50 YEARS ICAAC
BOSTON | SEPTEMBER 12–15, 2010
A-687

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

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2010 ICAAC, Boston, MA
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## Abstract

**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 to100 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.
**Conclusion:** 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.

## Introduction

Solithromycin (CEM-101), a novel fluoroketolide antimicrobial agent, has demonstrated substantial activity against both susceptible and macrolide resistant bacterial strains *in vitro* susceptibility testing (1-3). As part of the development of solithromycin the metabolism of solithromycin was investigated in mice, rats, monkeys and humans.

## Materials and Methods

CD-1 mice, Sprague Dawley rats and cynomologus monkeys were dosed once daily by oral gavage with repeat doses ranging from 20 to100 mg/kg in mice and rats (7 days) and in monkeys (28 days). In Phase 1 multidose studies, human subjects were dosed once daily with 200 to 600 mg for 7 days. PK of solithromycin and metabolites were evaluated. Blood samples were collected and analyzed by LC-MS. Authentic metabolite standards were prepared and characterized.

## Results

Solithromycin is metabolized to two primary metabolites, N-Acetyl-CEM-101 and CEM-214 in mice, rats, and monkeys. N-Acetyl-CEM-101 is formed by acetylation of the amino group of the aminophenyl-1,2,3-triazole moiety of solithromycin. CEM-214 is formed by loss of the aminophenyl-1,2,3-triazole moiety of solithromycin. The structures of the metabolites are shown in Figure 3. The two major metabolites are observed in all species however the degree of metabolism between species showed significant differences. In rats, solithromycin is extensively acetylated but the cleaved product was only detected at low levels. In rats, solithromycin is rapidly converted into N-Acetyl-CEM-101 which reaches a maximum concentration in approximately five hours as shown in Figure 1. Unlike rats, in monkeys both N-Acetyl-CEM-101 and the CEM-214 are present in substantial amounts. Conversely, in both mice and humans N-Acetyl-CEM-101 and CEM-214 are not found in significant amounts. The degree of metabolism in each species is shown in Figure 2.

**Figure 1. Time Course of CEM-101 Metabolite Formation in Rats**

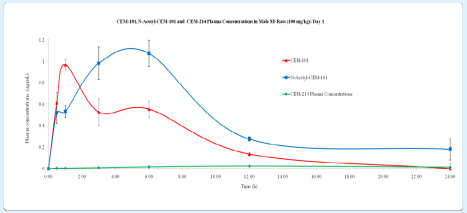
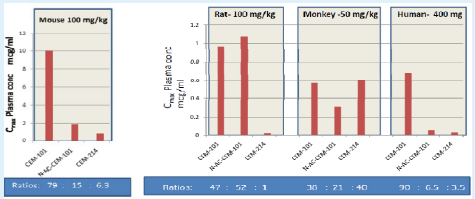



**Figure 2. The Degree of Metabolism in Each Species**



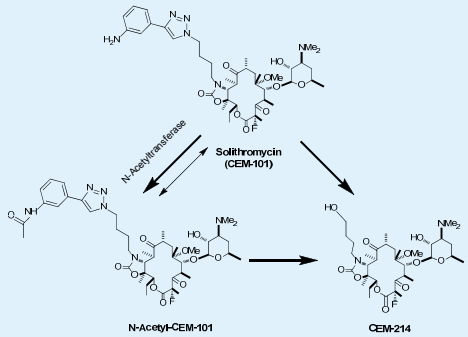

Both metabolites retain the macrolide core and have activity similar to solithromycin against susceptible strains of *S. pneumoniae*. The data is presented in Table 1. Against strains with *mef* resistance, N-Acetyl-CEM-101 MICs were typically decreased 1- to 8-fold relative to the parent compound, but activity was retained against *erm*B strains. CEM-214 MICs were decreased 2- to 64-fold for *erm*B and *mef* strains compared to solithromycin (CEM-101). Activity against gram-negative organisms was reduced for both metabolites.

The metabolism of solithromycin and the reduced activity of the major metabolites must be taken into account in efficacy and toxicity studies in different animal species, particularly the rat.

**Table 1. MIC's of CEM-101 and the major metabolites**

| Organism | Phenotype/ Genotype | CEM-101 | N-Acetyl-CEM-101 | CEM-214 |
|---|---|---|---|---|
| ***S. pneumoniae*** | | | | |
| ATCC 49619 | Pen-I; WT | ≤0.06 | ≤0.015 | 0.03 |
| 117-20B | WT | ≤0.06 | ≤0.015 | 0.03 |
| 014-4331A | *mef*A | 0.25 | 0.5 | 1 |
| 007-4589A | *erm*B | ≤0.06 | ≤0.015 | 2 |
| 120-1037B | *erm*B+ *mef*A | 0.12 | 16 | >16 |
| ***S. pyogenes*** | | | | |
| ATCC 19615 | QC | ≤0.015 | - | 0.03 |
| 129-7129A | ermA | ≤0.015 | - | 0.06 |
| 089-14217 | ermB | 0.12 | - | >16 |
| ***S. aureus*** | | | | |
| 024-11A | WT | ≤0.06 | 0.06 | 0.25 |
| ATCC 29213 | WT | ≤0.06 | 0.06 | 0.25 |
| BAA-977 | ermA | ≤0.06 | 0.06 | 0.25 |
| CAP D-05 | ermA | >64 | >16 | >16 |
| ***E. coli*** | | | | |
| | WT | 8 | 16 | >16 |

**Figure 3. Structures and Possible Route of Formation of Major Metabolites of CEM-101**




## Conclusions

**Conclusion:** Unlike other macrolides, the metabolism of CEM-101 in humans is significantly different than that in monkeys and rats, and is similar to mice. The major metabolites are not formed in significant amounts in humans or mice. These metabolism results must be borne in mind when interpreting data from animal studies and using them in predicting the effects of solithromycin in humans.

## References

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