

6-1-2000

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Recommended Citation

Opanuraks, J. and Kongkanand, A. (2000) "Safety and efficacy of transurethral alprostadil Inmen with erectile dysfunction :King Chulalongkorn Memorial Hospital experience," *Chulalongkorn Medical Journal*: Vol. 44: Iss. 6, Article 6.

Available at: <https://digital.car.chula.ac.th/clmjjournal/vol44/iss6/6>

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Safety and efficacy of transurethral alprostadil in
men with erectile dysfunction :
King Chulalongkorn Memorial Hospital experience

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Opanuraks J, Kongkanand A. Safety and efficacy of transurethral alprostadil in men with erectile dysfunction : King Chulalongkorn Memorial Hospital experience. Chula Med J 2000 Jun; 44(6): 433 - 40

Objective : *To evaluate the safety and efficacy of transurethral alprostadil for the treatment of men with erectile dysfunction.*

Materials and Methods : *In an outpatient setting, patients with erectile dysfunction from various organic causes were treated with transurethral alprostadil, in an open-label, dose-escalating study. Testing stopped when the dose provided an erection sufficient for intercourse, as assessed by the patient and the investigator. Patients, who achieved a sufficient response received medication at the selected dose for use at home for 3 months. After each home administration, patients recorded in diaries whether or not sexual intercourse occurred and any side effects to the drug.*

Results : *In - clinic titration phase: of the 38 subjects who entered, 5 dropped out due to reasons unrelated to efficacy and safety of the transurethral alprostadil. The remaining 33 patients completed the in-clinic titration. Of these, 27 patients (82 %) achieved an erection sufficient for intercourse and were provided with medication for*

home treatment. In the home treatment phase, 18 of the 27 (67%) had intercourse successfully at least once and 3 month follow - up. The most common side effect was penile pain and burning which occurred after 8 of the 27 (30%) alprostadil treatment. No patient reported priapism or developed penile fibrosis.

Conclusions : *Alprostadil delivered transurethally by this system was well tolerated, effective and safe in treating erectile dysfunction and was generally well accepted by the patients.*

Key words : *Transurethra, Alprostadil, Erectile dysfunction.*

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Received for publication. January 10, 2000.

จลินทร์ โอภาณุรักษ์, อภิชาติ กงกะนันท์. ประสิทธิภาพและความปลอดภัยของยาสอดทางทอ็บัสสาวะอัลพรอสตาดีลในผู้ชายหย่อนสมรรถภาพทางเพศ : ประสบการณ์จากการศึกษาในโรงพยาบาลจุฬาลงกรณ์. จุฬาลงกรณ์เวชสาร 2543 มิ.ย; 44(6): 433 - 40

วัตถุประสงค์ : เพื่อศึกษาถึงประสิทธิภาพและความปลอดภัยของยาสอดทางทอ็บัสสาวะอัลพรอสตาดีล ในผู้ชายหย่อนสมรรถภาพทางเพศ

วิธีการศึกษา : ที่คลินิกเสริมสร้างสมรรถภาพทางเพศผู้ป่วยที่มีปัญหาหย่อนสมรรถภาพทางเพศจากสาเหตุใดก็ตาม จะได้รับการรักษาด้วยยาสอดทางทอ็บัสสาวะอัลพรอสตาดีล และประเมินผลโดยดูการแข็งตัวของอวัยวะเพศชายที่สามารถมีเพศสัมพันธ์ได้ โดยผู้ประเมินเป็นแพทย์และตัวผู้ป่วยเอง และถ้าผู้ป่วยพึงพอใจในผลการรักษาแล้ว จะได้รับยากลับไปใช้ที่บ้านเป็นเวลา 3 เดือน โดยหลังการใช้ยาแต่ละครั้งผู้ป่วยจะบันทึกลงในไดอารี่ถึงผลการใช้ว่าสามารถมีเพศสัมพันธ์และมีผลข้างเคียงอย่างไร

ผลการศึกษา : ที่คลินิกเสริมสร้างสมรรถภาพทางเพศ, มีผู้ป่วยเข้ารับการรักษา 38 ราย, 5 ราย ออกจากการศึกษาเนื่องจากเหตุผลส่วนตัว, ที่เหลืออีก 33 ราย เข้ารับการทดสอบที่คลินิกจนครบ พบว่ามี 27 ราย (82 %) ที่สามารถมีการแข็งตัวของอวัยวะเพศชายที่สามารถมีเพศสัมพันธ์ได้และได้รับยากลับไปใช้ที่บ้านต่อ, ผลบันทึกในไดอารี่จากการใช้ยาที่บ้านพบว่า 18 จาก 27 ราย(67 %) สามารถมีเพศสัมพันธ์ที่พึงพอใจอย่างน้อย 1 ครั้ง และมารับยาจนครบ 3 เดือน ส่วนผลข้างเคียงที่พบบ่อยคือปวดที่บริเวณอวัยวะเพศ

สรุป : ยาสอดทางทอ็บัสสาวะอัลพรอสตาดีลมีประสิทธิภาพที่ดีและปลอดภัยในการใช้รักษาผู้ป่วยที่หย่อนสมรรถภาพทางเพศ

คำสำคัญ : ยาสอดทางทอ็บัสสาวะอัลพรอสตาดีล, ภาวะหย่อนสมรรถภาพทางเพศ

Erectile dysfunction is estimated to affect up to 10 % of the male population in the United States.⁽¹⁾ It becomes more frequent with age, but is not an inevitable consequence of normal aging. It is usually due to organic factors or diseases, such as pelvic vascular disease, diabetes mellitus, neurodegenerative disorders, side effects of medication, pelvic surgery and trauma. Erectile dysfunction impairs sexual performance, diminishes self-esteem, and disrupts personal relationships.

Although several treatments have been available for erectile dysfunction, including oral medications, vacuum pumps, vascular surgery, penile prostheses and intracavernosal injections, most patients remain untreated. The threshold at which a man will seek treatment for erectile dysfunction has been high, because of the social stigma and lack of convenient, safe and effective treatment.

Previous studies conducted in USA have shown that transurethral delivery of alprostadil (the medicated urethral system for erection, MUSE) is well tolerated and effective in the treatment of men with organic erectile dysfunction.⁽²⁾ Although one of the trials of transurethral alprostadil involved a large group of patients, the dose was not selected by an open-label stepwise titration, as would be expected in clinical practice and the study population was in the USA. Thus the conclusions from that study may not be applicable to a population in Thailand.

This study reports the results of an open-label, dose-escalating study of transurethral alprostadil in patients with erectile dysfunction in King Chulalongkorn Memorial Hospital in Thailand. This trial was conducted to confirm the efficacy and safety of transurethral alprostadil. The endpoints measured in this study

included erectile response on a five-point scale, sexual intercourse, patient comfort with the therapy, and adverse reactions.

Materials and Methods

Between June 1998 to March 1999, a total of 38 patients with erectile dysfunction were treated with transurethral alprostadil. Patients included in the study were restricted to those in whom healthy adult male 18 years or older with a subjective complaint of erectile dysfunction at the infertility and impotence clinic of King Chulalongkorn Memorial Hospital. They provided written informed consent, were willing and able to comply with all study requirements and visit schedules, and agreed not to use other forms of treatment of erectile dysfunction. Patients were excluded from this study as they had a known allergy or hypersensitivity to alprostadil, a history of myocardial infarction, uncontrolled congestive heart failure, abnormal penile anatomy or poor personal hygiene that interfere with intraurethral administration, and a history of urethral stricture, balanitis, urinary tract infection or STD. Patients with a current or prior penile implant were also excluded

Eligible patients were treated with transurethral alprostadil (PGE1) by using a proprietary drug delivery system (MUSE,[®] Vivus, Inc., Menlo Park, CA, USA). The system consisted of a polypropylene applicator with a hollow stem 3.2-cm long and 3.5-mm in diameter. The tip of each applicator contained a semisolid pellet of medication. Each single-use system was pre-filled with a specified dose of medication (250,500 or 1,000 mcg of alprostadil). Patients voided and subsequently inserted the stem of the applicator slowly and gently into the urethra;

the button on the end of the applicator was then depressed, depositing the pellet of medication in the urethra, and the applicator was removed. The medication pellet was then dispersed along the urethra by rolling the penis between the palms of the hands.

Patients were screened for eligibility by medical history, labs and physical examination and eligible patients entered an open - label, three - dose (250, 500 and 1000 mcg alprostadil), dose - escalating phase conducted in an out patient setting. After administering each dose, the patient and investigator graded the erectile response on a five - point erection assessment scales (EAS) where 1 = no response, 2 = some enlargement, 3 = full enlargement but insufficient for intercourse, 4 = erection sufficient for intercourse and 5 = full erection.⁽³⁾ They will be evaluated over a one hour period for blood pressure and pulse rate. Patients who achieved EAS scores of 4 or 5 on any dose were provided with the effective dose of alprostadil for 3 months of home treatment.

A three - month home treatment period with monthly interim visits was required for patient follow-

up and drug distribution. After each home administration, patients recorded in a diary the EAS score, whether or not sexual intercourse occurred, the level of discomfort associated with the treatment, and any adverse reactions for the patient. At the end of three months, patients were required to return all study supplies and have a physical exam.

Efficacy evaluations in this study were based on the percentage of patients who successfully progressed through the various phases of the study, the percentage of patients experiencing satisfactory sexual activity during home therapy and the percentage of patients with adverse reactions.

Results

From June to March 1999, a total of 38 patients entered the outpatient dosing phase. The demographic characteristics of the men studied are shown in Table 1. The baseline characteristics of the patients selected for home therapy generally reflected the characteristics of the outpatient group (Table 1). Previous therapies included band therapy, hormones, intracavernous injections, and vacuum pumps.

Table 1. The characteristics of the patients.

Characteristic	Men studied in the clinic (N = 38)	Men using treatment at home (N = 27)
Age (yr.)		
- Mean	53.87	55.81
- Range	29 - 75	29 - 75
Duration of dysfunction (mo.)		
- Mean	49.63	49.07
- Range	4 - 240	6 - 240
Capable of partial erection (% of men)	71	70
Previous Therapy (% of men)	40	48

The primary contributing factors of erectile dysfunction included aging, diabetes, surgery and trauma, alcohol abuse, tobacco abuse, hypertension, psychogenic factors and idiopathic factors and are summarized in Table 2.

Table 2. The primary contributing factors of the patients.

Primary contributing factors	%
Age	23
Hypertension	14
Diabetic mellitus	14
Alcohol	15
Trauma or surgery	8
Tobacco abuse	12
Psychogenic factors	2
Idiopathic factors	12

Responses in the clinic :

In the clinic, 38 patients enrolled in the study but 5 dropped out due to reasons unrelated to efficacy and safety of the transurethral alprostadil. The remaining 33 patients completed the in-clinic titration. Of these, 27 men (82 %) had maximal penile responses of 4 or 5 on the Erection Assessment Scale (i.e. an erection sufficient for intercourse or a full erection) and were provided with medication for home treatment. Doses of 1000 mcg of alprostadil were selected by 81.48 % (22 / 27) of the patients and 18.52 % (5 / 27) chose a 500 mcg. dose.

More than 90 % of patients experienced minimal discomfort or no discomfort with each dose; however, one case had reported bleeding from the urethra.

Responses at home :

Of the 27 men who took treatment at home, 24 reported their response to at least one dose and 18 men (67 %) completed the 3 months of treatment. Among the men who did not complete the study, 5 reported lack of efficacy, 3 discontinued due to adverse reactions and one was lost to follow - up.

Adverse reactions :

Drug - related urogenital pain was not reported by any of patients during the outpatient dosing (Table 3). One patient reported urethral bleeding. More than 90 % of the patients had minimal or no discomfort. In the outpatient setting, no dizziness and no hypotension had occurred. (Table 3)

During home treatment, drug - related urogenital pain was reported by 15 patients (56 %) and urethral bleeding by one (4 %). There were no episodes of syncope. Additionally, there were no reports of penile fibrosis or priapism (a rigid erection lasting > = 6 hr.) in the outpatient or home settings.

Discussion

Penile erection is a neurovascular process dependent upon the relaxation of the smooth muscle tissue in the erectile bodies of the penis (the corpora cavernosa and the corpus spongiosum). Alprostadil produces corporal smooth muscle relaxation that permits rapid arterial filling, resulting in engorgement of the sinusoids within the cavernosa and subsequent veno-occlusion.^(4,5) Pharmacotherapy with alprostadil previously required a direct injection into the corpora cavernosa.⁽⁶⁾ Transurethral therapy delivers alprostadil to the urethral mucosa for absorption into the surrounding corpus spongiosum. The route of drug

Table 3. The drug – related adverse reaction profile.

Adverse reaction	Out patient	At home
No. of patients	38	27
Urogenital effects (%)		
Urethral pain / burning	0	4 (15)
Penile pain	0	8 (30)
Testicular pain	0	3 (11)
Urethral bleeding	1 (3)	1 (4)
Priapism	0	0
Penile fibrosis	0	0
System effects (%)		
Dizziness	0	0
Hypotension	0	0

transfer has been suggested to be through small communicating veins draining the corpus spongiosum or through the deep dorsal vein, with retrograde transfer into the corpora cavernosa, producing an erection.⁽⁷⁾

The first phase of this study consisted of individual dose testing in an outpatient setting to find a dose that produced an erection sufficient for intercourse. Most patients (82 %) found a suitable dose and progressed to the home treatment phase. While some patients responded adequately to the lower doses of alprostadil, most patients (81 %) preferred the highest dose (1000 mcg) indicating greater effectiveness with higher doses. However, the selection pattern may have been influenced by the open-label study design; in a double-blind study conducted in the USA, only 41 % of men selected the 1000 mcg dose.⁽¹⁾ Reasons for not responding to alprostadil during outpatient dose-testing include lack of responsiveness to alprostadil

nervousness with the outpatient setting, or unfamiliarity with the new treatment.

During the 3 months of home treatment, 89 % of patients reported intercourse at least once and 67 % completed 3 months follow-up. This success rate was remarkably high in light of the severity of impairment in this study group; most patients had primary contributing factors of erectile dysfunction which was organic, all were unable to engage in sexual intercourse on any occasion for at least 3 months before study entry and the mean duration of erectile dysfunction was 49 months. The rate of efficacy appeared to be consistent over the 3 months of treatment.

Importantly, not all patients who achieved a sufficient erection in the outpatient setting reported intercourse at home. The development of marital and psychological problems during the prolonged period of erectile dysfunction may partially explain this discrepancy. The overall efficacy of transurethral

alprostadil can be calculated by multiplying the percentage that found an effective dose by the percentage who subsequently had intercourse at home. In this study, 82 % of patients achieved success during outpatient dosing and 67 % of patients subsequently reported intercourse at home; this corresponds to an intent-to-treat efficacy of 55 %. Some patients who were excluded from home treatment because they had an insufficient response to test doses might have been responsive in the home environment. Many patients may experience anxiety in the outpatient setting which interferes with their ability to achieve an erection.

The most common adverse reactions associated with this therapy occurred in the urogenital area; no serious adverse reactions related to the study drug, and no episodes of priapism or penile fibrotic complications were reported during this study. Three patients discontinued due to adverse reactions and 67 % of the patients completed the 3-month home treatment phase. Most patients found this method of therapy to be associated with minimal or no discomfort.

In conclusion, this 3-month study showed that transurethral alprostadil was broadly effective and well tolerated for the treatment of chronic erectile dysfunction. This method of therapy provides a useful treatment option for men with erectile dysfunction.

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