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Nightmares induced by montelukast in children and adults

To the Editors:

Montelukast, a leukotriene receptor antagonist, was approved in Spain in 1998 for the treatment of asthma in both adults and children. Sleep disturbances, including nightmares, related to leukotriene receptor antagonists have not been described in clinical trials. However, several cases of sleep abnormalities, including nightmares, have been reported in post-marketing experience in patients treated with montelukast [1].

Up to December 2011, the Spanish System of Pharmacovigilance had gathered 24 reports of nightmares in patients (17 children, seven adults) treated with montelukast (table 1). Of the 24 patients, 15 were males and nine were females. 14 patients presented with other concomitant psychiatric symptoms: insomnia (n=5), nervousness (n=4), hallucinations (n=3), aggressiveness (n=2), irritability (n=2) and anxiety (n=1). Cases with aggressiveness were rated as serious. In all cases the only suspect medicine was montelukast. Six patients had taken other medicines concomitantly, although on a long-term basis. In 18 patients the nightmares appeared within the first day of exposure (n=11) or within the first week of treatment (n=7). Nightmares rapidly resolved after montelukast discontinuation in 21 cases. Alternative causes other than montelukast were excluded in most reports. Three patients were re-exposed to montelukast after the nightmares resolved, and in all three patients the nightmares reappeared.

In a list of all reported adverse reactions with montelukast in the UK after the first 14 months of marketing, 13 cases of nightmares were included [2].

A total of 44 reports of psychiatric disorders in children during treatment with montelukast as a suspected drug were found in the Swedish Adverse Drug Reaction database (SWEDIS) up to 2007. There were 15 reports of nightmares induced by montelukast, eight (53%) of which occurred in children $\leqslant$5 yrs of age [3]. Details regarding clinical course and causal relationship with montelukast in these cases are similar to those of the paediatric cases in our series.

In the analysis of the psychiatric adverse drug reactions in the paediatric population registered to the SWEDIS database during the period 2001–2010, montelukast was the most frequently suspected drug (excluding vaccines). The most frequently reported psychiatric adverse drug reaction associated with montelukast was nightmares [4].

Nightmares are relatively common parasomnias, defined as an unpleasant or frightening dream usually occurring in rapid eye movement (REM) sleep. A number of different medicines have been involved in cases of nightmares. However, for most of them the eventual pharmacological mechanism is unknown. Various neurotransmitter modulating systems have been implicated in the mechanisms of dreaming and in nightmares. Drugs affecting norepinephrine, serotonin, dopamine, acetylcholine and gamma-aminobutyric acid, such as β-blockers, antidepressants, dopamine agonists, anticholinergic agents and benzodiazepines, have more often been associated with nightmares [5].

The incidence of nightmares is difficult to establish. 80% of the general adult population may suffer from sporadic nightmares [6]. Since children experience more REM sleep than adults, nightmares in childhood tend to be more common and sometimes relapsing [6]. Moreover, among patients with asthma, sleep problems are common complaints. Obstructive pulmonary disease disturbs sleep. Compared with the general population, patients with chronic respiratory conditions have a higher prevalence of sleep disorders, including nightmares [7]. The high proportion of children in our series may also reflect preferential prescribing of montelukast for children.

The higher background incidence of nightmares in patients with asthma adds difficulty to the causality assessment in the cases we present. However, the close time sequence between exposure to montelukast and nightmares, the fact that 18 out of 24 patients were not exposed to any other medicine, the quick recovery after montelukast withdrawal in most cases, and the positive re-challenge in three patients suggest a causal relationship and warrant a more detailed assessment of the risk.

We cannot suggest a mechanism for montelukast-induced nightmares. To our knowledge, nightmares have not been

TABLE 1 Reports of nightmares associated with montelukast

Sex	Age yrs	Adverse events	Induction period days	Dose mg·day^{-1}	Concomitant medication
Female	2	Nightmares, nervousness	12	4	None
Male	2	Nightmares, aggressiveness	8	4	None
Male	2	Nightmares	180	4	None
Male	3	Nightmares, insomnia	⩽1	4	None
Male	3	Nightmares, nervousness	6	4	None
Male	3	Nightmares	⩽1	4	None
Male	3	Nightmares, hallucination	⩽1	4	None
Male	3	Nightmares, irritability, insomnia	⩽1	4	None
Female	3	Nightmares, irritability	48	4	Salbutamol, fluticasone
Male	4	Nightmares	⩽1	5	None
Female	5	Nightmares, hallucination	⩽1	4	None
Male	5	Nightmares, insomnia	26	4	None
Male	6	Nightmares, anxiety	⩽1	4	None
Male	6	Nightmares	365	5	None
Male	7	Nightmares	⩽1	4	Fluticasone, cetirizine
Male	7	Nightmares, nervousness	1	4	None
Female	8	Nightmares, nervousness	6		None
Female	19	Nightmares	4	10	None
Male	30	Nightmares	⩽1	4	Budesonide
Female	36	Nightmares	7	10	None
Female	44	Nightmares	2	10	None
Female	49	Nightmares	8	10	Salmeterol, fluticasone
Female	61	Nightmares, insomnia	⩽1	10	Salbutamol, fluticasone, cetirizine, lorazepam
Male	66	Nightmares, insomnia, hallucination, aggressiveness	45	10	Salbutamol, fluticasone, losartan, torasemide

reported with zafirlukast, another leukotriene receptor antagonist. Zafirlukast is not approved for use in children <12 yrs of age, while in our case series most patients were aged 2–7 yrs. However, higher susceptibility of children to this adverse effect should not be excluded.

Factors predisposing to this adverse effect and its mechanism remain to be elucidated. Meanwhile, it is important to bear in mind that montelukast may be a cause of nightmares, particularly in children. Usually nightmares disappear after withdrawal of the drug. Unexplained nightmares can lead to unjustified psychiatric consultation and possibly to additional treatments, which can add more morbidity. Doctors, patients and their families should be fully informed about this risk.

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