Case Report

Zuclopenthixol Induced Ischemic Priapism: Case Report and Review of Literature

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Abstract

Objective: Present a case of zuclopenthixol associated priapism, literature review and focus on the stuttering priapism entity as a potential serious complication as well as providing information about possible preventive treatments.

Case report: A 44 year-old male patient with history of cocaine abuse with associated priapism presents with acute painful erection after starting zuclopenthixol for treatment of a psychotic episode. This episode was later followed by many other similar episodes defined as stuttering priapism.

Conclusion: Acute ischemic priapism is a potential serious side effect of antipsychotics that physicians especially psychiatrists needs to be aware of especially if the patient has previous episodes in order to prevent reoccurrence.

Keywords: Zuclopenthixol; Antipsychotics; Priapism

Introduction

Priapism is defined as a persistent erection lasting for at least 4 hours without continuous sexual stimulation (1). Priapism is subdivided into 3 subtypes: Ischemic priapism: A veno-occlusive low flow priapm, whereby the cavernous blood has limited flow, thus becoming hypoxic, acidotic and hypercapnic. It manifests with rigid and tender corpora. Non-ischemic priapism: An arterial high flow priapism, due to unregulated cavernous arterial flow. Manifests with non painful, and usually non rigid erection, often associated with cavernous artery-corpora cavernosa fistula that could be due to prior trauma. Stuttering priapism: an unusual form of low-flow priapism that usually results in cavernous ischemia with consequent damage of erectile function manifests as recurrent painful rigid erections with periods of detumescence in between. Ischemic (low-flow) priapism, most commonly occurs in children with sickle cell disease, due to the sickling of red blood cells in the sinusoids of the corpora cavernosa after normal erection, leading to obstruction of the venous outflow and thus causing venous stasis. Obstruction and subsequent stasis renders venous blood hypoxic and acidotic leading to further sickling (1). Other common causes of Low-flow priapism include leukemia and medication side effects most commonly PDE-5 inhibitors and antipsychotic medications (3, 4). The recommended management plan for ischemic priapism according to the American Urologic Association guidelines, includes intravenous

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corporal aspiration, and irrigation with sympathomimetic agents (ex. phenylephrine) (1). In cases where aspiration and irrigation fail, as in cases where priapism has been present for more than 48 hours resulting in acidosis and ischemia that impairs the response of intracavernous smooth muscles to sympathomimetic, corporoglanular shunt should be considered. For priapism resulting from sickle cell disease, exchange transfusion, alkalization, oxygen therapy, and pain control are adjunctive treatment options. For patients suffering from stuttering priapism, oral alpha-adrenergic agents such as pseudoephedrine, is the first line treatment.

Non-ischemic (high-flow) priapism most commonly occurs because of perineal trauma leading to laceration of the cavernous artery (such as straddle injury) (5- 7). In such case, Priapism occurs due to fistula formation between the cavernous artery and corpora cavernosa, often diagnosed using color Doppler ultrasonography. Non-ischemic priapism is usually self-resolving, however if persistent needs angiographic embolization (1, 5, 7, 8).

Among the most common causes of priapism, drug-induced priapism is accounting for the onset of 25 to 40% of cases (9). Drug induced priapism is often associated with low-flow (ischemic) priapism. Several classes of medications such as antidepressants, antihypertensive, alpha-blockers, anticoagulants, and some psychoactive substances (cocaine, cannabis, alcohol...) have been shown to cause priapism, however 50% of drug induced priapism is caused by antipsychotics medications. Both typical and atypical antipsychotic drugs have been proven to cause drug-induced priapism. Several mechanisms explaining APD induced priapism have been proposed the most common one being due to the alpha-adrenergic blockade effect of APDS on the corpora cavernosa of the penis. Zuclopenthixol is a thioxanthene first generation typical antipsychotic with a piperazine side chain used for the treatment of schizophrenia and other psychosis. Zuclopenthixol has a high affinity for dopaminergic receptors and a moderate affinity to alpha 1 adrenergic receptors. Zuclopenthixol induced priapism is thought to be due to the alpha 1 adrenergic blockage effect of this agent, which leads to arteriolar vasodilation and relaxation of the smooth muscle fibers of the penis which in turn impedes the venous drainage of the corpora cavernosa and detumescence leading to low flow priapism. The prolonged rise in the intra-cavernosal pressure reduces the arterial blood flow and produces ischemia and later fibrosis that could lead to permanent sequalae such as impotence, dysuria, and urinary retention (10). Following is a case of a 45 year-old male on the psychiatry ward that we were consulted for evaluation and management of drug-induced priapism.

Case report

This is a case of a 44 year-old male patient, with history of substance use disorder who presented to our institution for management of paranoid delusions and substance detoxification. Patient has a long history of substance use of cocaine and opioids (heroin, oxycodone), most recent history was 6 months prior to presentation during which the patient had been taking 5 mg of cocaine per day for around 3 years after which he started having paranoia and delusions. History is pertinent for 4 episodes of priapism, during the phase when the patient was abusing cocaine, one episode of which lasted more than 36 hours and was managed with intracavernosal aspiration and injection of phenylephrine. During his hospital stay patient was maintained on the following medications: Aripiprazole 15 mg daily, benzhexol 5 mg 3 times daily, Buprenorphine 2 mg, Haldol 10 mg intravenous (IV) twice daily, Valium 5 mg IV 4 times daily. Due to increased agitation, Zuclopenthixol (Clopixol Accuphase) 100 mg intramuscular (IM) daily was added to the current treatment regimen, 2 days later during midnight the patient complained of painful persistent erection lasting more than 4 hours, after which urology team was consulted. Upon examination patient had a hard painful erection, one sided (right side) intracavernosal puncture with a 19 gauge butterfly needle was performed followed by aspiration of intracavernosal blood (around 10 cc of dark blood was aspirated). However, erection persisted after aspiration, then the patient was attached to a monitor and 1 cc of phenylephrine diluted to a dose of 100 mcg/ml was injected into the corpora cavernosa. Over the course of the next 10 minutes, progressive detumescence was achieved. Over the next few days patient complained of subsequent episodes of self-resolving episodes of painful erection, lasting less than 4 hours.

Discussion

Among the drug-induced priapism published cases, second-generation antipsychotics (33.8%), other medications (11.3%), and alpha-adrenergic antagonists (8.8%) accounted for the greatest percentage (11).

Table 1: Pharmacotherapeutic drug doses and use instructions

Drug	Dose/Instructions for use
Phenylephrine	Intracavernous injection of 200 µg every 3-5 minutes. Maximum dosage is 1 mg within 1 hour. Lower doses are recommended in children and patients with severe cardiovascular diseases.
Etilephrine	Intracavernosal injection at a concentration of 2.5 mg in 1-2 mL normal saline.
Methylene blue	Intracavernous injection of 50-100 mg, left for 5 minutes. It is then aspirated and the penis compressed for an additional 5 minutes.
Adrenaline	Intracavernous injection of 2 mL of 1/100,000 adrenaline solution up to five times over a 20-minute period.
Terbutaline	Oral administration of 5 mg for priapism lasting more than 2.5 hours, after intracavernous injection of vasoactive agents.

Medical treatments of ischemic priapism are strongly recommended as first line treatment before any surgical attempt, however, when initiated beyond 48 hours, while relieving priapism, they have little documented benefit in terms of long-term potency. Such effect can be explained by the irreversible smooth muscle damage that begins to be established by approximately 48 hours of tissue hypoxia (12, 13). Historically, exercise, ejaculation, ice packs, cold baths, and cold water enemas were among the described first line non-surgical treatments (14). However, there is limited evidence for the benefit of such measures especially that they may exacerbate priapism in sickle-cell disease patients. It is difficult to make conclusions about the success of aspiration and irrigation alone since in most cases, they were combined with intracavernosal injection of sympathomimetic agents. A randomized control trial of 70 patients with ischemic priapism lasting more than 6 hours treated with aspiration and saline irrigation at different temperatures reported 85% success rate with optimal result achieved at 10°C saline irrigation (15). In other hand, there is until now insufficient data to support superiority of combining aspiration with saline irrigation to irrigation alone. Adding intracavernosal pharmacotherapy to the aforementioned combination is considered the standard of care (1, 14, 16). The pharmacologic agents used include sympathomimetic drugs or α-adrenergic agonists such as phenylephrine, etilephrine, ephedrine, epinephrine, norepinephrine and metaraminol with a resolution rate of up to 80% (14, 16-18). According to a literature review at the AUA, combining aspiration-irrigation to intracavernosal therapy had a resolution rate of 77% as compared with 58% in injection alone group (1). Following is a table summarizing the pharmacologic agents with their respective doses and instruction of use (Table 1).

Stuttering priapism is a common entity especially in SCD patients (42-64%), whereas it has lower incidence in adult population (35%) of whom 72% had history of stuttering priapism. Patients with ischemic priapism more than 4 hours (incidence increase with increasing duration of priapism) are at risk of developing stuttering priapism. Many studies have postulated several mechanisms including inflammation, cellular adhesion, NO metabolism, vascular reactivity and coagulation (14, 19-22). One interesting cellular mechanism is related to downregulation of cyclic guanosine monophosphate (cGMP)-dependent protein kinase and PDE5, which results in disturbance in the corporal smooth muscle tone (23). This finding is of utmost importance as it has a direct implication in the treatment of stuttering priapism. Paradoxically, PDE5 inhibitors in low doses are indicated in the cases of idiopathic and SCD-associated priapism (17, 20-25) which was prescribed to our patient with no recurrence noted till the time of writing this paper. Terbutaline - a beta agonist causing vasodilation, resulting in vascular smooth muscle relaxation- was studied in a randomized control trial for the prevention of stuttering priapism in particular with alprostadil-induced priapsim resulting in detumescence achievement in 42% of cases compared to 15% in the placebo group.

Conclusion

Pariapism is a urologic emergency that should not be missed and should be watched for, especially in substance abusers (that in most cases have a previous history of priapism) and patients newly started on antipsychotic medications. Triple therapy by adding pharmacotherapy to aspiration and irrigation is considered the first line intervention with a high success rate.

Conflict of Interests

Authors declare no conflict of interests.

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