# The Use of Alprostadil Sterile Powder in a Home Self-Injection Study of Asian Men with Erectile Dysfunction

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## ABSTRACT

This study evaluated the individual optimal dose of alprostadil in the office setting that could be used as the basis for effective home self-injection therapy. The study included 150 Asian men with erectile dysfunction (ED). The mean age of study participants was 48.3 years (range, 21 to 74 years), and the mean duration of ED was 3.6 years. The most common cause of ED was venogenic (24%), psychogenic (21%), arteriogenic (13%), neurogenic (0.7%), or a combination of these (41%). An optimal response was seen in 72% of patients (n = 108) in the office and 96% of patients (n = 100) at home. The mean ± SD office dose of alprostadil was 19.4 ± 12.8 μg versus 18.0 ± 12.2 μg at home. More than half of the patients (57% in an office setting and 53% at home) achieved an optimal response at a dose between 5 and 15 μg. By the 20-μg dose, 82% of patients had achieved an optimal dose at home compared with 70% of patients in the office. An optimal response was seen at the same dose in the office and home in 75% of patients; the dose at home decreased from the office dose for 16% of the patients and increased for 9%. There were 24 patients who experienced adverse events: penile pain after injection (18 patients), cold sweating (2 patients), pediculosis (1 patient), broken leg (1 patient), ankle pain (1 patient), and prolonged erection (1 patient). One patient discontinued the study because of penile pain. Alprostadil sterile powder offered safe and effective treatment of ED for home self-injection therapy. Once an optimal dose response had been established in the physician's office, further home adjustments were needed in 25% of patients. Penile pain, usually mild, was the most common, possibly related adverse effect reported.



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## INTRODUCTION

The use of prostaglandin $E_1$ ($PGE_1$) for the diagnosis and treatment of male impotence was first reported by Ishi et al[1] in 1986. In subsequent clinical studies, $PGE_1$ was reported to be as effective as or superior to other intracavernous agents for the treatment of erectile dysfunction (ED).[2] At a dose of 10 to 20 μg, 55% to 86% of men with ED were reported to have had complete functional erections after $PGE_1$ injections, depending on the study and the etiology of ED.[2–11]

$PGE_1$, normally in the form of alprostadil, has become the preferred vasoactive agent for the clinical diagnosis and treatment of ED, as papaverine and phentolamine have been shown to be associated with a higher incidence of serious side effects, such as priapism and other penile complications.[2–12]

Initially, the intracavernous injection of vasoactive drugs was used for the diagnosis of ED in the physician's office; however, the long-term therapeutic potential of these drugs was quickly recognized for patients with the motivation and discipline to learn self-injection techniques for the treatment of ED. Since 1990, more and more clinical trials have reported the effectiveness of long-term, home self-injection programs.[2,10,12–19] Consequently, in Europe and the United States, long-term, self-injection programs for the treatment of ED are now widely accepted.[2,12] In most Asian countries, however, alprostadil has not yet been approved for the treatment of male impotence; as a result, almost no clinical studies have investigated home self-injection therapy in Asian men with ED.[20,21]

The purpose of this open-label, dose-response study was to determine the individual optimal dose of alprostadil in an office setting and compare that dose with the dose needed for effective self-injection home therapy of 1 month's duration.

## PATIENTS AND METHODS

### *Patients*

A total of 150 men, 21 to 74 years of age (mean, 48.3 years) with ED from 4 months' to 35 years' duration (mean, 3.6 years), were enrolled in the study. The cause of ED was venogenic (24%), psychogenic (21%), arteriogenic (13%), neurogenic (0.7%), or of mixed origin (41%). (Etiology was determined by individual standard practice.) Patients were selected from 2 sites in Taiwan, 1 site in China, and 1 site in Thailand. After signing an informed consent form, all patients had a physical examination (including vital signs, bulbocavernous reflex, cremasteric reflex, and sphincter tone) and laboratory evaluations (including complete blood count and differential, urinalysis, and a Venereal Disease Research Laboratories antigen test for syphilis). The medical history included the nature and duration of ED, as well as smoking habits. The clinical assessment of the probable cause of ED was also determined according to the physician's routine practice.

Patients were excluded if they had a history of or propensity for priapism, an underlying disease such as sickle cell anemia or the sickle cell trait, untreated endocrine disorders, cavernous fibrosis or anatomic deformation of the penis, or Peyronie's disease. In addition, patients who had previously used intracavernous injections for ED treatment were excluded. Patients were also excluded if they had a recent onset of acute illness (eg, myocardial

infarction, stroke, or arrhythmias), a history of sexually transmitted diseases within the preceding 6 months, or were taking other investigational or hormonal medications.

### *Dosing Regimen*

In this open-label, dose-escalation study, each patient was started with a 5-μg dose. The dose was then titrated upward to 10-, 15-, 20-, 30-, 40-, or 60-μg doses with a minimum 1-day interval between doses until the patient reached an optimal response, defined as an erection sufficient to achieve vaginal penetration and lasting from 30 to 60 minutes. If a patient did not achieve an optimal response at the 60-μg dose, no additional higher doses were administered. The office dose at which the patient achieved an optimal response was used as the initial dose for the home self-injection phase of the study.

Alprostadil sterile freeze-dried powder* was the formulation used. When reconstituted with 1 mL of sterile water, it contains 20 μg/mL of $PGE_1$ in the form of alprostadil sterile powder, 172 mg/mL of lactose, and 47 μg/mL of sodium citrate with a pH of 4 to 6. Patients were not allowed to use other intracavernous drugs, and a record was kept of all concomitant medications.

### *Efficacy Measures*

*Office Injections*

Optimal response (as defined previously) was the primary efficacy measure. Secondary end points were the time to onset of erection, duration of erection, time to complete detumescence, and patient evaluation of response. Erections were evaluated at 10-minute intervals by the same trained observer according to a three-point scale as absent, partial, or full. Responders were followed up until they had achieved complete detumescence. Nonresponders were followed up for at least 60 minutes after injection. After an interval of 1 day, patients could receive the next higher dose.

*Home Self-Injection Phase*

Each patient who elected to continue at home was permitted to take up to 2 injections a week up to a maximum of 10 injections. Patients were trained in the self-injection technique during the office phase. Once the optimal office dose had been determined, this dose was used by the patient for the first home injection. Efficacy (full, partial, or absent), time to onset of erection, and duration of erection were recorded by the patient after each injection. Patients were to call the investigator the day after the first injection or after any dose change prescribed by the investigator to report the results. If any erection lasted more than 4 hours, the patient was to call immediately. Based on the results of this injection, the dose could be adjusted by the investigator. At the 1-month visit, the patient's self-injection diary and results were reviewed.

### *Safety Measures*

*Office Injections*

Patients were evaluated for the occurrence of any adverse events, and vital signs were recorded at baseline and at 5,

*Trademark: Caverject® (Pharmacia & Upjohn, Inc., Kalamazoo, Michigan).

15, 60, and 120 minutes after injection. The patient's evaluation of side effects after an injection was also recorded at the end of the 2-hour study. If the patient reported any pain, he was asked to assess it as mild, moderate, or severe. He was also asked about the potential impact of the pain, if it were to occur, on the feasibility of intercourse.

*Home Self-Injection Phase*

Patients recorded any adverse effects from alprostadil injections in their diaries. Any serious adverse effects or an erection lasting more than 4 hours was to be reported immediately.

### *Statistical Analysis*

Descriptive statistics were used for the primary analyses. All patients who received at least one dose of alprostadil were included in all efficacy and safety analyses. For optimal and minimal doses, the patient distribution was categorized by dose and setting (office vs home). The mean dose in both the office and home settings was calculated separately with 95% confidence intervals. For individual patients, the optimal office dose was compared with the most frequent and successful home dose, as well as with the last home dose recorded. Values are given as mean ± SD.

For the safety analysis, the first occurrence and total number of adverse events were tabulated for each patient at each dose.

## RESULTS

### *Efficacy*

Of the 150 patients enrolled in the study, 108 (72%) achieved an optimal response in the office. There were 104 men who participated in the home self-injection phase of the study, and 96% (n = 100) achieved a full erectile response at home. The table compares the mean optimal dose variables between responders in the office and home settings. The mean optimal dose in the office was 19.4 ± 12.8 μg versus 18.0 ± 12.2 μg at home. The mean time to onset of erection in the office was 10.6 ± 2.2 minutes versus 8.4 ± 4.9 minutes at home. The mean duration of erection in the office was 41.0 ± 11.1 minutes versus 48.6 ± 23.2 minutes at home.

Optimal responses at each of the dose levels are illustrated in Figure 1. More than half of the patients achieved an optimal response between 5 and 15 μg in both the office (57%) and home (53%) settings. By the 20-μg dose, 82% of patients achieved an optimal response in the home self-injection phase compared with 70% of patients in the office setting. An optimal response was seen at the same dose in the office and home in 75% of patients. The optimal dose decreased for 16% of patients and increased for 9% of patients in the home self-injection phase. The average number of home injections for 100 patients was 7 (±3).

Erections were evaluated as full, partial, or absent by the patient in both the office and home settings. There was good agreement between the patient assessment of erection for all doses except the 5-μg and 20-μg doses. When compared with patient assessment of erection, the physician usually rated an erection as full more often than the patient. However, when patient assessment was compared with optimal dose, there is almost complete concordance (Figure 2).

Table. Mean optimal dose-response variables: office versus home injections in responders.

| Optimal Dose Variables | Office Injections (n = 108) | | Home Injections (n = 100) | |
|---|---|---|---|---|
| | Mean ± SD | Median (Min-Max) | Mean ± SD | Median (Min-Max) |
| Mean optimal dose (μg) | 19.4 ± 12.8 | 15 (5–60) | 18.0 ± 12.2 | 15 (3–60) |
| Mean duration of erection (min) | 41.0 ± 11.1 | 40 (20–80) | 48.6 ± 23.2 | 40 (30–125) |
| Mean time to onset of erection (min) | 10.6 ± 2.2 | 10 (10–20) | 8.4 ± 4.9 | 7 (1–25) |
| Mean time to complete detumescence (min) | 72.6 ± 14.2 | 70 (40–110) | NA | NA |

Min = minimum; Max = maximum.

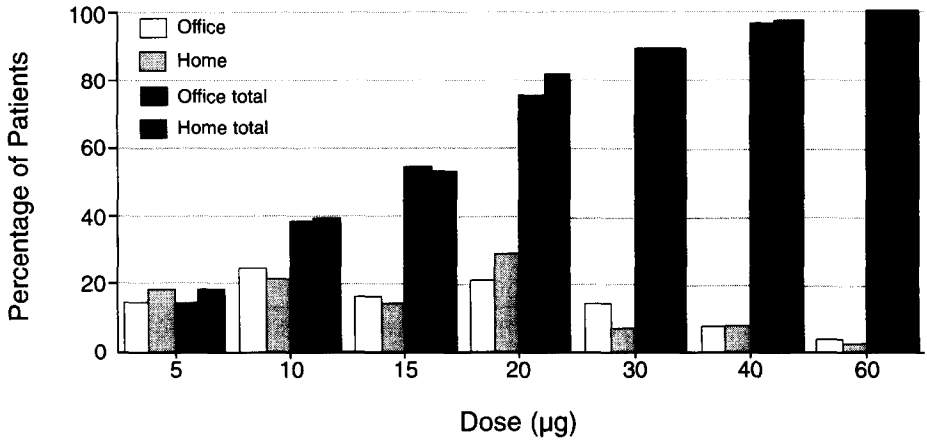



Figure 1. Percent optimal response. (Percentage of men having optimal response at each dose level and cumulative total.)

### *Cause*

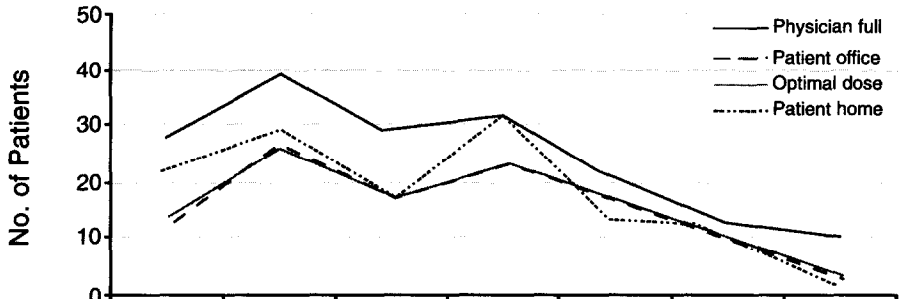
The cause of ED was correlated with dose and optimal response. The mean dose for venogenic patients was 20.7 μg; for arteriogenic patients, 25 μg; for psychogenic patients, 13.7 μg; for neurogenic patients, 15.0 μg; and for patients with mixed origin, 20.7 μg. The response rate showed a similar pattern with 42%, 65%, 85%, 100%, and 85%, respectively, achieving an optimal response.

### *Safety*

Penile pain after injection was reported by 18 (12%) patients. Penile pain was rated mild-to-moderate in 16 patients, moderate-to-severe in 1 patient, and severe in 1 patient. One patient discontinued the study because of penile pain. No episode of pain was considered serious, and all patients recovered with no residual effects. The other reported adverse events were cold sweating (2 patients), pediculosis (1 patient), broken leg (1 patient), and ankle pain (1 patient). One patient reported a prolonged erection (260 minutes) at a dose of 10 μg. There were no reports of penile hematoma, penile abnormalities, or abnormal clinical results.

## DISCUSSION

Reliable estimates of the incidence of ED in Asian countries have not yet been reported, but the frequency of ED is probably similar to that found in the United States.[22] Although Ishi et al[1] described the use of $PGE_1$ for the treatment of ED, there have been few subsequent studies in Asian countries since 1986. To date, the only major Asian study[20] evaluated self-injection therapy in 51 patients treated for an average of 11.8 months with either $PGE_1$ (n = 30) or papaverine (n = 21). The average effective dose of $PGE_1$ during the self-injection phase ranged from 5 to 40 μg, but




| | 5 | 10 | 15 | 20 | 30 | 40 | 60 |
|---|---|---|---|---|---|---|---|
| Physician full | 28 | 39 | 29 | 32 | 20 | 12 | 10 |
| Optimal dose | 14 | 26 | 17 | 23 | 15 | 9 | 4 |
| Patient office | 13 | 27 | 17 | 23 | 15 | 9 | 4 |
| Patient home | 20 | 30 | 17 | 32 | 13 | 10 | 3 |

Dose (μg)

Figure 2. Erection evaluations. Physician full = full erection of any duration; optimal dose = as determined by physician, full erection lasting 30 to 60 minutes; patient office = full erection (adequate for intercourse) evaluated by the patient in the office after injection; patient home = full erection evaluated by the patient at home after injection.

20 μg was the most frequent dose for 23 patients (76.7%), 10 μg for 3 patients (10%), and 5 μg and 40 μg for 2 patients (6.7%), respectively. Comparative results of the efficacy of the two drugs across doses were not reported, but patients in the $PGE_1$ treatment groups had fewer complications than patients in the papaverine group. Based on their results, Chiang et al[20] concluded that $PGE_1$ is a better agent than papaverine for long-term self-injection therapy in the treatment of ED.

The results of the present dose-response study of 150 Asian men with ED provide clinical evidence of the effectiveness of alprostadil for home self-injection therapy after an optimal dose is established by careful titration in the physician's office. Three quarters of the men who had an optimal response in the office were able to achieve satisfactory erections with the same dose at home. The mean dose required at home was lower, the mean time to onset of erection was shorter, and the mean duration of erection was longer. No subject experienced any serious side effects related to the injections, and only one man discontinued the study because of penile pain.

Although most early studies with regard to intracavernous injections reported that doses of alprostadil in the 10- to 20-μg range produced complete erections for most patients, a recent study[23] of 101 pa-

tients with vasculogenic impotence reported successful results with an average dose of 5.58 μg of $PGE_1$ in 70 patients using it for self-injection home therapy. For this reason, dose escalation starting as low as 2.5 μg[6] and titrating upward according to an individual patient's response is recommended.

The present study indicates that in the home environment, a dosage change may be required in 25% of patients. In the current study, more than half the men in the office and at home achieved an optimal response at a dose of between 5 and 15 μg. By the 20-μg dose, 70% of the patients reached an optimal response in the office, although the results were more notable in the home setting after self-injection treatment, in which 82% reached an optimal response by the 20-μg dose.

## CONCLUSIONS

Alprostadil sterile powder offers safe and effective treatment of ED for home self-injection therapy in Asian men with impotence of various causes. Once an initial optimal dose has been established in the physician's office through careful dose titration, further dose adjustments are needed during home self-injection therapy in about 25% of men. Side effects were neither serious nor frequent and did not interfere with a patient's ability to have successful intercourse. Doses between 5 μg and 20 μg produced satisfactory results for the majority of patients, especially for men with ED of psychogenic origin.

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## REFERENCES

1. Ishi N, Watanabe H, Irisawa C, et al. Studies on male sexual impotence report 18: Therapeutic trial with prostaglandin $E_1$ for organic impotence. *J Jpn Soc Urol.* 1986; 77:954–962.

2. Linet OI, Neff LL. Intracavernous prostaglandin $E_1$ in erectile dysfunction. *Clin Invest.* 1994;72:139–149.

3. Adaikan PG, Ng SC, Chan C, Ratnam SS. Why intracavernous $PGE_1$ for diagnosis and treatment of impotence? *Int J Impot Res.* 1990;2(Suppl 2):325–326.

4. Hwang TI-S, Yang C-R, Wang S-J, et al. Impotence evaluated by the use of prostaglandin $E_1$. *J Urol.* 1991;146:786–789.

5. Junemann K-P, Alken P. Pharmacotherapy of erectile dysfunction: A review. *Int J Impot Res.* 1989;1:71–93.

6. Lee LM, Stevenson WD, Szasa G. Prostaglandin $E_1$ versus phentolamine/papaverine for the treatment of erectile impotence: A double-blind comparison. *J Urol.* 1989; 141:549–550.

7. Ravnik-Oblak M, Oblak C, Vodusek DB, et al. Intracavernous injection of prostaglandin $E_1$ in impotent diabetic men. *Diabetes.* 1991;40(Suppl 1):533a. Abstract.

8. Sarosdy MF, Hudnall CH, Erickson DR, et al. A prospective double-blind trial of intracorporeal papaverine versus prostaglandin $E_1$ in the treatment of impotence. *J Urol.* 1989;141:551–553.

9. Schramek P, Waldhauser M. Dose-dependent effect and side-effect of prostaglandin $E_1$ in erectile dysfunction. *Br J Clin Pharmacol.* 1989;28:567–571.

10. Lewis RW. The pharmacologic erection. *Prob Urol.* 1991;5:541-548.

11. Data on file, Pharmacia & Upjohn, Inc., Kalamazoo, Michingan, 1994.

12. Porst H. Experience with alprostadil in diagnosis and therapy in Germany. In: Goldstein I, Lue TF, eds. *The Role of Alprostadil in the Diagnosis and Treatment of Erectile Dysfunction. Proceedings of a symposium, August 3–4, 1993; Brook Lodge, Kalamazoo, Michigan.* Princeton: Excerpta Medica; 1993:142–154.

13. Burgess TR, Earle CM, Glatthaar C, et al. Intracavernosal vasoactive agents, comparison of diabetic and non-diabetic impotent men. *Int J Impot Res.* 1990;2(Suppl 2):236–237.

14. Hirsch IH, Bagley DH, Christinzio J. Dosage considerations in the self-administration of $PGE_1$ for erectile dysfunction. *J Urol.* 1990;143(Suppl):305A. Abstract.

15. Porst H. Prostaglandin $E_1$ in male impotence—its diagnostic and therapeutic use in 2000 patients. *Int J Impot Res.* 1992;4 (Suppl 2):A88. Abstract.

16. Sister MP. Prostaglandin $E_1$ in erectile dysfunction: 20 Months of experience with 483 patients in a self-injection program. *Int J Impot Res.* 1990;2(Suppl 2):287–288.

17. Stackl W, Hasun R. Prostaglandin $E_1$—4 Years' experience of intracavernous injection. *Int J Impot Res.* 1990;2(Suppl 2): 255–256.

18. Weiske W-H. Long-term results in self-injection therapy (SIT) with $PGE_1$ in 220 patients. *Int J Impot Res.* 1992;4(Suppl 2):A87. Abstract.

19. Wetterauer U, Koppermann U, Bischoff R, Sommerkamp H. Intraindividual comparison of papaverine-phentolamine combination versus prostaglandin $E_1$ in intracavernous injection therapy for erectile dysfunction. *Int J Impot Res.* 1990;2 (Suppl 2):238–239.

20. Chiang H-S, Wen T-C, Wu C-C, Chiang W-H. Intracavernous self-injection therapy for the treatment of erectile dysfunction. *J Formos Med Assoc.* 1992;91: 898–901.

21. Hayashi S, Iwai Y, Yasumoto R, et al. Clinical evaluation of intracavernous self-injection of vasoactive drugs for impotence: A long-term follow-up observation. *Acta Urol Jpn.* 1994;40:37–41.

22. Feldman H, Goldstein I, Hatzichristou D, et al. Impotence and its medical and psychosocial correlates: Results of the Massachusetts Male Aging study. *J Urol.* 1994;151:54–61.

23. Von Heyden B, Donatucci CF, Kaula N, Lue TF. Intracavernous pharmacotherapy for impotence: Selection of appropriate agent and dose. *J Urol.* 1993;149: 1288–1290.