INTRACAVERNOSAL INJECTION THERAPY AND OTHER TREATMENT OPTIONS FOR ERECTILE DYSFUNCTION

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ABSTRACT

In the United States, almost 30 million men have complete or partial erectile dysfunction. This disorder occurs in approximately 52% of men between 40 and 70 years of age; 70% of affected men younger than 35 years of age have psychogenic causes, and 85% of men older than 50 years of age have organic impotence. Furthermore, erectile dysfunction is exacerbated by the presence of such conditions as heart disease, diabetes, and hyperlipidemia and the medications used to manage them. Thus, a widespread segment of the population is in need of a safe and effective treatment strategy for restoration of normal sexual function. The technique of intracavernosal injection therapy was initially described in the early 1980s. During the subsequent decade, the effectiveness of various drug combinations and the associated side effects were demonstrated. In 1995, prostaglandin E_1 was approved for intracavernosal pharmacotherapy. It has proved highly effective for neurogenic, vasculogenic, and psychogenic erectile dysfunction, with reported response rates of 75 to 92%. The major side effect (albeit uncommon) is corporal fibrosis. Other options for treatment of erectile dysfunction are vacuum-erection devices and penile prostheses. **(Endocr Pract. 1997; 3:54-59)**

INTRODUCTION

The first National Institutes of Health Consensus Conference on Impotence was a benchmark in furthering the understanding and treatment of male impotence (1). The 1992 conference recommended adoption and use of "erectile dysfunction" as the appropriate technical term to describe the inability to achieve or maintain an erection of sufficient rigidity to allow satisfactory sexual performance. As medical experts agreed on a new definition for this age-old condition, research into safe and effective therapies continued. Today, after 15 years of clinical testing with various intracavernosal therapies, patients have available a highly effective and safe pharmacotherapy for this medical disorder.

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Considerable advances in both the understanding of the mechanisms of erection and the treatment modalities have yielded enhanced public awareness of a problem long misunderstood and shrouded in myth. The National Institutes of Health has offered several critical points useful to both patients and physicians for understanding this condition and achieving the most successful treatment outcomes. Erectile dysfunction is a major public health issue that affects almost 30 million American men, who suffer from complete or partial erectile dysfunction. In most men older than 50 years of age, erectile dysfunction is due to organic causes and is exacerbated in the presence of heart disease, cigarette smoking, diabetes, hyperlipidemia, chronic renal insufficiency, spinal cord injury, and the medications used to control these conditions. Overall, erectile dysfunction affects approximately 52% of men between 40 and 70 years of age (2). The negative effect on these men has a profound social influence on quality of life issues, including increased anxiety, depression, substance abuse, inability to maintain work capacity, and deteriorating social, family, and intimate interpersonal relationships (3). Finally, the evaluation and treatment of erectile dysfunction are complex and necessitate a multidisciplinary approach to address both physiologic and psychologic causes.

AGE-RELATED FREQUENCY OF DYSFUNCTION

The most recent epidemiologic report on impotence was the Massachusetts male aging study, which was conducted from 1987 to 1989 and reported results on 1,290 nonhospitalized men who ranged in age from 40 to 70 years (2). The ratio of organic to psychologic male sexual dysfunction was found to be directly proportional to age, with 70% of men younger than 35 years of age having psychogenic causes and 85% of men older than 50 years of age having organic impotence. A threefold increase in the probability of complete impotence was found among men undergoing treatment for diabetes. In addition, complete impotence was more prevalent in men receiving vasodilators (36%), cardiac drugs (28%), hypoglycemic agents (26%), or antihypertensive drugs (14%). Although no correlation was found between complaints of impotence and serum testosterone or sex hormone-binding globulin levels, a correlation was noted with levels of the adrenal androgen metabolite dehydroepiandrosterone sulfate. Although this study clearly identified age as an associated factor, it also found that vascular risk factors and other potentially alterable age-related developments are important contributors to the presence of male sexual dysfunction.

PHYSIOLOGY OF ERECTION

Erection is both a complex hemodynamic and a neurophysiologic event. Hemodynamically, in the flaccid penis, the smooth muscles of the penile arteries, arterioles, and sinusoid spaces are in a contracted state. This increased resistance to arterial inflow in combination with unrestricted venous outflow results in the nonerect penis. Tumescence follows smooth muscle relaxation and subsequently decreased arterial resistance, increased arterial inflow, and sinusoidal engorgement. Venous outflow during an erection is considerably decreased because of distention of the blood-filled sinusoidal spaces compressing the veins against the inner layer of the noncompliant tunica albuginea (4). In addition, an erection is a coordinated neuropharmacologic event. Initially, sexual desire is registered within the medial preoptic area of the diencephalon influenced by dopaminergic and adrenergic receptors and is then transmitted to the sympathetic and parasympathetic nervous systems within the spinal cord, which facilitate flaccidity and erection, respectively. Smooth muscle contraction is maintained in the flaccid penis under sympathetic tone. An erection occurs as a result of a decrease in sympathetic tone and activation of parasympathetic neurotransmission. This cascade of events stimulates the release of nitric oxide, which is currently considered the primary mediator responsible for endothelial and cavernous smooth muscle relaxation (5).

HISTORY OF INTRACAVERNOSAL INJECTION THERAPY

The technique of injection therapy began in the early 1980s with reports by Virag (6) and Brindley (7), who observed that the injection of vasoactive agents directly into the corpora cavernosa produced a rigid erection on demand. Shortly thereafter, Zorgniotti and Lefleur (8) combined the two agents papaverine and phentolamine and noted a synergistic response. Papaverine, derived from the opium poppy, is a potent smooth muscle relaxant. After intracavernosal injection, the drug is relatively slow to clear the corpora, an action that may account for the sometimes prolonged erection it produces. An additional side effect is the elevation of liver transaminase levels. The agent phentolamine, while also having a direct relaxant effect on smooth muscle, acts primarily as an α-adrenergic antagonist. This combination of papaverine and phentolamine became the most widely used form of intracavernosal therapy until the late 1980s (9). During this period, various pharmacotherapies were used in an attempt to discover the effectiveness of drug combinations, related side effects, reports of penile pain, and patient response to injection therapy. Investigators demonstrated that prostaglandin E_1 (alprostadil), both a potent smooth muscle relaxant and an antiadrenergic agent, was a more suitable drug for intracavernosal pharmacotherapy because it most resembled the natural erectile cascade, was nontoxic, and was extensively metabolized locally within the penile corporal tissue (10). Prostaglandin E_1—either alone or, more commonly, in combination with papaverine and phentolamine—became the mainstay of intracavernosal injection therapy for erectile dysfunction, with reported overall effective response rates of 75 to 92% (11,12).

ALPROSTADIL STERILE POWDER

In July 1995, the US Food and Drug Administration approved the use of prostaglandin E_1 for intracavernosal pharmacotherapy. With this approval, the millions of American men experiencing impotence are now afforded a proven, highly effective, relatively low side-effect course of treatment. Intracavernosal pharmacotherapy is indicated for the treatment of erectile dysfunction caused by neurogenic, vasculogenic, psychogenic, or a combination of these factors. It is contraindicated in patients receiving monoamine oxidase inhibitors and those with sickle cell anemia, multiple myeloma, leukemia, or other conditions that predispose to priapism (13). In rigorous clinical trials encompassing more than 1,800 patients, 79 to 89% of patients achieved adequate erections sufficient for intercourse. This remarkable success takes into account appropriate dosing, with the mean optimal dose in one study being approximately 20 μg. A dose-related response to both rigidity and duration is apparent. In addition (and as expected), a cause-dose relationship exists whereby men with psychogenic erectile dysfunction respond to lower doses than do those with neurogenic and vasculogenic causes, whereas men with a mixed etiologic basis for their erectile dysfunction require the highest minimal effective dose (14,15). In populations of patients with diabetes, the prevalence of erectile dysfunction is estimated to be as high as 74%. In general, patients older than 60 years of age who have had diabetes for more than 10 years and who are dependent on insulin tend to respond less and require larger doses of this vasoactive agent (16). In contrast, some patients may respond to very low doses of alprostadil. Therefore, all patients with erectile dysfunction, regardless of the cause, should undergo a trial injection and subsequent titration under physician supervision.

Before initiation of intracavernosal pharmacotherapy, informed consent should be obtained. The patient needs to be educated about the various other treatment options and the indications, contraindications, and exclusions associated with this therapeutic modality. The patient should clearly understand that proper sterile technique must be used and that the predetermined titrated dose must never be increased without consulting the physician. Finally, the associated risks of pain, priapism, and corporal fibrosis must be discussed. The patient must be informed that, in the event of a prolonged erection, he must contact the physician immediately or go to the emergency department, and surgical intervention may ultimately be necessary. Therefore, the importance of careful, in-office titration and self-injection

instruction cannot be overemphasized, and the patient should initially be monitored by a physician. Patient follow-up at regular intervals is also critical because corporal fibrosis may increase progressively over time. The patient must be taught self-examination of the penis in the erect state to detect any plaques or nodules. In addition, the physician needs to examine the patient regularly.

Titration Guidelines for Neurogenic Cause

In the case of pure neurogenic impotence (for example, spinal cord injury), titration of intracavernosal pharmacotherapy should begin with a dose of 1.25 μg of prostaglandin E_1 (13). If a full erection occurs and does not last for more than 1 hour, this dose can be considered appropriate for future treatment. If no response occurs within 1 hour, one can inject again with 1.25 μg of prostaglandin E_1 (total of 2.5 μg); however, if this second injection also fails to elicit an adequate erection, one needs to wait at least 1 day before use of a higher dose. If the initial 1.25-μg dose produces a partial erection, after an interval of 24 hours the dose can be increased to 2.5 μg of prostaglandin E_1. If this second dose produces a full erection that does not last more than 1 hour, this amount can be considered the appropriate dose for future treatments. If, however, erectile response is partial, the dose can be increased to 5 μg after a 24-hour waiting period. This approach can be continued, with use of increases of 5 μg of prostaglandin E_1, until a full erection not lasting more than 1 hour is achieved.

Titration Guidelines for Mixed Causes

The following are dosage titration guidelines for intracavernosal pharmacotherapy for erectile dysfunction of vasculogenic, psychogenic, or mixed causes (13). In all cases, the dose should be carefully titrated and supervised by the physician. Titration should begin with a dose of 2.5 μg of prostaglandin E_1. If full erection occurs and does not last more than 1 hour, this dose can be considered appropriate for any future treatment. In the case of a starting dose of 2.5 μg that elicits no response within 1 hour, an additional dose of 5.0 μg can be given (total of 7.5 μg). Two doses may be given on the first day, but only one dose can be administered on subsequent days. If this dose produces a partial erection, the dose can be increased to 5.0 μg of prostaglandin E_1—but only after an interval of 24 hours. If this second dose achieves a full erection that does not last more than 1 hour, this amount can be considered the appropriate dose for future treatments. If a partial erectile response continues, however, the dose can be increased by adding 5 μg, again after waiting 24 hours. This method can be continued—increasing the dose by 5 to 10 μg of prostaglandin E_1 until a full erection not lasting more than 1 hour is achieved. Doses of more than 60 μg are not recommended, and doses that exceed 20 μg are rarely used clinically. In all cases, whether the response is full or partial, the patient must remain in the physician's office until complete detumescence occurs.

For men who fail to achieve adequate erections or who experience severe pain with single-agent intracavernosal injection therapy, additional agents can be used. Initially, a solution that contains prostaglandin E_1 and phentolamine is used; if this treatment fails, papaverine is added to form a Trimix solution (14). These highly effective (but not yet approved) combination solutions differ in their potency; thus, careful in-office titration is imperative, as is proper patient appreciation of the potential risks and benefits.

Related Side Effects

The most potentially significant adverse side effects associated with intracavernosal pharmacotherapy are local findings, including penile pain, priapism, and fibrosis. In clinical studies of up to 18 months' duration, penile pain was experienced on at least one occasion by 37% of the men. In most patients, this pain was reported to be mild or moderate, and only a small percentage (3%) discontinued treatment because of pain (15). Although the cause of the pain is unclear, it seems to be dependent on the dose. A recent study has suggested that the pain can be reduced by slow administration of the drug during a 30-second interval (17), whereas other studies have attempted to add a local anesthetic agent to the solution (procaine or lidocaine) (18). A major side effect previously associated with intracavernosal injection therapy was corporal fibrosis. Use of papaverine alone or in combination with phentolamine was associated with a high rate of clinically detected fibrosis (19). This finding differs dramatically from the fibrosis rate reported in long-term clinical trials of alprostadil, in which the incidence of corporal fibrosis at 6 months was 2.2 to 4.0% and at 18 months was 6.0 to 7.8% (13). The fibrosis observed has a clinical course similar to the plaques associated with Peyronie's disease, in which 35 to 50% resolve spontaneously. Therefore, although corporal fibrosis is uncommon with alprostadil therapy, it nevertheless can occasionally be severe and can necessitate surgical correction and possible insertion of a penile prosthesis (19).

PRIAPISM

Priapism, a medical emergency, is a painful erection that persists for more than 4 to 6 hours and may result in irreversible damage if left untreated. The type of priapism associated with intracavernosal therapy is defined as low flow or veno-occlusive and reflects a hypoxic, hypercarbic, and acidotic environment. The incidence of priapism ranges from 0.9 to 9.5% and is agent dependent. Use of papaverine alone is associated with the highest priapism rate (9.5%), in contrast to a much lower rate with prostaglandin E_1 (2.4%). With Trimix solutions (papaverine-phentolamine-prostaglandin E_1), reported priapism rates range from 0.9 to 2.7% (14). Currently, most cases of priapism are associated with the increased use of intracavernosal injection therapy for erectile dysfunction. The physician prescribing this treatment must be familiar with this emergency and all the available medical and surgical treatment options. Pharmacologically induced priapism needs to be treated within 3 to 4 hours; if present for less than 12 to 24 hours, it will most often respond to medical

intervention. Treatment consists of large-needle aspiration of the hypoxic blood coupled with irrigation and injection of an α-adrenergic agonist. The agent of choice is phenylephrine because of its pure α_1 and low β_1 activity. Careful patient monitoring of vital signs is necessary because the systemic absorption of phenylephrine will result in hypertension, headache, and possible cardiac ischemia. Those patients whose priapism is refractory to conservative therapy will require immediate intervention in the form of surgical shunting.

PATIENT SATISFACTION

Intracavernosal injection therapy, when successful, restores natural function. As with any effective treatment for erectile dysfunction, most patients report considerable benefit to their self-esteem. Studies have substantiated decreased anxiety and depression as well as overall improvement in sex life and quality of relationships (20). In the clinical trials, acceptance of and satisfaction with this technique were high—patients and partners reported that 87% and 86% of the injections, respectively, resulted in satisfactory intercourse (15). For those patients who initially reject this treatment because of the requirement for self-injection, the use of autoinjectors and ultrafine 29-gauge needles often substantially assists the patients in pursuing this effective treatment option.

Although the reported satisfaction rate is high, the home dropout rate is 30 to 60% (19). The causes for abandoning the therapy are numerous and may include loss of interest on the part of the patient or his partner, loss of response to the medication, cost, intercurrent illness, or return of spontaneous erections. The return of spontaneous erections—most often seen in patients with psychogenic impotence—is also occasionally observed in patients who have undergone radical retropubic prostatectomies.

VACUUM-ERECTION DEVICES

The noninvasive vacuum-erection device consists of a plastic cylinder with tubing connected to a handheld pump, which creates a vacuum seal and a negative pressure surrounding the penis. This negative pressure results in the passive accumulation of blood within the corpora and leads to an erection; then a constriction band is placed to maintain the erection. This device is associated with a high degree of patient acceptance. A recent survey of almost 1,600 users of vacuum-constriction devices indicated that 92% were able to achieve erection and nearly 80% had intercourse at least once every 2-week period (21). Other reports, however, noted a considerable dropout rate among users of the vacuum devices because of the mechanical nature and lack of satisfaction with the devices over time (22,23). Newer available units seem to be more comfortable, effective, and easier to use. Such devices are useful for a wide variety of patients with erectile dysfunction, including those with severe venous occlusive disease, and they may also be effective in men who have undergone removal of a failed penile prosthesis (24,25). Major complications of vacuum-erection devices are hematoma, ecchymosis, and penile necrosis, and minor complications include discomfort during sexual intercourse and pain during ejaculation.

PENILE PROSTHESIS

Beginning in the 1960s, the use of autologous bone grafts and, later, silicon implants were developed (26,27). Several types of penile prostheses are available: semirigid prostheses, inflatable prostheses, and a two-piece inflatable prosthesis. The prosthesis is placed directly into and replaces the two corpora cavernosa of the penis; when properly inserted, it provides adequate length and a relatively normal girth. The inflatable prosthesis was developed as a modification of the semirigid prosthesis. The multicomponent inflatable prosthesis consists of two inflatable cylinders that are placed within the penis, a pump that is placed within the scrotum, and a reservoir that is placed in the lower abdomen (25). These prostheses have the advantage of achieving near-natural flaccidity and, when activated, a rigid erection. The insertion of a penile prosthesis is essentially an irreversible procedure and often considered as a last resort after other more conservative types of therapy have failed or are unacceptable. Once a prosthesis has been inserted, however, the patient satisfaction rate is often the highest of the current therapies available (22). Complications from surgical procedures include prosthesis malfunction and infection (higher rates have been noted in patients with uncontrolled diabetes) (28). Of note, over time, substantial modifications have been made to the prosthetic devices, including fewer connections and use of nonkinking tubing, to decrease the malfunction rate.

FUTURE TREATMENT OPTIONS

Scientific researchers in the past decade and a half have made major strides toward improvement of both the diagnosis and treatment of erectile dysfunction and have contributed to the breaking down of the psychologic and emotional barriers surrounding this topic. Currently promising new and less invasive modes of delivery are undergoing clinical trials and may be available for use in the near future.

ORAL PHARMACOTHERAPY

An orally administered medication that has been available for some time for the treatment of erectile dysfunction is yohimbine hydrochloride, an α_2-adrenergic antagonist with both central and peripheral actions. It has demonstrated only a marginal improvement over placebo in men with organic impotence but may benefit a subgroup of men with early arteriogenic impotence and those with psychogenic erectile dysfunction (29). The efficacy of yohimbine may be enhanced by the addition of the antidepressant and serotonin agonist trazodone (30). Clinical trials reporting the efficacy of transbuccally administered

phentolamine or apomorphine taken only on demand before sexual activity are promising and warrant further study in larger patient populations (31,32). One of the most exciting oral agents currently being used in phase III clinical trials in the United States is the drug UK-92,480 (Sildenafil). This orally administered drug is a specific type V phosphodiesterase enzyme inhibitor, the predominant form of this enzyme found within the penis. Relaxation of the penile corpus smooth muscle is mediated by nitric oxide and its second messenger, cyclic guanosine monophosphate (cGMP). This class of enzymes is responsible for the breakdown of cGMP; thus, inhibition of phosphodiesterase enzyme type V would enhance erections mediated by nitric oxide-related cGMP by preventing its metabolism. At the annual meeting of the American Urological Association held in May 1996, preliminary data were presented from pilot studies performed in England. Those investigations suggested that this orally administered drug in a 50-mg dosage was extremely effective and well tolerated. This oral therapy has a physiologically sound mechanism of action and thus, pending further study, promises to be effective, selective, and safe for many men suffering from erectile dysfunction (33,34).

OTHER DRUG-DELIVERY SYSTEMS

Transdermal or transglandular delivery of agents to the corporal smooth muscle to elicit an erectile state has been attempted by using solutions of nitroglycerin, minoxidil, and prostaglandin E_1 (35,36). This type of drug delivery has not yet been sufficiently perfected to result in an adequate erectile response. A novel delivery system soon expected to be available is the transurethral approach. The absorption and transfer of prostaglandin E_1 into the corpora cavernosa are through the urethral mucosa, after pellets containing the drug have been dispensed into the distal urethra by means of an applicator. For achievement of penile erection, intraurethral doses as high as 125 to 1,000 μg of prostaglandin E_1 are needed. An estimated 20% of the drug is absorbed into the corpora cavernosa, and the other 80% of the drug that enters the systemic circulation is almost completely and safely metabolized on the first pass through the lungs. Initial results with this mode of delivery have been fair and suggest that, in a subgroup of men with impotence, this option may become a first-line therapy because of its noninvasive nature (37,38).

CONCLUSION

Research efforts during the past 15 years have resulted in the successful application of intracavernosal injection therapy for men with erectile dysfunction. Currently, alprostadil is a commercially available agent for intracavernosal injection that has been approved by the US Food and Drug Administration for use in the almost 30 million American men who suffer from this medical condition. Intracavernosal injection therapy is an excellent nonsurgical treatment option and has wide application in patients with impotence attributable to diverse causes. Physicians who treat men suffering from erectile dysfunction not only will experience the satisfaction of offering a safe and effective therapy but also, as a result, will observe an overall improved well-being in their patients.

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