Vol. 26, 1994

eau Official Organ of the European Association of Urology

European Urology

KARGER

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This extended issue was made possible through the generous support of the *Heinz Karger Memorial Foundation* in Basel.

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Michael C. Truss
Armin J. Becker
Walter F. Thon
Markus Kuczyk
Mohamad H. Djamilian
Christian G. Stief
Udo Jonas

Department of Urology, Medizinische Hochschule Hannover, FRG

Intracavernous Calcitonin Gene-Related Peptide Plus Prostaglandin E_1: Possible Alternative to Penile Implants in Selected Patients

Key Words
Impotence
Venous ligation
Smooth muscle physiology
Corpus cavernosum
Electromyography
Calcitonin gene-related peptide
Pharmacotherapy

Abstract
The implantation of a penile prosthesis is still the ultima ratio for patients with erectile dysfunction who fail other treatment options such as pharmacotherapy and penile venous surgery. Despite mostly favorable results regarding restauration of erectile capacity, penile allografts are often not accepted for various reasons. Therefore, pharmacotesting with a mixture of calcitonin gene-related peptide and prostaglandin E_1 (CGRP/PGE_1) was offered to different selected patients populations: 28 patients with erectile dysfunction and venous leakage who failed penile venous surgery, 28 patients with erectile dysfunction and venous leakage (who refused penile venous surgery) and 12 patients without venous leakage, but poor response to maximum doses of papaverine/phentolamine, received 5 μg CGRP plus 10 μg PGE_1. Erections sufficient for intercourse were noted in 19/28 (67.9%), 20/28 (71.4%) and 11/12 (91.7%) patients, respectively. Our data show that a combination of CGRP and PGE_1 may be an alternative to penile implants in selected patients.

Introduction

Cavernous smooth muscle tissue plays a major role in the induction and maintenance of a normal erection [1, 2]. In addition to adequate arterial inflow, relaxation of the cavernous smooth muscle is required, resulting in a strong reduction of venous outflow. Theoretically, insufficient venous outflow reduction can be caused by ectopic veins, incomplete cavernous relaxation or pathologic alterations of the tunica albuginea [3–5]. Standardized intracavernous pharmacotesting has been shown to be of high predictive value for the diagnosis of venous leakage [6]. However, in some patients not responding to repetitive maximum doses of conventional pharmacotherapy, no venous leakage is found by cavernosometry and cavernosography. In these patients the etiology of impotence remains obscure and cannot be assessed by current diagnostic tests when arterial disease has been ruled out.

In patients with venous leakage, penile venous surgery is a common treatment option. However, despite increasing knowledge about the pathomechanism of venoocclusive dysfunction, the results of venous ligation procedures often remain dissatisfying. The ultima ratio for patients who fail penile venous surgery and who do not respond to

Supported by grants from the Deutsche Forschungsgemeinschaft DFG Sti 96/2-2 and Tru 343/1-1.

Michael C. Truss, MD
Department of Urology
Medizinische Hochschule Hannover
Konstanty-Gutschow-Str. 8
D-30625 Hannover (FRG)

0302–2838/94/0261–0040
$5.00/0

conventional pharmacotherapy is still the implantation of a penile prosthesis.

This study was undertaken to identify therapeutic alternatives for patients who failed penile venous surgery, who do not respond to conventional pharmacotherapy or who refuse penile allografts for various reasons.

Patients and Methods

The routine workup of patients with erectile dysfunction in our impotence clinic consists of a detailed case history including a questionnaire, a sexual case history by a psychiatrist where indicated, a complete physical examination, routine blood laboratory, corpus cavernosum electromyography [7], pharmacotesting with a mixture of papaverine and phentolamine and Doppler ultrasonography. Where indicated, pharmacocavernosometry/-graphy and digital subtraction angiography are done.

Pharmacotesting was done in a relaxed atmosphere after informed consent had been obtained. Increasing doses of a mixture of papaverine (15 mg/ml) and phentolamine (0.5 mg/ml) were given, starting with a dose of 0.2 ml. Only 1 injection per day was given to avoid prolonged erections. The dose was increased to a maximum of 2.0 ml depending on the erectile response. Erections were evaluated by a urologist by inspection and palpation and graded as follows: E 0 = no response; E 1 = slight tumescence; E 2 = medium tumescence; E 3 = full tumescence; E 4 = full tumescence with medium rigidity sufficient for intercourse, E 5 = full erection. If 2 ml of the mixture failed to induce an erection sufficient for intercourse despite additional manual self-stimulation, venous leakage was suspected and the patient was offered pharmacocavernosometry/-graphy for evaluation of the venoocclusive system.

For corpus cavernosum electromyography (the term SPACE – single potential analysis of cavernous electrical activity – was abandoned in favor of the more precise and neutral term CC-EMG – corpus cavernosum electromyography – by the consensus committee at the First International Workshop on Smooth Muscle EMG Recordings/Leimyogram in Mannheim/FRG) [8] 2 coaxial needle electrodes (Dantec 9013 L) were inserted bilaterally into the cavernous bodies and advanced until the tips of the electrodes were located centrally. The signals were processed by different electrophysiological units (WIEST SPACE, Dantec Neuromatic 2000), displayed continuously on a monitor screen (Dantec 2000) and simultaneously recorded (WIEST SPACE). Interpretation of the recordings was done according to previously published data [7]. Since 9/92 EMG signals were recorded on-line with a personal computer and data were processed using an especially designed software on the basis of the Fast-Fourier analysis [9].

Doppler ultrasonography of the penile arteries was performed as described elsewhere [10]. For pharmacocavernosometry/-graphy the left corpus cavernosum was punctured with a 19-gauge needle under sterile conditions and connected to a perfusion pump. The right corpus cavernosum was punctured with a 26-gauge needle and connected to a transducer for pressure recording (WIEST Cavopump, Wiest, Germany). To induce cavernous smooth muscle relaxation, 30 mg of papaverine and 1 mg of phentolamine were injected intracavernously via the left cannula. After 10 min and subsequent to cavernous relaxation, cavernosometry was performed by perfusing the penis with warm (37 °C) saline with a flow rate of 150 ml/min. As soon as rigidity was reached, the minimum flow to maintain a full erection was determined ('maintenance flow'). After infusion of undiluted nonionic contrast medium, X-ray films were taken in anteroposterior and oblique (30°) positions. After opacification, the penis was perfused with normal saline to wash out the contrast medium. The needles were removed and the puncture sites were compressed manually. Flow rates exceeding 14 ml/min were considered abnormal [11–13].

All 129 patients with documented venous leakage were offered penile venous surgery and counseled about alternative therapeutic options.

Penile venous surgery was done as follows: A midline incision was done over the dorsum of the penis, then the superficial dorsal veins were ligated and the deep dorsal veins were resected from about 1 cm proximal to the suspensory ligament to the distal $^1/_3$ of the penile shaft.

Since previous studies showed a higher response rate of a combination of calcitonin gene-related peptide (CGRP) plus prostaglandin E_1 (PGE_1) as compared to PGE_1 alone [14], we offered this combination (5 µg CGRP plus 10 µg PGE_1) to patients with venous leakage who failed penile venous surgery, to patients with venous leakage who refused penile venous surgery and to patients without documented venous leakage who failed pharmacotherapy with papaverine/phentolamine. Prior to the injections all patients were extensively informed about the experimental character of this drug combination as well as possible side effects. The study protocol was approved by the Ethics Committee of the Medizinische Hochschule Hannover.

Results

After a comprehensive workup including pharmacotesting, venous leakage was suspected in 160/448 patients (35.7%). Insufficiency of the venoocclusive system was diagnosed in 129/160 (80.6%) or 129/448 (28.8%) patients, respectively. As therapeutic options penile venous surgery, implantation of a penile prosthesis, the use of a vacuum constriction device or a trial with CGRP/PGE_1 injections were offered. After extensive counselling, 84 patients underwent penile venous surgery, 28 patients opted for a trial with CGRP/PGE_1, 5 patients (all with concomitant Peyronie's disease) underwent implantation of a penile prosthesis and 2 patients with dysplastic arterial disease underwent arterial revascularization and penile venous surgery. The use of a vacuum constriction device was favored by 5 patients. The remaining 5 patients are either awaiting or refused further therapy (table 1).

In 31/160 patients (19.4%) without adequate response to 30 mg papaverine plus 1 mg phentolamine, venous leakage could not be documented by cavernosometry and -graphy. 28 patients who failed penile venous surgery underwent pharmacotesting with 5 µg CGRP plus 10 µg PGE_1. Of these, 19 (67.9%) achieved erections sufficient

Table 1. First-line management in 129 patients with erectile dysfunction and venous leakage

Penile venous surgery	84
CGRP/PGE_1 trial	28
Implantation of penile prosthesis	5
Vacuum constriction device	5
Arterial reconstruction (Hauri) and penile venous surgery	2
Awaiting therapy or refused treatment	5

Values are number of patients.

for intercourse. In addition, 28 patients with venous leakage who refused penile venous surgery and 12 nonresponders to papaverine/phentolamine (but without venous leakage) opted for pharmacotesting with CGRP/PGE_1. 20/28 (71.4%) and 11/12 (91.7%) patients had E 4 or E 5 responses. In the latter highly selected population the etiology of erectile dysfunction remained unclear despite a thorough diagnostic workup (significant arterial disease had been ruled out by Doppler ultrasonography).

The patients who responded to pharmacotherapy with CGRP/PGE_1 entered another study to evaluate the safety and efficacy of CGRP/PGE_1 autoinjection therapy. Up to now no significant side effects have been reported in this group after up to 80 and more autoinjections per patient [14]. Only 2/40 patients (5.0%) reported significant intrapenile pain associated with the injection.

A total of 13 patients (after failed penile venous surgery and/or failed CGRP/PGE_1 pharmacotesting) underwent implantation of penile allografts and 10 patients opted for a vacuum constriction device. The remaining patients refused further treatment.

Discussion

The management of erectile dysfunction associated with or due to venous leakage is far from being standardized despite better diagnostic tests to evaluate the etiology of impotence. As demonstrated in previous studies [6], standardized pharmacotesting with vasoactive substances was shown to have a high predictive value for the evaluation of the venoocclusive system. Although short-term results of the presumably causative therapy, penile venous surgery, often seemed to be promising [15], the outcome with longer follow-up tends to be disappointing [16]. Concomitant arterial disease was claimed to be one of the predisposing factors for the failure of venous surgery and, therefore, reconstructive vascular surgery was promoted with various intermediate and long-term results [17, 18]. Incomplete cavernous relaxation due to autonomic dysfunction or myogenic cavernous degeneration may be one of the possible etiologies of the insufficiency of the venoocclusive system [19]. Since CC-EMG was shown to be a minimally invasive and reproducible method for the evaluation of autonomic cavernous innervation and cavernous smooth muscle integrity [7], we evaluated our patient population after penile venous surgery in retrospect. Of the 38 patients who failed penile venous surgery, 30 (78.9%) had abnormal CC-EMG patterns, whereas 30/39 patients (76.9%) who had sufficient erections with or without additional intracavernous injections, had normal CC-EMG patterns. This difference was statistically highly significant ($p < 0.001$, χ^2 test) [own unpubl. data]. Thus, routine CC-EMG evaluation in patients with erectile dysfunction and venous leakage contributes significant predictive information and may alter the decision making in this patient population.

The ultima ratio after failed venous surgery and conventional pharmacotherapy remains the implantation of a penile prosthesis. However, despite mostly favorable results, many patients reject allografts for various reasons. In our experience, many patients also do not accept vacuum constriction devices due to their cumbersome handling. Since the classical drugs for autoinjection therapy (papaverine, papaverine plus phentolamine, PGE_1) induce a full erection in only 50–70% of an unselected population [20–25], newer, more potent substances or mixtures with a higher response rate are needed [26]. CGRP, along with other substances, was shown to play a possible role in the regulation of the smooth muscle tone [27]. Preliminary data show that a combination of CGRP and PGE_1 has a higher response rate than PGE_1 alone, with less side effects, such as intrapenile pain [28]. The pain reducing effect of CGRP/PGE_1 may be due to the anti-inflammatory effect of CGRP [29] and the reduced dose of PGE_1. We therefore offered, after extensive counseling about possible risks and side effects and after informed consent had been obtained, this combination to patients after failed penile venous surgery or as an alternative to penile venous surgery. In addition, patients without venous leakage as documented by cavernosometry and cavernosography but insufficient response to maximum doses of papaverine/phentolamine (despite the absence of significant arterial disease) were offered this drug combination. In these highly selected patient populations drugs with a higher erectile potential than papaverine/phentolamine or PGE_1 are needed. Pharmacotesting with CGRP/

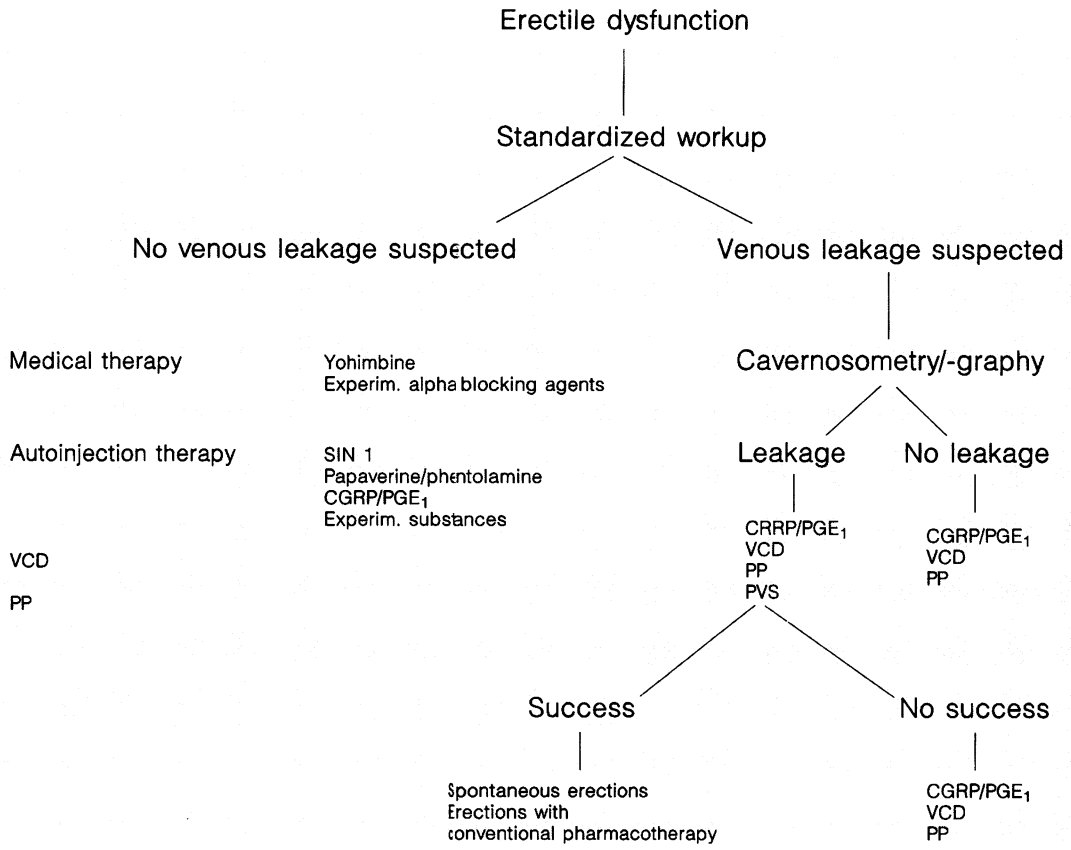

Fig. 1. Erectile dysfunction – current management at Medizinische Hochschule Hannover. VCD = Vacuum constriction device; PP = penile prosthesis: PVS = penile venous surgery.

PGE_1 induced sufficient erections in 67.9, 71.4 and 91.7% of patients, respectively.

The higher response rate of CGRP/PGE_1 compared to papaverine, papaverine/phentolamine or prostaglandin alone may be explained by the different and potentially additive effector mechanisms of CGRP and PGE_1. CGRP relaxes smooth muscle cells by hyperpolarization via potassium channel opening and cyclic adenosine monophosphate stimulation [30, 31]. PGE_1 acts through specific receptors on the smooth muscle cell surface.

In an ongoing study, the long-term efficacy and safety of this drug combination was evaluated with promising results; so far, no significant complications such as prolonged erections or fibrosis were noted after up to 80 and more injections per patient [14]. We therefore think that CGRP/PGE_1 may be a valuable alternative to penile implants as well as vacuum constriction devices in selected patients. However, it should be stressed that the experimental and clinical experience with this drug combination is still relatively limited. Despite favorable data, the use of CGRP/PGE_1 should currently be restricted to selected patients in well controlled clinical studies. For example, no data are yet available regarding the possible risk of prolonged erections in patients also responding to less potent substances like papaverine or prostaglandin alone. In addition, toxicological data for CGRP are restricted to the rabbit model, where human CGRP caused signs of slight to moderate inflammation [own unpubl. data]. Taken this together, the use of intracavernous CGRP/PGE_1 in patients with impotence should still be regarded as experimental and patients should be made aware of the experimental character of this treatment option.

The therapy of erectile dysfunction is nowadays too complex that it possibly could be a one-strategy or even a one-drug therapy. The increasing complexity of the etiologies and diagnostic modalities of erectile dysfunction requires the availability of drugs with different effector mechanisms and different erectile potentials. Currently, we recommend different substances to different patient populations: For a standardized dose response we use a mixture of papaverine and phentolamine. In case a patient responds very well or with a prolonged erection to small doses of this combination (<0.7 ml), we offer the nitric oxide donor linsidomin chorhydrate (SIN 1) [32]. The efficacy of this substance has been shown to be excellent in this patient population and no prolonged erections have been observed so far in more than 100 patients. In contrast, in patients who needed higher doses of papaverine/phentolamine (>0.7 ml) for the induction of an erection, the efficacy was significantly lower. These data demonstrate that SIN 1 is less potent but safer than papaverine/phentolamine [33]. Therefore, patients who respond well to moderate to maximum amounts or papaverine/phentolamine (0.8–2.0 ml) are maintained on this combination.

All other patients are offered cavernosometry and cavernosography and counseled about the possible alternatives: penile venous surgery, use of a vacuum constriction device, implantation of a penile prosthesis and autoinjection therapy with CGRP/PGE_1 (fig. 1). As stated before, CGRP/PGE_1 should currently not be regarded as a first-line treatment for an unselected patient population but should be considered for patients who need a more potent smooth muscle relaxing substance.

The finding 'venous leakage' may be a symptom of multifactorial etiology consisting of arterial, autonomic, myogenic, and venogenic pathology. Thus, evaluation of the autonomic cavernous innervation and smooth muscle intactness by CC-EMG provides additional predictive information in regard to the outcome of venous surgery. Based on the data of this study, we now routinely counsel our patients with erectile dysfunction and venous leakage and offer alternatives to penile venous surgery, such as pharmacotherapy with CGRP/PGE_1, use of a vacuum constriction device and implantation of a penile prosthesis.

In conclusion, our data show that success of penile venous surgery depends on proper patient selection; routine CC-EMG contributes significant predictive information in patients with erectile dysfunction and venous leakage. The combination of CGRP and PGE_1, as well as other possible substances or combinations of substances, may prove to be a valuable option in highly selected patients. Due to the experimental nature of new drug regimen, patients should be followed closely.

References

1 Juenemann KP, Lue TF, Fournier GR, Tanagho EA: Hemodynamics of papaverine and phentolamine-induced erections. J Urol 1986; 136:158–161.

2 Lue TF, Takamura T, Kuraiya M, Schmidt RA, Tanagho EA: Hemodynamics of canine corpora cavernosa during erection. Urology 1984;24:347–352.

3 Fournier GR, Juenemann KP, Lue TF, Tanagho EA: Mechanisms of venous occlusion during canine penile erection. J Urol 1987;137: 163–167.

4 Krane RJ, Goldstein I, Saenz de Tejada I: Impotence. N Eng J Med 1989;321:1648–1659.

5 Lerner SE, Melman A, Christ GJ: A review of erectile dysfunction: New insights and more questions. J Urol 1993;149:1246–1255.

6 Lue TF, Hricak H, Schmidt RA, Tanagho EA: Functional evaluation of penile veins by cavernosometry in papaverine-induced erection. J Urol 1986;135:479–482.

7 Stief CG, Djamilian M, Schaebsdau F, Truss MC, Schlick RW, Abicht JH, Allhoff EP, Jonas U: Single potential analysis of cavernous electric activity – a possible diagnosis of autonomic impotence? World J Urol 1990;8:75–81.

8 Jünemann KP, Bührle CP, Stief CG: Current trends in corpus cavernosum EMG. Conclusions of the 'First International Workshop on Smooth Muscle EMG Recordings/Leiomyogram', April 15 to 17, 1993 in Mannheim, Germany. Int J Impotence Res 1993;5:97–103.

9 Truss MC, Djamilian MH, Tan H, Stief CG, Jonas U: Single potential analysis of cavernous electrical activity – 4 years experience in more than 500 patients with erectile dysfunction. Eur Urol 1993;24:358–365.

10 Gall H, Bähren W, Scherb W, Stief CG, Thon W: Diagnostic accuracy of Doppler ultrasound technique of the penile arteries in correlation to selective arteriography. Cardiovasc Intervent Radiol 1988;11:225–231.

11 Stief CG, Wetterauer U, Sommerkamp H: Intra - individual study of dynamic and pharmacocavernography. Br J Urol 1989;64:93–97.

12 Kromann-Andersen B, Nielsen KK, Nordling J: Cavernosometry: methodology and reproducibility with and without pharmacological agents in the evaluation of venous impotence. Br J Urol 1991;67:517–521.

13 Vickers MA Jr, Benson C, Dluhy R, Ball RA: The current cavernosometric criteria for corporovenous dysfunction are too strict. J Urol 1992;147:614–617.

14 Djamilian M, Stief CG, Kuczyk M, Jonas U: Follow up results of a combination of CGRP and prostaglandin E_1 in the treatment of erectile dysfunction. J Urol 1993;149:1296–1298.

15 Wespes E, Schulman CC: Venous leakage: Surgical treatment of a curable cause of impotence. J Urol 1985;133:796–798.

16 Lewis RW, Puyau FA, Bell DP: Another surgical approach for vasculogenic impotence. J Urol 1987;136:1210–1212.

17 Hauri D: A new operative technique in vasculogenic erectile impotence. World J Urol 1986; 4:237–249.

18 Levine FJ, Goldstein I: Reconstructive vascular surgery for impotence; in Jonas U, Thon WF, Stief, CG (eds): Erectile Dysfunction. Berlin, Springer, 1991, pp 240–259.
19 Stief CG: Evaluation of the cavernous occlusive system; in Jonas U, Thon WF, Stief CG (eds): Erectile Dysfunction. Berlin, Springer, 1991, pp 162–170.
20 Brindley GS: Cavernosal alpha-blockade. A new technique for investigating and treating erectile dysfunction. Br J Psychiatry 1983;143: 332–335.
21 Ishii N, Watanabe H, Irisawa C: Intracavernous injection of prostaglandin E_1 for the treatment of erectile impotence. J Urol 1989;141: 323–325.
22 Juenemann KP, Alken P: Pharmacotherapy of erectile dysfunction. Int J Impotence Res 1989; 1:71–94.
23 Stackl W, Hasun R, Marberger M: Intracavernous injection of prostaglandin E_1 in impotent men. J Urol 1988;140:66–68.
24 Virag R: Intracavernous injection of papaverine for erectile failure. Letter to the editor. Lancet 1982;ii:938.
25 Zorgniotti AW, Lefleur RS: Auto-injection of the corpus cavernosusm with a vasoactive drug combination for vasculogenic impotence. J Urol 1985;133:39–41.
26 Montorsi F, Guazzoni G, Bergamaschi F, Ferini-Strambi L, Barbieri L, Rigatti P: Four-drug therapy for impotence due to corporeal veno-occlusive dysfunction. J Urol 1993;149:1291–1299.
27 Stief CG, Benard F, Bosch R, Aboseif S, Lue TF, Tanagho EA: A possible role for calcitonin-gene related peptide in the regulation of the smooth muscle tone of the bladder and penis. J Urol 1990;143:392–397.
28 Stief CG, Wetterauer U, Schaebsdau F, Jonas U: Calcitonin gene-related peptide: A possible role in human penile erection and its therapeutical application in impotent patients. J Urol 1991;146:1010–1014.
29 Raud J, Lundeberg T, Brodda-Janson G, Theodorsson E, Hedquist P: Potent anti-inflammatory action of calcitonin gene-related peptide. Biochem Biophys Res Commun 1991;180: 1429–1435.
30 Nelson MT, Huang Y, Brayden JE, Hescheler J, Standen NB: Arterial dilations in response to calcitonin gen-related peptide involve activation of K+ channels. Nature 1990;244:770–773.
31 Thiebaud D, Akatsu T, Yamashita T, Suda T, Noda T, Martin RE, Fletcher AE, Martin TJ: Structure-activity relationships in calcitonin gen-related peptide: Cyclic AMP response in a preosteoblast cell line (KS-4). J Bone Miner Res 1991;6:1137–1142.
32 Stief CG, Holmquist F, Djamilian M, Krah H, Andersson KE, Jonas U.: Preliminary results with the nitric oxide donor linsidomin chlorhydrate in the treatment of human erectile dysfunction. J Urol 1992;148:1437–1440.
33 Truss MC, Djamilian M, Kuczyk M, Stief CG, Jonas U: Follow up results of the nitric oxide donor linsidomine chlorhydrate in the diagnosis and treatment of erectile dysfunction. Accepted presentation. Annu Meet Am Urol Assoc, San Francisco, May 15–19, 1994.