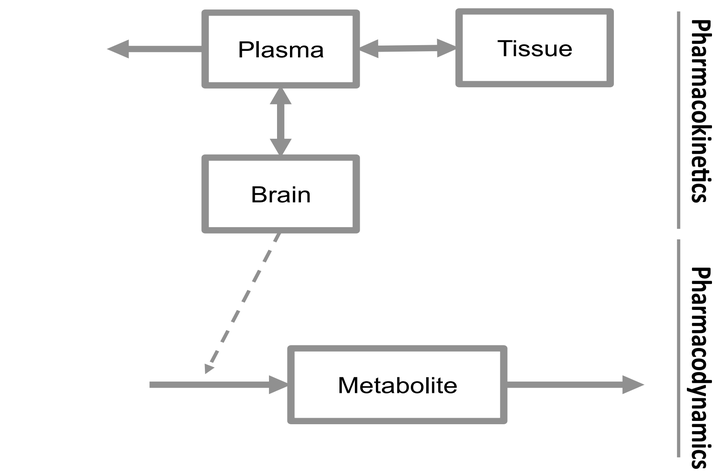
QUANTITATIVE PHARMACOLOGY OF 30 POTENTIAL BIOMARKERS FOR REMOXIPRIDE

W. van den Brink, R. Hartman, M. de Bruin, B. Gonzalez, J. Elassaiss-Schaap, P.H. van der Graaf, T. Hankemeier, E.C.M. de Lange

Cluster of Systems Pharmacology, LACDR, Leiden University, Leiden, The Netherlands

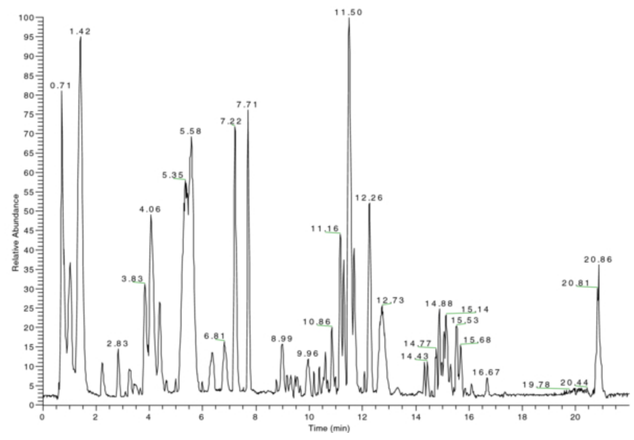
Background & Aim

PKPD modelling



- Provides quantitative insights in the relation between dose and biomarker response (e.g. efficacy, turnover rates)
- Guides dose selection for early clinical trials

Pharmacometabolomics



- Enables discovery of biomarkers of drug effect in a holistic manner
- Reveals drug-specific fingerprint biomarkers

Can we find a quantitative fingerprint biomarker of remoxipride?

Methods & Results

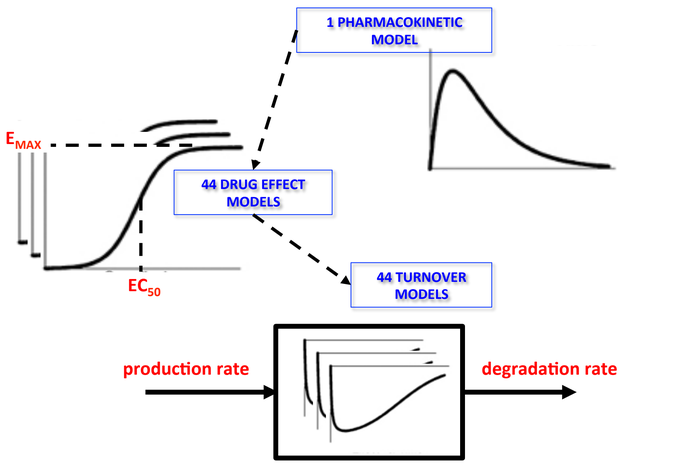


Figure 1. Schematic representation of 44 PKPD models that were fitted to 44 metabolites. Plasma and brain extracellular fluid samples were obtained in an experiment with different doses of the dopamine D2 antagonist remoxipride administered to rats. These samples were analysed for remoxipride and biogenic amines.

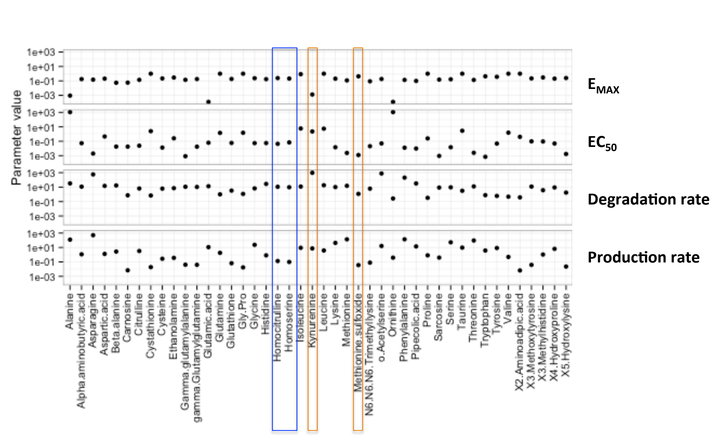


Figure 2. Overview of the model parameter estimates for each single metabolite. The blue box shows two metabolites with similar parameters and the orange boxes two metabolites with different parameter sets.

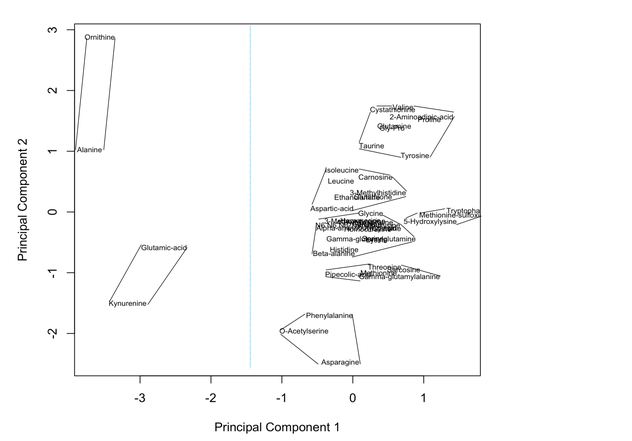


Figure 3. 8 clusters were identified with the 6 clusters on the right representing a response. Each cluster followed a different longitudinal dose-response pattern. A fingerprint PKPD model was developed with separate sub-models (drug effect + turnover) for each of the clusters.

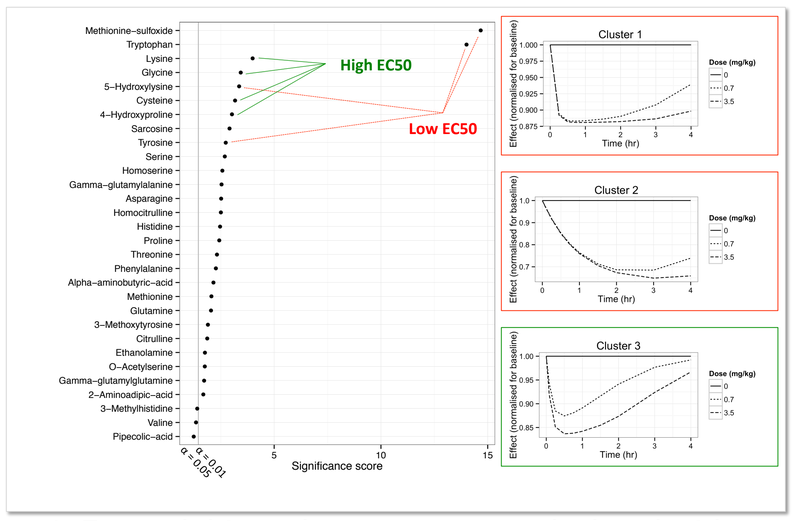


Figure 4. For each biomarker a score was calculated with a score > 1 showing a significant effect of remoxipride on the biomarker ($p < 0.05$). The fingerprint PKPD model informed on biomarker clusters with high EC50 (green) and low EC50 (red). This is visualised by the different dose response patterns on the right.

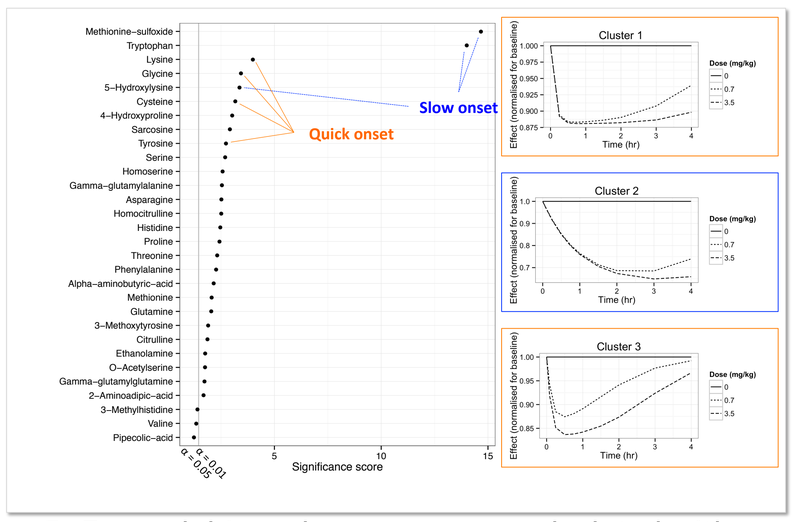


Figure 5. For each biomarker a score was calculated with a score > 1 showing a significant effect of remoxipride on the biomarker ($p < 0.05$). The fingerprint PKPD model informed onbiomarker clusters with slow onset of effect (blue) and quick onset of effect (orange). This is visualised by the different longitudinal profiles on the right

Conclusion

- 30 potential biomarkers were identified representing remoxipride fingerprint pharmacology
  - We could distinguish between biomarkers for high versus low EC50 (e.g. tyrosine versus glycine)
  - We could distinguish between biomarkers for quick versus slow onset of effect (e.g. tyrosine versus tryptophan)
- Additional studies with dopamine antagonists and agonists should reveal a dopamine-specific fingerprint biomarker that van be used to evaluate other compounds on dopaminergic activity

Contact: brinkwjvanden@lacdr.leidenuniv.nl

Universiteit Leiden The Netherlands

LACDR