The down-regulation of CYP3A4 and CYP2C19 in obese patients is restored after gastric bypass: PBPK modeling for omeprazole as a probe drug

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Objectives: Physiological models are promising simulation tools for dose optimization in special populations. Omeprazole, which is a known CYP3A4 and CYP2C19 probe drug, is frequently prescribed to prevent marginal ulcers after gastric bypass surgery. We aimed to simulate the effect of obesity and weight loss progression after gastric bypass on the metabolism and disposition of (*R*)- and (*S*)-omeprazole.

Methods: PBPK modeling was carried out in Simcyp V21 by integrating *in vitro*, *in silico*, and *in vivo* PK data to describe the disposition of (*R*)- and (*S*)-omeprazole, (*R*)- and (*S*)-5-hydroxy omeprazole. Drug parameters included the enantioselective enzyme kinetics and competitive and mechanism-based inhibition to capture the non-linear PK of omeprazole enantiomers. Healthy and morbidly obese populations were available in the simulator. The post-gastric bypass population accounted for increased gastric pH, reduced gastric volume, reduced gastric transit time, small intestine bypass, reduced intestinal CYP3A4, and altered SI motility and transit time [2]. Simulations in morbidly obese and post-gastric bypass models were verified using longitudinal clinical data in morbidly obese submitted to gastric bypass surgery [1].

Results: Simulated plasma concentrations captured the observed data in healthy volunteers, morbidly obese, and post-gastric bypass populations with 94% of predicted data within a 2-fold range. Obesity significantly reduces CYP3A4 and CYP2C19 activities, as reflected by the metabolic ratios of omeprazole sulphone/omeprazole and 5-hydroxy omeprazole/omeprazole. The down-regulation of CYP2C19 (1.8-fold) was implemented in the morbidly obese model, combined with the standard down-regulation of CYP3A4 (2-fold), to recapitulate the observed data [1]. Parameter sensitivity analysis (PSA) showed that intestinal CYP3A4, gastric pH, small intestine length (bypass), and the delay in the release of bile do not have a major influence on the AUC of either (*R*)- or (*S*)-omeprazole. The hepatic CYP3A4 had a major impact on the AUC of (*S*)-omeprazole, while hepatic CYP2C19 impacts the AUC of both (*R*)- and (*S*)-omeprazole. Obesity increases the AUC and reduces the C_{max} of both (*R*)- and (*S*)-omeprazole compared to non-obese status. The weight loss progression in post-RYGB restores the CYP3A4 and CYP2C19 activities and PK parameters as observed in non-obese.

Conclusions: The developed PBPK model provides a comprehensive understating of the complex non-linear PK of (*R*)- and (*S*)-omeprazole in obesity and after gastric bypass. Once omeprazole metabolic ratios are good predictors of the *in vivo* activity of major CYP enzymes, the current modeling approach will improve dose optimization of CYP3A4 and 2C19 substrates in obese and post-gastric bypass patients.

Citations:

[1] Mitrov-Winkelmolen, L. et al., 2016. https://doi.org/10.1007/s11695-016-2065-8
[2] Darwich, A. S. et al., 2012. https://doi.org/10.1111/j.2042-7158.2012.01538.x