

# Improvement in Digital Flexibility and Dexterity Following Ingestion of Sildenafil Citrate (Viagra) in Limited Systemic Sclerosis

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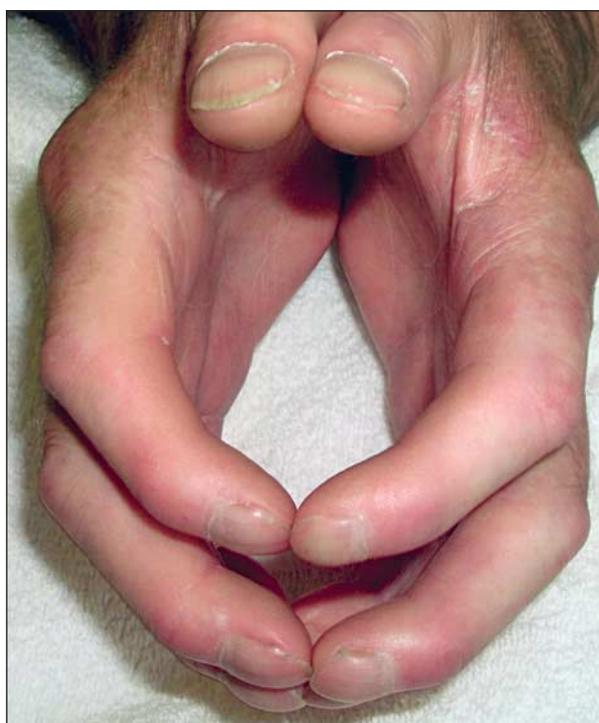
*The Cutting Edge: Challenges in Medical and Surgical Therapeutics*

## REPORT OF A CASE

A 66-year old man with a 20-year history of limited systemic sclerosis and discoid lupus erythematosus-induced scarring alopecia presented to our clinic for follow-up. He had an antinuclear antibody ratio (Hep-2) of 1:80; homogeneous staining pattern; negative extractable nuclear antibody screen findings (anti-Sm, Anti-RNP, anti-Ro, and anti-La); anti-double-stranded DNA antibody value of 22 IU/L (normal, <50 IU/L); and negative anti-Scl-70 findings. He had no history of diabetes mellitus, ischemic heart disease, or peripheral vascular disease. His skin conditions had been stable for 6 years under treatment with 200 mg of hydroxychloroquine daily, 20 mg of omeprazole daily, 2% ketoconazole shampoo, clobetasol propionate as needed (intermittently) for scalp lesions of discoid lupus erythematosus, and 2 annual prostacyclin infusions in the winter season.

On examination, he was found to have sclerodactyly affecting all the digits of his hand with associated fixed flexion deformities of the small joints of the hands giving rise to the "prayer sign" when the palms of his hands were opposed with maximum extension of the small joints of the hands (**Figure 1**). He was unable to clench his fist tightly without leaving spaces between the digits. He had a mouth opening distance of 4 cm and modified Rodnan score of 6. The modified Rodnan score comprises an aggregate skin score (0, normal; 1, thickened skin, able to pinch skinfold; 2, thickened skin, unable to pinch skinfold; or 3, thickened skin, unable to move skin) assessed in each of 17 areas (face, anterior chest, abdomen plus each limb individually [upper arm, forearm, dorsum of the hand, fingers, thighs, lower legs, dorsum of the foot]). The maximum potential score is 51.

The distance between the corresponding first metacarpophalangeal joints of both hands was 41 mm. The distance between the corresponding proximal interphalangeal joints of both hands was 40 mm. There were no signs of proximal, truncal, or perioral skin sclerosis. Findings of general examination were otherwise unremarkable apart from scarring alopecia of the scalp.



**Figure 1.** Flexion deformities before taking sildenafil citrate.

## CLINICAL CHALLENGE

Systemic sclerosis (or scleroderma) is broadly categorized into limited and diffuse cutaneous types based predominantly, but not solely, on the extent of sclerosis of the skin.<sup>1</sup> *Limited systemic sclerosis* is in general defined as the chronic presence of Raynaud phenomenon, peripheral skin involvement, calcification, telangiectasia, late onset of pulmonary hypertension, visible dilatation of the nail fold capillaries, and often (but not always) anticentromere antibodies. In contrast, *diffuse cutaneous systemic sclerosis* is in general characterized by a short interval (<1 year) between the onset of Raynaud phenomenon and development of truncal and peripheral skin changes, tendon friction rubs, internal organ complica-



**Figure 2.** Flexion deformities 12 hours after taking sildenafil citrate.

tions (such as pulmonary fibrosis, renal failure, gastrointestinal disease, and myocardial involvement), and visible nail fold–capillary loop dropout. Patients with the diffuse condition often have positive anti-Scl-70 but negative anticentromere antibody findings. Patients with either limited or diffuse systemic sclerosis may also develop ulcerations of the finger pulp, focal calcification of the subcutaneous tissue, and in some cases digital autoamputation due to occlusive vasculopathy. Systemic sclerosis differs from *mixed connective tissue disorder*, which may involve sclerosis of the skin in association with features of dermatomyositis (or polymyositis) and/or systemic (but not discoid) lupus erythematosus, often associated with positive anti-U<sub>1</sub>-RNP findings.<sup>2</sup>

Ninety percent of patients with systemic sclerosis also have Raynaud phenomenon and associated abnormal cold sensitivity, although they appear to have normal reflex response to heat stimuli.<sup>3-7</sup> Raynaud phenomenon can be ameliorated to varying degrees by keeping the hands protected from the cold and by using vasodilators.<sup>8</sup> In contrast, sclerodactyly is usually slowly progressive. Progressive sclerosis of the dermis is accompanied by an increase in thickness of the skin in the digits.<sup>9-14</sup> These changes alter the physical characteristics of the skin and lead to a reduction in the extensibility and elasticity of the skin, and as a result, there is gradual reduction and progressive loss of finger dexterity. This eventually leads to the development of fixed flexion deformities of the fingers and the prayer sign when both hands are held in opposition. Although many treatments have been used in systemic sclerosis, none has been clearly proven to im-

prove hand function or to arrest the sclerotic process that leads to progressive loss of function.<sup>15</sup>

## SOLUTION

Review of the patient's systems was remarkable for a 20-year history of erectile dysfunction. For the preceding 5 years, this was successfully treated with intermittent use of sildenafil citrate (Viagra; Pfizer Inc, New York, NY). The patient reported the expected acute adverse effects of flushing and headache. In addition, he also noted reduction in frequency of Raynaud phenomenon and improved function and flexibility of his fingers starting 2 hours after ingestion of sildenafil. These effects would last up to 3 days after each time he used sildenafil.

Results of physical examination 12 hours after taking 50 mg of sildenafil citrate showed that the interdigital distances between the corresponding metacarpophalangeal and corresponding proximal interphalangeal joints of both hands were 25 and 28 mm, respectively (**Figure 2**), and the patient could clench his fist, leaving no spaces between the digits. His modified Rodnan score was 6, and his mouth opening distance was 6 cm. These improvements were lost after 3 days.

## COMMENT

Sildenafil is the first member of a new group of drugs that inhibit guanosine monophosphate–specific phosphodiesterase type 5 and are designed specifically for the treatment of erectile dysfunction.<sup>16,17</sup> Sildenafil decreases the metabolism of cyclic guanosine monophosphate resulting in an increase in the level of nitric oxide, a potent vasodilator, which induces erection of the penis. Sildenafil is generally safe and has predictable adverse effects that occur in approximately 20% of patients.<sup>18</sup> Headache, nasal stuffiness, and flushing are the most common adverse effects. It is recommended that caution be exercised in patients with concurrent ischemic heart disease, but in a large meta-analysis no excess risk of cardiovascular deaths was apparent.<sup>16</sup> A single mortality due to sildenafil overdose has been reported.<sup>19</sup>

Nitric oxide metabolism is deranged in Raynaud phenomenon.<sup>20,21</sup> Exogenous nitrates have been shown to ameliorate Raynaud phenomenon.<sup>21</sup> In addition, genetic polymorphisms of endothelial nitric oxide synthetase have been reported in patients with scleroderma, which may predispose patients to develop scleroderma.<sup>22,23</sup> Infusions of sodium nitroprusside (a nitric oxide donor for endothelium) and oral L-arginine (the endothelial substrate for nitric oxide) have been reported to cause vasodilatation,<sup>24</sup> aid healing of digital ulcers in patients with scleroderma,<sup>25</sup> and reduce laboratory-induced Raynaud phenomenon.<sup>26</sup> However, studies using oral L-arginine report no apparent improvement in vasodilatation or Raynaud phenomenon.<sup>27,28</sup>

There has been 1 anecdotal report of improvement in Raynaud phenomenon and healing of digital ulcers with the use of sildenafil in 10 patients with connective tissue disease for whom treatment with calcium channel blockers had failed.<sup>29</sup> In this report, no improve-

ment in digital fixed flexion deformity or digital dexterity was mentioned.

In the present case, no improvement was noted in the modified Rodnan score, but objective improvement occurred in the flexibility of the patient's hands and in the mouth-opening distance. These findings are not surprising given that the hand assessment contributes only a small part to the overall modified Rodnan score.<sup>30</sup> We considered performing measurement with the Durometer (Type O, model 1700; Rex Gauge Company Inc, Buffalo Grove, Ill) to ascertain whether the observed effects resulted from softening of the skin, but the findings would be unreliable owing to the lack of flat surfaces and the presence of underlying bone in the digits.<sup>31</sup> We thought it highly unlikely that sildenafil could affect digital sclerosis in such a short time, and indeed, the skin scores for the fingers in the modified Rodnan score remained unchanged after the ingestion of sildenafil. We therefore postulate that the improvement in digital dexterity and flexibility that we observed in our patient might have occurred as a result of alteration of the viscoelastic properties of the skin due to improved warming due to sildenafil-induced vasodilatation.<sup>32</sup>

Our observation suggests that 5-phosphodiesterase inhibitors may have a role in the treatment of Raynaud phenomenon and in improving digital dexterity in patients with sclerodactyly, particularly in women, for whom unwanted penile erection would not be an issue. The dose-response relationship of these compounds with respect to improvements in Raynaud phenomenon and digital dexterity is unknown. Further studies are required to confirm the potential benefits of sildenafil. In addition, newer, long-acting 5-phosphodiesterase inhibitors may offer a more convenient and sustained therapeutic response.

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