Topical and Intra-Urethral Therapy

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SUMMARY

The management of erectile dysfunction (ED) has been completely transformed with the advent of effective oral therapy that occurred after the introduction of sildenafil in 1999. However, until the mid-1990s, the only practical method of delivering vasoactive substances to the penile erectile tissues was by direct injection into the copora cavernosa. Despite the introduction of orally effective agents, intracavernosal injection (ICI) continues to enjoy widespread acceptance by patients and urologists alike. However, despite its initial acceptance as a treatment alternative, 31–80% of men using such therapies eventually discontinue treatment for reasons relating to pain, loss of effectiveness, aversion to self-injection, and lack of interest, with drop out rates approaching 50% at 1 yr. This de facto dissatisfaction with proven effective treatments is the rationale for alternative routes for the delivery of vasoactive substances.

Intra-urethral and topical therapies for the treatment of ED have been proposed as a means to circumvent some of the negative factors associated with ICI and thus have an intrinsic appeal to many patients. Intra-urethral prostaglandin suppositories via the use of a commercial delivery system (Medicated Urethral System for Erection [MUSE]) gained Food and Drug Administration approval in 1997 and, despite recent advances and popularity in oral therapies, remain an important part of the treating physicians’ armamentarium. Currently, topical therapies for the treatment of erectile dysfunction remain in clinical trials and have yet to be approved for widespread use. They have the potential to avoid the systemic effects noted with oral therapies while being perceived as minimally invasive because they do not require needles or intra-urethral instrumentation. Topical and intra-urethral therapy may also provide benefits to patients unresponsive to systemic therapy or who use medications that cannot be taken along with such oral treatments (nitrate use).

Key Words: Erectile dysfunction; penis; topical delivery; intra-urethral delivery; MUSE.

INTRODUCTION

It is clear that there must be integrity of the neurovascular input to the corporal bodies for current oral therapies to be most effective. Men whose nerves are not spared during
radical prostatectomy generally respond more poorly to oral therapies than those whose nerves are spared (1–6). Therefore, there will continue to be a role for locally applied therapy in this subset of patients. Patients often inquire about less invasive therapies for the treatment of erectile dysfunction (ED) using oral, topical, or intra-urethral methods at the time of treatment discussion. Therefore, it is important that the practitioner be aware of the issues pertaining to such alternative therapies.

INTRA-URETHRAL THERAPY

General Principles of Intra-Urethral Agents

The concept of delivering medication via the urethra is not new. This method has been used in the treatment of urethral condyloma for years (7,8). The absorptive nature of the urethral mucosa was also demonstrated in several reports of systemic effects from urethrally instilled lidocaine, which is now commonly used as a local anesthetic for endoscopic procedures (9–11). Reports of priapism secondary to self-introduction of various substances to the urethra emphasized this as a potential route for drug therapy of ED (12,13). Despite these observations, the mechanism of translocation of vasoactive substances from the urethra into the corporal bodies has not been fully discerned. Although the urethral mucosa is not commonly used as a route of drug administration, the micro-environment theoretically appears more suitable for absorption than skin because of the presence of complex columnar cells rather than stratified squamous epithelium. Indeed, the absorption of intra-urethral prostaglandin is rapid, with less than 20% of the medication remaining in the urethra 20 min after dosing (14). Additionally, the existence of submucosal venules that communicate between the corpus spongiosum, which surrounds the urethra, and the cavernosal bodies provide a possible explanation for drug transfer. Corporal spongiosography has shown retrograde filling of the cavernous bodies through the deep dorsal vein and its circumflex branches after intra-urethral application of prostaglandin E (PGE)$_1$ (15). Regardless of the exact transfer mechanism, intra-urethral introduction of prostaglandin results in a rapid onset of hemodynamic effects in the penile vasculature—namely, increased corporal blood flow and increased arteriolar diameter, similar to those seen in intracavernosal injection (ICI) (16).

INTRA-URETHRAL THERAPY FOR ED: BACKGROUND

The use of intra-urethral delivery of a vasoactive substance as a therapeutic maneuver for ED was first published in 1993. Wolfson et al. (17) used PGE$_2$ vaginal suppositories to create a PGE$_2$ cream and then instilled this into the urethral meatus in 20 men with ED. Treatment response was determined after 20 min and was graded as no penile tumescence, partial tumescence, or full tumescence. Overall, they showed a 70% response rate, with 30% of men achieving full tumescence. After this initial report, several pilot studies using various formulations of PGE$_1$ showed promising results. Concurrently, a commercially available delivery system was developed using alprostadil (Medicated Urethral System for Erection [MUSE]). The system consists of a polypropylene applicator with a hollow stem that is 3.2 cm in length and 3.5 mm in diameter, with a tip containing a semisolid pellet of medication. The stem is inserted fully into the urethra, a button is depressed to dispense the medicated pellet, and the applicator is removed. It is important to have men urinate immediately before application because the residual urine helps facilitate insertion of the applicator and helps disperse the medicine. The applicators are avail-