Population Pharmacokinetic and Pharmacodynamic Modeling of Ramosetron for the Prophylaxis of Postoperative Nausea and Vomiting

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Objectives: Ramosetron, one of type 3 serotonin receptor antagonists, is used for the prevention and treatment of postoperative nausea and vomiting (PONV). The main objective of this study was to characterize the population pharmacokinetics and pharmacodynamics of ramosetron in adults.

Methods: Fifty elective surgical patients aged 19-80 years received one of an intravenous bolus dose of ramosetron (0.3 mg, 0.45 mg or 0.6 mg) 30 min before the end of surgery. Plasma concentrations of ramosetron in 462 plasma samples were measured, and the Rhodes Index for Nausea, Vomiting and Retching (RINVR) was assessed until 48 h after the administration of ramosetron as a surrogate measure for the antiemetic effect of ramosetron. Plasma concentrations and RINVR scores were analyzed with NONMEM. Based on the principles of allometry, body weight was incorporated in the base pharmacokinetic model, along with fixed allometric exponents. Covariate analysis was performed by means of a stepwise forward inclusion and backward elimination procedure. The exposure-response relationship was evaluated using the linear and sigmoid $E_{\text{max}}$ models.

Results: Pharmacokinetics of ramosetron were best described by a three-compartment mammillary model. Besides the priori-implemented body weight, only age had an effect on metabolic clearance. No other investigated covariates, including sex and other size descriptor (such as LBM) significantly affected the pharmacokinetics of ramosetron. The exposure-response relationship between ramosetron plasma concentration and RINVR score was not reliably described with the linear and sigmoid $E_{\text{max}}$ models.

Conclusions: A population pharmacokinetic model of ramosetron in adults was established and it described the data well. However, antiemetic effect of ramosetron was not described by simple pharmacodynamic models. Future modeling should focus on the prolonged effect of ramosetron and the natural extinction of PONV to clarify the exposure-response relationship.