Medical treatment of erectile dysfunction

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Summary

There has been a tremendous increase in demand for the treatment of erectile dysfunction in the last 10 years. This has occurred partly because of a greater understanding and awareness by both the general public and clinicians, and also because there now exists a range of effective treatments. The choice of treatments is increasing rapidly and novel delivery systems which may be more patient-friendly than intracavernosal injections are now becoming available. We review the published data on effectiveness and safety of the currently available treatments and discuss recent advances in oral therapy, as these drugs are likely to become available in the near future.

Keywords: erectile dysfunction; intracavernosal injections; testosterone supplementation; yohimbine

Impotence or erectile dysfunction is the inability to attain and/or maintain penile erection for satisfactory sexual intercourse. There has recently been an increase in interest in the management of erectile dysfunction, partly because of a greater awareness amongst clinicians and the public, but also because there is an increasing array of effective treatments.

Erectile dysfunction is recognised as a common problem with an overall incidence of around 10% throughout all ages.^{1–3} The incidence increases with age and is reported as 52% in men aged between 40–70 years old.⁴ At special risk are arteriopathies⁵ and diabetics. In a recent questionnaire study by Hackett of 250 diabetics and 981 age-matched controls in the community, the incidence was 53% and 26%, respectively.⁶

Erectile dysfunction is also a hidden condition; it is seldom inquired about as part of a routine consultation and the patient rarely volunteers information because of embarrassment and a feeling that little can be done. A recent study reported that 50% of sufferers had not discussed it with anyone and only 10% of non-diabetics with erectile dysfunction had approached their general practitioner.⁶ Of those who did discuss it with their general practitioner, no treatment was offered in 40% of cases and of those treated only 10% of patients found treatment to be satisfactory.

These figures for diagnosis and successful therapy are very low. We will describe the range of medical therapies for erectile dysfunction, which are often very effective and therefore reduce the significant morbidity associated with this condition.^{7,8}

Intracavernosal vasoactive injections

Since Virag's letter in the *Lancet* in 1982⁹ intracorporeal vasoactive agents have become a significant part of the diagnosis and treatment of erectile dysfunction. The technique is accepted as being very effective as long as there is no severe arterial or venoocclusive problem.⁸ Initially the agent of choice has been papaverine, sometimes given in combination with phentolamine. However, it is now generally agreed that prostaglandin E1 (alprostadil, PGE1) is the agent of choice because of efficacy and safety.

PROSTAGLANDIN E1 (PGE1)

Effectiveness

There are a multitude of publications on the use of PGE1. One large multicentre trial of 187 patients with erectile dysfunction reported good or very good patient satisfaction in 91% of patients.¹⁰ In a study by Stackl of 550 sufferers, 70% reported a full erection lasting for more than 30 minutes and all were adequate for vaginal penetration.¹¹ More recently, in an open flexible-dose study of 683 men with erectile dysfunction, 11 924 of 13 762 PGE1 injections given (87%) resulted in a satisfactory sexual performance.¹² Satisfaction rates of between 77% and 86% amongst partners was also reported.^{10,12}

Safety and side-effects

PGE1 occurs naturally in human tissues.¹³ There is no significant rise in levels of PGE1 in the systemic circulation on intracavernosal injection and it is metabolised by the lungs with a half-life of about 1 min.¹⁴ This perhaps explains why the rate of priapism, the most serious side-effect of intracavernosal injection therapy, is reduced with PGE1. With PGE1 the reported rate of priapism is 1–1.3%,^{12,14} compared with 2.3–15% on papaverine.⁸ The other frequently reported side-effect is pain on injection, sometimes as high as 16.8%. However, this is usually mild and rarely interferes with sexual intercourse.¹⁴ Also reported are haematoma (1.5%), local fibrosis, and haemosiderin deposits (0.1%).^{12,14}

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Prescribing and injecting

To find the lowest effective dose in patients with erectile dysfunction of a psychogenic or neurogenic aetiology, it is best to increase from 2.5 µg of PGE1 in 2.5-µg increments at different visits. In a recent single-blind dose escalation study of 201 men, the median effective (70% rigidity for >10 min by RigiScan testing) dose was 3.0, 4.0, and 5.0 µg in the psychogenic, neurogenic, and vasculogenic aetiological groups, respectively.¹² However, many patients with erectile dysfunction of a vasculogenic aetiology require a significantly higher dose of PGE1. In a recent study a maintenance dose of 20 µg was necessary in patients with erectile dysfunction of vasculogenic aetiology, compared with 5 µg in patients with a neurogenic aetiology. Therefore, in patients with erectile dysfunction of vasculogenic cause, an initial test dose of 10 µg is reasonable.¹⁵ Once the correct dose is determined, and after full discussion on the possible risks, including priapism, consent should be obtained before initiating home self-injection.

The majority of patients cope well with the injection, although abdominal obesity or poor eyesight can be significant obstacles. In these patients an autoinjector or teaching the partner to inject may help. Once confident to self-inject they should do so not more than every 3 days and if possible alternate the side to be injected.

OTHER INTRACAVERNOSAL AGENTS

Vasoactive intestinal polypeptide and phentolamine

Vasoactive intestinal polypeptide (VIP) is a postganglionic neurotransmitter which seems to have a role in the erectile process. VIP is described as a 'facilitator' of erections because intracavernosal injection leads to tumescence only.¹⁶ A combination of VIP and phentolamine can be very effective.^{17 18} In a study of 52 men with erectile dysfunction of mixed aetiology but full response to papaverine, intracorporeal injection of 30 µg of VIP and 0.5–2 mg of phentolamine led to a functionally rigid erection in 100% of cases.¹⁷ At 6 months follow-up no patient had complained of pain or suffered a complication such as corporeal fibrosis or priapism. VIP and phentolamine would seem to be a very promising, safe and efficacious treatment for erectile dysfunction and maybe an especially important alternative for patients who suffer PGE1-induced pain. At present this combination is currently only available on a named-patient basis in hospitals.

Moxisylyte hydrochloride

Moxisylyte is an α1-blocker and has erectogenic activity by antagonising noradrenaline. In a placebo-controlled study of men with neurogenic erectile dysfunction an injection of 10–30 mg of moxisylyte resulted in a full erection in 58% compared with none in the placebo group.¹⁹ More recently, in a comparative study, intracavernosal injection of moxisylyte resulted in successful sexual intercourse in 46% of patients compared with 81% of patients using PGE1. PGE1 is a more effective treatment for erectile dysfunction than moxisylyte but moxisylyte may have a role in patients with PGE1-induced pain, fibrosis, or priapism.

Linsidomine (SIN-1)

SIN-1 is the active metabolite of the anti-anginal drug molsinomine. It liberates nitric oxide (NO) and this leads to cavernosal smooth muscle relaxation through the cGMP pathway. Initial studies with SIN-1 appeared promising with 46% of men with erectile dysfunction of mixed aetiology attaining a functional erection,²⁰ while in a group of patients with psychogenic and neurogenic erectile dysfunction, 97.8% of patients were satisfied by their response to SIN-1.²¹ More recently, however, in a double-blind comparative cross-over study with SIN-1 and PGE1, SIN-1 did not produce a functional erection in any of the 40 patients. The authors concluded that PGE1 was superior and that "there can be no place for SIN-1 in the treatment of erectile dysfunction".²²

Nitroprusside

Nitroprusside also leads to cavernosal smooth muscle relaxation through cyclic GMP (cGMP) by its ability to release NO. In a single-blind cross-over study in 60 patients comparing 300 µg of nitroprusside with 20 µg of PGE1, 15% of patients attained a full erection with nitroprusside compared with 20% with PGE1.²³ However, nitroprusside is chemically unstable and can cause significant hypotension. For these reasons, its role in the treatment of erectile dysfunction would seem limited.

Figure 1 Vacuum device with diagrams showing components and use. By kind permission of Mentor Surgical Products

Calcitonin-gene-related-peptide

Calcitonin-gene-related-peptide is thought to be a parasympathetic neurotransmitter and has been shown *in vitro* to relax strips of cavernosal smooth muscle. By itself it has been shown to cause tumescence but not rigidity. In combination with PGE1, 56% of patients had a full erection, however, as there was no comparison with PGE1 alone in the study,²⁴ the role of calcitonin-gene-related-peptide is not clear. Also, to date, follow-up is too short to say whether its use leads to reduced pain, fibrosis, or priapism rate.

Chlorpromazine

In a 2-year study with 163 patients, a mixture of PGE1 and chlorpromazine was shown to be as effective as PGE1 and phentolamine.²⁵ Chlorpromazine may therefore be a useful substitute for phentolamine, as it is less expensive. It has also been shown that when chlorpromazine is substituted for phentolamine in combinations with papaverine or papaverine-plus-PGE1 there is no loss of efficacy.

External vacuum devices

For patients with erectile dysfunction who cannot tolerate or do not respond to intracavernosal injections, there is a choice between a penile prosthesis or a vacuum device. A vacuum device works by creating penile congestion and enough rigidity to allow penetration (figure 1).²⁶ There are no comparative controlled studies and most of the questionnaire reviews are carried out by the manufacturers themselves.²⁷ However, a satisfaction rate of 70% was reported by Price in diabetics, who also emphasized the importance of a stable relationship for success.²⁸ One major disadvantage to the patient is that these devices are not available on the National Health Service and cost £200 or more. Of the 60% who were able to get an adequate erection, only one third purchased a device, claiming price as the limiting factor.²⁹ There are few side-effects; some complained of pain and bruising at the site of the constricting rubber ring at the base of the penis and in a minority the partner found it an unacceptable method.²⁸

Although not universally popular, for some patients who cannot tolerate intracavernosal injections or are too elderly or unfit to be offered a penile prosthesis, a vacuum device may be a very effective treatment and it does not carry the risk of priapism.

Yohimbine

Yohimbine is an α_2 -adrenoreceptor blocker derived from the bark of the yohimbe tree. It has been used for many years as an aphrodisiac and as a treatment for erectile dysfunction. Its effectiveness has been controversial but there is enthusiasm.^{30 31 32} A double-blind cross-over trial with 82 patients showed a positive response in 34%.³⁰ In a controlled trial, Morales reported a good response in 43% but a high placebo response of 27%.³¹ Selection of patients seems to improve the success rate. Younger patients with recent onset (less than 2 years), less severe arterial or venous disease, and with testosterone levels at the higher end of the normal range seem to do better.³⁰ Side-effects such as anxiety and headache were reported as low and mild. Because of the low side-effect rate and the possible benefits it is reasonable to try yohimbine as a first-line treatment in selected patients. The therapeutic dose is variable and must be titrated up to eight tablets a day in divided doses. If there is to be any beneficial effect it usually takes 2 to 3 weeks before it becomes apparent.^{30 31} Alternatively, five tablets of yohimbine can be taken when required 30 minutes prior to sexual activity.

Testosterone replacement and supplementation

Testosterone can be given orally, by injection or implant, and now by a transdermal route (patch). Oral administration of testosterone is an unreliable route for increasing testosterone levels and injections or implants, both invasive techniques, are needed to sustain increased levels. The testosterone patch is a convenient and noninvasive method of obtaining controlled and sustained increases in testosterone levels.³³ However, the use of the testosterone patch has been limited to date, probably because of problems with skin irritation.

Testosterone replacement in men who are truly hypogonadal is generally accepted as beneficial.³⁴⁻³⁶ However, the relationship between erectile dysfunction and testosterone is controversial, although there is evidence that nocturnal erections are androgen dependent. However, hypogonadal men have been shown to have a normal erectile response to erotic stimuli,^{37 38} as have a group of sex

Table 1 Current medical therapies for erectile dysfunction.

	Advantages	Disadvantages
Intracavernosal injection		
PGE1	Effective Safe Priapism (<1%) Wide range of dose available Licensed for treatment	Pain (10%) Fibrosis (2%)
VIP and phentolamine Moxisylyte	Effective Pain not a problem No pain, fibrosis reported Good alternative if patient has complications of PGE1 therapy Very effective in psychogenic dysfunction Licenced for treatment	Available on named patient basis only Not as effective as PGE 1 Further trials and follow up required
Vacuum constriction device	Simple Effective	Patients and partner may have difficulty in acceptance. Different quality of erection, often cold penis and not full rigidity
Oral treatments		
Yohimbine	May be effective in selected patients and those with psychogenic dysfunction Few side-effects	Low effectiveness in majority of patients Cost to patient.
Testosterone	None	No beneficial effect on erections in eugonadal men Concern over stimulation of sub-clinical prostate cancer.

offenders on the anti-androgen cyproterone acetate.³⁹ Moreover, it has been shown that testosterone levels are similar in impotent and potent elderly men.⁴⁰

Many middle-aged men complain of a group of symptoms including mental and physical tiredness, lethargy and erectile dysfunction, which is increasingly attributed to a 'male menopause'. These men are usually eugonadal but their testosterone level may be at the lower end of the normal range. There is some evidence that their well-being and sexual interest can be increased by boosting their testosterone levels by supplementation,⁴¹⁻⁴³ although rarely to a level satisfactory to the patient.⁴³ However, none of the studies have shown any beneficial effect on erectile dysfunction. Testosterone supplements carry the credible risk of stimulating a latent hormone-sensitive prostatic carcinoma and as no benefits have been demonstrated for sufferers of erectile dysfunction, its use for this indication should be resisted.

Other treatments

ORAL AGENTS

Trazodone

The antidepressant trazodone was noted to occasionally induce priapism and therefore interest developed in its possible role in treatment of erectile dysfunction. There are reports of good erectogenic activity with trazodone,⁴⁴ although no significant benefit was found in a placebo-controlled trial.⁴⁵ There are also troublesome side-effects, including drowsiness, orthostatic hypotension, nausea and vomiting.

Sildenafil (Viagra®)

Sildenafil is a novel oral therapy currently under active investigation. It is a specific inhibitor of type 5 cGMP phosphodiesterase, which is the predominate isoenzyme in the cavernosal tissue of the penis. Its inhibition leads to increased local levels of the secondary messenger cGMP,^{46, 47} leading to relaxation of smooth muscle in the cavernosal tissue. This in turn increases blood flow into the corpora cavernosa, an essential stage in the erectile process.^{48, 49} In a double-blind cross-over study of 12 patients with erectile dysfunction of no established organic cause, an objective dose-dependent increase in erectile activity as determined by plethysmography (RigiScan, Dacomed Corporation, MN, USA) was demonstrated. Ten of 12 patients reported improved erectile activity in the sildenafil group compared with two of 12 taking placebo.⁵⁰ In another double-blind placebo-controlled study of 351 men with erectile dysfunction, outcome by patient and partner questionnaire confirmed a significant dose-dependent improvement on erectile activity.⁵¹ Side-effects such as facial flushing, headaches and dyspepsia were rare and mild. Sildenafil seems to be efficacious and safe and will undoubtedly play a major role in the treatment of erectile dysfunction in the future.

Apomorphine

Dopamine receptors situated in midbrain nuclei are known to have a role in the initiation of penile erection. Apomorphine is a short-acting dopamine agonist known to cause nausea, bouts of yawning, and erections, when given by subcu-

Figure 2 Intra-urethral applicator of the MUSE system. By kind permission of Astra Pharmaceuticals

taneous injection. Conventional oral administration of apomorphine tablets is associated with nausea as a side-effect. A new controlled-release tablet for sublingual administration has been found to be associated with a significant increase in erectile activity in two placebo-controlled double-blind variable-dose studies of men with psychogenic erectile dysfunction.^{52 53} Moreover, 70% of patients achieved successful sexual intercourse at home more than 50% of the time.⁵³ Apomorphine, especially in the sublingual form, therefore seems to be a promising oral treatment for psychogenic erectile dysfunction.

Phentolamine and prazosin

Alpha-adrenergic antagonists such as phentolamine and prazosin have been reported to have erectogenic activity by reducing the tone of the cavernosal smooth muscle. Erectile response rates of 30–40% were reported with buccal administration of phentolamine, compared with 15–20% with placebo.⁵⁴ Although some improvement in erectile activity compared with placebo was noted in men over 50 years of age, this increase did not reach statistical significance.⁵⁵ Oral prazosin was found to be significantly more effective than placebo in 65 men with psychogenic erectile dysfunction (response rate 70% *vs* 26% on placebo).⁵⁶ Alpha-adrenergic antagonists, of which yohimbine is also one, can be effective in the treatment of psychogenic erectile dysfunction but their role in organic erectile dysfunction is very limited. Patients may also be troubled by retrograde ejaculation as a side-effect of alpha-blocking medication.

Red ginseng

Ginseng has been associated with increased vitality and potency for many years. In two placebo-controlled studies in men with psychogenic erectile dysfunction, no increase in objective parameters of erectile function with RigiScan® monitoring or haemodynamic measurements were shown with Korean red ginseng.^{57 58} Both studies, however, showed significantly increased patient-perceived duration and rigidity of erections, and overall satisfaction with ginseng administration (effectivity 60% *vs* 30% on placebo).

PGE1: ALTERNATIVE ROUTES OF ADMINISTRATION

PGE1 can be given not only as an intracavernosal injection but also transurethrally,⁵⁹ known as MUSE (medicated urethral system for erection, figure 2), and topically as a gel.⁶⁰ Information regarding the effectiveness of topical PGE1 is limited but in one placebo-controlled study significant increases in cavernosal artery blood flow was noted, although only two of the nine men attained an erection.⁶⁰ The MUSE system involves the placement of a PGE1 pellet into the urethra by an applicator after the man has urinated.⁶¹ Up to 80% of the PGE1 is absorbed by the urethral mucosa within 10 minutes of administration and significant increases in cavernosal artery blood flow have been shown.⁶² The evidence of the safety and efficacy of the MUSE system comes from a double-blind placebo-controlled prospective study of 1511 men aged between 27 and 88 years with erectile dysfunction of varying aetiology.⁶¹ On clinic testing, an erection adequate for sexual intercourse was attained in 65.9% of administrations. In the home treatment phase of the study administration of PGE1 transurethrally was followed by sexual intercourse in 50.4% compared with 10.4% in the placebo group. The MUSE was effective regardless of age or the aetiology of the erectile dysfunction. Penile pain was noted in 10.8% of administrations of transurethral PGE1 and affected 32.7% of men. However, only 2.4% discontinued because of the pain. Other adverse effects such as dizziness, hypotension and urethral trauma occurred very rarely. In the 3 months of the study there was no evidence of penile fibrosis or any episode of priapism. It would seem that transurethral PGE1 is not only an attractive treatment option but is safe and effective. A study comparing MUSE with intracavernosal PGE1 is now required.

TOPICAL AGENTS

Glycerol trinitrate

A glycerol trinitrate cream has been shown to cause marked dilatation of the cavernosal arteries when applied to the penis; however, only tumescence occurred, with inadequate rigidity for penetration.⁶³ Not only is efficacy poor but side-effects, including hypotension and headache, are a problem.

Triple vasodilator combination

A topically applied cream containing three vasodilators (3% aminophylline, 0.25% isosorbide dinitrate and 0.05% co-dergocrine mesylate) was studied in a randomised double-blind placebo-controlled cross-over trial in 36 men with erectile dysfunction of mixed aetiology.⁶⁴ Overall, the results were encouraging,

Table 2 Effective medical treatments for erectile dysfunction in development

	Advantages	Disadvantages
Intraurethral PGE1 (MUSE)	Effective in 70% of cases No injection needed	High dose required Unpredictable response Longer follow-up and a comparative trial with intracavernosal PGE1 needed
Sildenafil (Viagra®)	Oral medication Very effective in cases of psychogenic aetiology Can be taken when required	Effectiveness in cases with organic aetiology to be determined

with 58% of men attaining an erection adequate for sexual intercourse with the active cream compared to 8% using the placebo. The cream was particularly effective in men with psychogenic erectile dysfunction, with eight of nine men responding fully. However, only two of seven men with arteriogenic erectile dysfunction responded adequately. In laboratory testing with duplex scanning, a significant increase in penile arterial flow was noted on application of the active cream compared to the placebo.

Conclusions

Erectile dysfunction is common, and its morbidity is significant, under-diagnosed and under-treated. Hackett reported that only 10% of a control group with erectile dysfunction had consulted their general practitioners, although 80% said they would like to discuss it if an effective treatment existed.⁶ More disappointing is that of those that were treated only 10% found it useful.

Effective medical treatment for erectile dysfunction does exist, intracavernosal injections and vacuum devices reportedly giving satisfactory treatment in more than 70% of cases. Although these techniques may seem unspontaneous or cumbersome, they are well tolerated by the patient and partner, especially if they are in a stable relationship.

Yohimbine has very few side-effects and can have a positive response; it is therefore worth trying in selected patients. Testosterone supplementation will have an effect on many systems and the risks and benefits are not known; there is no evidence that it is beneficial in the treatment of erectile dysfunction in patients with normal testosterone levels.

Although there are currently available treatments for erectile dysfunction which are safe and effective, what everyone would wish for is a convenient tablet that could be taken when sexual intercourse is desired. Although not yet available, the specific cGMP phosphodiesterase inhibitors such as sildenafil are a significant hope for the future.

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