Solithromycin (CEM-101) is a new fluoroquinolone 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. We tested to see if there is a potential for use in the treatment of malaria.

Solithromycin was compared by the semi-automated microdilution assay against intra-erythrocytic forms of P. falciparum derived from asynchronous cultures of the strain NF54, essentially as described (Mattie 1990). Parasite growth over 120h was measured by the incorporation of radiolabelled [3H] hypoxanthine (in hypoxanthine-free culture medium) added 24 hours prior to the termination of the test. Cultures were washed onto 0.45 µm filters and washed with distilled water. The radioactivity was counted the results recorded as counts per minute (cpm) per well at each drug concentration and expressed as a percentage of the untreated controls. Fifty percent inhibitory concentrations (IC₅₀) were estimated by linear interpolation (Huber 1993).

Method of Infection and Treatment of Animals

In vivo antimalarial efficacy studies were performed in C57BL/6 mice infected with Plasmodium berghei strain NF54, essentially as described (Matile 1990). The culture medium was a modification of that previously described (Dorn 1995, Trager 1976). Human erythrocytes served as host cells. The cultures were kept at 37°C in an atmosphere of 3% CO₂ and 97% N₂ in humidified modular chambers. Drug testing was carried out in 96-well microtiter plates.

In vitro Antimalarial Activity

Compounds were tested against intra-erythrocytic forms of P. falciparum derived from asynchronous stock cultures of the strain NF54 (airport strain of unknown origin), essentially as described (Desjardins 1979, Mattie 1990). The culture medium was a modification of that previously described (Dorn 1995, Trager 1976). Human erythrocytes served as host cells. The cultures were kept at 37°C in an atmosphere of 3% CO₂ and 97% N₂ in humidified modular chambers. Drug testing was carried out in 96-well microtiter plates. The compounds were dissolved prediluted in hypoxanthine-free culture medium and tested in duplicate over a 64-fold range. After addition of an equal volume of parasite culture with an initial parasitemia of 5% erythrocyte suspension, the test plates were incubated under the conditions described above for 72 hours (classical approach) or 120 hours.

Results

Solithromycin, clindamycin and azithromycin treatment at 4×100 mg/kg resulted in extended survival for clindamycin to 18-20 days. Azithromycin extended survival to 24-30 days but was not considered curative as parasites were still present by microscopy (Table 5). Solithromycin was curative with both 30 day survival and negative microscopic parasites, since a compound is considered curative if the animal survives up to Day 30 after infection with no detectable parasites by microscopy (Tables 4 and 5).

Discussion/Conclusions

- Solithromycin (CEM-101) showed delayed killing in vitro with little activity in the 72 hour and 96 hour assay.
- Solithromycin showed better activity than clindamycin, chloroquine, and artesunate in the 120 hour assay.
- Solithromycin dosed daily at 100 mg/kg for four days cured mice of P. berghei infection, unlike clindamycin or azithromycin.
- Solithromycin has activity similar to artesunate, which has demonstrated 30 day cures with a 4×100 mg/kg dose in this model.
- Solithromycin is active, in vitro, against multidrug resistant and azithromycin-resistant strains of P. falciparum.
- Solithromycin is the most active protein synthesis inhibitor in vitro and in vivo against Plasmodium species.

References
