Montelukast-induced metamorphopsia in a pediatric patient A case report and a pharmacovigilance database analysis

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Introdution

Metamorphopsia is a type of optic illusion in which the size, shape, or angulation of objects is perceived as altered. Individuals typically see lines as wavy or curly instead of straight and flat surfaces as curved [1]. It is a rare manifestation of an acute central nervous system insult, mainly to the visual or vestibular systems [1]. It is a symptom caused by disorders of the retina or choroid and frequently observed in age-related macular degeneration; it may occur, although less frequently, as the result of retinal detachments because of direct eye injuries or head trauma [2].

Metamorphopsia may also occur although rarely as an adverse drug reaction (ADRs); an analysis of case reports from the National Registry of Drug-Induced Ocular Side Effects of the United States of America reports has identified bisphosphonates, cetirizine, retinoids and topiramate as the drugs mostly involved in ocular ADRs [3].

To date, the ocular ADRs are not included in the side effects reported in the Summary of Product Characteristics (SPC or SmPC) of montelukast, a potent leukotriene-receptor antagonist, and the possible correlation between its use and the ocular event has not yet been investigated. Montelukast is administered once daily in the treatment of asthma and allergic rhinitis in children and adults [4]. Efficacy and safety profile data on montelukast from several paediatric studies have been published. While generally well tolerated, it may lead to clinical adverse reactions such as upper respiratory infection, worsening asthma, pharyngitis and headache [5-7].

In this study, we present the first case in which montelukast can be linked to the onset of metamorphopsia [8]. We then propose a possible mechanism leading to its insurgence and provide an analysis of international pharmacovigilance database to map its occurrence.

Detail of the case

A 12-years-old female suffering from asthma was treated with montelukast at the therapeutic dose (5 mg/day). Approximately an hour after the first oral administration of the drug, the patient experienced visual disturbance in which the perfectly straight lines appeared wavy, parts of the line appeared blank with flat surface bending. This visual disturbance lasted approximately 15 minutes. The patient was hospitalised. The neurological examination and the electroencephalogram revealed no abnormalities. The positive Amsler test confirmed the diagnosis of metamorphopsia. The patient received no other concomitant drug or herbal treatment and had no personal or family history of ocular diseases.

Considering the temporality between the drug intake and the appearance of the reaction, the treatment was discontinued and a diagnosis of iatrogenic metamorphopsia was performed by the clinician. The ADR resolved after drug withdrawal in few days. The patient no longer experienced ocular disturbances and remained metamorphopsia-free during a 3-month follow-up.

The positive dechallenge, the temporal association between drug's use and the onset of the reaction suggested a *possible* causal relationship between the metamorphopsia and montelukast administration, confirmed also by the Naranjo Algorithm.

Analysis of Pharmacovigilance databases

Montelukast-associated metamorphopsia has not previously been reported in the literature [8], although the main International pharmacovigilance databases contain several reports of ocular event referred to the leukotriene-receptor antagonist.

We retrieved 719 reports of ocular ADRs in which montelukast was the suspected drug involved, inserted into the following pharmacovigilance databases: the Danish Health and Medicines Authority, the Health Canada Vigilance Adverse Reaction Online Database, the Netherlands Pharmacovigilance Centre Lareb

Databank, the UK Medicines and Healthcare products Regulatory Agency, the FDA Adverse Event Reporting System (AERS), the Australian Adverse Event Reporting System (DAEN) (Table 1). Of 719 ocular ADR reports 4 of those in the AERS described metamorphopsia, representing the 0.5% of the total ocular events retrieved in our analysis. Of these, one refers of a 13-year-old male with multiple allergies who was placed on therapy with montelukast (strength, formulation and indication not reported). Approximately 5 minutes after montelukast administration, the patient experienced visual disturbance with metamorphopsia. The limit of this analysis is that the pharmacovigilance databases only receives reports of the most critical and severe cases; these numbers we retrieved may underestimate the complication rate of the drug.

Discussion

The adverse ocular drug-related events are scant in general and rare with montelukast. Previous studies have estimated that ocular disorders such as myopia and conjunctivitis can occur in patients taking montelukast with an incidence of 2%; mydriasis is among the most frequent adverse effects with overdosage of the drug [8, 12].

The pathogenic causes of montelukast associated metamorphopsia may be multiple and not necessarily mutually exclusive. Metamorphopsia, is often the result of progressive accumulation of fluid in the rear area of the ocular fundus, can lead to the perception of a visual field deformed [3]. It is therefore plausible that inflammation and peripheral oedema play an important role in this visual disturbance [18]. Inflammatory processes and the increase in vascular permeability are indeed responsible of macular oedema resulting in metamorphopsia. The release of inflammatory mediators such as histamine and products of arachidonic acid metabolism has been demonstrated in bronchoalveolar fluid of patients with asthma [19], and in some cases montelukast is able to cause peripheral oedema [17]. In the specific case we observed a partial inefficacy of montelukast in reducing pro-inflammatory mediators combined with a possible direct oedemigen effect of the drug may have synergised to trigger metamorphopsia [20].

A second possibility is headache, often associated with bizarre visual and spatial distortions [21]. Headache has been commonly reported (>1/100 to <1/10) in clinical studies enrolled asthmatic patients treated with montelukast. In our analysis, the ocular ADRs reports have frequently involvement of headache and migraine probably resulting in the predisposition of visual disturbance.

Finally, metamorphopsia can be also caused by psychiatric disorders [22], also detected in patients with asthma, who are at increased risk for a variety of mental disorders [23]. Montelukast can cause psychiatric adverse reactions; they are rare but involve mostly hallucinations including visual hallucinations [24,25]. It has been suggested that inhibition of leukotriene receptors in the brain could be responsible for these neuropsychiatric adverse effects [23]. Interestingly in one case montelukast was associated with the Alice-in-Wonderland syndrome that associate disorienting neurological conditions with metamorphopsia [9]. Also in this case no obvious trigger and negative magnetic resonance imaging and electroencephalography were reported [9-11].

Our current case report, along with previous data form literature and the International pharmacovigilance databases, identify in metamorphopsia a possible ADR by montelukast and provide a rationale for its occurrence. These results provide also means to help the physician to identify possible correlations between ocular side effects and montelukast for a prompt identification. An increased attention in pharmacovigilance to this ADR appears relevant because of the wide paediatric use of montelukast.

Table 1. Ocular ADRs in which montelukast was involved as suspected drug, inserted into the International pharmacovigilance databases.

Pharmacovigilance databases	**N° of ADR reports belong to SOC *Eye Disorder***	**N° of reports of *metamorphopsia***	**ADR belong to SOC *Eye Disorder* mostly reported**	**Period of observation (from-to)**
Danish Health and Medicines Authority	11	-	xerophtalmia, blepharospasm, eye swelling, periorbital oedema*****, eye pruritus, pupillary disorder, retinal deposits, visual impairment	1998-2015
Health Canada Vigilance Adverse Reaction Online Database	18	-	visual impairment, blindness transient, hyperhidrosis, periorbital oedema, blepharospasm, cough*****, drug ineffective*****, pyrexia*****, somnolence*****, dry eye, excessive eye blinking, eye movement disorder	1998-2015
Netherlands Pharmacovigilance	11	-	conjunctival haemorrhage, dry eye, visual impairment,	1998-2015

Centre Lareb Databank			lacrimal disorder, vision blurred	
UK Medicines and Healthcare products Regulatory Agency	62	-	Cataract, eye disorder periorbital oedema, eye pain, eye movement disorder, mydriasis, photopsia vision blurred, visual impairment	1998-2015
AERS	611	4	photopsia, eye disorder, dry eye, periorbital oedema, dizzness*, visual impairment, headache*, nausea*, anxiety*, vision blurred, visual disturbance, vision blurred, cataract, paraesthesia, visual field defect, eye pain	2004-2012
DAEN	6	-	headache*****, migraine*****, nausea*****, visual impairment, periorbital oedema, dizziness*****, fatigue*****, vomiting*****, photopsia, visual field defect, peripheral oedema *****	1998-2015
TOTAL	**719**	**4**		

- not reported

***** ADRs reported in association to ADRs detected using for the screening the SOC *Eye Disorder*

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