Effects of proton pump inhibitors on healing of gastric ulcerations induced by a continued non steroidal anti-inflammatory drug (NSAID) treatment

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Proton pump inhibitors promote ulcer healing in NSAID-treated patients with ongoing NSAID-induced gastric toxicity. However, the underlying mechanisms are unknown. This study examined the molecular pathways contributing to healing actions of esomeprazole (ESO) and lansoprazole (LAN) on NSAID-induced gastric ulcers after a continued NSAID treatment. Ulcers were induced in male rats by daily oral indomethacin (IND, 6 µmol/kg) for 14 days. Animals were then treated with IND (6 µmol/kg), alone or in combination with equivalent acid inhibitory doses of ESO (5 µmol/kg), LAN (15 µmol/kg) or famotidine (FAM, 20 µmol/kg) for 7 days. Stomachs were processed for: 1) histomorphometric analysis of mucosal injury; 2) mucosal levels of prostaglandin E_2 (PGE_2) and malondialdehyde (MDA); 3) expression of cyclooxygenase-2 (COX-2), VEGF and cleaved caspase-3 (Western blot); 4) expression of Ki-67 (immunohistochemistry). IND for 14 days induced mucosal damage (5.6±0.6%), reduced PGE_2 mucosal levels (54.5±21.4 pg/mg) and increased MDA (8.4±1.0 nmol/mg). IND for additional 7 days enhanced further the mucosal damage and MDA, while PGE_2 levels remained low. IND enhanced also the expression of COX-2 and caspase-3, reduced VEGF and Ki-67. In the presence of IND, treatment with ESO, LAN or FAM affected differentially most of the tested parameters. In particular: 1) ESO and LAN were more effective than FAM in reducing mucosal damage and MDA levels; 2) ESO and LAN, but not FAM, restored Ki-67 expression; 3) ESO, LAN and FAM partly counteracted IND-induced caspase-3 activation, without affecting the decrease in VEGF expression. The superiority of ESO and LAN over FAM in promoting ulcer healing in the presence of a continued IND treatment is likely to depend on both acid-dependent reduction of pro-apoptotic signalling and acid-independent restoration of repairing pathways.

Key words
Esomeprazole, lansoprazole, famotidine, indomethacin, non-steroidal anti-inflammatory drugs, stomach