Mechanistic Characterization of Adverse Events of Voriconazole and Telithromycin

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ABSTRACT

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 reasons for the “curare-like” effect on the neuronal junction seen with this antibiotic. This provides potential mechanistic links between the side effects of these drugs and those observed with telithromycin and the presence of a heterocyclic N in the pyridine side chain of voriconazole led us to test the effects of voriconazole in nAChR assays.

Methods: Electrophysiological studies were conducted using expression of human nAChR in Xenopus oocytes. Results: Telithromycin inhibits both the homeric (α7) and the heteromeric (α3β4) nAChR. It also inhibited the post-synaptic (α7) nicotinic junction receptors (nAChRj). The structure-adverse event relationship of the side effects is discussed.

CONCLUSIONS

Voriconazole and fluconazole are two molecules of the broader family of triazoles known to be effective against human fungal pathogens and similar in structure with the notable exception of a pyrimidine residue in voriconazole that is absent from fluconazole. Their similarity in visual effects observed between telithromycin and voriconazole and the presence of a receptor accessible pyrimidine moiety, we hypothesized that the side effects associated with this compound might arise from an interaction with neuronal nAChR.

INTRODUCTION

The lethal antibiotic telithromycin has been linked to many unusual side effects including visual disturbances, loss of consciousness, and severe aggravation of myasthenia gravis suggesting that this molecule or its metabolites might perturb neurotransmission at ganglia and the neuromuscular junction. A recent report demonstrated that some of these side effects are related to the profound inhibition of nicotinic acetylcholine receptors (nAChR) by telithromycin (1).

Telithromycin inhibits nAChRs in the low micromolar range, whereas the fluorescentable telithromycin (CEM-101) does not (Fig. 1) (1). This suggests a correlation between the chemical structure of telithromycin and the clinical observation. A closer analysis of the telithromycin structure compared to other macrolide antibiotics indicates that the inhibition might correlate with the presence of the pyridine moiety (Fig. 2). Two metabolites of telithromycin, telithromycin-N-oxide (RU76363), which retains the pyridine moiety, and RU76382, which does not, permit a means to further probe this structure side-effect hypothesis.

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METHODS

Oocyte preparation and injection. Xenopus oocytes were prepared and injected with cDNAs encoding for the human α7, α3β4, α7 and α3β2 using standard procedures (4).

Electrophysiological recordings. Brief solution change (Ach) test pulses were applied at regular intervals to assess the effect of the test compounds on the receptor activity. Currents evoked by Ach in the presence and absence of the test compounds were recorded.

RESULTS

Effects of telithromycin-N-oxide and RU76382 at the human α7 and α3β4 and μα1 receptors are shown in Figure 3. Telithromycin-N-oxide (B) caused a marked inhibition of the ACh-evoked current at the neuromuscular junction (α7) that was significantly larger than that caused by RU76382 (C). The inhibition of μα1 by telithromycin-N-oxide could augment the activities of the parent drug telithromycin at this receptor. These results, together with the antagonism of the pre-synaptic α3β2 receptors by telithromycin (D) which could explain the “curare-like” effect experienced by myasthenia gravis patients who received telithromycin (E, F).

Voriconazole caused profound inhibition at the μα1 receptor, with up to 62% reduction of the ACh-evoked current after 20 minutes of exposure (G).

Neither fluoroketolide solithromycin or voriconazole-N-oxide led to substantial inhibition at the μα1 receptor, illustrating the specificity of the molecular structure and supporting the hypothesis of a direct interaction of voriconazole with the receptors (E, F).

Fig. 1. Inhibition of ganglionic and central nAChRs by telithromycin. Concentration-inhibition curves for telithromycin (solid line) and solithromycin (CEM-101; open circles). Adapted from Bernhard et al. 2001. Avic 59:333–402.

Fig. 2. Chemical structures of the ketolide telithromycin, its metabolites telithromycin-N-oxide and RU76382, and the fluoroketolide solithromycin (CEM-101).

Fig. 3. Chemical structures of voriconazole, its major metabolite voriconazole-N-oxide, and fluconazole.

Fig. 4. Repression of nAChR activity by telithromycin metabolites. Telithromycin-N-oxide which retains the pyridine ring, displays a more potent inhibition of the α3β4 receptor than RU76382.

Fig. 5. Differential inhibition of ganglionic nAChRs by the triazole voriconazole and fluconazole. Voriconazole, which contains a pyrimidine moiety, is a strong inhibitor of the μα1 receptor.