for the 0.2 ml test dose. The general principal guiding therapy is to use a dose 0.1 ml lower than the tolerated test dose. Doses should

not be increased greater than 0.6 ml. There is limited experience with dosing greater than 5 times per day or with total daily doses greater than 20 mg.

Patients who fail to demonstrate a response for a particular "off" period should not repeat the dose of apomorphine for that episode. If a an interruption in therapy of greater than one week occurs, patients should be restarted on the 0.2 ml dose and titrated to effect.

Adverse Events (Safety Data) [5-8]

Deaths and Other Serious Adverse Events

There have been no reported deaths due to apomorphine in the pivotal or open label trials of this agent. The administration of apomorphine with ondansetron has resulted in profound hypotension and loss of consciousness. The use of the $5HT_3$ class of antiemetic agents is contraindicated for patients receiving apomorphine due to this serious adverse event.

Common Adverse Events

The manufacturer of apomorphine has maintained a database of 516 patients with PD who have received the agent in open trial format. These patients have experienced treatment periods from 4 months to over 12 months for 120 members of the population. Serious adverse events occurred in 16% and 19% discontinued the agent due to an adverse event. Common adverse events include dyskinesias, hallucinations and orthostatic hypotension. Termination of therapy was related to nausea (13 patients), vomiting (9), dizziness (9), somnolence (9), hallucinations (5) and dyskinesias (8).

In the North American efficacy trials of apomorphine, 107 patients were exposed to therapy. The commonly reported adverse events included nausea, vomiting, hallucinations, dyskinesias and yawning.

Patients receiving subcutaneous injections of apomorphine may also develop nodules at the site of injection.

Apomorphine has also been investigated as an erectile dysfunction agent. Use of apomorphine may result in priapism or prolonged erections, in the clinical trials this occurred in less than 1% of patients. Patients should be cautioned of this effect and understand the need to seek medical attention immediately.

Precautions/Contraindications [5]

Precautions

Apomorphine may exacerbate dyskinesias or cause development of new onset dyskinesia. In the clinical trials of the agent this event occurred in 24% of patients prompting withdrawal of apomorphine in 2% of cases.

Contraindications

Apomorphine contains sodium metabisulfite, which is capable of causing anaphylactic reactions in patients with sulfite allergy. Its use should be avoided in this patient population.

The administration of $5HT_3$ antiemetic agents (i.e., ondansetron, granisetron, dolasetron and palonosetron) may result in profound hypotension with apomorphine administration. The concomitant use of these agents is contraindicated for safety purposes.

Drug Interactions

Drug-Drug Interactions

The use of neuroleptic agents (i.e., phenothiazine, butyrophenones, thioxanthenes) or metoclopramide may diminish the effectiveness of apomorphine due to dopamine antagonism of the agents.

There may be an additive antihypertensive effect when apomorphine is given to patients receiving concurrent therapy with antihypertensive agents.

Efficacy Measures

There are no common laboratory measures that can follow the course of PD and serve as markers of treatment efficacy. The most clinically useful tools for monitoring PD progression and treatment effects include standardized scales that can rate disease severity.

Modified Hoehn & Yahr scale- this scale assesses disease severity from Stage 0, no sign of disease to Stage V, wheelchair bound or bedridden without assistance.

Unified Parkinson's Disease Rating Scale(UPDRS)- quantifies motor and behavioral status as well as disabilities. The entire scale can be viewed at http://www.wemove.org/par_rs.html. The UPDRS includes an evaluation of self-reported disability (i.e. the activities of daily living, ADL) as well as clinical scoring by a physician (i.e. the motor examination). A total of 199 points are possible with 0 representing no disability and 199 representing total disability.

Schwab and England Scale- measures the patients ability to perform activities of daily living in terms of speed and independence.

Parkinson's Disease Questionnaire (PDQ_39)- a self- administered, disease-specific instrument designed to measure aspects of health (scale of 0 to 100) that are relevant to patients with PD, and which may not be included in general health status questionnaires. Lower scores indicate a better-perceived health status. Higher scores are consistently associated with the more severe symptoms of the disease such as tremor and stiffness. The results are presented as eight discrete domain scores and not as a total score.

Clinical Trials [8-33]

Apomorphine was first produced in 1869. Since that time it has been investigated as a sedative, emetic and as a treatment for alcohol dependence. In 1951, trials of apomorphine as a therapy for PD were begun. At this time the pharmacology of the agent was unknown but with the discovery of its dopamine agonist effects in the 1960's subsequent trials of injectable routes of apomorphine began. Interest in its use tapered due to the lack of a delivery system and the profound nausea/vomiting and hypotension occurring during early trials. Since that time more convenient delivery forms have been developed and methods to manage the adverse effects have been developed. The agent has been available in Europe since 1993. Many investigations of apomorphine have used an open label design. Several trials have involved continuous infusions of apomorphine as well. The seven trials for subcutaneous therapy found apomorphine to result in decreased dyskinesia intensity; decreased time spent in "off" periods and allowed doses of levodopa to be decreased. These trials are summarized in **Table 1**. Recently, key trials have been conducted in North America that led to the approval of apomorphine in the US. The National Institute of Health Study (NIH) involved patients with a range of disability and concomitant medications. All patients demonstrated a response to apomorphine with some difference being found in the durations of effect among the subgroups. There was no difference in terms of threshold dose or optimal dose. This trial is summarized in **Table 2**. There have been several multicenter, randomized, double blind trials of apomorphine that were pivotal in the approval of the agent. These trials have demonstrated the efficacy of apomorphine in the decrease of hypomobility episodes associated with PD. While the number of patients involved in the trials may be small the effects seen were significant, both statistically and clinically. These trials have demonstrated an onset of action for apomorphine from 7.5 to 10 inutes, durations ranging from 60 to 120 min with an average dose of 4 mg. They are summarized in **Table 3**.

Table 1: Open Label experience with apomorphine

Reference	N	Duration of follow-up(months)	Time to onset (min)	% Improvement of "off" time
Stibe, 1988[9]	8	15	5-15	55
Powe, 1988[6]	17	3-15	NR	64
Frankel, 1990[10]	32	5-26	3.5-12.5	58
Deffond, 1993[11]	7	7.7	14	55
Peitz, 1998[12]	24	22	3-30	40

Table 2: NIH study of apomorphine[13]

	N	Response duration (min)	Dose a maximal benefit	Maximal Percent improvement
Dopa naïve	10	52	0.03	38.6±6.87
Stable L-dopa	9	44	0.06	46.2±5.79
Predictable off	8	33	0.06	75.88±3.51
Unpredictable off	7	28	0.06	75.29±3.66

Table 3: Pivotal Clinical Trials

Trial	N	Primary endpoint	Results	
APO-202[14] Phase I	29	Change in Part III of UPDRS	Apomorphine UPDRS change –23.9(±1.9) % change 62(±4.4)	Placebo -0.1(±1.3) -1(±3.7)
APO 202[14] Phase II	26	Percent of off state events aborted	95(±2.4)	23(±13)
APO301[15]	17	Change from baseline in UPDRS motor score	Baseline 41.3(±2.49) At 20 minutes 20±3.60	 40.1(±2.23) NS 3±2.24 P<0.0001
APO302[15]	A-37 P-27	Change from baseline in UPDRS motor score at 20 min	At 20 minutes -24.2	-7.4 P<0.0001
APO303[15]	51	Change from baseline in UPDRS motor score at 4 mg dose	-11	-3 p=0.0002

Acquisition Costs

Drug	Dose	Cost/Dose ($)	Cost/Day/patient ($)*	Cost/year/patient ($)
Apomorphine	0.2 ml	$3.95	$15.80	$5767.00
	0.4 ml	$ 7.90	$31.60	$11,534.00
	0.6 ml	$11.86	$47.44	$17,315.60
Trimethobenzamide	300 mg TID	$0.63	$1.89	$689.85

* Based on mean doses per day of 4

Sound alike look alike potential

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

LA/SA for generic name: apomorphine

Oxymorphone

Hydromorphone

Atomoxetine

Morphine

LA/SA for trade name: Apokyn™

Naprosyn

Unasyn

Zosyn

Cost Analysis

To date here have been no formal economic analysis of apomorphine.

Data Compilation Tables

Change in UPDRS from Dewey, et al[14]

(OUTCOME ON DRUG)	62%
(OUTCOME ON PBO)	1%
Treatment duration	I month
Absolute Risk Reduction (95% CI)	61% (±34%)
NNT	2

Conclusions

Apomorphine has been shown to consistently reduce the “off” episodes associated with PD. This has been demonstrated in both open label and double blind trials. Typical doses to demonstrate this effect have been 1-5 mg (0.1-0.5 ml) given subcutaneously. These doses can be repeated during the day as required up to approximately 10 times. The effects are fast acting and last up to 2 hours on average. The use of apomorphine has also been shown to enable a decrease in levodopa dose that can help lessen the occurrence of dyskinesias. Hypotension appears to be the most serious adverse effect and patients require monitoring during the titration phase of the agent. Other adverse effects include nausea, vomiting, yawning, hallucinations and injection site reactions.

Recommendations

Given the unique nature of this agent and its place in therapy, apomorphine should be added to the National Formulary with a restriction to neurology. This would also require the addition of the antiemetic agent trimethobenzamide with the same restrictions.

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