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Venlafaxine and extrapyramidal effects

Introduction

Venlafaxine (Efexor®) is an antidepressant, which has been approved for the Dutch market on June 6th, 1994. Venlafaxine and the active O-desmethyl metabolite inhibit the reuptake of serotonin, norepinephrin and dopamine. In doses of 75-150 mg daily, venlafaxine selectively inhibits the reuptake of serotonin, what makes it a selective serotonin reuptake inhibitor (SSRI). In doses of more than 150 mg daily, venlafaxine acts as a non-selective serotonin reuptake inhibitor [1].

The extrapyramidal system includes neural pathways that are responsible for the regulation of reflex movements such as balance and walk. Extrapyramidal disorders can cause a variety of symptoms such as tardive dyskinesia, parkinsonism, akathisia, bruxism and acute dystonia. The SPC of Efexor® mentions *increased muscle tone, tremor* and *myoclonus* as adverse drug reactions, but extrapyramidal symptoms (EPS) are not explicitly stated [2]. The SPCs of the SSRIs (Seroxat®, Cipramil®, Fevarin®, Zoloft®) do mention extrapyramidal symptoms as adverse drug reaction [3-6].

Reports

Up to May 2004, Lareb received 12 reports of extrapyramidal symptoms on venlafaxine (table 1). In all cases, the daily dose was 75 or 150 mg. The mean age was 42 years and time to onset varies from several hours to 2.5 years. None of the patients concomitantly used an antipsychotic. Eleven cases were reported by health professionals, one case (patient L) was reported by the MAH.

Table 1. Extra pyramidal symptoms in combination with venlafaxine reported to Lareb

Patient, sex, age	daily dose	extrapyramidal symptoms	concomitant medication	time to onset	remarks
A, F, 32	75 mg	increased muscle tone, trismus, convulsions.	none	4 hours	
B, M, 30	75 mg	dystonia/myoclonia of hands and face. rigidity limbs	oxazepam	19 days	pos. dechallenge
C, M, 51	150 mg	extrapyramidal symptoms (dystonia, trismus)	oxazepam, temazepam	10 days	pos, dechallenge
D, M, 29	75 mg	trismus	alprazolam, diazepam	1. 5 days	pos. de- and rechallenge
E, F, 20	75 mg	trismus	ethinylestradiol/levonorgestrel	several hours	pos. dechallenge, negative rechallenge
F, F, 40	75 mg	trismus	oxazepam,beclomethasone, acetaminophen/ propoxyphene	several hours	
G, F, 43	75 mg	lockjaw	none	2.5 years	
H, F, 56	75 mg	dystonia, tremor	zolpidem, enalapril	4 days	
I, F, 53	75 mg, 150 mg	dystonia	naproxen	12 hours	pos. dechallenge
J, F, 52	150 mg	parkinsonism	fluticason, s albutamol, salemterol/fluticason	1 year	pos. dechallenge
K, M, --	75 mg	muscle rigidity	flunitrazepam	3 hours	pos. dechallenge
L, M, 58	75 mg	bruxism	atorvastatin, hydrochlorothiazide/ losartan, vitamins	several hours	

Other sources of information

Literature

Most commonly, the antipsychotic drugs are associated with extrapyramidal symptoms, because of their dopaminergic inhibition. In addition, numerous articles and case-reports have been published about the occurrence of extrapyramidal effects in patients using SSRIs [7-9].
A literature search on extrapyramidal effects related to the use of venlafaxine yields two case reports and one abstract [7,10,11].

Databases

In the 4th quarter of 2003 the database of the WHO contained 14039 adverse drug reactions associated with the use of venlafaxine. A total of 398 ADRs concern a extrapyramidal disorder (expressed as extrapyramidal disorder, dystonia, dyskinesia, tardive dyskinesia and hypokinesia). Trismus and parkinsonism are not present in the WHO database.

Table 2. Extrapyramidal symptoms in association with venlafaxin in the WHO database

Extrapyramidal ADR associated with venlafaxine	Number of reports	ROR (95% CI)
Extrapyramidal disorder	102	2.03 (1.67 – 2.46)
Dystonia	119	2.67 (2.23 – 3.21)
Dyskinesia	105	3.00 (2.48 – 3.64)
Tardive dyskinesia	41	4.40 (3.22 – 5.99)
Hypokinesia	31	0.10 (0.07 – 0.14)
Total	**398**	**2.40 (2.17 – 2.65)**

Mechanism

A probable mechanism by which SSRIs cause extrapyramidal reactions is the serotonergic inhibition of dopamine neurotransmission in the striatum. This antidopaminergic effect disturbs normal coordination and movement, resulting in the typical extrapyramidal symptoms [8,9]. Because venlafaxine (selectively) inhibits the reuptake of serotonin, it will have the same serotonergic effects as the SSRIs.

Conclusion

Lareb received 12 reports of extrapyramidal adverse drug reactions in association with venlafaxine, for 7 of these reports, a positive dechallenge had been reported. Extrapyramidal associations are disproportionally present for venlafaxine in the WHO database. In addition literature is supportive and a plausible mechanism has been proposed.

References
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