Comparison of CEM-101 Metabolism in Mice, Rats, Monkeys and Human

Abstract A-687

D. Pereira*, T Degenhardt, P Fernandes
Cempra Pharmaceuticals, Chapel Hill, NC

Background:
Pharmacokinetic (PK) and toxicology studies in animal models are expected to be predictive of human safety and exposure. The metabolism of solithromycin (CEM-101), a potent new fluoroketolide was studied in mice, rats, monkeys and humans.

Methods:
CD-1 mice, Sprague Dawley rats and cynomologus monkeys were dosed by oral gavage with repeat doses ranging from 20 to 100 mg/kg in mice and rats (7 days) and in monkeys (28 days). In Phase 1 multidose studies, human subjects were dosed with 200 to 600 mg for 7 days. PK of CEM-101 and metabolites were evaluated.

Results:
Two major metabolites were identified; N-Acetyl-CEM-101 and CEM-214. N-acetyl-CEM-101 is as active as CEM-101 against macrolide susceptible bacteria; however against erm and mef strains it is 2-32 fold less active. CEM-214 is significantly less active (16-64 fold) than CEM-101. The formation of these metabolites is significantly different in each animal species (Figure 2). Surprisingly, the metabolism of CEM-101 in mice mirrors that found in humans, where CEM-101 is the predominant species and very little of these two metabolites are formed.

Figure 1. The Day 1 Plasma Cmax of Each Metabolite:

Conclusions:
Unlike other macrolides, the metabolism of CEM-101 in human is significantly different than that in monkeys and rats and is similar to mice. These results must be borne in mind while interpreting data from animal studies.