Title: Mechanism-based pharmacokinetic-pharmacodynamic modeling of erythroferrone offers an early prediction of long-term efficacy of erythropoietin in chemotherapy-induced anemia rats.

Author: Lin Zhang (1), Peng Xu (1), Xiaoyu Yan (1)
Institution: (1) School of Pharmacy, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong SAR.

Introduction:

Recombinant human erythropoietin (rHuEPO) has been used to treat chemotherapy-induced anemia, although with varying responsiveness [1]. Although hemoglobin (HGB) is the gold standard biomarker for evaluating response following rHuEPO treatment, the HGB response can take as long as two weeks, leading to a prolonged titration period and delaying chemotherapy. Erythroferrone (ERFE), an endogenous hormone, increases iron availability for erythropoiesis by lowering hepcidin levels [2]. ERFE is secreted by erythroid cells in response to erythropoietin (EPO), thus could potentially serve as an early biomarker to allow for early dose titration and prediction of rHuEPO responsiveness.

Objectives:

The current study aims to 1) develop a mechanism-based PK/PD model to quantify ERFE and HGB response to rHuEPO treatment in CIA rats 2) investigate the correlation between ERFE and HGB and the predictive ability of ERFE in predicting rHuEPO responsiveness.

Methods:

A single dose of rHuEPO (1350 IU/kg and 450 IU/kg) was given to carboplatin-induced anemia in rats. To simultaneously quantify both ERFE and HGB responses to rHuEPO, a pharmacokinetics and pharmacodynamics (PKPD) model was developed. A previously developed chemotherapy-induced myelosuppression model [3] was used as the starting point to build a CIA model by including the ERFE model. The model was fitted simultaneously to ERFE and HGB data obtained in rats. To investigate if there is a linear correlation between the change of ERFE and HGB after rHuEPO treatment, we then performed correlation analysis. Receiver operating characteristics (ROC) curve analysis was performed to test the predictive power of ERFE in predicting EPO responsiveness.

Results:

The PK model that best described EPO and Carboplatin was a two-compartment model with nonlinear elimination and a three-compartment model with linear elimination, respectively. The PD model included two sub-models, i.e., a CIA model that is linked by a series of transit compartments representing maturing erythroid cells at different stages, and an ERFE model that is linked to the last transit compartment representing the main cells that produce ERFE. The ERFE response to EPO was best described by an indirect response model with dual-input (i.e., a circadian input assuming cosine behavior and a first-order input) and a linear elimination. The estimated input rate constant (θ_{kin}) for ERFE was 1.4 /h. The estimated circadian mesor (θ_{Rm}) for ERFE was 3.53 ng/mL, representing the mean ERFE baseline of 3.53 ng/mL in CIA rats. The estimated circadian amplitude (θ_{Ra}) for ERFE was 1.13 ng/mL, representing the absolute ERFE change from baseline in the cosine function. The change of ERFE at 10 h after treatment was significantly correlated with the change of HGB by Day 6 in CIA rats after rHuEPO treatment (R = 0.77, P-value = 0.01). The ROC curve analysis identified the change of ERFE as a significant predictor of rHuEPO responsiveness (AUC = 0.88).

Conclusions:

The time course of ERFE and HGB following rHuEPO treatment in CIA rats was accurately characterized by a mechanism-based PK/PD model. The model allowed an accurate estimation of short-term biomarker ERFE as a predictor of HGB response following rHuEPO treatment. The modeling approach supports the development of limited sampling strategies that estimate biomarker profiles with a lower number of samples. This mechanism-based PK/PD model can be a useful add-on to future studies in the field of EPO therapy in anemic patients.

References:

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