Lareb
Nederlands Bijwerkingen Centrum
Netherlands Pharmacovigilance Centre

Paroxetine and restless legs

Introduction

Paroxetine is a selective serotonin re-uptake inhibitor (SSRI). It has been registered since 1991 in the Netherlands and is indicated for the treatment of *depressive episodes, obsessive-compulsive disorder, panic disorder with or without agoraphobia, social anxiety disorder/social phobia, generalised anxiety disorder and post-traumatic stress symptoms*.[1] Restless legs (RLS), is a sensorimotor disorder affecting about 7-10% of the population in the United States and Northern Europe. The incidence of women is twice that of men. Pregnant patients and patients suffering from iron deficiency, end stage renal disease and some neurological conditions such as spinal cerebellar atrophy, spinal stenosis and Parkinson's disease are more prone to develop the condition. The diagnosis is based on four essential criteria: (1) an urge to move, usually associated with paraesthesias, (2) onset or exacerbation of symptoms at rest, (3) relief of symptoms with movement and (4) symptoms manifesting in a circadian pattern.[2]
The paroxetine (Seroxat®) SmPC does not mention restless legs as possible ADR.[1] In this report, the association between paroxetine use and restless legs is described.

Reports

On May 19, 2008, the database of the Netherlands Pharmacovigilance Centre Lareb contained 23 reports concerning restless legs during SSRI use, This report is about the 18 patients who used paroxetine. In seven of the reports the reporter explicitly stated that the symptoms occurred in the evening/night or that the symptoms led to insomnia. The reports concerned 13 females and five males in the ages 24-64 years. The latency varied from days to years. In eight cases the drug was withdrawn, in six of the cases the patient had recovered at the time of reporting.

Table 1. Reports of restless legs associated with the use of paroxetine.

Patient, Sex, age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome
A 7635 M, 41	paroxetine not specified	cisapride	restless legs	4 weeks, dose not changed, outcome not reported
B 15007 F, 60	paroxetine not specified	flurazepam, ibuprofen, acetylcysteine, itraconazole	restless legs, myoclonic jerks	years after start, dose not changed, outcome not reported
C 17712 F, 58	paroxetine not specified	none	restless legs	days, action taken with the drug is unknown, not recovered at the time of reporting
D 18478 M, 43	paroxetine not specified	none	restless legs	1 week, dose not changed, outcome not reported

Patient, Sex, age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome
E 21109 M, 50	paroxetine depression	oxazepam	restless legs	latency was not reported, recovered after cessation
F 21257 F, 42	paroxetine depression and anxiety	none	restless legs	9 weeks, recovered with sequel after drug cessation
G 23501 F, 24	paroxetine depression	cetirizine, diclofenac, hydroxychloroquine	restless legs	8 months, dose increased, recovered
H 23782 M, 45	paroxetine depression	none	restless legs	latency is unknown, recovered after drug cessation
I 31614 F 49	paroxetine not reported	zopiclon ethinylestradiol/desogestrel	restless legs	12 days, recovered after dose reduction
J 32529 M, 49	paroxetine depression	metoprolol/hydrochlorothiazide	restless legs	2 months, recovered after drug cessation
K 33468 F, 51	paroxetine not specified	none	restless legs	8 weeks, dose not changed, outcome not reported
L 42025 F, 64	paroxetine not reported	none	restless legs	latency not reported, action taken with the drug is unknown, not recovered at the time of reporting
M, 45699 F, 34	paroxetine, 30 mg daily depression	norethisteron	restless legs	latency not reported, dose not changed, outcome not reported
N 53585 F, 30	paroxetine 20 mg daily depression	ibuprofen	restless legs	3 years, drug was withdrawn, not recovered at the time of reporting
O 60941 F, 32	paroxetine 40 mg OD depression	none	restless legs, insomnia, increased muscular tonus, yawning	4 days, drug was withdrawn, patient has not recovered at the time of reporting
P 63176 F 45	paroxetine 20 mg OD panic reactions	none	restless legs	weeks, dose not changed, outcome not reported
Q 64908 F, 33	paroxetine not reported	hydroquinine, oxazepam	restless legs	3 weeks, dose not changed, outcome not

Patient, Sex, age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome
				reported L
R 75817 F 30	paroxetine 20 mg OD depression methylphenidate 18 mg OD	none	restless legs, hyperhidrosis, fatigue	latency not reported, dose not changed, patient has not recovered

Other sources of information

Literature

In a recent prospective cohort study Rottach *et al.* followed new users of second generation anti-depressants to see if they developed RLS during treatment. In 24 of 271 patients (9%) RLS appeared or worsened as a side effect of antidepressant therapy, the incidence in the SSRI group - to which paroxetine belongs - was just below 5%. RLS as an adverse drug reaction occurred very early in the course of the treatment in this study, after a median of 2.5 days (range 1 to 23 days). In half of the cases the ADR led to a switch or discontinuation of treatment, in the other half of the patients the ADR was tolerable and did not affect further treatment. [3]
The prevalence of RLS in the general population was investigated in a cross-sectional study. In this study the use of SSRI's was identified as one of the factors increasing the risk of developing restless legs (OR= 3.1; 95% CI 1.6-5.8). [4]
Furthermore this association had been described in a few case-reports. [5-7]

Databases

On May 19 2008, the database of the Netherlands Pharmacovigilance Centre Lareb contained 18 reports of paroxetine and restless legs (ROR=11.2; 95%CI 6.6 - 18.8). On the same date the database of the WHO contained 445 reports of paroxetine and hyperkinesia (ROR=3.8; 95%CI 3.5 - 4.2). Hyperkinesia is the WHO-ART term corresponding to the MedDRA term restless legs.
On 8 June 2008, the Eudravigilance database contained 16 reports of restless legs syndrome associated with paroxetine. In four cases no co-medication was used. Eight times a medication with serotonin reuptake inhibiting properties was reported to be used concomitantly. Patients were predominantly of female sex (n=13). Two patients were less than 18 years (13 and 15 years), three were older than 65, the remaining were middle aged.

Mechanism

It is assumed that restless legs is caused by a dysfunction in the dopaminergic system, possible on the level of striatal and/or spinal dopamine receptors and the A11 neuron group localised in the hypothalamus. [8]
In a study by Sekine *et al.* it was investigated if the administration of an SSRI would alter the dopamine activity in midbrain neurons in rats. Single dose and repeated administration of paroxetine significantly increased spontaneously active dopamine neurons in the ventral tegmental area, part of the striatal area. However

the administration of paroxetine did not affect dopamine neurons in the substantia nigra pars compacta. [9]
It is possible that paroxetine can influence dopamine transmission in man in a similar way as in rats, which could be a possible mechanism for the development of restless legs during paroxetine use.

Conclusion

The Netherlands Pharmacovigilance Centre Lareb has received 18 reports linking the use of paroxetine with restless legs. The development of restless legs during paroxetine use has been described in literature, both in case-reports and epidemiological studies. A possible mechanism is that paroxetine alters the dopaminergic activity in certain areas of the brain. Restless legs should be mentioned as an ADR in all paroxetine containing products.

References

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This signal has been raised on July 2008. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbg-meb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).

- Restless legs should be mentioned as an ADR in all paroxetine containing products.