Combination of omeprazole with GLP-1 agonist therapy improves insulin sensitivity and antioxidant activity in liver in type 1 diabetic mice

Vishal Patel¹, Amit Joharapurkar¹, Nirav Dhanesha¹, Samadhan Kshirsagar¹, Jaysukh Detroja¹, Kartikkumar Patel¹, Tejal Gandhi², Kirti Patel², Rajesh Bahekar³, Mukul Jain¹

¹Department of Pharmacology and Toxicology, Zydus Research Centre, Cadila Healthcare Limited, Sarkhej-Bavla N.H. No.8A, Moraiya, Ahmedabad 382210, India
²Anand Pharmacy College, Anand 388601, India
³Department of Medicinal Chemistry, Zydus Research Centre, Cadila Healthcare Limited, Sarkhej-Bavla N.H. No. 8A, Moraiya, Ahmedabad 382210, India

Correspondence: Amit Joharapurkar, e-mail: amitjoharapurkar@zyduscadila.com

Abstract:
Background: Combination with suitable pharmacological agents can improve the antiobesity and antidiabetic actions of glucagon like peptide-1 (GLP-1) based therapies. GLP-1 agonist exendin-4 may have insulin-independent effects on amelioration of insulin resistance and hepatic steatosis by virtue of its action on hepatic GLP-1 receptors, and these effects can be improved by combination with proton pump inhibitors. However, it was not assessed whether omeprazole can improve the peripheral actions of exendin-4 in the state of insulin deficiency.

Methods: We investigated the effects of combination of omeprazole with GLP-1 agonist exendin-4 in multiple low-dose streptozotocin(STZ)-induced diabetes in C57BL/KsJ mice, a model of type 1 diabetes. Male diabetic mice were treated with exendin-4 and/or omeprazole for a period of 4 weeks.

Results: Omeprazole treatment had no significant effect on lowering the blood glucose levels of diabetic mice, when compared to control, although it improved the antihyperglycemic actions of exendin-4. Similarly, serum triglycerides and total cholesterol levels were significantly lower in the combination treated mice compared to either exendin-4 and omeprazole alone. In addition, the combination treatment significantly ameliorated lipid peroxidation and hepatic triglycerides in diabetic mice compared to either exendin-4 and omeprazole alone. The improvement in hepatic insulin sensitivity, as indicated by insulin tolerance test (ITT) and pyruvate tolerance test (IPPT), was correlated with the expression of nuclear factor erythroid-related factor 2 (Nrf2) and insulin receptor substrate-1 (IRS-1) and the combination treatment significantly improved the insulin sensitivity in comparison to vehicle control.

Conclusion: We conclude that combination with omeprazole improves the insulin sensitizing actions of GLP-1 therapy and these effects are partially mediated through the decrease in hepatic steatosis and improvement in antioxidant status in the liver.

Key words: GLP-1, exendin-4, omeprazole, type 1 diabetes, insulin sensitivity, Nrf-2, IRS-1