Management of Recurrent Ischemic Priapism 2014: A Complex Condition with Devastating Consequences

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ABSTRACT

Introduction. The management of recurrent ischemic priapism (RIP) is not clearly defined. Given the rarity of this condition, most treatment options are supported at best by level 3 or 4 evidence.
Aim. In this article, we review the current literature regarding the pathophysiology and management of RIP and discuss the risks and benefits associated with each option, which includes ketoconazole (KTZ), 5-α-reductase inhibitors and other hormonal therapies, phosphodiesterase type 5 (PDE5) inhibitors, intracavernosal sympathomimetic injection, oral sympathomimetic agents, and other investigational therapies.
Methods. A comprehensive literature review was performed regarding the management options for RIP.
Main Outcome Measure. To examine the pathophysiology of RIP and evaluate the treatment options.
Results. Multiple agents have been investigated to manage RIP. KTZ, finasteride, anti-androgens, gonadotropin-releasing hormone agonists, and estrogen have been shown to be effective in several reports, though some of these agents may have significant hormonal side effects. PDE5 inhibitors currently appear to be well tolerated in this patient population, though evidence of its efficacy is limited. Intracavernosal α-agonist therapy may be used to treat episodes of priapism after they occur. Very limited data suggest terbutaline, oral α-agonists, digoxin, hydroxyurea, and gabapentin may have a role in RIP management.
Conclusions. An ideal management strategy for RIP should focus on prevention of priapic episodes using an effective, well-tolerated, cost-effective medication. We currently have several proposed options, with varying efficacy rates and side effect profiles. While significant advancements in our understanding and management of stuttering priapism have been made within the past few years, clearly continuing research and clinical studies are needed to guide our management of this disease process. **Hoeh MP and Levine LA. Management of recurrent ischemic priapism 2014: A complex condition with devastating consequences. Sex Med Rev 2015;3:24–35.**

Key Words. Recurrent Ischemic Priapism; Stuttering Priapism; Ketoconazole; Sleep-Related Erections; Priapism

Introduction

Priapism is a persistent penile erection that continues greater than 4 hours, and may or may not be related to sexual stimulation [1]. It is divided into three main subtypes: ischemic, non-ischemic, and recurrent (or stuttering) priapism. Ischemic (veno-occlusive, low flow) priapism is a nonsexual, persistent erection characterized by little or no cavernous blood flow and hypoxic, hypercarbic, acidotic corporal blood gas. The corpora cavernosa are typically rigid and can be exquisitely tender to palpation. Ischemic priapism is considered a medical emergency, as it is associated with progressive fibrosis of the cavernosal tissues and potentially irreversible erectile dysfunction (ED) [2–4].

Recurrent ischemic priapism (RIP) is an uncommon form of ischemic priapism that is characterized by episodes of prolonged sleep-related erections (SREs) or "brief transitory attacks" of priapism. These prolonged SREs are associated

with pain and usually resolve spontaneously within 3–4 hours. They may progress to episodes of complete ischemic priapism in approximately one third of cases, necessitating emergent intervention [5]. Patients with stuttering priapism who experience erections lasting longer than 4 hours should be treated following the guidelines for ischemic priapism. Likewise, any man who has suffered from an acute ischemic priapic event is at risk for developing RIP. This pattern of recurrence challenges the physician to develop a management strategy to prevent future episodes of priapism. The following discussion provides a current literature review regarding RIP and the medical management options available.

Epidemiology and Risk Factors

Stuttering priapism appears to share its etiologies with ischemic priapism. While hematologic abnormalities are commonly present in children with RIP, the condition is often idiopathic in adults. The incidence of ischemic priapism is exceedingly rare, with overall reported rates from 0.34 to 1.5 per 100,000 men [6]. While priapism is rare and usually unpredictable, specific patient populations, specifically those with hematologic diseases such as sickle cell disease (SCD), glucose-6-phosphate dehydrogenase deficiency, leukemia, and hereditary spherocytosis are significantly more likely to experience ischemic priapism during their lifetime.

The Centers for Disease Control estimates that 90,000–100,000 individuals live with SCD in the United States, and worldwide, estimates are up to 20–25 million. SCD occurs in 1 out of every 500 African American and 1 out of every 36,000 Hispanic American births [7]. Adeyoju et al. conducted an international multicenter study in the United Kingdom and Nigeria investigating the incidence rate of priapism and stuttering priapism in patients with SCD. In this study, 35% of patients reported a history of priapism, and of these, 72% had a history of stuttering priapism [8]. The vast majority of patients with SCD and priapism are homozygous for hemoglobin S. However, priapism has also been noted in patients with sickle cell trait, sickle cell beta thalassemia, and hemoglobin SC disease [9]. Episodes of priapism may occur at any age in patients with SCD, but typically become a more significant clinical problem after puberty [10]. The mean age of onset is 12 to 15 years, with 75% to 90% of males reporting their first episode prior to 20 years of age, and approximately one third of males with SCD develop ED [8,11,12]. It is worth noting that men without prior knowledge of their SCD status may initially present with priapism, with a reported incidence as high as 10% [13]. It is our recommendation that a SCD hemoglobin analysis should be performed for all African American and Hispanic American men presenting with priapism or RIP symptoms if the individual's SCD status is unknown.

Stuttering priapism appears to occur less frequently in association with the other hematologic dyscrasias noted earlier, with several case reports described in the literature [14–16].

Multiple medications have also been associated with priapic episodes and should be considered in the differential diagnosis when hematologic dyscrasias are ruled out. These include antidepressants/mood stabilizers (such as bupropion, trazodone, fluoxetine, sertraline, and lithium), antihypertensives (such as prazosin), anticoagulants (including heparin and coumadin), methylphenidate and recreational drugs (including cocaine and amphetamines) [17,18].

Pathophysiology and Clinical Course

The pathophysiology of RIP is likely multifactorial and as noted earlier may share its etiologies with ischemic priapism. While intravascular occlusion likely plays a role in priapism related to SCD, it does not explain why RIP occurs in patients without hematologic dyscrasias. Elegant animal model studies suggest that RIP may in part be due to a downregulation of cyclic guanosine monophosphate-specific protein kinase 1, phosphodiesterase type 5 (PDE5), and RhoA/Rho-kinase pathways due to deficient endothelial nitric oxide (NO) synthase in corporal smooth muscle [19–21]. Oxidative stress due to disease processes such as SCD may also contribute to reduced bioavailability of endothelial NO in the corporal bodies [5].

SREs occur naturally during rapid eye movement (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, which can result in corporeal veno-occlusive ED [22]. Several 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 [22–24]. All men without physiologic ED have