Table 1 Comparison of C15-modified prostaglandins on the sheep blood pressure (intra-aortic injection)

	Equipotent molar ratios		
	Pressor response		*Depressor response*
ω-side chain characteristics	*PGD_2 analogues*	*$PGF_{2\alpha}$ analogues*	*PGE_2 analogue*
15(S)-hydroxyl	1.0	69	1.0
15(S)-methyl ether	5.6	107	> 100
15(R)-hydroxyl	1.9*	59*	550
15-oxo	8.4†	13	> 300
13,14-dihydro-15-oxo	5.7	550	> 300

Each ratio is the mean of at least three determinations.
* Racemic mixture
† Major component is the 12,13-ene isomer.

less active than $PGF_{2\alpha}$. (±)15(R) PGD_2 and 13,14-dihydro-15-oxo PGD_2 produced no effect at doses 100 and 330 times respectively, the threshold dose of $PGF_{2\alpha}$. Finally on the isolated rabbit jejunum, where PGD_2 is about 5 times less active than $PGF_{2\alpha}$, PGD_2 15-methyl ether and (±)15(R) PGD_2 are at least 100 times and the two 15-oxo PGD analogues at least 500 times less active than $PGF_{2\alpha}$.

Thus it would appear that simple chemical changes can be made at C15 which result in retention of PGD-like activity but loss of PGE- and PGF_α-like activities.

Prostaglandins were kindly supplied by I.C.I. Ltd and the Upjohn Co., Kalamazoo.

References

HORTON, E.W. & JONES, R.L. (1974). Biological activity of prostaglandin D_2 on smooth muscle. *Br. J. Pharmac.*, **52**, 110-111P.

HORTON, E.W. & MAIN, I.H.M. (1965). A comparison of the actions of prostaglandins $F_{2\alpha}$ and E_1 on smooth muscle. *Br. J. Pharmac.*, **24**, 470-476.

JONES, R.L. (1975). Actions of prostaglandins on the arterial system of the sheep: some structure–activity relationships. *Br. J. Pharmac.*, **53**, 464P.

Prostaglandins and changes in the gastric mucosal barrier and blood flow during indomethacin- and bile salt-induced mucosal damage

B.J.R. WHITTLE

Department of Pharmacology, Institute of Basic Medical Sciences, Royal College of Surgeons of England, London WC2A 3PN

The formation of gastric mucosal erosions by non-steroid anti-inflammatory drugs in the rat is greatly increased by the presence of bile acids in the gastric lumen (Semple & Russell, 1975), although this damage is prevented by prostaglandin methyl analogues (Whittle, 1975). Changes in gastric mucosal blood flow and in the resistance of the mucosa to acid back-diffusion (the mucosal 'barrier') have now been investigated as possible mechanisms underlying such erosion formation.

The gastric lumen of the urethane-anaesthetized rat was perfused with acidic saline (0.1-0.2 ml min^{-1}) and the loss of acid across the mucosa determined by titration. The potential difference (PD) across the mucosa, which is related to hydrogen- and sodium-ion flux and gives an indication of the integrity of the mucosal barrier (Chvasta & Cooke, 1972) was measured via calomel electrodes. Mucosal blood flow (MBF) was determined by [^{14}C]-aniline clearance (Main & Whittle, 1973).

During acid perfusion (100 mM HCl, pH 1), administration of sodium taurocholate (1 mg/ml, 2 mM) increased the acid-loss (from 0.48 ± 0.19 to 2.2 ± 0.3 μEq min^{-1} after 1 h; mean ± s.e. mean, $n = 4$), lowered PD (by −10.4 ± 1.5 mV, $n = 8$) and increased MBF (to 340 ± 15% of basal, $n = 4$). The rise in MBF appeared to correlate with acid back-diffusion and may represent a protective mechanism of the mucosa, since few erosions were seen after the 3 h perfusion. Indomethacin (20 mg/kg i.v.), injected during acid perfusion,

decreased MBF (by 30 ± 4% of basal, $n = 3$) but had no consistent effect on acid-loss or PD, and a low erosion 'score' was observed after 3 hours. However, during taurocholate perfusion, indomethacin reduced the elevated MBF (to 244 ± 17% of basal, $n = 4$) and led to a high incidence of erosions. The total acid-loss during taurocholate perfusion was 360 ± 50 μEq 3 h^{-1} ($n = 5$), and was 460 ± 40 μEq 3 h^{-1} ($n = 4$) following simultaneous administration of indomethacin (20 mg/kg s.c.).

The acid back-diffusion during combined taurocholate and indomethacin administration was reduced (20 ± 5%, $n = 8$) by the (15S)-15 methyl analogue of prostaglandin E_2 (5 μg $kg^{-1}h^{-1}$ s.c.), in a dose causing 53% inhibition of the erosions (Whittle, 1975). Intravenous infusion of the prostaglandin analogue (5 μg kg^{-1} over 1 h) increased PD (by −6.7 ± 0.9 mV, $n = 3$) and MBF (by 66 ± 13% of basal, $n = 3$) following taurocholate or indomethacin administration, and during resting conditions. Exogenous prostaglandins may therefore prevent erosions by actions on both MBF and mucosal permeability. However, the failure of parenteral indomethacin, alone, to markedly alter resting PD or acid-loss, in doses reducing mucosal prostaglandin levels (Main & Whittle,1975) may argue against a local role for endogenous prostaglandins in the maintenance of the rat mucosal barrier.

These results in the rat suggest that although a reduction in MBF, as observed with parenteral indomethacin, or an increased acid back-diffusion as seen with taurocholate, can lead to a low incidence of mucosal erosions, a combination of both produces extensive mucosal damage. Since several aspirin-like drugs are known to cause acid back-diffusion following intragastric administration, their potency in producing gastric erosions may be related to their concurrent effects on mucosal blood flow.

This work was supported by an M.R.C. grant to Professor G.P. Lewis. Prostaglandins were kindly supplied by the Upjohn Company, Kalamazoo.

References

CHVASTA, T.E. & COOKE, A.R. (1972). The effect of several ulcerogenic drugs on the canine gastric mucosal barrier. *J. Lab. clin. Med.*, **79**, 302-315.

MAIN, I.H.M. & WHITTLE, B.J.R. (1973). Gastric mucosal blood flow during pentagastrin- and histamine-stimulated acid secretion in the rat. *Br. J. Pharmac.*, **49**, 534-542.

MAIN, I.H.M. & WHITTLE, B.J.R. (1975). Investigation of the vasodilator and antisecretory role of prostaglandins in the rat gastric mucosa by use of non-steroidal anti-inflammatory drugs. *Br. J. Pharmac.*, **53**, 217-224.

SEMPLE, P.F. & RUSSELL, R.I. (1975). Role of bile acids in the pathogenesis of aspirin-induced gastric mucosal haemorrhage in rats. *Gastroenterology*, **68**, 67-70.

WHITTLE, B.J.R. (1975). Gastric acidity and the mechanisms by which prostaglandins prevent indomethacin-induced gastric erosions. *Br. J. Pharmac.* **55**, 242-243P.

The pro-inflammatory activity of E-, A-, D- and F-type prostaglandins and analogues 16, 16-dimethyl-PGE_2 and (15S)-15-methyl-PGE_2 in rabbit skin; the relationship between potentiation of plasma exudation and local blood flow changes

T.J. WILLIAMS (introduced by G.P.LEWIS)

Department of Pharmacology, Institute of Basic Medical Sciences, Royal College of Surgeons of England, London WC2A 3PN

Potentiation of inflammatory exudation by locally-injected prostaglandins has previously been described in guinea-pigs (Williams & Morley, 1973) and in rats (Moncada, Ferreira & Vane, 1973; Thomas & West, 1973). It was suggested (Williams & Morley, 1973) that this potentiation may be a consequence of the vasodilator activity of prostaglandins (PGs). This possibility has been investigated using a technique for the simultaneous measurement of local plasma exudation and blood flow changes in rabbit skin (Williams, 1975). The technique consists of intravenous injection of [^{131}I]-albumin, followed by intradermal injections of inflammatory agents mixed with ^{133}Xe in saline. After a fixed interval the animal is killed, skinned and punched-out lesions counted in a γ-counter. The ^{131}I counts then give a measure of plasma exudation and $\log_e$ ^{133}Xe counts are inversely proportional to local blood flow. Using this technique it was found that intradermal injections of prostaglandins alone produced insignificant