

Population pharmacokinetic analysis of ciprofloxacin in ICU patients

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Background and Objectives

Background: Although ciprofloxacin clearance (CL_{CIP}) substantially depends on kidney function in healthy volunteers, there is a weak relationship to measured creatinine clearance ($CRCL_M$) in critically ill subjects. Pathophysiological changes affect the pharmacokinetics of ciprofloxacin.

Objectives: To identify the best predictors of ciprofloxacin pharmacokinetics concerning kidney and liver function in ICU patients. To assess the need for dose reductions in isolated/combined kidney and liver dysfunction in critically ill patients.

Methods

Study design: A prospective observational clinical study was carried out on 15 ICU patients treated with intravenous infusions of 400 mg ciprofloxacin twice daily. 444 plasma concentrations were collected on four days. Clinical chemistry and hematology parameters were measured once per day.

Data analysis: A population pharmacokinetic model was developed stepwise using non-linear mixed effects modelling (NONMEM 7.4.1). We have first investigated the relationships between CL_{CIP} , $CRCL_M$ and Cockcroft-Gault creatinine clearance ($CRCL_{CG}$), and then evaluated liver function parameters [1]. A simulation study was conducted to integrate the new and previously published models [2-4].

Results

A two-compartment model with linear elimination and a combined error model appropriately described the pharmacokinetics of ciprofloxacin. Clearance and central volume of distribution increased from the first (16.2 [13.4 – 19.7] L/h and 24.2 [13.9-36.4] L) to the fourth (20.9 [17.8 – 25.8] L/h and 33.5 [21.3-48.8] L) study day (median [95% CI] from bootstrap), suggesting alterations of the pharmacokinetics of ciprofloxacin throughout the treatment course.

Bilirubin had the clearest relationship among liver parameters to ciprofloxacin clearance. $CRCL_M$ did not improve the model significantly while $CRCL_{CG}$ exhibited a stable relationship to clearance. Age and sex, but neither plasma creatinine nor body weight, had a clear relationship to ciprofloxacin clearance. The final covariate model consisted of age, sex and bilirubin (Eq. 1), which in total explained 60% of IIV (Figure 1).

$$\text{Eq. 1 } CL = TVCL * [1 + (49 - age) * 0.0153] * [1 - sex * 0.431] * [bili/1.85]^{-0.431}$$

The increase in the risk of overexposure ($AUC > 250 \text{ mg} \cdot \text{h/L}$) was small for subjects with reduced ($< 30 \text{ mL/min}$: risk of 0.7%) versus normal ($> 90 \text{ mL/min}$: risk of 0.06%) $CRCL_{CG}$, while the risk was remarkably increased in elderly female subjects with elevated bilirubin levels (risk of about 40% for 70 years old women with bilirubin 4 mg/dL) (Figure 2).

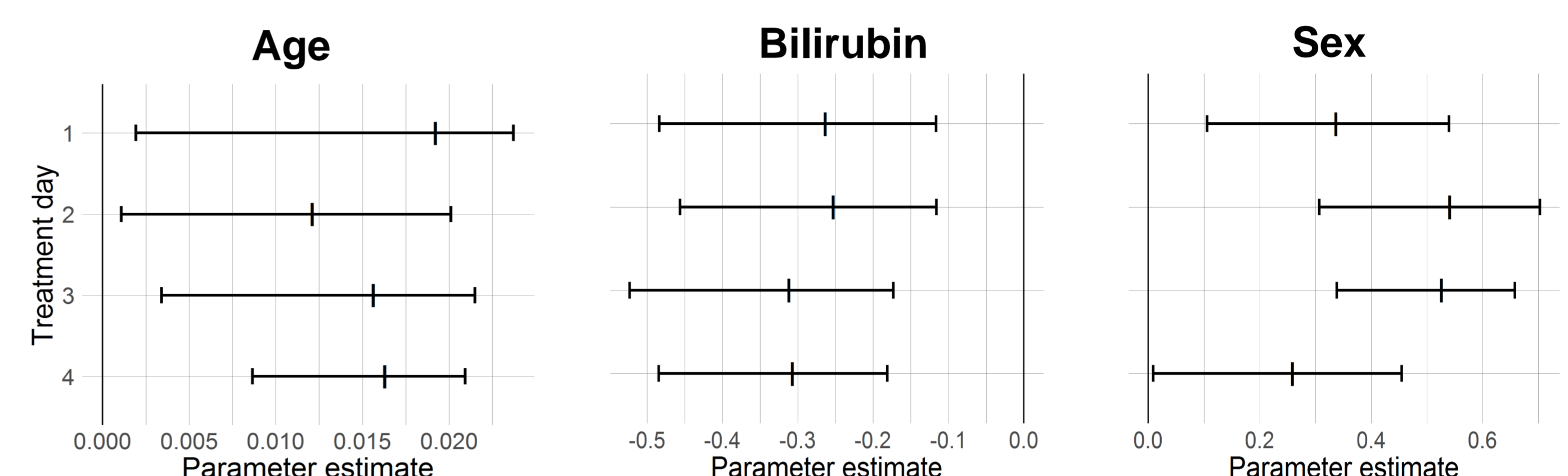
Daily doses of 1200 mg reached a PTA of 69% for an MIC of 0.5 mg/L while doses of 800 (400) mg/day were sufficient to attain a PTA of at least 90% for an MIC of 0.25 (0.125) mg/L in the entire population (Figure 3).

Conclusion

Total bilirubin, age and sex might be more relevant to predict ciprofloxacin pharmacokinetics in ICU patients. A dose reduction based on creatinine clearance is not supported while a reduction to 400 mg seems reasonable for female subjects with higher age and increased bilirubin if MIC values of the causative strains are $\leq 0.25 \text{ mg/L}$.

Results

Figure 1. Confidence intervals and medians of estimates of covariates



95% confidence intervals (bars) and medians (vertical lines) of estimated covariate parameters for age, bilirubin and sex based on a bootstrap with 1,000 samples for study days 1 to 4, respectively.

Figure 2. Probability of exceeding AUC limits of 250 mg*h/L depending on age, sex and bilirubin for a daily dose of 1200 mg ciprofloxacin

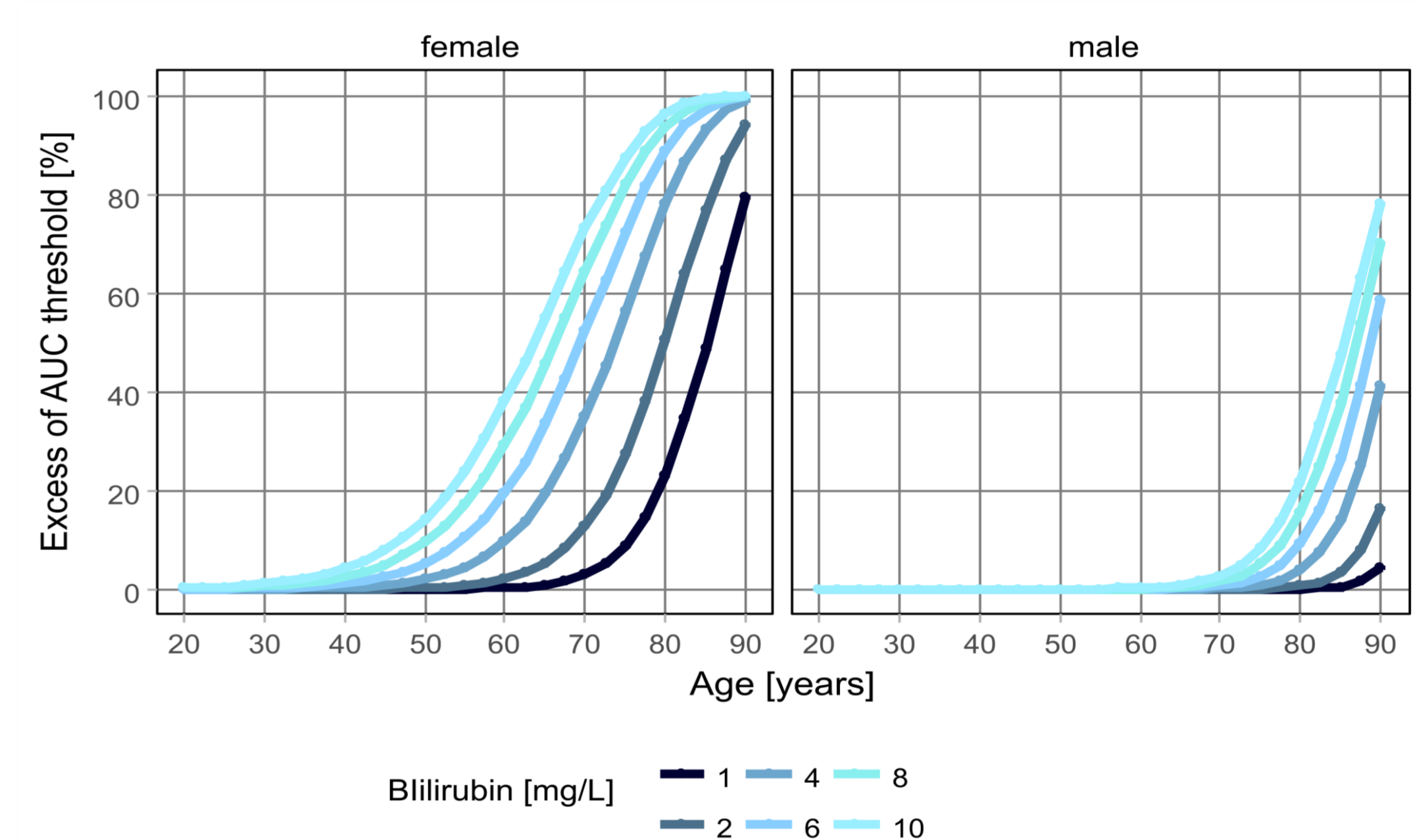
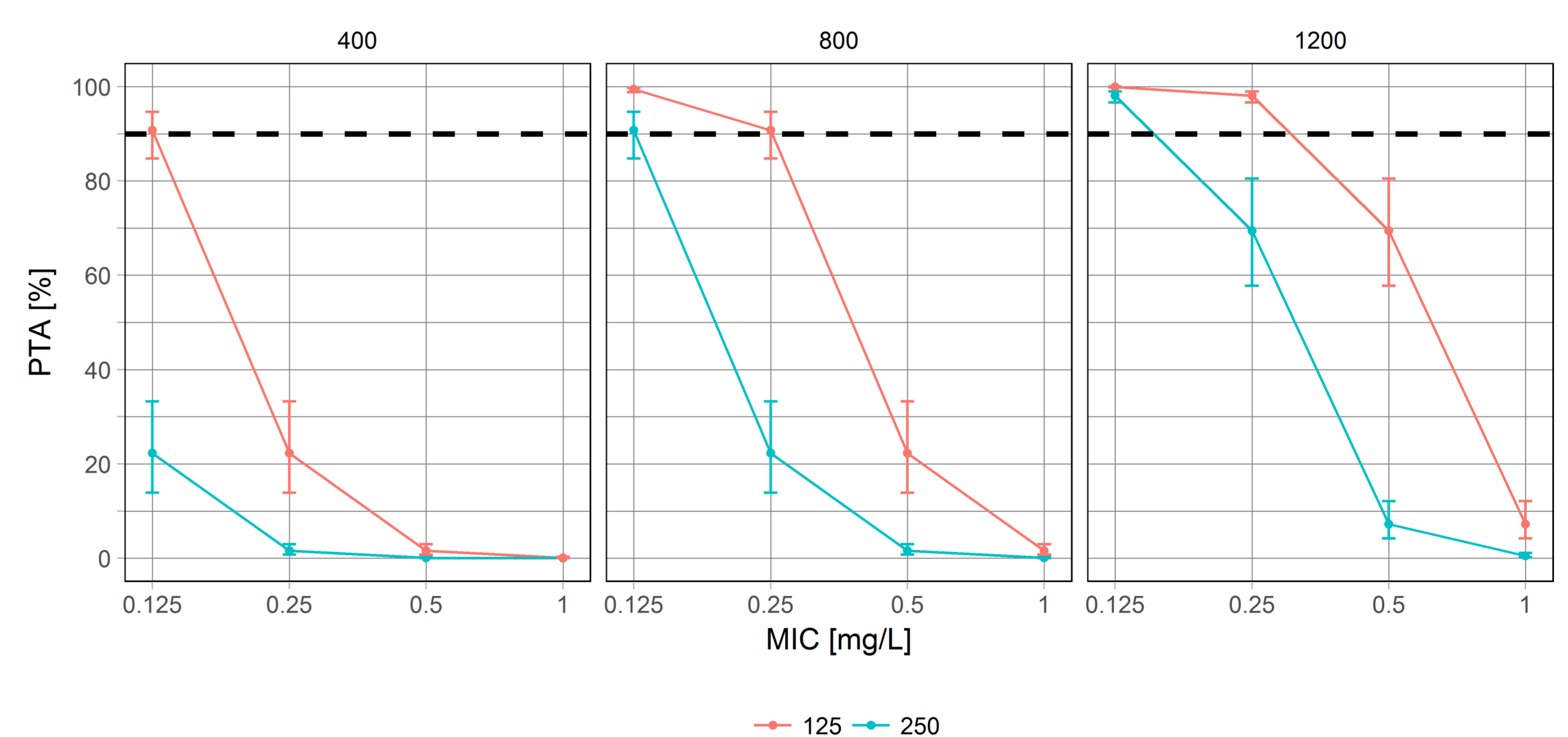


Figure 3. PTAs based on the joint evaluation of four models



The dashed line indicates the target PTA of 90%

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