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CASE REPORT

Crossover Reaction Between Mianserin and Trazodone for Restless Legs Syndrome

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A 58-year-old woman with a past history of mianserin-induced restless legs syndrome (RLS) developed the same syndrome on subtherapeutic doses of trazodone. However, neither nortriptyline nor imipramine at therapeutic doses caused RLS. The present report suggests that hyposerotonergic states are involved in the pathophysiology of RLS.

KEYWORDS—mianserin; trazodone; restless legs syndrome; serotonin

INTRODUCTION

Restless legs syndrome (RLS) is characterized by unpleasant creeping and restless sensations in the legs, and causes psychiatric complications such as insomnia and depression (Clough, 1987; Walters and Hening, 1987).

RLS has been reported in association with various drug treatments (Walters and Hening, 1987). We report a crossover reaction between mianserin and trazodone for RLS, which has not previously been reported. The present report sheds some light on the pathophysiology of RLS.

CASE REPORT

A 58-year old woman revisited our outpatient clinic because of a recurrence of depression. In the previous episode, she had developed RLS on subtherapeutic doses (10–30 mg/day) of mianserin (Otani *et al.*, 1992).

Her treatment was started with trazodone 150 mg at bedtime (22.00 h). At 22.30 h of the 9th day, she had creeping and restless sensations in her calves while dozing in bed. She could not keep her legs still because of these uncomfortable sensations. To seek relief, she vigorously moved and rubbed her legs. Thirty minutes later these symptoms subsided, and she could fall asleep. The same symptoms were observed for three consecutive days from the 13th day. From the 16th day the dose was decreased to 100 mg for 1 week, but restless legs were still observed on 4 days in a milder degree. Therefore, trazodone was switched to nortriptyline (25–75 mg at bedtime). Two weeks later, she was hospitalized at her own request. Nortriptyline had to be discontinued prematurely, since it was not available in our hospital pharmacy. Imipramine (50–150 mg at bedtime) was introduced instead, and her depressive symptoms improved in 4 weeks. Neither nortriptyline nor imipramine caused restless legs.

Plasma concentrations of trazodone and its active metabolite *m*-chlorophenylpiperazine (mCPP) (Kahn and Wetzler, 1991) at the dose of 150 mg/day were 187 ng/ml and 16 ng/ml, respectively. Plasma concentration of nortriptyline at the dose of 75 mg/day was 92 ng/ml, and that of imipramine plus desipramine at the dose of 150 mg/day was 224 ng/ml. The concentrations of nortriptyline and imipramine plus desipramine were within, while that of trazodone was lower than, the suggested therapeutic ranges (Orsulak, 1989).

DISCUSSION

The underlying pathophysiology in RLS has not been clarified yet (Clough, 1987; Walters and Hening, 1987). The possible mechanisms include underactivity of the GABA-ergic, serotonergic, dopaminergic, or endogenous opiate systems, and/or overactivity of the adrenergic system (Walters and Hening, 1987).

The present case developed RLS on subtherapeutic doses of mianserin and trazodone. However, neither nortriptyline nor imipramine at therapeutic doses caused RLS in the present patient, who was

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apparently very susceptible to this syndrome. These findings suggest that some biochemical effect(s) shared by mianserin and trazodone is involved in the pathophysiology of RLS.

Mianserin and trazodone are much more potent than nortriptyline and imipramine at blocking serotonin 5-HT_1 and 5-HT_2 receptors (Wander *et al.*, 1986). mCPP is a serotonin agonist (Kahn and Wetzler, 1991), but the concentration of mCPP in the present case was much lower than those in the previously reported 43 cases (Ishida *et al.*, 1995). In addition, only imipramine shows a significant serotonin uptake blockade (Wander *et al.*, 1986). Therefore, the present report suggests that hypo-serotonergic states are involved in the pathophysiology of RLS. The efficacy of clonazepam and carbamazepine for RLS (Clough, 1987; Walters and Hening, 1987) may support this hypothesis, since both clonazepam (Jenner *et al.*, 1975) and carbamazepine (Mizuno *et al.*, 1994) enhance serotonergic function.

Finally, the reason why the present case was susceptible to RLS was unknown, since none of the factors predisposing to this syndrome (Clough, 1987; Walters and Hening, 1987) was found.

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