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A comparison of the effects of stable endoperoxide analogues with PGE_2 and $PGF_{2\alpha}$ on rat gastric secretion, *in vivo* and *in vitro*

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Arachidonic acid (AA), like PGE_2, reduces rat gastric secretion and this effect is antagonized by indomethacin (Frame, Main & Melarange, 1977), an inhibitor of cyclo-oxygenase. Since the cyclic endoperoxide intermediates may themselves be important physiologically and may account for at least some of the action of AA, we have investigated the effects of two stable analogues of endoperoxide, Upjohn 44069 and 46619 (Bundy, 1975) on gastric secretion *in vivo* and *in vitro*.

In vivo studies were conducted using the lumen-perfused rat stomach preparation. Acid secretion, mucosal blood flow (MBF) (aniline clearance, Main & Whittle, 1973) and blood pressure (BP) were recorded. Acid secretion was stimulated by pentagastrin (0.33 $\mu g\ kg^{-1}\ min^{-1}$ infused intravenously throughout the experiment) and drugs were given by i.v. infusion for 30 min periods. The results are the mean $\pm$ s.e. mean of four observations.

In doses of 5 and 12.5 $\mu g\ kg^{-1}\ min^{-1}$, U44069 caused a maximum inhibition of acid secretion of $22.6 \pm 5.9\%$ and $33.3 \pm 9.7\%$ respectively while U46619 caused inhibition of $33.0 \pm 7.8\%$ and $53.3 \pm 4.8\%$ respectively. PGE_2 in doses of 0.25 and 0.5 $\mu g\ kg^{-1}\ min^{-1}$ inhibited acid secretion by $26.4 \pm 8.5\%$ and $33.8 \pm 6.2\%$ respectively. $PGF_{2\alpha}$ (5 and 12.5 $\mu g\ kg^{-1}\ min^{-1}$) produced variable effects on secretion (increased in 5 experiments and decreased in 3 experiments). The results suggest that U44069 and U46619 are qualitatively similar to PGE_2 but are respectively about 25 and 10 times less potent. Inhibition of acid secretion was always associated with an increase in the MBF/acid ratio.

The effects of endoperoxides on B.P. were mixed at the lower dose-level. The higher dose, however, predominantly decreased BP, as did PGE_2. $PGF_{2\alpha}$ usually produced a small initial increase in BP followed by a fall.

In vitro studies were carried out on the isolated mucosa (Hearn & Main, 1975). Acid secretion was measured by pH stat and secretory responses to histamine (2.6 to 5.2×10^{-5} M present in the serosal solution for 30 min) were obtained at 75 min intervals. Both U44069 and U46619, in concentrations of 0.8 to 1.64×10^{-6}M, added to the serosal solution for 15 min prior to histamine, inhibited the responses to histamine and were approximately 10–20 times less potent than PGE_2.

The results show that endoperoxide analogues have qualitatively similar effects to PGE_2 on acid secretion but are considerably less active. If the activity of the analogues reflects that of the natural endoperoxides, the latter are unlikely to contribute significantly to the inhibitory effect of AA. The contribution of other products of cyclo-oxygenase to this inhibitory effect remains to be established since the effects of thromboxanes and PGI_2 on gastric secretion have not yet been reported.

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