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Venlafaxine and severe respiratory disorders

Introduction

Venlafaxine is a serotonin and noradrenalin reuptake inhibitor that was approved for marketing in 1994. In the past years, the number of prescriptions for the drug have gradually increased (Figure 1). The drug is indicated *for the treatment of depression, especially when accompanied by vital signs, and for the treatment of generalised anxiety disorder* [1]. The most frequently reported ADRs are nausea, somnolence, dry mouth, insomnia, dizziness, constipation, weakness, nervousness, and sweating [2]. Disorders of the respiratory tract mentioned in the Summary of Product Characteristics (SPC) are: gasping, pharyngitis, rhinitis and sinusitis.

Recently, the possible relationship between venlafaxine and interstitial pneumonitis has received some media attention. This attention was raised by a case report in the American Journal of Respiratory and Critical Care Medicine [3]. The Netherlands Pharmacovigilance Centre Lareb has received one of the two cases described in that article.

In total, our centre has received four reports on severe respiratory disorders, but the possibility of such an association is not mentioned in the Dutch SPC of venlafaxine. Basically, two different types of pulmonary adverse reactions associated with venlafaxine seem to exist: eosinophilic pneumonia and non-eosinophilic pneumonitis[4].

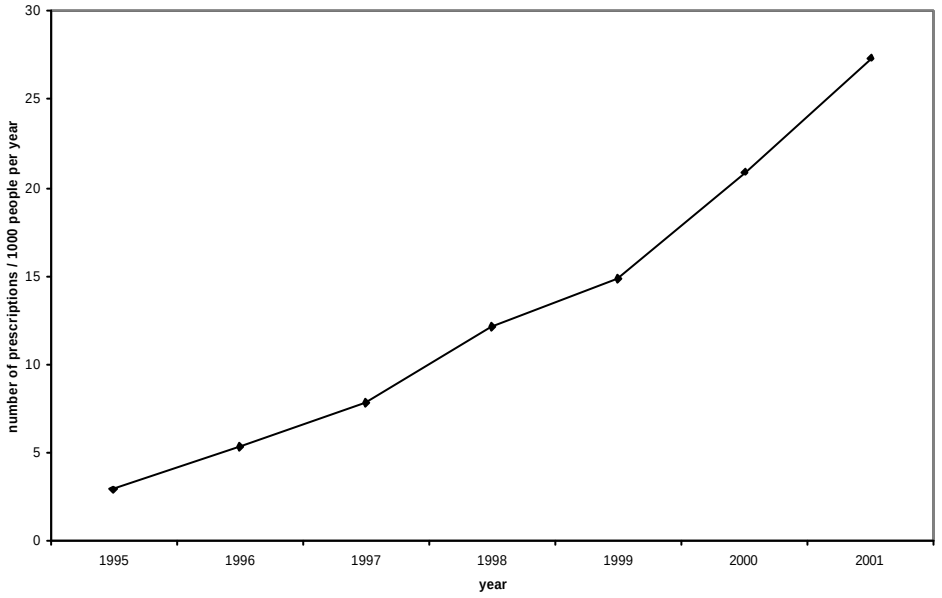

Fig 1: Number of prescriptions of venlafaxine per 1,000 persons/year (Source: GIP College Voor Zorgverzekeringen, Diemen)

Reports

Patient A is a 48-year-old female, who had been using venlafaxine 75 mg once daily for the treatment of her depression. There is no mention of the use of any concomitant medication. Severeral months after starting venlafaxine (the exact time to onset is not specified) she gradually developed progressive dyspnoea and a slight elevation of her body temperature (38.2°C). Bronchoalveolar lavage cultures were negative. A biopsy revealed an allergic alveolitis/eosinophilic pneumonia and possibly bronchiolitis obliterans.

Patient B is a 52-year-old female, who had used venlafaxine because of depressive episodes in the dosage of 37.5 mg twice daily. After three days, she developed progressive dyspnoea. She also used fluticason by inhalation for the treatment of her asthma. On an X-ray bilateral infiltrates could be localized. Bronchoalveolar lavage revealed 55% eosinophils. An eosinophilic pneumonia was diagnosed and she was treated with corticosteroids. After cessation of venlafaxine she gradually recovered within 12 days.

Patient C is a 20-year-old female, who used venlafaxine 37.5 mg twice daily. She used no concomitant medication. She was admitted to hospital because of progressive dyspnoea, non-productive coughing, severe weight loss and syncope. Time to onset of the symptoms involved was not specified. A chest radiograph showed subtle diffuse reticulonodular opacities throughout both lungs. In addition an cardiac ultrasound examination revealed a decreased left ventricular function. Bronchoalveolar lavage (BAL) fluid analysis yielded an increased total cell count predominantly consisting of lymphocytes (93.2%). A culture of BAL fluid remained sterile. Histological examination of material obtained by an open lung biopsy showed peri-bronchiolar inflammation and bronchiolitis. Venlafaxine was stopped but the glucocorticoid treatment that had been initiated earlier was continued. Her clinical condition improved within two weeks after venlafaxine cessation. Both the dyspnoea and cough disappeared and a chest radiograph showed no abnormalities. Moreover, her cardiovascular condition improved [3].

Patient D is a woman (estimated age 35 years), who had been using venlafaxine 75 mg once daily for the treatment of her depression. She developed a pneumonitis of which further specifications were lacking. She recovered after cessation of the drug. This report originated from the marketing authorisation holder; no additional information is available.

Table 1. Summary of the four reports concerning severe respiratory disorders associated with the use of venlafaxine

Patient, Sex, age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, outcome
A F, 48	venlafaxine 75 mg od depression	not reported	allergic alveolitis/ eosinophilic pneumonia	Recovered after cessation of drug
B F, 52	venlafaxine 37,5 mg td depression	fluticason inhaler	eosinophilic pneumonia	3 days
C F,20	venlafaxine 37,5 mg td depressive mood	none	pneumonitis cardiac failure	not reported, recovered after cessation of drug
D F, approx 35	venlafaxine 75 mg od depression nec	unknown	pneumonitis	not reported, recovered after cessation of drug

Other sources of information

Literature

Drent *et al*. [3] described two cases of interstitial pneumonia and cardiac failure in patients treated with venlafaxine. The first patient was reported to Lareb (Patient C). The second patient concerned a 62-year-old male with a history of myocardial infarction, chronic atrial fibrillation, and bronchoalveolar cell carcinoma. He developed progressive breathlessness 1 to 2 months after starting venlafaxine. Despite treatment, he died of multiorgan failure. Autopsy revealed interstitial fibrosis and organising pneumonia without eosinophils [3]. Fleisch et al. described a case of venlafaxine-induced acute eosinophilic pneumonia causing respiratory insufficiency. The diagnosis was established with BAL. The symptoms rapidly resolved upon cessation of the drug

and institution of corticosteroid treatment [5]. Oerman *et al*. described a case of eosinophilic pneumonia in a child [6].

Databases

On June 20th 2003, the database of the Netherlands Pharmacovigilance Centre Lareb contained 13 reports concerning respiratory disorders, associated with the use of venlafaxine. Four reports concerned severe respiratory disorders and are described in this message. Two reports concerned coughing; three mentioned dyspnoea and two cases concernede hyperventilation, one related to yawning and one report described a neonatal apnoeic attack of a child whose mother had been using venlafaxine during pregnancy.

The database of the Uppsala Monitoring Centre (WHO) contained 537 reports on venlafaxine and respiratory disorders. Except for yawning, the reported associations were not disproportionately present in the database. Dyspnoea was mentioned 183 times (34.1% of the respiratory disorders), followed by 'respiratory disorder', which was mentioned 31 times (5.8%). Allergic alveolitis and pneumonitis was mentioned 2 (0.4%) and 10 times (1.86%), respectively.

Mechanism

The exact mechanism for both eosinophilic pneumonia and non-eosinophilic pneumonitis is unknown. Drug-induced infiltrative lung disease is an established, although infrequent, complication of serotonin reuptake inhibitors [3]. Increased pulmonary capillary leakage secondary to increased levels of serotonin in the pulmonary vessels was considered a possible explanation for the cause of interstitial pulmonary damage in a patient treated with fluoxetine [7], which drug also inhibits the reuptake of serotonin. However, whether this mechanism also applies to venlafaxine is as yet not clear. Pneumonia has also been documented in relation to paroxetine [8].

In the liver and lungs, venlafaxine is partially metabolised by the CYP2D6. CYP2D6-inhibiting drugs or genetic variants in patients with a lower CYP2D6 activity may therefore contribute to accumulation of venlafaxine and enhance a toxic reaction [3].

Conclusion

The database of the Netherlands Pharmacovigilance Centre Lareb presently contains two reports of eosinophilic pneumonitis and two reports of pneumonitis associated with the use of venlafaxine. When we take the additional reports from the literature into account, we conclude that a causal relationship between the use of venlafaxine and severe respiratory disorders is likely.

References

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