

# Side Effects of Telithromycin and Voriconazole are Attributable to Nicotinic Acetylcholine Receptor Interactions

## Abstract A2-588

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### Background:

Some side effects caused by drug exposure can be understood by their molecular interactions with biochemical pathways while others remain obscure. An example of a now well understood side effect is the interaction of compounds with the cardiac potassium channel (hERG). Side effects caused by the ketolide, telithromycin, including reversible blurred vision, muscle weakness and liver failure were related to the profound inhibition of the  $\alpha 7$  and the ganglionic  $\alpha 3\beta 4$  nicotinic acetylcholine receptor (nAChR) (Antimicrob. Agents Chemother. 54: 5399-5402, 2010). The interaction of telithromycin metabolites with nAChRs are now reported. In view of the similarity of some of the side effects reported for patients treated with the antifungal voriconazole, but not fluconazole, experiments probing the effects of these compounds at the neuronal nAChR were conducted.

### Methods:

Human nACh receptors expressed in *Xenopus* oocytes were used forelectrophysiological studies.

**Results:** The telithromycin metabolite (telithromycin-N-oxide), which includes the pyridine moiety, inhibits the ganglionic  $\alpha 3\beta 4$  nAChR and the post-synaptic neuromuscular junction receptor (NMJE) whereas another metabolite without the pyridine moiety did not show significant inhibition. Voriconazole inhibits the human  $\alpha 3\beta 4$  resulting in 63% reduction of the ACh-evoked current, while only 10% inhibition of the  $\alpha 7$  receptor. Fluconazole caused no significant inhibition of the ACh-evoked currents.

### Conclusions:

Telithromycin-N-oxide contributes to the inhibition of the  $\alpha 3\beta 4$  and the post-synaptic NMJE nAChRs by telithromycin. Voriconazole, which possesses a pyrimidine moiety, inhibits the ganglionic  $\alpha 3\beta 4$  nAChR, which could be the origin of the visual disturbances observed in voriconazole treated patients. The absence of fluconazole effects at nAChR correlates with the absence of reported side effects. These data suggest that compounds containing pyridine or pyrimidine residues could interact with the nAChR resulting in clinical side effects.