International Journal of Medical and Health Research
ISSN: 2454-9142
www.medicalsciencejournal.com
Volume 4; Issue 1; January xxxx; Page No. xx-xx

Priapism as a Complication of High Dose Testosterone Therapy: A Medication Error [Case Report and a Review of Literature]

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Abstract
Priapism is defined as a prolonged, sustained penile erection without sexual stimulus. It rarely occurs in children, but may result in erectile dysfunction and sexual aversion behaviors as one gets older. Testosterone therapy is safely used in children with hypogonadism, delayed puberty, and micropenis. We report a rare case of testosterone-induced priapism in an 8-year-old boy with a micropenis, after receiving an incorrect dose of 500 mg of testosterone injection; his mother (a paramedic) administered it. The patient was managed with observation and cold compresses; without any surgical intervention. This case suggests that hormonal injections be administered by either registered nurses or physicians, "but not by relatives."

Keywords: Priapism, Testosterone, Micropenis, Medication Error

Introduction
The United State Institute of Medicine reports that '*To Err is Human'* in November 1999, which focused on preventable medical errors in order to build a safer health system and making patient safety the preeminent issue in health care. Over time, the concept of patient safety increased, and it became clear that the prescribing, dispensing, and administration of medications is the key of preventable medical errors [1]. The National Patient Safety Agency revealed the fact of those medication errors could occur at each stage of the medication treatment process. Children were more prone to these errors than adults. Medication errors in pediatrics have been estimated to be 3-37% during prescribing, 5-58% during dispensing, 72-75% during administration, and 17-21% during documentation [2].
Testosterone is a hormone used in children with micropenis, hypogonadism, constitutional delay of growth and puberty, hypospadias, and disorders of sexual differentiation. It is considered safe in both adults and children, with proper doses maintained, so that monitoring is recommended [3].
Kaplowitz studied the value of testosterone therapy in males with delayed puberty. He noted increased frequency of erections, but it was not excessive in any patient. This appears to be the case for the majority of patients, but it is important to be aware that priapism could occur during testosterone therapy [4-6].
Priapism is a prolonged complete or partial penile erection lasting more than four hours, but unrelated to sexual stimulus. There are three categories of priapism: ischemic priapism, which is considered the most common type in children, stuttering priapism (intermittent), and nonischemic priapism [7].
Priapism after administration a high dose of testosterone has been rarely reported in literature. There were 21-reported cases of priapism associated with testosterone therapy in English literature. Two cases were due to administering a high dose, whereas the rest were therapeutic doses [3, 5, 8-18]. We reported a case of an 8-year-old boy with micropenis and priapism, secondary to a high dose of testosterone in a medication administration error.

Case Report
An 8-year-old Yemeni boy was born prematurely after a 28-week gestation to no consanguineous parents. He is one twin in a pair of dizygotic twins, born with a birth weight of 1200 g and good Apgar scores. Presented to the Pediatric Endocrine Clinic with a history of micropenis (stretched penile length was equal to 3.7 cm, which is below the 10th percentile for ages plotted on the penile length chart). Testicular volume was 2 ml on both sides. No family history of micropenis or hypogonadism existed. His height was 110 cm (-3.71 standard deviation below the normal) and his weight was 16.5 kg (-3.02 standard deviation below the normal). He was otherwise healthy with no dysmorphic features and unremarkable systemic examinations. His initial work-up revealed a serum testosterone level of 0.087 nmol (normal 8.4-28.7 nmol/L), while follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were 0.2 (normally less than 2). Bone age according to Greulich and Pyle was that of a 7-year-old (delayed for chronological age). He had no risk factors for priapism: no history of trauma, sickle cell disease, or malignancies.
The patient was prescribed intramuscular testosterone injections of 50 mg, but received an accidently high dose of 500 mg by his mother who, as mentioned, is a paramedic personnel. Two hours after the injection, he started to have

painless prolonged erections for six hours in duration, but which resolved spontaneously and recurred again within hours; he continued to experience multiple erections, with six of them being more than 4 hours long (ranging from 6 to 12 hours), and accompanied by nocturnal erections. Both testicles became engorged, with a feeling of heaviness, discomfort, and darkness of scrotum color. His genital examination revealed a stretched penile length of 6 cm [**Figure 1**], with each testicular volume increased to 3 ml on both sides, along with pubic hair starting to appear at stage 2.

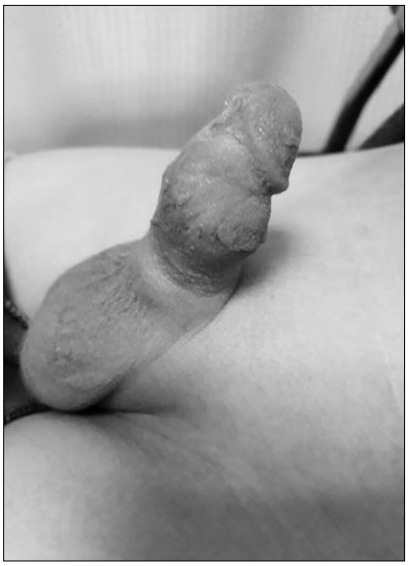

Fig 2: Erected patient's penis with penile length of 6 cm.

Our investigations were done to monitor precocious puberty (post high dose of testosterone) revealed that his serum testosterone was 23.54 ng/dL, LH 0.29 IU/L and FSH 0.11 IU/L. Testicular ultrasound showed prepubertal testicles size [**Figure 2**]. Complete blood count (CBC) and coagulation profile were otherwise normal with no evidence of anemia, polycythemia, thrombocytopenia, or thrombocytosis. Sickling test was negative.

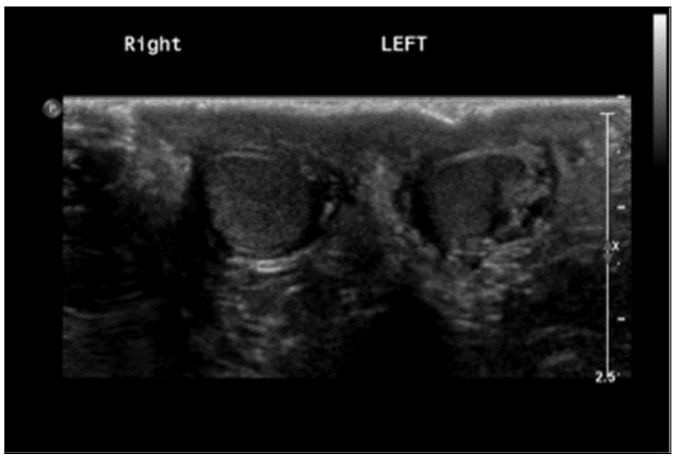

Fig 2: Ultrasound of testicles showed right testicles measures 1 x 0.8 x 1 cm and left testicle measures 1.4 x 0.8 x 0.8 cm.

There is no antidote for testosterone, so he was managed with cold penile compresses to decrease blood flow, daily monitoring of frequency and duration of erections, as a surgical shunt was planned if erections became worse; his erections were less frequent, however, along with shorter duration over time.

Discussion

This case suggests a strong association between a high dose of testosterone administration and development of priapism. This patient did not have a previous history or risk factors for it. Causes of priapism can involve sickle cell anemia, leukemia, malignancies, and trauma. Drugs have also been considered, but rarely has this been the situation. The World Health Organization (WHO) Uppsala Monitoring Centre received 122 reports of priapism from 1968 to 1987, containing 138 suspected drugs, although testosterone was not one of them [8].

Testosterone hormone is important for penile erections. Androgen receptors exist in large quantities in the immature phallus, including the erectile tissue, but decrease with age and present in low quantities in an adult phallus [19]. Androgens aid erection initiation by increasing nitric oxide synthase expression and activity. Increased nitric oxide causes cavernosal artery and sinusoidal smooth muscle relaxation, yet it also enhances phosphodiesterase type-5 that works on restoring the resting smooth muscle contractility [3]. The exact mechanism by which testosterone administration causes priapism is not clear yet.

In this reported case, priapism was obvious due to medication administration error. The patient was given a high dose of testosterone (500 mg) instead of the correct 50 mg by his mother (a paramedic) who erroneously read the written prescription. This is consistent with two other reported cases who developed priapism after a high dose of testosterone due to medication administration error. The first case was reported by Zargooshi, in a patient with hypogonadotropic hypogonadism, who had an increased dose from 250 to 500 mg. His conclusion was that testosterone-induced priapism is dose-dependent [13]. Ichoka reported a second case of testosterone-induced priapism in a patient with Klinefelter syndrome. The patient was given the third injection by mistake 12 days after the second injection, but the interval between the two injections was too short. Accumulation of testosterone enanthate, in addition to the supraphysiologic local testosterone level, could be the cause of priapism. Ichoka suspected that the sudden exposure to testosterone after a long period of deprivation could have caused priapism, via an increase in local sensitivity to testosterone [15]. This hypothesis was supported by other cases in the literature as well [**Table 1**]. Shergill reported a case of priapism after testosterone injection in a patient with Kallmann's syndrome [10], while Whalen reported two cases of priapism in patients receiving gonadotropin-releasing hormone (GnRH) for hypogonadotropic hypogonadism [9]. Zelissen reported a case of testosterone-induced priapism in a patient with idiopathic hypogonadotropic hypogonadism [8].

From previous reported cases, priapism can happen as a side effect of testosterone therapy itself, especially in patients deprived of testosterone, or as a complication of high doses.

The 21 cases found in a literature review [**Table 1**] found that most of them were in adolescence between 12 and 23 years. Four of them were above thirty, but no one was in the

childhood range, as was this indexed case. From these 21 patients, only one of them was documented to have micropenis, although no one was taking testosterone for isolated micropenis, as in this case. The onset of priapism after testosterone administration ranged from 2 to 10 days. In this patient, it started 2 hours after injection and continued for 6 hours, and resolved spontaneously; after that, he continued to have night and day erections with multiple episodes of priapism for one week until he sought medical advice.

To date, there is no antidote for testosterone overdose. Regarding priapism management and medical evaluation, it is recommended for any erection lasting more than 4 hours. Management and prognosis varies among cases. Initial management aims to determine the type of priapism and achieve detumescence. With the current treatments available, antiandrogens are seen as the optimal management of testosterone-induced priapism. However, they are relatively contraindicated in males who have not reached sexual or skeletal maturation. Opiate analgesia is required in ischemic priapism. Cold packs are also considered analgesic, and causing vasoconstriction and decreasing penile blood flow as that was effective in this indexed case. Aspiration of blood from the corpus cavernosum, along with irrigation, is the initial treatment in ischemic priapism. If not effective, an intracorporal injection of phenylephrine in a small dose should be performed. Last choice if the previous measures are not effective is surgery, with distal or proximal shunts being performed [6].

Follow-up of patients was not documented in most reports. Key reported a case of priapism after a therapeutic dose of testosterone for delayed puberty, who developed impotence one year after puberty [5].

Conclusion

Although a relative of the patient may work in the medical field, it is not advisable for that person to give the injection, as frequent errors can happen as a function of an emotional connection. For children, parents must be counseled before testosterone administration about its side effects - e.g., pubic hair appearance, frequent erections, and priapism, especially if given in too high a dose. Monitoring is needed for early puberty induction in these cases by regular examination of testicular size and Tanner's pubertal staging, in addition to biochemical monitoring of pubertal hormones and ultrasound monitoring of testicular size; this would naturally include serum testosterone levels returning to normal for his age.

Table 1: Reported cases of testosterone induced priapism

Year	Outcome	Onset from injections	Risk factors	Age of the patient	Disease	Agent used	Authors
1940	Resolved spontaneously	Not mentioned	-	12 year old	Eunuchoid	Testosterone propionate	Finkler20
1970	All these cases needed surgical intervention	Not mentioned	Previous Priapism before starting the therapy.	3 patients: 20, 20 and 31 year old	Sickle cell Disease	Testosterone, enanthate and cypionate.	Lundh12
1971	Not mentioned	Not mentioned	Dialysis	2 patients, age not mentioned	Renal Failure	Testosterone as a mixture of its ester	Shaldon18
1977	Not mentioned	Not mentioned	Dialysis	Not mentioned	Renal Failure	Testosterone as a mixture of its ester	Hartitzsch21
1983	Resolved after drug discontinuation	Not mentioned	-	19 year old	Sickle cell Disease	Clomiphene	Landefeld22
1987	Cavernosoglandular shunt had to be performed.	At the 17th day of treatment	Accumulation of globotriaosytceramide in autonomic ganglia,	17 year old	Fabry's disease	Testosterone undecanoate	Endres11
1988	Cavernosum-spongiosum shunt. Recurrent one day later and a second shunt operation was necessary.	Three days after third injection	-	20 year old	Idiopathic hypo-gonadotropic hypogonadism	Testosterone enanthate	Zelissen8
1989	Shunt operation was planned. At induction of anesthesia, penis detumescence occurred.	7 Days after first injection	-	15 year old	Delayed Puberty	Testosterone as a mixture of its ester	Ruch14
1989	Responded to irrigation But one year later, after puberty, he developed impotence.	5 days after first injection	Manipulation of the erected penis	14 year old	Delayed Puberty	Testosterone enanthate	Key LL5
	Responded to amyl nitrite therapy.	Following the initial dose	-	14 year old & 13 year old			

Table 2: Reported cases of testosterone induced priapism

Year	Outcome	Onset from injections	Risk factors	Age of the patient	Disease	Agent used	Authors
1991	Responded to injection of 1:100,000 epinephrine solution followed by aspiration	-	-	32 year old	Hypogonadism	Gonadotropin Releasing Hormone	Whalen9
	Shunt procedure was performed	-	-	38 year old			
1995	Respond to terbutaline + topical nitropaste	7 Days after first injection	-	14 year old	Sickle cell Disease	Testosterone enanthate	Slayton16
	Treated with aspiration	8 Days after first injection	-	13 year old			
2000	Corporeal glandular shunt was performed	Following the fourth injection	The patient increased the dose	23 year old	Hypogonadism	Testosterone enanthate	Zargooshi13

2003	Treated with aspiration but recurred within 24 hours. So, shunt was performed	10 Days after first injection	-	18 year old	Kallmann's Syndrome	Testosterone ester	Shergill10
2005	Treated by repeated aspiration and irrigation with phenylephrine	2 Days after second injection	-	14 years old	Constitutional delay of growth and puberty	Testosterone	Arrigo17
2005	Treated by aspiration and injection of adrenaline	8 Days after third injection	The interval between 2nd & 3rd injection was short	41 year old	Klinefelter syndrome	Testosterone enanthate	Ichoka15
2012	treated with insertion of bilateral T-shunts. After 24 hour Bilateral mid corporal corporotomies were performed.	7 Days after first injection	-	15 year old	Constitutional delay of growth and puberty	Testosterone ester	Donaldson3
	Treated with hyper hydration and analgesia.	3 Days after first injection	-	14 year old	Sickle cell Disease		

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