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Venlafaxine and hypertension

Introduction

Venlafaxine (Efexor®) has been approved for marketing in the Netherlands since June 1994. The therapeutic indications of venlafaxine are *episodes of depression and short term treatment of generalised anxiety disorder* [1]. According to the most recent practice guidelines on depression of the Dutch College of General Practitioners, treatment with an antidepressive agent should last for at least 6 months [2].
Venlafaxine is an antidepressant neither belonging to the tricyclic antidepressants, nor to the selective serotonin reuptake inhibitors. Venlafaxine is a non-specific serotonin reuptake inhibitor (NSRI) that inhibits neuronal uptake of serotonin, norepinephrine, and dopamine in order of decreasing potency.
Hypertension is mentioned in the SPC of venlafaxine as a frequent adverse drug reaction. The incidence as mentioned in the SPC is higher than 1:100. The SPC contains no information on the degree and severity of the hypertension that can be expected. According to the SPC it is a dose-dependent effect and the measurement of blood pressure of venlafaxine users is recommended.

Reports

Lareb received 11 reports of hypertension associated with the use of venlafaxine (seven reports from the MAH, 3 reports from specialist doctors and 1 report from a pharmacist).

Table 1. reports of hypertension associated with the use of venlafaxine

Patient, Sex, age	Daily dose	Tension (mm Hg)	Other symptoms	Concomitant medication	Time to onset, outcome after discontinuation
A: F,34	150 mg	unknown	palpitations	elanapril, ethinyl-estradiol/cyproterone	several weeks, unknown
B:F,46	37.5 mg	diastolic: 100-110	headache		unknown, recovered
C:M,45	75 mg	180/110	headache		1 month, recovered
D:F,33	300 mg	170/125		labetalol	2 weeks after increasing dose, recovered
E:M,75	150 mg	174/113			several months, unknown
F:F,31	37.5 mg	150/110	headache		4.5 months, unknown
G:F,52	75 mg	200/100	palpitations, arrhythmia	conjug. oestrogen/ medroxyprogesterone	2 weeks, recovered
H:M, unkn.	unknown	190/140		metoprolol	unknown, unknown
I:F,49	300 mg	unknown, hypertensive crisis		valproate	unknown, recovered
J:M,61	75 mg	200/130	tinnitus	mirtazapine, diazepam, cimetidine, unspec. asthma med.	9 months (several weeks after adding mirtazapine), unknown

Other sources of information

Literature

Meta-analysis of controlled clinical studies revealed an overall incidence of sustained elevation in supine diastolic blood pressure (DBP) in the acute phase of therapy (first 6 weeks) of 4.8% (p=0.015) for venlafaxine, and 2.1% for placebo. The incidence varied with the daily dosage of venlafaxine and appeared to be only statistically and clinically significant at dosages above 300 mg/day (incidence: 9.1%) During the continuation phase, 21 (4.5%) of 467 patients developed an elevated DBP (p=0.05). A sustained elevation of BP was defined as an elevated BP measured during at least 3 occasions with a systolic pressure of at least 140 mm Hg or a diastolic pressure of at least 90 mm Hg. Furthermore, 11.5% of 2495 venlafaxine users had higher diastolic blood pressures than 90 mm Hg (isolated measurement) after 6 weeks of therapy [3].

Another study investigated increases of blood pressure with the use of venlafaxine. A clinically significant change from baseline was defined as an increase of = 15 mm Hg and to = 105 mm Hg for diastolic blood pressure and an increase of = 20 mm Hg and to = 180 mm Hg for systolic blood pressure. The incidence of clinically significant changes of blood pressure was 1.3% for doses between 101 and 150 mg/day, 3.3% for doses between 151 and 200 mg/day, and 5.5% for doses > 200 mg/day. Among patients taking antihypertensive drugs before treatment with venlafaxine, the incidence of elevated blood pressure was 4.1% compared to 4.3% in the placebo group. Among patients with a supine diastolic blood pressure > 90 mm Hg before treatment with venlafaxine, the incidence of elevated blood pressure was 8.3% compared to an incidence of 4.8% in the total patient population [4].
According to the Physicians' Desk Reference the incidence of sustained increased DBP in premarketing studies was 3% for venlafaxine doses less than 100 mg/day, 5% for doses between 101 and 200 mg/day, 7% for doses between 201 and 300 mg/day, and 13% for doses greater than 300 mg/day. A placebo group had a 2% incidence of increased DBP. Most of the blood pressure increases were between 10 and 15 mmHg [5].

A case report published by Bakh *et al.* [6] mentions the occurrence of increased blood pressure at low doses of venlafaxine. The described patient was an Asian male with a history of essential hypertension. His blood pressure was, however, normal during the past three years without any antihypertensive treatment. The authors suggest that the hypertension caused by low-dose treatment of venlafaxine could be related to genetic polymorphism of CYP 2D6 or CYP 2C19, leading to slow metabolism of venlafaxine followed by high blood levels of venlafaxine.

Databases

Table 2. Overview of data of case/non-case approach of Lareb and WHO database

Database	n reports venlafaxine with hypertension	reporting rate (%)	n reports venlafaxine total	ROR	95% CI of the ROR
Lareb	11	2.8	390	5.0	1.8 – 13.6
WHO	698	5.3	13224	5.0	4.7 – 5.4

Mechanism

The hypertension induced by venlafaxine is a dose-dependent effect, resulting from the pharmacologic mechanism of action. This may be due to the fact that venlafaxine only inhibits the reuptake of norepinephrine in higher doses than 150 mg a day. Increases in blood pressure can easily be explained by the increasing effects of norepinephrine after inhibiting the reuptake of norepinephrine.

Discussion

It is not known whether the recommendation of monitoring blood pressure is implemented in daily clinical practice, but there is a realistic possibility that underdiagnosis of hypertension during the use of venlafaxine occurs. However, hypertension is one of the frequent ADRs of venlafaxine and it can be harmful for vascular health, especially when tensions as high as in the Lareb cases do exist over a prolonged period of time.

According to reports received by Lareb hypertension can also occur at lower doses, in contrast with the conclusions of Thase [3] that the incidence of elevated DBP was only statistically and clinically significant at dosages above 300 mg/day. In half of the Lareb reports the daily dose of venlafaxine is below 100 mg. The occurrence of hypertension at low-dose treatment with venlafaxine is also decribed in the literature [6].

In six cases the hypertension was accompanied by possible clinical symptoms of hypertension, such as headache, palpitations or tinnitus. On the other hand, headache and heart rhythm disorders are also mentioned as adverse drug reactions of venlafaxine.

In 3 reports the concomitant medication and the clinical information mention a pre-existing hypertension, controlled by medication. In the other cases, however, there are no indications of a pre-existing hypertension. Although venlafaxine-induced hypertension can easily be explained by the pharmacologic mechanism of action and therefore occurs in healthy people with no history of hypertension, this adverse drug reaction could occur more often and have a greater impact in patients with pre-existing hypertension. This is supported by the finding of Feighner that patients with a tension of > 90 mm Hg before treatment with venlafaxine had a higher incidence (8.3%) of clinically significant blood pressure elevations while on venlafaxine than the incidence in normotensive patients (4.8%) [4].

Because of the mechanistic background of venlafaxine induced hypertension, this effect is not expected with the use of SSRIs. However, hypertension theoretically can be expected with the use of antidepressants that increase the noradrenergic transmission, like tricyclic antidepressive agents and mirtazapine, but these antidepressants are also antagonist of postsynaptic alfa-1-receptors, preventing the hypertensive effects of norepinephrine on the vascular smooth muscle.

Conclusion

According to the therapeutic indication, venlafaxine is supposed to be used for at least 6 months. Therefore, the hypertension as serious as reported to Lareb in the above mentioned cases can be clinically significant and harmful. Extensive studies on the elevation of blood pressure during the use of venlafaxine are described in the literature supporting an estimated incidence of 5%. There are indications in the reported Lareb cases and in the literature that patients with pre-existing hypertension are more vulnerable to venlafaxine-induced hypertension than normotensive patients.

References

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