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Penile fibrosis in intracavernosal prostaglandin E1 injection therapy for erectile dysfunction

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Penile fibrosis (PF) may be a complication of intracavernosal injection therapy (ICI). It has been well documented as a side effect of papaverine, but there have been few reports associating penile fibrosis with prostaglandin E1 (PGE1, Alprostadil). Many authors did not find fibrotic changes in the penis while others reported penile fibrosis as a complication of intracavernosal PGE1 in only 0.76–2.1% of their patients. Recent studies, however, suggest that the incidence may be as high as 15%.

Three hundred consecutive patients who returned to our Institute for repeat prescription of PGE1 were asked about penile curvature and deformity and the penis was examined for fibrotic change. Twenty-two were excluded because of concurrent or previous use of papaverine and/or phentolamine, 30 patients had pre-ICI evidence of fibrotic change and 3 had incomplete data. Of the remaining 245 patients, 57 (23.3%) were found to have penile fibrosis. These men, mean age 62 y (21–79), had been self injecting an average of 5.2 times per month (1–16) for an average period of 29.2 months (2–86). The mean dose of PGE1 used was 13 μg (2–60) and an average of 65.6 μg of PGE1 (3–360) was used per month. The mean total number of injections was 142.4 (8–810) and the mean total amount of PGE1 1703 μg (105–11520).

Penile fibrosis is hence a significant complication of intracavernosal PGE1 therapy. It is mandatory to examine patients methodically for fibrotic changes in the penis prior to commencement of treatment and at subsequent regular reviews. Patients should be specifically warned of the possibility of penile fibrosis and should be instructed on self examination so that they may report early changes if and when these occur.

Keywords: penile fibrosis; intracavernosal injection; prostaglandin E1

Introduction

Penile fibrosis (PF) refers to fibrotic changes in the subcutaneous tissues, the tunica albuginea or intracavernosal sinusoids of the penis. The first popular description of penile fibrosis is generally attributed to Peyronie in 1743, although the condition was recognized as early as 1561 by Fallopius and Vasalius.[1,2]

There were apparently no reported cases of penile fibrosis as a complication of intracavernosal injection therapy (ICI)[2,3] until in 1987 when Hu *et al*[2] described penile curvature and fibrosis in three patients receiving treatment with papaverine and phentolamine. Since then fibrotic complications of papaverine have become well recognized and documented and the prevalence has been reported to be as high as 57%.[4–6]

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Prostaglandin E1 (PGE1) then became the vasoactive agent of choice for intracavernosal injection therapy because it was found to be more efficacious and because the risk of priapism and penile fibrosis was reported to be much lower.[7–10] Amar *et al*,[9] Arielly *et al*[10] and Nisen[11] in fact reported that there was no fibrosis of cavernosal tissues or scar formation in their patients treated with PGE1. Porst[12] in 1989 found penile fibrosis and deviation in only 4 (2.1%) of his patients who received PGE1 injections. Other authors reported incidences ranging from 0.76–2%.[8,13–15] In the Schwartz Pharma Scientific Product Information on Virilan (Alprostadil),[16] the incidence of penile fibrosis and of penile deviation was each listed as 0.05%, based on pooled data from 44 studies involving 6145 patients. Yet, in the Product Information on Caverject (Alprostadil) dated 17 March 1995,[17] Upjohn Pty. Ltd. warned of a frequency rate of 4.8% of penile fibrosis. Lakin *et al*[18] reported an even higher rate of 9% in patients after one year of self-injection therapy with PGE1. In a prospective study, Porst[19] found penile indura-

tions in 11.5% of his patients using PGE1, and Chen *et al*[20] reported an incidence of 15% in 68 of their patients without previous PF.

Patients and methods

Our study was undertaken to assess the frequency of fibrotic changes in the penis in patients receiving intracavernosal PGE1 for erectile dysfunction (ED). Between June 1995 and March 1996, 300 consecutive patients who returned to our Clinic for a further supply of PGE1 were each given a questionnaire and were asked to record the quality and duration of their erectile response and any adverse symptoms related to their use of PGE1 by self-injection. These patients were interviewed and a specific inquiry was made regarding penile curvature, deviation, deformity and any form of swelling in the penis. An examination of the external genitalia was performed and the patients were instructed on the technique of self-examination.

Statistical method

The proportion of men with hypertension and diabetes among patients with and without PF was analyzed using Chi-square test. Unpaired *t*-test was used to assess the significance of the difference between patients with or without PF for each of the measured variables, when the data was normally distributed. In the comparison of the total amount and total injections used by patients, with or without PF, the Wilcoxon Scores (Rank Sums) Test was used. The relationships between the percentage of patients with PF and age, total amount of PGE1 and total number of injections were analyzed using linear regression analyses.

Results

Of the 300 consecutive patients in the study, 55 were excluded from analysis. Of these, 22 had concurrent or previous use of papaverine and/or phentolamine. Thirty had PF detected prior to commencement of ICI therapy and 3 had incomplete data. PF was detected in 57 of the remaining 245 patients (23.3%). Fibrotic changes were found mostly in the dorsal part of the penile shaft (51/57). Thirteen of these men with PF had penile curvature and 14 had experienced pain with ICI. Penile ultrasound was performed on 28 patients. No echogenically evident fibrosis was detected in 12. Fibrotic change was reported in 16 with extensive fibrosis in 2 and calcification in 2 patients.

There were 17 men with hypertension and 7 with diabetes among the patients with PF. In the group without PF, 39 had hypertension and 14 had diabetes mellitus ($P > 0.1$ and > 0.2 respectively).

These men with PF, mean age 62 y (21–79), had been self-injecting an average of 5.2 times per month (1–16) for an average period of 29.2 months (2–86). The mean dose of PGE1 used was 13 μg (2–60) and an average of 65.6 μg of PGE1 (3–360) was used per month. The mean total number of injections used was 142.4 (8–810) and the mean total dose of PGE1 1703 μg (105–11520).

These findings were compared with those in patients who did not show clinical evidence of PF (Table 1). Although the duration of treatment, the dose of PGE1 per injection, the number of injections and the amount of PGE1 used per month were not statistically significantly different between the two groups, the total amount of PGE1 ($P = 0.0062$) and the total number of injections ($P = 0.0032$) over the whole treatment period were statistically significantly different. In addition there was a linear relationship ($P = 0.039$) between total amount of PGE1 used and the percentage of patients with PF (Figure 1). Age also appeared to be a significant factor ($P < 0.0176$) and, as in the case of total amount of PGE1 used, showed a linear relationship with the presence of PF, ($P = 0.047$) (Figure 2). No significant linear relationship was found between the total number of injections and the presence of PF.

Discussion

Whereas previously penile fibrosis was well recognized as a side effect of papaverine and PGE1 was thought to be rarely associated with this complication, the incidence of fibrotic changes in intracavernosal PGE1 therapy is now shown to be significant.

Chen *et al*,[20] in their review of 92 patients for penile scarring, reported that there was no significant difference in terms of the number of injections, injection frequency, dose per injection or total dose of PGE1. Our study showed that age, total number of injections and total amount of PGE1 are significantly different between the group of patients who developed PF and the group who did not.

Aboseif *et al*[21] found in their analysis of histological changes associated with intracavernosal injections of papaverine and PGE1 that, in contrast to papaverine, PGE1 led to very few changes without any complications or clinical evidence of fibrosis. The procedure of injection itself was found to produce mild inflammatory changes in the superficial dermis, deep dermis and the corpus cavernosum.[22] Virag *et al*,[23] in their attempt to evaluate the albugineal wall thickness (AWT), found that intracavernosal injection resulted in an increase of

Table 1 Comparison of treatment parameters in patients with and without penile fibrosis

	Patients with PF $n=57$	*Patients without PF* $n=188$	*Statistical significance*
Age (y)			
Range	21–79	26–83	$P=0.0176$
Mean	62.0	58.2	
Duration of treatment (months)			
Range	2–86	0.5–84	ns
Mean	29.2	24.6	
Dose of PGE1 per injection (μg)			
Range	2–60	0.5–50	ns
Mean	13.0	12.7	
No. of injections per month			
Range	1–16	0.3–18	ns
Mean	5.2	4.7	
Amount of PGE1 used per month (μg)			
Range	3–360	0.5–350	ns
Mean	65.6	57.5	
Total amount of PGE1 used over whole treatment period (μg)			
Range	105–11520	9–12100	$P=0.0062$
Mean	1703	1152	
Total no. of injections over whole treatment period			
Range	8–810	2–568	$P=0.0032$
Mean	142.4	99.6	

(ns—non-significant).

10.53–15.38% of AWT in various parts of the corpus cavernosum.

PF is probably not purely the result of trauma from repeated injections because, as observed by Chen *et al*,[20] PF in our patients occurred at locations where needles had not been inserted. The vast majority of our patients (51 out of 57) had PF along the dorsal aspect of the penile shaft. The fact that the total number of injections and total amount of PGE1 used over the whole treatment period were statistically significant factors appear to indicate a cumulative influence of PGE1 in the development of PF.

It is possible that PF commences as a vasculitis in the subtunical tissues[24] and continues as a chronic inflammation leading to perivascular fibrosis, dense plaque formation and sometimes calcification.[25,26] There may also be genetic predisposition to either a fibrotic tendency or an aberrant fibrotic reaction to injury or irritation.

The natural history of PF requires further elucidation. In a study reported by Linet and Ogrinc[27] involving 683 men receiving intracavernosal PGE1 over a period of 18 months for ED, 51 men (7.5%) developed PF. Fifteen of these men continued in the study despite the fibrotic changes and in 9 of them (60%) the fibrosis completely resolved. Porst[28] also

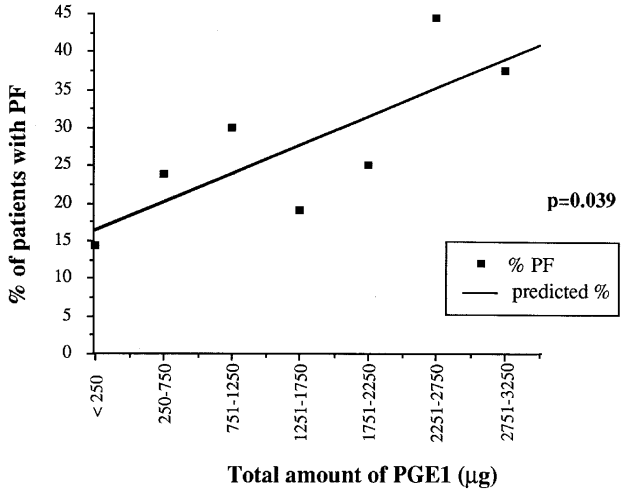

Figure 1 Total amount of PGE1 and PF-linear regression analysis. (Total amount of PGE1 > 3250 not included because of small numbers.)

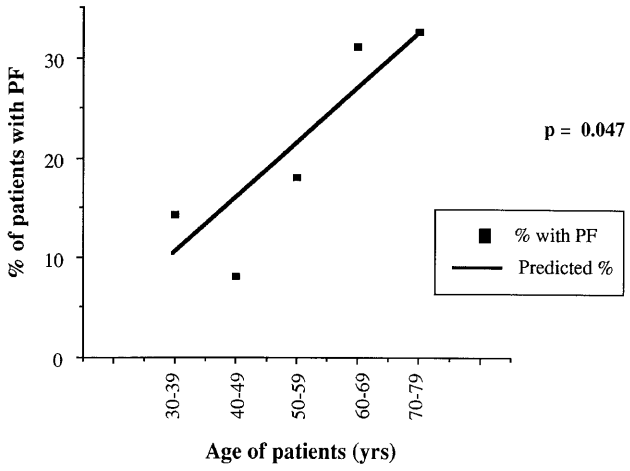

Figure 2 Age and prevalence of PF-linear regression analysis. (Ages 20–29 and 80–89 not included because of small numbers.)

reported the disappearance within three years of fibrotic changes in 9 of the 18 patients (50%) who developed PF in the course of ICI therapy with PGE1.

PF in impotent men is probably much more common than is generally recognized. Amin *et al*[29] found plaques, constriction and deformity of the penis in 55 of their 280 patients being assessed for erectile dysfunction (19.6%). This compares with the prevalence of 0.39% of Peyronie's disease in the general population.[30] Thirty of our 300 patients (10%) had fibrotic changes in the penis prior to intracavernosal injection therapy. It is important that the penis be examined methodically and any fibrotic changes carefully documented before therapy is initiated. This may be complemented by ultrasound examination of the penis. However we have not found penile ultrasound a sensitive way of diagnosing or confirming PF, nor an accurate way of assessing the extent and severity of fibrotic changes, as ultrasonographic evidence was positive in only 16 of our 28 patients with clinically evident PF (57%). Similarly Fedel *et al*[31] reported that ultrasound revealed evidence of morphological changes in only 59% of the palpable indurations. Lopez and Jarow[32] also remarked, in their study of Peyronie's Disease with duplex ultrasound, that ultrasonography was not as sensitive as palpation in identifying Peyronie's plaques.

From the medico-legal standpoint, patients must be specifically warned of risk of penile fibrosis. Where written informed consent form part of the protocol of an injection therapy programme, the possibility of penile fibrosis should be included in the patient information. There is no substitute for regular meticulous surveillance examination and patients need to be instructed on self-examination of their penis so that they may become aware of early fibrotic changes if and when these changes should occur.

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Editorial comment

Penile fibrosis in intracavernosal prostaglandin E1 injection therapy for erectile dysfunction — by K-K Chew *et al*

It is more than 10 years ago when Zorgniotti and Lefleur published the first time their experiences with self-injection therapy with the mixture of papaverine and phentolamine in a representative number of patients.[1] After some years of world-wide enthusiasm about this revolutionary new therapy in impotence papers on side-effects in self-injection therapy piled up with reports on priapisms and local penile alterations like nodules, indurations or curvatures. Not least by animal studies it seemed to be proven, that these local fibrotic changes were attributable to the toxic effects of papaverine[2,3,4] and so all the efforts aimed at a reduction of the dosage of papaverine. Nevertheless in some series the reported local fibrotic changes varied between 18% and 57%[5–7] revealing the necessity for the search for better tolerated vasoactive drugs. The use of prostaglandin E1 in the late eighties was associated with a reduction of priapisms below the 1% barrier as well as a considerably lower rate of local fibrotic changes in numerous publications. It was the merit of two comprehensive prospective multicenter clinical trials, launched by the pharmaceutical companies of Schwarz Pharma and Upjohn-Pharmacia and conducted according to the good clinical practice guidelines, to gain better insight into the side-effects on long-term follow-up with PGE1.

In the former clinical trial of Schwarz Pharma, which was conducted in eight European centers, the total rate of local fibrotic changes which occured during 3 y was 11.1% in 162 patients enrolled into the study, but half of these fibrotic alterations disappeared in the further course due to temporary discontinuation of self-injection therapy or improvement of the individual injection technique. Therefore a total of 5.6% of all enrolled patients showed local fibrotic changes after 3 y of follow-up.

In the latter European multicenter study of Upjohn-Pharmacia after 18 months of follow-up 7.5% of 683 involved patients developped local fibrotic changes.[8] Therefore in view of the abovementioned two prospective studies, as well as of the here presented retrospective study local fibrotic changes in the penile tissue have to be expected in 5–10% after intracavernous use of PGE1 for more than 2–3 years.

Although papaverine as well as the mixture of papaverine and phentolamine were considerably longer in use for self-injection therapy no single prospective GCP-Study of the long-term use of these drugs is available in the world-wide literature. And, in addition, nearly all of the reported retrospective studies are not considering long-term use of more than 2–3 y as well as the average number of the injections per patient.[9] Therefore from the scientific point of view, no comparisons between the different drugs are possible with reference to local fibrotic side-effects. With regard to the high local side-effects up to more than 50%, reported in some retrospective studies after papaverine and phentolamine, it must be feared, that local fibrotic changes may be two- or threefold higher than after PGE1, if these drugs would be followed-up in prospective long-term studies.

The authors make an effort to differentiate between drug-related and technique-related fibrotic side effects although it remains unclear on which basis this decision is made. Nevertheless they came to the conclusion, that in six cases the fibrotic changes were related to faulty injection-technique and in seven cases to the drug PGE1 itself.

In the prospective multicenter trial of Schwarz Pharma Company, which was headed by myself, it was obvious, that those patients with a higher rate of unsuccessful injections, not resulting in rigid erections, were at higher risk for development of local fibrotic changes. Both with respect to the present retrospective series of the authors and the cited prospective studies it seems convincingly, that a very thorough introduction into the self-injection technique, which will be indeed a time-consuming undertaking in the single patient, as well as the use of ultrathin needles (27–30 gauge) and permanent alternation of the injection site may provide appropriate precautions for diminuation of local side-effects. Last but not least the comment of the authors on the necessity of written informed consent has once more be emphasized in this context as nothing is more annoying than being involved in a lawsuit

where the patient is claiming, that he was not informed on such possible side-effects of self-injection therapy.

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