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Aspirin-induced gastric mucosal damage: prevention by enteric-coating and relation to prostaglandin synthesis

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1 Gastric damage induced by low-dose aspirin and the protective effect of enteric-coating was assessed in healthy volunteers in a double-blind placebo-controlled cross-over trial using Latin square design. Each was administered placebo, plain aspirin 300 mg daily, plain aspirin 600 mg four times daily, enteric-coated aspirin 300 mg daily, or enteric-coated aspirin 600 mg four times daily for 5 days. Gastric damage was assessed endoscopically, and gastric mucosal bleeding measured.

2 Aspirin 300 mg daily and 600 mg four times daily caused significant increases in gastric injury compared with placebo. Gastric mucosal bleeding was significantly more with the high dose, with a trend towards increased gastric erosions, compared with the low dose.

3 Enteric-coating of aspirin eliminated the injury caused by low dose aspirin and substantially reduced that caused by the higher dose.

4 All dosages and formulations caused similar inhibition of gastric mucosal prostaglandin E_2 synthesis.

5 Serum thromboxane levels were suppressed equally with plain and enteric-coated aspirin.

6 In this short-term study in healthy volunteers, gastric toxicity from aspirin was largely topical, independent of inhibition of prostaglandin synthesis, and could be virtually eliminated by the use of an enteric-coated preparation.

Keywords aspirin prostaglandin E_2 thromboxane gastric ulcer

Introduction

Aspirin and non-steroidal anti-inflammatory drugs are known to be harmful to the gastric mucosa and are associated with an increased incidence, prevalence and complication rate for peptic ulcers. Estimates of the level of risk vary. Prospective cohort studies suggest a 50% enhancement (Beard *et al.*, 1987; Carson *et al.*, 1987). Case control studies place the relative risk at between three and five (Armstrong & Blower, 1987; Faulkner *et al.*, 1988 & Somerville *et al.*, 1986), whilst uncontrolled endoscopic studies have suggested a much greater risk (Collins & du Toit, 1987; Farah *et al.*, 1988; Larkai *et al.*, 1987).

It is unclear whether there is a dose threshold or dose dependence. Graham & Lacey Smith (1986) have suggested that the effects of aspirin are dose dependent but this assessment may be subject to bias resulting from differential endoscopy rates. In contrast the US Physicians' Study of aspirin 325 mg on alternate days (Steering Committee of the Physicians Health Study Research Group 1989), found a highly significant increase in the number of patients developing melaena, with a relative risk of approximately 1.5, a figure identical to that reported in the only comparable cohort study of gastrointestinal bleeding in patients on full-dose NSAIDs (Carson *et al.*, 1987). The possibility that low dose aspirin causes a significant increase in peptic ulceration and upper gastrointestinal bleeding is supported by the study of Peto *et al.* (1988) of British doctors receiving aspirin 500 mg daily, whilst data from the UK Transient Ischaemic Attack Study (Antiplatelet Trialists' Collaboration, 1988) are less clear cut.

In view of the increasing use of low dose aspirin prophylaxis for cardiovascular disease it is important to define the level of risk pertaining to this treatment and to identify optimum methods to avoid gastric injury. We have previously shown that aspirin 75 mg or 300 mg daily causes significant gastric damage in humans, as assessed by gastric mucosal bleeding (Prichard *et al.*, 1989). We now report a comparison of gastric injury by aspirin 300 mg and 2.4 g daily, assessed endoscopically, and the effectiveness of enteric-coating as a means of avoiding it.

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Methods

Subjects

Twenty volunteers (10 male, ages 21–29 years) gave written, informed consent to participate in the study, which was approved by the Nottingham Medical School ethics committee. All were healthy, and had no history of gastro-intestinal disease, dyspepsia, easy bruising or bleeding or aspirin intolerance. All had a normal blood and platelet count, and prothrombin time prior to study entry. All subjects refrained from drugs (apart from the contraceptive pill) and alcohol during the study periods.

Trial design

There were five different treatments given to each volunteer: a) placebo; b) aspirin 300 mg daily; c) enteric-coated aspirin (Nu-Seals, Eli Lilly, Basingstoke, Hants UK) 300 mg daily; d) aspirin 600 mg four times daily; e) enteric-coated aspirin 600 mg four times daily.

Drugs were given with 50 ml of water at 07.00 h (except on study day when given at 05.30 h), 12.30 h, 17.30 h, 20 min before meals, and at 23.00 h (no food). The five treatments were given according to a Latin square design so that any sequence effect was eliminated, and administration was double-blind, by use of the double-dummy technique. Each treatment was given for 4 days with a final dose on the morning of the fifth day, which was the study day. There was a wash-out period of 10 days between each treatment.

Sample collection

Subjects fasted from midnight on the evening before the study day, and at 07.00 h, 90 min after the final dose of drug, they swallowed a French gauge 16 Salem sump orogastric tube as far as the 55 cm mark. Resting gastric juice was aspirated and the stomach rinsed rapidly three times with 100 ml distilled water. After 5 min 2 mg of phenol red was introduced in 15 ml of distilled water and dispersed around the stomach by a standard series of manoevres. Subjects lay on their left side to minimize loss of gastric contents through the pylorus. After nine minutes 100 ml distilled water was introduced, dispersed around the stomach, and aspirated at 10 min. Aspirated samples were saved on ice for assay of haemoglobin. The procedure was repeated three times, with two rapid washes between each to remove residual phenol red marker.

Concentration of blood in the gastric washings was measured by the orthotolidine method (Prichard *et al.*, 1989), and loss of gastric contents or failure of reaspiration corrected for by phenol red recovery, (measured spectrophotometrically at 560 nm).

Endoscopy

Subjects were then endoscoped using an Olympus GIF-XP20 endoscope. Intramucosal haemorrhages, haemorrhagic erosions and non-haemorrhagic erosions in the oesophagus, gastric fundus, gastric antrum, or duodenum were noted separately. Injury in each of these areas was quantitated by counting the number of lesions and by use of visual analogue scales. In addition, to relate our findings to those used in previous studies, adapted Lanza scores were also derived, (Table 1); similar to those used in other studies (Ehsanullah *et al.*, 1988; Lanza *et al.*, 1988).

Table 1 Endoscopic score (adapted from Lanza *et al.*, 1988; Ehsanullah *et al.*, 1988)

Score	*Endoscopic appearance*
0	Normal mucosa
1	Mucosal erythema
2	1–5 erosions
3	6–10 erosions
4	> 10 erosions

Observer variability

In 12 subjects two endoscopists scored the endoscopic appearance independently, and scores were compared to give the interobserver variability both according to the type of lesion, and also the area of stomach (body or antrum).

Gastric biopsies

After visual assessment, two pairs of biopsies were then taken from the dependent portion of the greater curve, between 45 and 55 cm from the incisor teeth. Each pair was placed in 1 ml of Tris saline (pH 7.4) in polypropylene Eppendorf vials on ice, for assay of *ex vivo* eicosanoid synthesis.

Biopsies were mechanically stimulated as previously described (Whittle, 1981). Pairs of gastric biopsies were vortex mixed for 6 s using a bench mixer (Whirli-mixer , Fisons PLC, Loughborough, U.K.), and then centrifuged in an Eppendorf bench centrifuge at 10,000 *g* for 10 s. The supernatant was discarded, and replaced by fresh Tris saline buffer. This wash was repeated and then the biopsies were vortex mixed for 1 min in 300 μl of buffer. They were then centrifuged again for 10 s and the supernatant was saved at −40° C. These were assayed by radioimmunoassay for prostaglandin E_2 (PGE_2), (antibody from Sigma Chemical Co., Poole, Dorset, U.K.), and thromboxane B_2 (TXB_2), (antibody provided by Professor L. Levine, Waltham, Mass. U.S.A.).

Serum thromboxane and salicylate determination

A blood sample was taken 3 h after the last dose of aspirin, through a 19 gauge needle, and incubated without anticoagulation for 1 h in glass tubes at 37° C. The serum was then saved at −40°C for thromboxane B_2 radioimmunoassay. Blood (5 ml) was also taken for serum total salicylate determinaton.

Statistics

The endoscopic signs of mucosal injury with different aspirin doses and preparations were compared using the non-parametric Friedman analysis of variance technique. Individual differences were than identified using the Wilcoxon test. These data were expressed as median and

interquartile range. Correlations between gastric mucosal bleeding and serum salicylate levels were assessed by Spearman rank correlation and regression slope compared for plain and enteric-coated preparations.

Data for gastric mucosal bleeding were log transformed to approximate a normal distribution and compared by analysis of variance for subject and treatment. Data are expressed as geometric mean and 95% confidence limits. Factorial analysis of variance was used to quantitate the dose dependence of aspirin and the protective effect of enteric coating against mucosal bleeding.

Results

Gastric damage: endoscopic assessment

Inter-observer agreement Inter-observer correlation of endoscopic damage scores was good; Spearman correlation coefficient was 0.63 ($P < 0.001$) for overall number of lesions, and 0.85 ($P < 0.001$) for visual analogue score. When analyzed separately according to type of lesion, it was found that correlation was poor for intramucosal haemorrhages, ($r_s = 0.34$, $P = 0.043$), (which were few in number compared with haemorrhagic erosions), but much better for haemorrhagic erosions and non-haemorrhagic erosions ($r_s = 0.7$ and 0.83 respectively, $P < 0.001$). Subsequent data analysis includes only erosions, haemorrhagic or non-haemorrhagic.

Effect of aspirin Both doses of aspirin caused a similar pattern of gastric mucosal injury. The most common lesions were harmorrhagic erosions in the body where virtually no non-haemorrhagic erosions were seen (Figure 1a and 1c). The pattern of injury in the antrum was different: non-haemorrhagic erosions were most common although haemorrhagic erosions were also seen (Figures 1b and 1d). Haemorrhagic erosion scores in the body increased from 0 (median, interquartile range 0–0.25) on placebo to 2 (0–5) on aspirin 300 mg daily ($P < 0.01$) and to 4 (0.5–8.5) on aspirin 2.4 g ($P < 0.01$). Differences between the two doses of aspirin did not achieve statistical significance. The increase in non-haemorrhagic erosions in the antrum was significant for aspirin 2.4 g daily (Figure 1d), but not for aspirin 300 mg daily. These changes were generally reflected in assessments of injury using visual analogue scales, but here differences between the score for antral injury with aspirin 300 mg (11 [0–16]) and with aspirin 2.4 g (28 [18–43]) were significant ($P < 0.05$), (Table 2).

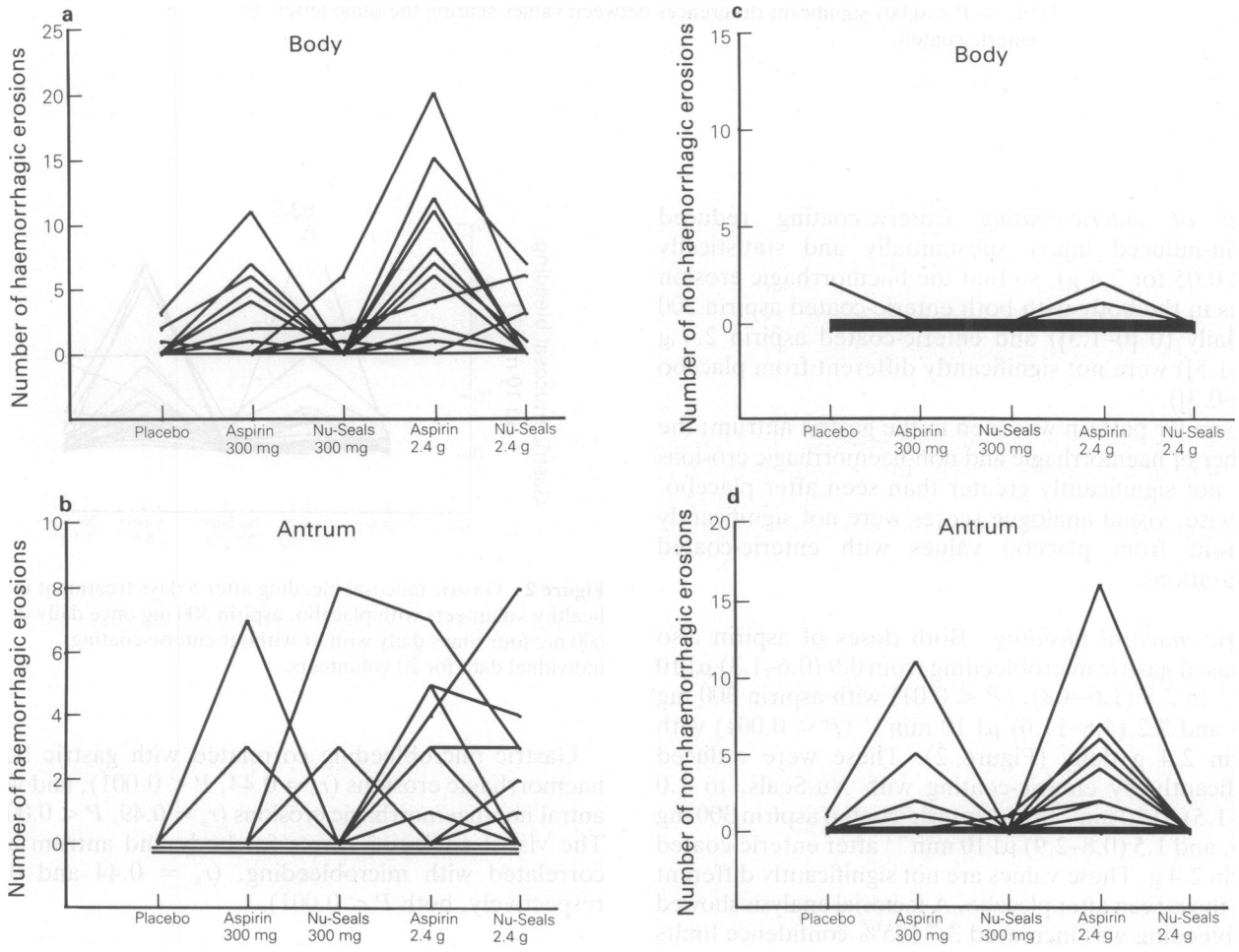

Figure 1 Effect of 5 days treatment in healthy volunteers with placebo, aspirin 300 mg once daily or 600 mg four times daily with or without enteric-coating; number of lesions observed endoscopically in 15 volunteers, individual data shown. a) gastric body haemorrhagic erosions; b) gastric antrum haemorrhagic erosions; c) gastric body non-haemorrhagic erosions; d) gastric antrum non-haemorrhagic erosions.

Table 2 Gastric mucosal damage: effect of 5 days treatment in healthy volunteers with placebo, aspirin 300 mg once daily or 600 mg four times daily with or without enteric-coating; assessment by adapted Lanza score of lesions, and visual analogue damage score (n = 15), and by microscopic bleeding (n = 20)

	Placebo	*Aspirin 300 mg*	*Aspirin-EC 300 mg*	*Aspirin 2.4 g*	*Aspirin-EC 2.4 g*
Gastric body					
Haemorrhagic* erosion score	0 (0–0.3)	2^{b} (0–5)	0^{e} (0–1.3)	4^{bde} (0.8–8.8)	0^{d} (0–1.5)
Non-haemorrhagic erosion score*	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
Visual analogue score*	0 (0–8)	5 (0–31)	0^{e} (0–8)	$24^{aee'}$ (14–52)	$3^{e'}$ (0–17)
Gastric antrum					
Haemorrhagic erosions*	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–3.3)	0 (0–0.3)
Non-haemorrhagic erosions*	0 (0–0)	0 (0–0.3)	0^{e} (0–0)	$2^{bee'}$ (0–5)	$0^{e'}$ (0–0)
Visual analogue score*	0 (0–6)	11^{ad} (0–16)	$0^{d'}$ (0–14)	$28^{bdd'}$ (18–43)	10 (0–18)
*Gastric mucosal bleeding (μl 10 min^{-1})***					
	0·9 (0·6–1.3)	2.8^{bde} (1.6–4.8)	1.0^{ef} (0.6–1.5)	7.2^{cdf} (4.8–11)	1.5 (0.8–2.9)

* – Median (interquartile range); ** – Geometric mean (95% confidence intervals); [a] – $P < 0.05$, [b] – $P < 0.01$, [c] – $P < 0.001$ compared with placebo; [d] – $P < 0.05$, [e] – $P < 0.01$, [f] – $P < 0.001$ significant differences between values sharing the same letter. EC – enteric-coated.

Effect of enteric-coating Enteric-coating reduced aspirin-induced injury substantially and statistically ($P < 0.05$ for 2.4 g), so that the haemorrhagic erosion scores in the body with both enteric-coated aspirin 300 mg daily (0 [0–1.3]) and enteric-coated aspirin 2.4 g (0[0–1.5]) were not significantly different from placebo (0 [0–0.3]).

A similar pattern was seen in the gastric antrum; the number of haemorrhagic and non-haemorrhagic erosions were not significantly greater than seen after placebo. Likewise, visual analogue scores were not significantly different from placebo values with enteric-coated preparations.

Gastric mucosal bleeding Both doses of aspirin also increased gastric microbleeding from 0.9 (0.6–1.3) μl 10 min^{-1} to 2.8 (1.6–4.8), ($P < 0.01$) with aspirin 300 mg daily and 7.2 (4.8–11.0) μl 10 min^{-1} ($P < 0.001$) with aspirin 2.4 g daily (Figure 2). These were reduced significantly by enteric-coating with Nu-Seals, to 1.0 (0.6–1.5) μl 10 mn^{-1} after enteric-coated aspirin 300 mg daily, and 1.5 (0.8–2.9) μl 10 min^{-1} after enteric-coated aspirin 2.4 g. These values are not significantly different from those seen after placebo. A factorial analysis showed that bleeding was increased 3.7 (95% confidence limits 2.2–6.1)-fold by aspirin 2.4 g daily compared with aspirin 300 mg daily and that the effect of enteric-coated aspirin was to reduce gastric microbleeding by a factor of 2.2 (1.3–3.7).

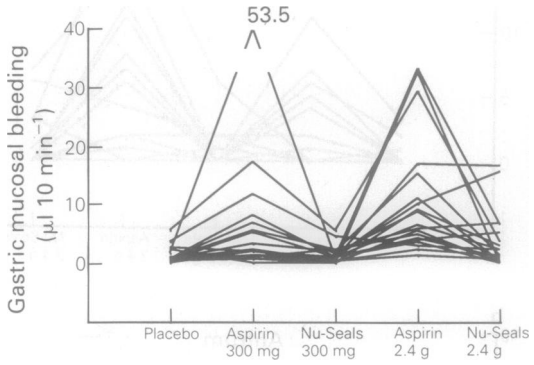

Figure 2 Gastric mucosal bleeding after 5 days treatment in healthy volunteers with placebo, aspirin 300 mg once daily or 600 mg four times daily with or without enteric-coating; individual data for 20 volunteers.

Gastric microbleeding correlated with gastric body haemorrhagic erosions ($r_s = 0.44$, $P < 0.001$), and with antral non-haemorrhagic erosions ($r_s = 0.49$, $P < 0.001$). The visual analogue scores for body and antrum also correlated with microbleeding, (r_s = 0.44 and 0.47 respectively, both $P < 0.001$).

Gastric mucosal PGE_2 and serum TXB_2 synthesis All doses of aspirin were associated with significantly reduced gastric mucosal synthesis of PGE_2 and TXB_2 (Figure 3a and 3b, Table 3). PGE_2 synthesis was reduced from 18

Table 3 *Ex vivo* PGE_2 and TXB_2 synthesis from gastric biopsies stimulated by vortex mixing for 1 min as described in text ($n = 15$), serum salicylate levels ($n = 20$) and serum TXB_2 levels (expressed as percentage of value after placebo) after 5 days treatment with aspirin 300 mg daily or 600 mg four times daily, with plain or enteric-coated preparation. Median and interquartile range

	Placebo	*Aspirin 300 mg*	*Aspirin-EC 300 mg*	*Aspirin 2.4 g*	*Aspirin-EC 2.4 g*
Gastric mucosa PGE_2 synthesis (pg mg^{-1})	18 (1–51)	0.7 (0.4–11)	1.8 (0.5–9.2)	2.8 (1.2–7.6)	0.6 (0.4–18)
Gastric mucosa TXB_2 synthesis (pg mg^{-1})	19 (4.1–37)	1.4^{c} (1.1–1.9)	2.5^{a} (1.1–5.2)	1.2^{c} (1.0–2.0)	1.4^{c} (1.2–1.7)
Serum salicylate (mg l^{-1})	< 5	16^{cdf} (10–20)	$7^{bdf'}$ (5–16)	91^{cf} (64–123)	$84^{cf'}$ (39–115)
Serum TXB_2 (% of placebo value)	—	0.4^{c} (0.2–1.1)	0.3^{c} (0.2–0.9)	0.3^{c} (0.1–1.0)	0.2^{c} (0.1–0.7)

[a] – $P < 0.05$, [b] – $P < 0.01$, [c] – $P < 0.001$ compared with placebo; [d] – $P < 0.05$, [f] – $P < 0.001$ significant differences between values sharing the same letter. EC – enteric-coated.

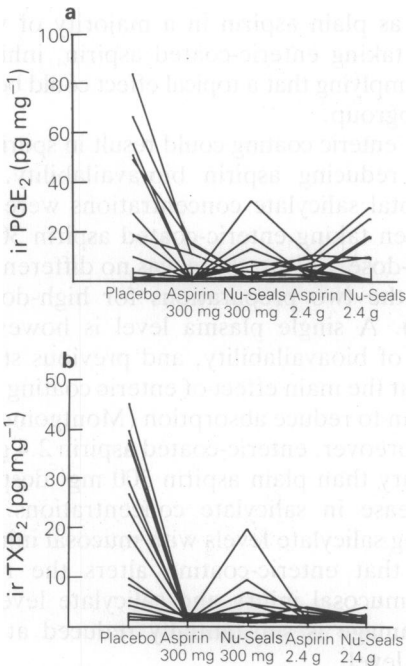

Figure 3 *Ex vivo* synthesis of PGE_2 (Figure 3a) and thromboxane B_2 (Figure 3b) from gastric mucosal biopsies stimulated by vortex mixing, after 5 days treatment in healthy volunteers with placebo, aspirin 300 mg once daily or 600 mg four times daily with or without enteric-coating; individual data for 15 patients shown.

(1–51) pg mg^{-1} on placebo to 0.7 (0.4–11) pg mg^{-1} on aspirin 300 mg, 1.8 (0.5–9.2) on enteric-coated aspirin 300 mg, to 2.8 (1.2–7.6) pg mg^{-1} on aspirin 2.4 g, and to 0.6 (0.4–18) pg mg^{-1} on enteric-coated aspirin 2.4 g daily. Differences between doses and preparations were not significant. There was however a trend towards less TXB_2 and PGE_2 inhibition with enteric-coated preparations. In contrast, there was near complete (more than 99.5%) suppression of serum TXB_2 (Table 3) with both plain and enteric-coated aspirin.

Serum salicylate Serum salicylate levels were undetectable at the end of the placebo period. They rose to 16 (10–20) mg l^{-1} after aspirin 300 mg and 7 (5–16) mg l^{-1} after enteric-coated aspirin 300 mg. Differences between the two preparations at this dose were statistically significant ($P < 0.05$). With aspirin 2.4 g daily, the levels were much higher and there were no significant differences between plain and enteric-coated aspirin (Table 3).

Relationship of mucosal injury to serum salicylates There was a significant correlation between both gastric microbleeding and serum salicylate ($r_s = 0.42$, $P = 0.007$, slope = 0.04 μl 10 min^{-1} bleeding for every 1 mg l^{-1} rise in serum salicylate), and between visual analogue score (summed score for body and antrum) and serum salicylate ($r_s = 0.63$, $P < 0.001$, slope = 0.3 increase in visual analogue score for every 10 mg l^{-1} rise in serum salicylate), (Figure 4). The effect of enteric-coated aspirin was to reset this relationship, reducing the slope of the regression correlation from 0.04 to 0.001 for microbleeding and from 0.3 to 0.07 for the visual analogue score. The relationship between microbleeding and serum salicylate was flat suggesting that mucosal microbleeding had become independent of effects reflected in the serum salicylate.

Oesophagus and duodenum No abnormalities were observed in the oesophagus during aspirin treatment. In the duodenum four non-haemorrhagic erosions were observed in one volunteer after aspirin 300 mg daily; after high dose aspirin, multiple haemorrhagic erosions were noted in one, multiple non-haemorrhagic erosions in four volunteers, while one had both lesion types. Two volunteers had haemorrhagic erosions after enteric-coated aspirin 2.4 g daily, but none after low-dose enteric-coated aspirin.

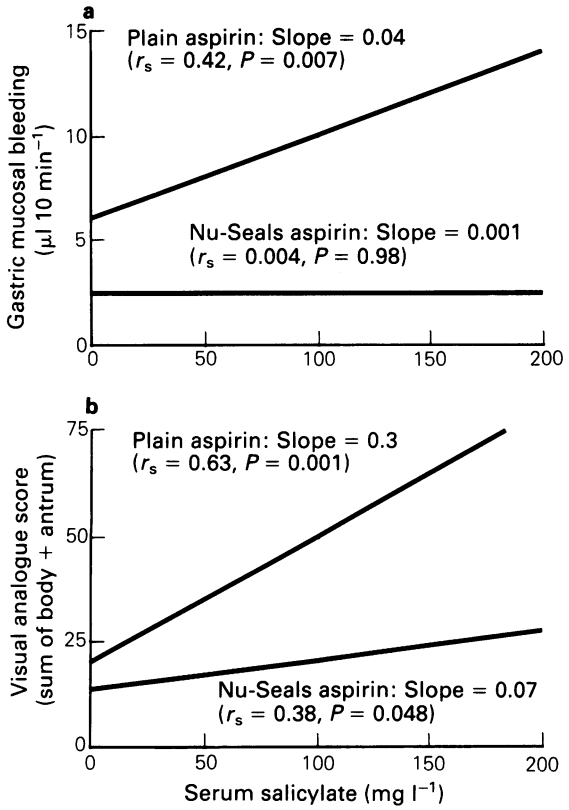

Figure 4 Correlation between serum salicylate level and gastric mucosal bleeding (Figure 4a) and summed visual analogue score for gastric body and antrum. Data for both 300 mg and 2.4 g doses of aspirin from 15 patients. Effect of enteric-coating of aspirin.

Discussion

In this study 300 mg daily caused significant gastric mucosal injury compared with placebo. Aspirin 2.4 g daily caused greater gastric mucosal bleeding than with the low dose, and there was a trend towards greater numbers of haemorrhagic erosions. Both doses caused a similar pattern of injury with haemorrhagic erosions in the gastric body and a mixture of haemorrhagic and non-haemorrhagic erosions in the gastric antrum. We cannot be certain that the short term toxicity of low dose aspirin translates into long term disease, but against the background of epidemiological studies suggesting substantial risk with low dose aspirin, this seems reasonable. Moreover, previous reports suggest that higher doses of aspirin induce mucosal adaptation (Graham *et al.*, 1988), so that the capacity to cause injury diminishes, whereas our previous data with 75 mg and 300 mg (Prichard *et al.*, 1989) daily suggest that this is not so with lower doses.

The second important conclusion from our study is that enteric-coating offers effective protection against gastric mucosal injury. Our data confirm two small earlier studies of protection against aspirin 2.4 g (Hoftiezer *et al.*, 1982) or 3.9 g (Lanza *et al.*, 1980) daily and extend these observations to show that the protection against low-dose aspirin, 300 mg daily, is so effective that mucosal appearances are not different from those seen with placebo. Conclusions cannot be drawn about small intestinal damage from this study but there is little evidence that this is a clinically important site of damage. These data suggest that enteric-coated aspirin should be an extremely suitable preparation for long term cardiovascular prophylaxis.

Three possible mechanisms could underlie the protection we have observed. Firstly, it is known that salicylates can cause topical injury, independent of any inhibition of prostaglandin synthesis. Enteric-coating may protect against this. Some experiments have shown gastric damage after parenteral administration of non-steroidal drugs (Grossman *et al.*, 1961) but this work has been criticized for using toxic concentrations of drugs, and other workers using therapeutic intravenous doses have failed to produce damage, (Cooke & Goulston, 1969; Ivey *et al.*, 1980). Rectal administration of aspirin in rats does not produce gastric damage, whereas rectal indomethacin and diclofenac do (Ligumsky *et al.*, 1990).

Secondly, enteric coating may prevent inhibition of prostaglandin synthesis in the gastric mucosa. It has been suggested that low dose aspirin (of any preparation) may undergo sufficient first pass metabolism for no systemic effects to be exerted on endothelial prostacyclin production. If this were also true in the stomach, inhibition of prostaglandin synthesis could only arise topically and would be prevented by enteric coating. Our data show that this is not the case, since enteric-coated aspirin caused as much inhibition of gastric mucosal prostaglandin synthesis as plain aspirin in a majority of volunteers. In a few taking enteric-coated aspirin, inhibition was reduced, implying that a topical effect could be important in this subgroup.

Finally, enteric coating could result in spurious protection, by reducing aspirin bio-availability. Although plasma total salicylate concentrations were somewhat lower when taking enteric-coated aspirin 300 mg than plain low-dose aspirin, there was no difference in levels between the two preparations for high-dose aspirin, (Table 3). A single plasma level is however a poor indicator of bioavailability, and previous studies have shown that the main effect of enteric coating is to delay, rather than to reduce absorption (Montgomery & Sitar, 1986). Moreover, enteric-coated aspirin 2.4 g caused no more injury than plain aspirin 300 mg, despite a four-fold increase in salicylate concentrations. Our data correlating salicylate levels with mucosal injury (Figure 4) show that enteric-coating alters the relationship between mucosal injury and salicylate levels, so that gastric damage is substantially reduced at any given salicylate level.

In conclusion, our data show that in the short term, in healthy volunteers, mucosal integrity can be preserved and gastric damage virtually eliminated by using enteric-coated aspirin, despite significant and substantial reductions in prostaglandin synthesis, and emphasise the importance of topical injury by aspirin in its gastric mucosal toxicity. Enteric-coating did not prevent inhibition of serum thromboxane, and so this preparation would appear to be suitable for cardiovascular prophylaxis. Further studies would be needed to confirm whether low dose enteric-coated aspirin reduces gastric ulcers and bleeding when used for long-term cardiovascular prophylaxis.

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