Case Report

Priapism associated with pregabalin

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Abstract

Priapism is a well-known cause of erectile dysfunction. There are a wide variety of causes, including hemoglobinopathy, neurological diseases, and drugs. We present a case report of an Asian man who presented with priapism that was continuous for 3 days after taking three doses of pregabalin for chronic back pain. Cavernous aspiration, phenylephrine injection, and a winter shunt all failed to achieve detumescence. The patient then presented to our institution on the 5th day of his initial presentation, and an El-Ghorab shunt was performed, after which detumescence and pain relief were achieved. We suggest that pregabalin might induce tumescence through acting on the $\alpha 2\delta 1$ subunit of voltage-gated calcium channels in the penile smooth muscle or by presynaptic inhibition of noradrenaline release. Further studies are warranted regarding the action of pregabalin and its effect on penile physiology.

Key Words: Drug-induced priapism, pregabalin, priapism

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INTRODUCTION

Priapism is defined as a prolonged erection without sexual stimulation or excitement for an interval of 4 hours or more. It is generally classified into two types, ischemic and non-ischemic priapism.[1,2]

Idiopathic priapism accounts for nearly half of all cases; several etiologies have been found to be associated with priapism. These etiologies include hematologic diseases such as sickle-cell anemia; neurological diseases such as syphilis infection, brain tumors, epilepsy, intoxication, and brain and spinal cord injuries; malignancies such as chronic granulocytic leukemia and penile, bladder, prostate, kidney, and sigmoid colon cancers; and drugs.

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There are several types of drug-induced priapism, which fall into either of two categories: (a) priapism induced by erectile dysfunction treatments such as phosphodiesterase type 5 (PDE5) inhibitors and intra-cavernous vasoactive agents and (b) priapism induced by non-erectile dysfunction medications. There are many medication classes that might cause priapism, including antihypertensive medications such as hydralazine, guanethidine, and α-adrenergic antagonists; psychotropic and antidepressant medications such as phenothiazines; sedative-hypnotics; selective serotonin reuptake inhibitors; trazodone; immunosuppressants such as tacrolimus; and anticoagulants such as heparin. In addition, heavy alcohol intake, topical and intranasal cocaine, and scorpion toxin have been linked to priapism.[1]

Herein, we present a case report of pregabalin-associated priapism. To our knowledge, this is the first case reported in the literature.

CASE REPORT

A 39-year-old Asian man presented to our emergency department with a painful erection that had lasted for 5 days. He had a history of back pain, for which he was under treatment

with pregabalin (75 mg twice daily). After his first dose of pregabalin, he noticed a prolonged morning erection that lasted for 2 h and resolved spontaneously. The following day and after receiving the 3rd dose of pregabalin, he had an erection that became painful, but he did not seek medical advice until 36 h later. At that time, cavernous blood aspiration and irrigation were performed combined with the intra-cavernous injection of phenylephrine, and partial detumescence was achieved. He was advised to stop pregabalin, but 6 h later, he suffered another attack of priapism. A winter shunt was performed, resulting in a short-lived detumescence lasting less than 6 h. At this point, the patient presented to our care on the 5th day after his first episode of priapism.

The patient had no past medical history of priapism, hemoglobinopathy, or neurological illness. He had no previous history of genital trauma or surgery. He was not under treatment with any medication other than pregabalin and had no drug allergies. He had no history of alcohol or drug abuse.

On examination, the patient had a rigid, erect, tender penis with a soft glans. There were penile bruises related to previous sites of evacuation and irrigation. No inguinal lymphadenopathy was detected. The rest of the examination was unremarkable. Investigations including a complete blood count, coagulation profile, electrolyte analysis, and renal and liver function tests were performed. All results were within normal limits.

The patient underwent an El-Ghorab distal cavernoso-spongiosal shunt with satisfactory detumescence and pain relief. He was kept in the hospital under observation for 2 days with no other attack of priapism; he was then discharged. At a 12-month follow-up, the patient reported no recurrent episodes of priapism. He reported occasional morning erections, but the erections were not sufficient for vaginal penetration.

DISCUSSION

Although most cases of priapism are idiopathic, it is well known and well documented that some medications may cause priapism.[1]

Pregabalin is a compound that is chemically and structurally similar to gabapentin, with antiepileptic, analgesic, and anxiolytic properties. Pregabalin is used for the management of various conditions, including partial seizures, diabetic neuropathy, surgical dental pain, and other pain syndromes, post-herpetic neuralgia, and social anxiety disorders.[3] Its mechanism of action is not clear, but it is thought to target the α2δ1 subunit of voltage-gated calcium channels, which leads to decreased calcium influx into excitable cells and a subsequent decrease in the release of excitatory neurotransmitters. Pregabalin is well absorbed after oral administration; it is eliminated largely by renal excretion, and has an elimination half-life of approximately 6 h.[3-6]

It is widely accepted that continuous penile detumescence is caused by continuous tone of the cavernous sinuses and cavernous arteriole smooth muscle contraction induced by increased free cytosolic calcium. The intracellular levels of calcium are controlled by several mechanisms, including norepinephrine, endothelin, and prostaglandin F2α (PGF2α). Increased levels of free cytosolic calcium lead to decreased blood flow in the cavernous tissues. In fact, norepinephrine has generally been accepted as the principal neurotransmitter that controls penile flaccidity and detumescence through its action on adrenergic α_{1a}- and α_{1d}-receptors, which are widely distributed in the cavernous tissues.[7] On the other hand, a decreased level of cytosolic free calcium leads to smooth muscle relaxation, which increases corporal blood flow and penile erection. Voltage-dependent calcium channels are also a source of free intracellular calcium, and it was found that deactivation of these channels by hyperpolarization can lead to smooth muscle relaxation[7] [Figure 1].

Due to the wide distribution of the α2δ1 subunit of voltage-dependent calcium channels in the body, which has been found in all the tissues analyzed so far,[6] we hypothesize that pregabalin might induce erection by direct action on smooth muscles, blockage of voltage-dependent calcium channels, and a subsequent decrease of the free cytosolic calcium level, which in turn may lead to penile tumescence [Figure 2]. Another hypothesis is that pregabalin might inhibit the pre-synaptic stimulation of sympathetic control of the corporal smooth muscle, acting on

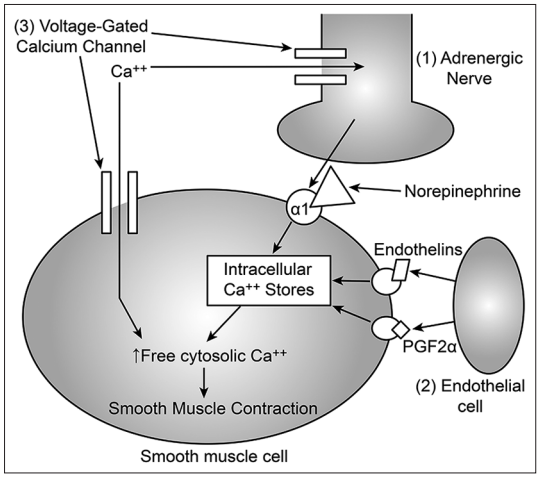

Figure 1: Schematic representation of free cytosolic calcium: (1) Adrenergic nerve fiber endings and (2) endothelial cells release norepinephrine, endothelins, and PGF2α, which lead to initiate the cascade of reactions that eventually result in elevation of free cytosolic Ca++ concentrations. (3) Voltage-gated calcium channels are another source of free cytosolic calcium that lead to an increase in the level of free cytosolic Ca++ due to an influx of extracellular calcium. Voltage-gated calcium channels in the nerve fibers are thought to aid in depolarization leading to the release of neurotransmitters

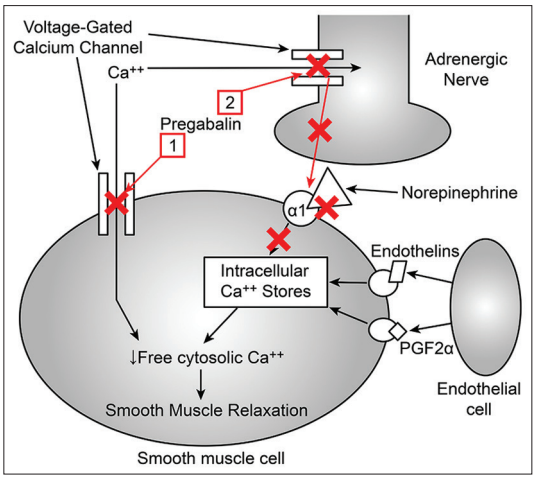

Figure 2: Pregabalin targets the voltage-gated calcium channels, leading to inhibition of Ca++ influx into excitable cells. (1) Pregabalin acts on voltage-dependent Ca++ channels of the corporal smooth muscle, leading to decrease in Ca++ influx into the smooth muscle and a resultant decrease in free cytosolic Ca++ level and, ultimately, smooth muscle relaxation. (2) Pregabalin acts on the voltage-dependent Ca++ channels of the adrenergic nerves, which leads to decrease in the excitability of nerves and decrease in norepinephrine release, resulting in a decrease in the release of intracellular Ca++ stores

the voltage-dependent calcium channels of the sympathetic nerve fibers, which, in turn, may lead to inhibition of norepinephrine release and subsequent inhibition of the release of stored intracellular calcium [Figure 2]. This effect is similar to the effect of adrenergic α-receptor blockers on cavernous smooth muscle, which is a well-known cause of drug-induced priapism.[7,8]

We suggest further investigations of the effects of pregabalin on penile physiology and priapism.

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