Lareb
Nederlands Bijwerkingen Centrum
Netherlands Pharmacovigilance Centre

Montelukast and depressive symptoms

Introduction

Montelukast (Singulair®) is a leukotriene receptor antagonist available on the Dutch market since 1998. It is indicated for *the treatment of asthma as combination therapy for patients with light to moderate forms of chronic asthma which cannot be adequately controlled by inhalation corticosteroids and short-acting ß-agonists. For asthma patients for whom montelukast is indicated as asthma treatment it can also relieve symptoms of seasonal allergic rhinitis. Montelukast is also indicated in asthma prevention, if exercise-induced bronchoconstriction is the main factor [1].*

Reports

On September 20, 2006 the database of the Netherlands Pharmacovigilance Centre Lareb contained four reports of depressive reactions associated with the use of montelukast.

Patient A is a female aged 55 who used montelukast 10 mg once daily for asthma associated with COPD. Concomitant medication included ipratropiumbromide inhalation, salmeterol inhalation, fluticasone inhalation, acetylcysteine, budesonide nose spray and desloratadine. Two weeks after montelukast therapy was initiated the patient experienced nightmares, a depressive symptoms, fatigue and increased dyspnoea. When montelukast was withdrawn, the first three symptoms resolved. It is not known if the dyspnoea resolved. The reporting pneumonologist stated that the increased dyspnoea also could be a sign of progressing COPD.

Patient B, reported by a pneumonologist, is a female aged 39 who used montelukast 10 mg once daily for asthma. Concomitant medication included salmeterol/fluticasone inhalation, mebeverine and psyllium seed. One week after starting montelukast treatment the patient experienced chest discomfort, malaise, depressive symptoms and dizziness. Montelukast was withdrawn, patient outcome is unknown.

Patient C, reported by a pharmacist, is a male aged 46 who used montelukast 10 mg once daily for asthma. Concomitant medication included omeprazole, salbutamol inhalation and budesonide/formoterol inhalation. Six days after starting montelukast treatment the patient got in a depressed state. The patient continued to use montelukast for four weeks but the depression did not resolve. When montelukast was withdrawn, the patient recovered.

Patient D, reported by a pharmacist, is a female aged 59 who used montelukast 10 mg once daily for mild to moderate asthma. Concomitant medication included mometasone nose spray, salmeterol/fluticason inhalation, oxazepam and paroxetine. Three days after starting treatment with montelukast the patient experienced insomnia and aggravation of her depression. When montelukast was withdrawn the symptoms resolved.

Other sources of information

Literature

Several drugs are known to cause depressive symptoms. However montelukast has not been associated with depressive symptoms earlier [2]. A Medline search based on the MeSH terms montelukast, leukotriens, depressive disorder and mood disorders did not yield any relevant publication.

Databases

On September 20, 2006 the database of the Netherlands Pharmacovigilance Centre Lareb contained four reports of depression associated with the use of montelukast (ROR 2.1 95% CI 0.8 - 5.7). The same day the database of the WHO contained 3466 reports on montelukast, 43 of these concerned depression (ROR 1.2 95% CI 0.9 – 1.6)

Mechanism

The mechanism of montelukast-induced depressive symptoms is unknown. However montelukast has earlier been associated with adverse drug reactions such as abnormal dreaming, nightmares, hallucinations, agitation with aggressive behavior, irritability and restlessness, which suggests that montelukast can penetrate the blood brain barrier and exert an effect in the brain [1,3].

Discussion and conclusion

Lareb received four reports of depressive symptoms in patients using montelukast. Possible confounding includes that asthma itself has been associated with the development of depression [4]. Inhalated corticosteroids can also exert effects on the central nervous system. Fluticason in combination with salmeterol which is used by patients A, B and D, is associated with hyperactivity and irritability where as budesonide, which is used by patient C also has been associated with depression [5,6]. The latency of montelukast-induced depressive symptoms varies from 3-14 days. In three of the cases a positive dechallenge was seen.

The fact that the patients (except for one) did not suffer from depressive symptoms before they started montelukast, the short latency, and recovery after withdrawal of the drug all strengthen our hypothesis that depressive symptoms are an ADR related to the use of montelukast. According to the Marketing Authorisation Holder of montelukast, depression will be added to the product information.

References
1. Dutch SPC Singulair®. (version date 11-7-2005) http://www.cbg-meb.nl/IB-teksten/23164.pdf.
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3. Price D. Tolerability of montelukast. Drugs 2000;59 Suppl 1:35-42.
4. Goldney RD, Ruffin R, Fisher LJ, Wilson DH. Asthma symptoms associated with depression and lower quality of life: a population survey. Med J Aust. 2003;178(9):437-41.
5. Dutch SPC Seretide®. (version date 12-8-2005) http://www.cbg-meb.nl/IB-teksten/23529-23530-23531.pdf.
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