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Effect of lignocaine on eicosanoid synthesis by pieces of human gastric mucosa

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Abstract—Lignocaine can affect prostaglandin synthesis in various tissues, and it has anti-inflammatory activity. No studies have been made previously on human isolated gut tissues. When concentrations of 5, 50 and 250 μg mL^{-1} lignocaine were incubated with human gastric mucosa/submucosa at 37°C for 30 min, only the highest concentration reduced the levels of prostaglandin E, thromboxane B_2 and 6-keto-$PGF_{1\alpha}$ in the incubates, and leukotriene C_4/D_4 was unaffected. Therapeutically relevant amounts of lignocaine given parenterally would therefore seem unlikely to alter gastric mucosal prostanoids, but high doses can be given orally because of extensive first-pass metabolism in the liver.

Inflammatory mechanisms play a central role in the pathophysiology of several bowel diseases, such as ulcerative colitis and obstructive ileus. Various studies have shown that local anaesthetics have marked anti-inflammatory effects on leucocytes, including inhibition of their migration and metabolic activation (Hammer et al 1985; Rimback et al 1988; Eriksson et al 1992), and lysosomal enzyme release (Peck et al 1985; Sasagawa 1991).

In-vivo, local anaesthetics lessen oedema in peritonitis (Rimback et al 1988) and burns (Cassuto et al 1990), and reduce the fluid loss in obstructive ileus triggered by pronounced gut inflammation (Cassuto et al 1987). Clinical studies have shown that local anaesthetics counteract the severe mucosal inflammation of interstitial cystitis (Asklin & Cassuto 1989) and ulcerative colitis (Bjorck et al 1989). Because eicosanoids have roles in inflammation and gastric mucosal protection, we set out to investigate the effects of lignocaine on eicosanoid production by human gastric mucosa in-vitro.

Materials and methods

Lignocaine HCl was diluted in water to give stock concentrations of 50, 500 and 2500 μg mL^{-1}. These were diluted 10-fold with phosphate-buffered saline pH 7·4 (PBS) on the day of incubation to give final solutions of 5, 50 and 250 μg mL^{-1}.

Human gastric tissue was removed surgically from patients with benign or malignant diseases. Samples were taken at least 5 cm from any macroscopically detected lesions, transported to the laboratory in PBS and handled using latex gloves in a Class 2 safety cabinet. The layer of mucosa/submucosa was carefully removed from the underlying muscle while the tissue was bathed in PBS. After cutting into pieces of 3–5 mm^2, washing in PBS and blotting to remove excess fluid, carefully weighed samples (100 ± 5 mg) were pre-incubated (1 mL PBS, 0°C 30 min) in the absence or presence of lignocaine 5, 50 and 250 μg mL^{-1}. This pre-incubation fluid was discarded and replaced by fresh PBS (± drug) which was removed after incubation at 37°C for 30 min, and stored at −20°C for eicosanoid assays 5–10 days later.

The measurements were carried out by radioimmunoassay in duplicate using suitable dilutions of specific antisera and tritiated standards (Jaffe & Behrman 1974). Assay sensitivities were about 20 pg for prostanoids and 50 pg for leukotriene C_4/D_4 (LTC_4/D_4). Intra- and inter-assay coefficients of variation were 5–9% and 10–11%, respectively, depending on the eicosanoid measured.

Tritiated prostanoids were from Amersham Radiochemical Centre (Amersham, UK), and tritiated LTC_4 was from New England Nuclear (Dupont, Stevenage, UK). The prostaglandin E (PGE) antiserum was from ICN (High Wycombe, UK), and the thromboxane B_2 (TXB_2) and 6-keto-$PGF_{1\alpha}$ antisera were from Wellcome (Beckenham, UK). Cross-reactions were as previously reported (Tavares et al 1987; Goel et al 1989). The PGE antiserum does not distinguish between PGE_1 and PGE_2 (hence the values are expressed as PGE), and the leukotriene antiserum does not distinguish between LTC_4 and LTD_4 (hence the values are expressed as LTC_4/LTD_4). The percent cross-reactions of the leukotriene antiserum, kindly provided by Dr J. Zakrzewski, Department of Thoracic Medicine, King's College School of Medicine and Dentistry, were: LTC_4 100; LTD_4 29·4; LTE_4 0·7; LTB_4 0·05; PGE < 0·05; arachidonic acid < 0·05.

Results

Results are expressed as means ± s.e. and the raw data analysed statistically by Student's *t*-test for paired data (2-tailed).

Lignocaine 250 μg mL^{-1} reduced the amounts of PGE, TXB_2, and 6-keto-$PGF_{1\alpha}$ (all $P < 0.05$) but lignocaine 5 and 50 μg mL^{-1} had no significant effect (Table 1).

The LTC_4/D_4 accumulating in the gastric mucosal incubates showed no significant change with lignocaine 5, 50 or 250 μg mL^{-1} (Table 1).

Table 1. Effect of different concentrations of lignocaine on the accumulation of endogenous eicosanoids in incubates of human gastric mucosa/submucosa.

Lignocaine (μg mL^{-1})	PGE	TXB_2	6-Keto-$PGF_{1\alpha}$	LTC_4/D_4
0	112·4 ± 24·5	60·7 ± 13·4	87·2 ± 31·9	3·8 ± 0·6
5	120·3 ± 34·7	71·9 ± 21·7	89·0 ± 33·5	3·1 ± 0·7
50	98·6 ± 33·2	49·8 ± 13·7	87·0 ± 41·7	3·5 ± 0·8
250	75·4 ± 16·1*	39·2 ± 15·6*	57·9 ± 23·6*	3·1 ± 0·7

The values are ng (g wet tissue)$^{-1}$/30 min (means ± s.e., n = 5). *$P < 0.05$ compared with PBS control (lignocaine 0 μg mL^{-1}).

Discussion

Some studies have found inhibition of prostaglandin synthesis by local anaesthetics (Kunze et al 1974; Horrobin & Manku 1977; Nellgard et al 1992), but others showed a stimulation (Casey et al 1980; Jones & Hurley 1984). We found that lignocaine 250 μg mL^{-1}, but not 5 or 50 μg mL^{-1}, inhibited the gastric mucosal formation and release of PGE, TXB_2 and 6-keto-$PGF_{1\alpha}$, but there was no significant effect of any concentration on LTC_4/D_4. Release of LTB_4 and interleukin-1 from from human leucocytes in-vitro was inhibited by 500 μg mL^{-1} lignocaine or bupivacaine (Eriksson et al 1992), so that the effect on LTC_4/D_4 may depend on the drug concentration or on the tissue.

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The metabolic inhibition by local anaesthetics of antigen/antibody-induced activation of leucocytes harvested from the subcutaneous tissue by a titanium chamber (Eriksson et al 1992) does not seem to explain the inhibition of prostanoid release; otherwise, presumably leukotriene synthesis would also be inhibited, but this did not occur in our mucosal study.

The highest concentration of lignocaine that we used (250 μg $mL^{-1} = 0{\cdot}025\%$) is well below topical concentrations in-vivo that induce marked anti-inflammatory effects in laboratory animals (Cassuto et al 1990) and in man (Asklin & Cassuto 1989; Bjorck et al 1989). Plasma lignocaine concentrations allowed in patients are sufficient in-vivo to inhibit anion release from human leucocytes (Peck et al 1985) but are much lower than the 250 μg mL^{-1} required to inhibit the formation of human gastric mucosal prostanoids in-vitro. Nevertheless, with local application where the concentrations can be much higher, inhibition of prostanoid formation and release by local anaesthetics may contribute to the clinical inhibition of inflammation such as interstitial cystitis and ulcerative proctitis (Asklin & Cassuto 1989; Bjorck et al 1989). Higher concentrations of lignocaine are also feasible within the stomach compared with systemic levels, because most of the drug absorbed from the alimentary tract is degraded by first-pass metabolism in the liver. However, since lignocaine is mainly ionized at gastric pH, its absorption by the gastric mucosa is low. It remains to be seen whether lignocaine may be of use in gastric inflammation.

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