Mechanistic Characterization of Adverse Events of Voriconazole and Telithromycin

Abstract 644

Daniel Bertrand[1], Sonia Bertrand[1], David Pereira[2], *Prabhavathi Fernandes[2]

[1]HiQScreen Sàrl, 15, rue de l'Athénée, Geneva Switzerland; [2]Cempra Pharmaceuticals Inc. Chapel Hill, NC 27517 USA

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 α3β2 nAChR and its major metabolite, telithromycin-N-oxide, caused > 80% sustained inhibition of the ganglionic α3β4 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 α3β4 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 α3β4 and α7 nAChRs by telithromycin is further enhanced by the inhibition of the α3β4 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.