PPI PROTECTION AGAINST NSAID-INDUCED GASTROTOXIC DAMAGE: MORE THAN ANTISECRETORY ACTION

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Background and aim: Proton pump inhibitors (PPIs) are effective in both the prevention and healing of non steroidal anti-inflammatory drug (NSAID)-induced gastric lesions by acting as antisecretory agents. Besides gastric acid and pepsin, oxidative stress induced by tissue antioxidant depletion and uncoupling of mitochondrial oxidative phosphorylation are considered potential mechanisms of mucosal injury in NSAID gastropathy. It has been proposed that PPIs may exert their gastroprotective action also through antioxidant mechanisms. In this study, we examined the effects of esomeprazole sodium on reduced glutathione (GSH) levels as an index of non-proteic sulfhydryl compounds, and on mitochondrial oxidative phosphorylation, in the gastric mucosa of rats treated with indomethacin. **Materials and methods**: Male albino Wistar rats, 200-225 g body weight (n=8/group), received one of eight treatments by intragastric gavage: 1% methocel as vehicle (controls), esomeprazole 10, 30 or 60 µmol/kg, indomethacin 100 µmol/kg, esomeprazole 10, 30 or 60 µmol/kg and indomethacin 100 µmol/kg. In rats treated with esomeprazole and indomethacin, esomeprazole was administered 30 minutes before indomethacin. The animals were sacrificed 4 hours after indomethacin administration, and the stomachs were processed for the evaluation of mucosal levels of GSH, whereas mitochondrial fraction from gastric mucosa was processed for citrate synthase and respiratory chain complexes (NADH-ubiquinone oxidoreductase, succinate dehydrogenase, rotenone-insensitive cytochrome c reductase, cytochrome oxidase) specific activities. **Results**: Esomeprazole alone failed to affect GSH levels and specific mitochondrial enzymatic activities. Esomeprazole (10-60 µmol/kg) dose-dependently reversed the inhibitory effect of indomethacin on GSH levels up to control values. With regard to mitochondrial enzyme activities, esomeprazole at the dose of 30 µmol/kg completely reversed the effects of indomethacin on the assessed parameters. An histomorphometric analysis showed that esomeprazole dose-dependently reduced mucosal injuries induced by indomethacin, with the dose of 30 µmol/kg being effective on superficial lesions only. **Conclusions**: The present study shows that esomeprazole dose-dependently counteracts the effects of indomethacin on gastric mucosal glutathione levels and on mitochondrial enzyme activities. This supports the view that, in addition to inhibiting acid secretion, the protective effects exerted by esomeprazole against indomethacin-induced gastric damage can be ascribed to a reduction of gastric oxidative injury.