Prevention of Recurrent Ischemic Priapism with Ketoconazole: Evolution of a Treatment Protocol and Patient Outcomes

Michael P. Hoeh, MD and Laurence A. Levine, MD

Department of Urology, Rush University Medical Center, Chicago, IL, USA

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ABSTRACT

Introduction. The management of recurrent ischemic priapism (RIP) is not clearly defined. Ketoconazole (KTZ) is used to treat RIP and produces a temporary hypogonadal state to suppress sleep-related erections (SREs), which often evolve into episodes of ischemic priapism in this population.

Aim. We review our experience to prevent RIP using KTZ and present our outcomes using a decreased dose regimen.

Methods. A retrospective chart review and phone survey of 17 patients with RIP was performed. KTZ inhibits adrenal and gonadal testosterone production with a half-life of 8 hours. By suppressing testosterone levels, SREs are interrupted. We compared our previous protocol of three times daily (TID) KTZ dosing with prednisone for 6 months with our current regimen of initiating KTZ 200 mg TID with prednisone 5 mg daily for 2 weeks and then tapering to KTZ 200 mg nightly for 6 months.

Main Outcome Measures. The primary outcome was the prevention of RIP using KTZ. Secondary outcomes included side effects secondary to KTZ use and patient satisfaction.

Results. All men experienced daily or almost daily episodes of prolonged, painful erections prior to starting KTZ. The mean number of emergency room (ER) visits per patient prior to starting KTZ was 6.5. No patient required an ER visit for RIP while on KTZ. Sixteen of 17 patients (94%) had complete resolution of priapism while on KTZ with effects noted immediately after starting therapy and no reported sexual side effects attributed to KTZ. One man stopped therapy after 4 days because of nausea/vomiting. Fourteen of 16 men eventually discontinued KTZ after a median duration of 7 months. Twenty-nine percent reported no recurrent priapic episodes after discontinuing. A total of 78.6% had partial or complete resolution of symptoms persisting after KTZ was discontinued with a mean post-treatment follow-up of 36.7 months.

Conclusion. No reliable effective preventative therapy has been identified for RIP. In our relatively sizable single-center experience, KTZ appears to be a reasonably effective, safe, and inexpensive treatment to prevent RIP while preserving sexual function. We now recommend our tapered dose regimen listed above. After 6 months, we recommend stopping the medication as we have found a majority of patients will not need to resume nightly KTZ.

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Key Words. Recurrent Ischemic Priapism; Stuttering Priapism; Ketoconazole; Sleep-Related Erections; Priapism; Induced Hypogonadal State and Recurrent Priapism

Introduction

Priapism is defined as a prolonged penile erection lasting greater than 4 hours which may or may not be triggered by sexual stimulation or desire. Priapism is divided into three main categories: ischemic, nonischemic, and recurrent priapism. Recurrent ischemic priapism (RIP), also known as stuttering priapism, is an uncommon form of ischemic priapism. Patients with RIP typically present with episodes of prolonged sleep-related erections (SREs) or "brief transitory attacks" of priapism. These SRE, although painful, usually last less than 3–4 hours. However, this disorder is known to progress to major episodes of ischemic priapism in 28% of cases necessitating

emergent intervention [1]. Likewise, any man who has suffered from an acute ischemic priapic event is at risk for developing RIP. Left untreated, this disease process may lead to irreversible corporal fibrosis and erectile dysfunction (ED) [1–5].

Elegant animal model studies have suggested that the pathophysiology of RIP may be based on dysregulation of nitric oxide (NO) and phosphodiesterase type 5 (PDE5) inhibitors in corporal smooth muscle [6]. Hematologic disorders such as sickle cell disease (SCD) and glucose 6-phosphate dehydrogenase deficiency (G6PDD) are more commonly present in children with RIP, whereas the disease is often idiopathic in adult-onset RIP. Those with SCD are affected with ischemic and recurrent priapism at a much greater frequency. Men diagnosed with SCD have an estimated lifetime probability for the development of clinically significant priapism as high as 42% and the rate of subsequent ED up to 30% [7–11]. G6PDD may also lead to an increased frequency of RIP, possibly secondary to hemolytic anemia and subsequent oxidative stress to the penis, affecting NO and PDE5 response [12].

SREs occur naturally during REM sleep in healthy men, and their purpose is believed to provide engorgement of the corpora cavernosa, which in turn leads to increased tissue oxygenation and prevention of cavernous fibrosis, the histopathological etiology for corporeal venooclusive ED [13]. Various human and animal studies have shown that androgens appear to play a key role in the regulation of SRE, in contrast to the erectile response to tactile and/or visual erotic stimuli during waking hours, which predominantly involves an androgen-independent system [13–15]. All men without physiologic ED experience SRE approximately three to seven times during sleep. These erections resolve spontaneously and typically do not cause pain [14]. SREs in men with RIP, however, may be prolonged and are characteristically painful and may eventually lead to episodes of priapism.

The first-line therapy for men experiencing episodes of acute ischemic priapism secondary to RIP remains the same as for any ischemic priapism: aspiration/irrigation in combination with intracavernous α-agonist injection therapy [2]. There are multiple pharmacologic treatments proposed for the management and prevention of RIP, including hormonal agents such as ketoconazole (KTZ) [16].

KTZ is an orally active antifungal drug known to inhibit androgen production in both the testicle and adrenal gland. As a result, high-dose KTZ (400 mg orally three times a day) is a standard treatment option for hormone-refractory prostate cancer and is typically given with 5 mg prednisone to prevent adrenal insufficiency which is known to occur with continuous 24-hour dosing of KTZ. Adverse effects of KTZ tend to be dose dependent and include nausea and vomiting in up to one-half of patients on high-dose regimens, skin rash in 10%, weakness/fatigue, nail dystrophy, and gynecomastia. Gastrointestinal side effects typically improve or resolve with dose modification. Hepatotoxicity is a rare (<1%) but potentially life-threatening adverse reaction. *The FDA recommends that* all patients undergoing KTZ therapy have liver function tests (LFTs) performed prior to initiation, at weeks 2 and 4 following initiation, and monthly thereafter until the medication is discontinued. If LFTs increase greater than three times the upper limit of normal or if patients develop clinical signs/symptoms of hepatotoxicity, the treatment should be discontinued [17–19].

KTZ typically has rapid absorption in fasting men, with peak serum concentrations achieved within 2 hours after administration. The mean elimination half-life values are 7.5–8 hours [20]. Santen et al. found that after administration of low dose KTZ (200 mg KTZ daily), total and free plasma testosterone levels fall to levels 60% below baseline levels within 4–8 hours before returning to basal values within 24 hours [21]. In 2009, we reported our initial positive experience with the management of RIP using KTZ in eight patients with an average follow-up of approximately 1.5 years. We have revised our protocol in this report.

Material and Methods

Seventeen patients were referred to our center with RIP for management who were ultimately treated with our revised KTZ protocol. In 2009, our treatment protocol was KTZ 200 mg three times daily (TID) with prednisone 5 mg daily for 6 months [16]. These 17 new patients were treated with a revised protocol of 2 weeks KTZ 200 mg TID with prednisone 5 mg once daily. If there were no breakthrough priapisms, the protocol was adjusted to KTZ 200 mg nightly without prednisone for a total of 6 months. The average follow-up was approximately 3 years. LFTs were obtained prior to initiation, at weeks 2 and 4, and monthly following initiation.

A chart review and subsequent phone survey were obtained for each patient. All patients were