

Proposed Mechanisms to Explain the Unusual Visual Disturbances Associated with Telithromycin.

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Background:

Reports of macrolides causing “blurred vision” prompted investigation of the possible mechanisms of action. A first clue about blurred vision came from the relatively high prevalence of such symptoms reported by subjects exposed to telithromycin compared to structurally related macrolides (clarithromycin or azithromycin). As macrolides do not readily cross the blood brain barrier, blurred vision must arise from disruption of function in the peripheral nervous system. Since cholinergic neurotransmission plays a determinant role in peripheral nervous transmission we evaluated the possible interaction of macrolides with neuronal nicotinic acetylcholine receptors (nAChR) and compared the effects of telithromycin, clarithromycin, azithromycin and CEM-101, a novel fluoroketolide.

Methods:

Effects of macrolides at human neuronal nAChRs were assessed using electrophysiological recordings in receptors expressed in *Xenopus* oocytes.

Results:

Exposure to low concentrations of telithromycin (2 μ M) for 15 minutes caused pronounced inhibition at the α 3 β 4 (90 \pm 10%) and α 7 (85 \pm 3%) receptor. Inhibition was significantly less with the other macrolides tested. Clarithromycin and azithromycin respectively inhibited the α 3 β 4 receptor by 40 \pm 7% and 56 \pm 10%, and the α 7 receptor by 49 \pm 4% and 51 \pm 16%. CEM-101 inhibited the α 3 β 4 receptor by 61 \pm 4% and, importantly, had no effect at the α 7 receptor (<6 \pm 3%). As the α 3 β 4 and α 7 receptors are the major constituents of ganglionic transmission, inhibition of their activity will impair or even suppress neurotransmission in peripheral ganglia.

Conclusions:

Dysfunction of the ciliary ganglion is expected to cause a loss of control of pupillary constriction and ciliary muscle contraction. Both effects thereby may combine to produce a reduction in the depth of field and of accommodation and cause a loss of focusing. This should result in profound vision disturbance and blurred vision for objects in the near and intermediate vision.