

Medical Management of Peyronie's Disease

Review

WAYNE J. G. HELLSTROM

From the Department of Urology, Tulane University School of Medicine, New Orleans, Louisiana.

ABSTRACT: Peyronie's disease (PD) is a wound-healing disorder in which a fibrotic plaque forms in the tunica albuginea layer of the penis. It clinically presents as any combination of penile pain, angulation, and erectile dysfunction. Recent studies indicate that PD has a prevalence of 3%–9% in adult men. Although the exact etiology has not been established, PD likely results from a predisposing genetic susceptibility combined with an inciting event such as microtrauma during intercourse. During the initial acute phase (6–18 months), the condition may progress, stabilize, or regress. For this reason authorities recommend a more conservative treatment approach, with a trial of oral and/or intralesional pharmacotherapy, before surgical reconstruction is considered. Oral therapies most commonly employed include tocopherol (vitamin E) and para-aminobenzoate (Potaba), with colchicine, tamoxifen, propoleum, and acetyl-L-carnitine being used less often. There are a limited number of long-term placebo-controlled studies with these oral agents, and for the most part, studies have failed to show a consistent beneficial

effect. Intralesional injection therapy for PD is more commonly used as a first-line therapy. The current standard of care includes injection with interferon- α -2b, verapamil, or collagenase. Interferon- α -2b, in particular, has been documented in a large, multicenter, placebo-controlled study to show significant benefit over placebo in decreasing penile curvature, plaque size, penile pain, and plaque density. However, intralesional interferon is associated with posttreatment flu-like symptoms unless patients are premedicated with a nonsteroid anti-inflammatory agent. Other available therapies that have not consistently shown efficacy in placebo-controlled studies include corticosteroids, orgotein, radiation, and extracorporeal shockwave therapy. Surgery is considered when men with PD do not respond to conservative or medical therapy for approximately 1 year and cannot perform satisfactory sexual intercourse. Ongoing basic research in PD will likely identify future targets for medical exploitation.

Key words: Penis, erectile dysfunction, penile curvature.

J Androl 2009;30:397–405

Peyronie's disease (PD) is a localized connective tissue disorder characterized by changes in the collagen composition that cause abnormal scar formation in the tunica albuginea of the penis. Although the condition was recognized earlier in the medical literature, the eponymous term arose after Francois Gigot de la Peyronie, the personal physician to King Louis XV of France, reported on a series of 3 patients with nodules and curvature of the penis in 1743.

PD has historically been thought to be a rare, insignificant condition. The first description of the natural history of PD (Williams and Thomas, 1970) reported that the disease was one of "gradual resolution." They further stated that none of the 21 patients described in their study experienced a worsening of their condition. This led them to advocate observation and reassurance as

primary therapy. Their study was hindered by a small number of study subjects, inadequate follow-up, and lack of a standardized approach and evaluation of patients with PD. Nevertheless, the results of this study led clinicians to adopt a conservative approach of watchful waiting as standard treatment for PD.

In 1990, a questionnaire-based study (Gelbard et al, 1990) revealed that among 97 patients with PD, only 13% experienced a resolution of their symptoms. They further noted that 40% of respondents perceived that their disease had progressed, and 48% considered that their condition had remained unchanged at follow-up. In addition to disease progression, these authors reported that 77% of patients experienced detrimental psychological consequences as a result of their disease process. Another study (Kadioglu et al, 2001) provided additional support to the idea that PD was a progressive condition in a retrospective review of 307 men with this condition. They reported that spontaneous resolution was a rare occurrence and that 30.2% of those not receiving any treatment experienced substantial deterioration. Additionally, 62.5% of patients found their disorder to be "disabling," and poorer outcomes and symptoms were associated with the presence of coexisting diabetes mellitus, hypertension, or lipid abnormalities. Results from these studies suggested that despite a

This paper is based on a presentation at a Special Symposium on April 12, 2008, "Therapeutic Strategies for Male Sexual and Hormonal Health", associated with the American Society of Andrology Annual Meeting, for which the presenting author received an honorarium.

Dr Hellstrom has nothing to disclose.

Correspondence to: Dr Wayne J. G. Hellstrom, Tulane University School of Medicine, Department of Urology SL-42, 1430 Tulane Ave, New Orleans, LA 70112-2699 (e-mail: whellst@tulane.edu).

Received for publication July 29, 2008; accepted for publication October 30, 2008.

DOI: 10.2164/jandrol.108.006221

general perception that the condition was benign, PD is progressive and can result in significant emotional and psychological consequences in the afflicted.

Current epidemiological estimates of the prevalence of PD range from 3.2%, as described in a 1999 questionnaire study involving 4432 respondents from Cologne, Germany (Schwarzer et al, 2001), to 8.9%, as reported in a 2004 study of 534 men who presented to American urologists for routine prostate screening (Mulhall et al, 2004). Disease onset is commonly associated with preceding trauma and most often occurs in older men (mean age, 53 years; range, 19–83 years), although reports (Mulhall et al, 2006) have documented that the majority of men with PD in their series had no specific recollection of trauma and 10% of patients experienced symptom onset before 40 years of age.

Pathophysiology

Despite PD being recognized by the medical community for >250 years, there has been meager advancement by researchers toward understanding the underlying etiology of PD and providing effective modalities for preventing and curing the condition. PD is commonly perceived to be a disorder of inappropriate wound healing, with its development probably resulting from an underlying genetic predisposition in addition to the presence of an inciting event (Bjekic et al, 2006). As mentioned, microtrauma has been hypothesized to contribute to the initiation of PD.

Evidence for an underlying genetic predisposition towards PD can be found in its association with other collagen diseases such as Dupuytren's disease. One study comparing the gene expression profiles of patients with PD and Dupuytren's found similar alternations in genes responsible for collagen degradation, ossification, and myofibroblast differentiation (Qian et al, 2004).

Clinical Evaluation

No standard clinical assessment of PD has been established to date. Patients presenting with PD typically exhibit any single presentation or a combination of penile plaque, curvature, penile pain, and erectile dysfunction (ED). Plaques are typically located on the dorsal or lateral aspect of the penis, causing an upward or lateral deflection during erection. As many patients are embarrassed by or unaware of the presence of PD, they are unlikely to mention the topic unless specifically questioned about it by a treating physician.

All assessments of PD should begin with a thorough history, gathering information about disease onset and duration, the presence of precipitating trauma, the degree of penile deformity, curvature and erectile rigidity/dysfunction, and the subjective level of sexual

ability. It is also important to understand the degree of emotional and psychological impact that this disease has on the patient's interpersonal relationships, as this may encourage a more thorough and possibly aggressive treatment approach. A more detailed medical and sexual history can often be rapidly obtained through the use of standardized questionnaires, such as the International Index of Erectile Function (IIEF) and the Peyronie's Disease Index (Levine et al, 2003). These may also serve as means for the objective follow-up to measure treatment efficacy over time. Information obtained about a patient's medical history should focus on risk factors associated with ED, such as hypertension, hyperlipidemia, diabetes, or the presence of coronary artery disease.

Physical examination begins with a standard genitourinary evaluation and includes observation for the presence of Dupuytren's contracture or Lederhose scarring (plantar fibromatosis), both of which are associated with an increased incidence of PD. Objective measurements include documentation of the stretched penile length, plaque characteristics, location and size, and the presence or absence of tenderness to palpation.

Laboratory studies do not serve an essential role in the diagnosis or management of PD, but may include serum testosterone, glucose, prostate-specific antigen, and lipid panel according to the clinical presentation (eg, ED). Objective imaging may be obtained via penile duplex Doppler ultrasonography (PDDU) to record penile vascular flow, venous leakage, and erectile response, as well as plaque size and location and presence of calcifications. Penile curvature can be measured by using a standard instrument, such as a protractor, or by using photographs taken from multiple angles. Although vasoactive injections can cause bruising, pain, and prolonged erections, obtaining accurate baseline measurements is valuable. These measurements provide a standard against which progression or regression of the disease can be measured at future visits.

Taking into account the natural history of PD and the results of appropriate clinical evaluation, considerations for appropriate therapy can be made on the basis of the patient's erectile status, the presence of bothersome symptoms such as pain, the patient's motivation for treatment, and the patient's overall psychological status (Levine and Greenfield, 2003). In most patients, the standard of care involves an initial trial of either oral or intralesional therapies during the first 6–12 months of treatment (Kendirici and Hellstrom, 2004). Commonly prescribed oral therapies include tocopherol (vitamin E) and para-aminobenzoate (Potaba), with colchicine, tamoxifen, propoleum, and acetyl-L-carnitine used less frequently. Intralesional therapy involves repeated injections of verapamil, interferon- α -2a or -2b, or

Table 1. Oral therapy: summary of oral and injection pharmacotherapies for Peyronie's disease, focusing on proposed mechanisms and adverse effects

| Drug | Proposed Mechanism of Action | Adverse Effects |
|-----------------------------|---|---|
| Tocopherol (vitamin E) | Antioxidant effect, DNA repair, immune modulation | Nausea, vomiting, diarrhea, fatigue, weakness, blurred vision |
| Para-aminobenzoate (Potaba) | Enhancement of oxygen uptake, GAG secretion and monoamine oxidase activity | Nausea, anorexia, pruritus, anxiety, chills, cold sweats, confusion, difficulty concentrating |
| Colchicine | Reduction in lactic acid production by leukocytes, decreased activity of phagocytes, anti-inflammatory effect | Nausea, vomiting, bone marrow depression (aplastic anemia, agranulocytosis, or thrombocytopenia), peripheral neuritis |
| Tamoxifen | Modulation of TGF β secretion from fibroblasts | Hypercalcemia, peripheral edema, depression, dizziness, headache |
| Propoleum | Unknown | Skin irritation (rash, pruritus, erythema, edema) |
| Acetyl-L-carnitine | Unknown | Nausea, vomiting, diarrhea |

Abbreviations: GAG, glycosaminoglycan; TGF β , transforming growth factor β .

collagenase directly into the penile plaque over 2-week intervals (biweekly) for approximately 6 months. Other available intralesional therapies include corticosteroids and orgotein, which have not shown any efficacy to date.

Oral Pharmacotherapy

Oral pharmacotherapies and their proposed mechanisms and effects are summarized in Table 1.

Tocopherol (Vitamin E)—Tocopherol is a fat-soluble compound that functions as a natural antioxidant to reduce the number of oxygen free radicals produced in energy metabolism. It has also been shown to play a role in DNA repair and in immune modulation (Traber et al, 1999). The widely accepted use of tocopherol in the treatment of PD has been hypothesized to inhibit fibrosis by acting as a scavenger of oxygen free radicals. In vitro studies examining the effect of free radicals on human cavernosal cells have exhibited a direct association with increased collagen production (Ahuja et al, 1999). It is logical to conclude that inhibition of free radicals (ie, with use of tocopherol) should decrease the rate and degree of fibrosis. However, in vivo data have failed to show any benefit in patients with PD to date.

The first reported use of tocopherol was in a 1948 study of 23 patients that found a 91% reduction in plaque size with complete resolution of pain and a 78% decrease in penile curvature (Scardino and Scott, 1949). However, a double-blinded, placebo-controlled, crossover study (Pryor and Farrell, 1983) failed to show similar beneficial effects for tocopherol relative to placebo. In this study, of 40 patients with PD, an improvement in pain was noted among 35% of those receiving tocopherol, but no significant changes were observed in plaque size or penile curvature.

Despite the lack of definitive evidence for tocopherol in the treatment of PD, urologists commonly prescribe this agent at once-daily doses of 400 IU because of its wide availability, low cost, and minimal to absent adverse effects. Additionally, because many patients

with PD experience psychological effects, tocopherol may also serve to provide a psychological placebo benefit to patients wishing to do something (as opposed to nothing) to alter the course of their disease.

Para-aminobenzoate (Potaba)—Para-aminobenzoate (Potaba) is a compound that was introduced in 1959 as a possible therapy for PD after it was shown to decrease collagen production in vitro when added to fibroblast cell cultures (Zarafonitis and Horrax, 1959). Its mechanism of action is hypothesized to involve the enhancement of 3 endogenous antifibrotic properties of tissues: oxygen uptake, glycosaminoglycan (GAG) secretion, and monoamine oxidase activity. Monoamine oxidase is known to break down circulating monoamines that include adrenaline, noradrenaline (epinephrine, norepinephrine), dopamine, and serotonin. Therefore, increased monoamine oxidase activity decreases serotonin, which may play a role in preventing fibrogenesis.

Despite its long history of use, human study data on the efficacy of para-aminobenzoate for PD are limited.

Currently, para-aminobenzoate is considered to be a first-line therapy for PD. Its adverse effect profile is minimal, with nausea and anorexia occurring most frequently. A recent German questionnaire study of 636 urologists treating PD revealed that the majority of their patients (76%) were treated with either para-aminobenzoate (46%) or tocopherol (29%) (Hauck et al, 2005). A recent double-blinded, placebo-controlled PD trial has shown that para-aminobenzoate showed a response rate of 74.3% over placebo 50.0% ($P = .016$) (Weidner et al, 2005). These authors suggested that this oral agent may stabilize the disorder and prevent progression of penile curvature.

Colchicine—Colchicine is a medication that is commonly employed in the treatment of acute attacks of gout. Its exact mechanism of action in PD is unknown but is hypothesized to involve a reduction in lactic acid production by leukocytes (thus leading to decreased uric

acid deposition) and decreased phagocytosis (with resultant anti-inflammatory effects). It is postulated that the anti-inflammatory properties of colchicine may decrease collagen synthesis and up-regulate collagenase activity.

One study (Kadioglu et al, 2000) examined the efficacy of colchicine administered to 60 men with PD presenting in the acute phase of the disease process. Patients had mean disease duration of 5.7 ± 4.3 months at the time of treatment, and results at follow-up (10.7 ± 4.7 months later) showed improvement in penile deformity in 30% of men, no improvement in 48.3%, deterioration in 21.7%, and resolution of pain in 95%. The authors concluded that the best results were observed in patients exhibiting no vascular risk factors or ED, those presenting within 6 months of disease onset, and those with $<30^\circ$ of curvature. Because this study lacked appropriate controls, few conclusions can be drawn from it about the efficacy of colchicine in patients with PD.

To date, there is no general consensus regarding the use of colchicine in the treatment of PD. The efficacy of treatment increases when the drug is given to patients with fewer vascular risk factors, no comorbid ED, and less significant curvature ($<30^\circ$), and those presenting early in their disease process. Colchicine, when administered in a regimen of 0.5 mg 3 times daily, is most commonly associated with adverse gastrointestinal effects (nausea, vomiting, diarrhea), but it is generally considered to be a safe medication for the long term.

Tamoxifen—Tamoxifen is a nonsteroidal estrogen receptor antagonist that is most commonly employed in patients with estrogen receptor-positive breast carcinoma. One proposed mechanism of action in patients PD is modulation of transforming growth factor β secretion from fibroblasts.

Tamoxifen was first used as a potential treatment for PD in a 1992 study that treated 32 patients with PD with tamoxifen 20 mg twice daily over a 3-month period (Ralph et al, 1992). Tamoxifen improved penile pain in 80%, reduced erectile deformity in 35.5%, and was associated with plaque shrinkage ≥ 1 cm in 34.3% of patients. Greater improvement was observed in patients who were in the earlier stages of PD (<4 months) than in those receiving treatment later in the disease process.

However, the efficacy of tamoxifen in PD was called into question by the results of a 25-patient, placebo-controlled study of tamoxifen 20 mg twice daily for 3 months (Teloken et al, 1999). Investigators used penile radiography, ultrasound, and pharmacologically induced erections (using alprostadil [prostaglandin E₁]) to objectively compare baseline status prior to treatment with follow-up 4 months later. No statistically significant differences between tamoxifen and placebo with

respect to decreased penile pain (66.6% vs 75%, respectively), reduction in penile deformity (46.1% vs 41.7%, respectively), or decrease in plaque size (30.7% vs 25%, respectively) were observed. Critics of the study point out that patients with PD would probably have experienced better results had they received tamoxifen treatment earlier in the course of the disease. However, in the absence of more conclusive data demonstrating a beneficial effect of tamoxifen on PD, this drug cannot be recommended for routine treatment in patients with PD.

Propoleum—Information regarding the composition, mechanism of action, and efficacy of propoleum is limited, because the substance is patented in Cuba and its use restricted to that country. Propoleum came into use after a Cuban patient with PD began taking the substance for giardiasis and noted that his PD had improved.

Because there is little information regarding the properties of propoleum, and the substance cannot be obtained outside of Cuba, clinical knowledge of the drug is limited. Appropriately designed, placebo-controlled, double-blinded efficacy studies performed by additional research groups are necessary to support or dispute currently published findings (Lemourt et al, 1998, 2003).

Acetyl-L-Carnitine—To date, only 1 study has been conducted to evaluate the efficacy of acetyl-L-carnitine. It is hypothesized to inhibit acetyl coenzyme A. In this randomized study involving 48 patients with PD, subjects were given either tamoxifen 20 mg twice daily or acetyl-L-carnitine 1 g twice daily for 3 months (Biagiotti and Cavallini, 2001). Penile curvature, plaque size, and pain were assessed using PDDU. Results comparing acetyl-L-carnitine with tamoxifen showed that acetyl-L-carnitine was significantly more effective than tamoxifen at reducing pain (92% vs 50%, respectively) and inhibiting disease progression (92% vs 46%, respectively), whereas both drugs were statistically shown to significantly reduce mean plaque size. Only acetyl-L-carnitine was statistically shown to significantly reduce penile curvature (from 15.9° to 8.9°). Although no control was provided in the study, because tamoxifen has been previously shown to be similar to placebo, it can be inferred that acetyl-L-carnitine is possibly effective at reducing pain and at decreasing overall disease progression in patients with PD.

Pentoxifylline—There have been anecdotal reports (not placebo-controlled) about various agents (eg, pentoxifylline) (Brant et al, 2006; Bella et al, 2007; Taylor and Levine, 2008). Although such reports are interesting, they underscore the need to perform large-scale placebo-controlled studies to further explore novel mechanisms of action in clinical cases of PD.

Table 2. Intralesional injection therapy

| Drug | Proposed Mechanism of Action | Adverse Effects |
|---------------------------------|--|---|
| Corticosteroid | Anti-inflammatory effect, inhibition of phospholipase A ₂ , immune suppression | Local tissue atrophy, thinning of the skin, systemic effects rarely seen |
| Orgotein | Conversion of superoxide radicals to H ₂ O ₂ and O ₂ , anti-inflammatory effect | Pain, edema, stiffness, dysesthesias, skin rash |
| Collagenase | Degradation of interstitial collagens | Injection-site pain, ecchymosis, corporal rupture |
| Verapamil | Inhibition of calcium-dependent transport of extracellular matrix molecules (collagen, fibronectin, GAGs), increased collagenase activity, modification of inflammatory response, inhibition of fibroblast proliferation | Nausea, lightheadedness, penile pain, ecchymosis, no cardiovascular events reported |
| Interferon- α -2a or -2b | Regulation of immune responses, inhibition of fibroblast and collagen production | Myalgias, arthralgia, sinusitis, fevers, flu-like symptoms |

Intralesional Pharmacotherapy

In addition to oral treatments for PD, another option for conservative therapy is injection of pharmacologically active agents directly into penile plaques (Table 2). One advantage of intralesional treatment compared with oral treatment is localized delivery of a particular agent, which provides higher concentrations of the drug than might be tolerated if given systemically. Several drugs have been used to treat penile plaques with varying degrees of efficacy, including corticosteroids, orgotein, collagenases, verapamil, and interferon- α -2a or -2b.

Corticosteroids—Corticosteroids are candidates for treatment of PD because of their anti-inflammatory effects via inhibition of phospholipase A₂ and suppression of the immune response (Tranchant et al, 1989). The first documented use of intralesional corticosteroids for PD (Bodner et al, 1953) reported a decrease in plaque size and penile pain following dexamethasone injection. A second study (Winter and Khanna, 1975) of 21 patients with PD conducted in 1975 failed to confirm these earlier findings, even though a high percentage of the patients who had previously failed other therapies noted decreased pain and plaque size. Investigators concluded that the results of intralesional corticosteroid injections did not differ significantly from what would be expected from the natural history of the disease.

Because of the lack of conclusive evidence showing benefit and because of the adverse effects experienced with long-term use of corticosteroids (eg, local tissue atrophy, thinning of skin, immune suppression), corticosteroid injections are not currently advocated as an intralesional therapy for PD.

Orgotein—Orgotein is a pharmaceutical version of copper/zinc superoxide dismutase that possesses anti-inflammatory properties. Superoxide dismutase occurs physiologically in cells, such as polymorphonuclear leukocytes, and generates large amounts of superoxide radicals for various biological purposes, including the destruction of foreign materials (tissue, bacteria). Through its actions, superoxide radicals are converted

to the more benign H₂O₂ and O₂ molecules. Because superoxide radicals have the potential to further exacerbate inflammation and generate fibrosis, it was hypothesized that orgotein might potentially reduce the fibrosis associated with PD.

Although orgotein had been used in the treatment of inflammatory urinary tract conditions as early as 1974, its first use as an intralesional injection in patients with PD was not until 7 years later. Two independent studies involving a total of 45 patients found that patients treated with orgotein exhibited decreases in penile pain, curvature, and plaque size, and 19 of 22 patients who previously were unable to engage in sexual activity displayed marked improvement, with some experiencing a complete restoration of normal erectile function (Bartsch et al, 1981; Gustafson et al, 1981). However, these preliminary studies were limited by lack of appropriate controls and flawed experimental design.

Although additional uncontrolled studies have since reported the beneficial effects of intralesional orgotein, no randomized, placebo-controlled, double-blinded studies have been published to date that clearly identify a statistically significant effect of this therapy (Revelli et al, 1990; Primus, 1993). Adverse effects reported for orgotein include pain, swelling, stiffness, dysesthesias, and skin rashes (Uthman et al, 2003). Because information on orgotein is limited, in part by its restricted use in the United States because of reported toxicity with off-label use, it is unlikely to be prescribed for the intralesional therapy of PD.

Collagenase—Collagenase is a physiological enzyme (also classified as specific matrix metalloproteinase 1, 8, and 13) that is capable of degrading interstitial collagens, such as type II collagen. The first examination (Gelbard et al, 1980) of the effect of collagenase on PD plaques took place in 1985. These investigators utilized highly purified clostridial collagenases (PCCs) to test their effect on various human tissues in vitro, including human pericardium, human corpus cavernosum, tunica albuginea, and PD plaques. Results from these exper-

iments demonstrated a considerable reduction in the size of the PD plaque, along with microscopic fraying and dispersal of collagen bundles, when compared with plaques injected with normal saline. Predictably, elastic fibers, vascular smooth muscle, and axonal myelin sheaths were not affected by collagenase application.

Following up on these in vitro results, this research team performed an in vivo pilot study that involved injecting intralesional PCC (mean dose 2328 units) in 31 men with PD (Gelbard et al, 1985). After 4 weeks of treatment, 65% of patients exhibited objective improvement, 93% reported elimination of pain, and the ability to have intercourse was restored in 75% of patients. Additionally, the researchers noted that penile plaques were either altered significantly or absent in 4 patients and reduced by 20%–100% in 16 others.

Interestingly, a study evaluating the presence of IgG antibodies to collagenase in healthy men vs those with PD found that antibodies were present in 34% of healthy men vs 58% of men with PD (Hamilton et al, 1986). These data suggest the possibility that collagenase activity is up-regulated in patients with PD or that effective collagenase activity is decreased because of an autoimmune response against the protein.

Because of its documented efficacy, intralesional collagenase therapy has been used to treat patients with PD; nevertheless, further studies are necessary to confirm a beneficial response to PCC. A multicenter, controlled study is currently being initiated in the United States.

Verapamil—Verapamil is a calcium channel antagonist that is thought to selectively inhibit calcium ion flux in both cardiac muscle and cells responsible for intracardiac conduction, as well as in coronary and systemic arteries. The rationale for its use in the intralesional treatment of patients with PD is based on in vitro data that demonstrate transport of extracellular matrix molecules that include collagen, fibronectin, and GAGs as a calcium-dependent process (Roth et al, 1996). In addition to resulting in decreased intracellular calcium, verapamil has been shown to increase collagenase activity, affect cytokine expression associated with early inflammation and wound formation, and inhibit in vitro fibroblast proliferation in PD plaques (Roth et al, 1996; Mulhall et al, 2002).

Use of intralesional injections of verapamil in patients with PD was popularized in a nonrandomized, uncontrolled study (Levine et al, 1994) of biweekly injections of verapamil 10 mg given over a 6-month period that led to subjective decreases in penile narrowing (reported by 100% of patients) and curvature (among 42% of patients) and objective decreases in plaque volume of $\geq 50\%$ demonstrated in 30% of patients. Patients also

reported benefits with respect to plaque softening and erectile function.

There has only been 1 randomized, placebo-controlled, single-blinded study of verapamil (Rehman et al, 1998). This study included 14 patients with PD and consisted of weekly injections of verapamil or placebo for 6 months with pretreatment and posttreatment PDDU used to objectively measure results. Comparing verapamil with placebo, the data obtained showed statistically significant improvements in mean plaque-associated penile narrowing, statistically significant subjective improvements in mean erectile function (42.87% vs 0%, respectively) and subjective softening of plaques in verapamil-treated patients. The mean change in penile curvature with verapamil was not statistically significant (reduction from 37° at baseline to 29°; $P < .07$).

In patients with PD, adverse effects of the therapy that have been reported thus far include nausea, lightheadedness, penile pain, and ecchymosis. No cardiovascular events have been documented, and the adverse effects of verapamil are generally considered to be mild. Because only 1 study evaluating the efficacy of verapamil has included a placebo arm, additional studies are required to more fully document the benefit of verapamil in terms of altering the natural history of PD.

Interferon- α -2a or -2b—Interferons are a class of endogenously produced, low-molecular-weight cytokines that function to regulate the normal immune response to foreign antigens. Currently, 3 types of natural interferons have been identified: α , β , and γ . The first suggested use of interferons for the treatment of PD was initiated in a study (Duncan et al, 1991) that treated cultured fibroblasts derived from PD plaques with a human recombinant interferon. Results showed that although the α , β , and γ forms of interferon led to inhibition of fibroblast and collagen production, interferon- γ also caused an increase in GAG and fibronectin production. From these data, the authors hypothesized that interferon- α and - β were reasonable agents for use as intralesional therapies for PD.

The first placebo-controlled study involving interferon- α -2b (Judge and Wisniewski, 1997) examined the effects of interferon 1.5×10^6 units administered intralesionally 3 times weekly over a 3-week period in 13 patients with PD of ≥ 12 months' duration. These investigators found that 6 of 10 patients achieved complete resolution of erectile discomfort and significant improvements in penile deformity (mean improvement 20°), with those presenting with smaller initial plaque lengths (< 4 cm) showing the greatest improvements. One interesting study that employed magnetic resonance imaging (MRI) to quantitatively assess

plaque size in patients with PD prior to and following treatment with interferon- α -2a supported the finding that interferon therapy was more likely to benefit patients presenting with smaller plaques (Polat et al, 1997). Among subjects classified as having plaques 0.5–1 cm in length, complete resolution (at least below the resolution capacity of MRI) was seen, whereas those with plaque lengths of 1.5 and 2 cm achieved mean plaque reductions of 90% and 83.3%, respectively.

The most scientifically definitive study to date on the efficacy of intralesional interferon- α -2b in PD is a single-blinded, multicenter, placebo-controlled, parallel study involving 117 patients published in 2006 (Hellstrom et al, 2006). Fifty-five patients were given interferon- α -2b 5×10^6 units at 2-week intervals over a period of 12 weeks, and each patient was evaluated for penile curvature, plaque characteristics (size, density), penile pain, erectile function, and penile hemodynamics using PDDU and IIEF questionnaires. Significant improvement was seen in actively treated patients compared with placebo (intralesional injection of the same volume of saline) for mean penile curvature (reduction from 49.9° to 36.4° in the interferon group vs 50.9° to 46.4° in the placebo group), mean penile plaque size (reduction from 4.8 to 2.2 cm² in the interferon group vs 4.5 to 3.6 cm² in the placebo group), mean plaque density (reduction from 2.29 to 1.52 in the interferon group vs 2.07 to 1.84 in the placebo group [range 0–3 for both groups]), pain resolution (67.7% of patients in the interferon group vs 28.1% of patients in the placebo group), and penile blood flows, whereas mean IIEF scores were not significantly different before and after treatment (interferon 18.3 to 20.8 vs placebo 17.9 to 19.0). These results provide the best efficacy evidence to date supporting the use of intralesional interferon in patients with PD.

Transdermal Pharmacotherapy

In addition to oral and injection routes of drug delivery, topical and transdermal approaches to the treatment of PD have been investigated. Topical preparations of β -aminopropionitrile, hydrocortisone, and verapamil have been reported in uncontrolled trials to have effects ranging from none to significant reductions in pain, penile deviation, and size of PD plaques (Gelbard et al, 1983; Miller and Ardizzone, 1983). However, the true efficacy of topical preparations was called into question following a study (Martin et al, 2002) in which verapamil levels were measured in excised samples of tunica albuginea following 2 applications of topical verapamil. This study showed that verapamil was not present in any of the tunical samples obtained and was recovered in small amounts in the urine. Despite minimal systemic absorption, the lack

of demonstrable verapamil in sampled tunica albuginea suggests that there is no scientific basis for its use. As such, topical therapies are not currently recommended by any credible erectile authorities in the treatment of PD. However, a recent publication by Fitch et al (2007) suggests that long-term (9-month) therapy does provide benefit. Obviously a multicenter placebo-controlled study is needed.

To overcome limitations of topical therapies, emphasis has more recently been placed on testing modalities such as iontophoresis, which enhances the local uptake of drugs. Iontophoresis involves the application of an external electric force to induce further (electromotive) penetration of topical medication and has been evaluated to date with topical verapamil, dexamethasone, and orgotein (Schieroni et al, 1985). This is in contrast to a later study (Martin et al, 2002) that demonstrated no uptake of verapamil in tunica albuginea following topical application. A study (Levine et al, 2003) reported that 71.5% of excised tunica albuginea samples from 14 men who received iontophoresis and topical verapamil therapy prior to undergoing surgical treatment for PD were found to contain measurable levels of verapamil. A subsequent prospective, controlled study evaluated the efficacy of electromotive verapamil and dexamethasone vs electromotive lidocaine (lignocaine) in 96 men with PD (Di Stasi et al, 2004). Men were randomized to receive either verapamil 5 mg \pm dexamethasone 8 mg or 2% lidocaine with a 2.4-mA electric current for 20 minutes, 4 times weekly for 6 weeks. Compared with baseline, significant decreases in median plaque volume (reduction from 824 to 348 mm³) and penile curvature (reduction from 43° to 21°) were seen in the actively treated groups, whereas no changes in plaque volume or curvature were seen in the control group. Significant pain relief was experienced transiently in the control group and permanently in the treatment arm. These results support those of a previous uncontrolled study that reported plaque reduction in 82%, curvature decrease in 84%, and pain elimination in 88% of 49 men who received verapamil and dexamethasone treatment with iontophoresis (Di Stasi et al, 2003).

Conclusions

PD is a common disorder that often presents with any combination of penile pain, curvature, penile plaque, or ED. The disorder may have an underlying genetic predisposition and become manifest with an inciting event such as trauma. Following the initial evaluation of a patient presenting with PD, the recommended standard of care involves an initial trial of oral and/or intralesional pharmacotherapy in the acute phase (first year) of this condition.

Among available oral treatments, tocopherol paraminobenzoates are the most commonly prescribed agents because they are inexpensive, have a mild adverse effect profile, and provide a psychological placebo benefit. Colchicine, tamoxifen, propoleum, and acetyl-L-carnitine are additional oral therapies that are also occasionally prescribed in other countries and are still considered investigational in nature. Oral treatments are more likely to be successful if initiated early in the course of a patient's disease and, for the most part, prevent progression rather than curing the condition.

Intralesional injection therapies have become more popular over the last 2 decades and provide an additional minimally invasive modality for patients with PD. The intralesional approach allows for direct delivery of a particular agent at concentrations that might otherwise be toxic systemically. Use of corticosteroids or orgotein is not currently recommended, and there have been no randomized, placebo-controlled studies clearly documenting their efficacy. Use of collagenase is supported by the results of studies that have revealed significant benefits for this therapy when employed early in the course of PD. Verapamil has been shown in 1 placebo-controlled and numerous uncontrolled studies to have beneficial effects in PD. Interferon- α -2a or -2b has been reported in peer-reviewed multicenter placebo controlled studies to have efficacy in improving penile curvature, plaque size and density, and to reduce penile pain.

As the definitive pathophysiology of PD has yet to be elucidated, further research is required in this area. Currently, oral pharmacotherapy has shown negligible success in improving penile pain, curvature, and plaque size in patients with PD. Intralesional therapy using various agents (eg, collagenase, verapamil, and interferon) is growing in clinical acceptance and popularity as a minimally invasive approach for the initial treatment of PD. As our scientific understanding of the underlying mechanisms of this perplexing condition increase we can anticipate the development of novel medical therapies for PD.

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