

FDA Advisory Committee

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Visual Adverse Effects of Telithromycin

A Neuro-ophthalmologist Expert's Perspective

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What We Know About the Visual Side Effects

- The symptoms can be bilateral blurred vision, dimming of vision “difficulty focusing”, or double vision
- Characteristically, the onset of symptoms usually occurs within 1-3 hours of taking the dose, and resolve after cessation of treatment
- There is no case of permanent damage to the visual system attributable to telithromycin
- Most patients with visual symptoms still maintain normal activities, but activity should be modified on an individual basis, as some may not be able to drive or work.

“Dimming” of Vision: Is This a Worrisome or Dangerous Symptom?

- Clinical cases of dimming or darkening of vision are usually of vascular origin, can be vision threatening, and are worrisome
- Unilateral cases are due to either retinal or optic nerve ischemia
- Bilateral cases are usually hypotensive, affecting either the retinae/optic nerves at the end organ or visual cortex at the occipital pole (susceptible watershed vascular area). They are almost always accompanied by presyncopal-like symptoms

The cases of telithromycin associated dimming of vision are very rare, reversible, can last up to hours, are bilateral and have not been associated with syncopal-like hypotensive symptoms

What is Causing the Blurring and Dimming Visual Symptoms?

- Unlikely to be a pure accommodative (focusing) end organ effect or lens effect because:
 - patients experiencing “blurring” or “focusing problems” do not have a shifted near or far focal point, as would be expected with paresis or over-stimulation of focusing muscles in the ciliary body of the eye.
 - Lack of muscarinic, adrenergic, or acetylcholinesterase effects of telithromycin at therapeutic doses, argues against direct effect on ciliary body smooth muscle
 - Some elderly patients with side effect of blurred vision lack focusing due to underlying presbyopia or pseudophakia from cataract surgery with intra-ocular lens implant, so accommodative mechanism is unlikely in these patients

What is Causing the Blurring and Dimming Visual Symptoms?

- Unlikely to be an effect on the cornea:
 - There have been no dry eye or tear film symptoms or findings and the time of onset and duration are not compatible with this mechanism
 - Edema of the cornea or surface abnormalities have not been found in patients examined and these do not normally resolve quickly

What is Causing the Blurring and Dimming Visual Symptoms?

- This leaves the following possibilities:
 - A drug adverse effect interfering with the neuronal firing or conduction at either the retina or visual cortex (primary or higher cortical areas)
 - A vascular effect is less likely, considering the bilaterality and long duration of symptoms, reversibility, lack of presyncopal symptoms, predominance of “blurring” symptoms, and rarity of “dimming” or “darkening”
 - The mechanism could depend on a given patient’s underlying susceptibility to the action of the drug at the neuronal level (i.e. mitochondrial genetic susceptibility, or membrane ion channel characteristics)

How Might the FDA and Industry Approach This in the Future?

- Detailed first-hand description of symptoms from affected patients reported via a website or telephone interview would be helpful – direct communication with the patient
- A guide for patients on what to expect and how to check their vision when symptoms occur would improve the quality of symptom reporting
- An opportunity to speak to or email a designated visual expert could be offered patients to allow a more direct assessment of the visual symptoms; re-challenge in a monitored setting could be requested

What Do Reports Mean to Me As a Visual Expert?

- All of the reports have been reversible, leading me to conclude that there is no known perceived permanent damage to the visual system
- The incidence of adverse visual effects is rare (less than 1%) implying an underlying susceptibility in a minority population of patients
- Severe visual symptoms are even rarer, but patients need to be warned of this possibility and its potential impact on driving and their visual performance

Would I Take Telithromycin?

- I would take this drug for the time period over which it is prescribed
- I would discontinue the drug if I were one of the few patients that experienced visual adverse effects –visual symptoms produce anxiety
- I believe that the reports of transient and reversible visual adverse effects are benign and would not prevent me from taking telithromycin, if prescribed