Case Report

Severe Raynaud's Phenomenon with Yohimbine Therapy for Erectile Dysfunction

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ABSTRACT. Yohimbine is a selective α-2 adrenergic antagonist that has been used in the pharmacologic management of erectile dysfunction (ED). We describe a patient with CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia) who paradoxically experienced worsening of Raynaud's phenomenon when using yohimbine for ED. (J Rheumatol 2003;30:2503–5)

Key Indexing Terms:
YOHIMBINE CREST RAYNAUD'S IMPOTENCE SILDENAFIL

Yohimbine is a selective α-2 adrenoreceptor antagonist extracted from the bark of the African *Pausinystalia yohimbe* tree. It is an indole alkaloid, which increases noradrenaline release and the firing rate of central noradrenergic cells. This results in increased sympathetic tone and decreased outflow of blood from the corporeal bodies of the penis, facilitating erection[1-3].

Maurice Raynaud described digital vasospasm induced by cold exposure or emotional stress in 1862[4]. Raynaud's phenomenon (RP) may occur in any acral region of the body, including the nose or penis. Secondary RP is associated with CREST (calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia), scleroderma, vaso-occlusive disease, or exposure to vibrating power tools or drugs[5]. Drug-induced RP is described with ß blockers, vinca alkaloids, and bleomycin. One report described a Raynaud's-like phenomenon with yohimbine[6]. Although RP of the penis has been described, erectile dysfunction (ED) with RP has not been reported[5].

CASE REPORT

A 65-year-old computer programmer presented with a 3-year history of RP associated with CREST syndrome. RP affected all toes and fingers, excluding thumbs. Episodes lasted 10–15 minutes, and were relieved with heat. He also noted painful RP of his penis. He had no history of hypertension, diabetes, peripheral vascular, cardiac or renal disease. He was taking no medications. His family history was negative for arthritis, RP, or scleroderma. He is a lifelong nonsmoker.

Three months prior to presentation, he started yohimbine for erectile dysfunction (ED). His ED was investigated by urology, and diagnosed as nonpsychogenic. Vascular studies of his penis were not performed. With yohimbine he had no significant improvement in his ED. He noted increased frequency and severity of his digital RP while taking yohimbine. These attacks lasted more than 60 minutes, occurred many times daily, and were no longer relieved by warming the digits.

Examination revealed a healthy looking man, with a few facial telangectasiae. Blood pressure was 118/70. The cardiorespiratory, neurologic, and joint examinations were unremarkable. He had sclerodactyly of fingers, but no nailfold capillary dilatation, calcinosis, or evidence of previous digital infarction. He had mild acrocyanosis of the toes, and poor capillary refill despite good pedal pulses.

Investigations revealed a positive antinuclear antibody titer of 1:2560, speckled pattern. Centromere antibodies were present. Digit plethysmography revealed abnormal waveforms with decreased amplitude. Cold stress caused severe dampening of waveforms in 9 of 10 fingers.

He continued yohimbine for 4 weeks, while he maintained a detailed daily record of his RP. While taking yohimbine, his daily felodipine 10 mg was ineffective in controlling RP or improving ED.

Within 48 hours of discontinuing yohimbine, his RP improved significantly. There were fewer daily episodes, of less than 10 minutes' duration. There was less pain. He also noted improvement in sensation, and was able to return to typing. Within 48 hours of rechallenge with yohimbine, he developed more severe RP. Attacks would occur without cold exposure, many times daily. Painful RP episodes increased and many episodes took more than 1 hour to resolve. He was unable to work at the computer, due to poor sensation in his fingers.

There was no improvement in his ED with stopping yohimbine, and continuing felodipine. However, application of 1 inch of nitroglycerin (NTG) ointment to his penis resulted in dramatic improvement in ED. He was able to resume normal sexual relations. Fortuitously, NTG applied to the penis (or the chest) also improved his digital RP. Digit plethysmography was repeated, taking the combination of felodipine and NTG. The severity of the vascular waveform dampening was reduced and the baseline temperature of the digits improved (Tables 1 and 2). He refused further investigations of his RP, which involved ongoing treatment with yohimbine. Yohimbine was discontinued. His ED also responded to sildenafil, which inhibits phosphodiesterase type 5, thereby enhancing the vasodilatory and muscle relaxing properties of nitric oxide and cyclic guanosine monophosphate in the corpus cavernosum[7]. He chose instead to use topical NTG and felodipine to control his RP and ED, as sildenafil precludes the use of concurrent NTG, due to the risk of severe hypotension[8].

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Table 1. Digital temperature before and after yohimbine cessation.

	Yohimbine With Felodipine and Nitropaste (° C)	Mean (°C)	Felodipine and Nitropaste (°C)	Mean (°C)
Left Fingers				
1	31.6		32.0	
2	31.9		32.0	
3	29.1	31.5	30.4	32.0
4	31.5		32.6	
5	33.4		33.1	
Right Fingers				
1	33.2		33.3	
2	31.2		33.0	
3	25.8	31.5	32.2	33.3
4	33.3		34.0	
5	34.2		34.1	

Table 2. Digital temperatures before and after yohimbine cessation.

	Yohimbine With Felodipine and Nitropaste (° C)	Mean (°C)	Felodipine and Nitropaste (°C)	Mean (°C)
Left Toes				
1	24.9		30.8	
2	23.8		30.3	
3	23.5	23.8	30.4	30.4
4	23.6		30.4	
5	23.4		30.3	
Right Toes				
1	25.7		29.8	
2	25.7		31.7	
3	25.5	25.7	30.4	30.9
4	25.8		31.1	
5	26.0		31.6	

DISCUSSION

We describe a patient with CREST and RP, aggravated by oral yohimbine used for ED. Yohimbine has been reported to have different effects on the vasculature when administered orally versus intravenously. Freedman, *et al* noted improvement in primary RP, with intravenous yohimbine[9]. He found that cold-induced vasospasm in primary RP was abolished by blockade of peripheral α-2 receptors. This was shown with regional infusion of yohimbine into the brachial artery to eliminate the confounding effects resulting from blockade of central α-receptors.

In contrast, oral yohimbine has been reported to cause a Raynaud's-like phenomenon in the digits[6]. Yohimbine has been shown to be 50 to 100 times more active at presynaptic than postsynaptic receptors[1]. Intravenous infusion of yohimbine improves Raynaud's through its selective blockade of peripheral α-2 receptors. However, oral administration has not been shown to be beneficial because of the predominant antagonism of central α-2 receptors resulting in increased sympathetic outflow and increase in plasma noradrenaline concentrations. While many studies have reported therapeutic doses of yohimbine increase noradrenaline levels, the same doses do not produce clinically significant hemodynamic changes in normotensive patients[10]. Recent data suggest that there is marked interindividual variability in yohimbine metabolism. Patients who are slow metabolizers may have an increased catecholamine response due to prolonged terminal elimination half-life and drug accumulation with repeated dosing[11,12]. Our patient agreed to discontinue and rechallenge himself with yohimbine. Taking yohimbine he documented an increase in the severity of RP and was unable to use his fingers for keyboarding. These symptoms improved markedly when yohimbine was discontinued. He achieved control of his RP and ED with a combination of felodipine and NTG. He preferred this combination since the concomitant administration of NTG and sildenafil is contraindicated[8]. He refused further yohimbine challenge; therefore, we were unable to perform serial measures of hemodynamic status to confirm that he was an atypical slow yohimbine metabolizer. In patients with a similar clinical presentation, this may be a useful means of detecting this phenotypic state. His benefit from NTG suggests intact endothelial function, while clinical deterioration on oral

yohimbine suggests a dominant α-2 adrenergic effect as postulated by Flavahan, *et al*[13].

We have described a patient with CREST syndrome and erectile dysfunction who noted worsening RP when he took yohimbine. He may be a slow metabolizer of yohimbine, resulting in increased catecholamine release and decreased clearance, thereby stimulating α-2 adrenergic receptors, causing worsening of his symptoms. This is the first report of aggravation of RP with yohimbine, and improvement of RP and ED with a combination of felodipine and topical nitroglycerin.

REFERENCES

1. Ernst E, Pittler MH. Yohimbine for erectile dysfunction: a systematic review and meta-analysis of randomized clinical trials. J Urol 1998;159:433-6.
2. Goldberg MR, Robertson D. Yohimbine: a pharmacological probe for study of the alpha-2 adrenoreceptor. Pharmacol Rev 1983;35:143-80.
3. Baum N. Treatment of impotence. 1. Nonsurgical methods. Postgrad Med 1987;81:133-6.
4. Raynaud M. De la gangrene symetrique des extremites. Paris: Universite de Paris; 1862.
5. Towheed T, Dewar C. A practical approach to Raynaud's syndrome. Medicine N Am 1996;19:56-60.
6. Sandler B, Aronson P. Yohimbine-induced cutaneous drug eruption, progressive renal failure, and lupus-like syndrome. Urology 1993;41:343-5.
7. Corbin JD, Francis SH, Webb DJ. Phosphodiesterase type 5 as a pharmacologic target in erectile dysfunction. Urology 2002;60:4-11.
8. Kloner RA, Zusman RM. Cardiovascular effects of sildenafil citrate and recommendations for its use. Am J Cardiol 1999;84:11N-17N.
9. Freedman RR, Baer RP, Mayes MD. Blockade of vasospastic attacks by alpha-2 adrenergic but not alpha-1 adrenergic antagonists in idiopathic Raynaud's disease. Circulation 1995;92:1448-51.
10. Tam SW, Worcel M, Wyllie M. Yohimbine: a clinical review. Pharmacol Ther 2001;91:215-43.
11. Sturgill MG, Grasing KW, Rosen RC, et al. Yohimbine elimination in normal volunteers is characterized by both one- and two-compartment behavior. J Cardiovasc Pharmacol 1997;29:697-703.
12. Le Corre P, Dollo G, Chevanne F, Le Verge R. Biopharmaceutics and metabolism of yohimbine in humans. Eur J Pharm Sci 1999;9:79-84.
13. Flavahan NA, Flavahan S, Liu Q, et al. Increased alpha-2 adrenergic constriction of isolated arterioles in diffuse scleroderma. Arthritis Rheum 2000;43:1886-90.