Model-based analysis of biomarkers in the evaluation of cardiovascular safety.

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Introduction: Cyclo-oxygenase inhibitors remain widely used. However, concerns regarding the long term safety of these compounds have shifted from the established association with ulcerative processes to cardiovascular adverse events [1]. As understanding of biomarkers and their relationships to cardiovascular safety improves, the early characterisation of drug-induced effects on biomarkers becomes an important tool for the evaluation of safety. Since long term adverse events have become a major regulatory concern, it is also paramount to identify tools which enable quantitative assessment of risk and risk-benefit ratio associated with these therapies [2].

Currently used approaches rely on empirical evidence and are therefore unsuitable to allow accurate characterisation of long term safety profile. Here we use naproxen as a paradigm to assess the ability of current preclinical experimental designs to provide necessary information for the prospective prediction of drug-induced effects on biomarkers in humans using nonlinear mixed effects modelling (NLME). The aim is to demonstrate NLME as a feasible alternative to empirical methods and assess the accuracy of predicted biomarker concentrations in humans.

Methods: A rodent general toxicity study was conducted according to standard practices with the exception of biomarker samples being collected from animals at the time of pharmacokinetic sampling. A pharmacokinetic (PK) model was fit to the data and combined with prostaglandin E₂ (PGE₂) and thromboxane B₂ (TXB₂) to obtain a full pharmacokinetic-pharmacodynamic (PKPD) model. Translation of preclinical findings into drug effects in humans was then performed taking into account differences in the therapeutic exposure observed in patients. The accuracy and precision of predictions were assessed using literature data in humans.

Results: The PKPD model yields parameter estimates with adequate precision for the purposes of simulation and extrapolation, including estimates of between-subject variability. The predicted cumulative AUC, which was used as measure of drug exposure, was comparable to the observed data in the published literature.

Discussion/conclusions: A model-based approach was used which enables the characterisation of pharmacokinetics and PKPD relationships for relevant biomarkers without increasing the experimental burden of preclinical cardiovascular safety experiments. Integrated NLME analysis is recommended as the decision tool in the early assessment of cardiovascular risk.
