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COMMUNICATIONS

Effect of time of dosing relative to a meal on the raft formation of an anti-reflux agent

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Abstract—Gamma scintigraphy was used in twelve healthy volunteers to establish whether the time of dosing of Liquid Gaviscon relative to a meal influenced its therapeutic action. Indium-113m labelled Liquid Gaviscon was administered to fasted subjects, 30 min after a technetium-99m labelled meal or immediately before ingestion of the meal. The time for 50% of the Gaviscon to empty from the stomach was 0·36 ± 0·13 h, 3·10 ± 0·31 h and 0·68 ± 0·04 h (s.e.m.), respectively. The preparation was found to empty rapidly from the fasted stomach and could not be floated on a meal consumed subsequently. For raft formation to occur, Liquid Gaviscon should be taken 30 min after a meal.

Anti-reflux formulations are usually classed with antacids; however, they are specifically advocated for the treatment of gastro-oesophageal reflux and not dyspepsia. Liquid Gaviscon (Reckitt and Colman Pharmaceuticals, UK) is the most widely used anti-reflux agent in the UK. It contains sodium alginate and sodium bicarbonate; the sodium bicarbonate reacts with gastric acid to produce bubbles of carbon dioxide, and the acid forms alginic acid gel from the soluble sodium alginate. The gas bubbles become entrapped in the alginic acid gel, thus giving it sufficient buoyancy to form a floating layer on the gastric contents. Raft formation has been demonstrated to occur in-vivo when 10 mL of the product has been administered 30 min after a liquid meal (375 mL Clinifeed-ISO, Roussel Laboratories) or a scrambled egg meal (May et al 1984; Washington et al 1987).

The amount of acid available is critical for raft formation to occur, although food stimulates acid secretion, it also both buffers and dilutes the acid. Dosing schedules of antacids with respect to meals have been reported. Fordtran & Collyns (1966) and Deering & Malagelada (1977) found that antacids administered 1 h after a meal elevated the stomach pH for longer than when they were administered after 3 to 4 h. This is primarily due to the presence of food slowing the rate of delivery of the antacid to the duodenum.

Antacids given to fasted subjects are used inefficiently (Grossman 1956) since they are emptied from the stomach, usually within 20 min (Jenkins et al 1983). The efficacy of anti-reflux agents has been examined by Laitinen et al (1985), however, the formulations were administered half an hour before meals which does not conform to the manufacturers recommended dosing schedule for these types of material.

We have performed two scintigraphic studies to evaluate the importance of the dosing schedule of an anti-reflux agent with respect to a meal. One study was carried out to determine the gastric distribution and residence time of Liquid Gaviscon in fasted volunteers and to compare this to the residence time of the same dose of Liquid Gaviscon when administered 30 min after a test meal. The second study examined whether the anti-reflux agent given to fasted volunteers, would float on a meal taken subsequently.

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Materials and methods

The test meal used (2 slices toasted white bread (60 g), 200 mL unsweetened orange juice, 25 g butter, 30 mL milk, 2 scrambled eggs) produced a total calorific value of 1693 kJ (405 kcalories), had a nutritional breakdown of 34·1 g protein, 46·9 g fat and 51·4 g carbohydrate. The weight of the meal was 435 g with a volume of 430 mL.

The eggs were labelled by incorporation of 3 MBq of technetium-99 m sulphur colloid before cooking. The technetium was eluted from a generator as the pertechnetate which was used to label sulphur colloid using a commercial kit (Mallinckrodt Inc). The integrity of this method of labelling the meal has been well established and the release of the label into the liquid phase correlated with the digestion of egg by the pepsin in the simulated gastric juice (USP formulation) at 37°C (Feldman et al 1984; Washington et al 1987). The anti-reflux formulation used was Liquid Gaviscon (Reckitt and Colman, UK, Batch no F08547) as supplied by the Hospital Pharmacy, Queen's Medical Centre, Nottingham. The formulation was labelled by inclusion of a small quantity of indium-113m alginate. The 3 MBq of ^{113m}In indium chloride solution in 0·04 M HCl was added to 25 mg of sodium alginate powder and this was stirred until a gel of alginic acid had formed. Ten millilitres of Liquid Gaviscon was then added slowly, with stirring between each addition (May et al 1984; Bennett et al 1984).

Healthy male and non-pregnant female volunteers, age range 19 to 24, were recruited from the University student population. Subjects who had a history of gastrointestinal disturbances, excessive smoking, diabetes or allergies to any of the test meal ingredients were excluded from the study. Any reason to suspect that a female subject was pregnant excluded her from the trial. The volunteers were given written and verbal information as to the nature of the trial. Each subject was required to give written, informed consent before entry into the study and fill in a questionnaire concerning exclusion criteria. The study had approval from the Nottingham University Hospital Ethics Committee and permission was granted by the Department of Health and Social Security to administer the radioisotopes.

Fasted versus fed study. Six subjects participated, they fasted overnight and on the following morning three were given the test meal, radiolabelled with 3 MBq technetium-99m, and the other three remained fasted. The fasted group was given 10 mL Liquid Gaviscon radiolabelled with 2 MBq of indium-113m. The fed group received the labelled Gaviscon 30 min after the test meal. The subjects remained seated during the study, but stood for the imaging.

Radioactive anterior and posterior markers were placed on the thorax opposite the stomach to allow accurate alignment of

subsequent images. Anterior and posterior images of 30 s duration were obtained at 10 min intervals by the gamma camera until all activity had left the stomach. Images were taken simultaneously in the indium and technetium channels, and stored separately on the computer for subsequent analysis. One week later the treatments were reversed.

Effect of dosing immediately before a meal on the flotation of Liquid Gaviscon. This study was similar to that previously described and also used six volunteers. All subjects were asked to swallow a 10 mL bolus of Liquid Gaviscon radiolabelled with 2 MBq of indium-113m and then to consume the labelled test meal immediately afterwards. Anterior and posterior images of 30 s duration were taken at approximately 15 min intervals for the following 3 h, or until all activity had left the stomach. This study was not crossed-over.

Data analysis. Data was analysed blind. Each image was analysed by creating three regions of interest, one around the whole stomach, a second around the upper half of the stomach, to assess the extent to which the formulation or food remained in this region, and a third to assess background activity. Due to overlap of the indium isotope into the technetium channel the entire stomach outline was clearly visible in the technetium channel. Consequently it was possible to divide the stomach into an upper and lower half by bisecting the greater and lesser curvatures (Washington et al 1987). This resulted in two regions with approximately the same number of pixels in each. The total counts from the regions of interest around the stomach were corrected for background radiation and decay of the isotope. The technetium-99m count rates were also corrected for indium-113m overlap into the technetium channel. The activity in the stomach was calculated as the geometric mean of the anterior and posterior images to correct for the movement of the isotope from the fundus to the antrum, since the fundus is closer to the posterior of the body (Hardy & Perkins 1985).

Graphs of the percentage of the meal and the formulation remaining in the stomach with time were constructed for each subject. The graphs were then interpolated to produce a mean graph and the standard errors of the mean were calculated. The significance of the results was tested by *t*-test after normality checking.

Results

Fasted/fed study. The mean curves for gastric emptying of Liquid Gaviscon, in fasted and fed subjects, are shown in Figs 1 and 2a, respectively. The mean time for half the Gaviscon to empty from the stomach (T50) was 0·36±0·13 h (±s.e.m.) in the fasted subjects (n=5) and 3·10±0·31 h in the fed subjects (n=6). One subject was excluded from the fasted group because it was apparent from the scintigraphic images that he had ingested a significant volume before the experiment.

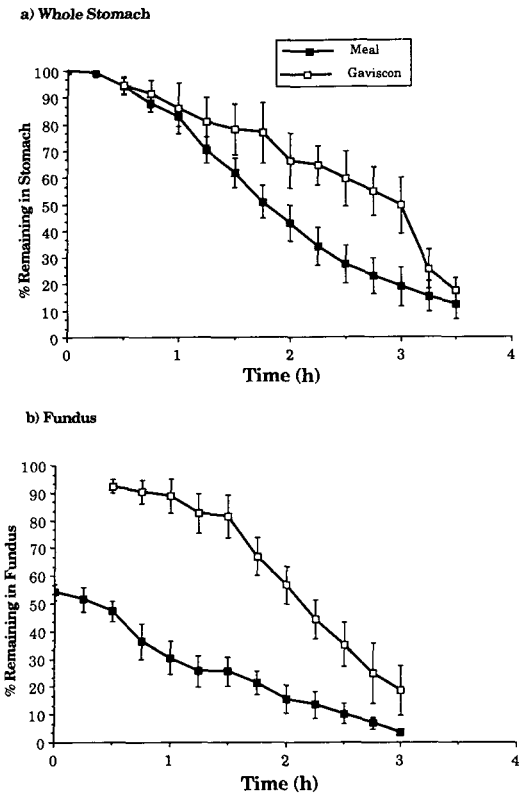

FIG. 2(a) Gastric emptying curves from subjects who were given 10 mL Liquid Gaviscon 30 min after a meal (n=6, ±s.e.m.). (b) Percentage of Gaviscon remaining in the fundus in subjects who were dosed 30 min after a meal (n=6, ±s.e.m.).

Examination of the activity in the top half of the stomach in the fed subjects showed that greater than 80% of the radiolabelled Gaviscon remained in the upper half of the stomach for approximately 1 h after ingestion (Fig. 2b). Only 50% of the food was found in the fundal region of the stomach initially. In one subject, Gaviscon, instead of floating to the top of the stomach, as observed with the remaining subjects, sank to the

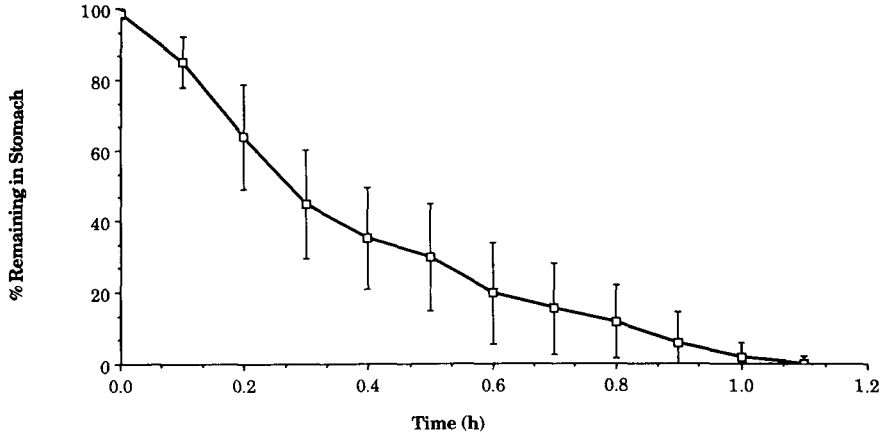

FIG. 1. Gastric emptying curve for Gaviscon in fasted subjects (n=5, ±s.e.m.).

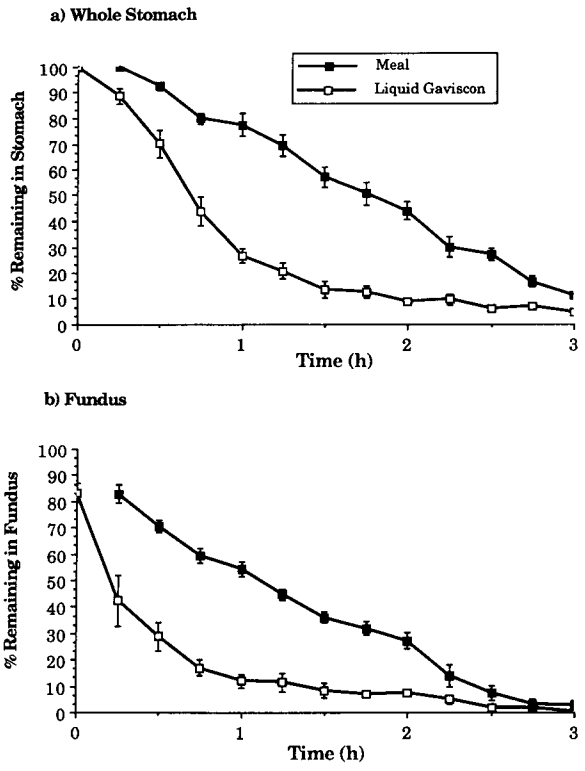

FIG. 3(a) Gastric emptying curves from subjects for Liquid Gaviscon and the test meal when the test meal was administered immediately after ingestion of 10 mL Liquid Gaviscon (n = 6, ± s.e.m.). (b) Percentage of Gaviscon remaining in the fundus in subjects who were dosed 30 min before a meal (n = 6, ± s.e.m.).

pyloric antrum then floated up the pyloric canal and emptied ahead of the food. However, there was no reason to exclude these data from the mean curves.

Effect of dosing Liquid Gaviscon 30 min before a meal. The mean curve for the gastric emptying of Liquid Gaviscon and the test meal when the Gaviscon was administered 30 min before consumption of the meal is shown in Fig 3a; the T50 was 0·68 ± 0·04 h, and for the test meal, 1·71 ± 0·27 h (n = 6). Fig. 3b demonstrates that Gaviscon did not localize in the fundus when this dosing regimen was followed. The gastric emptying curves for the test meal in the fasted/fed group (T50 = 1·84 ± 0·27 h) and the group dosed with Gaviscon immediately before feeding (Figs 2a, 3a) were not significantly different.

Discussion and conclusion

The gastric residence time of the Liquid Gaviscon in fasted subjects resembled that obtained for the same volume of antacid administered to fasted volunteers (Jenkins et al 1983). This demonstrated that Gaviscon did not possess an inherent ability to be retained in the stomach in the absence of food and did not have significant mucoadhesive properties. In the study of Laitinen et al (1985), where the formulation was administered 30 min before the meal, it is possible that approximately 70% of the formulation would have already left the stomach by the time the meal was eaten, hence the Gaviscon could not exert significant therapeutic benefit since it could not form a raft. It has been demonstrated that the particulate antacids within an anti-reflux formulation become entrapped in the alginate gel, leading to a reduction in their neutralization capacity (Washington et al 1986a). However, it is likely that some local neutralization of the small volume of acid in the fasted stomach would occur, particularly if the formulation of the preparations used by Laitinen et al contained materials such as aluminium hydroxide (Washington et al 1986b). The formulation used in the present study contained only enough sodium bicarbonate to elevate the raft. Formulations from different manufacturers contain varying amounts of particulate antacids which have been demonstrated to influence their in-vitro properties (Washington et al 1986b).

When the radiolabelled Gaviscon was administered 30 min before the test meal 80% of the dose initially remained in the fundus. Ingestion of the food caused half of the Gaviscon in the fundus to be pushed into the antrum. Once the Gaviscon had been displaced to the antrum by the food it was effectively removed from the acid secreting areas of the stomach since the antrum does not possess any parietal cells. Therefore, because of lack of gastric acid, raft formation did not occur so the formulation emptied from the stomach before the food. The food did significantly delay the emptying of the Gaviscon when compared with the fasted group ($P < 0.01$). However, emptying was much faster than in the group in which the Gaviscon was taken after the meal ($P < 0.01$). It is essential for the preparation to be taken at least 30 min after a meal if a raft is to be formed on the gastric contents. This allows acid secretion to overcome the diluting and buffering effect of the meal, while still providing sufficient gastric volume to position the raft in the fundus.

We have reported on the emptying of a multiparticulate system dosed in a hard gelatin capsule immediately before a meal (O'Reilly et al 1987). Unlike the Liquid Gaviscon, the multiparticulate mixed and emptied with the meal. The pellets used were between 0·7 and 1·3 mm in diameter and had a density of 1·2 g cm^{-3}. The initial phase of emptying of the pellets was exponential and it was thought that they were emptied in the volume of water used to swallow the capsule. A later phase of emptying was linear as the pellets become distributed within the food. In the present work, Liquid Gaviscon, which is viscous, showed mixing with the meal taken subsequently; hence its emptying from the stomach followed exponential pattern typical for liquids.

In conclusion, Liquid Gaviscon did not prolong gastric emptying time of the meal. Raft formation was due to the presence of both sufficient gastric contents to float the raft and, by the reaction with the sodium bicarbonate, adequate free hydrogen ions to produce the necessary buoyancy. It was essential for the formulation to be taken after a meal to enable raft formation to occur and for it to be located in the fundal region of the stomach where it could afford protection to the oesophagus.

This study has demonstrated the importance of the dosing schedule of anti-reflux agents with respect to food intake if the therapeutic action of the formulation is to be maximized. It should be made clear to patients that anti-reflux agents, if they are to exert a significant therapeutic benefit, should be taken after consumption of a meal.

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Improved synthetic routes to the novel thromboxane receptor antagonist ICI 192605: activity of synthetic 1,3-dioxane intermediates

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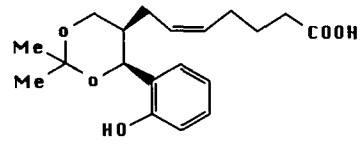
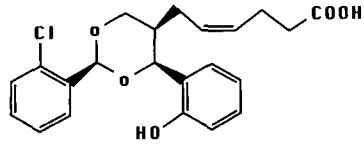
Abstract—A study of the synthetic routes to the thromboxane receptor antagonist ICI 192605 4(Z)-6-(2-*o*-chlorophenyl-4-*o*-hydroxyphenyl-1,3-dioxan-*cis*-5-yl) hexenoic acid is described which led to an improvement in overall synthetic yield from 20 to 55%. In-vitro thromboxane receptor antagonist data are reported for the novel 1,3-dioxane synthetic intermediates. These data indicated that shortening of the side chain in an appropriately substituted 2,2-dimethyl-1,3-dioxane (e.g. ICI 180080) from a heptenoic acid, to a hexenoic acid, had little effect on thromboxane receptor antagonist potency ($pA_2 = 7.5$ rabbit thoracic aorta for the heptenoic acid ICI 180080 and $pA_2 = 6.9$ for the corresponding hexenoic acid. Human platelet aggregation pA_2 values were 6.7 and 7.0, respectively).

Thromboxane A_2 is an unstable metabolite of arachidonic acid which is both a constrictor of smooth muscle and a blood platelet aggregator. These pharmacological actions may play a role in the pathology of a number of life threatening diseases (Fitzgerald et al 1988) such as angina, stroke and asthma. Blockage of the actions of thromboxane A_2 by a selective thromboxane receptor antagonist may facilitate the study of these diseases and eventually establish thromboxane receptor antagonists as novel therapeutic agents.



Structure 1



Structure 2

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We have previously described the original synthesis and pharmacological properties of the novel 1,3-dioxane thromboxane antagonists ICI 180080 (**1**) (Brown & Foubister 1986) and its more potent and stable analogue 4(Z)-6-(2-*o*-chlorophenyl-4-*o*-hydroxyphenyl-1,3-dioxan-*cis*-5-yl)hexenoic acid, ICI 192605 (**2**) (Brown et al 1988). We now report an investigation of the synthetic routes to **2** aimed at improving the synthesis for the preparation of sufficient material for pharmacological and pre-development work. Included are the in-vitro thromboxane receptor antagonist activities of the novel synthetic intermediates involved.

Materials and methods

Chemistry. To prepare the desired thromboxane antagonist (**2**) from the intermediate (**3**) (Brown et al 1988) two synthetic operations are required (Fig. 1): demethylation of the methyl phenyl ether group under non-acidic conditions and replacement of the 2,2-substituted methyl groups of the 1,3-dioxane ring of **3** with an ortho-chlorophenyl ring, either by direct exchange or via a ring opened 1,3-diol such as **6**. By variation of the sequence of these steps, four different preparative routes to the dioxane (**2**) resulted (Routes A, B, C_1 and C_2, Fig. 1) and were compared.

In route A, demethylation of the methyl ether (**3**) with sodium thioethoxide to the corresponding phenol (**4**) using six molar equivalents of the thiol reagent improved the yield from 31% (Brown et al 1988) to 84%. Demethylation of **3** with diphenyllithium phosphide (Ireland & Walba 1977) resulted in the lower yield of 54%. Route A was completed by acetal exchange with 2-chlorobenzaldehyde. In route B, acetal exchange was carried out before demethylation but in the subsequent demethylation with sodium thioethoxide, lower yields of the phenol (**2**) were obtained, presumably due to some attack of the thiol reagent at the aryl chlorine atom. Cleavage of the 1,3-dioxane ring of **3** with dilute hydrochloric acid afforded the 1,3-diol (**6**) in quantitative yield. Sodium thioethoxide ether fission (Route C_1) of the diol (**6**) to give the triol (**7**) was also high yielding, but ring closure with 2-chlorobenzaldehyde gave **2** in only 43% yield. 1,3-