

Phosphodiesterase Type 5 Inhibition Is a Novel Therapeutic Option in Raynaud Disease

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Background: Raynaud disease (RD) is a common disorder affecting 3% to 5% of the healthy population, and occurs in more than 90% of patients with connective tissue diseases. The therapeutic options remain limited, particularly in patients with secondary RD due to connective tissue disease. Theoretical considerations lead to the expectation that phosphodiesterase type 5 inhibitors may improve clinical symptoms and digital blood flow in patients with RD.

Methods: We conducted an open-label pilot study in 40 patients with RD, 33 (82%) of whom had secondary and 7 (18%) of whom had primary RD. Digital blood flow was measured by laser-Doppler flowmetry at room temperature and during the cold-exposure test before medical treatment, 1 hour after the initial intake, and after 2 weeks of continuous treatment (10 mg twice a day) with the novel phosphodiesterase type 5 inhibitor vardenafil. Clinical symptoms were recorded by a patient questionnaire and summarized as the Raynaud condition score.

Results: Laser-Doppler flowmetry revealed that vardenafil improved digital blood flow in 28 (70%) patients, whereas 12 (30%) did not respond. In individuals responding, digital blood flow significantly increased by a mean \pm SEM of $21.0\% \pm 4.9\%$ and $30.0\% \pm 5.7\%$ at 1 hour and 2 weeks of treatment at room temperature, respectively, and by $18.8\% \pm 4.4\%$ and $35.1\% \pm 7.5\%$ at 1 hour and 2 weeks during the cold-exposure test, respectively ($P < .01$ for all). Consistently, clinical symptoms improved in 27 (68%) of the 40 patients, and the Raynaud condition score declined from a mean \pm SEM of 5.05 ± 0.38 to 3.54 ± 0.31 ($P < .001$).

Conclusion: Our data indicate that phosphodiesterase type 5 inhibition significantly improves peripheral blood flow and clinical symptoms in a large subset of patients with RD and, thus, may provide a novel therapeutic approach in such individuals.

Arch Intern Med. 2006;166:231-233

ACCORDING TO POPULATION-based surveys of various ethnic groups, the prevalence of Raynaud disease (RD) in the healthy population is 3% to 5%.¹ This syndrome, which was first described by Maurice Raynaud in 1862, is defined as episodic cold- or emotional stress-triggered ischemic vasospasms of the digital arteries and precapillary arterioles, which may lead to superficial ulcerations and—in severe cases—can even result in deep tissue necrosis with gangrene and require amputations.¹ Primary RD is distinguished from secondary RD, which frequently occurs in patients with connective tissue diseases (ie, systemic sclerosis [SSc]). Thus far, medical therapy of this condition remains unsatisfactory, particularly in patients with secondary RD. Therapeutic effects (reduction of frequency, duration, and severity of RD-related attacks) have been demonstrated for calcium channel blockers (CCBs), the angiotensin type 1 receptor antagonist losartan, the α_1 -adrenoceptor blocker prazosin, and the selective serotonin reuptake inhibitor fluoxetine.¹ However, treatment with these agents was suc-

cessful only in a subset of patients and had to be discontinued in approximately 15% because of significant adverse effects. Medical therapy of primary RD is mostly successful, whereas the treatment of RD secondary to connective tissue diseases, particularly SSc, is often complicated. The intravenous application of prostacyclin analogues (iloprost) was effective for the short-term palliation of severe SSc-associated RD, whereas orally administered prostaglandins (iloprost, cicaprost, and beraprost) or arginine have not proved effective.¹

Phosphodiesterase type 5 (PDE5) inhibitors, such as sildenafil citrate, which mediate vasodilatory effects via accumulation of cyclic guanosine monophosphate in vascular smooth muscle cells, are effective in the treatment of erectile dysfunction and pulmonary hypertension.^{2,3} It was recently reported that medical treatment of pulmonary hypertension with sildenafil in a patient with lung fibrosis secondary to SSc was associated with a significant improvement of coexisting RD.⁴ Because PDE5 inhibitors are known to exert vasodilatory properties, particularly in diseased tissue,⁵ and, furthermore, were recently shown to exhibit antiproliferative effects,⁶ a therapeutic

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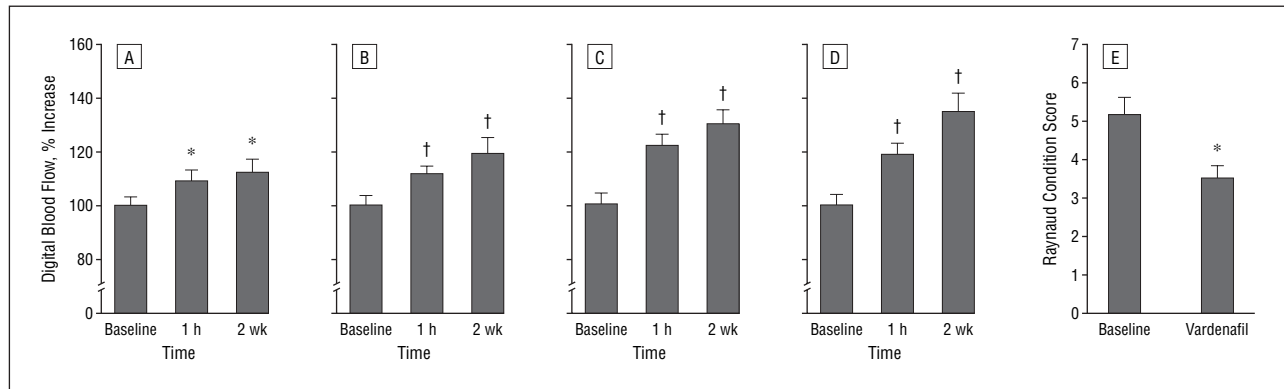


Figure. Mean \pm SEM results of laser-Doppler flowmetry after treatment with the phosphodiesterase type 5 inhibitor vardenafil, 10 mg twice a day, in all patients (N=40) at room temperature (RT) (A) and during the cold-exposure test (CET) (B) and in treatment responders (n=28) at RT (C) and during the CET (D) and mean \pm SEM data for the Raynaud condition score in all patients (N=40) during the 7 days before therapy (baseline) and during the second week of continuous vardenafil treatment (E). In A through D, data are given as the relative increase of blood flow after treatment compared with basal values. $P < .025$ was considered statistically significant (Bonferroni correction). The asterisk indicates not significant; and the dagger, $P < .01$. In E, the asterisk indicates $P < .001$.

tic potential of PDE5 inhibitors in patients with RD may indeed be expected. Therefore, we conducted an open-label pilot study, in which we investigated the effects of the novel PDE5 inhibitor vardenafil⁷ on clinical symptoms and peripheral blood flow in patients with RD of various causes.

METHODS

Forty patients (3 men and 37 women; mean \pm SEM age, 49 \pm 13 years) with a definite diagnosis of RD (typical clinical symptoms, impaired digital blood flow, and history of RD-related attacks for at least 1 year) were included. The study was approved by the local ethics committee, and written informed consent was obtained from each patient. All vasoactive agents (eg, CCBs and nitrates) were discontinued at least 1 week before study inclusion. Vardenafil, 10 mg twice a day, was administered over 2 weeks. Peripheral blood flow in the index finger was measured by laser-Doppler flowmetry after adjustment to room temperature (24°C) at time point 0 (baseline), 1 hour after the initial intake, and after 2 weeks of continuous therapy. Measurements were repeated during a cold-exposure test (CET) at 4°C, and nail fold capillary microscopy was also performed for each condition. All measurements were made in a fasting state at the same time of day. The frequency, total daily duration, and severity of RD-related attacks were recorded by a patient questionnaire and summarized as the Raynaud condition score (RCS). Based on the previously described conditions, patients were asked to rate the difficulty they had with their RD on a scale ranging from 0 (none) to 10 (very severe) on each day throughout the study period. A detailed description of the questionnaire and the RCS is given by Black et al.⁸

All data are expressed as mean \pm SEM. Statistical analysis of the mean intraindividual percentage change of digital blood flow $[(\text{treatment}/\{\text{basal} - 1\}) \times 100\%]$ was assessed by the 2-tailed 1-sample *t* test with Bonferroni correction (adjusted $\alpha = .025$, vs 0). The mean absolute change of the RCS was analyzed by a 2-tailed paired-sample *t* test ($\alpha = .05$). Statistical evaluation was performed using a commercially available software program (SPSS, 10.0 for Windows; SPSS Inc, Chicago, Ill).

RESULTS

Of the 40 patients enrolled, 7 (18%) had primary RD (no history or physical findings suggestive of a secondary cause, healthy nail fold capillaries, and negative test results for specific autoantibodies) and 33 (82%) had secondary RD (clinical

features suggestive of a connective tissue disease, enlarged and disarranged and/or decreased number of capillary loops and/or hemorrhages on nail fold capillary microscopy, and presence of specific autoantibodies). Twelve patients (30%) were smokers, whereas 28 (70%) were non-smokers. All smokers abstained from smoking at least 12 hours before testing. Laser-Doppler flowmetry revealed improved digital blood flow during vardenafil treatment in 28 (70%) patients, whereas 12 (30%) did not respond to therapy. When all patients were pooled, laser-Doppler measurements showed a tendency toward increased digital blood flow at room temperature at 1 hour (9.9% \pm 4.4%) and 2 weeks (12.9% \pm 5.5%) of vardenafil treatment compared with baseline values ($P = .03$ for both) (Figure, A). During the CET, however, vardenafil significantly increased blood flow by 11.0% \pm 3.7% at 1 hour (97.5% confidence interval [CI], 2.2%-19.9%) and by 19.7% \pm 6.6% (97.5% CI, 4.1%-35.4%) at 2 weeks ($P < .01$ vs baseline for both) (Figure, B). In patients responding to vardenafil (n=28), there was a highly significant increase of digital blood flow at room temperature and during the CET at both time points: room temperature, 21.0% \pm 4.9% (97.5% CI, 8.8%-33.1%) at 1 hour and 30.0% \pm 5.7% (97.5% CI, 16.2%-43.8%) at 2 weeks (Figure, C); CET, 18.8% \pm 4.4% (97.5% CI, 8.0%-29.5%) at 1 hour and 35.1% \pm 7.5% (97.5% CI, 16.9%-53.2%) at 2 weeks (Figure, D) ($P < .01$ vs baseline for all). As expected, capillary microscopy showed no differences during the 2-week observation periods. Consistent with the improvement of digital blood flow in 28 (70%) of the patients, 27 (68%) reported a distinct improvement of clinical symptoms due to RD. Twenty-four (60%) of the 40 patients reported a reduction of the total daily duration of RD-related attacks, and the number and severity of attacks were reduced in 50% (20/40) and 53% (21/40) of patients, respectively. Consequently, the RCS of all patients significantly decreased from 5.05 \pm 0.38 during the 7 days before treatment to 3.54 \pm 0.31 during the second week of vardenafil therapy ($P < .001$) (Figure, E), resulting in a decrease of 1.51 \pm 0.29 (95% CI, 0.91-2.11).

Vardenafil treatment caused a modest decrease of systolic blood pressure and had no effect on heart rate. No severe adverse events (symptomatic hypotension, myocardial infarction, stroke, or death) were recorded, and the

typical adverse effects of PDE5 inhibitors occurred at the expected frequencies. Eight patients (20%) experienced headaches; 6 (15%), flush; 4 (10%), dyspepsia; 3 (8%), running nose; 3 (8%), visual abnormalities; and 1 (2%), ischemia of the index finger. Treatment was prematurely discontinued in the patient with severe ischemia of the index finger.

COMMENT

These data demonstrate that PDE5 inhibition by vardenafil significantly improved digital blood flow in patients with RD within 1 hour, and this effect persisted throughout the observation period of 2 weeks, suggesting a novel indication for PDE5 inhibitors in clinical practice. The CET was able to identify individuals who are likely to respond to vardenafil. When compared with other studies, the response rate and therapeutic efficacy of vardenafil were at least equal to those of established agents, such as CCBs. Two recent meta-analyses revealed that the therapeutic effects of CCBs in patients with RD are rather moderate. A mean reduction of 2.8 to 5.0 attacks per week and a 33% reduction in severity were observed in primary RD, and a mean reduction of 8.3 attacks in 2 weeks and 35% less severity were observed in patients with RD secondary to SSc.^{9,10} In the present study, 68% of the patients reported a significant improvement of clinical symptoms on vardenafil treatment, which was due to a reduction of the duration, frequency, and severity of attacks. As a result, the RCS significantly declined from 5.05 ± 0.38 to 3.54 ± 0.31 . More important, the improvement of clinical symptoms, which was observed in most patients, was confirmed by objective measurement of digital blood flow in each patient, using laser-Doppler flowmetry. This seems particularly promising because most patients (82%) had secondary RD, mostly due to SSc, which is particularly difficult to treat.

In contrast to a recent study¹¹ demonstrating that sildenafil improved endothelial dysfunction only in nonsmoking individuals, we found no difference in the response rates of smokers (8 [67%] of 12) vs nonsmokers (20 [71%] of 28) on digital blood flow and clinical improvement of RD. Furthermore, the response rates of patients with primary (6 [86%] of 7) or secondary (21 [64%] of 33) RD to vardenafil treatment were quite similar. Thus, the reason for the failure of some patients to respond to vardenafil, while others responded quite well, remains unclear.

Within the study period of 2 weeks, no severe adverse events occurred. This is consistent with previous reports^{12,13} demonstrating that long-term treatment with PDE5 inhibitors is not associated with increased cardiovascular risk or mortality. The frequencies of other adverse events (headache, flush, dyspepsia, running nose, and visual abnormalities) were within the range that was previously reported for PDE5 inhibitors, and did not exceed the frequency of adverse effects during the standard therapy with CCBs.^{8,9} In one patient, vardenafil treatment was prematurely stopped because of severe ischemia of the index finger; however, a causal relationship was not proved and, based on much literature on PDE5 inhibitors, this case should be considered a coincidence. Because PDE5 inhibitors and CCBs exert their vasodilative properties through distinct mechanisms, it can be specu-

lated that combination therapy with these agents may enhance the therapeutic effect. Such a combination seems to be safe because no increase of adverse events was observed during the concomitant intake of PDE5 inhibitors and antihypertensive agents, including CCBs.^{14,15}

In summary, our findings indicate that PDE5 inhibitors like vardenafil significantly improve peripheral blood flow and clinical symptoms in a large subset of patients with RD and, thus, may provide a novel therapeutic approach in such individuals. Based on these findings, a placebo-controlled trial and a comparison and/or combination with established medications (eg, CCBs) are highly warranted.

Accepted for Publication: August 9, 2005.

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Author Contributions: Dr Rosenkranz had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Financial Disclosure: None.

Funding/Support: This study was supported by a research grant from Bayer Vital GmbH, Leverkusen, Germany.

Role of the Sponsor: The funding body had no role in data extraction and analyses, in the writing of the manuscript, or in the decision to submit the manuscript for publication.

Acknowledgment: We thank Martin Hellmich, MD, Institute of Medical Statistics, Informatics and Epidemiology, Universität zu Köln, for statistical evaluation of the data.

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