International Journal of Impotence Research (2001) 13, 317–321
© 2001 Nature Publishing Group All rights reserved 0955-9930/01 $15.00
www.nature.com/ijir

Intracavernosal alprostadil is effective for the treatment of erectile dysfunction in diabetic men

JPW Heaton[1]*, D Lording[2], S-N Liu[3], AD Litonjua[4], L Guangwei[5], SC Kim[6], JJ Kim[7], S Zhi-zhou[8], D Israr[9], D Niazi[9], R Rajatanavin[10], S Suyono[11], F Benard[12], R Casey[13], G Brock[14] and A Belanger[15]

[1]*Queen's University, Kingston, Canada;* [2]*St Francis Xavier Cabrini Hospital, Melbourne, Australia;* [3]*National Cheng-Kung University, Tainan, Taiwan;* [4]*Medical Center, Makati City, Philippines;* [5]*China-Japan Friendship Hospital, Beijing, China;* [6]*Chung-Ang University, Seoul, Korea;* [7]*Korea University, Seoul, Korea;* [8]*Huashan Hospital, Shanghai, China;* [9]*Allam Iqbal Medical College, Lahore, Pakistan;* [10]*Theptarin General Hospital, Bangkok, Thailand;* [11]*Cipto Mangunkusumo Hospital, Jakarta, Indonesia;* [12]*Hospital St-Luc, Montreal, Canada;* [13]*Male Health Center, Oakville, Canada;* [14]*St Joseph Health Center, London, Canada; and* [15]*Laval Clinical Research Center, Laval, Canada*

The efficacy and safety of intracavernosal alprostadil was evaluated for the treatment of erectile dysfunction in men with type I or type II diabetes mellitus. This was an open-label, flexible dose-escalating study involving 336 men (77% of whom were Asian/Oriental) enrolled by 15 centres in Australia, Canada and seven countries in Asia. The effective alprostadil dose, ie the dose producing penile rigidity adequate for intercourse and lasting up to 60 min, was established by titration at the clinic prior to entry into the 6 month self-treatment home phase. All men were fully trained in the self-injection technique before entry into the home phase. Efficacy and safety were assessed using patient and partner diaries and by interview at clinic visits during the titration phase and after 1, 3 and 6 months of treatment. An effective home dose was established by titration for 94% of the 336 men (median dose 20 μg, range 2.5–60 μg). Of 278 (83%) men who entered the home phase, 277 men (247 with type II diabetes and 30 with type I diabetes) had evaluable data for alprostadil dosage and clinical response. During the home phase, a satisfactory erectile response was achieved after 99% of injections, and the median alprostadil dose remained unchanged. The initial home dose and clinical response were similar in type I and type II diabetic men. Treatment was generally well tolerated with a low incidence of penile pain (24%) In conclusion, intracavernosal alprostadil was effective and well tolerated in type I and type II diabetic men with erectile dysfunction of mixed aetiology. *International Journal of Impotence Research* (2001) **13,** 317–321.

Keywords: erectile dysfunction; diabetic men; alprostadil; efficacy; safety

Introduction

Erectile dysfunction (ED) is a common and often neglected complication of diabetes mellitus. Compared with the general population, the prevalence of ED is higher in diabetic men (up to 75%)[1] and increases substantially with increasing age.[2] Although the aetiology of ED in diabetic men is probably multi-factorial, vascular and neurogenic complications associated with the natural history of diabetes are thought to be the main causes.

Intracavernosal alprostadil (prostaglandin E_1, PGE_1) injection is a safe and effective treatment for ED. Alprostadil is effective in 70–80% of non-diabetic men and has a good safety profile provided that the effective dose is first established by careful titration.[3,4] Preliminary data[5,6] suggest that alprostadil is also effective and well tolerated in diabetic men with ED, and warrant further investigation. The aim of this open-label, flexible dose-escalating study was to investigate the efficacy and safety of intracavernosal alprostadil for the treatment of ED in a large group of men with type I (insulin-dependent) or type II (non-insulin-dependent) diabetes mellitus.

Materials and methods

A total of 15 centres in nine countries (Australia, Canada, China, Indonesia, Korea, Pakistan, Philippines, Taiwan and Thailand) participated in this

*Correspondence: JPW Heaton, Department of Urology, Queen's University and Kingston General Hospital, 76 Stuart Street, Kingston, Ontario, Canada K7L 2V7.
E-mail: heatonj@post.queensv.ca
Received 9 August 2001; accepted 24 August 2001

study. Men aged at least 18 y with controlled type I or type II diabetes mellitus (defined by fasting blood glucose < 250 mg% or glycosylated haemoglobin A_{1c}[HbA_{1c}] $> 10\%$) and documented ED for at least 4 months, who had not previously received treatment for ED, were recruited from the urology clinic at each centre. Assessment of the aetiology of ED was based on medical history and physical examination. Men in whom diabetes mellitus was due to pancreatic disease or hormonal causes, with evidence of cavernosal fibrosis, anatomical deformation of the penis, Peyronie's disease or penile plaques, abnormal testosterone, prolactin or thyroid tests, a history of priapism, or who did not have a stable, heterosexual partner, were excluded. Additional exclusion criteria included uncontrolled hypertension (blood pressure $> 180/110$ mmHg), electrocardiographic (ECG) evidence of previous acute myocardial infarction or ischaemia, serious systemic or major organ diseases or psychiatric disorders in the last 6 months, human immunodeficiency virus (HIV) — positive or sexually transmitted diseases in the last 60 days, or drug or alcohol abuse in the last 12 months prior to entry. Treatment with other investigational medications within 21 days prior to entry, or concomitant treatment with testosterone or anticoagulants during the study was prohibited. Treatment with any medication known to cause ED (for example, beta-blockers, phenothiazines, hydrochlorothiazide, or antidepressants) was continued provided that the medication was started at least 3 months prior to entry and dosing remained constant throughout the study.

The study was approved by the ethics committee responsible for each centre and conducted according to the Declaration of Helsinki (South Africa Revision, 1996). All men gave written informed consent prior to entry.

Study design

Following screening for study eligibility, including physical examination and clinical and laboratory safety assessments, the men entered the titration phase of the study. During this phase the effective dose of alprostadil, defined as the dose producing penile rigidity adequate for intercourse and lasting up to 60 min, was established. The evaluation of erection was done at each centre by only one trained person by observation and manual palpation using the following rating: 0 = no response, 1 = partial response, tumescence but insufficient rigidity for intercourse, and 2 = full response, rigidity adequate for intercourse. At the first clinic visit, the men were injected with 5 μg of alprostadil, and if there was an inadequate response within 1 h, a 10 μg dose was administered on the same day. If response was suboptimal, the men were injected with increasing doses of alprostadil to a maximum of 60 μg, with an interval of at least 1 day between doses, until the effective dose was achieved. Erection was assessed by observation and manual palpation and rated using a three-point scale as 'none', 'partial' or 'full erection'. The latency and duration of response was also recorded. Standing blood pressure and pulse were measured before and up to 2 h after each injection.

On completion of the titration phase, and prior to entry into the home maintenance phase, all men were fully instructed in the preparation and storage of alprostadil, and trained in the injection technique. Men were instructed to self-inject the effective dose of alprostadil about two to three times per week and to complete a diary after each injection. The date, timing and dose of alprostadil, duration of erection, evaluation of erection ('none', 'partial' or 'full') and sexual activity ('satisfactory' or 'unsatisfactory') were documented and any adverse events noted. Subject to their consent and agreement, the partners also evaluated sexual activity ('satisfactory' or 'unsatisfactory'). Men were advised to contact the clinic immediately if they experienced an erection that lasted longer than 4 h.

The men attended the clinic after 1, 3 and 6 months of treatment or at withdrawal. At each clinic visit, physical and penile examination were repeated, vital signs were measured, patient and partner diaries were reviewed and additional treatment packs with injections were dispensed. Dose adjustment (to a maximum of 60 μg) due to efficacy and/or tolerability considerations was permitted. In addition, at visits after 1 and 6 months of treatment, blood and urine samples were taken for measurement of haematology and clinical chemistry safety variables. Any spontaneously reported or observed adverse events were recorded throughout the study.

Study treatment

Alprostadil (Caverject® Injection, Pharmacia & Upjohn) was supplied as a kit containing freeze-dried sterile powder in 5 ml clear glass vials and was reconstituted with 1 ml of sterile bacteriostatic water to give a solution containing alprostadil 20 μg/ml. Different volumes of this stock solution were injected to obtain the appropriate doses of alprostadil.

Statistical analysis

Clinical response was defined as penile rigidity sufficient for sexual intercourse. During the titration phase, response was based on the investigator's

assessment of erection. During the home phase, response was based on each man's assessment of erection, his satisfaction with sexual activity following injection, and his partner's satisfaction with sexual activity following injection. The primary efficacy variable was the initial dose used during the home maintenance phase. Subgroup analyses with an analysis of variance (ANOVA) model were used to investigate the effect of diabetes diagnosis (type I or type II) on the initial home dose. All statistical tests were two-sided and the level of significance was 0.05. All other efficacy and safety data were analysed descriptively.

Results

Demographics

A total of 336 men (mean age, 55.3 y; mean duration of ED, 3.3 y; mean duration of diabetes, 8.4 y) entered the titration phase of the study and were treated with alprostadil. The majority of men (77%) were of Asian/Oriental ethnicity. Most men (89%) had type II diabetes and were receiving oral therapy (Table 1). Only 11% of the men had been previously treated for ED. Details of the disposition data are presented in Table 2. Fifty-nine (17.5%) of the 336 enrolled men withdrew during the titration primarily due to lack of efficacy, lost to follow-up and adverse events (AEs). Thus, 277 (82%) of the 336 enrolled men entered the home maintenance phase and administered at least one dose of alprostadil. Overall 210 (63%) men completed the whole study. The main reasons for withdrawal during the home phase were similar as during the titration phase.

Titration phase

During the titration phase 316 out of 336 men exposed to alprostadil, ie 94% responded either with full or partial erection to at least one dose of alprostadil. For the 292 men who completed the titration phase, the median effective dose was 20 μg (range: 2.5–60 μg), with 90% of the doses between 2.5 μg and 40.0 μg. The median latency of erection at effective dose was 7 min (range: 3–44 min) and median duration of erection was 55 min (range: 3–390 min).

Home treatment phase

Of the 278 men who entered the home phase, 277 men (247 with type II diabetes and 30 with type I diabetes) had data for alprostadil dosage and clinical response (data were not recorded by one man). The distribution of alprostadil doses at entry to home phase is presented in Table 3. The median effective dose in these 277 men was 20 μg. For type I and type II diabetic men, the median effective dose was 15 and 20 μg, respectively (Table 3). During the home phase the initial effective dose of alprostadil

Table 1 Characteristics of men enrolled in the study ($n=336$)

Age; (y)	55.3 (30–75)
Race; *n* (%)	
Oriental/Asian	258 (77)
White	71 (21)
Other	7 (2)
Weight (kg)	73.4 (44–149)
Height (cm)	169.2 (152–194)
Diabetes history	
Duration; (y)	8.4 (0.1–40)
Type II (non-insulin dependent); *n* (%)	299 (89)
Treated with[a]	
Oral agent	234 (78)
Diet only	35 (12)
Insulin	44 (15)
Type I (insulin-dependent)	37 (11)
Erectile dysfunction history	
Duration; (y)	3.3 (0.3–30)
Aetiology; *n* (%)	
Vasculogenic[b]	126 (38)
Neurogenic	75 (22)
Psychogenic	26 (8)
Mixed	109 (32)
Previous therapy; *n* (%)	36 (11)

Data are given as mean (range) except where indicated otherwise.
[a]Patients may have been treated with more than one agent.
[b]Includes arteriogenic aetiology.

Table 2 Disposition data ($n=336$)

	No. (%) of Men
Withdrew during titration ($n=44$)	
Lack of efficacy	21 (6)
Adverse events	11 (3)
Lost to follow-up	7 (2)
Non-compliance	1 (<1)
'Other'[a]	4 (1)
Completed titration, did not enter home phase ($n=15$)	
Lost to follow-up	11 (3)
'Other'[b]	4 (1)
Entered home phase (277)	
Withdrew ($n=67$)	
Lack of efficacy	20 (6)
AEs	17 (4)
Lost to follow-up	13 (4)
Non-compliance	6 (4)
'Other'[c]	11 (3)
Total withdrawn	126 (37)
Completed study	210 (63)

[a]Fear of needle (three), Peyronie's disease (one).
[b]Problem with partner (two), work commitment (two).
[c]Personal reasons (six), recurrence of spontaneous erections (two), partner problem (one), fear of needle (one), premature ejaculation (one).

remained unchanged in 72% (199/277) of men, increased in 20% (54/277) of men and decreased in 7% (20/277) of men. Data were missing for a further four (1%) men. Overall, 80% of doses administered at 6 months were in the range of $>5-40\,\mu g$ (median: $20\,\mu g$).

During the home phase, a total of 6756 injections were self-administered by the 277 men. Full erection was reported after 83% (5584/6756) of injections. The response rates in terms of full erection were similar in the type I and type II diabetic men, ie 705/821 (86%) and 4869/5931 (82%) of injections, respectively. Clinical response, defined as a satisfactory erectile response, was reported after 99% (6659/6756) of injections. Response rates were again similar in men with type I or type II diabetes (99.8% and 98%). Table 4 shows high satisfaction with sexual activity after alprostadil injections in both men and their partners throughout the whole home phase.

Adverse events

All men who received at least one dose of alprostadil ($n=336$) were included in the safety evaluation. Table 5 summarises adverse events judged by the investigators to be related to alprostadil. 'Penis disorder', which encompassed a variety of events such as penile pain, penile ecchymosis, prolonged erection, penile edema and rash, was reported by 71/336 (21%) of men. Taking into account all men who reported penile pain and/or injection site pain, the overall incidence of any penile pain was 24% (82/336; Table 5). Although most treatment-related adverse events were of mild to moderate intensity and self-limiting, 6% (21/336) of men subsequently discontinued treatment, in most cases due to penile pain (17/336, 5%). Two men each developed prolonged erection and priapism ($>6\,h$) respectively. All these events resolved spontaneously. Treatment was discontinued for one of these men following recovery. One man developed a penile nodule during the study. The use of alprostadil was not associated with any clinically relevant changes in laboratory safety variables or vital signs.

Table 3 Distribution of alprostadil doses at entry to home phase. All evaluable men

Dose (μg)	*All men (n = 277)*	*Type I diabetic men (n = 30)*	*Type II diabetic men (n = 247)*
≤ 2.5	3 (1)	2 (7)	4 (2)
$>2.5-5$	35 (13)	3 (10)	22 (9)
$>5-10$	54 (19)	5 (17)	37 (15)
$>10-15$	15 (5)	6 (20)	22 (9)
$>15-20$	78 (28)	5 (17)	75 (30)
$>20-30$	37 (13)	5 (17)	24 (10)
$>30-40$	29 (11)	2 (7)	30 (12)
$>40-50$	2 (1)	0 (-)	4 (2)
>50	24 (9)	2 (7)	29 (11)
Median (range)	20 (2.5–60)	15 (0.5–60)	20 (0.5–60)

Table 4 Satisfaction with sexual activity after alprostadil injections — home phase

Time of visit	*No. of evaluated injections*	*Satisfaction* n	*Satisfaction* %
Men			
Month 1	1589	1194	75
Month 3	2347	2020	86
Month 6	2818	2600	92
Whole study	6754	5814	86
Partners			
Month 1	1139	872	77
Month 3	1697	1498	88
Month 6	2071	1932	93
Whole study	5660	4302	76

Discussion

This is the first large multinational study which has specifically investigated the efficacy and safety of long-term intracavernosal alprostadil self-injection therapy for treatment of ED in men with type I or type II diabetes, the majority of whom were of Asian/Oriental ethnicity.

The results of this study showed that alprostadil was effective in treating ED in diabetic men, possibly more so than in non-diabetic men, as had been suggested in a previous report.[7] During the 6 month treatment period, a satisfactory erectile response was reported after 99% of injections, and this compared favourably with response rates of 93–94% reported in Asian and Caucasian non-diabetic men.[4,8] Moreover, most men (72%) who entered the home phase remained on the same initial effective dose of alprostadil. At the end of 6 months, sexual activity following injection was judged by men to be satisfactory after 92% of injections. Partner satisfaction rates with sexual activity after injection were also high (93%)

Table 5 Adverse events related to penis and associated with alprostadil[a] ($n=336$)

Event	n	%
Pain	82	24
Ecchymosis	7	2
Edema	3	<1
Prolonged erections[b]	2	<1
Priapism[a]	2	<1
Rash	2	<1
Nodule	1	<1

[a]Investigator's judgement.
[b]Resolved spontaneously.

comparable to reported in studies involving non-diabetic men (90%[4]; Table 4).

As microangiopathy is the main factor implicated in ED in type I diabetes, intracavernosal vasoactive therapy for ED is generally considered to be less effective in this group than in men with type II diabetes.[9] However, studies of penile blood flow in men with type I or type II diabetes[9,10] have not demonstated any significant differences in cavernosal arterial insufficiency between these two groups. In the current study, response rates did not differ between type I or type II diabetic men (99.8 and 98%, respectively). Although the median effective dose of alprostadil was slightly lower in type I rather than type II diabetic men (15 and 20 μg, respectively), both doses were generally consistent with the median effective alprostadil dose reported in a large study of non-diabetic men (18.6 μg).[11] Because of small subgroup numbers (there were only 30 men with type I diabetes compared with 247 men with type II diabetes), it is difficult to draw any conclusions about possible differences in alprostadil dosage in each subgroup of men.

The attrition rate observed in our study was higher than previously reported in studies in non-diabetic men (37 *vs* 20–27.5%, respectively).[4,12,13] However, only 41 (12%) men were withdrawn due to lack of efficacy, with half of these withdrawals occurring prior to entry into the home phase, and only 28 (8%) men were withdrawn due to AEs. Thus it would appear that the reason for the higher attrition rate observed in this study is not due to a higher incidence of objective reasons such as lack of efficacy, side effects or discomfort, and may instead reflect cultural differences between the different study populations possibly with respect to patient and partner problems with the concept of penile injection.[14] This is supported by the failure of partners to record their assessment of sexual activity following a high proportion of injections (27%).

Intracavernosal alprostadil was well tolerated. The incidence and profile of treatment-related adverse events observed in this study were consistent with previous reports in non-diabetic men.[3,4] The overall incidence of penile pain was 24%, which is lower than expected from data sheet information (37%).[15] The incidence of other events known to be associated with intracavernosal alprostadil injection, such as penile ecchymosis (2% [7/336]), rash (<1% [2/336]), and penile edema (<1% [3/336]), was generally consistent with the known adverse event profile of alprostadil.[15] Prolonged erection or priapism occurred in 1% of patients and resolved completely without medical treatment. One patient developed a penile nodule which resolved following withdrawal.

Conclusions

Intracavernosal alprostadil administered to type I and type II diabetic men was effective and had the expected safety profile. There were no apparent differences in efficacy between type I and type II diabetic men.

Acknowledgement

This study was supported by a grant from Pharmacia & Upjohn AB, Sweden.

References

1 McCulloch DK *et al*. The prevalence of diabetic impotence. *Diabetologia* 1980; **18**: 279–283.
2 Dunsmuir WD, Holmes SAV. The aetiology and management of erectile, ejaculatory and fertility problems in men with diabetes mellitus. *Diabetic Medicine* 1996; **13**: 700–708.
3 Linet OI, Ogrinc FG. Efficacy and safety of intracavernosal alprostadil in men with erectile dysfunction. *New Engl J Med* 1996; **334**: 873–877.
4 The European Alprostadil Study Group. The long-term safety of alprostadil (prostaglandin-E1) in patients with erectile dysfunction. *Br J Urol* 1998; **82**: 538–543.
5 Ravnik-Oblak M *et al*. Intracavernous injection of prostaglandin E_1 in impotent diabetic men. *Int J Impot Res* 1990; **2**: 143–150.
6 Losada F *et al*. Prostaglandin E_1 en el tratamiento de la impotencia erectil del diabetico. *Endocrinologia* 1993; **40**: 186–188.
7 Bancroft J, Gutierrez P. Erectile dysfunction in men with and without diabetes mellitus: a comparative study. *Diabetic Medicine* 1996, **13**: 84–89.
8 Choi HK *et al*. A dose–response study of alprostadil sterile powder (S. Po.) (Caverject) for the treatment of erectile dysfunction in Korean and Indonesian men. *Int J Impot Res* 1997: **9**: 47–51.
9 Metro MJ, Broderick GA. Diabetes and vascular impotence: does insulin dependence increase the relative severity? *Int J Impot Res* 1999; **11**: 87–89.
10 Wang CJ *et al*. Penile blood flow in diabetic impotence. *Urol Int* 1993; **50**: 209–212.
11 Linet OI, Alprostadil Study Group. Long-term safety of Caverject™ (alprostadil S. Po., PGE_1) in erectile dysfunction (ED). In: Meuleman E, Lycklama a Nijeholt G, Vanderschureren D, eds. *Proceedings of the 3rd world meeting on impotence research*, Amsterdam, The Netherlands, 24–28 August 1998. Monduzzi Editore: Bologna, 1998, pp 251–254.
12 Lehmann K, Casella R, Blochlinger A, Gasser TC. Reasons for discontinuing intracavernous injection therapy with prostaglandin E1 (alprostadil). *Urology* 1999; **53**: 397–400.
13 Gupta R, Kirschen J, Barrow RC II, Eid JF. Predictors of success and risk factors for attrition in the use of intracavernous injections. *J Urol* 1997; **157**: 1681–1686.
14 Mulhall JP *et al*. The causes of patient dropout from penile self-injection therapy for impotence. *J Urol* 1999; **162**: 1291–1294.
15 Alprostadil Data Sheet, Pharmacia & Upjohn.