

Validation of the novel Basel Phenotyping Cocktail Capsule – a useful tool for quantifying human CYP450 metabolism in physiological and semi-physiological models

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Objectives

Cytochrome P450 (CYP) are the main metabolic pathway of numerous endogenous and xenobiotic compounds. Hence, estimates of CYP activity is relevant for clinical decision making in drug therapy as well as in drug development. Drug interactions and disease states, such as inflammation or chronic liver disease, potentially alter CYP function substantially, regardless of the underlying genotype. Altered CYP function may result in changed systemic drug exposure, which in its extremes causes either increased pharmacodynamic effects, even toxicity or therapeutic failure. Hence, attempts were made assessing CYP phenotype for estimating metabolic capacity in humans in vivo. The application of CYP isoform specific probe drugs has been shown to be a safe and reliable phenotyping test: By calculating the ratio (i.e. the metabolic ratio, MR) between concentrations of parent drug and metabolite the capacity of CYP under investigation can be assessed [1][2]. As we have shown, quantitative ranking of metabolism status can be done by putting MRs in relation to ratios obtained in induced and inhibited states [2]

We selected and tested 6 CYP isoform-selective probe drugs in a clinical trial, combined in a single capsule, to reduce drug amount to low- or even micro-doses and to allow a convenient administration [3]. The aim of the present study was to select CYP isoform-selective probe drugs, combined in a single capsule and obtain PK profiles in healthy volunteers, check for tolerability, and calculate MRs. In addition, we aimed to determine a reduced optimal sampling regimen for the newly defined probe drug cocktail.

METHODS

We performed an open-label randomized 2-period crossover PK study in 12 healthy volunteers using the Basel phenotyping cocktail capsule. Non-compartmental analysis was performed for each compound using the package NonCompart in R to obtain basic PK parameters and calculate MR for each sampling time point and AUC_{0-12h}. As a preliminary analysis, we fitted a linear model to determine sampling time points which correlate best with MRs calculated of AUC_{0-12h}.

RESULTS

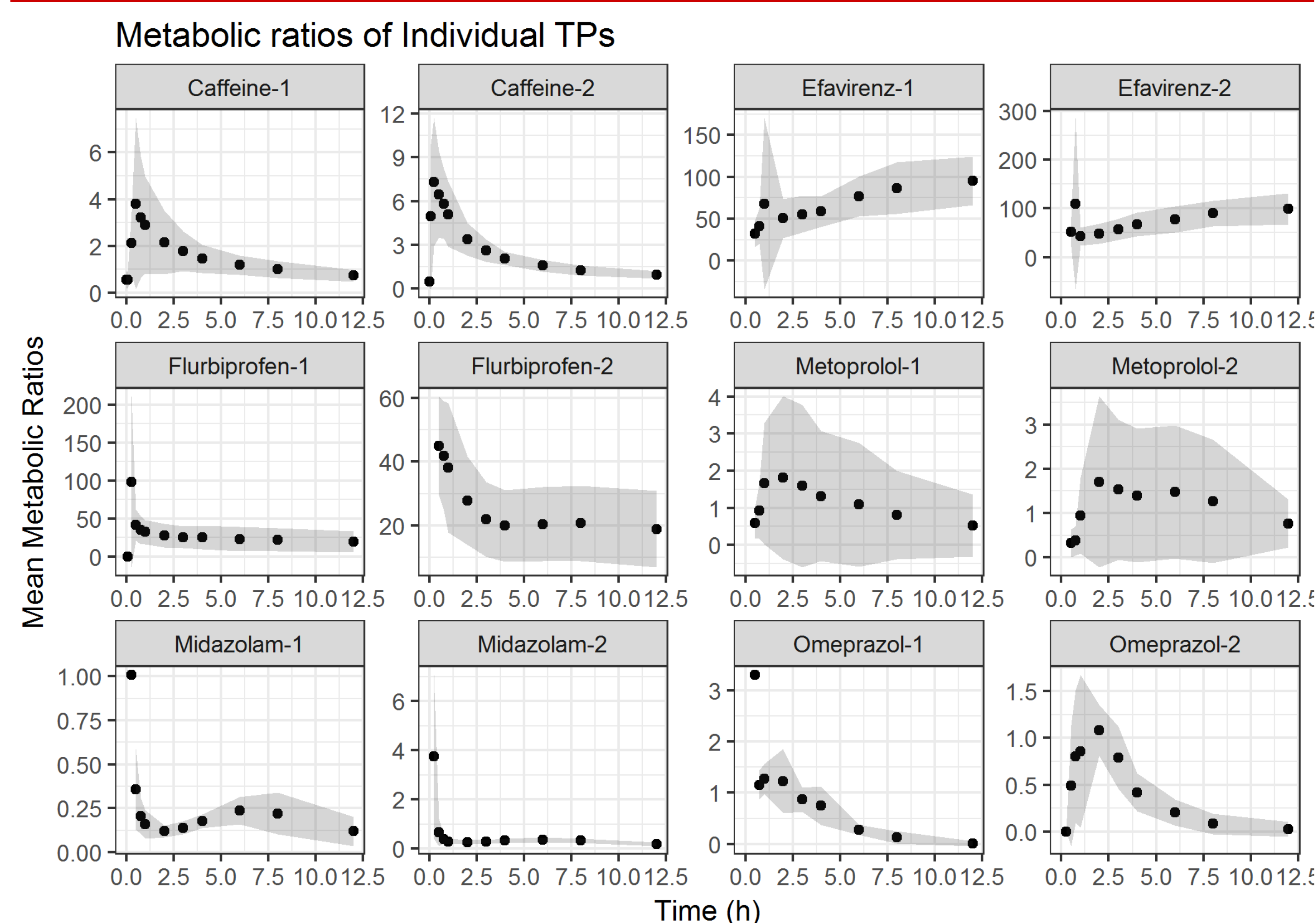


Fig.1 Single time point ratios: Capsule vs individual components. Capsule formulation is indicated by compound name and «1», individual components by compound name and «2». Black dots indicate mean MR values, grey ribbon indicates +/- SD.

PK profiles from parent compound and metabolite were obtained and a non-compartmental analysis was performed. MRs of single TP measurements as well as MRs of AUC_{0-12h} were calculated. We found for flurbiprofen (CYP2C9) one subject with rapid metabolizing phenotype, while for metoprolol (CYP2D6) there were two poor metabolizer phenotypes.

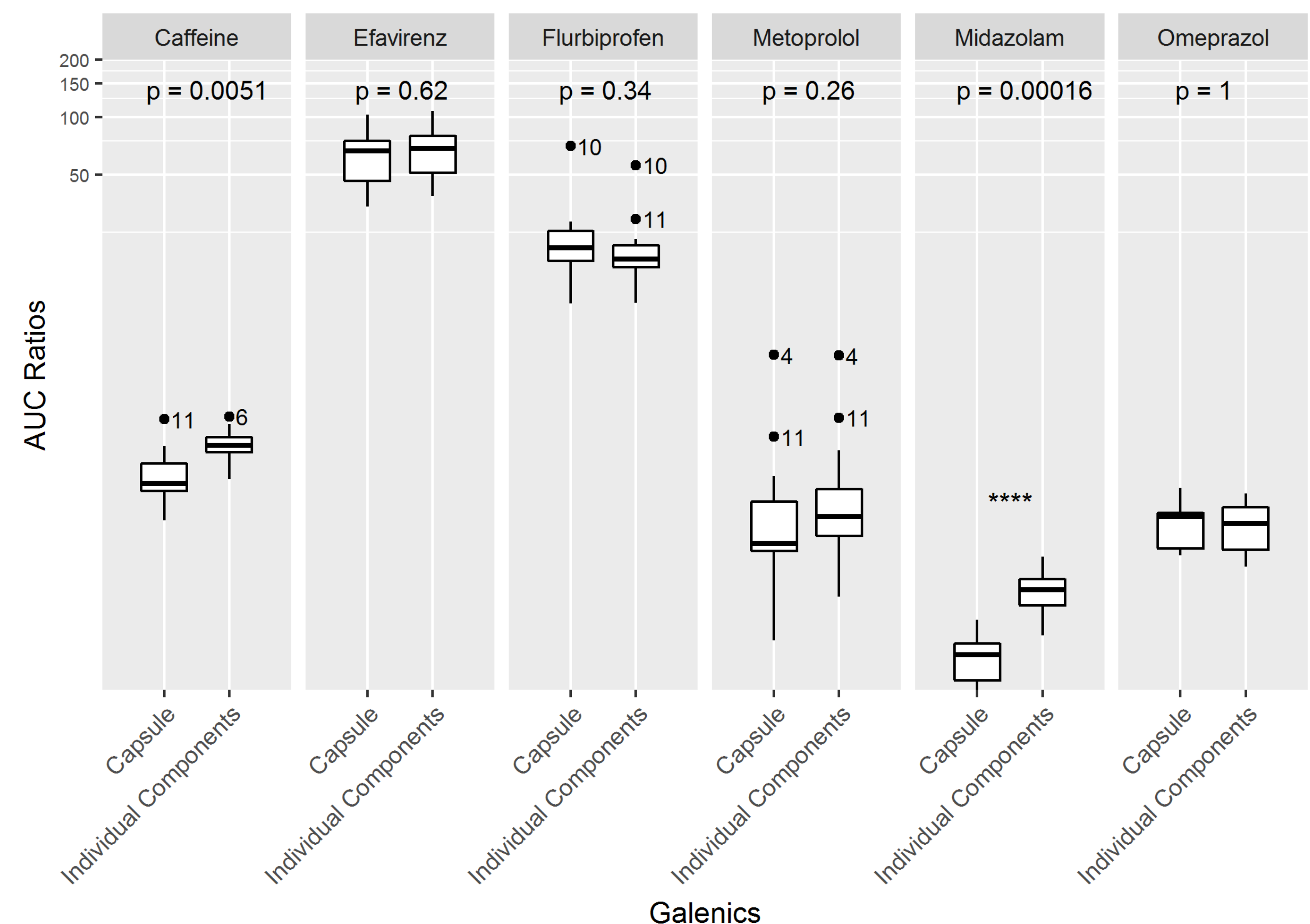


Fig. AUC_{0-12h} ratios: Capsule vs Individual components. No statistically significant difference between AUC ratios of the two formulations, except for midazolam ($p < 0.001$). This could be caused by a formulation effect as we used a midazolam-solution as individual component (vs mini tablets in the capsule), which is faster absorbed and, in addition, might have escaped some first pass metabolism, as it was dosed into the buccal cavity.

Because of large differences in PK profiles, sampling time points could not be collapsed to a single measurement for the phenotyping cocktail. For the capsule formulation, MRs at 2h correlated best with midazolam (CYP3A4, adj.R²: 0.88, $p < 0.001$) and caffeine (CYP1A2, adj.R²: 0.94, $p < 0.001$) AUC ratios, while for efavirenz (CYP2B6, adj.R²: 0.9, $p < 0.001$), flurbiprofen (CYP2C9, adj.R²: 0.99, $p < 0.001$), and omeprazole (CYP2C19, adj.R²: 0.75, $p < 0.001$) best fits were achieved at 6h. Metoprolol showed excellent fits at both of these time points (CYP2D6, adj.R²: 0.99, $p < 0.001$).

These proposed sampling time points shifted for individually administered components to 1h for midazolam (CYP3A4, adj.R²: 0.88, $p < 0.001$) and omeprazole (CYP2C19, adj.R²: 0.74, $p < 0.001$) and to 6h post dose for caffeine (CYP1A2, adj.R²: 0.76, $p < 0.001$) efavirenz (CYP2B6, adj.R²: 0.96, $p < 0.001$), flurbiprofen (CYP2C9, adj.R²: 0.99, $p < 0.001$), and metoprolol (CYP2D6, adj.R²: 0.99, $p < 0.001$), respectively.

Conclusion

The information of such experiments is valuable to individualize and inform physiological and semiphysiological models. Further studies are currently ongoing in our group to characterize patients at different stages of liver cirrhosis by means of the Basel Phenotyping capsule. In a next step, we plan to adapt a Population Optimum Design of Experiments (PODE) approach to predict MR_{AUC} from a minimum of PK samples.

REFERENCES

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