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Mirtazapine-Induced Restless Legs

JUHA MARKKULA[1] and HANNU LAUERMA[2*]
[1]*Turku Psychiatric Clinic, Finland*
[2]*Psychiatric Clinic, University Central Hospital of Turku and Mental Hospital for Prisoners, Turku, Finland*

Two cases of restless legs syndrome in association with mirtazapine treatment of 5–6 weeks are presented. Rather than akathisia related to serotonine reuptake inhibitors, which usually emerges during the first weeks of treatment, our cases resemble previously described mianserin-induced RLS cases. This suggests that although blockade of 5-HT2 receptors by mirtazapine may be protective against acute akathisia, it does not protect against slowly developing restless legs syndrome similar to that induced by mianserin. © 1997 John Wiley & Sons, Ltd.

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INTRODUCTION

Restless legs syndrome (RLS) is characterized by feelings of discomfort or unease that predominantly affect the legs and induce an urge to keep the limbs in motion. It is closely associated with periodic movements in sleep (PMS), whereas its relation to akathisia is unclear and controversial (Barnes and Braude, 1985; Gibb and Lees 1986; Montplaisir *et al*., 1986). RLS frequently results in insomnia which may be severe. The two most effective medications for RLS are levodopa (Becker *et al*., 1993) and clonidine (Wagner *et al*., 1996).

In 1989 Paik *et al*. first reported on three cases of mianserin-induced RLS. Mianserin is known to occasionally cause unexpected agitation and paradoxical insomnia. Winsberg *et al*. (1987) reported on akathisia as a possible side-effect of mianserin in their study of six hyperkinetic children. However, Poyurovsky *et al*. (1995) reported on low-dose mianserin as a remedy for fluvoxamine-induced akathisia in a single case-study. They suggested that the ameliorating effect of low-dose mianserin on akathisia may be caused by postsynaptic 5HT2A/5HT2C antagonist activity, whereas higher doses of mianserin might cause akathisia and RLS by potentiating noradrenergic and/or serotonergic transmission. Akathisia is a recognized side-effect of selective serotonin reuptake inhibitor (SSRI) antidepressants (Lipinski *et al*., 1989; Power and Cowen, 1992). The mechanism of pathogenesis may be serotonin-induced decrease of dopaminergic activity in the ventral tegmental area. RLS does not seem to have such a clear link to SSRI medication, which suggests at least partially separate pathways in pathogenesis. Both neuroleptic-induced and SSRI-induced akathisia have been suggested to lead to suicidal tendencies, although there is no conclusive data concerning this question (Power and Cowen, 1992).

Mirtazapine or 6-azamianserin (Org 3770) is a novel sedative antidepressant with prominent alpha 2-adrenergic auto- and heteroreceptor antagonistic properties and no effect on monoamine reuptake. As measured with microdialysis in freely moving rats, mirtazapine caused a concurrent increase in 5-HT while mianserin did not (de Boer *et al*., 1996). Blockade of 5HT2 and 5HT3 receptors caused by mirtazapine has been suggested to prevent side-effects associated with nonselective 5HT activation and to contribute to the known anxiolytic and sleep-improving properties of mirtazapine (de Boer, 1996). A Medline database search up to December 1996, using the words mirtazapine or Org 3770 and restless legs or akathisia did not lead to any reports.

*Correspondence to: Hannu Lauerma, Medical Director, Mental Hospital for Prisoners, P.O. Box 49, SF-20251 Turku, Finland. Fax: 358-2-2301563. E-mail hanlau@utu.fi.

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Drug-induced motor restlessness may be underdiagnosed because it is sometimes difficult to distinguish from hypomania or psychomotor agitation associated with depression or anxiety. We present here two cases of RLS in association with mirtazapine that we have identified.

CASE REPORTS

Patient 1

A 55-year-old woman sought help for her incapacitating insomnia and exhaustion. She had suffered from depression and severe insomnia 2 years earlier and the condition was treated successfully with fluoxetine. As a part of a general medical examination at the time small old lesions of infarctation were detected in CT, but were not considered to be causal in relation to the depression. Apart from this there were no other signs or symptoms of a CNS incident. A year after the first episode of depression she started to suffer from a progrediating insomnia again and started to use her former adjuvant medication, clonazepam 0·5–1 mg at night. However, her early morning insomnia worsened until she felt that she could sleep practically no more than 1 or 2 h and could not go to work any more because of extreme fatigue.

At the first appointment the patient appeared slightly tearful. She had lost feelings of pleasure and interest in a substantial proportion of her hobbies. Her appetite had decreased as well as her ability to concentrate, and making decisions had become difficult. Since the rest of the diagnostic criteria were met, a diagnosis of major depressive episode was made. In a recent medical check-up (including laboratory tests) no indication of a general medical condition was found. Because insomnia was a major problem, mirtazapine 30 mg at night was started. To avoid rebound anxiety she was also prescribed diazepam 5 mg at night, which she was able to discontinue gradually within 3 weeks. After that she used occasionally zolpidem 5–10 mg at night. Her insomnia along with the rest of the symptoms of her depression improved steadily over the weeks and she returned to work successfully after 2 weeks sick-leave. Suddenly, after 5 weeks on mirtazapine, she started to experience at night, approximately 1 h after she had taken the medicine, most unpleasant restless feelings in her feet, which then spread to the upper extremities and the whole body, resulting in inability to sleep and an urge to keep moving. After a few nights she discontinued the medication, which resulted in the disappearance of the restless feeling. The patient began to sleep relatively well again with zolpidem 10 mg.

When the restlessness first appeared the patient got scared as she thought that she was becoming 'crazy'. At first she found it hard to believe that the feelings were caused by the medicine as the treatment effect appeared to be excellent. After a pause of 1 week she recontinued mirtazapine. The restlessness reappeared immediately and disappeared again when the patient discontinued the treatment after a few days. After this the patient consulted her psychiatrist. Fluoxetine 20 mg a day was substituted for mirtazapine. In follow-up of 2 months, the patient continued to work and feel well and only occasionally used zolpidem 5–10 mg. Her depression had remitted.

Patient 2

A 26-year-old man complained of difficulties in initiating sleep and waking up too early in the morning, daytime fatigue, concentration and memory problems, absent-mindedness, irritability, lack of interest and low spirits. As he was found to fulfill the diagnostic criteria for major depression, moclobemide 150–300 mg a day was initiated. During this treatment he reported worsening insomnia and unpleasant feelings which 'resembled that caused by drinking too much coffee'. Fluvoxamine 100 mg, which was substituted for moclobemide, caused slight akathisia. No signs of psychosis or mania were detected. When mirtazapine 30 mg was substituted for fluvoxamine, the patient began to sleep considerably better after a few days. During the following 5 weeks his condition continued to improve until quite abruptly after 6 weeks on mirtazapine he started to experience restlessness in his legs which resulted in insomnia. He reported the feeling to resemble that caused by fluvoxamine except for the fact that it bothered him predominantly at night when he was trying to go to sleep. The symptoms fit the picture of restless legs and disappeared immediately after the medication was discontinued. In a medical check-up including sleep laboratory and other laboratory tests no indication of a general medical condition or specific sleep-disorder was detected.

DISCUSSION

The signs and symptoms of both patients meet the criteria of RLS as proposed by Gibb and Lees (1986). The following features are common to both patients.

(1) Initially there was a good response to mirtazapine.
(2) The restlessness started quite abruptly after treatment of 5–6 weeks.
(3) The restlessness occurred in the evening approximately 1–2 h after taking the medication, and the symptoms disappeared after the medication was discontinued.
(4) No signs of psychosis, a general medical condition or hypomania were detected.

Although depression may be associated with restlessness and insomnia, the re-challenge of patient 1 as well as the close temporal relationship between the cessation of medication and disappearance of RLS favour the assumption that the symptoms were caused by mirtazapine. The side-effect seemed to occur quite close to the average peak plasma concentration after taking the medicine and seemed to last a few hours at a time.

Patient 2 had previously suffered from slight fluvoxamine-induced akathisia, which may be considered a variant of RLS or vice versa. Although akathisia and RLS resemble each other, the time schedules of development of motor side-effects in this patient were different. Rather than SSRI-related akathisia which usually occurs during the first weeks of treatment, our cases resemble previously described mianserin-induced RLS cases (Paik *et al*., 1989; Markkula and Lauerma, in press). We suggest that there is a mechanism common for mianserin and mirtazapine and different from that leading to SSRI-induced akathisia, which may lead to development of RLS after several weeks of treatment. Although blockade of 5HT2 receptors seems to be effective against drug-induced akathisia, it does not appear to protect against slowly-developing RLS.

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