

Solithromycin (CEM-101) - A New Fluoroketolide with Antimalarial Activity

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Solithromycin (CEM-101) is a new fluoroketolide antibiotic under clinical development for the treatment of community-acquired bacterial respiratory tract infections. In this study, we evaluated its in vitro and in vivo activity against different species of *Plasmodium* parasites to see if there is a potential for use in the treatment of malaria.

Solithromycin was tested by the semi-automated microdilution assay against intra-erythrocytic forms of *P. falciparum* derived from asynchronous cultures of the strain NF54, essentially as described (Matile 1990). Parasite growth over 120h was measured by the incorporation of radiolabelled [³H] hypoxanthine (in hypoxanthine-free culture medium) added after 96h of drug incubation and 24h prior to the termination of the test. Because of its slow mode of action, solithromycin was followed for 120 hrs vs. the usual 72h assay. The test was run 3 times, and at lower concentrations, because it was more active than expected.

In vitro *P. falciparum* data for solithromycin in the 120h assay (96h + 24h) showed an IC₅₀ against NF54 of 2.4 compared to artesunate with an IC₅₀ of 3.3, clindamycin 5.3 and chloroquine 4.7 ng/ml.

Based on its promising in vitro activity, solithromycin was tested in the murine *P. berghei* model as described (Vennerstrom 2004). Solithromycin was first studied after a single dose of 100 mg/kg either in DMSO or HPMV. In the second experiment, solithromycin was given at a dose of 100 mg/kg daily for 4 days in both vehicles. Following the single dose, solithromycin showed antiparasitic activity of 80.05% and 81.45% and mouse survival in days was 15.2 and 12.7 days, respectively. Following daily doses of 100 mg/kg for 4 days solithromycin showed antiparasitic activity of 99.79% in both vehicles. The mice survived for 30 days in both experiments and thus solithromycin is considered to be fully curative in this model.

Solithromycin has been shown to have excellent in vitro and in vivo activity against *Plasmodium* species. This data would support future studies to determine solithromycin's potential for the treatment of blood stage malaria in combination with a fast-acting antimalarial. It may also have additional benefits because of its activity as an antibiotic.