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Case Report: Avoidance of Palpable Corporal Fibrosis Due to Priapism with Upregulators of Nitric Oxide

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ABSTRACT

Introduction. Recent evidence suggests that blocking inducible nitric oxide (NO) synthase in the penis may exacerbate fibrotic processes and that application of medications known to increase NO in tissues may prevent fibrosis.

Aim. To report the use of an antifibrotic regimen consisting of medications known to upregulate NO production in two patients with refractory priapism.

Methods. Two patients presented with priapism of greater than 48-hour duration. After corporal aspiration/irrigation and shunting procedures failed, both were prescribed a daily antifibrotic regimen comprising the phosphodiesterase inhibitors pentoxifylline and sildenafil, and the NO precursor, L-arginine.

Results. At 1 year, both patients were found to have supple corpora without evidence of corporal fibrosis.

Conclusions. An antifibrotic regimen consisting of upregulators of NO production may ameliorate the corporal fibrosis associated with recalcitrant priapism. **Rajfer J, Gore JL, Kaufman J, and Gonzalez-Cadavid N. Case report: Avoidance of palpable corporal fibrosis due to priapism with upregulators of nitric oxide. J Sex Med 2006;3:173–176.**

Key Words. Priapism; Oral Vasoactive Agents; Nitric Oxide

Introduction

Priapism, if left unresolved, results in localized ischemia to the corporal tissue that may lead to the development of corporal fibrosis [1]. Pathologically, corporal fibrosis is identified by the loss of corporal smooth muscle cells and an excess of collagen deposition. Clinically, these fibrotic corpora can lead to erectile dysfunction and may make placement of a penile prosthesis a difficult surgical procedure.

Biochemically, the processes involved in the development of fibrosis in any tissue involve mitochondrial dysfunction, impaired adenosine triphosphate (ATP) synthesis, and the development of reactive oxygen species (ROS) that ultimately lead, via lipid peroxidation and DNA damage, to cellular apoptosis and replacement of the cells by collagen [2]. One consistent feature of tissues undergoing oxidation and cell death is the presence of inflammatory cells expressing nitric oxide (NO) [3]. It was always assumed that NO expressed by these inflammatory cells was in someway proapoptotic and profibrotic [3,4]. However, this view has recently been challenged by the demonstration that: (i) blocking inducible nitric oxide synthase (iNOS) in such situations exacerbated the profibrotic process in the tissue; and (ii) upregulators of NO appear to be antifibrotic [5]. In animal models of Peyronie's disease, treatment with L-arginine, pentoxifylline, and sildenafil, all upregulators of NO, seems to attenuate and/or prevent fibrosis [6].

On the basis of these experimental observations and in an attempt to determine whether upregulators of NO could ameliorate fibrosis, we treated two priapism patients who failed both medical and surgical therapy with a combination of these three aforementioned compounds and observed their responses over 1 year of continuous treatment.

Case 1

A 50-year-old male who had taken trazodone for insomnia presented to the emergency room with a 96-hour erection. Attempted irrigation of the corpora with large bore needles and dilute epinephrine was unsuccessful in relieving the priapism. A bilateral corpus spongiosal-corpus cavernosal (CS-CC) shunt was performed after a Winter shunt initially failed. Although detumescence occurred, the corpora remained indurated and woody. At discharge a few days later, the patient was prescribed L-arginine 1 gm PO bid and pentoxifylline 400 mg PO tid. At 2 weeks follow-up, he was started on sildenafil 50 mg nightly, in addition to the L-arginine and pentoxifylline that he was taking daily. Five weeks later, the corpora were minimally indurated, and at 4 and 12 months later, the penis was normal to palpation without any evidence of induration. The patient has had neither spontaneous erections nor any recurrent bouts of priapism.

Case 2

A 55-year-old man presented with priapism of 48-hour duration, refractory to corporal aspiration and irrigation. He had been taking trazodone for insomnia and had no prior history of priapism. Bilateral perineal CS-CC shunts were performed, which failed to resolve the priapism, and the patient was discharged home with a classic semi-rigid postpriapism penis. He was then started on pentoxifylline 400 mg PO tid and L-arginine 1 gm PO bid. At 2 weeks after discharge, sildenafil 25 mg was added nightly, and this was titrated to 50 mg nightly 1 month later. At 6 months, while still on the triple antifibrotic regimen, the entire corporal bodies, both distal and proximal, were completely soft to palpation. The patient continues to have satisfactory intercourse with oral on-demand phosphodiesterase (PDE) type 5 inhibitors. He has had no recurrent bouts of priapism.

Discussion

These two patients, both with long-standing priapism refractory to medical and surgical intervention, demonstrate that it may be possible to intervene in the latter stages of the condition in order to preserve the integrity of the corporal tissue. The use of L-arginine, pentoxifylline, and sildenafil as antifibrotic agents is based on data obtained in animals that showed that penile fibrosis, albeit in an animal model of Peyronie's disease, could be prevented with this regimen [6]. The scientific rationale for using L-arginine, pentoxifylline, and sildenafil relies on their ability to upregulate the effects of NO, specifically from iNOS. L-arginine is the metabolic precursor of NO; pentoxifylline and sildenafil are PDE4 and PDE5 inhibitors, respectively. Pentoxifylline also suppresses tumor necrosis factor alpha, a potent proinflammatory cytokine. Although it may be counter-intuitive to use NO donors and PDE inhibitors, the latter known to be proerectile, in a condition such as priapism, NO has myriad effects on cellular function depending on the tissue and the isoform of NOS that is affected.

iNOS expression is normally restricted to macrophages and Kupfer cells, where it is intimately involved in mollifying cellular inflammation. In the penis, increased iNOS expression may be seen either with an inflammatory reaction, as in cavernositis or Peyronie's disease, or simply with aging, where the tissue becomes relatively fibrotic without any relationship to an inflammatory reaction [7]. The end result of any inflammatory reaction, regardless of the tissue involved, may be fibrosis of the tissue. Although it has always been assumed that the presence of iNOS in tissues other than macrophages and Kupfer cells may represent the innate response of the tissue undergoing inflammation, in experimental studies where NO production from iNOS has been blocked, tissue fibrosis is exacerbated, thereby challenging the formerly held concept that NO from iNOS was a profibrotic mediator [5].

With an inflammatory response, ROS is believed to be the main chemical responsible for the development of fibrosis. Because NO is a known quencher of ROS and iNOS inhibition promotes fibrosis, it was hypothesized that upregulating NO from iNOS may be antifibrotic in its action. Indeed, the oral administration of the NO upregulators L-arginine, pentoxifylline, and sildenafil, when used individually in an experimental model of penile fibrosis, was shown to ameliorate the fibrosis [6]. Further proof of this concept came from Davila et al., who demonstrated a similar outcome when the cDNA for iNOS was injected directly into a penile plaque [8].

The dosages of the three compounds that we used in our two patients were empirically selected to provide a continuous level of NO production

throughout the day. This consisted of 1 gm of L-arginine twice daily, pentoxifylline 400 mg thrice daily, and sildenafil 25–50 mg once daily. Whether these dosages are optimal or whether each compound could be used individually, as shown in our animal studies, rather than in combination, as we have empirically performed, remains to be determined. Neither patient experienced any adverse effects, including prolonged erections, from this triple combination.

Although it seems counter-intuitive to use PDE inhibitors in patients with priapism, studies have shown that the nonerectile properties of these medications may play a constructive role in this condition. In sickle cell anemia, sildenafil reduces the sludging of blood within the corpora through the anticoagulatory effects of NO via its inhibition of platelet aggregation [9]. In three such patients, prompt resolution of the priapistic episode and relief of pain was noted within 1 hour of sildenafil administration [9]. However, caution should be exercised regarding the use of PDE5 inhibitors in this population, as priapism has been induced in men who have taken PDE5 inhibitors for the on-demand treatment of erectile dysfunction [10]. In our two patients with priapism treated with PDE inhibitors daily as part of their antifibrotic regimen, one recovered his erectile function partially, while the other has not. Until biopsies of their corpora can be performed to show otherwise, our two patients described herein appear clinically to have benefited from this antifibrotic therapy, avoiding the development of clinically palpable cavernosal fibrosis that typically occurs in patients with recalcitrant priapism.

Our study has obvious limitations. First, priapism remains a relatively rare condition, and the natural history of refractory priapism is poorly defined. Our experience with the inevitable development of palpably indurated corporal bodies in refractory priapism has been corroborated in prior retrospective investigations [11]. However, it is possible that some patients may have an inexplicable spontaneous resolution of corporal induration. Second, without corporal biopsies, we define corporal induration solely on the basis of physical examination. Both patients were offered biopsies to confirm resolution of corporal fibrosis at 6 months following admission; however, both refused. Finally, although the use of sildenafil is contraindicated in patients with an anatomical abnormality such as corporal fibrosis and in conditions that predispose patients to priapism, the drug has been used to treat certain patients with priapism [9]. Therefore, it is conceivable that the antifibrotic properties of sildenafil and other PDE inhibitors may be utilized in the future to treat conditions for which it is currently contraindicated. However, such a recommendation requires confirmation in clinical trials prior to generalized adoption.

In summary, it appears that the corporal fibrosis that is the ultimate result of prolonged untreated priapism may be attenuated by drugs that upregulate the effects of NO. Although the use of these compounds to treat postpriapistic fibrosis, either individually or in combination, is to be considered investigational at this point, if clinically successful in future randomized, double-blind clinical trials, one may speculate that upregulators of NO may be useful in the management of other conditions characterized by fibrosis.

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Conflict of Interest: None.

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