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Effects of prostaglandin E_2 methyl analogues on the anti-inflammatory and gastric erosive activity of indomethacin

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The inhibition of prostaglandin synthesis has been proposed as a mechanism for both the anti-inflammatory actions (Vane, 1971) and gastrointestinal side effects (Robert, 1974; Main & Whittle, 1975a) of non-steroid anti-inflammatory drugs. Prostaglandins E_1 and E_2, on local administration, potentiate carrageenan-induced oedema formation in the paw of rats pretreated with indomethacin (Moncada, Ferreira & Vane, 1973). These prostaglandins (PGs), when administered systemically, can also inhibit the formation of rat gastric mucosal erosions induced by indomethacin (Whittle, 1975). In the present study, we have investigated whether the potent gastric-antisecretory methyl analogues of PGE_2 (Robert & Magerlein, 1973; Main & Whittle, 1975b), in doses which inhibit erosion formation, also inhibit the reduction of rat paw oedema by indomethacin.

Oedema formation in the hind paw of male Wistar rats (180–210 g) was induced by injecting 0·1 ml of a carrageenan suspension (Marine Colloids, batch RE 7179; 2% in saline) into the subplantar region. The change in volume of the paw was measured every 45 min with a mercury displacement plethysmograph connected to a transducer-pen recorder system (Van Arman, Begany & others, 1965). Prostaglandins, stored in methanol (—5°) and made up freshly in aqueous solution as required, were injected either locally (0·1 ml) into the hindpaw, or subcutaneously into the flank. Indomethacin (10 mg ml^{-1}) was dissolved in 5% w/v $NaHCO_3$ solution (pH 8) and immediately injected subcutaneously. The formation of gastric erosions following indomethacin administration to fasted (18 h) rats was assessed as described previously (Main & Whittle, 1975a) and expressed as an erosion index.

Administration of carrageenan caused a rapid increase in paw volume (of 660 ± 154 μl after 3h, mean ± s.e.m.; n = 5). In rats pretreated with indomethacin (20 mg kg^{-1}, s.c., 1 h before carrageenan) the increase in paw volume was significantly less (133 ± 31 μl, n = 16; $P<0{\cdot}01$). This oedema formation was maximal after 3 h in rats given carrageenan alone, whereas in those pretreated with indomethacin, plateau values were obtained after 1 h, and remained steady over the next 4 h. Local administration of PGE_2 (0·1–1·0 μg), into the hind paw, 2·25 h after carrageenan administration to indomethacin-pretreated rats caused dose-dependent increases in paw volume (Table 1), whereas there was no significant change following local saline (0·1 ml) administration. These results confirm the finding of previous workers (Moncada & others, 1973; Smith, Ford-Hutchinson & others, 1974; Lewis, Nelson & Sugrue, 1975) that prostaglandins of the E series can increase rat paw oedema.

Similarly, local administration of (15S)-15-methyl PGE_2 methyl ester or 16,16 dimethyl PGE_2 (0·1–1·0 μg) significantly increased rat paw oedema, and appeared to be less potent than PGE_2 in the range investigated. In contrast, systemic administration of the (15S) or 16,16-dimethyl PGE_2 analogues (5–20 μg kg^{-1}, s.c.) had no significant effect on paw oedema (Table 1).

Indomethacin, in the anti-inflammatory doses used in these experiments (20 mg kg^{-1}, s.c.), caused a time-dependent rise in the incidence and severity of gastric mucosal erosions, as reported previously (Main &

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Table 1. *Change in paw volume following prostaglandin administration in rats treated with carrageenan (0·1 ml, 2% locally) and indomethacin (20 mg kg^{-1}, s.c.; 1 h before carrageenan).* Prostaglandins administered 2·25 h after carrageenan, and volume change determined 1·5 h later. Results are expressed as mean ± s.e.m., where n is the number of values, and the significance of the change was evaluated using Student's *t*-test for paired data. * $P<0.05$ ** $P<0.01$ *** $P<0.001$.

	Dose	route	n	Δpaw volume (μl)
Saline		local	26	2·7 ± 25
Prostaglandin E_2	0·1 μg	local	6	340 ± 51**
	1·0 μg	local	8	438 ± 40***
16, 16 dimethyl E_2	0·1 μg	local	7	196 ± 92**
	1·0 μg	local	4	365 ± 96*
(15S)-15 methyl E_2	0·5 μg	local	6	300 ± 80*
(15S)-15 methyl E_2	5 μg kg^{-1}	systemic	9	17 ± 25
	10 μg kg^{-1}	systemic	3	17 ± 16
16, 16 dimethyl E_2	20 μg kg^{-1}	systemic	8	6·7 ± 41

Whittle, 1975a). Simultaneous administration of the PGE_2 methyl analogues (0·3–5·0 μg kg^{-1}, s.c.) caused a dose-dependent inhibition of these erosions. From a study using 50 rats, the dose causing 50% inhibition of 3 h-developed indomethacin-induced gastric erosions was 0·6 μg kg^{-1}, subcutaneously for both analogues. There was greater than 90% inhibition of the erosion formation with either analogue at doses of 2·5 μg kg^{-1}, subcutaneously.

These results indicate that, as with the parent prostaglandin, local administration of the methyl analogues of PGE_2 increases carrageenan-induced paw oedema in indomethacin-pretreated rats. Whereas these analogues are 30–100 times more active than the parent prostaglandin, following systemic administration, in causing such actions as stimulation of intestinal motility, inhibition of gastric secretion and inhibition of gastric erosions (Main & Whittle, 1975b; Whittle 1975), in the present study on paw oedema they were only approximately equipotent to PGE_2 following local administration. It is of interest that the vasoactive potency of these analogues (as depressors of rat systemic arterial blood pressure) is also only comparable to PGE_2 (Weeks, DuCharme & others, 1973; Main & Whittle, 1975b) since it has been suggested that the pro-inflammatory action of prostaglandins may be related to their local vasodilator properties (Williams & Morley, 1973; Williams, 1976). This lower relative potency of the methyl analogues on paw oedema following local administration may also be accounted for by increased absorption and removal from the site of injection. Alternatively, these results may indicate a low activity of the 15-hydroxyprostaglandin dehydrogenase at this site; decreased inactivation of the methyl analogues, as compared with PGE_2, by the dehydrogenase enzyme system has been proposed as a mechanism for the generally-found increased potency of these analogues (Weeks & others, 1973).

The present findings in the rat suggest that systemic administration of the potent methyl analogues of PGE_2, in doses greater than those required to inhibit indomethacin-induced gastric erosions, does not inhibit the anti-inflammatory activity of indomethacin. This raises the possibility that concurrent administration of low doses of a prostaglandin analogue could prevent the gastric irritancy associated with the use of non-steroid anti-inflammatory agents, without suppressing their therapeutic actions.

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