

Characterization of the Mechanism of Nicotinic Acetylcholine Receptor Inhibition That is Likely Linked to the Off-Target Activity by Telithromycin

Abstract P1418

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Objectives:

Previous studies carried out with telithromycin at the nicotinic acetylcholine receptors have clearly illustrated that the pyridine moiety in the side-chain of telithromycin inhibits the $\alpha 7$ and $\alpha 3\beta 4$ receptors. Similarly, the visual effects of voriconazole led us to the characterization of the inhibition of $\alpha 3\beta 4$ nAChRs by its heterocyclic N in the pyrimidine side chain. The aim of this study was to examine the mode of action of telithromycin at the human $\alpha 7$ and $\alpha 3\beta 4$ nAChRs.

Methods:

Electrophysiological studies were conducted using expression of human nAChRs in *Xenopus* oocytes. ACh dose-response curves were obtained in the absence or presence of a fixed concentration of telithromycin to determine the mode of action of telithromycin. Competitive antagonists are characterized by the fact that blockade caused by the antagonist can be surmounted by the appropriate increase in the agonist concentration. On the contrary, non-competitive antagonists are characterized by the fact that blockade is insurmountable.

Results:

Data obtained for $\alpha 3\beta 4$ with 2 μM telithromycin suggests that telithromycin might have a dual action with competitive and non-competitive inhibition. The dual mode of action of telithromycin was confirmed by examining the time course of the ACh response measured at a low ACh concentration (10 μM) and at a high ACh concentration (1280 μM). Inhibition caused by telithromycin is not accompanied by a modification of the response time course at 10 μM ACh, whereas a profound modification of the decay time was observed at the high ACh-concentration. The difference in the response time course, with a faster decay time observed at ACh concentrations >160 μM , indicates that inhibition is not caused by competition only, but that telithromycin probably enters the channel pore and blocks ionic conduction by steric hindrance. Exposure of cells expressing the human $\alpha 7$ to telithromycin (20 μM) causes a shift in the concentration activation curve towards higher ACh concentrations indicative of a competitive inhibition of $\alpha 7$. Similarly to $\alpha 3\beta 4$ at high ACh concentrations (>600 μM), telithromycin causes an additional inhibition probably due to open channel blockade.

Conclusions:

Mechanistic characterization of the side effects of drugs helps to optimize the side-effect profiles of drugs in development. These studies can mechanistically differentiate new macrolides/ketolides from telithromycin.