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Recurrent Priapism from Therapeutic Quetiapine

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Priapism is rarely related to use of non-erectile related medications. The objective was to educate about the multiple possible causes of priapism and to provide treatment recommendations for the different types of priapism. We present the case of a 43-year-old African American male with a history of schizoaffective disorder who presented to our emergency department multiple times over a three year period with priapism, each episode related to the ingestion of quetiapine. Following penile aspiration and intercavernosal injection of phenylephrine, this patient had resolution of his priapism. This case demonstrates an unusual case of recurrent priapism. [West J Emerg Med. 2014;15(1):114–116.]

INTRODUCTION

Priapism is defined as persistent penile erection or clitoral engorgement not accompanied by sexual desire or stimulation, usually lasting more than 4 to 6 hours. It is considered a urologic emergency that should be treated promptly as it can lead to erectile dysfunction in 30-90% of patients.¹ In general, priapism is divided into 2 types: high-flow and low-flow. High-flow priapism is non-ischemic and is often caused by increased flow through arteries due to trauma. Low-flow priapism is a result of blood collecting within the corpora and is caused by erectile dysfunction medications, hyperviscosity syndromes, trauma, tumor, neurologic conditions, and medication side effects. Various psychoactive medications are also known to cause low-flow priapism, with trazodone the most commonly implicated member of this group. Quetiapine is an atypical antipsychotic originally designed for use in schizophrenia, but it is now also used to treat a multitude of other psychiatric disorders, including schizoaffective disorder, bipolar disorder, anxiety, and depression.² We report the first case of recurrent priapism as a result of standard doses of quetiapine after first use and with multiple subsequent uses.

CASE REPORT

A 43-year-old African American man with a history of schizoaffective disorder and ulcerative colitis presented to the emergency department (ED) for a painful erection lasting 15 hours. He reported noncompliance with sulfasalazine for ulcerative colitis but intermittent use of quetiapine, 100 mg every morning and 200 mg every evening, for his

schizoaffective disorder. Prior to the ED visit, previous doses of quetiapine resulted in erections lasting 3 hours every morning that resolved spontaneously. He denied any history of trauma, sickle cell disease or trait, illicit drug use, vasoactive agents, including nitrates, recent intercourse, or use of any medications or devices for sexual enhancement. Examination demonstrated a tender and erect phallus without evidence of injury, fibrosis, angulation, lesions, or discharge. Testicles were normal, and no hernias were present.

Subcutaneous terbutaline and oral pseudoephedrine were administered with no effect. Aspiration of 10 cc of intracavernosal blood followed by intracavernosal phenylephrine injection led to successful detumescence. The patient was advised to discontinue use of quetiapine and arrange follow-up with his primary care physician.

The patient returned to the ED 4 times over the course of the next year. Each time the patient had a morning erection lasting 6 to 9 hours following 200 mg of quetiapine ingestion the prior evening. Detumescence was achieved successfully with aspiration and intracavernosal phenylephrine injection. The patient was ultimately transitioned from quetiapine to ziprasidone and amitriptyline with resolution of his recurrent priapism.

Three years after his initial presentation, the patient returned to the ED with yet another episode of priapism. He reported accidentally taking 100 mg of quetiapine instead of his normal dose of amitriptyline the evening prior to presentation. He awoke with an erection and came to the ED after the erection failed to resolve spontaneously after 8

hours. Detumescence was again achieved with intracavernosal aspiration and injection of phenylephrine. Intracavernosal blood was found to contain quetiapine with a level of 502 ng/ml. The patient was discharged home and advised to dispose of any excess quetiapine.

DISCUSSION

The case presented is the first reported case of recurrent priapism due to therapeutic doses of quetiapine. There have been several previous case reports implicating quetiapine as a cause of priapism. Quetiapine was initially approved by the U.S. Food and Drug Administration for the treatment of schizophrenia in 1997. The first report of priapism was in 2001 by Pais and Ayzvazian;³ a 45-year-old male attempted suicide by ingesting 27 quetiapine (65 mg/tablet) pills, which resulted in priapism requiring a cavernosal-glanular shunt to achieve detumescence.

Du Toit et al reported priapism due to therapeutic doses of quetiapine in 2004.⁴ Their patient developed priapism 24 hours after being transitioned from risperidone and trazodone to quetiapine. Symptoms resolved after being started on loxapine, an antipsychotic with minimal alpha1 adrenoceptor blockade. The patient had no difficulty with risperidone and trazodone for 2 years prior to the event but developed diabetes over the course of his 2 years of treatment. Thus, Du Toit et al concluded that the “risk of ischemic (low-flow) priapism from a range of atypical antipsychotics is aggravated by diabetes.”

In a letter to the editor, Harrison et al describe a 46-year-old African American/Native American man on mirtazepine and quetiapine who developed priapism requiring surgical intervention after taking amphetamines 24 to 48 hours prior to presentation.^{5,6}

The case presented by Davol and Rukstalis provided the best evidence for therapeutic quetiapine alone as a cause of priapism.⁷ They described priapism in a 25-year-old African American man without a history of sickle cell disease or trait, who had been taking quetiapine for over a year, was taking no other medications, and received his medications at the prison infirmary.

The pharmacologic mechanism of drug-induced priapism is believed to be related to the blockade of alpha1 adrenoceptors. Alpha-adrenergic blockade allows for relaxation of cavernosal trabecular smooth muscle resulting in engorgement of the corpora cavernosa. Examples of medications that act via this mechanism include yohimbine or delequamine.

Antipsychotics are also believed to cause priapism by blocking alpha1 adrenoceptors. A study of reports of antipsychotic-induced priapism in the United States Adverse Event Reporting System database found that high alpha1 affinity antipsychotics (quetiapine, chlorpromazine, risperidone, ziprasidone) were associated with priapism requiring medical intervention (reporting odds ratio 13.7;

10.1-18.5) while low and medium affinity antipsychotics such as loxapine, haloperidol, and aripiprazole were not associated with priapism requiring intervention (reporting odds ratio 2.2; 0.9-4.1).⁸

Our patient developed recurrent priapism after taking relatively low (100 to 200 mg) doses of quetiapine. Transition to another antipsychotic resulted in resolution of symptoms. After not using quetiapine and being symptom free for over two years, the patient developed priapism after a single dose of quetiapine. The expected therapeutic serum steady-state level of quetiapine is 100-1000 ng/ml. While an intercavernosal level is not directly comparable to serum levels and serum levels were not measured in this case, the intracavernosal level of 502 ng/ml demonstrates the presence of quetiapine within the corpora after only a single dose.

One possible difficulty in interpretation of reported cases is that most cases of priapism due to quetiapine use are African American patients. All of the patients described denied a history of sickle cell disease or trait and any other symptoms consistent with such a history, yet none of the case patients were ever tested for sickle cell trait or disease. However, development of priapism during adulthood in sickle cell disease is uncommon: 75% of male sickle cell patients have the first occurrence of priapism before the age of 20 with a mean age of 12 to 15 years.⁹ In vitro studies of quetiapine metabolism have shown that quetiapine is metabolized by both CYP3A4 and to a lesser degree CYP3A5, which is expressed in 60% of African Americans versus only 10-30% of whites.¹⁰ This raises the possibility that priapism due to quetiapine use may be affected by differences in metabolism.

Knowing that priapism is rare, practitioners may be unfamiliar with the standard therapeutic treatment plan for priapism. High-flow versus low-flow states may be established by history and physical exam, cavernosal blood gas or color duplex ultrasonography of the penis.¹¹ High-flow priapism is most commonly caused by penile arterial laceration and resultant excessive inflow of arterial blood. Low-flow priapism presents with a painful erection, engorged corpora cavernosa and (in contrast to normal erection) a flaccid corpus spongiosum and glans penis. While the diagnosis and treatment of priapism is similar in both adults and children, causes of low-flow priapism that must be elucidated through careful history and physical examination in children include bleeding disorders, Kawasaki disease, leukemia, and sickle cell disease. For cases in which differentiating high- versus low-flow priapism is challenging, intracavernosal blood gas analysis will demonstrate arterial blood in high-flow priapism versus low pH, low oxygen tension, and high carbon dioxide in low-flow priapism.

Initial treatment should include analgesia. Opioids and anxiolytics may be used parentally. A dorsal penile nerve block using local anesthesia using a wheal of lidocaine *without* epinephrine dorsally one centimeter distal to the pubic bone and scrotal insertion may be a helpful adjunct in pain control.

Treatment of any primary disorder that may be causing the priapism is integral to the initial therapy. In sickle cell disease, this treatment includes hydration and oxygenation.

For high-flow priapism, arterial flow is maintained and there is no concern for immediate ischemia; as a result, a period of observation is appropriate prior to selective arterial embolization.¹² Another option that has been attempted successfully in case reports includes applying direct pressure to the arteriovenous fistula under Doppler ultrasound guidance.^{13,14} Regardless, urologic consultation should be made from the ED and will likely guide treatment in high-flow priapism.

For low-flow priapism, the most proven treatment requires aspiration of cavernosal blood and direct cavernosal injection of phenylephrine (or epinephrine in some reports).^{15,16} For phenylephrine, 1 mg of 1 mg/mL phenylephrine can be mixed into a syringe with either 9 or 99 cc of normal saline thereby creating a 100 mcg/1cc or 100 mcg/10cc concentration respectively.¹⁷ A butterfly needle should be placed perpendicularly to the penis into the corpora cavernosa (the two corpora cavernosa are connected and therefore only a single side approach is necessary). Five to 10 cc of blood should be aspirated using an empty syringe, and 100-200 mcg of phenylephrine should be injected. This can be repeated every 5-10 minutes to a maximum dose of 1000 mcg. Vital signs including blood pressure should be monitored, as some phenylephrine will be absorbed systemically. If aspiration fails, the next step is surgical intervention and the creation of a cavernosal-corpora spongiosa shunt.

Consultation with a urologist is recommended in all cases of pediatric priapism, persistent low-flow priapism, and high-flow priapism. Patients with persistent priapism or underlying disorders such as leukemia or sickle cell disorder require inpatient hospitalization. If the priapism is treated successfully, then the patient can be observed and discharged home with urologic specialist follow-up as an outpatient.

CONCLUSION

Use of quetiapine continues to increase. While initially approved for schizophrenia, quetiapine is now approved for mania-associated bipolar disorder, and has also been used in the treatment of myriad disorders including depression, obsessive-compulsive disorder, post-traumatic stress disorder, restless leg syndrome, Tourette's syndrome, and as a sedative. Given past case reports and our case of recurrent priapism, it is important that physicians come to recognize priapism as a serious side effect of quetiapine and are prepared to treat it appropriately when diagnosed.

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