

## Relation between Intracavernosal Dose of Prostaglandin Pge 1 and Mean Duration of Erection in Men with Different Underlying Causes of Erectile Dysfunction

Dejan Bratuš, Gregor Hlebič, Tine Hajdinjak

Department of Urology,  
Teaching Hospital Maribor,  
Maribor, Slovenia

**Aim** To analyze differences in effect of intracavernosally applied alprostadil (prostaglandin PGE 1) on men with different underlying causes of erectile dysfunction.

**Methods** Forty eight men with erectile dysfunction lasting for at least six months were stratified according to the etiology of erectile dysfunction into one of 4 groups comprising 12 patients. The groups were the following: psychogenic, arteriogenic, veno-occlusive, and neurological erectile dysfunction group. All men filled out International Index of Erectile Function (IIEF)-5 questionnaire, which is a 5-question version of International Index of Erectile Function Questionnaire, underwent clinical examination including neurological assessment, were tested for nocturnal penile tumescence, and had Doppler color sonography of penile arteries. Intracavernosal alprostadil was then applied to the patients, starting with a 5 µg dose and then increased in 5 µg increments until the final dose of 20 µg was reached. We measured the time from the moment of application until the start of erection and time of erection duration. For statistical analysis, non-parametric Friedman test for significant differences between repeated measurements in small groups and Wilcoxon test for differences between doses were used.

**Results** Significant relation was found between the applied dose of intracavernosal alprostadil and the duration of erection in all 4 groups of men with erectile dysfunction. In patients with arteriogenic erectile dysfunction, mean ( $\pm$ standard deviation) duration of erection for consecutive doses of alprostadil 5µg, 10 µg, 15 µg, and 20 µg were  $40.0 \pm 20.6$ ,  $54.6 \pm 23.6$ ,  $65.0 \pm 29.6$ , and  $82.1 \pm 35.4$  minutes, respectively, with significant increase for each dose. In patients with veno-occlusive dysfunction, mean durations of erection significantly increased from  $8.2 \pm 7.8$  minutes at 10 µg to  $17.3 \pm 9.5$  minutes at 20 µg. In patients with neurogenic erectile dysfunction, mean durations of erection were  $40.4 \pm 16.6$ ,  $61.7 \pm 24.7$ ,  $82.5 \pm 34.4$ , and  $101.0 \pm 28.5$  minutes respectively, with significant increase for each dose. In patients with psychogenic erectile dysfunction, mean durations of erection were  $32.4 \pm 15.4$ ,  $45.8 \pm 15.1$ ,  $69.9 \pm 23.5$ , and  $98.3 \pm 37.9$  minutes respectively, with a significant increase for each dose.

**Conclusion** Men with different underlying cause of erectile dysfunction show different response to the intracavernosally applied alprostadil. In order to achieve the optimal result, the treatment should be started with the smallest doses which are gradually increased until the maximum effect is reached.

> **Correspondence to:**

Dejan Bratuš  
Department of Urology  
General Hospital Maribor  
Ljubljanska 5  
2000 Maribor, Slovenia  
[bratus.dejan@sb-mb.si](mailto:bratus.dejan@sb-mb.si)

> **Received:** June 8, 2006  
> **Accepted:** December 1, 2006

> **Croat Med J. 2007;48:76-80**

Erectile dysfunction is a condition that affects a many men. Epidemiological studies have shown that more than half of the men between 40 and 70 years have at least some degree of erectile dysfunction (1). This is also a social problem, since it negatively affects the quality of the relationship with their partner. The treatment of this condition is very important for both the affected man and his partner and should be started as soon as possible (2).

In recent years, orally effective agents (phosphodiesterase type 5 inhibitors) became the most frequently prescribed treatment for erectile dysfunction (3-7). However, some men do not respond to oral treatment or have contraindications for such a treatment. For this group of men, intracavernosal application of vasoactive agents is the second best choice, which is still widely used (8). Prostaglandin PGE1 (alprostadil) was proven to be the safest vasoactive agent, as well as an effective one (8-13). In order to maximize the effects and minimize the potentially dangerous side effects, such as priapism, it is very important to carefully select the starting dose of this medication in men with different underlying causes of erectile dysfunction. The aim of this study was to evaluate the response to different doses of intracavernosally applied alprostadil in this population of men.

## Subjects and methods

### Patients

Forty eight men with moderate to severe erectile dysfunction lasting for at least six months were included in the study. The study was done entirely in our department between January 2002 and June 2005 and was not funded by any outside source. The patients were selected among the patients who had visited our outpatient clinic for erectile dysfunction and the first 12 patients that fulfilled the criteria for inclusion into one of the four groups were selected. The primary inclusion criterion was the score of less than 21 on the 5-item International Index of Erectile Function (IIEF-5) questionnaire (14). From all patients, a detailed history was taken and a clinical examina-

tion performed, including a neurological evaluation. Also, the presence or absence of nocturnal penile tumescence was confirmed using the snap-gauge band (15). In further evaluation, Doppler color sonography of the penile arteries was performed. We measured two parameters, peak systolic velocity and end diastolic velocity. Peak systolic velocity above 25 cm/s indicated a normal arterial inflow. End diastolic velocity below 5 cm/s was considered normal, excluding the presence of veno-occlusive dysfunction (16). In cases with elevated end diastolic velocity, pharmacocavernosography was performed to confirm or exclude the presence of veno-occlusive dysfunction.

Patients were stratified into one of the 4 groups with 12 patients in each. Patients with normal penile sonography, present nocturnal tumescence, and absent neurological deficits were stratified in the group with psychogenic cause of erectile dysfunction (17). Patients with low peak systolic velocity, normal end diastolic velocity on sonography, absent nocturnal tumescence, and normal neurological findings were stratified into the group with arteriogenic erectile dysfunction (16). Patients with veno-occlusive dysfunction, confirmed by pharmacocavernosography, normal peak systolic velocity, elevated end diastolic velocity, absent nocturnal tumescence, and normal neurological findings were stratified in the group with veno-occlusive dysfunction (16). The last group was formed of patients who had normal penile sonography, absent nocturnal penile tumescence, a clinically evident neurological lesion in the S2-S4 region, and absent bulbocavernosus reflex. To be sure that the underlying cause of erectile dysfunction in this group of patients was neurological, only the patients after the traumatic lesion of the lower spine with no residual reflex erections were included (18,19).

### Procedure

Alprostadil (Caverject, Pfizer, New York, NY, USA) was applied intracavernosally to each patient in increasing doses. The starting dose was 5

$\mu\text{g}$  and the doses were increased by 5  $\mu\text{g}$  each time until the final dose of 20  $\mu\text{g}$  was reached or the erections became too long (more than 120 minutes), allowing a possibility of prolonged erection by further increase in the dose. The applications were done not less than 3 days and not more than 14 days apart, by the same person. We used 28-gauge needles and the application was done laterally on the shaft of the penis, 1 cm behind the glans penis (20). We measured the time from the moment of the application until the start of the erection and then until the end of the erection. The start of the erection was determined as 20% increase in the penile diameter, while the end of erection was confirmed when the penile diameter returned to the starting value (21). The measurement of the penile diameter was made by previously designed frames. The duration of the erections was calculated as the time from the start till the end of the erection.

The study was approved by the medical ethics committee of the Republic Slovenia and all procedures were in accordance with the Helsinki declaration and good clinical practice principles.

#### **Statistical analysis**

Data were presented as mean and standard deviations (SD), using the Statistical Package for the Social Sciences, version 10.0.1 for Windows (SPSS Inc., Chicago, IL, USA). Although the variables were normally distributed, due to the small number of subjects per group, non-parametric tests were used to determine the relationship between the doses and the duration of the erections – Friedman test for significant differences between repeated measurements within groups and Wilcoxon signed rank test for differences between pairs of doses.  $P < 0.050$  were considered statistically significant.

### **Results**

#### **Arteriogenic erectile dysfunction**

Mean age  $\pm$  SD of the patients in this group was  $59.3 \pm 11.1$  years. Mean peak systolic velocity in

this group was  $20.3 \pm 3.6$  cm/s, and mean end diastolic velocity was  $0.3 \pm 0.8$  cm/s. Mean duration of erection significantly increased with the increasing dose, from  $40.0 \pm 20.6$  at 5  $\mu\text{g}$  to  $82.1 \pm 35.4$  at 20  $\mu\text{g}$  (Friedman test,  $P < 0.001$ ; Figure 1A). Wilcoxon signed rank test revealed a significant increase in duration of erection with each higher dose (Figure 1A).

#### **Veno-occlusive dysfunction**

Patients in this group had a mean age of  $37.6 \pm 22.0$  years, mean peak systolic velocity of  $29.6 \pm 2.4$  cm/s, and mean end diastolic velocity of  $8.2 \pm 0.7$  cm/s. Some of the patients in this group did not achieve an erection after the application of certain doses (6 patients at 5  $\mu\text{g}$ , 5 patients at 10  $\mu\text{g}$ , 3 patients at 15  $\mu\text{g}$ , and 2 patients at 20  $\mu\text{g}$ ). In statistical analysis, the value of zero (0) minutes was used for these patients. Mean duration of the erections increased  $5.8 \pm 6.7$  minutes at the 5  $\mu\text{g}$  to  $17.3 \pm 9.5$  minutes at the 20  $\mu\text{g}$  (Friedman test,  $P = 0.005$ ; Figure 1B). Wilcoxon signed rank test revealed significant increase in duration of erection with highest dose, but not in low dose range of alprostadil (Figure 1B).

#### **Neurogenic erectile dysfunction**

The mean age of patients in this group was  $43.1 \pm 8.0$  years, mean peak systolic velocity was  $33.6 \pm 4.3$  cm/s, and mean end diastolic velocity  $-0.3 \pm 0.7$  cm/s. Two of the patients in this group did not receive 20  $\mu\text{g}$  dose because their response to 15  $\mu\text{g}$  dose was so intense (120 and 150 minutes duration of erection) that there was a reasonable fear that 20  $\mu\text{g}$  dose could result in a dangerously prolonged erection or even priapism.

The erection duration significantly increased from average of  $40.4 \pm 16.6$  minutes at 5  $\mu\text{g}$  to  $101.0 \pm 28.5$  minutes at 20  $\mu\text{g}$  (Friedman test,  $P < 0.001$ ; Figure 1C). Wilcoxon signed rank test significant increase in duration of erection with higher each dose of alprostadil (Figure 1C).

### Psychogenic erectile dysfunction

The patients in this group were on the average  $38.1 \pm 7.6$  years old and had a mean peak systolic velocity of  $34.3 \pm 3.4$  cm/s, and mean end diastolic velocity of  $-0.3 \pm 0.9$  cm/s.

Mean duration of erections in this group increased from  $32.4 \pm 15.4$  minutes at  $5 \mu\text{g}$  to  $98.3 \pm 37.9$  minutes at  $20 \mu\text{g}$  (Friedman test,  $P < 0.001$ ; Figure 1D). Again, Wilcoxon signed

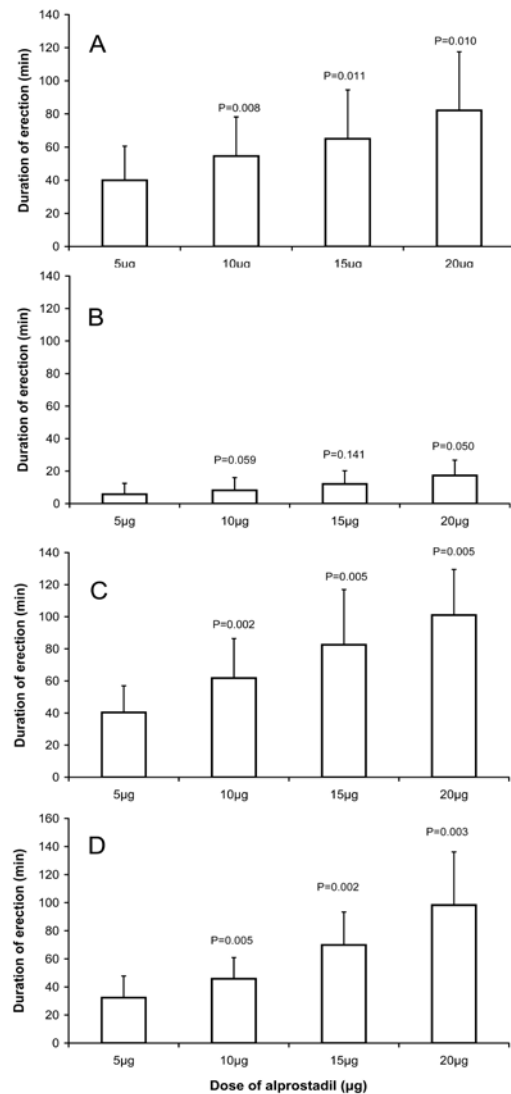
rank test revealed a significant increase in duration of erection with each higher dose of alprostadil.

During the whole study, we had no side effects, there was not a single case of priapism, and no reports of any significant local hematomas. Only a few patients reported mild local pain at the injection site, but the pain was not serious enough for patients to quit the study.

### Discussion

Our study showed a statistically significant increase in the duration of the erections with increase in the dose of applied alprostadil in all the groups. There were some differences in the response between the groups with different underlying causes of erectile dysfunction. The strongest response was in the group with neurogenic erectile dysfunction, where lower starting doses are recommended to avoid a possible prolonged erection or priapism. The highest doses should be cautiously used in this group of the patients. On the other hand, the response was smaller in the group with veno-occlusive dysfunction and some of the patients in this group showed no response even with the highest doses. The lack of the response at lower doses does not, however, rule out the possibility of an effective treatment with higher doses. Therefore, administration of high doses of intracavernosal alprostadil should be considered before other more aggressive forms of treatment.

Our results are well in accordance with previous knowledge about the effects of the intracavernosal use of alprostadil in men with erectile dysfunction. Many studies dealt with the efficacy of self-administered vasoactive drugs, mainly comparing the overall efficacy of different vasoactive substances. As for the overall efficacy, side effects, and tolerability of this type of treatment, our results are well in accordance with these other studies (8,11,12,21). To our knowledge, our study was the first detailed analysis on treatment response in men with different underlying causes of erectile dysfunction, so we can only rely on our



**Figure 1.** Duration of erection in men with different causes of erectile dysfunction (mean $\pm$ SD). (A) arteriogenic erectile dysfunction; (B) veno-occlusive erectile dysfunction; (C) neurogenic erectile dysfunction; (D) psychogenic erectile dysfunction. P values represent results of comparisons in erection duration with a first lower dose (Wilcoxon signed rank test).

results. The drawback of our study is a relatively small number of patients, which is why larger studies are needed to confirm the external validity of our conclusions.

Our study shows that the application of intracavernosal alprostadil remains an effective and safe treatment of erectile dysfunction. The starting doses should be adjusted individually according to the suspected underlying cause of erectile dysfunction, in order to avoid possible prolonged erections or priapism. The relation between the higher subsequent doses and the duration of erections has proven to be positive linear, so we can expect longer erection times with the increase in the dose in all the patients. If the increase in the dose is made in small increments, one can avoid the possible side effects. In our study we did not observe any side effects, such as prolonged erection or priapism.

Intracavernosal application of vasoactive agents remains one of the modalities for the treatment of erectile dysfunction. In the era of orally effective agents, it is considered to be a secondary treatment, used mainly when oral agents yield no response or are contraindicated. Nevertheless, intracavernosal injections are still widely used and knowledge about the exact effects of different doses is important if we want to satisfy our patients' need for an adequate treatment without the risk of potentially dangerous side effects.

#### References

- Johannes CB, Araujo AB, Feldman HA, Derby CA, Kleinman KP, McKinlay JB. Incidence of erectile dysfunction in men 40 to 69 years old: longitudinal results from the Massachusetts male aging study. *J Urol.* 2000;163:460-3. [Medline:10647654](#)
- Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol.* 1994;151:54-61. [Medline:8254833](#)
- Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. *N Engl J Med.* 1998;338:1397-404. [Medline:9580646](#)
- Porst H, Rosen R, Padma-Nathan H, Goldstein I, Giuliano F, Ulbrich E, et al. The efficacy and tolerability of vardenafil, a new, oral, selective phosphodiesterase type 5 inhibitor, in patients with erectile dysfunction: the first at-home clinical trial. *Int J Impot Res.* 2001;13:192-9. [Medline:11494074](#)
- Hellstrom WJ, Gittelman M, Karlin G, Segerson T, Thibonnier M, Taylor T, et al. Vardenafil for treatment of men with erectile dysfunction: efficacy and safety in a randomized, double-blind, placebo-controlled trial. *J Androl.* 2002;23:763-71. [Medline:12399521](#)
- Martin-Morales A, Rosen RC. Effective treatment of erectile dysfunction with vardenafil. *Drugs Today (Barc).* 2003;39:51-9. [Medline:12669108](#)
- Gresser U, Gleiter CH. Erectile dysfunction: comparison of efficacy and side effects of the PDE-5 inhibitors sildenafil, vardenafil and tadalafil – review of the literature. *Eur J Med Res.* 2002;7:435-46. [Medline:12435622](#)
- Linet OI, Neff LL. Intracavernous prostaglandin E1 in erectile dysfunction. *Clin Investig.* 1994;72:139-49. [Medline:8186662](#)
- Hedlund H, Andersson KE. Contraction and relaxation induced by some prostanoids in isolated human penile erectile tissue and cavernous artery. *J Urol.* 1985;134:1245-50. [Medline:3903226](#)
- Ishii N, Watanabe H, Irisawa C, Kikuchi Y, Kawamura S, Suzuki K, et al. Studies on male sexual impotence. Report 18. Therapeutic trial with prostaglandin E1 for organic impotence [In Japanese]. *Nippon Hinyokika Gakkai Zasshi.* 1986;77:954-62. [Medline:3773397](#)
- Lui SM, Lin JS. Treatment of impotence: Comparison between the efficacy and safety of intracavernous injection of papaverine plus phentolamine (Regitine) and prostaglandin E<sub>1</sub>. *Int J Impot Res(Suppl).* 1990;2:147-51.
- Lee LM, Stevenson RW, Szasz G. Prostaglandin E1 versus phentolamine/papaverine for the treatment of erectile impotence: a double-blind comparison. *J Urol.* 1989;141:549-50. [Medline:2918589](#)
- Zorgniotti AW, Lefleur RS. Auto-injection of the corpus cavernosum with a vasoactive drug combination for vasculogenic impotence. *J Urol.* 1985;133:39-41. [Medline:2578067](#)
- Rosen RC, Cappelleri JC, Smith MD, Lipsky J, Pena BM. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. *Int J Impot Res.* 1999;11:319-26. [Medline:10637462](#)
- Chen J, Greenstein A, Sofer M, Matzkin H. RigiScan versus snap gauge band measurements: is the extra cost justifiable? *Int J Impot Res.* 1999;11:315-8. [Medline:10637460](#)
- Lue TF, Hricak H, Marich KW, Tanagho EA. Vasculogenic impotence evaluated by high-resolution ultrasonography and pulsed Doppler spectrum analysis. *Radiology.* 1985;155:777-81. [Medline:3890009](#)
- Lue TF. Impotence. Diagnostic methods. *Problems in urology.* 1991;5:519-26.
- Bors E, Comarr AE. *Neurological urology.* Basel: S Karger;1971.
- Bors E, Comarr AE. Neurological disturbances of sexual function with special reference to 529 patients with spinal cord injury. *Urol Surv.* 1960;10:191-222.
- Patient instructions for Caverject (alprostadil injection) aqueous. Kalamazoo (MI): Pharmacia and UpJohn; 1999.
- Watters GR, Keogh EJ, Earle CM, Carati CJ, Wisniewski ZS, Tulloch AG, et al. Experience in the management of erectile dysfunction using the intracavernosal self-injection of vasoactive drugs. *J Urol.* 1988;140:1417-9. [Medline:3193507](#)