

Protective effects of rifaximin against experimental enteropathy induced by indomethacin in rat

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Nonsteroidal anti-inflammatory drugs, besides exerting detrimental effects on the upper digestive tract, can also damage the small and large intestine (Wallace, 2013). Although the underlying mechanisms remain unclear, there is evidence that enteric bacteria play a pivotal role (Syer et al., 2015). The present study examined the protective effects of rifaximin, a poorly absorbed antibiotic with a broad spectrum of antibacterial activity, in a rat model of indomethacin (IND)-induced enteropathy. Small intestinal injury was induced in 40-week-old male rats by intragastric (i.g.) IND administration (1.5 mg/kg BID) for 14 days (Fornai et al., 2014). Rifaximin polymorph-alpha as an extended intestinal release (EIR) formulation, consisting of coated microgranules (REIR, 50 mg/kg BID, i.g.), was administered 1 hour before IND. Subgroups of rats treated with IND or REIR+IND also received omeprazole (OME, 0.7 mg/kg OD, i.g.), as inhibitor of gastric acid secretion. At the end of treatments, blood samples were collected to evaluate haemoglobin (Hb) concentration (as an index of digestive bleeding). Small intestine was processed for: 1) histological assessment of intestinal damage (percentage length of lesions over the total length examined); 2) assay of tissue myeloperoxidase (MPO), as an index of neutrophil infiltration; 3) assay of tissue malondialdehyde (MDA), as an index of lipid peroxidation. Rats treated with IND displayed a 13.3% mortality rate, while in groups treated with REIR+IND or OME+IND the mortality rate was lower (8.3% and 6.7%, respectively). No deaths were observed in controls or animals treated with OME+REIR+IND. IND significantly decreased Hb levels (by 28%). The Hb decrease was not affected by OME, while it was significantly lessened in rats treated with REIR+IND or OME+REIR+IND. IND treatment was associated with the occurrence of lesions in the jejunum and ileum. In both intestinal regions of rats treated with REIR+IND or OME+REIR+IND the percentage of lesions was significantly lower, as compared with rats receiving IND alone. The severity of lesions induced by IND was reduced by co-treatment with OME in the jejunum, but not in the ileum. MPO and MDA levels in the jejunum and ileum from IND-treated rats were significantly increased, as compared with controls. In rats treated with REIR+IND or OME+REIR+IND, MPO and MDA levels did not differ significantly from those recorded in controls, while OME was unable to affect these parameters. The overall results are summarized in the Table. In conclusion, treatment with REIR significantly prevents IND-induced intestinal damage, this entero-protective effect being associated with a decrease in digestive bleeding, tissue inflammation and oxidative stress. The co-administration of OME does not appear to affect the parameters related to intestinal damage, with few minor exceptions.

Wallace (2013). *World J Gastroenterol.* 19:1861-1876

Syer et al. (2015) *J Gastroenterol.* 50:387-393

Fornai et al. (2014). *J Pharmacol Exp Ther.* 348:86-95