An Open-Label, Uncontrolled Dose-Optimization Study of Sublingual Apomorphine in Erectile Dysfunction

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ABSTRACT

Background: Because apomorphine is a dopamine agonist that acts on areas of the central nervous system believed to mediate penile erection, its use in erectile dysfunction (ED) has been investigated. However, it also produces nausea by dopamine-receptor stimulation of the chemotrigger zone in the brain. Therefore, a low plasma concentration, achieved rapidly, would be selective for the desired erectile response but would be below the dopamine threshold for nausea.

Objective: We evaluated the efficacy and tolerability of a dose-optimized regimen of a sublingual formulation of apomorphine (apomorphine SL) in the treatment of ED.

Methods: This was a multicenter, open-label, uncontrolled, Phase III dose-optimization study of apomorphine SL in heterosexual men with ED. The 2-week screening period, during which baseline severity of ED was determined using the International Index of Erectile Function, was followed by a 3-week dose-optimization period beginning at a dose of 2 mg. Patients were to make at least 2 attempts at intercourse per week throughout the study, placing 1 apomorphine tablet under the tongue beforehand. At the end of the first week, the dose could be increased to 3 mg at the discretion of the investigator; at the end of the second week, the dose could be increased to a maximum of 4 mg or decreased as needed. In the following 4-week treatment period, patients took their individual optimal doses. The primary efficacy variable was the percentage of attempts resulting in erections firm enough for intercourse, as assessed by investigators' review of data from patients' diaries. Secondary variables included the percentage of attempts resulting in successful intercourse, time to erection, and duration of erection. Information about adverse events, including their severity and relation to treatment, was determined on the basis of direct questioning, spontaneous reports, and review of patient diaries.

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Results: The study enrolled 849 heterosexual men whose ages ranged from 31 to 78 years (mean, 58.1 years). They had a mean 5.7-year history of ED of various causes. ED was mild in 11.5% of the men, moderate in 23.8%, and severe in 48.1%. When results of the last 8 attempts were pooled, representing the period during which patients were taking their optimal doses of apomorphine SL, the mean percentage of attempts resulting in erections firm enough for intercourse was 39.4%, compared with 13.1% at baseline; attempts resulting in intercourse increased from a mean of 12.7% at baseline to 38.3% with treatment. The average median time to erection was 23 minutes, and the average median duration of erection was 13 minutes. Nausea, the most common treatment-related adverse event (11.7%), was dose related and diminished with continued dosing. One patient had a single syncopal episode that was judged to be related to apomorphine SL.

Conclusions: In the present study, a dose-optimization regimen of apomorphine SL—with dosing initiated at 2 mg and adjusted up to a maximum of 4 mg as needed—was effective and well tolerated in the treatment of ED, regardless of its cause or severity.

Key words: apomorphine, dopamine agonist, dose-optimization, erectile dysfunction, ED. (*Clin Ther.* 2001:23:1260–1271)

INTRODUCTION

Erectile dysfunction (ED) is the inability to achieve or maintain an erection sufficient for satisfactory sexual performance.[1] This definition, by distinguishing ED from difficulties with libido, orgasm, and ejaculation, permits a more accurate estimate of its prevalence. According to the National Institutes of Health, 5% of men in the United States experience complete ED at the age of 40 years; at ≥65 years, the rate increases to 15% to 25%.[1] When partial or occasional ED is included, the overall prevalence approaches 30 million in the United States and nearly 140 million worldwide. A community-based random survey conducted in Massachusetts found that 52% of 1290 men between 40 and 70 years of age had at least some degree of impotence (39% at age 40; 67% at age 70).[2] Of the men in this survey, 81% reported either minimal or moderate ED. It must be recognized that the prevalence of ED differs according to the definition used, which is somewhat subjective, often representing the failure of a man's performance to meet his own expectations, which are largely dictated by cultural and societal factors.

Although age is by far the strongest predisposing factor,[1] ED may be a surrogate marker for certain organic disorders known to be direct risk factors (eg, atherosclerosis, diabetes mellitus, hypertension, and chronic renal failure). Moreover, drugs used to treat atherosclerosis and other diseases are responsible for an estimated 25% of cases of ED.[1]

Because apomorphine is a dopamine agonist that acts on areas of the central nervous system believed to mediate penile erection, its use in ED has been investigated. However, apomorphine produces nausea by dopamine-receptor stimulation of the chemotrigger zone, which lies in the area postrema of the brain outside the blood-brain barrier, where it is exposed to plasma drug concentrations.[3] Therefore, a low plasma concentration of apomorphine, achieved rapidly, would be selective for the desired erectile response but would be below the dopamine threshold for nausea.[3]

Whereas oral formulations are limited by rapid first-pass metabolism and injectable formations are generally less acceptable to patients, sublingual apomorphine (apomorphine SL) has the desired properties. It is structurally similar to dopamine and exhibits dopamine-agonist activity.[4] It is highly lipid soluble and quickly reaches an equilibrium between the blood and tissue compartments. Apomorphine SL has a half-life of 2 to 3 hours and is metabolized by hepatic glucuronidation. Metabolites are renally excreted. The desired penile erectile response is the result of enhanced cerebral neural signaling.[5]

In a placebo-controlled dose-optimization study in 569 patients,[6] improvement in erectile function was significantly greater with apomorphine SL 2 to 6 mg than with placebo ($P \leq 0.001$). Heaton[7] reported that the efficacy of apomorphine SL was dose dependent in 3 studies comparing apomorphine 2 and 4 mg in 854 patients with ED; the most common side effect was mild to moderate dose-related nausea, the incidence of which diminished after the first dose. Vasovagal syncope has been reported with apomorphine, predominantly at doses ≥4 mg; for example, Heaton[7] reported this event in 0.6% of patients taking 4 mg. In 87.2% of cases on file with the manufacturer, clear prodromal symptoms (nausea, sweating, dizziness, and/or pallor) preceded these events. All patients recovered without sequelae.

To assess the efficacy and tolerability of a dose-optimization regimen of apomorphine SL in the treatment of ED, we designed a protocol that at least partially mimicked the circumstances encountered by actual patients receiving a prescription for apomorphine SL—along with information about vasovagal symptoms—and using the drug at home.

METHODS

Inclusion and Exclusion Criteria

Adult men who had been in a stable heterosexual relationship for at least 6 months were eligible for study participation if at least 50% of their attempts at intercourse had failed in the 3 months before the study because of an inability to attain and sustain a sufficiently firm erection. Their general health and literacy had to be adequate for participation in a clinical trial. Patients with concomitant organic diseases such as hypertension, diabetes mellitus, coronary artery disease, and benign prostatic hyperplasia could participate provided their condition was controlled.

Patients with uncontrolled cardiovascular disease—unstable angina, hypertension (resting systolic blood pressure >180 mm Hg and/or resting diastolic blood pressure >100 mm Hg) or hypotension (standing systolic blood pressure <90 mm Hg)—with symptoms or clinically significant abnormal electrocardiographic (ECG) findings were excluded. Additional reasons for exclusion were clinically significant neurologic disease, including spinal cord injury and multiple sclerosis, cancer in remission for <5 years, HIV, and AIDS. Also excluded were men who had undergone radical prostatectomy, had received a penile prosthesis, had a major penile deformity, had serum testosterone levels <240 ng/dL, or had used other interventions for ED within 1 month of taking the first dose of apomorphine SL. Hypersensitivity to morphine and a history of recent drug or alcohol abuse were additional exclusions. The exclusion criteria were intended to ensure tolerability, but were also designed to limit the population to men who had intrinsic penile function.

Concomitant use of metoclopramide or cisapride was prohibited, because these drugs may inhibit the central nervous system effects of apomorphine. Because anxiolytics and selective serotonin reuptake inhibitors are known to confound the manifestation of ED, introduction of these drugs (or a change in dose) was not permitted; however, patients taking stable maintenance doses of these agents were allowed to continue doing so.

The protocol was approved by the institutional review board for each participating center, and the study was conducted in conformity with the Declaration of Helsinki and the requirements of good clinical practice. Patients and their partners gave their written informed consent before entering the study.

Study Design

This was a multicenter, open-label, uncontrolled, Phase III dose-optimization study involving an escalating-dose regimen of apomorphine SL in heterosexual men with ED of various causes. During a 2-week screening period, patients underwent a complete physical examination that included medical and sexual histories, assessment of vital signs (including blood pressure and pulse in both the supine and standing positions), an ECG, and laboratory tests. To establish the presence and severity of ED and to assess patients' erectile function after treatment, patients completed the International Index of Erectile Function (IIEF)[8] at baseline and at the week-3 and week-7 visits. The IIEF contains 15 questions divided into 5 domains: erectile function, intercourse satisfaction, overall satisfaction, orgasmic function, and sexual drive. The severity of ED was determined based on the sum of the scores of questions 1 through 5 and question 15. Scores ≤10 indicated severe ED; scores from 11 to 16, moderate ED; and scores from 17 to 24, mild ED.

Participants were asked to attempt sexual intercourse at least twice a week during the screening period. After being counseled about potential side effects, including nausea and syncope, they were instructed to place 1 apomorphine tablet under the tongue when intercourse was desired and proceed when ready. After each attempt, they were to answer 2 questions in a patient diary: "Did you attain and maintain an erection firm enough for intercourse?" and "Did you have intercourse with your wife/partner?" They then entered a 3-week dose-optimization period at an initial apomorphine SL dose of 2 mg. They agreed to make at least 2 attempts at intercourse per week throughout the study, with a minimum of 8 hours between doses.

Patients returned to the clinic at the end of the first week, at which time the dose could be increased to 3 mg at the discretion of the investigator. At the end of the second and third weeks, the dose could be increased to a maximum of 4 mg or decreased as needed. After week 3, each patient received a 4-week supply of apomorphine SL (20 tablets) at his optimal dose level, as determined by the investigator. Throughout the study, each apomorphine dose and subsequent attempts at sexual intercourse were recorded in patients' diaries, which were to be completed within 12 hours of taking the drug.

Patients returned to the clinic at weeks 1, 2, 3, and 7 for assessment of efficacy and adverse events. Information about adverse events was obtained by questioning patients about symptoms, recording their spontaneous comments, and reviewing their diaries. The physician assessed the

severity of the reported events and their relationship to apomorphine SL on the basis of the patient's history and appropriate clinical examination. Brief physical examinations, including recording of vital signs, were performed at all visits during the treatment period, and patients underwent a complete physical examination at the final visit.

Efficacy Measures

The primary efficacy variable was the percentage of attempts resulting in an erection sufficiently firm for intercourse, as recorded in patients' diaries. A secondary variable was the percentage of attempts resulting in intercourse. Additional efficacy variables included time to erection and duration of erection.

Statistical Procedures

For the analysis of attempts resulting in an erection firm enough for intercourse and the percentage of attempts resulting in intercourse, percentages were calculated for individual patients and then averaged across all patients. Baseline diary responses were summarized and compared with responses recorded during the treatment period. Because the last 8 doses taken by those who completed the study represented use of apomorphine SL at optimal levels, similar analyses were performed on these data. Both time to erection and duration of erection were determined by computing the median for each patient and then averaging the medians across patients for those attempts that resulted in an erection firm enough for intercourse.

Adverse events (including severity and relation to treatment) were summarized, as was use of the antiemetic prochlorperazine. Changes from baseline in vital signs and laboratory results were analyzed using paired *t* tests. Between-dose differences in efficacy or adverse events were not submitted to statistical analysis, because only 14.5% of patients remained at the 2- or 3-mg dose level throughout the study.

RESULTS

The study enrolled 849 heterosexual men from 99 sites throughout the United States. The men ranged in age from 31 to 78 years (mean, 58.1 years), and the majority were white (730 [86.0%]) (Table I). Their mean duration of ED was 5.7 years. Nearly half (408 [48.1%]) had severe ED (IIEF[8] score ≤10); 202 (23.8%) had moderate dysfunction (score 11–16); and 98 (11.5%) had mild dysfunction (score 17–24). (IIEF responses were insufficient to establish the severity of ED in 140 men [16.5%].) At baseline, the men reported having an average of 13.1% erections firm enough for intercourse. A total of 585 patients (68.9%) presented with preexisting organic disease controlled by medication, including hypertension (371 [43.7%]), benign prostatic hyperplasia (259 [30.5%]), diabetes mellitus (196 [23.1%]), and coronary artery disease (143 [16.8%]). The majority (541 [63.7%]) were alcohol users. Three patients continued taking stable maintenance doses of anxiolytics and selective serotonin reuptake inhibitors.

Of the 849 patients who took at least 1 dose of apomorphine SL, 641 (75.5%) completed the 7-week study. (Reasons for discontinuation are shown in Table I.) After discussion with their physicians, most patients (726 [85.5%]) decided to optimize their dose to the 4-mg level, suggesting that tolerability was not affected by dose. Forty-nine (5.8%) patients remained at 2 mg, and 74 (8.7%) remained at 3 mg.

Table I. Characteristics and disposition of patients with erectile dysfunction (N = 849).

Age, y	
Mean	58.1
Range	31–78
Height, in	
Mean	70.1
Range	56–79
Body weight, lb	
Mean	204.1
Range	115–371
Race, no. (%)	
White	730 (86.0)
Black	67 (7.9)
Hispanic	38 (4.5)
Other	14 (1.6)
Coexisting organic disease, no. (%)	
Hypertension	371 (43.7)
Benign prostatic hyperplasia	259 (30.5)
Diabetes mellitus	196 (23.1)
Coronary artery disease	143 (16.8)
Alcohol users, no. (%)	541 (63.7)
Cigarette smokers, no. (%)	165 (19.4)
Baseline severity of erectile dysfunction	
Severe	408 (48.1)
Moderate	202 (23.8)
Mild	98 (11.5)
None	1 (0.1)
Unspecified*	140 (16.5)
No. (%) discontinuing the study	208 (24.5)
Primary reason for discontinuation, no. (%)	
Lack of efficacy (partial/complete)	110 (13.0)
Adverse event	42 (4.9)
Noncompliance or loss to follow-up	39 (4.6)
Patient or partner request	15 (1.8)
Other	2 (0.2)

*These patients did not answer questions on the International Index of Erectile Function[8] in a way that allowed assessment of severity

The figure illustrates the mean percentage of attempts resulting in an erection firm enough for intercourse and the mean percentage of attempts resulting in intercourse based on patients' diaries. When results of the last 8 attempts were pooled, representing the period patients were taking their optimal doses, the mean percentage of attempts resulting in erections firm enough for intercourse was 39.4%, compared with 13.1% at baseline. Attempts resulting in intercourse increased from 12.7% at baseline to 38.3% with treatment. Patients with severe ED showed the greatest improvement from baseline over the last 8 attempts (from 4.8% to 31.0%). Erectile function in those with moderate ED increased from 24.0% to 55.1%, and in those with mild ED from 41.1% to 66.4%. The results in patients with comorbidities were similar to those in the population as a whole. For example, in the 196 patients with diabetes mellitus, the rate of baseline attempts resulting in erections firm enough for intercourse was 8.9%, compared with 27.4% across all attempts after treatment.

When analyzed by dose, the mean percentage of attempts resulting in an erection firm enough for intercourse was 27.5% in the 2-mg group, 31.5% in the 3-mg group, and 38.6% in the 4-mg group. However, results at the lower doses should be interpreted cautiously given that 726 (85.5%) patients took only a few doses at the 2- and 3-mg levels.

The average median time to erection was 23 minutes, with 55 patients (6.5%) achieving erection within 10 minutes of dosing; the average median duration of erection was 13 minutes. Overall, IIEF[8] results in all 5 domains showed significant change from baseline at all time points ($P < 0.001$).

Adverse Events

Of the 849 patients who received at least 1 dose of apomorphine SL, 250 (29.4%) reported adverse events considered by the investigator to be related to treatment. Of these, 69.6% were mild, 27.2% were moderate, and 3.2% were severe. The incidence of adverse events was generally lower with the 2- and 3-mg doses. As expected, nausea was the most common adverse event at all doses, occurring with an incidence of 3.2% at 2 mg, 4.7% at 3 mg, and 7.2% at 4 mg. Nausea was mild in most patients (72 [72.7%]) and severe in 1. Most episodes of nausea were transient, lasting <1 hour, and the need for antiemetics was low (1.5%). Treatment-related headache and dizziness were reported by 60 (7.1%) and 49 (5.8%) patients, respectively. The severity of headache and dizziness was considered mild by the majority of patients (47/60 [78.3%] and 34/49 [69.4%], respectively). One patient had a single episode of treatment-related syncope. He did not take another dose of apomorphine SL and discontinued the study 7 days later. Table II presents drug-related adverse events reported by >1.5% of patients.

The overall incidence of adverse events in patients with comorbidities was similar to that in patients without concomitant disease. Physical examinations, vital signs, and ECGs yielded unremarkable findings both during and at the end of the study, and no clinically meaningful changes in laboratory values were observed.

DISCUSSION

A variety of treatments have been used for ED, ranging in invasiveness from surgi-

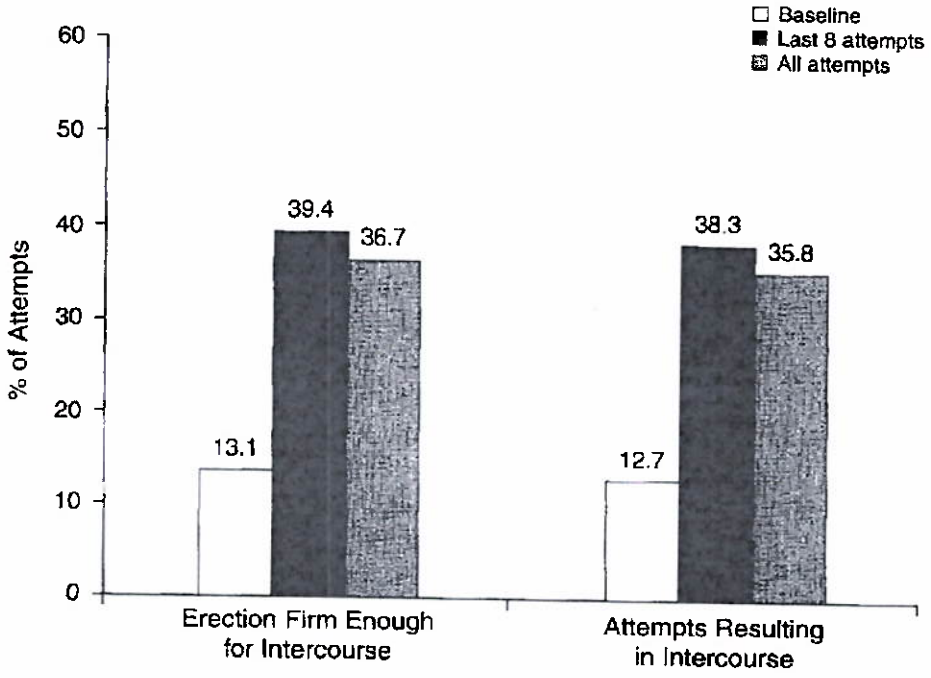

Figure. Response to a dose-optimization regimen of sublingual apomorphine.

cally implanted prostheses (rods or inflatable cylinders) and vacuum devices to drugs injected or inserted into the urethra and locally applied creams and unguents. Although many of these interventions have been successful in inducing or enhancing erection, many men discontinue treatment because of inconvenience or discomfort.[9] Even before the introduction of sildenafil in 1998, myriad orally administered drugs with potential efficacy in ED were investigated, including L-arginine, the precursor of nitric oxide (the principal mediator of erection), alpha-1– and alpha-2–receptor antagonists (phentolamine, trazodone, yohimbine), peripherally active vasodilators such as prostaglandin E_1 (limaprost), and the opiate antagonist naltrexone.[10]

The etiology of ED may be organic, psychogenic, or both, but most patients have ED of mixed origin.[11] The majority of men in our study (71.9%) entered with moderate to severe ED according to IIEF criteria,[8] with 68.9% having at least 1 coexisting organic disease. After taking apomorphine SL, 39.4% of attempts resulted in erections firm enough for intercourse, compared with 13.1% at baseline.

In our experience, it is not unusual for patients to choose higher doses of drugs in clinical trials that allow them the choice. Indeed, most patients (85.5%) in our trial chose the 4-mg dose of apomorphine SL, which suggests that tolerability was not a problem in these patients. Although the erectile response while patients were taking apomorphine SL 3 mg increased from 12.8% at baseline to 31.5% after treatment, too few patients remained at this dose level for conclusions about its efficacy to be drawn. Nonetheless, our findings agreed with those of a controlled clinical trial by Dula et al,[12] who reported that apomorphine SL 3 mg provided efficacy comparable to that of 4 mg with substantially fewer side effects.

Apomorphine SL was well tolerated in the present study. Dose-related nausea was the most common adverse event. Its severity was mild in 73.0% and moderate in 26.0% of patients, and symptoms improved with repeated use of the medication. The

Table II. Treatment-related adverse events reported by >1.5% of patients, by number (%) of patients (N = 849).

	Dose Level			
Adverse Event	2 mg (n = 849)	3 mg (n = 804)	4 mg (n = 747)	Overall* (N = 849)
Nausea	27 (3.2)	38 (4.7)	54 (7.2)	99 (11.7)
Headache	19 (2.2)	29 (3.6)	22 (2.9)	60 (7.1)
Dizziness	17 (2.0)	13 (1.6)	24 (3.2)	49 (5.8)
Vasodilatation	8 (0.9)	7 (0.9)	14 (1.9)	25 (2.9)
Sweating	2 (0.2)	8 (1.0)	14 (1.9)	22 (2.6)
Vomiting	5 (0.6)	0 (0)	11 (1.5)	16 (1.9)
Somnolence	6 (0.7)	6 (0.7)	6 (0.8)	16 (1.9)

*Patients who experienced adverse events at >1 dose level were counted only once in the overall total.

overall incidence of nausea was 11.7%; when assessed by dose, the respective incidence of nausea with doses of 2, 3, and 4 mg was 3.2%, 4.7%, and 7.2%. These figures are lower than the incidence seen in fixed-dose analyses[7]: in 3 double-blind, fixed-dose, crossover studies, the incidence of nausea after a 4-mg dose was 20.4%. We believe that the dose-optimization schedule used in our study may account for the reduced incidence of nausea.

At the First International Consultation on Erectile Dysfunction, held in Paris in 1999, an expert panel recommended the use of oral agents as first-line therapy for the treatment of ED, regardless of its source. Apomorphine SL is a centrally acting oral agent that appears to be effective and well tolerated in an ED population representative of that seen in clinical practice. On the whole, because the patient trying a new erectogenic agent is most concerned with his ability to achieve coitus, we believe the end points used in this trial are clinically meaningful and the most rigorous used to date in ED drug trials. Despite the fact that no placebo control was used, the questions "Did you attain and maintain an erection firm enough for intercourse?" and "Did you have intercourse with your wife/partner?" represent a direct assessment of the success of this or any other erectogenic agent.

CONCLUSIONS

The results of this study suggest that a dose-optimization regimen of apomorphine SL—with dosing initiated at 2 mg and adjusted up to a maximum of 4 mg as needed—is effective and well tolerated in the treatment of ED, regardless of its cause. Physicians are encouraged to work with patients to establish an optimal dose, to discuss possible side effects of new drugs for ED, and, ideally, to involve the patient's wife or partner in the treatment program.

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