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Failure of the inhibition of rat gastric mucosal 5-lipoxygenase by novel acetohydroxamic acids to prevent ethanol-induced damage

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1 The role of leukotriene B_4 (LTB_4) and LTC_4 as mediators of gastric mucosal damage following ethanol challenge *in vivo* has been investigated using two selective 5-lipoxygenase inhibitors, BW A4C and BW A137C.

2 Oral administration of ethanol to rats *in vivo*, induced macroscopic damage to the gastric mucosa and markedly increased the formation of the 5-lipoxygenase products, LTB_4 and LTC_4, from the mucosa *ex vivo*.

3 Pretreatment with the acetohydroxamic acids BW A4C and BW A137C (5–50 mg kg^{-1} p.o.) dose-dependently reduced ethanol-stimulated LTB_4 and LTC_4 formation by the gastric mucosa, with an ID_{50} of approximately 5 mg kg^{-1} p.o.

4 A single oral dose of BW A4C (20 mg kg^{-1}) induced near-maximal inhibition of mucosal LTB_4 formation within 30 min, which was well maintained for 5 h, whereas BW A137C (20 mg kg^{-1} p.o.) induced maximal inhibition between 30 and 60 min after administration, which then diminished over the subsequent 5 h.

5 The mucosal formation of the cyclo-oxygenase product, 6-keto-prostaglandin $F_{1\alpha}$, which was unaltered following ethanol challenge, was not inhibited by the acetohydroxamic acids. Likewise, the small increase in mucosal thromboxane B_2 formation following challenge was not inhibited by BW A4C.

6 Neither BW A4C nor BW A137C, at doses that almost completely inhibited the mucosal synthesis of LTB_4 or LTC_4, reduced the macroscopic gastric mucosal damage induced by ethanol.

7 Pretreatment with the lipoxygenase inhibitor BW 755C (5–50 mg kg^{-1} p.o.) did reduce mucosal damage, but there was a dissociation between the degree of protection and the inhibition of leukotriene biosynthesis.

8 Oral administration of high doses of either BW A4C or BW A137C (300 mg kg^{-1}) did not induce macroscopic gastric damage over a 3 h period.

9 These findings suggest that the leukotrienes, LTB_4 and LTC_4 are not the primary mediators of ethanol-induced acute mucosal damage, but do not exclude their role in more chronic gastric damage and inflammation.

Introduction

A number of observations have led to the proposition that the arachidonic acid metabolites of the 5-lipoxygenase pathway, particularly leukotriene C_4 (LTC_4), may have a role as mediators of gastric ulceration. When applied locally to the rat gastric mucosa *in vivo*, LTC_4 produced venular constriction and vascular stasis in the submucosa (Whittle *et al.*, 1985). The effects of ethanol on the gastric mucosal microvasculature, particularly stasis of blood flow (Guth *et al.*, 1984; Szabo *et al.*, 1985) are similar to those described for LTC_4. In addition, the gastric mucosal damage induced by ethanol is accompanied in both a time- and concentration-dependent manner by the enhanced formation of LTC_4 by the gastric mucosa (Peskar *et al.*, 1986).

Gastric mucosal damage induced by oral ethanol administration to rats is substantially reduced by BW 755C (Wallace & Whittle, 1985), which inhibits leukotriene synthesis in inflammatory exudates (Higgs *et al.*, 1980) and inflamed colon (Boughton-Smith *et al.*, 1988b) in the rat. Pretreatment with the lipoxygenase inhibitor, nordihydroguiaretic acid

(NDGA) reduces both the gastric mucosal damage and the increased LTC_4 release produced by ethanol (Peskar *et al.*, 1986). Protection against ethanol-induced damage by prostaglandin E_2 (PGE_2) does not affect the enhanced leukotriene formation (Dreyling *et al.*, 1986; Boughton-Smith & Whittle, 1987). However, the stable prostaglandin analogue, 16, 16 dimethyl PGE_2 and the anti-ulcer drug, carbenoxolone both protect against ethanol-induced damage and reduce the gastric mucosal formation of leukotrienes (Peskar *et al.*, 1986; Boughton-Smith & Whittle, 1987). These observations, therefore, make it unclear whether the enhanced leukotriene formation that accompanies ethanol challenge contributes to or is a consequence of the resulting gastric mucosal damage.

To study further the relationship between ethanol-induced gastric mucosal damage and the release leukotrienes, the effects of two novel compounds have been investigated, N-(3-phenoxycinnamyl)-acetohydroxamic acid (BW A4C) and N-(4-benzyloxybenzyl)-acetohydroxamic acid (BW A137) (Jackson *et al.*, 1988). These acetohydroxamic acids are potent and selective inhibitors of 5-lipoxygenase, when incubated *in vitro* with human polymorphonuclear leucocytes, and after oral administration to rats, when eicosanoid formation was assessed in whole blood stimulated *ex vivo* with calcium ionophore (Bhattacherjee *et al.*, 1988; Tateson *et al.*, 1988).

A preliminary account of some of this work has been presented to the British Pharmacological Society (Boughton-Smith *et al.*, 1988a).

Methods

Ethanol-induced gastric mucosal damage

Absolute ethanol (1 ml) was administered orally to rats (male, Wistar, 200–220 g) which had been deprived of food overnight (18–20 h) but allowed free access to water. The rats were killed 5 min later by cervical dislocation, and the stomachs removed, opened along the greater curvature and gently rinsed under tap water. The stomachs were pinned out flat on wax blocks and photographed with a Polaroid camera, and the area of mucosal damage was subsequently measured from the photograph by use of computer-aided planimetry (Apple II). In most experiments, segments of mucosa were taken for measurement of eicosanoid formation as described below.

Drug treatment

Individual drugs were investigated by a random experimental design that ensured that different treatments were equally distributed in each experiment. The drugs were suspended in 1% w/v methyl cellulose, using an homogenizer (Ultra-turrax, 30 s), and administered orally 30 min before ethanol. The drugs used were the novel acetohydroxamic acids, BW 4AC and BW A137C (5–50 mg kg^{-1}), and BW 755C (5–50 mg kg^{-1}). Control animals received 1% methyl cellulose only (1 ml kg^{-1} p.o.).

Gastric mucosal eicosanoid formation

The corpus mucosa (100 mg) was stripped from the underlying muscle layer, chopped with scissors (15 times) and incubated in Tyrode solution (1 ml) for 20 min (37°C). Following centrifugation (800 *g*, 4°C; 2 min) in a bench top centrifuge (Hettich, Micro rapid/k) the supernatants were placed in boiling water for 2 min, to remove protein, as described by Peskar *et al.* (1986), and after a further centrifugation (800 *g*, 4°C; 2 min), eicosanoids in the boiled supernatant were subsequently determined by specific radioimmunoassays (RIA).

Radioimmunoassay

The levels of the eicosanoids LTB_4, LTC_4, 6-keto-$PGF_{1\alpha}$ and in some experiments thromboxane B_2 (TXB_2), were measured directly from the final mucosal supernatants after appropriate dilution. Cross-reactivities have previously been determined for anti-sera to LTB_4 (Salmon *et al.*, 1982), LTC_4 (Aehringhaus *et al.*, 1982) 6-keto-$PGF_{1\alpha}$ and TXB_2 (Salmon, 1978). The anti-sera to LTC_4 cross-reacts by up to 40% with LTD_4 (Aehringhaus *et al.*, 1982). However, the immunoreactive-LTC_4 formed by the rat gastric mucosa after ethanol challenge co-migrates on reverse phase-h.p.l.c. almost exclusively with LTC_4 (Peskar *et al.*, 1986; Boughton-Smith & Whittle, 1988).

Time course studies

A single oral dose of BW A4C or BW A137C (20 mg kg^{-1}) was administered to fasted rats, as described above. In the dose ranging studies, this dose produced near-maximal inhibition of leukotriene formation after 30 min. Groups of treated rats were challenged with ethanol at intervals of 0.5 to 8 h later and mucosal damage and eicosanoid formation measured as described above.

Acute effects of acetohydroxamic acids on the gastric mucosa

Rats (male, Wistar, 165–185 g) were housed individually and fasted overnight but allowed free access to water. The acetohydroxamic acids (suspended in 1% methyl cellulose) were administered orally

($1\,ml\,kg^{-1}$) at a dose of $300\,mg\,kg^{-1}$. Aspirin ($200\,mg\,kg^{-1}$) and indomethacin ($10\,mg\,kg^{-1}$) were administered orally in the same manner, and in another group of rats, indomethacin (dissolved in 2.5% w/v $NaHCO_3$) was administered by the subcutaneous route. After 3 h, the rats were killed by cervical dislocation, the stomachs removed, opened along the lesser curvature and macroscopic gastric mucosal lesions assessed in a randomized, blinded fashion using a scoring system based on the number and length of lesions (Whittle, 1976). This method of lesion measurement was adopted since the nature and extent of the lesions were not of sufficient intensity to be assessed accurately as % area of mucosa.

Drugs and materials

The acetohydroxamic acids, BW A4C and BW A137C (N-(3-phenoxycinnamyl) and N-(4-benzyloxybenzyl)-acetohydroxamic acid) were synthesized as described by Jackson *et al.* (1988) in the Dept. of Therapeutic Chemistry, Wellcome Research Laboratories, Beckenham, Kent. Indomethacin and aspirin were obtained from Sigma Chemical Company (St Louis, U.S.A.). BW 755C (3-amino-[m-(trifluoromethyl)-phenyl]-2-pyrazoline) as the hydrochloride, absolute alcohol (99.7%) and Tyrode solution were from the Wellcome Research Laboratories.

Statistical analysis

Eicosanoid formation by the gastric mucosa following the 20 min incubation was calculated as $ng\,g^{-1}$ tissue. In the drug studies, the results are expressed as % of the ethanol control. Mucosal damage induced by ethanol was calculated as % of the total area of the mucosa. The results are presented as the mean ± s.e.mean and statistical significance calculated by use of Student's unpaired *t* test (two tailed) with a value of $P < 0.05$ being taken as significant.

Results

Ethanol-induced gastric damage

Oral administration of absolute ethanol resulted, after 5 min, in haemorrhagic damage involving 40 ± 3% of the total mucosal area (mean ± s.e.mean, $n = 29$, $P < 0.01$).

The mucosal damage was accompanied by changes in mucosal eicosanoid formation (Figure 1). The corpus mucosa from control stomachs formed significant amounts of immunoreactive

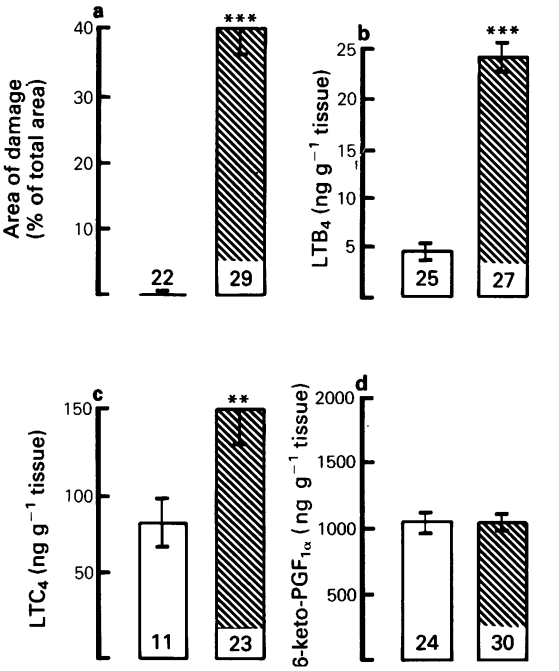

Figure 1 Gastric mucosal damage and eicosanoid formation after oral administration of absolute ethanol (1 ml, 5 min) (hatched columns). The area of gastric mucosal damage (% of total area) (a) and mucosal formation of eicosanoids; (b) leukotriene B_4 (LTB_4), (c) LTC_4 and (d) 6-keto-prostaglandin $F_{1\alpha}$ ($ng\,g^{-1}$ tissue) are the mean of (*n*) experiments (figures in columns); vertical bars indicate s.e.mean. Statistically significant difference from control (open columns) is shown as $^{**}P < 0.01$, $^{***}P < 0.001$.

LTB_4 ($4.5 \pm 0.4\,ng\,g^{-1}$ tissue, $n = 25$), LTC_4 ($68 \pm 14\,ng\,g^{-1}$, $n = 11$) and 6-keto-$PGF_{1\alpha}$ ($1057 \pm 88\,ng\,g^{-1}$, $n = 24$). Following mucosal damage by ethanol there were marked increases in the mucosal formation of LTB_4 (5.3 fold) and LTC_4 (2.2 fold), whereas the formation of 6-keto-$PGF_{1\alpha}$ was unchanged (Figure 1). In some experiments where TXB_2 was measured as an additional cyclooxygenase product, there was a small but significant increase in the mucosal formation of TXB_2 following ethanol-induced damage (from $219 \pm 21\,ng\,g^{-1}$, $n = 11$ to $364 \pm 33\,ng\,g^{-1}$, $n = 14$, $P < 0.01$).

Effect of acetohydroxamic acids

Pretreatment with BW A4C ($5–50\,mg\,kg^{-1}$ p.o.) resulted in a dose-related inhibition in the formation of LTB_4 and LTC_4 by the mucosa after ethanol challenge ($ID_{50} \leqslant 5\,mg\,kg^{-1}$ p.o.) (Figure 2). The gastric mucosal damage induced by ethanol was not

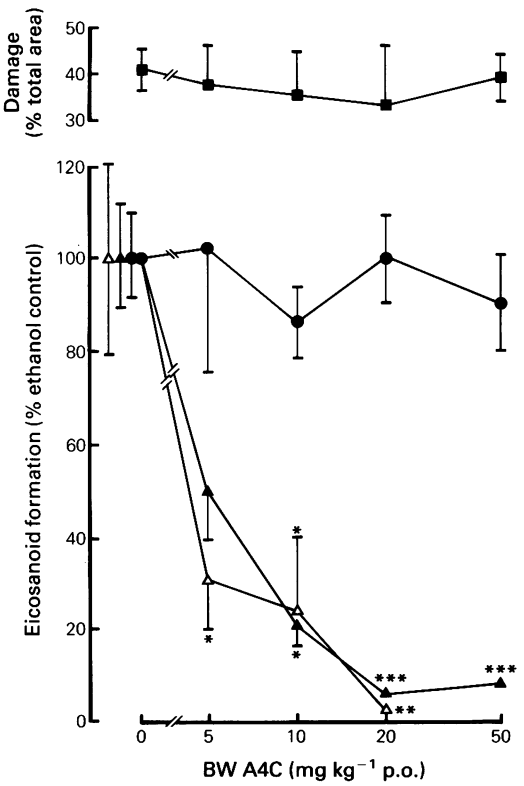

Figure 2 Effect of BW 4AC on ethanol-induced gastric mucosal damage (■) and the formation of leukotriene C_4 (LTC_4) (△), LTB_4 (▲) and 6-keto-prostaglandin $F_{1\alpha}$ (●). Rats were dosed with BW 4AC (5–50 mg kg^{-1} p.o.) 30 min before absolute ethanol (1 ml, p.o.). The gastric mucosal damage (% total area) and eicosanoid formation by segments of mucosa (calculated as % ethanol control) are the mean of 5–6 animals per experimental group and vertical lines indicate s.e.mean. Statistical significance, compared to ethanol control, is shown as $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

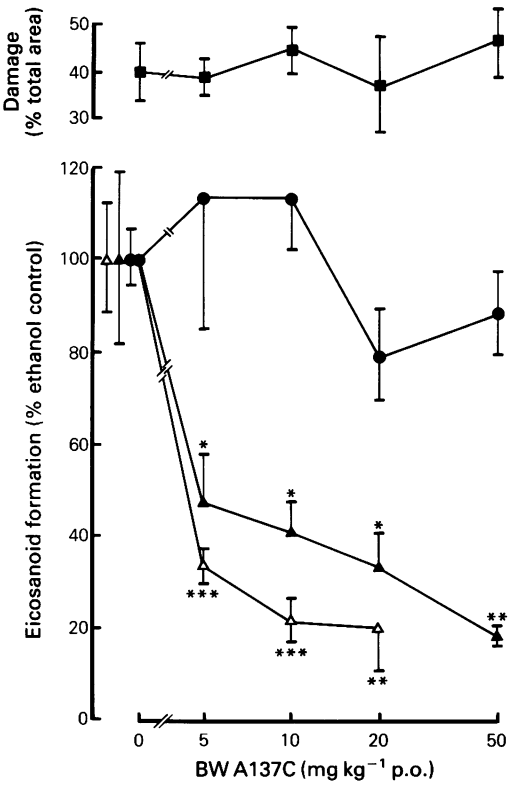

Figure 3 Effect of BW A137C on ethanol-induced gastric mucosal damage (■) and the formation of leukotriene C_4 (LTC_4) (△), LTB_4 (▲) and 6-keto-prostaglandin $F_{1\alpha}$ (●). Rats were dosed with BW A137C (5–50 mg kg^{-1} p.o.) 30 min before ethanol (1 ml, p.o.). The gastric mucosal damage (% total area) and eicosanoid formation by segments of mucosa (calculated as % ethanol control) are the mean of 5–6 animals per experimental group and vertical lines indicate s.e.mean. Statistical significance, compared to ethanol control, is shown as $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

affected by BW A4C, even at doses (20 mg kg^{-1} p.o.) that near-maximally inhibited the formation of both LTB_4 ($94 \pm 1\%$ inhibition, $n = 6$, $P < 0.001$) and LTC_4 ($97 \pm 1\%$ inhibition, $n = 6$, $P < 0.001$). None of the doses of BW A4C used significantly affected the mucosal synthesis of 6-keto-$PGF_{1\alpha}$ or the other cyclo-oxygenase product, TXB_2.

Similar effects on eicosanoid formation were seen following pretreatment with BW A137C. This acetohydroxamic acid also dose-dependantly inhibited the mucosal formation of LTB_4 and LTC_4, having a similar potency to BW A4C ($ID_{50} \leqslant 5$ mg kg^{-1} p.o.). However, even at a dose (20 mg kg^{-1} p.o.) which produced substantial inhibition of the formation of LTB_4 ($67 \pm 8\%$ inhibition, $n = 6$, $P < 0.05$) and LTC_4 ($79 \pm 10\%$ inhibition, $n = 6$, $P < 0.05$), BW A137C had no effect on gastric mucosal damage induced by ethanol (Figure 3). The synthesis of 6-keto-$PGF_{1\alpha}$ was not affected by treatment with BW 137C (Figure 3).

Time course studies

A single oral dose of BW A4C (20 mg kg^{-1}) resulted in near-maximal inhibition of the mucosal formation of LTB_4 within 30 min and this was maintained for up to 5 h (Figure 4). By 8 h, the mucosal formation of LTB_4 had returned towards control levels. Inhibition of LTB_4 formation by BW A137C (20 mg kg^{-1}) was maximal at 30 min and 1 h but thereafter

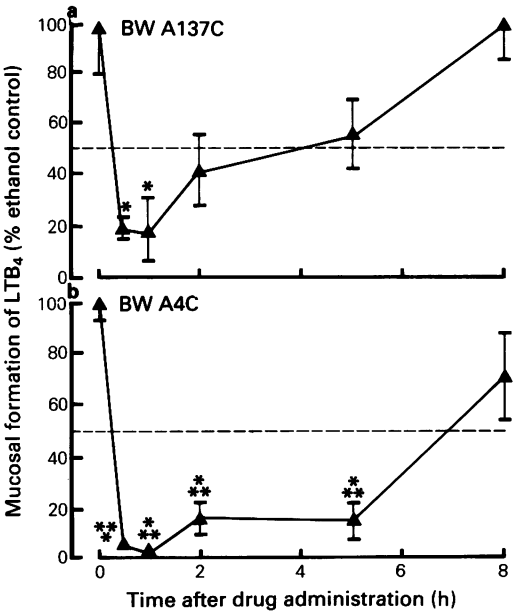

Figure 4 Time course studies on the effects of a single oral dose (20 mg kg^{-1}) of (a) BW A137C or (b) BW A4C on ethanol-induced (1 ml, p.o.) gastric mucosal leukotriene B_4 (LTB_4) formation. The results expressed as % of the ethanol control are the mean of 5–6 animals in each experimental group; vertical lines indicate s.e.mean. Statistical significance, difference from the ethanol control is shown as $*P < 0.05$, $***P < 0.001$.

returned towards control levels. At none of the time periods after administration of BW A4C or BW A137C was there a significant reduction in the mucosal damage produced by ethanol or in the synthesis of 6-keto-$PGF_{1\alpha}$.

Effects of BW 755C

Pretreatment with BW 755C had no effect on eicosanoid formation at doses up to 10 mg kg^{-1} although at this dose there was a significant reduction in ethanol-induced damage ($45 \pm 11\%$ inhibition, $n = 5$, $P < 0.05$). Higher doses of BW 755C (20 mg kg^{-1}) substantially inhibited the mucosal formation of LTB_4 ($79 \pm 4\%$ inhibition, $n = 5$, $P < 0.01$) and LTC_4 ($92 \pm 2\%$ inhibition, $n = 5$, $P < 0.01$) but there was no further reduction in damage. However, at the highest dose of BW 755C (50 mg kg^{-1}) the mucosal damage was further reduced (to $63 \pm 12\%$ inhibition, $n = 5$, $P < 0.01$), whereas there was no further reduction in leukotriene synthesis (Figure 5). BW 755C had no significant effect on the mucosal synthesis of 6-keto-$PGF_{1\alpha}$ or TXB_2 at the doses used.

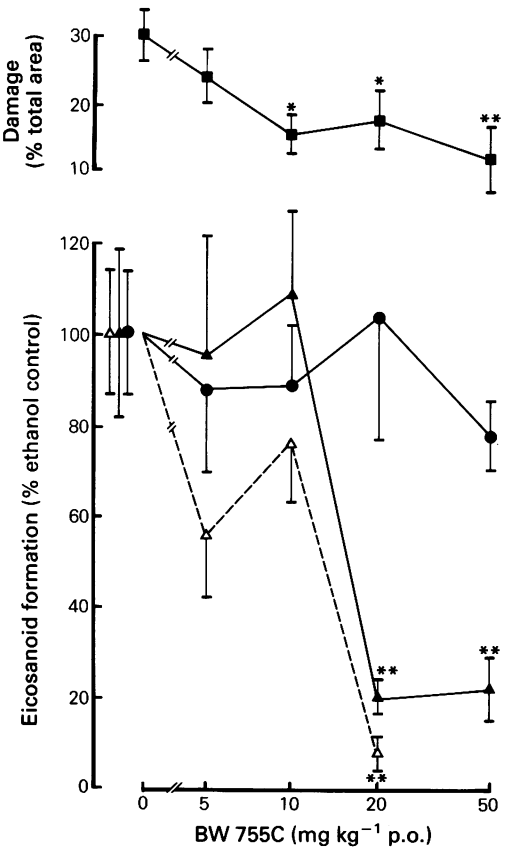

Figure 5 Effect of BW 755C on ethanol-induced gastric mucosal damage (■) and the formation of leukotriene C_4 (LTC_4) (△). LTB_4 (▲) and 6-keto-prostaglandin $F_{1\alpha}$ (●). Rats were dosed with BW 755C (5–50 mg kg^{-1} p.o.) 30 min before ethanol (1 ml, p.o.). The gastric mucosal damage (% total area) and eicosanoid formation by segments of mucosa (calculated as % ethanol control) are the mean of 5–6 animals per experimental group and vertical lines indicate s.e.mean. Statistical significance, compared to ethanol control, is shown as $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

Acute effects of acetohydroxamic acids on the gastric mucosa

Three hours after the oral administration of either BW A4C or BW A137C (300 mg kg^{-1}) there were no macroscopically-apparent lesions in the gastric mucosa. In contrast, 3 h after either oral or subcutaneous administration of indomethacin (10 mg kg^{-1}), there were discrete haemorrhage lesions on the rugal folds of the mucosa, as previously described (Whittle, 1976). Similarly, oral administration of aspirin (200 mg kg^{-1}) resulted in the appearance of haemorrhagic lesions in the gastric mucosa (Figure 6).

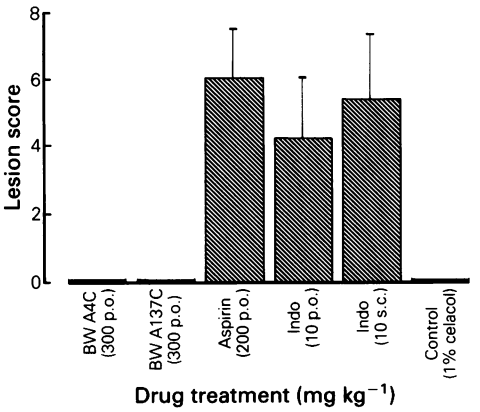

Figure 6 The macroscopically-assessed effects on the rat gastric mucosa, 3 h after oral administration of BW A4C or BW A137 (300 mg kg^{-1}), aspirin (200 mg kg^{-1}) or indomethacin (Indo; 10 mg kg^{-1}). In a further group, indomethacin (10 mg kg^{-1}) was also administered subcutaneously. Drugs were suspended in 1% methyl cellulose and lesion scores (assessed from the number and length of mucosal lesions) are the mean from 8–10 rats per group; vertical bars show s.e.mean.

BW A4C and BW A137C (300 mg kg^{-1}) had no significant effect on the mucosal synthesis of 6-keto-$PGF_{1\alpha}$ (99 ± 12% and 113 ± 22% of control respectively, $n = 6$ for both), determined 3 h after oral administration. In contrast, oral administration of indomethacin (10 mg kg^{-1}) or aspirin (200 mg kg^{-1}) significantly inhibited the gastric mucosal formation of 6-keto-$PGF_{1\alpha}$ (76 ± 6% and 94 ± 3% inhibition respectively; $n = 6$, $P < 0.001$ for both), determined after 3 h.

Discussion

The gastric mucosal damage induced by ethanol was accompanied by increases in the mucosal synthesis of LTC_4 and LTB_4 as described before (Peskar *et al.*, 1986; Boughton-Smith & Whittle, 1987). We have previously confirmed the identity of the ethanol-stimulated mucosal leukotrienes by reversed phase h.p.l.c., where the peaks of the immunoreactive LTB_4 and LTC_4 co-eluted virtually exclusively with the authentic standard leukotrienes (Boughton-Smith & Whittle, 1988). The mucosal formation of the cyclo-oxygenase metabolite prostacyclin, determined as its stable breakdown product 6-keto-$PGF_{1\alpha}$, was unchanged after challenge with ethanol, while there was a small increase in mucosal TXB_2 formation.

The novel acetohydroxamic acids used in the present study, BW A4C and BW A137C were potent and selective inhibitors of ethanol-stimulated mucosal leukotriene synthesis. The acetohydroxamic acids were approximately equi-potent inhibitors of the mucosal synthesis of LTC_4 and LTB_4, indicating an inhibitory action on the common 5-lipoxygenase enzyme pathway required for the synthesis of these different leukotrienes. The results, therefore, support previous findings in which the acetohydroxamic acids selectively inhibited 5-lipoxygenase when incubated *in vitro* with human polymorphonuclear (PMN) leucocytes and also after oral administration to rats, when eicosanoid formation was estimated in whole blood challenged with calcium ionophore *ex-vivo* (Bhattacherjee *et al.*, 1988; Tateson *et al.*, 1988). In other studies in the rat, BW A4C exhibited a comparable potency following oral administration to that in the present study, for the inhibition of LTB_4 formation in inflammatory exudates (Higgs *et al.*, 1988). In addition, both BW A4C and BW A137C reduced the leukotriene-dependant component of anaphylactic bronchoconstriction in the guinea-pig (Payne *et al.*, 1988).

Neither acetohydroxamic acid prevented the gastric mucosal damage produced by ethanol, even at doses that near-maximally inhibited the mucosal synthesis of LTB_4 and LTC_4. These results therefore, provide evidence against a role for these leukotrienes as primary mediators of the acute mucosal damage induced by ethanol in the rat.

The lipoxygenase inhibitor, BW 755C, prevented the gastric mucosal damage induced by ethanol, as previously demonstrated using acidified ethanol (Wallace & Whittle, 1985). As shown before, BW 755C did not inhibit the formation of the cyclo-oxygenase products, 6-keto-$PGF_{1\alpha}$ and TXB_2 (Whittle *et al.*, 1980; Wallace & Whittle, 1985). In the present study, BW 755C was shown to inhibit the mucosal synthesis of LTB_4 and LTC_4. However, the potency of BW 755C in preventing ethanol-induced damage was not directly correlated with inhibition of leukotriene synthesis. Thus, BW 755C reduced damage at a dose which did not affect leukotriene synthesis, and conversely when leukotriene synthesis was near-maximally inhibited by BW 755C, there was still significant damage produced by ethanol.

It is possible, therefore, that BW 755C may protect the gastric mucosa by a mechanism unrelated to inhibition of leukotriene synthesis, perhaps by its anti-oxidant properties (Marnett *et al.*, 1982; Pekoe *et al.*, 1982). Indeed, the powerful free radical scavenger, nordihydroguiaretic acid (NDGA) also prevents ethanol-induced gastric damage (Peskar *et al.*, 1986). These authors suggested that the protection of the gastric mucosa by NDGA was through the observed inhibition of LTC_4 synthesis (Peskar *et al.*, 1986). However, the reduced mucosal synthesis of LTC_4 may occur in part as a consequence of a

reduction in ethanol-induced damage. Although NDGA is a potent inhibitor of lipoxygenase enzymes *in vitro* (Hamberg, 1986; Bhattacherjee *et al.*, 1988) we have been unable to demonstrate inhibition of lipoxygenase by NDGA in rat whole blood *ex vivo* (Bhattacherjee *et al.*, 1988). A further possibility is that BW 755C may act by inhibiting 12- or 15-lipoxygenase (Randall *et al.*, 1980) and that products from these enzyme pathways, such as hydroperoxy metabolites, are involved in ethanol-induced damage. In this respect, the acetohydroxamic acids are at least 24 times less potent inhibitors of 12- and 15-lipoxygenase *in vitro* compared to 5-lipoxygenase enzymes (Bhattacherjee *et al.*, 1988; Tateson *et al.*, 1988).

The acetohydroxamic acids, even in high doses, did not affect the synthesis of 6-keto-$PGF_{1\alpha}$ by the gastric mucosa. Furthermore, BW A4C did not inhibit the mucosal formation of TXB_2, thus supporting previous studies in which the acetohydroxamic acids did not inhibit TXB_2 formation in rat whole blood *ex vivo* (Tateson *et al.*, 1988). In contrast to the cyclo-oxygenase inhibitors, aspirin and indomethacin, administered at doses that inhibited mucosal prostaglandin formation, oral administration of the acetohydroxamic acids, even at doses some 50 times those required to inhibit gastric mucosal leukotriene formation, did not produce gastric mucosal lesions over a three hour period. These results indicate that unlike inhibition of the formation of protective prostaglandins, inhibition of leukotriene synthesis does not compromise the integrity of the gastric mucosa.

The failure of the acetohydroxamic acid 5-lipoxygenase inhibitors to prevent ethanol-induced acute gastric damage, while suggesting that LTB_4 and LTC_4 are not the primary mediators of acute damage, does not preclude a role for the leukotrienes in the pathogenesis of other forms of gastric damage, or as mediators of chronic gastric ulceration or mucosal inflammation. The potent actions of the leukotrienes on the mucosal vasculature and on the activation of inflammatory cells may be important in maintaining more chronic gastric mucosal damage, especially where there is an inflammatory infiltrate. If the leukotrienes are involved in aspects of chronic gastric ulceration and inflammation, inhibitors of gastric mucosal 5-lipoxygenase, such as the acetohydroxamic acids may facilitate repair of the gastric mucosa and therefore could have clinical value. The lack of gastric toxicity of these compounds, as demonstrated in acute studies by macroscopic observation, will be of considerable advantage in any other future clinical use of these acetohydroxamic acids, for example, in the treatment of asthma.

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