Development of a quantitative systems pharmacology model for prediction of mineralcorticoid receptor antagonists-induced hyperkalemia

Tomohisa Nakada1,2, Maithreye Rengaswamy1, Krishnakant Dasika3, Rukmini Kumar3, Ryuta Saito2

1DMPK Research Laboratories, Mitsubishi Tanabe Pharma Corporation, Japan; 2Discovery Technology Laboratories, Mitsubishi Tanabe Pharma Corporation, Japan; 3Vantage Research, India

Objectives: Mineralcorticoid receptor antagonists (MRA) were used for the treatment of hypertension and diabetic nephropathy (DN) in combination with renin angiotensin aldosterone system (RAAS) inhibitors. The objectives in this study were to evaluate predictabilities of MRA effects using a quantitative systems pharmacology (QSP) model of hypertension regulation with RAS incorporating reabsorption of potassium in the renal tubule.

Methods: To describe serum potassium behavior after oral administrations of MRA such as eplerenone, a simulation model for potassium regulation was developed based on a hypertension model with RAAS previously reported1). The model for potassium regulation was verified by being confirmed whether the simulation of losartan therapy can be reproduced with the clinical trial or not2). In MRA therapy, the pharmacokinetics model of MRA was incorporated onto the model to reproduce the plasma concentration-time profile of drugs, and then elevation of serum potassium was simulated to compare with the actual data3).

Results: The serum potassium level during losartan therapy using the model was well predicted to the actual clinical data in DN patients2). In DN patients administered eplerenone (50mg and 100mg, bid) in combination with RAAS inhibitors, mean changes from baseline in glomerular filtration rate (GFR) and urinary-albumin excretion ratio (UACR) were decreased from -3% to -6% and from -28% to -37%, respectively, covering the reported values3). Likewise, the tendency of increases in serum potassium was able to be reproduced using the model.

Conclusions: The QSP model enabled us to predict the efficacy of MRA treatment. These findings suggest to help us minimize the risk of hyperkalemia during MRA therapy and support an effective clinical design for drug development.