International Journal of Impotence Research (1997) 9, 39–42
 0955-9930/97 $12.00

Experience with intracavernous PGE-1 in the treatment of erectile dysfunction: dose considerations and efficacy

M Ismail, L Abbott and IH Hirsch

Department of Urology, Jefferson Medical College, Philadelphia, PA 19107, USA

The recommended dose of PGE-1 as treatment for erectile dysfunction has ranged from 10–60 mcg in various studies. We conducted the present study to identify factors that influence dose tritration and maintenance.

From 96 patients who presented to our institution with erectile impotence, 40 elected self injection with PGE-1. Erectile response to intracavernous injection was assessed in the course of office-based dose titration. Patients were stratified into different groups based on age and etiology of erectile dysfunction. The mean maintenance dose was calculated in each group. Patients were evaluated quarterly by physical palpation of the penis, complete blood count, serum electrolytes, and liver function tests in order to assess safety of therapy. The average maintenance dose varied with the etiology of erectile dysfunction and age of the patient. The central neurogenic group was the most responsive to PGE-1 therapy, requiring an average maintenace dosage of 5 mcg. Men with vascular etiologies required the largest maintenance dosage of 20 mcg. Furthermore, dosage requirement increased linearly with age. We conclude that dosing considerations vary widely in a clinical setting and their determination is greatly facilitated if primary and associated causes of erectile dysfunction and the age of the patient are considered.

Keywords: prostaglandin E1; erectile dysfunction; intracavernous injection; dose considerations; efficacy; side effects

Introduction

The discovery that intracavernous injection of vasoactive agents induces penile erection makred one of the most dramatic advances in diagnosis and treatment of erectile dysfunction. Papaverine and phentolamine, either alone, or in combination has offered convincing success rates regardless of the etiology.[1] Nonetheless, fibrotic, hepatic, and cardiovascular complications have been reported with these agents.[2] In addition, the risk of prolonged erection requiring intervention may approach 10% in the initial dosing phase of treatment.[3] Subsequently, safer vasoactive agents have been investigated for their efficacy in intracavernous therapy programs. Prostaglandin E-1 (PGE-1) has been shown to relax corporal smooth muscle *in vitro* studies.[4] Its efficacy as a direct smooth muscle relaxant[4,5] has been substantiated in various clinical studies.[6] Since systemic and local side effects have been observed far less frequently, interest in PGE-1 has grown rapidly as a diagnostic and therapeutic agent. Encouraging initial experience with PGE-1 in 12 patients was reported in 1987.[7] Subsequent reports have confirmed the efficacy and relative safety of PGE-1.[8–10] We report our experience with PGE-1 considering initiation and maintenace dose requirements, efficacy, and safety in treatment of erectile dysfunction.

Correspondence: Dr I Hirsch, Associate Professor of Urology, Jefferson Medical College, 1025 Walnut St. (Rm. 1103), Philadelphia, PA 19107 USA.
Received 15 July 1996; accepted 27 November 1996

Materials and methods

A multi-disciplinary approach was undertaken in 96 men who presented to our institution with the complaint of erectile impotence. The mean age of the patient population was 52 ranging from 17–75 y. All men were evaluated by detailed sexual and medical histories, physical examination, hormonal profile, penile brachial systolic index. Bulbocavernosus reflex latency, nocturnal penile tumescence studies, color Doppler imaging, and dynamic infusion cavernosometry and cavernosography were also performed when indicated. The various diagnostic studies utilized are shown in Table 1.

Patients were classified according to six etiologic causes for their erectile dysfunction, including vascular, neurogenic, psychogenic, diabetic, hormonal, and combined. In addition, the neurogenic

Table 1 Methods of evaluation used to determine etiology and the number of patients undergoing each study

Evaluation	*Number of patients*	*%*
Interview and physical exam	96	100%
Penile brachial index	70	76%
Color Doppler imaging	20	19%
Nerve conduction studies	48	50%
Nocturnal penile tumescence	30	28%
Dynamic infusion cavernosometry and cavernosography	8	7%

group was further subdivided into those patients with central lesions (spinal cord injuries, herniated disc, or multiple sclerosis) and those patients with peripheral lesions (pelvic surgery or prostatectomy). Table 2 shows the total number of patients within each etiologic category, including the relative percentage of the total number of patients.

As a treatment goal, specific therapy for the predominant cause of erectile dysfunction was encouraged. Patients were excluded from intracavernosal therapy if they had a history of sickle cell disease, Peyronie's disease, or idiopathic priapism.

From the various surgical and non-surgical treatment alternatives, 40 men of the 96 total men evaluated elected self-administered PGE-1 therapy and were followed for a period of 3–18 months. PGE-1 injections were prepared by dilution of a standard 500 mcg/ml vial (Prostin VR, Upjohn Laboratories, Kalamazoo, MI) with sterile normal saline to yield a concentration of 10 mcg/ml. Diluted solutions were drawn up in pre-filled synringes according to specified dose requirements and dispensed to patients through out institution's pharmacy at a cost of $5 per ml. Injections were administered with a 27 gauge needle in either a tuberculin or 3 cc syringe. Digital compression of the injection site was maintained for a minimum of 3 min following each injection with patients observed for systemic and local effects, as well as the quality and duration of erection.

Erectile response to intracavernous injection was assessed by subjective observation of rigidity and tumescence and in some men, by objective measurement of axial buckling pressure using a rigidometer (Promini, Sao Paulo, Brazil). Men with central neurogenic impotence, from either multiple sclerosis or spinal cord injury, were given initial doses of 2.5 mcg and advanced to maintenance dose by 2.5 mcg increments. All other patients began initial dosing at 10 mcg and were advanced to maintenance dose by 5 mcg increments. Following acquisition of intracorporeal injection techniques and assessment of optimal dosage, patients were discharged on a self-administered program of home injection, after a mean of 2.72 teaching sessions. They were dispensed with a four week supply of dose specific, pre-filled syringes, and instruction for home use, followed after one month and then quarterly with a physical examination and subjective assessment of erectile response, complete blood count, serum electrolytes and liver function tests in order to monitor safety of treatment.

Table 2 The number of patients within each etiology initially evaluated, and electing intracavernous injection (ICI)

Etiology	*Age (average)*	*Number of patients*		*% of patients electing ICI*
		Evaluated	*Injected*	
Vascular	58.3	33	8	20%
Neurogenic				
Central[a]	34.9	17	9	22.5%
Peripheral[b]	59.2	10	3	7.5%
Psychogenic	49.5	11	6	15%
Diabetic	54.6	8	6	15%
Hormonal	27.3	4	2	5%
Combined	52.5	13	6	15%

[a]Central neurogenic erectile dysfunction includes men with spinal cord injury, multiple sclerosis, and herniated disc as a source of neurogenic erectile dysfunction.
[b]Peripheral neurogenic erectile dysfunction includes men with erectile dysfunction following prostatectomy or pelvic surgery.

Results

The average maintenance dosage of PGE-1 varied for each etiologic group. The central neurogenic group was most responsive to PGE-1 injection therapy, requiring an average maintenance dosage of only 5 mcg. Moderate dose requirements were observed in diabetic (12 mcg), psychogenic (13 mcg) and hormonal (13 mcg) subgroups. Patients with peripheral neurogenic lesions on average required 18 mcg while the men with combined causes (vascular and others) required an average maintenance dosage of 19 mcg. Finally, the men with vascular etiologies required the largest maintenance dosages, at an average of 20 mcg. Furthermore, dosage requirement increased linearly with age, as shown in Figure 1.

The quality of the erection was rated both objectively and subjectively during the dose titra-

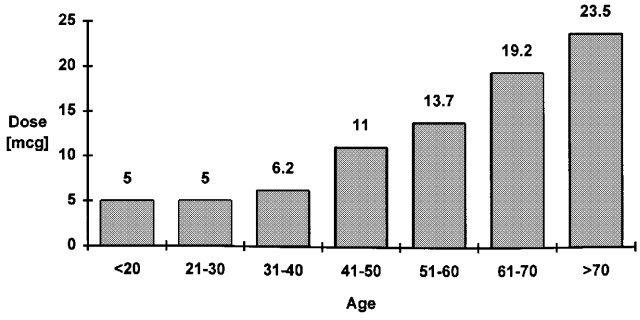

Figure 1 Linear relationship between age and maintenance dosage of prostaglandin E1.

Table 3 Subjective and objective evaluation of quality of erection

	Tumescence	*Axial buckling pressure*	*Office*	*Home*
Excellent	> 80%	> 150 mm Hg	37	35
Good	60–79%	100–150 mm Hg	3	5
Fair	< 60%	< 100 mm Hg	0	0

tion phase and during the course of follow-up. An erection was considered 'excellent' if patient reported greater than 80% rigidity, 'good' if it was rated between 60–79%, and 'fair' if less than 60%. Ninety-three percent of the erections induced at the office were rated as excellent, with an axial buckling pressure in excess of 150 mm Hg. Of the erections induced at home, 88% were considered 'excellent'. Furthermore, no erections were rated less than 'good', and all patients considered the erectile quality satisfactory for sexual intercourse. These data are summarized in Table 3.

Pain described as mild discomfort was noticed in 40% of patients, but not severe enough to interfere with sexual activity or to discontinue therapy. In the course of the physical exam, no fibrotic plaques were found on palpation. WBC, RBC, Hgb, and platelet counts showed no significant changes after treatment when compared to baseline pretreatment levels. Liver function tests, although showing mild increase after treatment, were all in the normal range and the changes were not statistically significant. There were no episodes of prolonged erection or priapism during the course of the study.

Discussion

Review of literature shows that the dose of PGE-1 used for treatment of erectile dysfunction has ranged from 10–60 mcg. Clinical observations suggest that the dose response of PGE-1 depends on the etiology. Various studies,[9,11] noted an overall response rate of 79% for PGE-1, however, the response rate was 100% in patients with psychogenic or neurogenic erectile dysfunction. Earle and associates observed that doses as low as 1–2 mcg of PGE-1 produced full erections in some patients with spinal cord injury.[12] We previously reported successful results in patients with neuropathic erectile dysfunction with a mean dose of 6.2 mcg.[13]

Alternatively the mean dose of PGE-1 was much higher in patients with vasculogenic impotence compared to those with psychogenic or neurogenic impotence in another study.[14] In another study the median effective dose was 3, 4 and 5 mcg in psychogenic, neurogenic and vasculogenic groups respectively, and 4–5 mcg in the combined groups.[15] Our results support a direct dose-etiology correlation and reaching the correct maintenance dose is facilitated by defining the primary and contributing causes of impotence. Interestingly, patients with central neurogenic erectile dysfunction generally required much lower doses than men with peripheral causes. This may be related to the older age of men with peripheral neurogenic impotence and the fact that these patients often suffer associated post-surgical erectile dysfunction and vascular and cavernous insufficiency.

Another important determinant of dose requirement is the patient's age as our data demonstrates a linear relationship between dose and age. Moreover in patients with vascular and peripheral neurogenic etiologies, requiring higher doses, the average age tends to be higher as shown in Table 2. In a study using papaverine, it was found that the geriatric population required 50% higher dosage to achieve an adequate erection as compared to younger patients.[16]

Our study, in addition, confirms the efficacy with intracavernosal PGE-1 and a low incidence of complications. The degree of efficacy reaching 100% in our study is probably related to proper patient selection and dose escalation. A number of studies have shown PGE-1 alone to be at least as effective as papaverine and phentolamine in inducing erections in impotent men.[8–10] The incidence of corporal fibrosis with chronic papaverine use has been reported to range from 3–37%.[2,16] Although none of our patients developed fibrous plaques on clinical palpation, we previously reported an incidence of 16.5% of men on chronic intracavernous PGE-1 who developed new echogenic foci detected by penile ultrasound.[17] While the significance of these subclinical lesions is unknown, they may represent histological changes associated with any chronic intracavernosal therapy regardless of the agent used. This theory is supported by the experimental findings of Aboseif, *et al*,[18] who observed that monkeys injected with saline and those injected with PGE-1 demonstrated comparable and uncommon smooth muscle changes.

Another concern associated with intracavernous therapy using papaverine and phentolamine is elevation of liver enzymes. Some clinical studies had noted mild to moderate increases in LDH and alkaline phosphatase levels.[2] Our results show that there was a very slight increase in both of these values in the 40 patients evaluated in this study, however, these values did not approach a level of statistical significance. Therefore, while PGE-1 appears safe, periodic monitoring seems advisable in men with known hepatic dysfunction.

The incidence of priapism following PGE-1 has been reported to be in the 1% range.[19] Many series have reported episodes of priapism to be more prevalent during treatment with papaverine or phentolamine, compared to PGE-1 treatments.[9,11] The results of our study demonstrating the absence

of priapism is the result of careful dose titration and escalation monitored in an office setting prior to self administered home use.

Given the safety from adverse side effects such as fibrotic plaques, priapism, and liver dysfunction, PGE-1 seems to be a preferable alternative to other drugs for intracavernous injection therapy, and is currently the only FDA approved drug for intracavernous therapy. Dosing considerations are clearly age and etiology-dependent and are greatly facilitated if the primary and associated causes of erectile dysfunction are known.

References

1 Zornigiotti AW, Lefleur RS. Autoinjection of the corpus cavernosum with a vasoactive drug combination for vasculogenic impotence *J Urol* 1985; **133**: 39–41.
2 Levine ED, Resnick MI. Side effects of self administration of intracavernous papaverine and phentolamine for treatment of impotence. *J Urol* 1989; **141**: 54–57.
3 Padma-Nathan H, Goldstein I, Payton T, Krane RJ. Intracavernosal pharmacotherapy: The pharmacologic erection program. *World J Urol* 1987; **5**: 160–165.
4 Adaikan PG, Karim SM, Kottegoda SR,Ratman SS. Cholinereceptors in the corpus cavernosum muscle of the human penis. *J Auton Pharmacol* 1983; **3**: 107.
5 Hedlund H, Anderson KE. Contraction and relaxation induced by some prostanoids in isolated human penile erectile tissue and cavernous artery. *J Urol* 1985; **134**: 1245–1250.
6 Juneman KP, Alken P. Pharmacotherapy of erectile dysfunction: A review. *Int J Impot Res* 1989; **1**: 71–94.
7 Virag R, Adaiken PG. Effects of prostaglandin E1 on penile erection and erectile failure (letter). *J Urol* 1987; **137**: 1010.
8 Earle CM *et al*. Prostaglandin E1 therapy for impotence, comparison with papaverine. *J Urol* 1990; **143**: 57–59.
9 Mahmoud KZ, Eldakhli MR, Fahmi IM, Abdel-Azis AB. Comparative value of prostaglandin E1 and papaverine in treatment of erectile failure. Double blinded crossover study among Egyptian patients. *J Urol* 1990; **143**: 57–59.
10 Lee LM, Stevenson RW, Szasz G. Prostaglandin E1 versus phentolamine/papaverine for the treatment of erectile dysfunction. A double blind comparison. *J Urol* 1989; **141**: 549–550.
11 Hwang TI *et al*. Comparison of penile vascular effect induced by intracavernous injection of papaverine and prostaglandin E1. *J Formo Med Assoc* 1989; **88**: 1038–1041.
12 Earle CM *et al*. Intracavernosal injection therapy for impotence due to spinal cord injury. *Int J Impot Res* 1990; **2 (Suppl. 2)**: 297–298.
13 Hirsch IH *et al*. Use of intracavernous injection of prostaglandin E1 for neuropathic erectile dysfunction. *Paraplegia* 1994; **32**: 661–664.
14 Glenn SG, Laurence AL. Pharmacological erection program using prostaglandin E1. *J Urol* 1991; **46**: 786–789.
15 Otto IL, Francis O. Efficacy and safety of intracavernosal Alprostadil in men with erectile dysfunction. *N Eng J Med* 1996; **334**: 873–877.
16 Kerfoot WW, Carson CC. Pharmacologically induced erections among geriatric men. *J Urol* 1991; **146**: 1022–1024.
17 Hirsch IH *et al*. Sequential penile ultrasound monitoring of patients treated with chronic intracavernous prostaglandin E1. *Urol* 1994; **45**: 1037–1041.
18 Aboseif SR *et al* Local and systemic effects of chronic intracavernous injection of papaverine, prostaglandin E1 and saline in primates. *J Urol* 1989; **142**: 403–408.
19 Chen J, Godschalk M, Katz PG, Mulligan T. The lowest effective dose of prostaglandin E1 as treatment for erectile dysfunction. *J Urol* 1995; **153**: 80–81.