



Letter

Seizures as a rare but serious adverse effect of leukotriene receptor

Leukotriene receptor antagonists (LTRAs) are used widely in the treatment of allergic rhinitis and asthma in children.^{1,2} LTRAs are safe in combination with antihistamines in patients with chronic urticaria who respond inadequately to antihistamines alone.³ Several clinical trials have emphasized that LTRAs can be considered safe. Nevertheless, many adverse effects associated with LTRAs have been reported. Most of the adverse events are mild (headache, gastrointestinal disorders, pharyngitis, fatigue, upper respiratory tract infection, cutaneous rash, and reversible changes in the serum transaminase levels). Although adverse events, such as seizures, are probable, no case reports of LTRAs leading to or triggering convulsions have been reported.^{1,2}

We describe 3 patients who had convulsions after beginning treatment with LTRAs. Patient 1 was a 15-year-old girl with atopic asthma who was monitored for 2 years. She started using valproic acid for epilepsy 1 year ago. No seizures were observed while she was taking inhaled corticosteroids and valproic acid. Three days after adding an LTRA to her asthma treatment, she started having seizures during sleep. Initially, her physicians and family did not associate the convulsions with the LTRA. While she was hospitalized for her convulsions, the LTRA could not be given because the family left it at home. No seizures were observed during the hospitalization, and the patient was discharged. When she returned home and started using the LTRA again, the seizures during sleep returned. Consequently, the LTRA was blamed for triggering the seizures and was stopped. seizure further seizures were observed.

Patient 2 was a 6-year-old girl who had been followed up with a diagnosis of epilepsy for 1.5 years. She was using antiepileptic medication but had not had any seizures in the last year. When she had attacks of wheezing, an LTRA was added to treat mild persistent asthma. With resumption of use of the LTRA, she started having seizures again. The family suspected the LTRA and discontinued its use. The seizures disappeared. A few weeks later, when the patient's asthmatic symptoms increased, the patient started using the LTRA again, and the seizures returned. We recommended discontinuing use of the LTRA, and the seizures were controlled.

Patient 3 was a 2½-year-old boy with an episode of urticaria that lasted for 1.5 months and was treated with antihistamines. His pediatrician added an LTRA to the treatment when the antihistamines failed to control the urticaria. Three days after adding the LTRA to his treatment, the patient had an afebrile convulsion for the first time in his life. At that time, the antihistamines were held responsible for the seizure. All medications were cut for 1 week, and the patient's seizures disappeared. Three days after starting use of only an LTRA for the ongoing urticaria, the patient had another

seizure. The LTRA was withdrawn, and the patient had no further seizures (Table 1).

Several clinical trials have emphasized that montelukast can be considered a safe drug. However, many adverse events associated with LTRAs have been reported. Although adverse events of LTRAs, such as seizures, are probable, no report has found that LTRAs can lead to or trigger convulsions.^{1,2}

We treated 3 children who had convulsions that emerged with or were triggered by LTRAs. Associations between LTRAs and disorders of the immune, nervous, and uropoietic systems and psychiatric, hepatobiliary, pancreatic, skin, and subcutaneous tissue disorders have been reported.^{1,2,4,5} Psychiatric and nervous system disorders were observed most commonly, including agitation with aggressive behavior or hostility, anxiety, depression, disorientation, dream abnormalities, hallucinations, insomnia, irritability, restlessness, somnambulism, suicidal ideation and behavior, tremor, dizziness, drowsiness, paresthesia or hypoesthesia, sleep talking, sleepwalking, and, very rarely, seizures.^{1,6}

Although most of these adverse events are mild, the US Food and Drug Administration issued a warning regarding the potential of montelukast and other LTRAs to lead to suicidality in 2009. However, in a subsequent study of 20,000 adult and pediatric patients, no case of suicide was reported, a similar frequency was found in the control group, and this warning was disregarded.¹ The reported neuropsychiatric adverse events associated with LTRAs occur more frequently in patients who have a psychiatric disorder before starting use of the drug, although the cause of these neuropsychiatric adverse effects is not known.^{1,4,7} Although studies of children are lacking, we hypothesized that blocking cysteinyl leukotriene 1 by specific antagonists can cause neuropsychiatric adverse reactions in susceptible pediatric patients.

During postmarketing surveillance of montelukast, reported adverse effects included agitation with aggressive behavior or hostility, anxiety, depression, disorientation, dream abnormalities, hallucinations, insomnia, irritability, restlessness, somnambulism, suicidal ideation and behavior (suicidality), tremor, dizziness, drowsiness, paresthesia or hypoesthesia, sleep talking, sleepwalking, and, very rarely, seizures.¹

Sleep disturbances, especially nightmares, are the most frequently reported neuropsychiatric adverse effects of LTRAs.^{6,7} LTRAs are thought to have the potential to cause seizures, although no cases have been reported.¹ Moreover, they have been found to prevent convulsions in mice.⁸ It has also been proposed that LTRAs can be used as anticonvulsants,⁹ and LTRAs might be an option for preventing seizures in patients with epilepsy who also have allergies because seizures can be triggered by antihistamines.¹⁰ However, this is not a viable option because LTRAs can lead to seizures, as seen in our patients.

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Table 1
Characteristics of the Study Patients

Patient No.	Age, y	Sex	Indication	Dose, mg/d	Duration, d	Concomitant treatment	Adverse effects	Prognosis
1	15	F	Athma	10	3	Valproic acid and budesonide, 400 µg/d	Convulsions	Resolved
2	6	F	Asthma	5	4	Valproic acid	Convulsions	Resolved
3	2.5	M	Urticaria	4	3	Ketotifen	Convulsions	Resolved

We report convulsions observed as a rare adverse effect of LTRAs in 3 patients. Two of these patients were being treated for epilepsy, and the seizures were under control. The third patient had no prior history of seizures. Note that seizures were observed in sleep in 2 of our patients with epilepsy after starting LTRA treatment.

A Swedish study conducted from 1998 to 2007 examined neuropsychiatric adverse effects reported during LTRA therapy in children younger than 18 years. In order of decreasing frequency, they included nyctophobia, aggressiveness, anxiety, sleep disorders, insomnia, irritability, hallucination, hyperactivity, and personality changes. In 80% of the cases, the adverse effects appeared in the first week after initiating use of the medicine.⁶ No convulsions were reported in this study. In all 3 of our patients, the convulsions were observed within 1 week after initiating use of the medication. In 2012, Cereza et al⁷ reported no seizure activity in 24 adult and pediatric patients who used LTRAs and had nightmares.

In conclusion, although they generally have mild, reversible adverse effects, LTRAs should be administered cautiously in patients with preexisting epilepsy history.

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