International Journal of Impotence Research (2002) 14, Suppl 1, S70–S81
 0955-9930/02 $25.00
www.nature.com/ijir

Current status of local penile therapy

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Guidelines for management of patients with erectile dysfunction indicate that intraurethral and intracavernosal injection therapies represent the second-line treatment available. Efficacy of intracavernosal injections seems superior to that of the intraurethral delivery of drugs, and this may explain the current larger diffusion of the former modality. Safety of these two therapeutic options is well established; however, the attrition rate with these approaches is significant and most patients eventually drop out of treatment. Newer agents with better efficacy-safety profiles and using user-friendly devices for drug administration may potentially increase the long-term satisfaction rate achieved with these therapies. Topical therapy has the potential to become a first-line treatment for erectile dysfunction because it acts locally and is easy to use. At this time, however, the crossing of the barrier caused by the penile skin and tunica albuginea has limited the efficacy of the drugs used.
International Journal of Impotence Research (2002) **14,** Suppl 1, S70–S81. DOI: 10.1038/sj/ijir/3900808

Keywords: erectile dysfunction; local penile therapy; topical therapy; alprostadil

Introduction

Management of patients with erectile dysfunction has been recently grouped into three different levels.[1] Initially, patients should be advised to control every clinical abnormality or lifestyle factor associated with a higher risk of erectile dysfunction. Usually this first step alone does not significantly improve the patient's erectile function and first-line therapy is considered. This includes oral pharmacotherapy, the use of the vacuum device, and psychosexual therapy. Most patients who are currently seen for erectile dysfunction are prescribed either sildenafil or sublingual apomorphine, the two drugs that are officially marketed. This happens because the efficacy and safety of the oral approach have been clearly established and because most of the patients would rather use such a simple-to-use therapy. Patients who do not respond to oral therapy are considered for second-line treatment, which includes the intraurethral and intracavernosal administration of vasoactive drugs. It is rare to prescribe one of the second-line therapies when choosing treatment for the first time; this used to happen when sildenafil was the only oral drug on the market because patients using nitrates had a definite contraindication to the use of sildenafil. A second patient category might be represented by those requesting a fast response, which cannot be obtained by sildenafil; however, sublingual apomorphine is characterized by a fast onset of action and may represent an effective solution for these patients.[2] In conclusion, intraurethral and intracavernosal therapy are currently used almost exclusively in patients who do not respond to oral therapy; however, when counseling the patient with erectile dysfunction on the treatment options available, every alternative should be extensively detailed at the first office visit.

Topical administration of vasoactive agents represents a potentially reliable option that would certainly be appealing for many patients because it works directly at the penile level, thus lacking any systemic influence, and it is easy to use.[3] Any effective drug with an adequate system of administration has the potential to become a first-line therapy for erectile dysfunction.

The aims of this article are to review the latest results shown with these therapeutic options and to demonstrate the correct approach to determining which patients are candidates for these therapies.

Intracavernosal injection therapy

The pharmacological erection program

When a patient is considered to be a potential candidate for vasoactive injection therapy, the

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characteristics, potential limitations, and adverse effects of the treatment are extensively explained to the patient. The patient is asked to read and sign a detailed informed consent. Patients with a history of hemoglobinopathy, bleeding diathesis, Peyronie's disease, or idiopathic priapism are excluded from treatment. In addition, patients with poor manual dexterity, poor visual acuity, or morbid obesity or those in whom a transient hypotensive episode may have a deleterious effect (for example, unstable cardiovascular disease and transient ischemic attack) are not ideal candidates for this treatment. Finally, patients with serious psychiatric disorders or patients who might misuse or abuse this therapy should be excluded from treatment.

The first phase of the program consists of the dose titration of the drug or mixture used for injections. Patients are placed in the sitting position on the examination couch during each injection and kept in this position for 30 min. Systemic blood pressure is recorded at baseline in the event of syncope and to check for hypertension. The right side (lateral aspect) of the penis is cleansed with an alcohol swab. The first injection is then performed with a very small amount of either the drug or the mixture. At our clinic, three versions of a four-drug mixture composed of papaverine, phentolamine, alprostadil, and atropine sulfate are used, and 0.05 mL is usually injected first.[4–6] The needle is inserted by a quick jab up to the hilt of the needle so that the tip of it reaches the center of the right corpus cavernosum. Injections must not be performed on the dorsal and ventral aspects of the penis to avoid damage to the dorsal neurovascular bundle of the penis and urethra, respectively.

Immediately after injection, the base of the penis is squeezed firmly between the right thumb and index finger, while the accessible portion of the penis is massaged for up to 5 min by squeezing it laterally along the length of the shaft between the left thumb and index and middle fingers, thus distributing the drug throughout the pendulous shaft. Patients are then left alone to watch an erotic video and they are invited to masturbate without ejaculation to optimize sexual stimulation. The erectile response is then assessed by the physician and patient. The dose of the injected drug or mixture is considered adequate when it produces an erection that is equal to 50–75% of the maximal erectile response reported by the patient. If a patient reaches a maximal rigid erection during the titration phase in the clinic, a lower dose is suggested for home use since the erectile effect induced by the drug or mixture during sexual activity is usually greater than that observed under laboratory conditions. If the first injection does not produce a satisfactory erectile response (that is, less than 50% of the maximal potential response), the patient is reinjected after at least 24 h and the dose is slightly increased (at our clinic we use 0.05-mL increments). The titration process proceeds until the optimal dose is identified or the maximal injected volume (at our clinic, 0.5 mL) is reached.

If after the injection a full rigid erection persists for longer than 1 h, 20–40 μg of adrenaline are injected intracorporeally to obtain complete detumescence. Appropriate electrocardiographic and blood pressure monitoring is used during this procedure. Patients are contacted by telephone the next day to verify persistence of detumescence.

After the proper dose of the drug or mixture has been determined, patients watch the thorough demonstration of both a conventional insulin syringe and an automatic self-injection system (Disetronic Pen, Medis, Milan, Italy) (Figure 1) with which multiple injections can be performed, thus avoiding the maneuvres needed before each injection performed with the insulin syringe (preparation of the syringe, needle, and the appropriate amount of the drug).[7] The pen consists of a capsule that is screwed together with the adapter after inserting the filled glass cartridge. The needle is then screwed into the adapter. The glass cartridge consists of a rubber piston and a conus in front, which is closed with a cap. The cartridge set contains a pull rod and a needle in addition to the glass cartridge (Figure 2). To fill the cartridge, the pull rod is screwed into the thread of the rubber piston and, after removing the cap, the needle is stuck on the conus. The glass cartridge volume is 3 mL. At our clinic the cartridge is filled with the four-drug vasoactive mixture mentioned previously, which will be described in detail later. Because the average volume of mixture used at each injection by our patients is below 0.2 mL, every cartridge has a drug load that is

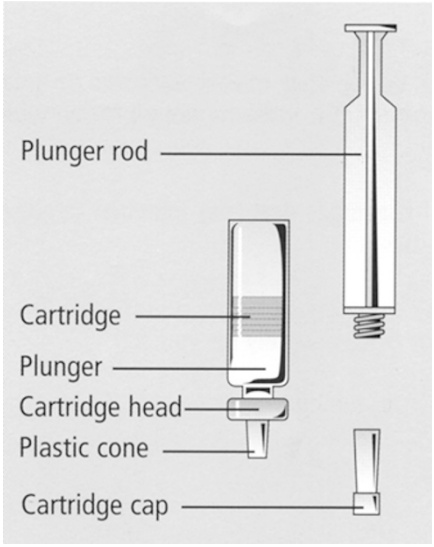

Figure 1 Self-injection system (Disetronic Pen) in use at our institution.

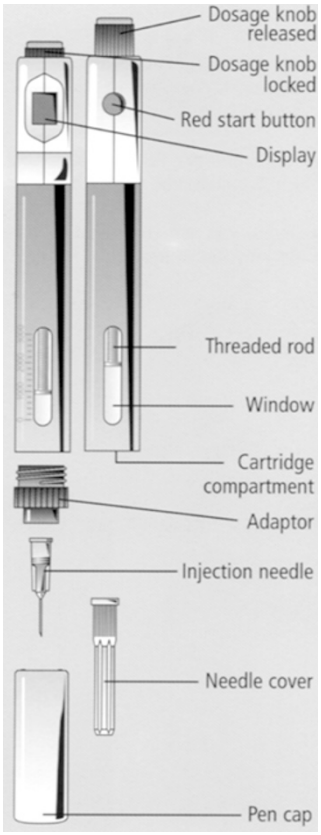

Figure 2 Different components of the system.

usually enough for 8–10 injections. We supply 29-gauge needles for injections.

To prepare the pen for injections, the adapter is first removed from the capsule. The full glass cartridge is then inserted into the capsule with the conus pointing forward. The adapter is screwed firmly into the capsule. The needle is removed from the blister and screwed together with the cap into the adapter. The needle cap is pulled out and, while holding the pen with the needle pointing upward, the knob is pressed slowly until it reaches the top. Some drops of liquid should come out, but if this does not occur, the knob is turned clockwise for approximately two to three clicks and is slowly pressed until it stops. The knob is slowly released, drops are shaken off and the cap is put into the adapter. To inject the drug, the needle is inserted into the corpus cavernosum and the pen knob is gently depressed until it stops. Two models of this system are currently available, which differ only in the volume (20 or 50 μL) of liquid released with every click of the knob. We use the 20 μL model for pure psychogenic and neurogenic patients and the 50 μL model for vasculogenic cases.

Patients are instructed to limit injection use to three times a week, with no more than one injection in any 24-h period. They are also taught to inject the right and left cavernous body alternatively. Patients are then warned to return immediately to the emergency department if erection persists for longer than 3 h. Patients are also told to refrigerate the drug or mixture if it contains prostaglandin E_1 (PGE_1) and to examine the drug or solution for changes in color or the formation of a precipitate.

Patients are reassessed once a month for the first 2 months and subsequently every 3 months. At each follow-up visit, injection frequency, duration and consistency of erections, and patient satisfaction are recorded. The penis is carefully examined for nodules, hematomas, or areas of induration. Liver function test results are assessed every 6 months. Penile ultrasonography is performed to verify any clinical findings on digital palpation of the penis.

Results and complications of vasoactive intracavernous injection therapy

The follow-up of approximately 4000 patients treated worldwide with papaverine alone or in combination with phentolamine has been previously published;[8] in addition, long-term results with intracavernous injection therapy based on PGE_1 have been reported.[9–13] Reported adverse effects have included hematomas, burning pain after injection, urethral damage, cavernositis or local infections, fibrotic changes of the corpora cavernosa, curvature, and prolonged erections or priapism. The two most important complications are prolonged erections and localized fibrotic changes of the corpora cavernosa. Prolonged erections are usually encountered during the dose titration phase and have been reported in 2–15% of patients treated.[8,9] The development of painless fibrotic nodules within the corpora cavernosa may lead to penile curvature. This problem has been reported in 1.5–60% of patients treated for 1 y.[8,9] We believe that most of the fibrotic nodules occur in patients who inject themselves very frequently (multiple traumas to the corporeal tissue) and who do not compress the injection site for a sufficient amount of time, with the subsequent development of intracavernous hematomas.

The increase in the frequency of spontaneous erections and the decreased need for treatment are common findings during follow-up of intracavernous vasoactive injection therapy. It has been demonstrated that the long-term use of PGE_1 intracavernous injections is able to markedly improve cavernosal artery function as shown by color Doppler sonography.[14] The improved hemodynamic response seen in patients injecting themselves regularly may be explained on a microvascular level. It has been shown that the long-term administration of vasoactive agents in monkeys causes

hypertrophy of sinusoidal smooth muscle at the ultrastructural level. Both papaverine and PGE_1 lead to a hypertrophic response, but papaverine results in a combination of hypertrophy, atrophy, and fibrosis, whereas with PGE_1, the normal cellular architecture is preserved. With the sinusoidal muscle 'toned up' after long-term self-injection with PGE_1, the efficiency of sinusoidal smooth muscle action may improve, leading to the observed increase in cavernosal artery flow.

In addition, it has been shown that PGE_1 may improve the hemodynamic response partly by promoting neovascularization.[14] This issue remains controversial because Wespes *et al*[14] were unable to demonstrate any significant changes of the intracavernous structure following long-term treatment with intracavernosal alprostadil. In this study, 10 patients underwent biopsy of the corpora cavernosa before and after a 3-y treatment with alprostadil (overall, 150–250 injections per patient). No histological difference was observed with classic staining. A reduction was noted in the percentage of intracavernous smooth muscle after treatment in two of five patients on the side of injection, but there was no difference with the other corpus cavernosum. No difference was observed in the percentage of intracavernous smooth muscle between both corpora in the five patients with biopsies performed only after treatment.

Recently, Brock *et al*[15] reported on the return of spontaneous erections during long-term intracavernosal alprostadil treatment. In this study, 70 men with a stable heterosexual partner entered the titration phase, and the effective alprostadil dose was determined before entry into the 12-month self-treatment home phase. Duplex ultrasonography was used to measure the peak systolic velocity and diameter of the cavernosal arteries throughout the study. An effective dose was established for 67 (96%) of the 70 men (median dose of alprostadil, 15 μg). During the home phase, 94% of men responded to alprostadil and the median dose remained unchanged. Complete duplex ultrasound data were obtained for 38 men and showed significant increases in postinjection peak systolic velocity in both cavernosal arteries ($P < 0.001$ at 12 months) and between the preinjection and postinjection cavernosal arterial diameters ($P = 0.0001$) compared with baseline. Reports of a return of spontaneous erections increased throughout the study compared with baseline (37%, 26 of 70) and were confirmed by interview for 46 (85%) of 54 men with available data overall.

The issue of the curative effects of intracavernosal injection therapy still remains controversial, since in another study nocturnal penile tumescence activity remained unchanged after long-term intracavernous injections use.[16] In this study, 19 men with organic erectile dysfunction underwent nocturnal penile tumescence testing before and after alprostadil-based intracavernous injection therapy at least 6 months in duration. A 5-item questionnaire was used to assess subjective changes in erectile activity over time. In this study, mean time of intracavernous injection therapy was 2.4 y and mean injection frequency was 3.7 times monthly. Nine patients believed that unaided erection improved after intracavernosal injection, and six achieved intercourse without injection who were unable to do so before injection. However, no statistically significant changes were noted in any of the five objectively measured nocturnal penile tumescence parameters.

Many drugs have been tested for intracavernous use. The following section discusses the mechanisms of action, results, and complications seen with the more widely used drugs.

Clinical experience with approved agents

Papaverine. Papaverine hydrochloride is an opium alkaloid that acts at a postreceptor level via the inhibition of phosphodiesterase, leading to an accumulation of cyclic adenosine monophosphate (cAMP), which attenuates the α_1-receptor–mediated contraction of the smooth muscle cell, possibly by interfering with the calcium ion mobilization. This drug facilitates erection by relaxation of smooth muscles in the sinusoids and dilation of helicine arteries.[17] Doses ranging from 10 to 60 mg are usually given when papaverine is used as a single agent. At present, however, papaverine is usually used in combination either with phentolamine alone or with phentolamine and prostaglandin to increase the overall erectogenic effect and reduce toxicity.

It is well known that intracavernous injections of papaverine may induce corporeal fibrosis. This is thought to be due to the acidity of papaverine solutions (ranging from 3 to 4 pH), which, unfortunately, cannot be corrected by the use of a buffer because the papaverine solution precipitates at a pH greater than 5. Papaverine is extensively metabolized in the liver, and papaverine-induced hepatotoxicity in the form of increase of liver transaminases and drug-induced hepatitis has been reported.[18] A recent study has demonstrated that to avoid adverse effects the single injection dose of papaverine should not exceed 4.5 mg.[19] Reported efficacy rates with doses between 30 and 110 mg varied between 27% and 78% and were dependent on dosage and the patient population investigated.[21] A literature analysis of 19 publications that included 2181 patients overall demonstrated that papaverine produced an average response rate of 61% in in-office testing.[20] The most important adverse effect was priapism in 3–18.5%, which mostly occurred during the titration phase. Fibrotic alterations were seen in 5–30% of patients, with an

average of 5.7% in 15 retrospective studies.[20] Because of safety concerns, monotherapy with papaverine has been discontinued in most industrialized countries. However, because of its considerably low cost, self-injection monotherapy with papaverine still continues in many developing countries.

Phentolamine and papaverine–phentolamine combination. Phentolamine mesylate is an α_1- and α_2-adrenergic receptor blocking agent that dilates arterial vessels and abolishes sympathetic inhibition of erection. Lack of effect on venous return by intracavernous phentolamine has been demonstrated both in animal and human studies.[21] Since a single intracavernous phentolamine injection does not produce a satisfactory erectile response, the drug is not used alone but in combination with papaverine and PGE_1.[4–6] The most frequently used doses of phentolamine are listed in Table 1. The most common adverse effects observed after intravenous administration of phentolamine are orthostatic hypotension and tachycardia. The combination of papaverine and phentolamine is marketed in several European countries (Androskat): this solution has a pH that varies between 3.1 and 3.5 and is stable for 2 to 3 y. Combining the cyclic nucleotide cAMP and cyclic guanosine monophosphate (cGMP) accumulating effects of papaverine and the α-adrenoceptor blocking effects of phentolamine results in an increased average response rate of up to 60–70% observed during in-office testing. With home use, response rates as high as 90% have been reported.[22] The global efficacy rate of this combination as evaluated in large retrospective studies is 68.5%.[20] Frequent adverse effects were similar to those of papaverine. Priapism was reported in 6–15% and fibrosis in an average of 12% of patients treated.[10,20]

PGE_1 (alprostadil). PGE_1 has α_1-blocking properties mediated through a membrane receptor and relaxes the cavernous and arteriolar smooth muscle while causing restriction of venous outflow. PGE_1 produces full erections at doses as low as 2.5 μg. When used as a single agent, the maximal injected dose usually ranges from 30–40 μg. PGE_1 is the most widely used component of multidrug vasoactive mixtures, which permit a reduction in the doses of the single agents, thus reducing adverse effects. The most frequently reported adverse effect of PGE_1 intracavernous injections is local corporeal pain, which occurs in 13–80% of the patients and is dose related (occurring more frequently at doses greater than 15 μg). Three hypotheses have been suggested to explain pain: (1) the pain is related to the acidity of the injected agent, as has been described with local anesthetics; (2) the pain is caused by pharmacologically induced vasodilation and represents vascular pain; and (3) the pain is caused by the direct activation of pain receptors via PGE_1. To avoid this adverse effect, 7.5% sodium bicarbonate or 20 mg of procaine should be added to the PGE_1 solution.[23,24]

In contrast to papaverine or to the papaverine–phentolamine combination, large worldwide prospective studies have been conducted in accordance with good clinical practice guidelines for both alprostadil preparations (alprostadil sterile powder [Caverject] and alprostadil alfadex [Viridal or Edex]), with long-term follow-ups of 4–5 y.[25–27] A review of these large studies shows that the efficacy rate of alprostadil during in-office titration varied between 70% and 75% in more than 10,000 patients.[20] In a variety of prospective self-injection trials, the success rates (defined as successful penetration per injection) varied between 89% and 96%; this is higher than any reported efficacy rate among all the available marketed vasoactive drugs.[28] The positive effect of alprostadil injections on quality of life has been demonstrated.[29] Clinical and self-reported measurements were used to assess physiological and psychological status at baseline and at 3, 6, 12, and 18 months for 579 patients who entered the self-injection phase of an open-label, flexible-dose clinical trial. Quality of life was measured using the Center for Marital and Sexual Health Sexual Functioning Questionnaire, which focuses on the psychosocial and physical dimensions of erectile dysfunction; the Brief Symptom Inventory, which measures mental health; and the Duke Health Profile, which measures general quality of life.

It was clear from this study that clinical improvements in erectile function due to alprostadil therapy were associated with improvements in sexual activity, sexual satisfaction, and overall mental health. Adverse effects seen with alprostadil treatment include the above-mentioned penile pain; priapism, which is seen during the dose titration phase; and corporeal fibrosis, which is encountered in 7.5–11.7% of patients during the 4–5 y of long-term follow-up. Between 33% and 47% of penile fibroses healed spontaneously, suggesting that the incidence of persistent penile fibroses in patients

Table 1 Vasoactive mixtures for intracavernous injection therapy[a]

Drug	*Amount of drug in solution*					
Prostaglandin E_1 (μg)	100	200	30	80	200	300
Papaverine (mg)	300	300	150	80	240	300
Phentolamine (mg)	10	20	5	20	20	20
Atropine (mg)	0	0	0	3	3	3
Saline (mL)	0	0	2.4	0	0	0

[a]The amounts in the first two columns are those used in the study by Montorsi *et al*,[3] the amounts in the third column are those used in the study by Govier *et al*,[45] and the remaining amounts are mixtures currently used at our institution.

undergoing long-term self-injection therapy is between 5% and 7%.[26–28]

Moxisylyte. Moxisylyte is known to be a competitive norepinephrine antagonist, acting on postsynaptic α-receptors. *In vivo* it clearly decreases the spontaneous activity, amplitude, and tone of the contractions of cavernous smooth muscle in dogs, and it relaxes *in vitro* norepinephrine-contracted corporeal smooth muscle strips.[30] Intracavernous injection of 10, 20, or 30 mg of moxisylyte is able to induce an adequate erection for intercourse in 85% of patients.[31] The most interesting characteristic of this drug is its very low rate of adverse effects, including priapism (<1%) and fibrosis (<2%). However, in all published moxisylyte trials, clinically relevant drops in blood pressure accompanied by orthostatic symptoms and dizziness were described in 5–8% of patients.[32]

Vasoactive intestinal polypeptide–phentolamine combination. Because vasoactive intestinal polypeptide (VIP) alone injected intracorporeally in volunteers did not result in rigid erections, a combination of VIP and phentolamine was developed for self-injection therapy.[33] In a large prospective trial with 289 patients, 77% responded with grade 3 erections, considered by the investigators to be sufficient for intercourse.[34] In this study, two priapisms (0.6%) were observed. In a large, multicenter study from the UK, an efficacy rate consistently higher than 80% was seen in all patient categories, irrespective of the origin of the disease; however, the total dropout rate was 65%, which is considerably higher than in all other alprostadil injection trials.[28] The greatest advantage of the Invicorp preparation is its high availability in a ready-to-use, automatic, single-injection device equipped with a 29-gauge needle.[35,36]

Clinical experience with agents under investigation

Calcitonin gene-related peptide. Calcitonin gene-related peptide (CGRP) relaxes smooth muscle cells by hyperpolarization via potassium channel opening and cAMP stimulation. In patients, intracavernous injections of CGRP induced dose-related increases in penile arterial inflow, cavernous smooth muscle relaxation, cavernous outflow occlusion, and an erectile response. In the literature, CGRP (5 μg) has been used in combination with PGE_1 (10 μg) in patients who did not respond to the papaverine–phentolamine combination, including patients with hemodynamically proven veno-occlusive dysfunction.[37] Full erections were obtained in more than 70% of patients. No significant complications were seen with this drug at low doses; however, facial flushing and hypotension were reported at higher doses (25 μg).[38] Because of the limited number of patients treated to date and the short follow-up, CGRP is not yet suggested as a first-choice drug to be used in all candidates for injection therapy but should be considered when PGE_1 or other drugs alone fail to produce a full erectile response.

Linsidomine. Linsidomine chloridrate is the active metabolite of the antianginal drug molsidomine, and it is believed to liberate nitric oxide nonenzymatically (nitric oxide donor), which in turn stimulates guanylate cyclase, leading to an increase in the intracellular concentration of cGMP. Linsidomine also hyperpolarizes the cell membrane by influencing the sodium–potassium pump, thus rendering the smooth muscle cell less responsive to adrenergically mediated contraction.

Linsidomine has been tested with a single injection dose of 1 mg, and in these conditions its effectiveness was comparable to the combination of papaverine and phentolamine,[39] whereas the injection of 20 μg of PGE_1 produced greater erectile effects than linsidomine in most patients.[40] In addition, linsidomine did not prove to be effective in the treatment of patients with corporeal veno-occlusive dysfunction.[41]

No adverse effects, including pain, priapism, or corporeal fibrosis, have been reported after injection of linsidomine. The drug safety profile and its low cost make linsidomine an appealing drug for patients responding to the papaverine–phentolamine combination.

Sodium nitroprusside. Sodium nitroprusside, a nitric oxide donor similar to SIN-1, was evaluated in a comparative trial with alprostadil. In a total of 95 patients, 49% responded with partial and 15% with complete rigidity to 300–400 mg doses of nitroprusside compared with 54% and 20%, respectively, after 20 μg of alprostadil. With nitroprusside doses of 600 mg, global response rates of 84% were achieved. Because alprostadil produced better response rates and sodium nitroprusside was incriminated with hypotonic blood pressure reactions in up to 15% of the patients, this compound did not enter the phase of multicenter trials.[42]

Atropine. The use of atropine sulfate in pharmacological erection programs was first reported by Virag *et al*.[43] It is now known that atropine sulfate in low doses (10^{-8} M) blocks muscarinic receptors, thereby diminishing cholinergic inhibition of the adrenergic and cholinergic excitation of the nonadrenergic, noncholinergic neuroeffector systems that control neurogenic corporeal smooth muscle relaxation. However, in large pharmacological doses

(10^{-30} M), atropine causes release of the endothelium-derived relaxing factor, which has recently been identified as a neurotransmitter involved in penile erection.

Atropine has never been suggested for single-drug injections but has always been included in multidrug vasoactive mixture. Recently, however, Sogari *et al*[44] questioned the actual adjunctive role of atropine when added to a three-drug mixture and used in the pharmacological erection test. At our clinic, 3 mg of atropine sulfate is part of a four-drug mixture (Table 1).

Multiple-drug mixtures. The association of multiple vasoactive drugs is designed to use the synergistic effect derived from the different mechanisms of action that produce the erectogenic effects. None of the drugs mentioned herein are able to produce a full erectile response in all types of impotent patients participating in the pharmacological erection program. Patients with severe penile vascular impairments, especially those with marked veno-occlusive dysfunction of the corpora cavernosa, are poor responders to single-drug intracavernous vasoactive injection therapy. In addition, adverse effects observed during intracavernous pharmacotherapy are mainly drug related, that is, they are due to the chemical composition of the drug itself, to the total dose of the drug used for a single injection, and to the total volume injected. On the contrary, the association of multiple vasoactive drugs produces a full erectile response in more than 90% of patients with an average volume of injected mixture and an extremely limited drug dose.

The most frequently used combinations are shown in Table 1.[3,45,46] It is generally agreed in the literature that these multidrug combinations achieve the greatest rate of responders with the lowest rate of complications. However, the main drawback of multidrug injection therapy is that none of these pharmacologic combinations has been approved by the national health care authorities (the only exception being the papaverine–phentolamine combination in some European countries), and they therefore have to be prepared by the hospital pharmacy because they are not available in the market.

It is the authors' feeling that only patients who may not be treated by multidrug preparations are those requiring a very limited amount of a single conventional drug. However, in our practice, we prefer to use a multidrug mixture (prepared in three different versions: mild, normal, strong) with each patient entering the pharmacological erection program. Patients with pure psychogenic or neurogenic impotence are treated with the mild mixture, patients with mild vasculogenic impotence are treated with the normal mixture, and patients with significant cavernosal artery occlusive disease or corporeal veno-occlusive dysfunction are treated with the strong mixture. The mean ($\pm$s.e.) volume per injection used by our first 600 patients treated is 0.21 ± 0.09 mL, 0.18 ± 0.05 mL, and 0.20 ± 0.04 mL for the mild, normal, and strong mixtures, respectively.

Intracavernosal injection therapy vs *sildenafil treatment*

The advent of sildenafil has revolutionized the management of patients with erectile dysfunction as oral therapy has progressively gained the position of first-line option among the patient's choices. In a large, multicenter study,[48] patients with erectile dysfunction of various causes who were under treatment with alprostadil for at least 6 months and who were reporting satisfactory erections with intracavernosal treatment were switched to sildenafil starting at the dose of 50 mg, which was then titrated according to the patient's needs. At the end of a 12-week treatment with sildenafil, 69% of the patients elected to continue to use the oral treatment. The Erectile Dysfunction Inventory of Treatment Satisfaction questionnaire was used to compare treatment satisfaction in both groups and similar results were found. However, alprostadil injections achieved a higher rate of erections resulting in intercourse compared with sildenafil. Hatzichristou *et al*[48] evaluated patient preference with regard to sildenafil and injection therapy in a group of impotent men on intracavernous injection therapy for more than a year. In phase 1 of this study, the efficacy of sildenafil, 50 and 100 mg, was determined with home use. In phase 2, responders to sildenafil were asked to use the preferred dose orally for a month and choose intracavernous injection or sildenafil. In phase 3, patients were asked to continue either treatment for 3 more months. Of 155 men who had been undergoing intracavernous injection therapy for at least 1 y, 74.8% responded to sildenafil during study phase 1. After 1 month of treatment, 61.2% of responders preferred to continue with the oral drug, 26.7% returned to intracavernous injections, and 12.1% used each drug alternately. Three months later, 63.8% of responders preferred oral treatment and 32.8% chose intracavernous injection, whereas 3.4% continued to use each treatment alternately. These studies show that patients undergoing intracavernous injection therapy should be given the option to try sildenafil because most of them will ultimately elect to use oral treatment. It is also clear that a significant subset of patients, however, will decide to use injections most of the time or at least sporadically.

An interesting issue is related to sildenafil nonresponders. Shabsigh *et al*[49] studied patients who did not respond to an open-label trial of

sildenafil up to 100 mg. These patients entered an alprostadil alfadex in-office titration phase to determine the optimal dose of the drug, up to 40 μg, which was then used during a 6-week home trial. The alprostadil alfadex use at home resulted in improvements of questions 3 and 4 of the International Index of Erectile Function in 89.6% and 85.1% of patients, respectively. The most common adverse effect seen with alprostadil alfadex use was penile pain (29.4%). This study clearly demonstrated that most patients in whom sildenafil fails can be salvaged by intracavernosal alprostadil therapy.

The opposite finding was also demonstrated by McMahon *et al*,[50] who studied 93 patients who did not respond to a home trial with high-dose alprostadil or a three-drug mixture. A total of 34% of these patients responded to sildenafil (most at the 100-mg dose). Another 47.5% of the patients responded to the sildenafil-injection therapy combination. The most interesting finding of this study is the evidence that combining sildenafil and intracavernosal injection therapy may salvage a significant proportion of patients in whom injections alone fail.

Intraurethral therapy

A novel approach derived from transdermal application is transurethral drug delivery, which allows the transfer of drugs from the urethra directly into the corpora cavernosa. In a retrograde urethrogram study using contrast media with the proximal urethra constricted, Vardi and Sáenz de Tejada[51] demonstrated vascular communications between the spongiosal and cavernosal compartments. Their study documented the ability to transfer the drug by vascular communications from the corpora spongiosa (urethra) to the cavernosal spaces. All the intraurethral drugs for erection are postulated to work by this transfer mechanism.

Intraurethral alprostadil

Intraurethral alprostadil has been developed and marketed by Vivus (Menlo Park, CA). The Medicated Transurethral System for Erection (MUSE) consists of a polypropylene applicator with a hollow stem 3.2 cm in length and 3.5 mm in diameter. The tip (measuring 3 or 6 mm in length) contains a semisolid pellet of medication that is available in four dose strengths: 125, 250, 500, and 1000 μg. Alprostadil is administered while the subject is in a sitting or standing position by fully inserting the stem of the applicator into the distal urethra. A button is depressed to deposit the pellet. A gentle rocking of the applicator from side to side will separate the medicated pellet from the applicator tip. The patient should urinate immediately before administration, because the medicated pellet has been developed specifically to dissolve in the small quantity of urine that remains in the urethra after urination. After removing the applicator, massaging the penis for 30–60 s allows the compound to spread out and be absorbed fully.

The mechanism of action of transurethral alprostadil is based on its absorption from the urethra and transport throughout the erectile bodies by communicating vessels between the corpus spongiosum and the corpora cavernosa. Initial clinical studies have shown that more than 60% of men using MUSE in the office achieved erections rigid enough for penetration.[52–54] Results with home use were defined as a successful penetration occurring at least once during the trial: this occurred in 65–70% with MUSE *vs* 10–20% with placebo. Most of the patients used the 500 dose and 1000-μg doses, and it has actually been suggested to start treatment with the 500-μg.[55] When special patient categories were evaluated, such as spinal cord and radical prostatectomy patients, MUSE achieved erection rates that were lower than those seen in the general population.[56,57] In some of these patients, a constrictive band placed at the base of the penis would facilitate blood entrapment within the penis, resulting ultimately in better erections. An interesting application for MUSE was the treatment of the soft glans syndrome in penile implant patients.[58,59] Williams *et al*[60] demonstrated that the resumption of sexual life with MUSE led to the improvement in several important quality-of-life domains in patients and their partners.

In these studies, penile pain was the most frequent adverse effect, occurring in approximately 10% of the patients. Interestingly, Fulgham *et al*[61] followed the algorithm recommended by the manufacturer and used MUSE in the office in 115 consecutive men with erectile dysfunction. By using a 5-point scale to measure penile rigidity, they achieved a maximum score of 4–5 in 13.2% of patients using the 500-μg dose and 30% of patients using the 1000-μg dose. A significant proportion of these patients showed some decrease of both systolic and diastolic blood pressure after the administration of MUSE. A total of 20% of patients experienced at least one adverse event. The authors concluded that no more than 30% of patients at any given time using any dose achieved erections sufficient for intercourse during in-office testing. Of note, because of this limited efficacy, discomfort, pain, and burning associated with treatment, and cost, more than 80% of patients did not continue to use MUSE at home. The latter study seems be to somewhat confirmed by Mydlo *et al*,[62] who showed that most patients who did not respond to MUSE did respond to sildenafil, whereas patients in whom sildenafil failed responded to MUSE in less than 1%

of cases. The same authors[63] also showed that a significant proportion of patients who did not respond to either intraurethral alprostadil or sildenafil monotherapy did respond to the combination of the two drugs. Patients with a higher education, greater persistence, and more realistic expectations were more satisfied with combined therapy.

Trials comparing intracavernosal vs *intraurethral therapy*

Intracavernosal injection therapy with alprostadil seems to offer a better efficacy profile than the intraurethral route with the same drug. Shabsigh *et al*[64] performed a crossover, randomized, open-label, multicenter study in 111 patients with erectile dysfunction of at least 6 months' duration that compared the efficacy, safety, and patient preference of intracavernous injections of alprostadil alfadex (EDEX) with MUSE plus optional ACTIS. The study showed that more EDEX than MUSE administrations resulted in an erection sufficient for sexual intercourse (82.5% *vs* 53.0%) and that significantly more patients using EDEX achieved at least one erection sufficient for sexual intercourse (92.6% *vs* 61.8%, $P < 0.001$). Patient and partner satisfaction was greater with EDEX, whereas overall adverse events were similar with both treatments. Porst[65] reported similar results in 103 unselected patients treated with MUSE up to 1000 μg and intracavernous alprostadil up to 20 μg. There was a significant difference in cavernosal artery end-diastolic velocity at duplex examination performed after administration of either intraurethral or intracavernosal alprostadil, showing that the former treatment was not able to induce complete smooth muscle relaxation. Interestingly, adverse effects, namely penile pain, were greater in the MUSE-treated patients. The finding that intracavernosal alprostadil is able to produce erections with better rigidity compared with intraurethral alprostadil has also been shown by other investigators.[66,67] However, MUSE has been reported to be effective in 58% of patients who did not previously respond to intracavernosal injections of alprostadil.[68]

Topical pharmacological therapy

Nitroglycerin

Organic nitrates are potent dilators of arteries and veins and relax most smooth muscles. The vasodilating effects of topical nitrates have been used successfully in the management of ischemic heart disease and Raynaud disease. Clear effects of nitroglycerin have been demonstrated also on penile erectile tissue. A measurable vasodilatory response to nitroglycerin ointment has been shown by color Doppler sonography, and a definite relaxation of strips of penile cavernous tissue induced *in vitro* by nitroglycerin has also been demonstrated.[69]

Placebo-controlled studies have shown the occurrence of partial or full erections after topical administration of nitroglycerin in patients with psychogenic and organic impotence, neurogenic impotent patients being the most responsive to the drug.[69,70]

Nitroglycerin is usually applied on the penile shaft and glans penis either as 2% ointment (2 cm) or as a plaster that releases 10 mg of nitroglycerin throughout 24 h. The ointment is usually applied 30–60 min before intercourse, whereas the plaster is usually applied for 2–4 h and removed immediately before intercourse. Both these methods include the use of a condom to prevent the transmission of the drug to the partner, with potential adverse effects such as spousal headache. It has also been reported that the application of nitroglycerin ointment to the perineal area exclusively caused erectile responses similar to those observed after genital application of the drug, and this obviated the need to wear a condom to prevent adverse effects to the partner. Adverse effects reported by patients included mild headache, with only rare instances of other systemic effects.

Isosorbide nitrate, another nitric oxide donor, has been used in combination with aminophylline and co-dergocrine mesylate in 36 men with erectile dysfunction. Of these, 21 reported full erection and satisfactory intercourse without major adverse effects.[71] However, this positive result was not confirmed by others.[72]

Minoxidil

Minoxidil is a vasodilator that acts directly on arterial smooth muscle and has been used to treat hypertension. The primary mechanism of action of minoxidil is by opening potassium channels in the membrane of vascular smooth muscle cells. The commercially available form is a 2% solution and a maximum dose of 1 mL (0.28 mg) is suggested by the manufacturer. Conflicting results have been reported in the literature regarding the erectogenic effects of minoxidil. Under laboratory conditions, application of 1 mL of a 2% minoxidil solution on the glans penis caused greater changes of penile tumescence and rigidity and of arterial function rather than administration of 2.5 g of 10% nitroglycerin ointment and placebo.[73] However, when the same doses of minoxidil were used in a clinical setting, this drug appeared to be of minimal utility in improving patients' sexual activity.[74,75] This

striking difference may be due to different criteria in assessing the erectile response, that is, in the clinical studies only patients achieving erections adequate for vaginal penetration were considered responders.

Adverse effects after topical administration of minoxidil were minimal and included a burning sensation on the glans penis in a few patients.

Papaverine

The effect of topical administration of papaverine under the form of a 7.5%, 15%, and 20% gel has been recently assessed in a phase 1, placebo-controlled study.[76] Drug amounts applied ranged from 133 to 500 g in a dose-ranging fashion. After application of this papaverine base gel to the scrotum, perineum, and penis of 20 patients with organic impotence, cavernous artery diameter was significantly increased in most. However, full clinical erections were present in only 15% of patients but were also present with the placebo preparation. Topical papaverine gel appears to be well tolerated after genital and forearm application. A significant diminution in blood pressure was present at 15 and 30 min after application to the forearm. Papaverine gel is not as effective as intracavernous injection therapy but could be promising at higher concentrations or in combination with other skin enhancers.

Prostaglandin E_1

PGE_1 has been combined with SEPA (2-n-nonyl-1, 3-dioxolane), a transdermal permeation enhancer that in an *in vitro* study was shown to enhance the transport of alprostadil across human skin *in vitro*. McVary *et al*[77] evaluated and compared the use of this transdermal permeation enhancer in a gel formulation containing alprostadil for systemic effects, local tolerance of the penis, and effectiveness in inducing erection in patients with erectile dysfunction. Application of PGE_1 gel correlated positively with erectile response since 67–75% of patients had an erection compared with 17% of controls ($P < 0.001$).

Conclusions

At present, oral pharmacotherapy represents the first-line option for most patients with erectile dysfunction. Patients who do not respond to oral therapy or those who are not eligible for this treatment are considered for second-line treatments, which include intracavernosal injections, intraurethral suppositories, or topical agents. Currently, intracavernosal injection therapy is associated with the highest efficacy within this group; however, the major limitation of this approach is represented by its high attrition rate.[78–80] In addition, intraurethral administration of alprostadil seems to have a limited role in the future in view of the close advent of new extremely safe and effective oral drugs. Topical agents remain a very attractive option with a potential to become the preferred first-line treatment if an effective system to facilitate skin and tunica permeation is found.

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Appendix

Open discussion following Dr Montorsi's presentation

Dr Porst: We saw in all the injectable trials dropout rates after 18 months or after 2 y of around 50–55%. We now see the same dropout rates with Viagra. There's no difference at all. That means we see no difference between the injectables and the orals. What is the reason behind this?
Dr Montorsi: It could be that all of the patients have the same feelings. It's not related to the difficulty in using the injection. The major causes are always lack of efficacy and sometimes dissatisfaction with treatment. Cost is another issue, and there is a cost issue also for the oral pills. Lack of support is another issue. I strongly believe that patients who are using oral drugs, not only injections, also need to be supported.
Dr Riley: The other reason, of course, is the partner.
Dr Nehra: We all see these dropout rates at 18–24 months with both oral and injectables. The question is, do you think that this is progression of disease or deterioration of function? It's not lack of efficacy.
Dr Pryor: No, it's not a lack of efficacy. Honestly, it remains in secrecy for me. What I learned was that many patients who are also responding to Viagra are not refilling their prescription. Maybe the secrecy is the attitude of the spouse. We don't have any data about this. I guess we have to do a lot of research in this direction to learn more about the reasons for dropouts in both local and oral therapies.
Dr Althof: I don't think we're asking the right questions. People come in and we ask, 'Does the drug work?' which is, of course, the first question. However, I don't think we're asking the right question after that. Examples include 'what was the experience like for you' or 'what obstacles did you have to overcome in order to use the medication?' The drugs work, but the explanation for the difference between the efficacy rate and the discontinuation rate lies outside the medical arena. That's the gap that can be explained most likely by nonmedical factors: the biopsychosocial factors that the man, the woman, and the couple have.
Dr Meuleman: We recently did a long-term follow-up of our penile implantation program, and it turned out that 35% of all the men with the prosthesis didn't use it any more.
Dr Nehra: After how long?
Dr Montorsi: The mean fallout was about 7 y.
Dr Carson: Those were our data too. We look at it as the glass half full, though. I mean, 70% were using it after 10 y. But it's still the same; a third are not using it.