Endocrine, *vol. 23, nos. 2–3, 149–155, March–April 2004* 0969–711X/04/23:149–155/$25.00

Intracavernous Pharmacotherapy for Erectile Dysfunction

Anthony J. Bella and Gerald B. Brock

The Department of Surgery, Division of Urology, St. Joseph's Health Center, The University of Western Ontario, London, Ontario, Canada

With the advent of phosphodiesterase type-5 inhibition as oral therapy, intracavernous injection of vasoactive agents has been relegated to second-line therapy for most patients with erectile dysfunction. However, the future of this category of agents remains bright as an ever-expanding number and combination of agents in use and under investigation will likely make intracavernous injection more appealing as greater efficacy, tolerability, and more rapid onset is attained. In this article, functional anatomy and physiology of human penile erection is reviewed, as are current clinical vasoactive agents including prostaglandin E-1, papaverine, and phentolamine. Emerging therapies discussed include guanylate cyclase activators, potassium channel openers, nitric oxide donors, vasoactive intestinal polypeptide, calcitonin gene-related peptide, selective alpha-1 receptor antagonists, and gene therapy. Ongoing research continues to define new roles for this effective and safe technique, which has withstood the test of time, restoring erectile function among patients with diverse ED etiologies and a variety of co-morbidities.

Key Words: Impotence; penile erection; pharmacotherapy; vasodilator agents; injections.

Introduction

The modern era of impotence research and treatment of erectile dysfunction (ED) was sparked by the introduction of intracavernous vasoactive drugs as agents inducing penile rigidity. In the early 1980s, Virag's report of incidental erection through intracavernous injection of papaverine and the dramatic demonstration by Brindley at the annual meeting of the American Urological Association heralded the discovery of reversible pharmacotherapy able to stimulate a natural erection *(1,2)*. Within 2 yr, intracavernous injection (ICI) was widely available for home use, and provided men with an option other than surgical intervention or external appliances to restore erectile function *(3)*. Not only has ICI gained worldwide acceptance as a safe and effective treatment for ED *(4,5)*, but many of the treatment advances over the past two decades can be traced to research in erectile physiology ignited by the landmark discovery that direct injection into the corpora cavernosa created an erection *(6–8)*.

Clinically, prostaglandin E-1 (PGE-1), phentolamine, and papavarine remain the most commonly used injectable vasoactive agents for the diagnosis and treatment of ED. Continuing research has expanded our knowledge of the underlying mechanisms of ED and identified several new potential intracavernous agents. Among those agents currently under investigation are nitrosylated-adrenergic receptor antagonists *(9)*, nitric oxide donors *(10)*, vasoactive intestinal polypeptide (VIP) *(11)*, potassium-channel openers *(12)*, calcitonin gene-related peptide *(13)*, selective alpha-1-receptor antagonists *(14)*, and gaunylate cyclase activators *(15)*. The use of direct penile injection, serving as a route of delivery, holds great promise for these agents, which target a multitude of physiologic sites.

With the advent of phosphodiesterase type-5 (PDE5) inhibition as oral therapy for ED, ICI has been relegated to second-line therapy for most patients. Although ICI therapy produces a predictable clinical effect with reduced systemic absorption and side effects, the need for local needle delivery and the effectiveness of oral agents has resulted in only 14% of clinicians using ICI as their primary modality for treatment of ED *(16)*. Current treatment algorithms advocate a minimalist evaluation prior to instituting treatment with adjunctive diagnostic maneuvers suggested only in cases where a lack of satisfactory results are obtained. Guidelines, such as those published by the Canadian Urologic Association, highlight the evolving use of a minimally invasive, patient self-directed goal-oriented approach to evaluation and treatment using oral agents as first-line therapy based on efficacy, side effect profile, and ease of use *(17)*. Second-line therapies include injectable and intraurethral vasoactive agents, as well as vacuum devices. Approaches such as these are both time and cost effective, allowing for the majority of patients to achieve an effective result, without the need for extensive or specialized testing.

ICI remains a mainstay of ED management as local vasoactive therapy offers numerous potential advantages to the patient *(18)*. This nerve-independent form of reversible ther-

Received September 15, 2003; Revised November 14, 2003; Accepted December 8, 2003.

Author to whom all correspondence and reprint requests should be addressed: Anthony J. Bella, St. Joseph's Health Center–Department of Surgery, Division of Urology, F-122, 268 Grosvenor Street, London, Ontario, Canada, N6A 4V2. E-mail: susans2@sjhc.london.on.ca

Table 1
Ideal Candidates for Intracavernous Injection Therapy

Failure of first-line oral therapy
Patient use of nitrates or potential use of nitrates
Neural injury from pelvic surgery, trauma, or radiation
Diabetic patients or severe vasculopaths (often after failed first-line therapy)
Patient desire for rapid onset of erection
Patient desire for greater rigidity and duration of erection than achievable with oral agents

Table 2
Absolute and Relative
Contraindications for Intracavernous Injection Therapy

History of priapism with vasoactive drug use
Severe penile fibrosis
Use of MAOIs (monoamine oxidase inhibitors) which would limit use of phenylephrine for potential priapism
Poor visual acuity limiting needle delivery

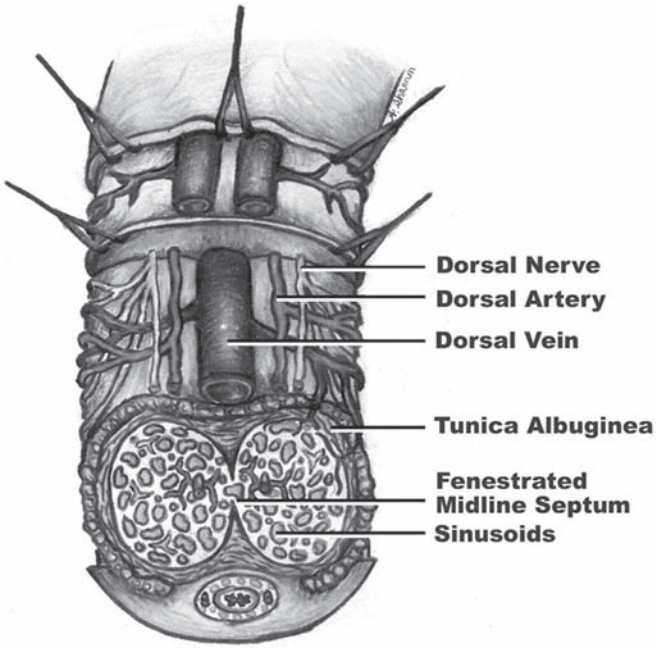

Fig. 1. Cross-sectional anatomy of the human penis.

apy simulates a natural erection with rapid onset of action and a reduced incidence of systemic complications and drug interactions compared to systemic treatment, and is efficacious for vascular and non-vascular (psychogenic, hormonal, neurogenic) forms of ED. In fact, high local concentrations are attainable even with severe forms of vascular insufficiency. In our view, for patients who fail, cannot tolerate, or are contraindicated to first-line treatments, ICI represents an important treatment option (Tables 1 and 2) *(19)*.

Recent advances in the understanding of normal erectile function, especially the role of nitric oxide (NO)–cyclic guanosine monophosphate (cGMP) second messenger pathways *(20)*, has ensured that the future of this category of agents remains bright. Novel substances, as well as standard vasoactive agents, continue to be evaluated for effect on cavernous smooth muscle and vascular function. The role of ICI in disease modification and recovery of spontaneous erectile function continues to be defined, especially for patients at greatest risk, such as those who experience a period of post-operative neuropraxia following radical prostatectomy *(21)*. The potential of PGE-1 to upregulate nitric oxide synthase activity via a high-flow effect is also under current investigation *(22)*. Perhaps the most exciting developments in ED research are in the realm of gene therapy, with trial agents delivered directly into penile circulation via ICI *(23–25)*.

Functional Anatomy and Physiology

It is the incomplete midline septum between paired corpus cavernosum of the human penis that accounts for free communication of vasoactive agents between the erectile bodies. This anatomic finding allows injection into a single corpora with rapid infusion of drug into both. Upon injection, a rapid bilateral increase in cavernous blood flow is noted, creating an equalized pressure in both corpora. This occurs in the presence of normal bilateral cavernosal artery flow, asymmetrical flow, or unilateral arterial injury. The cavernous arteries are positioned asymmetrically as shown in Fig. 1. Injury by needle puncture is unlikely, as these vessels are found in close proximity to the midline septum and in most cases a small gauge needle (27–30g) is used *(26)*. The depth of needle advancement can be gauged by the tunica albuginea, serving as a landmark anatomic structure *(27)*.

The cavernosal smooth muscles are found deep to the tunica albuginea, arranged as a series of sinusoids or potential spaces lined by endothelium *(28)*. These are separated by smooth muscle trabeculae surrounded by elastic fibers, collagen, and loose areolar tissue *(29)*. A misdirected needle during injection is easily recognized as a higher-pressure injection or patient discomfort. In our experience, we recommend rotating the needle, as the bevel will usually dislodge from the trabeculae and the vasoactive agent will enter the penis at minimal pressure. Ideally, self-injection is performed on the dorsolateral aspect of the penile shaft, staying away from the dorsal nerve, artery, and vein *(30)*. Following injection and sexual stimulation, rigidity is achieved within 2–10 min as a rapid increase in cavernosal artery blood flow leads to compression of subtunical venules located between smooth muscle of the corpora cavernosa and the inner tunica albuginea. With venous outflow blocked, intracavernous pressures reach greater than 100 mmHg. Vasoconstriction and the loss of penile rigidity occurs as a result of an increase in sympathetic tone coincident with ejaculation *(6)*.

Intracavernous injection has proven to be a robust means of treating ED owing to the underlying simplicity of agent and delivery *(31)*. Any substance that induces smooth muscle relaxation within the penis may potentiate an erection, independent of neural non-adrenergic non-cholinergic pathways. Agents in use today produce an erection by relaxing smooth muscle directly by altering calcium or potassium ion channel permeability or through direct activation or decreased degradation of second messenger molecules such as cGMP and cAMP. Recent research in laboratory animals has shown that calcium-dependent chloride channels may also serve as a future ion target for vasoactive agents *(32)*. The neural independence of ICI has resulted in efficacious treatment of ED in spinal cord injury, diabetic, and early post-prostatectomy patients *(21,33,34)*.

Prostaglandin E-1

Although prostaglandins were first discovered by Kurzrok and Lieb in 1930 *(35)*, it was not until 1986 that both Ishii and Adaikan described the potential of PGE-1 as an effective vasoactive agent for intracavernosal use in impotence *(36,37)*. Over the past two decades, PGE-1 has become the best studied of all vasoactive agents and gained widespread use for intracavernous injection and intraurethral delivery *(38)*. In 1996, PGE-1 became the first and only FDA-approved penile injectable for the management of ED.

PGE-1 modulates adenyl cyclase, upregulating the production of cAMP in the penis and leading to a decrease in free calcium concentration and subsequent cavernous smooth muscle relaxation *(39)*. Vasodilation is mediated via gap junctions within the penis. PGE-1 acts upon presynaptic neurons to modulate noradrenaline release, inhibiting sympathetic activity and further enhancing pro-erectile function *(40,41)*.

Metabolism of injected PGE-1 is through rapid pulmonary clearance of up to 90% during first passage through the lung. Plasma half-life is less than 1 min. The liver, kidney, and local metabolism within the penis contribute to the conversion of PGE-1 to inactive metabolites *(38,42)*. Rates of priapism, a potentially devastating adverse effect of ICI, are low with compiled rates between 1% and 3% *(43, 44)*. Our own clinical experience suggests that these events are often the result of rapid dose progression by the patient, missed initial injection with second attempt, or use among young and/or neurogenic patients. Gradual and progressive dose escalation by the patient will prevent most occurrences of priapism *(45)*.

Our current protocol for use of PGE-1 is focused upon informing the patient about the agent, its use, and possible side effects, as well as teaching self-injection in a comfortable, monitored environment (Fig. 2). An initial dose of 5–10 μg for the vasculogenic male is recommended, while patients with neurogenic ED or suspected normal vasculature inject with a lower dose of 2.5 μg. Under supervision, the patient himself performs the injection, followed by sexual self-stimulation in private. Adjustments are made based on response and duration of action with a goal of rigidity persisting for 15–45 min. All patients are given an illustrated information packet, which includes information on priapism, penile fibrosis and scarring, injection technique, and dose adjustment. Recommended dose increases are in increments of 2.5–5 μg, with a minimum 24 h between injections. Careful physical examination is performed prior to onset of treatment at home, with all patients informed of any penile abnormalities including preexisting fibrosis (Table 3).

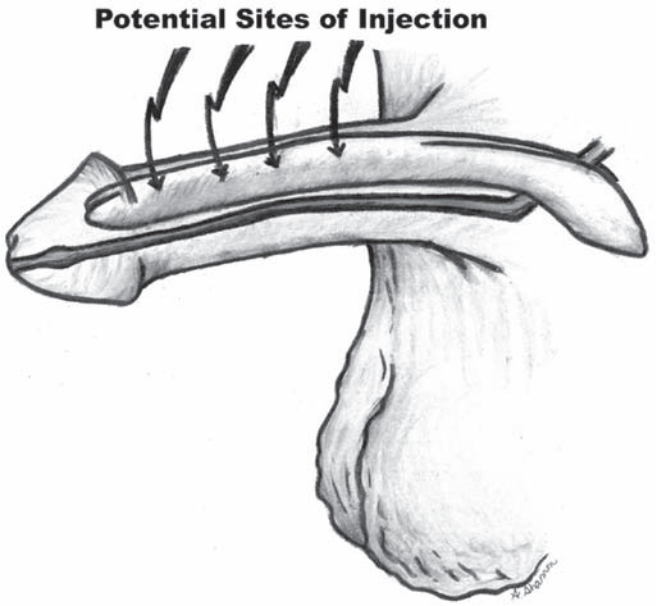

Fig. 2. Sites for intracavernous injection therapy.

Table 3
Strategies to Optimize Intracavernous Injection Therapy

Direct injection into proximal corpora
Gentle local pressure applied to injection site (2–3 min)
Comfortable, stress-free environment
Sexual stimulation following injection
Incremental dose increases if unsuccessful, until recommended dose maximum achieved (minimum 24 h between attempts)
Patient information and support

PGE-1 is the most widely utilized injectable vasoactive agent. Since its introduction for treatment of ED, a vast body of knowledge has accumulated describing the efficacy and safety of this drug. Cumulative data yield a success rate of 70–75% across ED etiologies, utilizing a median dose of 12–15 μg *(4,38,44)*. Common adverse effects include burning sensation at time of injection and bruising, with priapism (1%) and penile fibrosis (1–3%) occurring much less frequently *(4,43,44,46)*.

The question of whether long-term use of vasoactive agents promotes a return of spontaneous erection remains unanswered. Recent reports describe increased incidence of

spontaneous erection, disease modification, and improved hemodynamic parameters following long-term use of PGE-1 *(47–49)*. Objective measures have shown that PGE-1 therapy significantly increases peak systolic velocity and cavernosal arterial diameter *(50)*. Although studies report increased arterial flow enhances vasodilatation secondary to up-regulation of nitric oxide, there are conflicting clinical reports that fail to consistently demonstrate significantly improved nocturnal erections *(47,49,51)*. With further studies needed to identify which ED populations are most likely to experience genuine erectile enhancement from vasoactive drug use, we presently inform our patients that improved spontaneous sexual function may occur for a significant minority of men, but few reach the point of not requiring medication.

Patients who have failed first-line oral pharmacotherapy constitute the largest group of men considering ICI and PGE-1 *(52)*. Several recent reports have specifically addressed efficacy in this population, including Shabsigh and colleagues reporting data from a large multicenter trial using intracavernous alprostadil alfadex treatment for patients not responding to sildenafil. Prior to enrollment, patients were retried on sildenafil at 100 mg and failed as measured by the International Index of Erectile Function (IIEF) questionnaire. Patients noted 89.6% and 85.1% improvements in the ability to achieve and maintain an erection (questions 3 and 4 of the IIEF) *(53)*. The significant response rate demonstrated among sildenafil non-responders indicates that progression to second-line injection therapy is appropriate.

Discontinuation of ICI therapy remains high, with most series describing long-term dropout rates of 40–60%. Interestingly, patient attrition is often not based on objective side effects such as penile pain, fibrosis, and priapism. Rather, major determining factors include lack of patient motivation, and dissatisfaction with treatment and drug-induced erection *(54–56)*. The high dropout rate noted during the initial treatment period, and ineffectiveness as the most cited reason, underlines the importance of close patient monitoring in early therapy (Tables 4 and 5) *(57)*.

In addition to its therapeutic role, PGE-1 is frequently used in a diagnostic capacity to assess vascular flow in men with erectile dysfunction. A complete erection following intracavernous injection indicates a reasonable response to the vasoactive agent but provides no insight about the neural axis. Recent work by Elhandbly and colleagues suggests a nonresponse is due to incompetent veno-occlusive function and/or severe arterial insufficiency *(58)*.

Table 4
Inadequate Response
to Intracavernous Injection Therapy: Common Causes

Inadequate dose
Misdirected injection into wrong location (subcutaneous or trabecular)
Leakage of vasoactive agent prior to injection
Inadequate sexual stimulation
Premature ejaculation

Table 5
Common Steps
to Correct Inadequate Therapeutic Response

Reassess dose and increase until therapeutic response achieved
Review of injection technique
Evaluate timing with regards to injection and sexual stimulation
Change to more potent vasoactive agent or combination therapy if at maximum recommended dose
Use combination therapy if pain is limiting factor
Involve partner and reassure

Papaverine

Discovered by Merck in 1848, papaverine is an opium alkaloid originally isolated from the poppy *Papaver somniferum*. This agent induces relaxation of cavernous smooth muscle and penile vessels via nonspecific inhibition of phosphodiesterase, leading to increased levels of cGMP and cAMP, as well as impairment of calcium influx through blockage of voltage-dependent calcium channels *(59)*. Metabolism is hepatic, with a plasma half-life of 1–2 h.

Following Virag's report in 1982 *(1)*, papaverine was the most commonly administered vasoactive agent until the introduction of PGE-1 into clinical practice. Usually delivered in doses between 20 and 80 mg (range 5–160 mg), efficacy as monotherapy is about 55%. Although papaverine is inexpensive, effective, and stable at room temperature, compiled reports indicate an increased rate of priapism (1–6%) and fibrosis (6–12%) observed in comparison to other agents *(60,61)*. Penile pain is common following injection, likely due to the acidity of the papaverine hydrochloride formulation *(62)*. Unlike PGE-1, papaverine has not been reviewed or approved by the FDA for treatment of ED, thus limiting its use as monotherapy.

Phentolamine

The vasoactive potential of phentolamine was discovered in 1978, with early animal studies suggesting effective blockade of the epinephrine pressor response and a smaller sympatholytic effect *(63)*. An alpha-adrenergic antagonist with equal affinity for α_1 and α_2 receptors, monotherapy with phentolamine has been disappointing *(64)*. It is hypothesized that although intracavernous injection of phentolamine increases corporal blood flow, a concurrent increase in norepinephrine prevent sinusoidal relaxation *(65)*. Clinically, the role of phentolamine in the modern era is limited to use as a component of vasoactive drug combinations.

Drug Combinations

Zorgniotti and Lefleur first reported clinical use of combination therapy for self-injection in 1985, combining papa-

Table 6
Comparison of Single Agent Vs Combination Intracavernous Injection Therapy

Drug	Dose	Efficacy (%)	Priapism > 6 hours (%)	Fibrosis (%)	Drop-out rate (%)
Prostaglandin E-1	12–15 mg (range 5–40 mg)	70–75	1	1–3	40–60
Papaverine	20–80 mg (range 5–160 mg)	55	1–6	6–12	35–50
Phentolamine/papaverine	10 mg/1.25 mg–60 mg/2 mg	70	7	6–12	30–45
Trimix (PGE-1, papaverine, phentolamine)	10 mg/8 mg/0.2 mg–20 mg/20 mg/0.5 mg	75–85	1–3	2–5	25

vine and phentolamine *(66)*. Multiple series, including a review of 13,030 injections in 160 patients by Armstrong and associates, have demonstrated patient satisfaction greater than 75% and low rates of priapism or fibrosis *(67, 68)*. The main advantage of the bimix combination versus trimix (papaverine, phentolamine, and PGE-1) is stability without refrigeration *(69)*. This three agent formulation was introduced in 1991, with subsequent reviews demonstrating a level of patient satisfaction approaching 90% with decreased incidence of painful erection when compared to papaverine/phentolamine or alprostadil (PGE-1) therapy *(70,71)*. Although not approved by the FDA for treatment of ED, these drug combinations are widely available and most often utilized as second-line ICI agent therapy for men who have failed or experienced significant penile pain with PGE-1 (Table 6) *(72,73)*.

Emerging Therapies

Guanylate Cyclase Activator

YC-1 and A-350619 are novel soluble guanylate cyclase (sGC) activators, which have been shown to increase intracavernous pressure in rabbit and rat penile preparations *(15,74)*. BAY41-2272, a pyrazolopyridine derivative, has recently been shown to relax human corpus cavernosum with or without the presence of nitric oxide (NO) *(75)*. NO is released from erectile-autonomic nerves, activating soluble guanylyl cyclase, which converts GTP to cyclic GMP as part of a cascade resulting in smooth muscle relaxation, neurotransmission, inhibition of platelet aggregation, and immune response. In the penis, cGMP second messenger relaxes cavernous smooth muscle and increases blood flow into the corporal bodies, thereby eliciting and maintaining penile erection *(6,76)*. This class of agent is unique in that the potential exists for ED treatment of patient subsets lacking or having reduced endogenous NO production, such as diabetics *(77)*.

Vasoactive Intestinal Polypeptide

VIP, a potent smooth muscle relaxant isolated from small intestine, was first described as a neurotransmitter for penile erection in 1986 *(78)*. While VIP receptors are present in cavernous smooth muscle, initial studies using intracavernosal VIP alone produced disappointing penile responses. However, a combination of papaverine and VIP produced penile rigidity similar to that with papaverine and phentolamine *(11,79,80)*. The potential clinical role of VIP appears to be in combination therapies, as was shown in a recent double-blind, placebo-controlled study of phentolamine and VIP which reported an efficacy approaching 85% *(81)*.

Nitric Oxide Donors: Sodium Nitroprusside and Linsidomine (SIN-1)

Early animal studies reported that sodium nitroprusside, a nitric oxide donor, increased nitric oxide release in a dose-dependent manner *(82)*. By relaxing vascular smooth muscle, sodium nitroprusside dilates peripheral arteries and veins. Although its half-life is only 1–2 min, the potential exists for systemic hypotension with this agent *(83)*. The lower potency of sodium nitroprusside compared to PGE-1 and a risk of hypotension not fully elucidated currently limits the clinical application of this agent *(84)*.

Linsidomine (SIN-1) also upregulates cGMP production by releasing nitric oxide. Clinical trials have shown that intracavernous SIN-1 is well-tolerated but has a lower smooth muscle relaxing effect than either PGE-1 or phentolamine/papaverine *(85)*. Given the observed erectile and hemodynamic response to SIN-1, research continues into combinations with other vasoactive agents which may yield therapeutic synergies salvaging some men who are otherwise unresponsive to current ICI regimens *(11,86)*.

Calcitonin Gene-Related Peptide (CGRP)

A potent vasodilator, CGRP has been shown to induce dose-related increases in penile blood flow with CGRP-specific receptors that are located in cavernosal nerves, arterial walls, and smooth muscle *(13,87)*. A trial of combined CGRP and PGE-1 therapy has been reported in 59 men with no response to papaverine–phentolamine and 6 with cavernous fibrosis; 35 and 5 patients had an erectile response, respectively *(88)*. These early results may indicate that combined CGRP and PGE-1 therapy may have a role in future treatment of selected ED patients *(89)*.

Selective Alpha-1 Receptor Antagonists and Nitrosylated-Adrenergic Receptor Antagonists

Clinically less potent than phentolamine and papaverine, selective alpha-1 receptor antagonists such as moxisylyte

and abanoquil are considered safe vasoactive agents due to their short duration of action (half-life 3–4 h), low systemic side-effects, and low incidence of priapism *(90,91)*. By competitive blockage of α_1 adrenoreceptors, these drugs relax cavernous smooth muscle precontracted by norepinephrine. Clinically, Buvat and colleagues were able to demonstrate a 68% satisfactory erectile response with moxisylyte, compared to 79% with papaverine, with a significant reduction in priapism (1.3% vs 8.8%) and corporeal fibrosis (1.3% vs 32%) *(92)*.

Nitrosylated-adrenergic receptor antagonists are a new class of molecule that have been shown to induce concentration-dependent relaxation of rabbit and human corpus cavernosum in in vitro studies. This agent's dual function of nitric oxide donor and alpha-ARA also induced penile erection in animal models, suggesting possible therapeutic value as a potential agent for treatment of impotence *(9)*.

Potassium-Channel Openers

This class of vasoactive agent, which includes PNU-83757, nicorandil, pinacidil, and cromakalim, has been shown to induce relaxation of penile erectile tissue through opening of potassium channels and subsequent hyperpolarization in various animal models *(93,94)*. Further experiments utilizing human corporeal tissue strips demonstrated potassium channel modulation of corporeal smooth muscle membrane potential and transmembrane calcium flux *(95)*. The efficacy, safety, and tolerability of PNU-83757 has been studied in a single-dose, single-blind, placebo-controlled clinical trial involving 66 men with ED of vascular etiology. Encouraging results demonstrated 24 of 25 patients receiving active drug obtaining a partial (15) or full (9) erection with no cardiovascular side-effects or penile pain noted *(96)*.

Gene Therapy

Preclinical work is ongoing and has clearly demonstrated "proof-of-concept" for the utility of gene therapy for the treatment of erectile dysfunction. Various targets including nitric oxide synthase and calcitonin gene-related peptide are under current investigation through the use of ICI in animal models *(23–25,96,97)*. In his review of clinical development of gene therapy for treatment of ED, G.J. Christ remarks that the limiting step "will not lie in the ability to identify relevant molecular targets that are amenable to gene therapy for erectile dysfunction, but rather in the safety, specificity and longevity of those targets" *(98)*. Clearly much work remains, but the future role of ICI in this realm of treatment possibilities continues to expand.

Conclusion

Intracavernous delivery of vasoactive drugs remains essential to the comprehensive therapeutic management of male erectile dysfunction. This effective and safe technique has withstood the test of time, restoring erectile function among patients with diverse ED etiologies and a variety of co-morbidities. In the near term, its role will likely remain as the most important means of salvaging men who fail or cannot tolerate oral agents. In addition to its role in the direct delivery of gene therapy agents into penile circulation, the ever-expanding number and combination of vasoactive agents in use and under investigation will likely make ICI more appealing as greater efficacy, tolerability, and more rapid onset is obtained. Indeed, the future of this category of agents for treatment of erectile dysfunction remains bright.

References

1. Virag, G. (1982). *Lancet* **ii,** 938.
2. Brindley, G. (1983). *Brit. J. Psychiatry* **143,** 332–337.
3. Zorgniotti, A. W. and Lefleur, R. S. (1985). *J. Urol.* **133,** 39–41.
4. Porst, H., Buvat, J., Meuleman, E., Michal, V., and Wagner, G. (1998). *Int. J. Impot. Res.* **10,** 225–231.
5. Sunderam, C. P., Thomas, W., Pryor, L. E., Sidi, A. A., Billups, K., and Pryto, J. L. (1997). *Urology* **49,** 932–935.
6. Andersson, K. E. and Wagner, G. (1995). *Physiol. Rev.* **75,** 191.
7. Burnett, A. L. (1997). *J. Urol.* **157,** 320.
8. Stief, C. G., Uckert, S., Becker, A. J. et al. (1997). *J. Urol.* **157, 355** (abstract).
9. de Tajada, I. S., Garvey, D. S., Schroeder, J. D., et al. (1999). *J. Pharmacol. Exp. Ther.* **290(1),** 121–128.
10. Truss, M. C., Becker, A. J., Djamilian, M. H., Stief, C. G., and Jonas, U. (1994). *Urology* **44,** 553–556.
11. Sazova, O., Kadioglu, A., Gurkan, L., et al. (2002). *Int. J. Impot. Res.* **14,** 44–49.
12. Vick, R. N., Benevides, M., Patel, M., et al. (2002). *J. Urol.* **167,** 2618–2623.
13. Bivalacqua, T. J., Champion, H. C., Abdel-Mageed, A. B., Kadowitz, P. J., and Hellstrom, W. J. (2001). *Biol. Reprod.* **65,** 1371–1377.
14. Marquer, C. and Bressolle, F. (1998). *Fund. Clin. Pharmacol.* **12,** 377–387.
15. Mizusawa, H., Hedlund, P., Brioni, J. D., et al. (2002). *J. Urol.* **167,** 2276–2281.
16. WHO International Society for Impotence Research: (2000). *Erectile dysfunction*, Health Publication Ltd.
17. Canadian Urological Association Guidelines Committee**.** (2002). *Can. J. Urol.* **9,** 1583–1587.
18. Porst, H. (2000). *Int. J. Impot. Res.* **12(Suppl. 4),** S91–S100.
19. Nehra, A. (2001). *Curr. Urol. Rep.* **2,** 468–472.
20. Lue, T. F. and Dahiya, R. (1997). *Mol. Urol.* **1,** 55.
21. Montorsi, F., Guazzoni, G., Strambi, L. F., et al. (1997). *J. Urol.* **158,** 1408–1410.
22. Escrig, A., Marin, R., and Mas, M. (1999). *J. Urol.* **162,** 2205–2210.
23. Andersson, K. E. and Hedlund, P. (2002). *Int. J. Impot. Res.* **14(Suppl. 1),** S82–S92.
24. Magee, T. T., Ferrini, M., Garban, H. J., et al. (2002). *Biol. Reprod.* **67,** 1033–1041.
25. Christ, G. J., Rehman, J., Day, N., et al. (1998). *Am. J. Physiol.* **275,** H600.
26. deGroat, W. C. and Steers, W. D. (1988). In: *Contemporary management of impotence and infertility*. Tanagho, E. A., Lue, T. F., and McClure, R. D. (eds.). Williams & Wilkins: Baltimore.
27. Hsu, G. L., Brock, G. B., Martinez-Pineiro, L., et al. (1992). *Int. J. Impot. Res.* **4,** 117–129.
28. Aboseif, S. R. and Lue, T. (1998). *Urol. Clin. North Am.* **15,** 1–7.
29. Moreland, R. B. (2000). *Int. J. Impot. Res.* **12(Suppl. 4),** S39–S46.

30 Benard, F. and Lue, T. F. (1990). *Drugs* **39,** 394–398.
31 Richter, S., Vardi, Y., Ringel, A., et al. (2001). *Int. J. Impot. Res.* **13,** 172–175.
32 Karkonis, T., DeYoung, L., Brock, G. B., and Sims, S. M. (2003). *J. Appl. Physiol.* **94,** 301–313.
33 Zaslau, S., Nicolis, C., Galea, G., Britanico, J., and Vapnek, J. M. (1999). *J. Spinal Cord. Med.* **22,** 303–307.
34 Heaton, J. P., Lording, D., Liu, S. N., et al. (2001). *Int. J. Impot. Res.* **13,** 317–321.
35. Kurzrock, R. and Lieb, C. (1930). *Proc. Soc. Exp. Biol. Med.* **28,** 268.
36. Adaikan, P. G., Kottegoda, S. R., and Ratnam, S. S. (1986). In: *Abstract Book 2nd World Meeting on Impotence*. Prague Czechoslovakia.
37. Ishii, N., Watanabe, H., Irisawa, C., et al. (1986). In: *Abstract Book 2nd World Meeting on Impotence*. Prague Czechoslovakia.
38 Porst, H. (1996). *J. Urol.* **155,** 802–815.
39. Paoletti, R. (1986). In: *Prostaglandin E1 in atherosclerosis*. Sinzinger, H. and Rogatti, W. (eds.). Springer-Verlag: New York.
40. Molderings, G. J., van Ahlen, H., and Gothert, M. (1992). *Int. J. Impot. Res.* **4,** 19.
41. Italiano, G., Calabro, A., Pescatori, E. S., Marin, A., and Pagano, F. (1994). *Int. J. Impot. Res.* **6(Suppl. 1),** A22.
42 Cawello, W., Schweer, H., Dietrich, B., et al. (1997). *J. Urol.* **158,** 1403–1407.
43. The European Alprostadil Study Group. (1998). *Br. J. Urol.* **82,** 538–543.
44. Linet, O. I. and Ogrinc, F. G. (1996). *N. Engl. J. Med.* **334,** 873–877.
45. Choi, H. K., Adimoelja, A., Kim, S. C., et al. (1997). *Int. J. Impot. Res.* **1,** 47–51.
46. Hauck, E. W., Altinkilic, B. M., Schroder-Printzen, I., Rudnick, J., and Weidner, W. (1999). *Andrologia* **31,** S99–S103.
47. McMahon, C. G. (1992). *Int. J. Impot. Res.* **4,** 179–186.
48. Wespes, E., Sattar, A. A., Noel, J. C., and Schulman, C. C. (2000). *J. Urol.* **163,** 464–466.
49. Maniam, P., Seftel, A. D., Corty, E. W., Rutchik, S. D., Hampel, N., and Althof, S. E. (2001). *J. Urol.* **165,** 830–832.
50. Brock, G., Lei, M. T., and Linet, O. I. (2001). *Urology* **57,** 536–541.
51. Simonsen, U., Garcia-Sacristan, A., and Prieto, D. (2002). *J. Vasc. Res.* **39,** 283–303.
52. Nehra, A. (2001). *Curr. Urol. Rep.* **2,** 468–472.
53. Shabsigh, R., Padma-Nathan, H., Gittleman, M., et al. (2000). *Urology* **55,** 477–480.
54. Rowland, D. L., Boedhoe, H. S., Dohle, G., and Slob, A. K. (1999). *Int. J. Impot. Res.* **11,** 145–151.
55. Mulhall, J. P., Jahoda, A. E., Cairney, M., et al. (1999). *J. Urol.* **162,** 1291–1294.
56. Purvis, K., Egdetveit, I., and Christiansen, E. (1999). *Int. J. Impot. Res.* **11,** 287–299.
57. de la Taille, A., Delmas, V., Amar, E., and Boccon-Gibod, L. (1999). *Eur. Urol.* **35,** 312–317.
58. Elhanbly, S., Schoor, R., Elmogy, M., et al. (2002). *J. Urol.* **167,** 192–196.
59. Brading, A. F., Burdyga, T. V., and Scripnyuk, Z. D. (1983). *J. Physiol.* **334,** 79–89.
60. Kattan, S., Collins, J. P., and Mohr, D. (1997). *Urology* **37,** 516–518.
61. Sahin, M., Basar, M. M., Bozdogan, O., and Atan, A. (2001). *Urology* **58,** 487–492.
62. Moriel, E. Z. and Rajfer, J. (1993). *J. Urol.* **149(Pt. 2),** 1299–1300.
63. Domer, F. R., Wessler, G., Brown, R. L., and Charles, H. C. (1978). *Invest. Urol.* **15,** 404–407.
64. Stief, C. G. and Wetterauer, U. (1988). *J. Urol.* **140,** 1415–1416.
65. Juenemann, K. P., Lue, T. F., Fournier, G. R., and Tanagho, E. A. (1986). *J. Urol.* **136,** 158–161.
66. Zorgniotti, A. W. and Lefleur, R. S. (1985). *J. Urol.* **133,** 39–41.
67. Keogh, E. J., Watters, G. R., Earle, C. M., et al. (1989). *J. Urol.* **142,** 726–728.
68. Armstrong, D. K., Convery, A., and Dinsmore, W. W. (1993). *Int. J. STD AIDS* **4,** 214–216.
69. Soli, M., Bertaccini, A., Carparelli, F., et al. (1998). *J. Urol.* **160(2),** 551–555.
70. Bennett, A. H., Carpenter, A. J., and Barada, J. H. (1991). *J. Urol.* **146,** 1564–1565.
71. McMahon, C. G. (1991). *Int. J. Impot. Res.* **3,** 113.
72. Shmueli, J., Israilov, S., Segenreich, E., Baniel, J., and Livne, P. M. (1999). *Int. J. Impot. Res.* **11(1),** 15–19.
73. Baniel, J., Israilov, S., Engelstein, D., Shmueli, J., Segenreich, E., and Livne, P. M. (2001). *Urology* **56,** 647–652.
74. Miller, L. N., Nakane, M., Hsieh, G. C., et al. (2003). *Life Sci.* **72,** 1015–1025.
75. Kalsi, J. S., Rees, R. W., Hobbs, A. J., et al. (2003). *J. Urol.* **169,** 761–766.
76. Andersson, K. E. (2001). *Pharmacol. Rev.* **53,** 417.
77. Brioni, J. D., Nakane, M., Hsieh, G. C., et al. (2002). *Int. J. Impot. Res.* **14,** 8–14.
78. Adaikan, P. G., Kottegoda, S. R., and Ratnam, S. S. (1986). *J. Urol.* **135,** 638–640.
79. Kiely, E. A., Bloom, S. R., and Williams, G. (1989). *Br. J. Urol.* **64,** 191–194.
80. Becker, A. J., Uckert, S., Stief, C. G., et al. (2002). *World J. Urol.* **20,** 59–63.
81. Sandhu, D., Curless, E., Dean, J., et al. (1999). *Int. J. Impot. Res.* **11,** 91–97.
82. Trigo–Rocha, F., Martinez–Pineiro, L., Donatucci, C. F., Hsu, G. L., Lue, T. F., and Tanagho, E. A. (1995). *Int. J. Impot. Res.* **7,** 49–56.
83. Brock, G., Breza, J., and Lue, T. F. (1993). *J. Urol.* **150,** 864–867.
84. Martinez-Pinerio, L., Cortes, R., Cuervo, E., Lopez-Tello, J., Cisneros, J., and Martinez-Pineiro, J. A. (1998). *Eur. Urol.* **4,** 350–354.
85. Stief, C. G., Holmquist, F., Djamilian, M., Krah, H., Andersson, K. E., and Jonas, U. (1992). *J. Urol.* **148,** 1437–1440.
86. von Heyden, B., Brock, G. B., Martinez-Pineiro, L., and Lue, T. F. (1996). *Eur. Urol.* **30,** 502–505.
87. Stief, C. G., Benard, F., Bosch, R., et al. (1993). *Urology* **41,** 397–401.
88. Djamilian, M., Stief, C. G., Kuczyk, M., and Jonas, U. (1993). *J. Urol.* **149(Pt. 2),** 1296–1298.
89. Truss, M. C., Becker, A. J., Thon, W. F., et al. (1994). *Eur. Urol.* **26,** 40–45.
90. Giraldi, A., Wyllie, M., and Wagner, G. (2000). *Int. J. Impot. Res.* **12(S1),** S37–S40.
91. Marquer, C. and Bressolle, F. (1998). *Fundam. Clin. Pharmacol.* **12,** 377–387.
92. Buvat, J., Buvat-Herbaut, M., Lemaire, A., and Marcolin, G. (1993). *Contracept. Fertil. Sex.* **21,** 173–176.
93. Hedlund, P., Holmquist, F., Hedlund, H., and Andersson, K. E. (1990). *J. Urol.* **144,** 146–151.
94. Trigo-Rocha, F., Donatucci, C. F., Hsu, G. L., Nunes, L., Lue, T. F., and Tanagho, E. A. (1995). *Int. J. Impot. Res.* **7,** 41–48.
95. Venkateswarlu, K., Giraldi, A., Zhao, W., et al. (2002). *J. Urol.* **168,** 355–361.
96. Tirney, S., Mattes, C. E., Yoshimura, N., et al. (2001). *Mol. Urol.* **5,** 37–43.
97. Bivalacqua, T. J., Champion, H. C., Abdel-Mageed, A. B., Kadowitz, P. J., and Hellstrom, W. J. (2001). *Biol. Reprod.* **65,** 1371–1377.
98. Christ, G. J. (2002). *Curr. Opin. Urol.* **12,** 497–501.