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Topical effects of 16,16 dimethyl prostaglandin E_2 on gastric acid secretion and mucosal permeability to hydrogen ions in dogs[1]

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SUMMARY The effects of luminal instillation of 16,16 dimethyl PGE_2 ($dmPGE_2$) on gastric acid secretion and back diffusion of H^+ were studied in anaesthetised dogs which were prepared with a segment of the greater curvature of the stomach mounted in a double lumen chamber. This model permitted simultaneous evaluation of two segments of mucosa, one control and the other test, supplied by the same vascular pedicle. Infusion of histamine (1·0 μg/kg/min, intravenously) stimulated brisk acid secretion in both chambers. Topical application of 25 μg $dmPGE_2$ in 20 ml 0·3 M HCl to the test chamber for 30 minutes prevented acid secretion from the test mucosa during a second histamine infusion. Since the control chamber showed no evidence of inhibition this indicates that $dmPGE_2$ acted directly on the secretory cells, rather than after absorption from the bloodstream. This observation, however, does not exclude a possible local effect on mucosal blood flow. Direct exposure of the gastric mucosa to $dmPGE_2$ increased the rate of back diffusion of H^+ because of disruption of the permeability barrier, indicated by increased H^+ back diffusion, Na^+ efflux, and a reduction in potential difference. However, H^+ loss was small compared to the reduction in acid output.

Prostaglandins (PGs) of the E group are potent inhibitors of gastric acid secretion in animals and man (Mihas *et al.*, 1976; Robert *et al.*, 1976). Recent studies have shown that 16,16 dimethyl PGE_2 ($dmPGE_2$) is active orally, with relatively few undesirable side-effects (Nylander *et al.*, 1974; Robert *et al.*, 1975; Wilson *et al.*, 1975). Nylander *et al.* (1974) demonstrated that $dmPGE_2$ failed to inhibit human gastric secretion when administered directly into the upper jejunum, whereas it was very effective when given intragastrically. This observation indicates a direct action on the secretory cells, which could be desirable in the treatment of peptic ulcer because systemic side-effects may be minimised. Alternatively, $dmPGE_2$ might be largely absorbed through the stomach or the reduction in gastric acid output after intragastric administration might be partly due to increased back diffusion of H^+. O'Brien and Carter (1975) reported that in dogs $dmPGE_2$ in the Heidenhain pouch significantly increased H^+ back diffusion.

The present study evaluates further the topical effect of $dmPGE_2$ on secretory inhibition, using a double-lumen chamber *in vivo*, which permitted simultaneous observation of two segments of mucosa supplied by the same vascular pedicle. Thus, a topical effect in the treated mucosa could be distinguished from a systemic effect in the untreated control mucosa. In addition, this study also determined the effect of $dmPGE_2$ on the mucosal permeability barrier.

Methods

Mongrel dogs weighing 20 to 25 kg were anaesthetised with sodium pentobarbital (25 mg/kg) and maintained on a Harvard respirator throughout each experiment. Polyvinyl catheters (ID 0·145 mm) were placed in both femoral veins for infusion of fluids and histamine. Arterial pressure was monitored through a left femoral arterial catheter (Statham transducer P23AA, Hewlett-Packard recorder). A segment of

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gastric corpus with an isolated vascular pedicle, prepared as described by Moody and Durbin (1965), was placed in a double-lumen chamber which provided two mucosal compartments, each 17 cm^2. The fluid in both chambers was removed at 15 minute intervals and replaced by isotonic HCl (0·3 M). Secretory volume was calculated as the change in weight between the instilled and recovered solutions. H^+ flux was determined by potentiometric titration of instillate and recovered samples to pH 6·5 (Radiometer, Copenhagen) with 0·1 M NaOH. Na^+ concentration of the gastric sample was determined by flame photometry (Radiometer FLM2). Polyvinyl catheters (ID 0·85 mm), filled with saturated KCl in 5% agar to provide electric contact to saturated calomel electrodes (K4112, Radiometer, Copenhagen), and subcutaneous reference electrodes, measured mucosal potential difference on a Radiometer TTTI pH meter.

Each experiment began with four 15 minute control periods to allow the mucosa to reach a stable resting state. Submaximal acid secretion was then stimulated with histamine 1·0 μg/kg/min intravenously. After a steady rate of secretion was reached, the histamine infusion was discontinued and secretion was allowed to return to a resting level. $dmPGE_2$ (5, 10, or 25 μg) was added to the bathing solution of 20 ml 0·3 M HCl in the test chamber for two periods; the control chamber was instilled with 20 ml HCl alone. Histamine was then re-infused (1·0 μg/kg/min intravenously) until a steady rate of secretion was again obtained in the control chamber. To study mucosal permeability $dmPGE_2$ 25 μg was then added to the bathing solution (20 ml HCl) in the test chamber for four periods.

The chambers for test and control experiments were alternated. For each period, the net H^+ flux, Na^+ flux, and potential difference across the stomach wall were measured.

Results

Figure 1 shows the effects on histamine-stimulated acid output of topical treatment of gastric mucosae with 20 ml HCl alone (control) or containing 5, 10, or 25 μg $dmPGE_2$. In control chambers, the first and second infusions of histamine stimulated comparable acid outputs. The acid output after treatment of 5, 10, or 25 μg $dmPGE_2$ was significantly reduced ($P < 0.05$) compared to the first histamine infusion

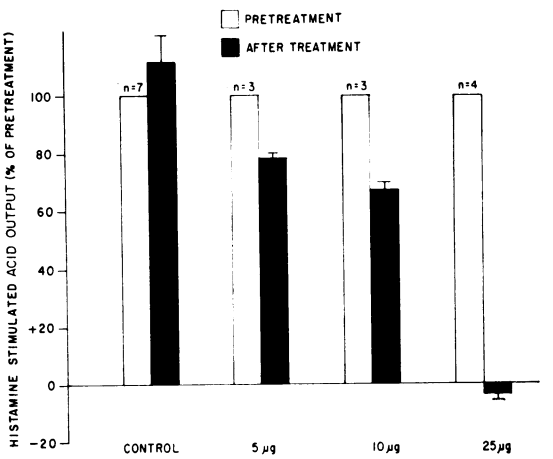

Fig. 1 *Percent reduction in acid output after topical treatment of the gastric mucosa with 0·3M HCl alone (control), and 5, 10, and 25 μg of $dmPGE_2$ in HCl for 30 min. The acid output before treatment or during first histamine infusion is represented as 100%. n represents the number of experiments (mean ± SEM).*

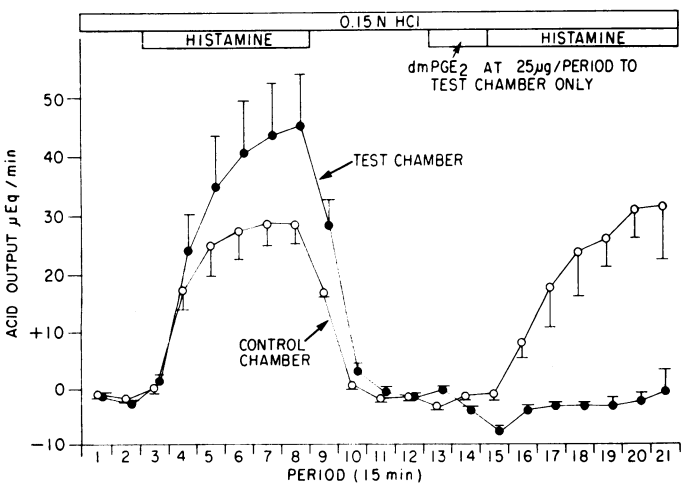

Fig. 2 *Sequential changes in acid output from control and test chambers before and after topical instillation of 25 μg $dmPGE_2$ in 20 ml 0·3M HCl (mean ± SEM, four experiments).*

Table *Effects of dmPGE$_2$ on gastric mucosal permeability barrier*

	Before dmPGE$_2$		*Exposure to dmPGE$_2$*	
	Control mucosae	*Test mucosae*	*Control mucosae*	*Test mucosae*
PD (mV)	62·5 ± 2·2	61·8 ± 1·7	62·3 ± 2·0	43·8 ± 2·0*
H^+ loss (μmol/min)	1·4 ± 0·3	1·3 ± 0·2	0·7 ± 0·2	3·1 ± 0·5*
Na^+ gain (μmol/min)	0·8 ± 0·2	0·7 ± 0·1	0·6 ± 0·2	13·1 ± 1·9*

*P < 0·05, †P < 0·001 when compared to control mucosae.
All values represent the mean ± SEM (12 experiments in three dogs).
(μmol = μequiv).

The exposure of mucosa to 5 and 10 μg dmPGE$_2$ for 30 minutes resulted in a 22 ± 2 (SE)% and a 33 ± 3% reduction in acid output respectively; 25 μg dmPGE$_2$ eliminated acid output with the second histamine infusion.

Figure 2 illustrates the sequential changes in acid output from control and test chambers. Before exposure to dmPGE$_2$, both mucosal areas were stimulated to secrete with histamine ($P < 0·01$) and then returned to a resting level after histamine infusion was discontinued. After pretreatment with 25 μg dmPGE$_2$ for two 15-minute periods, acid output was completely inhibited in the test chamber during the second histamine infusion ($P < 0·001$), whereas output from the control mucosa was comparable to that during the first histamine infusion.

The effects of 25 μg dmPGE$_2$ on gastric mucosal permeability barrier as indicated by potential difference, H^+ and Na^+ fluxes are shown in the Table. Before instillation of dmPGE$_2$, both control and test mucosae were comparable in potential difference, H^+ loss, and Na^+ efflux. dmPGE$_2$ did not alter the PD and the ion fluxes in the control chamber, but reduced that in the test mucosa ($P < 0·05$), and significantly increased H^+ back diffusion ($P < 0·05$) and sodium efflux ($P < 0·001$) (Fig. 3). These effects were observed immediately after the exposure of mucosa to dmPGE$_2$. However, the H^+ loss following dmPGE$_2$ was only 3·1 ± 0·5 μmol (μequiv)/min, less than 10% of the H^+ output stimulated by histamine.

Discussion

This model provided two segments of fundic mucosae supplied by the same vascular pedicle, thus eliminating many of the uncontrolled variables encountered in other experimental and clinical models. In addition, the experimental design ensured that both mucosae were secreting comparably before exposure to dmPGE$_2$. The lack of inhibition in the untreated (control) mucosa indicates a direct effect of dmPGE$_2$ rather than a systemic effect following absorption. However, a local effect on mucosal blood flow cannot be excluded.

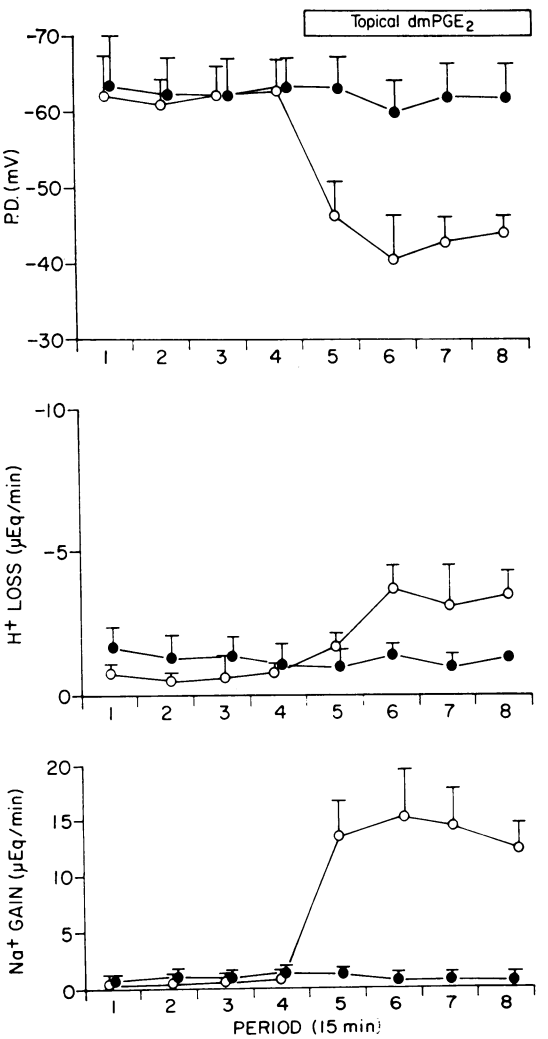

Fig. 3 *Sequential changes in potential difference (PD), H^+ loss and Na^+ efflux. All data are expressed in terms of mean ± SEM, four experiments. Topical dmPGE$_2$ (25 μg) was added to the bathing solution of the test chamber (20 ml 0·3M HCl) from period 5 through 8.*

The increased back diffusion of H^+, effiux of Na^+, and reduction in PD indicate that $dmPGE_2$ disrupted the mucosal barrier. Nonetheless, the amount of H^+ back diffusion was small compared to the reduction of acid output. O'Brien and Carter (1975) reported much greater H^+ back diffusion following instillation of $dmPGE_2$ into canine Heidenhain pouches, but they used 300 μmol (μ equiv) in 20 ml of acid solution which was more than 10 times the dose we found prevented acid secretion (25 μg in 20 ml of acid solution).

Increased H^+ back diffusion has been said to be associated with gastric mucosal injury. Recent studies have evolved some new concepts of the gastric mucosal barrier and its relationship to mucosal ulceration (Silen, 1977). The absolute amount back diffused may be less important in the pathogenesis of ulceration than the tolerance of mucosa to withstand H^+. In our model, we could observe the mucosa continuously, and found no evidence of gross mucosal injury following the topical administration of $dmPGE_2$.

$dmPGE_2$ is a much more potent inhibitor of gastric acid secretion than is PGE_2 (Robert *et al.*, 1976). The dose required for inhibition in our study was slightly lower than that reported by Robert *et al.* (1976), who demonstrated that 7·5 μg/kg orally inhibited acid output by 50% in dogs. However, the mucosal surface within our chamber was much smaller than in a Heidenhain pouch.

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