Brimonidine “Rebound:” Worsening of Rosacea Following Topical Application of Brimonidine Gel

Sir,

Brimonidine is a selective alpha-2 adrenergic agonist. It has a vasoconstrictive action on small distal resistance arteries by way of postsynaptic alpha-2 adrenergic receptor signaling on the vascular smooth muscle. The enlarged superficial cutaneous vessels that contribute to the fixed background facial redness of rosacea remain vasoactive to sympathetic nervous system innervation.[1] This makes the adrenergic agonists such as brimonidine and oxymetazoline (which is an alpha-1 receptor agonist) effective for rosacea. Brimonidine gel was approved in 2013 by the US Food and Drug Administration for persistent erythema of rosacea. It has been available in India for over a year.

A 23-year-old female presented with erythematous plaques and papules on both cheeks for the past 7–10 days [Figure 1]. She had been applying brimonidine tartrate (0.33%) gel daily in the morning for the past 6 weeks for rosacea. Her redness had improved considerably after starting the treatment. However, after using the gel for around 4 weeks, she noticed that redness returned by evening and was accompanied by burning sensation. Hence, she started applying brimonidine in the evenings too. On further inquiry, she reported that the symptoms improved for a couple of hours after application, but returned with greater severity later. Initially, only the redness was worse, but later, the skin started thickening. On suspicion of brimonidine rebound/contact dermatitis, the patient was asked to discontinue brimonidine and only apply a bland emollient. She was put on doxycycline 100 mg BD for 10 days. On follow-up, the plaques and papules had reduced, and erythema had improved. She was put on isotretinoin 10 mg once daily and given two sessions of intense pulse light at
15-day interval. After 2 months of isotretinoin, she was clear of all lesions and her flushing was very well controlled [Figure 2].

Rebound erythema constitutes rebound dilation of the capillaries caused by downregulation of alpha-2 adrenergic receptors,[2] secondary beta-receptor stimulation, and rebound increase in parasympathetic activity.[3] This may be similar to “rhinitis medicamentosa,” observed with overuse of alpha-adrenergic agonist nasal sprays (e.g. oxymetazoline and xylometazoline). Thus, it has been proposed to be named as “dermatitis medicamentosa.”[4]

The product insert has no mention of “rebound,” although it mentions that 1% patients may get erythema/flushing or contact dermatitis. Although in phase 2 trials, no cases of rebound were observed,[5] in phase 3 studies, flushing and erythema were reported at a higher incidence in the brimonidine treatment arm compared to the vehicle arm. In a retrospective review of clinical studies, flushing and erythema were the most commonly reported adverse events, occurring in a total of 5.4% of individuals in the phase 3 studies and in 15.4% in the long-term study.[6] Some people relate wearing off of the effect at the end of the day to a worsening, and this is more pronounced in the active than the vehicle group.[7] Real-world use has shown that approximately 10%–20% treated with brimonidine experience a worsening of erythema.[8] There are many online posts of rebound by patients on rosacea blogs.

The term “rebound” has been used to describe several physiologically distinct events.[8] It probably encompasses wearing off, flushing, erythema, contact dermatitis, as well as compensatory vasodilatation. Having prescribed brimonidine to over 40 patients, the author has come across at least four patients with complaints of worsening of their rosacea. Two patients (including this case) reported getting plaques and papules of rosacea, although they had only flushing or erythematotelangiectatic rosacea before starting therapy with brimonidine. One patient reported that her whole face became “tomato red” at 5 pm every evening, presumably the time when the vasoconstrictive effect wore off. Her rosacea was only centrofacial before, but now, the entire face “including the sides” was affected.

Such a side effect is counterproductive to the management of rosacea. To avoid such cases, patients should be asked to discontinue use if they notice worsening of their condition. It must be studied if brimonidine is more suitable for temporary use, like the alpha-adrenergic nasal sprays, rather than for long-term use. It can be applied before important events rather than as an everyday application.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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96

Letters to Editor

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Sir,

Cutaneous mastocytosis (CM) in children is a rare benign cutaneous proliferative disorder caused by mast cell proliferation in the dermis. It presents with highly itchy skin lesions on body which may show blistering at times. The condition is known to resolve slowly, but it may progress to systemic dissemination in some cases if not treated. Traditional treatments aim at only controlling itching and are partially effective. We report an uneventful therapy of diffuse CM with imatinib mesylate in a 14-month-old boy.

A 14-month-old boy was brought to our dermatology outpatient department with multiple, severely itchy, skin-colored–to-erythematous lesions all over his body [Figure 1]. The child was irritable and was unable to have a peaceful sleep due to severe itching. The patient was treated with multiple courses of oral antihistamines and steroids with partial improvement.

Cutaneous examination showed multiple skin-colored–to-yellowish xanthomatous papules and plaques over entire skin surface. After informed consent, a lesional skin biopsy was done. Histology showed diffuse dermal infiltrate of mast cells occupying the entire papillary and reticular dermis. On clinicopathological correlation, a diagnosis of CM was made and was confirmed by metachromatic special stain (Toluidine blue) showing purple staining granules [Figure 2a and b]. Systemic involvement was ruled out by clinical, laboratory, and radiological investigations. Final diagnosis of diffuse CM was made. Genetic analysis was done from skin biopsy for KIT mutation, which turned out to be negative.

Figure 2:
(a) Typical “fried egg” appearance of mast cells (H and E, ×10). (b) Toluidine blue stain showing pink cytoplasmic granules with degranulation (Toluidine blue under oil immersion).

Figure 1: Multiple skin-colored papulonodules over back with positive Darier's sign.