

# Mechanistic Characterization of Adverse Events of Voriconazole and Telithromycin

Abstract 644

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## Background:

Mechanistic characterization of the side effects of drugs helps to optimize the side-effect profiles of drugs in development. We have previously described the inhibition of neuronal nicotinic acetylcholine receptors (nAChR) by telithromycin, which contains a pyridine in its side chain. In this report we have characterized the reason for the “curare-like” effect at the neuromuscular junction seen in myasthenia gravis patients treated with telithromycin. Similarities in the visual effects of voriconazole to those observed with telithromycin and the presence of a heterocyclic N in the pyrimidine side chain of voriconazole led us to test the effects of voriconazole in nAChR assays.

## Methods:

Electrophysiological studies were conducted using expression of human nAChRs in *Xenopus* oocytes.

**Results:** Telithromycin inhibits the presynaptic  $\alpha 3\beta 2$  nAChR and its major metabolite, telithromycin-N-oxide, caused > 80% sustained inhibition of the ganglionic  $\alpha 3\beta 4$  nAChR. It also inhibited the post-synaptic neuromuscular junction receptors (NMJ) (50% inhibition). This structure-adverse event relationship correlated with the insignificant inhibition by another telithromycin metabolite lacking the pyridine moiety. The  $\alpha 3\beta 4$  receptor found in the ciliary ganglion of the eye was strongly inhibited by telithromycin-N-oxide (80% reduction) and also by voriconazole (63% reduction). Fluconazole, which has had no visual side effects, caused no significant inhibition of nAChRs.

## Conclusions:

The cumulative effects of telithromycin and telithromycin-N-oxide can explain the curare-like neuromuscular effects seen after telithromycin administration. The visual effects resulting from the inhibition  $\alpha 3\beta 4$  and  $\alpha 7$  nAChRs by telithromycin is further enhanced by the inhibition of the  $\alpha 3\beta 4$  nAChR by the N-oxide metabolite of telithromycin. The heterocyclic N in the pyrimidine of the side chain of voriconazole possesses nAChR inhibitory activity, which could be the origin of the adverse events observed with voriconazole.