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Transdermal nitroglycerin prevents nonsteroidal anti-inflammatory drug gastropathy

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Abstract

The application of a transdermal nitroglycerin patch (2–30 μg/3 h/rat) protected, in a dose-dependent manner, the rat gastric mucosa against damage induced by the nonsteroidal anti-inflammatory agent indomethacin (20 mg/kg s.c.).

Keywords: NSAID (non-steroidal anti-inflammatory drug); Gastric mucosal injury; Nitric oxide (NO)

The development of life-threatening gastroduodenal hemorrhage during the long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) has placed a significant limitation on their use. Recent studies have shown that nitric oxide (NO) plays an important role in maintaining the integrity of the gastric mucosa. Endogenous NO modulates mucosal blood flow (Piqué et al., 1989), reduces leucocyte-endothelial cell adherence (Kubes et al., 1991), and increases mucous gel layer thickness (Brown et al., 1992); factors presumably involved in the pathogenesis of NSAID-induced gastroduodenal injury. The exogenous administration of NO-releasing compounds has been shown to protect the gastric mucosa against damage by various agents, including NSAIDs (Wallace et al., 1994). However, the clinical utility of such agents is limited by their short duration of action.

In view of the above, we hypothesized that a clinically used, safe and effective mode of continuous administration of an NO donor, namely the nitroglycerin patch, would provide protection against indomethacin-induced gastric mucosal injury in the rat.

Sprague-Dawley rats (225–275 g), fasted for 20 h, had a nitroglycerin patch (Nitro-Dur 10 or 15, Schering-Plough) applied to a shaved dorsal cervical area. Patches were cut to produce doses of nitroglycerin of 2, 7, 15 and 30 μg/3 h/rat. On a μg/3 h/kg basis, these doses are within the range used clinically in man. Placebo patches of analogous sizes and composition, but without nitroglycerine, were used in control rats. In preliminary experiments in urethane-anesthetized rats the highest dose of nitroglycerine used in our gastric damage studies (30 μg/3 h/rat, $n = 4$) had no significant effect on arterial blood pressure, with values which remained between 86 and 99 mm Hg throughout the experimental period (180 min) and were not significantly different from those present in animals treated with placebo patches (90–102 mm Hg, $n = 3$). Fifteen minutes after patch placement, 20 mg/kg indomethacin (Sigma) was administered subcutaneously. Three hours later, the animals were killed and the stomachs removed, opened along the greater curvature and the mucosal surface photographed. From the photographs, the lengths of all individual lesions in each rat were measured and added to provide a total lesion length for each rat.

As shown in Fig. 1, in control rats the administration of 20 mg/kg indomethacin s.c. resulted in a total lesion length of 30 ± 5 mm. Pretreatment with nitroglycerin at doses of 2, 7, 15 or 30 μg/3 h, resulted in a dose-dependent reduction in damage, with lesion length decreasing by 13, 31, 63 and 68% respectively.

The data presented in this paper demonstrate that

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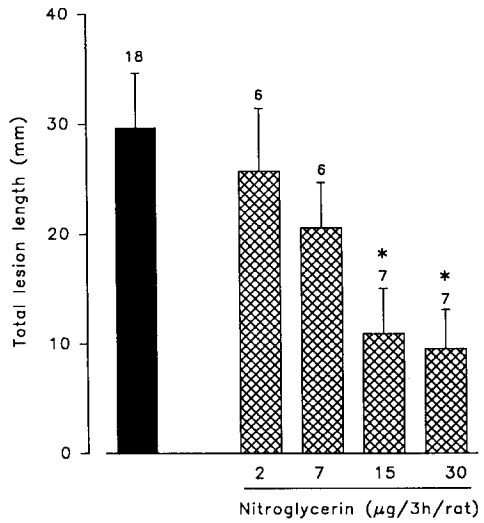

Fig. 1. Effects of different doses of nitroglycerin administered via a transdermal patch on indomethacin-induced gastric mucosal injury in the rat. Each column and bar represent the mean and S.E.M., and the number above is the number of rats used. * $P < 0.05$ vs. control, analysis of variance (ANOVA) followed by Bonferroni post-hoc test.

the application of a transdermal nitroglycerin patch, in doses that on a weight basis are analogous to those used in man, protects the rat gastric mucosa against damage induced by the NSAID indomethacin. In the studies of gastric protection with NO donors, the donor has been administered orally (Wallace et al., 1994), intraluminally (Brown et al., 1992) or close intra-arterially (López-Belmonte et al., 1993). In the present study protection was achieved by a clinically used method of systemic administration. The promising initial results reported here with acute NSAID injury warrant further study.

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