DOI:10.1111/j.1365-2125.2005.02481.x

Mirtazapine-induced arthralgia

Anneke Passier & Eugène van Puijenbroek
Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, the Netherlands

Correspondence
Anneke Passier, PhD, Netherlands Pharmacovigilance Centre Lareb, Goudsbloemvallei 7, 5327 MH 's-Hertogenbosch, The Netherlands.
Tel: +31 73 6469718
Fax: +31 73 6426136
E-mail: A.Passier@Lareb.nl

Keywords
Mirtazapine, arthralgia, adverse drug reaction, serotonin, 5HT1-receptors

Received
20 December 2004
Accepted
3 June 2005

Aim
With this article, we intend to corroborate the assumed association between mirtazapine and arthralgia by presentation of eight case reports, and we describe a possible mechanism of action.

Methods and results
The Netherlands Pharmacovigilance Centre Lareb received eight case reports on arthralgia associated with use of mirtazapine. These case reports are presented in short. We also present worldwide data on this association.

Conclusions
The Lareb reports support the association between mirtazapine and arthralgia. A comparison is made between mirtazapine, mianserin and nefazodone, as these antidepressants show similarities in their mode of action and are all associated with arthralgia. We suggest that this adverse drug reaction may be induced by enhanced 5HT1-mediated neurotransmission.

Introduction

Mirtazapine (Remeron®) is a tetracyclic piperazinoazepine analogue of mianserin used for treatment of depression. The compound has a chemical structure closely related to mianserin but unrelated to other drugs used in the treatment of depression, like tricyclic antidepressants (TCAs), monoamino oxidase inhibitors (MAOIs), or selective serotonin reuptake inhibitors (SSRIs). Mirtazapine was approved for marketing in the Netherlands in 1994 [1]. Due to its mode of action, mirtazapine can be described as a noradrenergic and specific serotonergic antidepressant (NaSSA) [2].

Although both arthralgia and myalgia are described as possible adverse drug reactions in the product information of mirtazapine, this association has seldom been described in literature. The Netherlands Pharmacovigilance Centre Lareb, maintaining the voluntary adverse drug reaction reporting system in the Netherlands on behalf of the Dutch Medicines Evaluation Board, received eight reports on arthralgia or arthralgia-related symptoms in association with mirtazapine. In this article, we present a short overview of these reports.

Methods and results

From May 1995 until October 2004, the Netherlands Pharmacovigilance Centre Lareb received eight reports of arthralgia or arthralgia-related symptoms in association with the use of mirtazapine. Details on all eight cases are presented in Table 1.

The time to onset was reported for all patients and was short; varying from 2 to 22 days. Six of the eight

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Table 1
Characteristics of reports of arthralgia and/or arthritis associated with mirtazapine submitted to the Netherlands Pharmacovigilance Centre between May 1995 and October 2004

Patient, Sex, age	Dose, indication	Concomitant medication	Reported ADR Time to onset	Action taken, Outcome	Remarks
A F, 52	30 mg daily depression	None/unknown	Arthralgia like pain in hip, extending to knee, unilateral 2 days	Drug withdrawn, patient recovered	
B F, 42	45 mg daily depression	None/unknown	Severe myalgia and arthralgia 22 days	Drug withdrawn, patient recovered	
C M, 58	30 mg daily depression	Psyllium laxative	Arthralgia in hips and shoulders, myalgia in legs and fingers 3 days	Drug withdrawn, patient recovered	
D M, 46	30 mg daily depression	None/unknown	Painful, stiff hands, swollen, stiffness of the entire musculo-skeletal system 17 days	Drug withdrawn, patient recovered	
E F, 46	30 mg daily depression	Lorazepam oxazepam	Myalgia, arthralgia, stinging 17 days	Drug withdrawn, patient recovered	Patient has fibromyalgia
F M, 61	30 mg daily depression	Pantoprazole, alfuzosine, hydro-exocobalamin, beclomethason	Diffuse pain in joints of hips, knees and hands 3 weeks	Drug withdrawn, patient recovered	No symptoms of arthritis
G M, 46	30 mg daily depression	Diazepam, alprazolam	Pain in shoulder joints 6 days	Unknown	
H M, 62	30 mg daily indication unknown	Diazepam, alprazolam, loprazolam, flunisolide nasal	Painful knees, hips, elbows 2 days	Unknown	Simultaneous: withdrawal of alprazolam

patients discontinued the use of mirtazapine and recovered rapidly. One patient was reported with a disorder in her medical history that may have contributed to the reported symptoms. Nevertheless, the mirtazapine-associated stinging musculoskeletal and joint pain experienced by the 46-year-old female with fibromyalgia (patient F) disappeared 2 days after withdrawal of the medication.

Up to March 2004, the worldwide database of the WHO Monitoring Centre contained a total of 4578 reports of adverse drug reactions on mirtazapine. One hundred and ten of these (2.4%) concern reports of arthralgia. It is statistically significant that arthralgia is reported in association with mirtazapine more often than expected (odds ratio 1.95; 95% CI 1.61–2.36).

Discussion

The association between mirtazapine and arthralgia, demonstrated in both the Lareb and the WHO worldwide databases, is not commonly described in the literature. To our knowledge (Medline search October 2004), Jolliet *et al.* were the first and only ones to describe two case reports on this association [3, 4]. The reports in this article make a considerable contribution to this number. Arthralgia is also reported in association with other antidepressants, but only for mirtazapine and

mianserin this association was found to be significant in both the Lareb and the WHO databases (WHO odds ratio on mianserin and arthralgia 3.45; 95% CI 2.97–4.00)*.

The mechanism by which mirtazapine causes this adverse drug reaction is unclear. Mirtazapine has a specific mode of action: it induces enhanced noradrenergic and serotonergic neurotransmission by antagonizing presynaptic α2-receptors. The increase in serotonin synaptic concentrations indirectly enhances 5HT1-mediated neurotransmission, since 5HT2 and 5HT3-receptors are potently blocked by mirtazapine [1, 2, 5]. This specific effect on the 5HT1-receptors may be a relevant factor in inducing specific adverse drug reactions, including arthralgia.

Jolliet *et al.* suggested that the structural similarity with mianserin (a tetracyclic antidepressant that is associated with arthralgia more frequently) may be a relevant factor [3]. It should be noted that, besides their striking structural similarity, mianserin and mirtazapine also show similarity with respect to their mechanism of action. Both antidepressants act as central presynaptic α2-adrenergic antagonists and they both antagonize postsynaptic 5HT2-receptors. In line with this hypothesis is the finding that nefazodone, another antidepressant unrelated to TCA, MAOIs or SSRIs, is also associated with arthralgia in the WHO database (odds ratio 1.26; 95% CI 1.05–1.51) (not significant in the Lareb database). Although there is hardly any structural similarity between nefazodone and mirtazapine/mianserin, all three products are known to be 5HT2-antagonists. Hood *et al.* [6] also suggested that the blockade of 5-HT2a-receptors is of importance in induction of arthralgia, based on the mechanism of action of nefazodone.

**The views expressed are purely those of the authors and may not in any circumstances be regarded as stating an official position of WHO.*

Competing interests: None declared.

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