

Priapism, pomegranate juice, and sildenafil: Is there a connection?

Subramanian Senthilkumaran, Namasivayam Balamurugan, Ponuswamy Suresh, Ponniah Thirumalaikolundusubramanian¹

Department of Emergency and Critical Care, Sri Gokulam Hospitals and Research Institute, Salem, ¹Department of Internal Medicine, Chennai Medical College and Research Center, Irungalur, Trichy, Tamilnadu, India

Abstract We report the development of low flow priapism in three patients related to simultaneous consumption of sildenafil with pomegranate (*Punica granatum*) (POM) juice. There were no other concurrent diseases, intake of drugs, and chemicals or other risk factors in these patients. We want to create awareness among patients and practitioners for recognition and timely intervention. Probable mechanisms are highlighted.

Key Words: Alternative medicine, complementary, cytochrome, pomegranate, priapism, sildenafil

Address for correspondence:

Dr. S. Senthilkumaran, Department of Accident, Emergency and Critical Care Medicine, Sri Gokulam Hospital and Research Institute, Salem - 636 004, Tamilnadu, India. E-mail: maniansenthil@yahoo.co.in

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INTRODUCTION

Sildenafil citrate is a potent and selective inhibitor of cyclic guanosine monophosphate (cGMP). It has been widely prescribed for erectile dysfunction.^[1] The adverse events reported are flushing, dizziness, headache, tachycardia, chest pain, drowsiness, hypotension, nausea, and syncope.^[2] However, priapism with isolated use of sildenafil in therapeutic dose has been documented rarely.^[3] Medications containing nitrates, alpha blockers, HIV protease inhibitors, and St. John's wort has to taken very cautiously. Also, use of potent cytochrome P450 (CYP) 3A4 inhibitors namely macrolide and imidazole antimicrobials as well as non-specific CYP inhibitor cimetidine are associated with increased plasma levels of sildenafil and may aggravate the actions of sildenafil.


Pomegranate (*Punica granatum*) (POM) juice has a high

content of polyphenolic flavonoid. The flavonoids have potent anti-oxidant and anti-atherosclerotic properties. Owing to these nutritional characteristics, HEART-UK and the cholesterol charity encourages consumption of POM as part of a routine heart healthy diet.^[4] This endorsement motivates people to drink the juice for its potential health benefits. Priapism following concurrent use of sildenafil and POM juice is reported for the first time in the literature to create awareness on this entity.

CASE REPORTS

Case 1

A 46-year-old man presented to the emergency room with a persistent and painful penile erection that had lasted for 5 hours after sexual intercourse with his wife. He was diagnosed to have psychogenic type erectile dysfunction and the urologist prescribed sildenafil. He took 50 mg sildenafil on alternative days for past 30 days which produced hard erections that detumesced immediately after intercourse. He was advised by an alternative medicine practitioner to drink 200 ml of pomegranate juice daily to improve the vigor and vitality. After taking pomegranate juice first time along with a dose of 50 mg of sildenafil for the first time, he had an erection within

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15 minutes that was sustained even after ejaculation. He was not on any concurrent medications or herbal agents. He denied previous events of priapism, genital trauma, substance abuse, and other chronic illness. Examination showed an engorged, edematous, erect penis with tense and tender corpus cavernosa sparing the corpus spongiosum and glans. The testis and the prostate were normal.

Complete blood count, blood chemistries including liver function test, and coagulation profile were within normal limits. No dysmorphic red blood cells were seen on microscopic examination. Aspiration of cavernosa yielded a dark blood and analysis of the aspirate confirmed a venous composition of pH of 6.90, PCO₂ of 65 mmHg, and PO₂ of 15 mmHg, which were consistent with low-flow priapism. His priapism was refractory to analgesics, ice packing, and subcutaneous terbutaline. Hence, epinephrine along with 2% lidocaine was injected into each corpus after aspiration of venous blood. Total detumescence occurred within 15 minutes. The patient was discharged uneventfully and was instructed not to drink pomegranate juice while on sildenafil. He continues to use sildenafil 50 mg, which produces erections that subside immediately after orgasm.

Cases 2 and 3

Two brothers of a same family aged 35 and 27, who were married and healthy and did not take any medications presented to the emergency room with 8 hours history of priapism. They consumed sildenafil 50 mg occasionally in order to increase their orgasm. Incidentally, they were advised by practitioner of naturopathy to drink freshly prepared POM juice. On the day of concomitant use of POM juice with sildenafil 50 mg, they had erections that did not detumescence. There was no previous history of priapism or other risk factors. Laboratory studies were within normal limits. On examination, the corpora cavernosa were rigid and tender with soft corpus spongiosum and glans. Detumescence was achieved within 10 minutes following an intracavernous injection of epinephrine along with 2% lidocaine (as an anesthetic). The response was soon probably because it was a drug-induced priapism and not due to associated/underlying pathological causes. They were counseled not to use sildenafil as an aphrodisiac agent. On follow-up at 3 months, they reported normal erections with no further episodes of priapism.

DISCUSSION

After oral administration, sildenafil is rapidly absorbed and the bioavailability reaches around 40% only due to extensive first-pass metabolism. This is also influenced by age of the patient and liver and kidney function. Warrington *et al.* reported that about 79% of the intrinsic clearance of

sildenafil is attributable to cytochrome P450 (CYP) 3A4 and remaining to CYP2C9.^[5] The pharmacokinetic properties of sildenafil predispose it to drug interactions. Laboratory studies have shown that POM juice inhibits key cytochrome P450 enzymes, which are involved in sildenafil metabolism similar to grape juice.^[6] Based on the circumstantial evidence in our patient who had a previously well-controlled sexual activity without changes in dosage, the concomitant intake of POM juice might have resulted in priapism by inhibition of CYP3A4-mediated first-pass metabolism and increased the bioavailability of the drug as observed by Lee *et al.*^[7] It is also possible that the inherent antioxidant properties of POM juice might have enhanced the bioavailability of endothelial nitric oxide (NO) levels and acted directly on the endothelium as reported by Ignarro and colleagues.^[8] In addition, an additive or synergistic effect between sildenafil and POM juice might have also contributed for priapism. Occurrence of priapism with concomitant use of POM juice and sildenafil among the brothers (case 2 and 3) of the same family indicate the probability of genetic predisposition. Rechallenge could not be done as these patients refused. However, further studies are needed to confirm or refute these issues in indigenous medical practice. POM juice has been recommended in the treatment of erectile dysfunction.^[9] An effect of grapefruit juice on the pharmacokinetics of sildenafil was documented earlier.^[10] Many drug interactions are a result of inhibition or induction of CYP enzymes.^[11] The limitations of this report being lack of rechallenge and non-estimation of serum sildenafil level.

CONCLUSION

This report highlights on the interaction of POM juice with sildenafil and the development of low-flow priapism, an emergency which requires immediate attention to alleviate complications and minimize the risk of impotence. We also suggest that patients taking sildenafil should be aware of this potential interaction and warned about concurrent use in future. In the meantime, the manufacturers should be advised to include this in patient information leaflet. Also, clinicians and practitioners should be aware of this interaction while treating and prescribing sildenafil.

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