

Andrology

Peyronie's disease continues to be a fascinating topic for urologists, and two papers in this section, one from Rome and one from Los Angeles, describe new insights into this disease.

Authors from the UK write about the current practice of vasectomy reversal and the management of unobstructive azoospermia in a region of that country. Although this is a questionnaire-based survey, a 74% response rate justifies the authors' conclusions and their comments, which will be of value to the reader.

Transdermal electromotive administration of verapamil and dexamethasone for Peyronie's disease

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Accepted for publication 14 February 2003

OBJECTIVE

To evaluate the effects of the transdermal electromotive administration of verapamil and dexamethasone on plaque size, penile deviation, pain, erectile function and capacity for vaginal penetration in patients with Peyronie's disease.

PATIENTS AND METHODS

Forty-nine patients were treated four times weekly for six consecutive weeks. During each session the drug mixture was administered from a receptacle fixed to the skin overlying the plaques, using 2.4 mA pulsed current for 20 min. Plaque size and penile deviation were evaluated by dynamic penile duplex ultrasonography, X-ray and photographs; pain, erectile function and capacity for vaginal penetration were assessed using a questionnaire. Vital signs and side-effects were recorded. Differences before and after treatment were assessed.

RESULTS

The plaque disappeared in 8% of patients, with a measurable reduction in volume in 74% and no change in 18% ($P < 0.001$). Penile deviation resolved in 10% of the men, decreased in 74% and remained unchanged in 16% ($P < 0.001$). The plaque volume was

halved in two-thirds of the men, to a mean (SD) of 515 (301) mm³, and the penile deviation halved in 45% of patients, to 24 (5)°; pain was completely eliminated in 88% ($P < 0.001$). Erectile function was completely restored in 42% of patients with initial erectile dysfunction and improved in 17% ($P < 0.001$); vaginal penetration improved in 73%. No toxicity was noted, except for a transient skin erythema at the site of the penile and dispersive electrodes.

CONCLUSION

The transdermal electromotive administration of verapamil and dexamethasone is clinically safe and appears to be an effective treatment in patients with Peyronie's disease.

KEYWORDS

Peyronie's disease, dexamethasone, verapamil, electric current

INTRODUCTION

Peyronie's disease is characterized by localized inflammation with subsequent plaque and eventual scarring involving the tunica albuginea [1]. The result is bending and deformity of the erect penis, development of pain in the penis, difficulty in vaginal

penetration, changes in erectile capacity and/or erectile dysfunction (ED) [2]. While severe penile deformity and ED are best treated with surgery, several conservative treatment options have been used to resolve pain, minimize penile deformity and arrest the progression of the disease [3,4], but the lack of placebo-controlled, randomized studies makes evaluation difficult. Also, there are systemic and local side-effects with oral therapy and intraplaque injection [3,4].

Absorption through the skin is an important alternative or adjunct to traditional methods of drug delivery. In patients with Peyronie's disease transdermal iontophoretic administration of steroids [5–7] or orgotein [8,9] has shown promising results without the side-effects associated with oral or intraplaque injection therapies. Two clinical studies using different methods showed that transdermal electromotive administration (TEA) of verapamil and dexamethasone, with or without lidocaine, was beneficial in patients with Peyronie's disease [10,11]. Two electrokinetic forces form the basis of this treatment; (i) iontophoresis, which repels positively charged verapamil ions, and (ii) electro-osmosis or solvent drag of dexamethasone (phosphate) against its coulombic gradient [12], with acceleration of both drugs into underlying tissues. Recently it was reported that TEA of verapamil into the tunica albuginea provides measurable drug levels in plaque tissue [13].

In an effort to define the benefits and limitations of TEA we used it to deliver verapamil and dexamethasone in a carefully selected and motivated group of patients with Peyronie's disease. Objective and subjective measurements of plaque size, plaque stage (fibrous or calcified), penile deviation, pain, erectile capacity and difficulty with intercourse were used to investigate the effects of a standardized TEA regimen and to identify factors that may predict treatment outcome.

PATIENTS AND METHODS

Forty-nine patients attending an outpatient urology clinic were enrolled. After institutional ethics committee approval, all patients were informed about the scientific nature of the study and gave written consent. Inclusion criteria were clinical evidence of Peyronie's disease (plaque, deformity of the

penis and pain on erection, or nonspecific genital pain) and the discontinuation of any previous relevant treatment for at least 6 months. Exclusion criteria were: (i) a history of recent treatment with calcium-channel blockers or dexamethasone; (ii) therapies interfering with calcium-channel blockers or dexamethasone; (iii) ED of causes other than Peyronie's disease on sexological, psychological, vascular, hormonal, and neurological evaluation. A history of penile trauma before the development of disease, and previous treatments and the time of onset of symptoms were recorded.

The treatment plan included four sessions a week for 6 consecutive weeks; during each session with the patient supine, a 5-mL plastic self-adhesive receptacle containing a silver electrode (CT-DAS 500 Ag, Physion srl, Medolla, Italy) was fixed to the penile skin overlying the plaque. The receptacle was filled with a solution of 8 mg dexamethasone and 5 mg verapamil diluted to 5 mL with water. There were no difficulties in applying the receptacle. The anode of the current generator (Physionizer 30, Physion srl, Medolla, Italy) was connected to the receptacle and the cathode to a skin electrode which was placed on to the lower abdomen. Pulsed direct current of 2.4 mA at 2500 Hz was applied for 20 min. Blood pressure and heart rate were monitored throughout the procedure and after each therapy session. The incidence of systemic, local, acute or chronic toxicity was recorded.

The reliability of objective measurements of plaque size and penile deviation, and subjective score scales of the questionnaire, were determined using a test-retest pilot study. In a random sample, 15 men with Peyronie's disease were identified who met the eligibility criteria. Each patient was evaluated by a physical examination, photographs, duplex ultrasonography (DU) and plain X-ray of the penis at a maximum pharmacologically induced erection, and were given the questionnaire. Two weeks after the first evaluation the same objective measures were repeated and an identical questionnaire administered. Eleven patients returned the first questionnaire and 10 returned both. The test-retest reliability of the objective measures and the questionnaire were 91% and 89%, respectively. The methods of objective measurement and the questionnaire were refined after reviewing the comments from patients and physicians.

Patients were assessed clinically and the objective variables measured before and 4 weeks after the end of treatment. Plaque and penile deviation were evaluated by physical examination, photographs, DU and a plain X-ray of the penis on full pharmacologically induced erection. The subjective symptoms (pain, erectile function and capacity of vaginal penetration related to penile deviation) were evaluated by the questionnaire, which was completed and returned to the interviewer.

For DU a 7.5 MHz transducer was used with the penis fully erect, after an intracavernosal injection with 20 µg of prostaglandin-E1. The stage of the plaque, fibrous or calcified, was evaluated by DU and X-ray, with plaque length measured using callipers and from DU, and volume estimated by multiplying the plaque length, width and depth. Penile deviation and the location of the angle were assessed by photography of the penis when fully erect in three planes, following previous criteria [14].

The final plaque volume and penile deviation after therapy were assigned to one of four categories, i.e. unchanged, improved by less than half, improved by more than half, and 'disappeared'. Pain was assessed using a four-step ordinal descriptive scale (none, mild, moderate, severe).

Patients were asked to rate their erectile function during sexual intercourse on a four-step scale (no tumescence, partial tumescence, full tumescence but insufficient rigidity, full rigidity). Erectile function was also evaluated objectively by the intracavernosal injection during DU of the penis. Vaginal penetration related to penile deviation was defined as impossible, difficult, or possible.

Univariate differences both in continuous (plaque size and penile deviation) and ordinal data (pain, erectile function and vaginal penetration) measured before and after treatment were assessed using the paired Wilcoxon signed-rank test. Summary results for continuous data are presented as the median (interquartile range, IQR), as the data distribution was skewed. To evaluate the effect of disease severity before TEA (plaque volume, stage, penile deviation, age, duration of disease, traumatic aetiology and pain at rest) on the four-step ordinal outcome scale, Fisher's exact test for contingency tables was

Median (IQR)	Before	After	P*	TABLE 1 Descriptive statistics before and after therapy
Plaque:				
Length, mm	13.5 (9.6)	8.9 (9)	< 0.001	
Width, mm	12.5 (5)	7.7 (5.2)	< 0.001	
Depth, mm	3.8 (1.5)	2.2 (2.3)	< 0.001	
Volume, mm ³	705.2 (628.1)	130.5 (428.1)	< 0.001	
Penile deviation, °	33 (10)	16 (14)	< 0.001	
Number:				
Pain				
None	0	43		
Mild	15	4	< 0.001	
Moderate	34	2		
Erectile function:				
Full rigidity	8	25		
Full tumescence/ partial rigidity	30	20	< 0.001	
Partial tumescence	11	4		
Vaginal penetration:				
Possible	9	36		
Impaired	29	8	< 0.001	*Wilcoxon paired signed rank test.
Not possible	11	5		

After TEA the pain was completely eliminated in 88% of patients, improved in 8% and remained unchanged in 4% (Table 1).

Before TEA, 41 patients (84%) described having ED (Table 1); afterward erectile function was completely restored in 17 (42%), relatively improved in seven (17%) and remained unchanged in 17 (42%). Before TEA, 40 patients (82%) reported impossible or difficult vaginal penetration (Table 1); afterward 27 (68%) reported possible penetration, two (5%) improved from impossible to difficult and 11 (28%) remained unchanged.

No patients had a decrease in blood pressure or related cardiac effects, and no systemic, local, acute or chronic toxicity was detected, except for a transient skin erythema at the site of the penile and abdominal electrodes.

used, both for plaque volume and penile deviation outcomes. For simplicity the data for plaque volume and penile deviation before treatment were dichotomized (≤ 1000 vs > 1000 mm³ and $\leq 35^\circ$ vs $> 35^\circ$, respectively) and age and duration of disease were respectively classed as < 50 , 50–60, > 60 years and < 6 , 6–12, 12–24, > 24 months, and finally, stage, traumatic aetiology as well as pain at rest were considered as dichotomous (fibrous vs calcified, yes/no, yes/no); significance was indicated as $P < 0.05$.

RESULTS

The median (range) age of the patients was 58 (29–68) years; seven (14%) recalled penile trauma during intercourse before developing the disease. Twenty-five patients (51%) had been treated unsuccessfully with oral vitamin E and/or intralesional injection of betamethasone (17) or orgotein (four), or local laser therapy (four). The mean duration of disease before the start of the study was 17.5 (3–72) months. All enrolled patients completed the treatment programme and underwent 1176 therapy sessions.

Plaques were predominantly dorsal in 32 patients (65%), left- or right-sided in 17 (35%), fibrous in 30 (61%) and calcified in 19 (39%). The median (IQR) plaque dimensions

before and after therapy are shown in Table 1. After treatment the plaque totally disappeared in four patients (8%), reduced by less than half in 29 (59%) and by more than half in seven (14%); the plaque remained unchanged in nine (18%). From the univariate analysis (Table 2) the reduction was greater in small plaques that were not calcific or traumatic, and with no pain at rest. The initial penile curvature, age, or duration of disease did not affect the reduction in plaque volume.

Before therapy penile curvature was ventral in four patients (8%), dorsal in 22 (45%) and lateral in 23 (47%). The median (IQR) penile deviations before and after therapy are also shown in Table 1. The penis became completely straight in five patients (10%). The deviation after TEA improved by more than half in 17 patients (35%) and by less than half in 19 (39%), with no change in eight (16%). From the univariate analysis (Table 2) there was a greater reduction in small, uncalcified lesions causing less initial deviation. Age, duration of disease, traumatic aetiology and the presence of pain at rest had no effect on the reduction in deviation.

Both general genital pain and pain on erection was present initially in 13 (27%) and 36 (74%) of the patients, respectively; there was relief on TEA with verapamil and dexamethasone from the start of therapy.

DISCUSSION

In this phase-2 study the therapeutic efficacy of TEA of verapamil and corticosteroid was assessed in Peyronie's disease. The results suggest that the treatment is effective, well tolerated and better for smaller, uncalcified plaques. Peyronie's disease frequently develops in response to acute or repetitive trauma to the erect penis, with microvascular injury and fibrin deposits, leading to the recruitment and activation of inflammatory cells, followed by matrix formation and the development of a fibrotic plaque [15]. The efficacy of combined verapamil and dexamethasone can be explained in two ways. As Peyronie's disease is associated with inflammation-dependent pathology, anti-inflammatory approaches may be beneficial. Indeed, corticosteroids were among the first drugs injected into plaque to reduce the fibrous tissue and related symptoms [3,4]. The use of verapamil was based on its ability to alter fibroblastic production of extracellular matrix macromolecules and collagenase [16–18]. Both of these functions are involved in scar-tissue formation and remodelling, which are known to be mediated by intracellular calcium levels. Intraplaque injection with verapamil appears to be effective in reducing pain and penile deviation, and can contribute to subjective improvement in sexual function and erectile capacity [19].

In recent years markedly more patients with Peyronie's disease have been referred to

TABLE 2 The four-step ordinal outcome scale for plaque volume and penile deviation with initial status, by univariate analysis

Initial class (n)	Plaque volume				P*	Penile deviation				P*
	No change	< 50%	> 50%	Disappeared		No change	< 50%	> 50%	Disappeared	
Plaque volume, mm ³										
≤ 1000 (35)	2	4	25	4		1	14	15	5	
> 1000 mm ³ (14)	7	3	4	0	0.001	7	5	2	0	0.001
Penile deviation, °										
≤ 35 (26)	5	3	14	4		4	12	5	5	
> 35 (23)	4	4	15	0	0.282	4	7	12	0	0.027
Plaque stage										
Fibrous (30)	2	2	22	4		1	8	16	5	
Calcific (19)	7	5	7	0	0.002	7	11	1	0	< 0.001
Age classes, years										
< 50 (7)	1	2	2	2		1	2	2	2	
50–60 (24)	3	3	16	2		2	10	9	3	
> 60 (18)	5	2	11	0	0.165	5	7	6	0	0.310
Disease duration, months										
< 6 (13)	2	2	8	1		1	4	6	2	
6–12 (15)	2	1	9	3		2	5	5	3	
12–24 (9)	2	2	5	0		2	4	3	0	
> 24 (12)	3	2	7	0	0.867	3	6	3	0	0.733
Aetiology										
Traumatic (7)	1	2	2	2		1	2	2	2	
Not traumatic (42)	8	5	27	2	0.040	7	17	15	3	0.410
Pain at rest										
Yes (13)	4	4	4	1		4	5	3	1	
No (36)	5	3	25	3	0.045	4	14	14	4	0.438

*Fisher's exact test. > or < 50%, improvement by more than or less than half.

urologists, probably caused by an increasing incidence combined with decreasing reticence by the patients [20]. Therefore, the wide variety of treatments available for an ill-understood disease that waxes, wanes and occasionally resolves, is now subject to more critical scrutiny. Oral therapy with numerous drugs has provided inconsistent therapeutic benefits [3,4] and consistent side-effects with all except vitamin E. Intraplaque injections ameliorate the symptoms [3,4] but are painful and it is almost impossible to achieve an even drug distribution by injecting into the hardened tissue of a plaque. Technically correct and meticulous surgery gives good results but most procedures are surprisingly extensive, with prolonged time to full healing, subject to the usual side-effects of all surgery and, if the disease recurs, an expensive wasted effort.

Dexamethasone and verapamil were used in all TEA because applying electric current to solubilized drugs significantly increases the transport rates [21]. Furthermore, this method of localized drug administration has some

distinct advantages; it is painless, gives an even distribution throughout the plaque, has no risk of infection and a minimal risk of systemic side-effects from the drugs. There is always a risk of thermal damage to the skin, although this did not happen in the present patients.

An important concern raised by this uncontrolled study is the true efficacy of TEA; can the results be explained by spontaneous remission of the disease? We regard this as most unlikely; what reports there are on the natural history of Peyronie's disease indicate that spontaneous improvement rates vary from 7% [22] to an enthusiastic 29% (in 12 patients) [23], and far less than that achieved in the present series.

Finally, there are two issues of considerable practical importance. The incidence of severe, or even distressing, side-effects caused by electromotive drug administration is very low (none in the present series). Second, pain relief is almost universal [10] and is usually achieved within the initial three to four

treatment sessions. Patients scheduled for surgery for severe and painful disease obtain relief from the interim three to four sessions, and some reconsider their forthcoming surgery.

In conclusion, TEA of verapamil and dexamethasone is a safe and seemingly effective treatment for Peyronie's disease, reducing plaque volume, penile deviation and pain, and can contribute to the subjective improvement in erectile capacity and sexual function. These findings need to be confirmed in a phase-3 study using a placebo-controlled, randomized and stratified design. We are now assessing the tissue penetration of verapamil and dexamethasone, and the mechanism of action of TEA, together with the optimum dosage and duration of treatment.

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Abbreviations: TEA, transdermal electromotive administration; DU, duplex ultrasonography; ED, erectile dysfunction.