Rheumatology 2003;42:601–602
doi:10.1093/rheumatology/keg137

Serotonin reuptake inhibitors, Raynaud's phenomenon and erythromelalgia

SIR, We read with great interest the report by Coleiro *et al.* [1] describing a pilot study on the tolerability and efficiency of fluoxetine for the treatment of Raynaud's phenomenon. This study confirmed previous case reports suggesting the usefulness of selective serotonin reuptake inhibitors (SSRIs) in the management of Raynaud's phenomenon [2, 3]. Here we describe for the first time two patients who experienced, when given SSRIs, disappearance of Raynaud's phenomenon but occurrence of erythromelalgia.

A 60-yr-old woman suffering from Raynaud's phenomenon for 2 yr noted the relief of her symptoms 1 month after she was given sertraline (50 mg/day) for depression. However, painful erythema of the hands and feet consistent with the diagnosis of erythromelalgia occurred concomitantly. There was no improvement when sertraline was replaced by paroxetine or with low-dose aspirin. The second patient was a 68-yr-old woman with Raynaud's phenomenon and Sjögren's disease treated with hydroxychloroquine. As she suffered from depression, treatment with fluoxetine was introduced (20 mg/day) without benefit. When she was given 40 mg daily, she observed the disappearance of Raynaud's phenomenon and the occurrence of erythromelalgia. Pulse and neurological examination, nailfold capillaroscopy and ultrasound Doppler results were normal for both patients. Symptoms disappeared only when SSRI treatment was discontinued in both patients. Plasma serotonin levels were undetectable under SSRI treatment and returned to the normal value only 3 months after SSRI discontinuation.

Raynaud's phenomenon and erythromelalgia are both vascular acrosyndromes. Erythromelalgia is a rare painful disorder of the extremities characterized by redness, a burning sensation and an increase in skin temperature exacerbated by exposure to heat [4]. The pathophysiology of these syndromes is not well understood. Moreover, serotonin may cause vasoconstriction or vasodilatation depending on the vessels involved and the integrity of the endothelium. Serotonin has been involved in the pathogenesis of both Raynaud's phenomenon and erythromelalgia [2, 4].

SSRIs inhibit the reuptake of serotonin with a decreased storage of 5-hydroxytryptamine in platelets leading to symptomatic platelet dysfunction. In our patients, the strong temporal association between SSRI administration,

the relief of Raynaud's phenomenon and the occurrence of erythromelalgia suggests that serotonin metabolism (and SSRI) is involved in the pathophysiology of Raynaud's phenomenon and erythromelalgia. As some patients with Raynaud's phenomenon experienced marked clinical improvement in their symptoms when given SSRIs [1–3], it is possible that vasodilatation related to plasma serotonin depletion induced by SSRIs explained the erythromelalgia. Erythromelalgia has also been reported to occur in association with other drugs inducing vasodilatation such as calcium-channel blockers [4]. An erythromelalgia-like syndrome associated with nifedipine has also been described in a patient suffering from Raynaud's phenomenon [5]. Our case reports confirm that SSRIs might be of value in some patients with Raynaud's phenomenon, as described in the report by Coleiro *et al*. [1], but they can also induce erythromelalgia. However, variability in the response to treatment was noted in the report of Coleiro *et al*. [1], where the greatest benefit was seen in females and in patients with primary Raynaud's phenomenon. The response may be dose dependent as observed in our second patient. SSRI treatment for Raynaud's phenomenon could induce a stronger vasodilatation effect in some predisposed patients leading to erythromelalgia. Moreover, our case reports demonstrated that peripheral vascular effects of SSRI are complex, as suggested by the observations of worsening of pre-existing Raynaud's phenomenon with digital infarction [6] or improvement of erythromelalgia during SSRI treatment [7]. As suggested by Coleiro *et al*. [1], this variability may be partly explained by differences in serotonin metabolism. Further studies are needed to confirm our observations.

J. Rey, E. Cretel, R. Jean, M.-J. Pastor[1], J.-M. Durand

Service de Médecine Interne, Hôpital de la Conception and [1]*Service de Pharmacovigilance, Hôpital St Marguerite, Marseilles, France*

Accepted 16 September 2002

Correspondence to: J.-M. Durand. E-mail: jean-marc.durand@ap-hm.fr

1. Coleiro B, Marshall SE, Denton CP *et al*. Treatment of Raynaud's phenomenon with the selective serotonin reuptake inhibitor fluoxetine. Rheumatology 2001;40:1038–43.
2. Jaffe IA. Serotonin reuptake inhibitors in Raynaud's phenomenon. Lancet 1995;345:1378.
3. Bolte MA, Avery D. Case of fluoxetine-induced remission of Raynaud's phenomenon—a case report. Angiology 1993;44:161–3.
4. Davis MDP, O'Fallon WM, Rogers RS III, Rooke TW. Natural history of erythromelalgia: presentation and outcome in 168 patients. Arch Dermatol 2000;163:330–6.
5. Sunahara JF, Gora-Harper ML, Nash KS. Possible erythromelalgia-like syndrome associated with nifedipine in a patient with Raynaud's phenomenon. Ann Pharmacother 1996;30:484–6.
6. Bell C, Coupland N, Creamer P. Digital infarction in a patient with Raynaud's phenomenon associated with treatment with a specific serotonin reuptake inhibitor. A case report. Angiology 1996;47:901–3.
7. Rudikoff D, Jaffe IA. Erythromelalgia: response to serotonin reuptake inhibitors. J Am Acad Dermatol 1997;37:281–3.