Inhibition of prostacyclin (PGI_2) formation in the rat small-intestine and gastric mucosa by the ulcerogen, indomethacin

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Administration of indomethacin to rats leads to the acute formation of gastric mucosal erosions within 3 h and to the more chronic development of lesions in the small-intestine after 3–5 days. Inhibition of prostaglandin biosynthesis (Vane, 1971) may be implicated in the pathogenesis of both types of lesions (Robert, 1974; Main & Whittle, 1975), both being prevented by the concurrent administration of various prostaglandins (Robert, 1974; Whittle, 1976). The different time-course of lesion development in the two tissues may result from different sensitivities of their cyclo-oxygenase to inhibition, or from different duration of inhibition, perhaps due to the reported enterohepatic recirculation of indomethacin (Duggan, Hooke, Noll & Kwan, 1975). The effect of indomethacin, in a single dose, on prostacyclin formation by the rat gastric mucosa (Moncada, Salmon, Vane & Whittle, 1978) and small-intestine has been investigated.

Strips (0.2–0.4 g) of gastric mucosa or ileum from which the mesentery had been removed were incubated in buffer (50 mM Tris: pH 8.4, 1 ml) by vortex mixing (1 min, 22°C). The supernatant was immediately tested for its ability to inhibit human platelet aggregation and this prostacyclin-like activity, characterised as previously described (Moncada *et al.*, 1978), was assayed against authentic prostacyclin.

The mucosal extracts contained significantly ($P < 0.01$) greater levels (99 ± 9 ng/g tissue, mean ± s.e. mean; $n = 24$) than the ileal extracts (43 ± 5 ng/g tissue; $n = 24$). Indomethacin (2.5–10 mg/kg s.c.) caused a dose-dependent reduction of prostacyclin-like activity in extracts of both the mucosa and the ileum, cyclo-oxygenase inhibition *in vivo* thus being reflected by decreased prostacyclin formation *in vitro*.

Indomethacin (10 mg/kg s.c.) inhibited the formation of prostacyclin-like activity from the mucosa by $95 \pm 1\%$ ($n = 15$), and from the ileum by $86 \pm 3\%$ ($n = 15$), 3 h after administration. After 24 h, this inhibition was significantly ($P < 0.05$) reduced to $77 \pm 5\%$ ($n = 6$) and $76 \pm 3\%$ inhibition ($n = 6$) for mucosa and ileum respectively. There was no significant inhibition of prostacyclin formation in either mucosal or ileal extracts after 48 hours. Following indomethacin (10 mg/kg s.c.), the mucosal erosion index (see Whittle, 1976) was 6.1 ± 1.6 ($n = 18$) after 3 h and 2.3 ± 0.8 ($n = 18$) after 24 hours. No mucosal erosions were observed 48 h after indomethacin. In contrast, the formation of intestinal lesions, consisting of nodules or adhesions in the jejunal and ileal region, was only macroscopically apparent after 24 h to 48 h, with gross adhesion and perforation being observed after 72 hours.

These experiments show a temporal relationship between cyclo-oxygenase inhibition, as measured by prostacyclin generation, and the formation of gastric mucosal erosions by indomethacin. The rapid healing of the erosions may reflect the return of prostacyclin formation by the mucosa within 24 to 48 h; prostacyclin administration has been shown to prevent these erosions (Whittle, Boughton-Smith, Moncada & Vane, 1978). The degree and duration of cyclo-oxygenase inhibition by indomethacin in the ileum was comparable to that in the mucosa. Hence, if inhibition of cyclo-oxygenase activity and prostacyclin formation is involved in the formation of intestinal ulcers by indomethacin, then such lesions must result from primary damage within the initial 24 h period following administration. These lesions then develop further, despite the return of the tissue's cyclo-oxygenase activity and capacity for endogenous prostacyclin formation.

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