

Population pharmacokinetic analyses of regorafenib and capecitabine in patients with locally advanced rectal cancer (SAKK 41/16 RECAP)

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Background and objectives

- Despite anticancer therapy, patients with locally advanced rectal cancer frequently suffer from relapses.
- Recent studies in which sorafenib or cediranib, both tyrosine kinase inhibitors (TKI) were added to the standard therapy consisting of capecitabine, a prodrug of the antimetabolite 5-fluourouracil, showed promising results [1, 2].
- Regorafenib, a multitarget TKI was investigated in combination with capecitabine in the phase Ib trial “**Neoadjuvant treatment with Regorafenib and Capecitabine combined with radiotherapy in locally advanced rectal cancer (SAKK 41/16 RECAP)**” (NCT02910843) conducted by the Swiss Group for Clinical Cancer Research (SAKK).
- So far, the combination of capecitabine and regorafenib has never been investigated before.
- Population pharmacokinetic (PopPK) models of both regorafenib and capecitabine and their metabolites were implemented in this study to analyze possible drug-drug interactions (DDI).

Methods

- Pharmacokinetic data from 12 patients enrolled in the RECAP trial were used for model development using NONMEM.
- Patients received 825 mg/m² capecitabine twice daily from day 1 to 38.
- Regorafenib was administered in three dose levels (40, 80 and 120 mg) once daily from day 1 to 14 and day 22 to 35.
- Plasma samples were collected on day 1 (0.5, 1, 2, 3, 4 and 6 h after dosing), followed by random sampling on day 2, 4, 8, 15, 22, 29 and 36.
- Plasma concentrations of regorafenib and its metabolites M-2 and M-5 and plasma concentrations of capecitabine and its metabolites 5'-deoxy-5-fluorocytidine (DFCR) and 5'-deoxy-5-fluorouridine (DFUR) were quantified using validated assays by liquid chromatography coupled to tandem mass spectrometry [3, 4].
- PopPK parent-metabolite models were built sequentially and used to generate drug exposure parameters (concentrations over time, cumulative area under the curve [AUC] over time).
- These parameters were tested as covariates within the respective other PopPK model in order to investigate possible DDI.
- In addition, demographic data (e.g. sex, age, body surface area), bilirubin and hemoglobin were tested as covariates as well.
- Model evaluation was performed using goodness-of-fit plots and visual predictive checks.

Results

Regorafenib

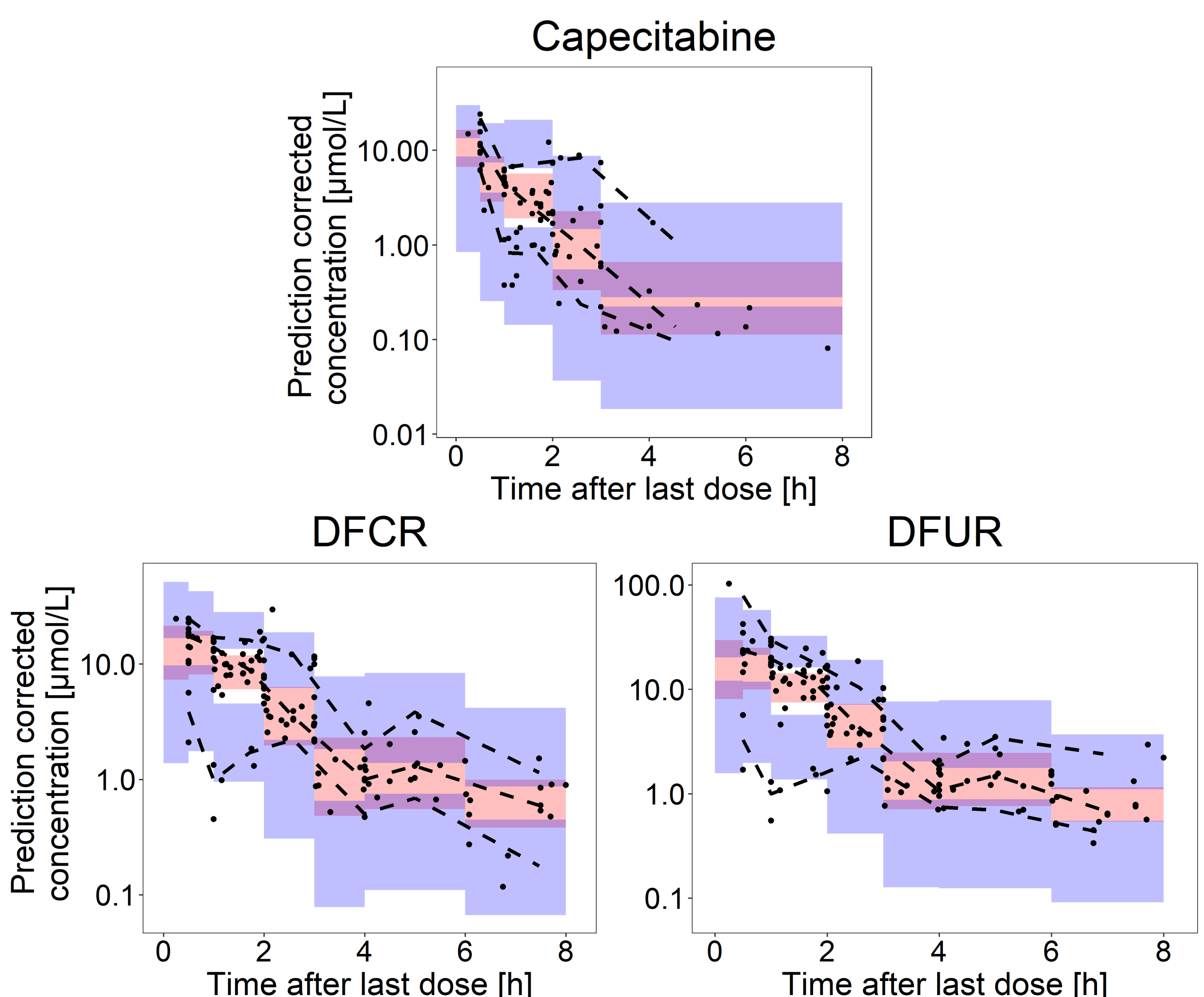
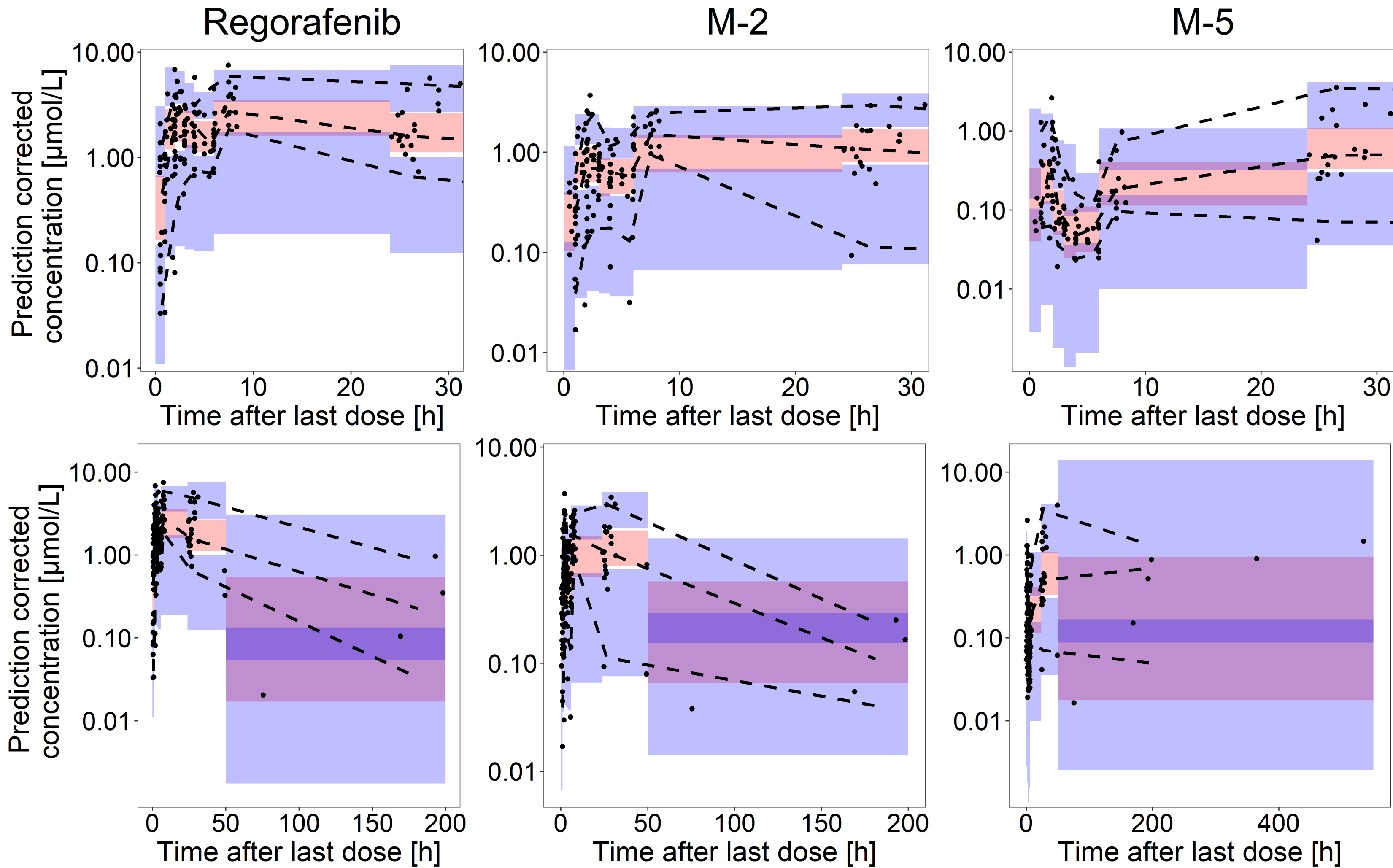
- Regorafenib, M-2 and M-5 pharmacokinetics were described by two-compartment models.
- A transit compartment model was used for the description of regorafenib absorption.
- The formation of M-2 from regorafenib was best described by presystemic metabolism.
- Since the fractions metabolized were unknown, it was assumed that M-2 and M-5 volumes of distribution were the same as that of regorafenib.
- Model parameters were precisely estimated (relative standard errors <30%, except for the shared volume of distribution).

Capecitabine

- Capecitabine, DFCR and DFUR pharmacokinetics were described by one-compartment models.
- Parallel first- and zero-order absorption processes were chosen for the capecitabine absorption model.
- Model parameters were precisely estimated (relative standard errors <30%).
- Regorafenib M-2 cumulative AUC over time as linear covariate significantly improved the capecitabine model fit and reduced capecitabine clearance estimates:

$$CL_{Pop,Capecitabine} = 272 \frac{L}{h} - 0.119 \times AUC_{M-2,cumulative} \left[\frac{\mu mol \times h}{L} \right]$$

Visual Predictive Checks



Conclusions

- The developed PopPK models of regorafenib, capecitabine and their respective metabolites described the observed data well.
- The influence by M-2 cumulative AUC over time on capecitabine clearance suggests a decreased formation of the metabolite 5-fluorouracil by the addition of regorafenib.
- The inhibition of ABC efflux transporters by regorafenib could be a possible explanation for the current finding assuming that M-2 inhibits these transporters like regorafenib [5–7].

Acknowledgements

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