2017

Similar Adverse Events from Two Disparate Agents Implicate Lipid Inflammatory Mediators for a Role in Anxiety States

Gordon McCarter
Touro University California, gordon.mccarter@tu.edu

Lauren B. Blanchard

Recommended Citation

McCarter, G., & Blanchard, L. B. (2017). Similar Adverse Events from Two Disparate Agents Implicate Lipid Inflammatory Mediators for a Role in Anxiety States. *Oxford Medical Case Reports, 2017* (11), [Article omx060]. https://doi.org/10.1093/omcr/omx060

OMCR

Oxford Medical Case Reports, 2017;11, 233–235

doi: 10.1093/omcr/omx060
Case Report

CASE REPORT

Similar adverse events from two disparate agents implicate lipid inflammatory mediators for a role in anxiety states

Gordon C. McCarter[1,*] and Lauren B. Blanchard[2]

[1]Department of Biological and Pharmaceutical Sciences, Touro University California, College of Pharmacy, Vallejo, CA, USA, and [2]Family Medicine Oakland, Oakland, CA, USA

*Correspondence address. Department of Biological and Pharmaceutical Sciences, Touro University California, College of Pharmacy, 1310 Club Drive, Vallejo, CA 94592, USA. Tel: +1-707-638-5919; Fax: +1-707-638-5266; E-mail: gordon.mccarter@tu.edu

Abstract

We recently reported a case in which a 54-year-old male experienced maintenance insomnia, generalized anxiety and panic symptoms associated with consumption of a fish oil supplement enriched in eicosapentaenoic acid (EPA). We report here that the same patient has experienced identical but more severe symptoms in response to the use of the leukotriene receptor antagonist montelukast, in accordance with other cases reported to the Food and Drug Administration. Since omega-3 fatty acids like EPA are precursors for the biosynthesis of eicosanoids including leukotrienes, a common factor to these psychiatric adverse events may be perturbations in this highly complex system of lipid inflammatory mediators.

INTRODUCTION

Montelukast (Singulair®, Merck & Co.) is a leukotriene receptor inhibitor that specifically antagonizes the cysteinyl leukotriene type 1 receptor (CysLTR1). Biological agonizts of the CysLTR1 include leukotrienes-C4, -D4 and -E4, which are released by immune cells to mediate inflammation of airways, the nasal mucosa and other tissues [1]. Thus, montelukast and another CysLTR1 antagonist, zafirlukast, are effective treatments for asthma and allergic rhinitis [2]. The Food and Drug Administration has received numerous reports of neuropsychiatric adverse events associated with montelukast, including suicidality, depression, abnormal behavior, aggression, anxiety, insomnia, nightmares, and night terrors [3] and special attention has been paid to these effects in pediatric populations [4, 5]. In this case report, we describe a patient who experienced severe anxiety and maintenance insomnia with panic symptoms temporally correlated with a month-long trial of montelukast, prescribed for mild asthma. This case is unique in that the patient had previously experienced similar symptoms associated with consumption of a fish oil supplement enriched in the omega-3 fatty acid eicosapentaenoic acid (EPA) [6]. That such disparate agents caused similar psychiatric adverse events may shed light on whether and how lipid inflammatory mediators could affect fear circuits in the brain.

CASE REPORT

The patient is a 56-year-old male in very good health. He exercises regularly, primarily walking, running, and bicycling, and has an excellent cardiovascular profile with a body mass index of 23. He is educated at the doctoral level and is medically literate. As reported previously [6], he was diagnosed with major depressive disorder at age 42 and was treated with fluoxetine, omega-3 fatty acids and psychotherapy which were eventually

Received: March 28, 2017. **Revised:** July 11, 2017. **Accepted:** August 1, 2017

effective, with the depression going into a yet-continuing remission starting at age 53. The patient had discontinued the fluoxetine more than 6 months after the depression had gone into remission. Of note, he had not experienced significant anxiety symptoms until age 54, which at that time were associated with the use of EPA-enriched fish oil supplements. The patient had taken the same refined fish oil supplements for over 5 years and he partially attributes the remission of his depression to them, but they gradually began causing the anxiety and insomnia symptoms, which became noticeable by age 54 and abated when he temporarily stopped taking the fish oil supplements. A subsequent challenge with the fish oil triggered the symptoms again, so the patient stopped taking them altogether after which the anxiety and insomnia symptoms were largely eliminated [6]. He was prescribed lorazepam for the anxiety symptoms, which by agreement was restricted to no more than 12 1 mg tabs per 6 months to prevent dependence.

During a recent annual physical exam, his primary care practitioner suggested montelukast for his mild chronic asthma. Two to three weeks after initiating montelukast at 10 mg/day he noticed gradually worsening generalized anxiety and began waking suddenly after several hours of sleep. During his awakenings, he often experienced strong sympathetic activation, with increased heart rate, flushing and a loosening sensation in his viscera. These panic symptoms were associated with ruminative thoughts in which routine life concerns led to the imagination of catastrophic outcomes for himself, his family and society at large. He described one night in which he experienced nasal congestion and had persistent, intrusive fears of suffocation should his mouth somehow be forced shut. He is experienced in somatic quieting and cognitive self-soothing [7] but found these difficult to execute in these night-time panic episodes. Instead, he chose to get out of bed and read until he was calm enough to resume sleep. On a few occasions he took 0.25–0.5 mg of lorazepam, often with a glass of wine. The only other medications the patient used were fluticasone 100 mcg-salmeterol 50 mcg inhalation powder (Advair®, GlaxoSmithKline) and albuterol HFA, both for occasional asthma exacerbations. The anxiety symptoms occurred virtually every night by the fourth week of taking montelukast.

The patient reported that in the daytime he was also frequently overcome by morbid fears of such things as aging in loneliness, his children failing at life or worldwide economic collapse. At other times he would suddenly feel extreme anxiety about expectations of him at his workplace, in which he experienced a wave of sympathetic arousal, mainly felt as flushing and an increased heart rate. Because of the night-time awakenings he was chronically sleep-deprived during this period, to which, based on experience, he attributed the fact that he felt restless and 'jittery,' and had a pounding heart throughout much of the day. The patient recognized that the current symptoms were very similar to those associated with fish oil supplements, but he considered them significantly more intense than the previous episode.

The patient did not associate his anxiety symptoms with the new medication until it was time to refill his prescription. He researched the adverse events associated with montelukast and immediately decided to discontinue the drug after ~1 month of daily use. The panic symptoms during night-time awakenings abated within a few days, while the awakenings themselves and the general anxiety took a few weeks to largely resolve. Several months after the discontinuation of montelukast the patient reported that he felt a 'normal' mild degree of daytime anxiety and experienced mild maintenance insomnia less than once a week with no panic symptoms.

DISCUSSION

Post-marketing vigilance has resulted in the collection of many reports of neuropsychiatric adverse events associated with montelukast, particularly in the FDA Adverse Event Reporting System (FAERS) database [3, 4, 8]. The most frequently reported neuropsychiatric adverse events with 'serious outcomes' in the FAERS database were suicidal ideation, depression, aggression, abnormal behavior, anxiety and insomnia. However, there have been few specific, detailed reports of such adverse events in the literature [9, 10]. The current report is unique in the extended history of the patient and his medical literacy—he lectures on psychiatric medicines in both a Doctor of Pharmacy program and a graduate counseling psychology program—as well as the close temporal correlation of the use of montelukast with his anxiety symptoms. The reaction to montelukast described in this report is strikingly similar to a previous incident in the same patient 18 months earlier, in which the symptoms of daytime anxiety and maintenance insomnia with night-time panic symptoms were evoked by the consumption of 2 g/day high-EPA fish oil supplements [6]. The symptoms provoked by both the fish oil and montelukast were much more intense than what had become the moderate background level of anxiety symptoms for the patient at age 56. Because, the intense anxiety symptoms occurred only in conjunction with consumption of the two agents and were qualitatively very different from any previous symptoms experienced by this patient, it is unlikely that the episode described here was a coincidental exacerbation in the natural history of his psychological health.

In this patient, two disparate manipulations of the eicosanoid signaling system had very similar effects on the expression of fear and worry behaviors. EPA is a metabolic precursor to many eicosanoids and leukotrienes, and the reaction of the global eicosanoid/leukotriene signaling system to an exogenous increase in EPA is likely to be quite complex and variable between individuals and possibly within individuals over time [11]. In addition, blockade of the CysLTR1 by montelukast may have wider effects on this system beyond the prevention of leukotrienes-C4, -D4 and -E4 from promoting inflammation. Interestingly, expression of a key protein regulating eicosanoid metabolism was strongly correlated with anxiety-like behavior in mice [12]. Since montelukast and fish oil are widely used agents and the vast majority of patients who use them experience no neuropsychiatric side effects, the subject of the current report may have an uncommon or idiosyncratic physiological reaction to these agents. His response to high-EPA fish oil changed in his early fifties from apparently beneficial to demonstrably aversive, which may simply be associated with normal aging, as manifested perhaps by reduced testosterone. Clinicians treating both respiratory and psychiatric disorders should be aware of possible idiosyncratic adverse events related to the use of medicines that affect the lipid inflammatory signaling system. More research is needed into the effects of this system on the amygdalae and other neural elements mediating fear.

CONFLICT OF INTEREST STATEMENT

None declared.

FUNDING

No sources of funding.

ETHICAL APPROVAL

None required.

CONSENT

The patient described has signed a Patient Consent form.

GUARANTOR

Gordon C. McCarter, PhD.

REFERENCES

1. Peters-Golden M, Henderson WR Jr. Leukotrienes. *N Engl J Med* 2007;**357**:1841–54.
2. Scott JP, Peters-Golden M. Antileukotriene agents for the treatment of lung disease. *Am J Respir Crit Care Med* 2013; **188**:538–44.
3. Updated Information on Leukotriene Inhibitors: Montelukast (marketed as Singulair), Zafirlukast (marketed as Accolate), and Zileuton (marketed as Zyflo and Zyflo CR). Washington, D.C.: Food and Drug Administration 2009; http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm165489.htm. (27 January 2017, date last accessed).
4. Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review. Washington, D.C.: Food and Drug Administration 2014; https://www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/ucm434555.htm. (1 August 2017, date last accessed).
5. Aldea Perona A, Garcia-Saiz M, Sanz Alvarez E. Psychiatric Disorders and Montelukast in Children: A Disproportionality Analysis of the VigiBase®. *Drug Saf* 2016;**39**: 69–78.
6. Blanchard LB, McCarter GC. Insomnia and exacerbation of anxiety associated with high-EPA fish oil supplements after successful treatment of depression. *Oxf Med Case Rep* 2015;**3**: 244–5.
7. Kabat-Zinn J. *Full Catastrophe Living: Using the Wisdom of Your Body and Mind to Face Stress, Pain, and Illness*. New York: Bantam Books, 2013.
8. Philip G, Hustad C, Noonan G, Malice MP, Ezekowitz A, Reiss TF, *et al*. Reports of suicidality in clinical trials of montelukast. *J Allergy Clin Immunol* 2009;**124**:691–6. e696.
9. Callero-Viera A, Infante S, Fuentes-Aparicio V, Zapatero L, Alonso-Lebrero E. Neuropsychiatric reactions to montelukast. *J Investig Allergol Clin Immunol* 2012;**22**:452–3.
10. Calapai G, Casciaro M, Miroddi M, Calapai F, Navarra M, Gangemi S. Montelukast-induced adverse drug reactions: a review of case reports in the literature. *Pharmacology* 2014; **94**:60–70.
11. Norris PC, Dennis EA. Omega-3 fatty acids cause dramatic changes in TLR4 and purinergic eicosanoid signaling. *Proc Natl Acad Sci USA* 2012;**109**:8517–22.
12. Joshi YB, Pratico D. The involvement of 5-lipoxygenase activating protein in anxiety-like behavior. *J Psychiatr Res* 2013; **47**:694–8.