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ONLINE FIRST

Carvedilol for the Treatment of Refractory Facial Flushing and Persistent Erythema of Rosacea

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Rosacea is a common facial disorder characterized by centrofacial erythema, flushing, telangiectasia, edema, papules, pustules, ocular lesions, and rhinophyma in various combinations.[1-4] The skin lesions most commonly affect the convex areas of the nose, cheeks, chin, and forehead. Rosacea is classified as erythematotelangiectatic (ETR), papulopustular, and phymatous subtypes, and as ocular and granulomatous variants.[2-4] The ETR subtype is typified by frequent episodes of facial flushing, telangiectasias, and persistent centrofacial erythema and may be accompanied by facial edema, burning, or stinging. Severe flushing can cause significant physical discomfort and emotional stress to the patients, and currently no satisfactory treatments are available.

REPORT OF A CASE

A 48-year-old woman presented with facial flushing with persistent erythema, and edema accompanied by burning and itchy sensation that were provoked by various stimuli, including heat, sun exposure, cold weather, stress, spicy food, alcohol, and cosmetics. She began to have facial flushing and erythema about 11 years previously, shortly after glycolic acid treatments on the face. Since then, she had visited many dermatology clinics for help, and despite treatments with doxycycline, fexofenadine hydrochloride, cetirizine hydrochloride, low-dose prednisolone, topical corticosteroid preparations, metronidazole gel, and pimecrolimus cream in various combinations, there were only partial beneficial effects. Topical and systemic corticosteroids provided better control, but symptoms would flare or rebound when these treatments were discontinued.

The patient underwent bilateral endoscopic thoracic sympathectomy for the severe ETR 8 years previously. The facial symptoms showed a moderate improvement after sympathectomy. But about half a year later, she began to experience severe compensatory hyperhidrosis over the back and legs that necessitated a change of clothing up to 6 times per day in summertime. Meanwhile, the facial erythema and flushing persisted, and to treat it she received stellate ganglion block periodically along with oral clonidine hydrochloride, 0.15 mg 3 times daily, for the next few years. Despite these treatments, she still had a severe hot flush with a burning sensation and persistent facial erythema that required consistent air conditioning or a fan blowing to the face even in bed. Moreover, her daily life was very much restricted because of so many triggering or aggravating factors that she had to avoid. She also experienced chronic insomnia and constipation. In March 2009, she came to us for help. Examination revealed diffuse fiery red erythema of the cheeks and some background atrophy and telangiectasia of the skin (**Figure 1**). She was otherwise in good health. Laboratory tests, including hemogram and antinuclear antibody test, showed no abnormal findings. The clinical diagnosis was severe rosacea with a component of steroid rosacea.

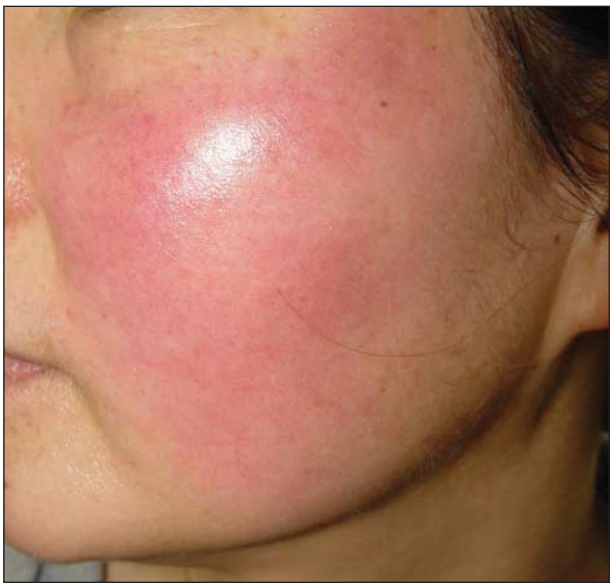

Figure 1. Severe erythematotelangiectatic rosacea before carvedilol treatment.

Despite 4 weeks of treatment consisting of doxycycline, fexofenadine hydrochloride (60 mg twice a day), dexamethasone (5 mg/d), aspirin (100 mg/d), clonidine hydrochloride (0.15 mg 3 times a day), and topical hydrocortisone ointment, 1%, and pimecrolimus cream, 1%, there was only slight clinical improvement. Her face remained very warm and red. The temperature of her cheek was 37°C (ear temperature, 36.3°C).

THERAPEUTIC CHALLENGE

Many treatment options are available for rosacea and provide varying degrees of success,[5-12] including topical metronidazole, oral tetracyclines, azithromycin, β-adrenergic blockers,[5,6] clonidine,[7,8] naloxone hydrochloride,[9]

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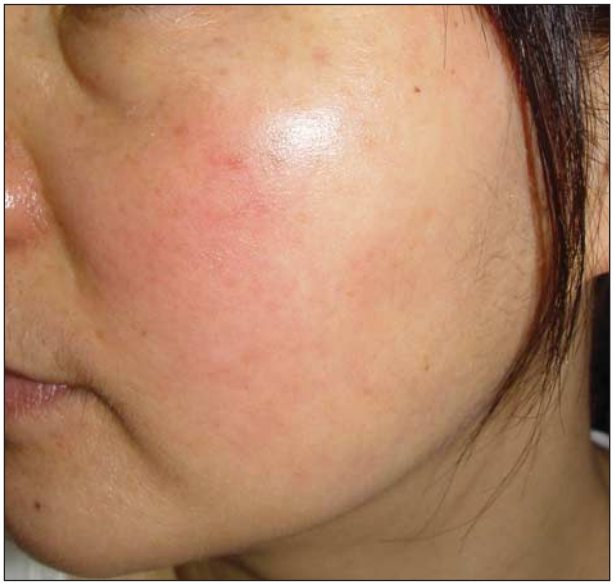

Figure 2. Dramatic clinical improvement after adding carvedilol, 6.25 mg twice daily for 1 week and 3 times daily for the next week.

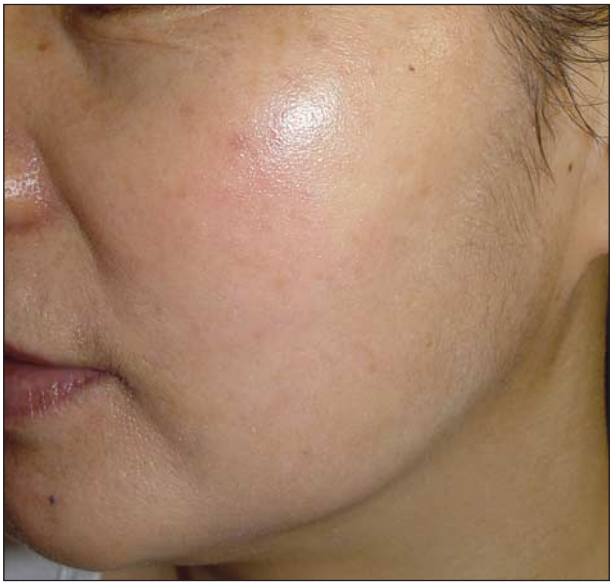

Figure 3. Minimal facial erythema while maintaining therapy with carvedilol, 6.25 mg 1 to 3 times a day for 16 months.

ondansetron hydrochloride,[10] as well as vascular laser therapy and endoscopic thoracic sympathectomy.[11,12] However, severe ETR often responds poorly to treatment. The facial flushing, persistent erythema, and discomfort (burning and itchiness) in our patient were very severe and proved refractory to many of the aforementioned therapies over the course of 11 years. She was in desperate need of a more effective treatment to relieve her severe physical and emotional stresses.

SOLUTION

The traditional β blockers nadolol[5] and propranolol hydrochloride[6] can suppress flushing reactions in some patients, particularly when associated with anxiety.[6] Because patients with ETR are often normotensive, some patients are less able to tolerate the hypotension and bradycardia caused by these traditional β-blockers. This problem prompted us to find other β-blockers that might have less hypotensive adverse effects. The frequency of hypotension during carvedilol, atenolol, and nadolol therapy for hypertension was 1.8%, 4%, and 1%, respectively.[13-15] Carvedilol is also approved for treating mild-to-moderate congestive heart failure and in a study[16] was well tolerated even in elderly patients with low rates of hypotension (3.3%) and bradycardia (1.7%). Our patient agreed to have carvedilol added to her current medications after being informed about the potential adverse effects. Carvedilol, 6.25 mg twice a day, was prescribed for the first week, followed by 3 times a day thereafter. She monitored her blood pressure and pulse rate regularly at home, and no hypotension or bradycardia was noted.

A dramatic improvement in the erythema and telangiectasia was noted in 2 weeks (**Figure 2**). The temperatures of the cheek and ear were measured before and after carvedilol treatment. The patient's cheek temperature was reduced by 6.9°C (from 36.9°C to 30.0°C). The corresponding ear temperature decreased from 36.2°C to 35.9°C. The patient's own assessment of the clinical severity based on a 10-point visual analog score showed a reduction of 9 points (from 10 to 1). Her blood pressure was reduced from 130/70 mm Hg to 110/60 mm Hg. The symptoms of ETR continued to improve with minimal facial erythema and only transient flushing episodically without a hot or burning sensation (**Figure 3**). We were able to taper and eventually discontinue her fexofenadine, dexamethasone, and aspirin in 2 months. As of March 2011, the patient was receiving maintenance therapy of carvedilol (6.25 mg 1-3 times a day), doxycycline (100 mg every other day to once a day), and topical pimecrolimus, 1%, for 23 months without adverse effects. She needed to take only 6.25 mg daily in summertime when she could use an air conditioner or was able to dissipate the body heat by sweating. The patient was extremely satisfied with this new treatment.

COMMENT

Rosacea flushing is often difficult to control by standard treatments for rosacea. Wilkin[7] reported that clonidine (α-adrenergic agonist) reduced the malar temperature in patients with ETR, despite no improvement of redness after provocative maneuvers. Although β-blockers have not demonstrated objective laboratory evidence for direct effects on cutaneous blood vessels during flushing episodes, fewer symptoms have been noted in some patients.[5,6] The mechanism of β blockers in treating ETR may be by way of blocking the β_2-adrenergic receptor on the smooth muscle of cutaneous arterial blood vessels, resulting in vasoconstriction.[4] Moreover, nonselective β-blockers also reduce the symptoms of anxiety and tachycardia that often intensify flushing symptoms.[5,6] Carvedilol is a nonselective β-adrenergic blocking agent with α_1-blocking activity and has a ratio of α_1- to β-adrenoreceptor blockade of 1:10.[17] For reducing blood pressure in patients with mild to moderate hypertension, carvedilol, 50 mg twice daily, was as effective as pro-

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pranolol hydrochloride, 80 mg twice daily.[17] For facial flushing, the dose of propranolol hydrochloride needed to achieve symptomatic control varied from 20 to 40 mg taken 2 to 3 times a day.[6] In our patient, a low dose of carvedilol was very effective in treating ETR, with fast onset of symptom control. It also allowed tapering and eventual cessation of her long-term oral and topical corticosteroid therapy. She felt that a maintenance therapy with carvedilol was necessary for control of her facial symptoms.

Low-dose carvedilol therapy in the present case represents a novel use of this drug, and the positive effect suggests that carvedilol may be an effective alternative for severe rosacea flushing. Low-dose carvedilol is well tolerated even in elderly patients with heart failure.[16] Nevertheless, it is important to monitor patients for potential adverse effects such as hypotension, bradycardia, bronchospasm, hyperglycemia, fatigue, dizziness, erectile dysfunction, and atrioventricular block.[13]

Chronic inflammation is believed to account for some symptoms of rosacea, and reactive oxygen species released by local inflammatory cells may contribute to the inflammation in rosacea.[18,19] Some antibiotics, such as doxycycline, metronidazole, and azithromycin, have anti-inflammatory effects or antioxidant properties, which have been shown to play an important role in the treatment of rosacea.[18,20] Interestingly, carvedilol also demonstrated more potent antioxidant properties compared with other β blockers[21] and may offer an added advantage over the traditional β blockers. Prospective clinical trials are warranted to evaluate its full therapeutic potential and optimal regimen in treating rosacea, especially ETR.

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