Progress report

Antacids and peptic ulcer—a reappraisal

There is a considerable difference of opinion between clinicians on opposite sides of the Atlantic about the role of antacid therapy in peptic ulcer. As a result of Doll’s work\(^1\) most clinicians in the United Kingdom have considered antacids to be of symptomatic benefit only, but without effect on the natural history of disease. In the United States, however, antacids have remained the basic medical treatment for peptic ulcer and large quantities are prescribed in intensive regimens with the belief that they accelerate ulcer healing. Such a difference of opinion usually means that the treatment in question is without any dramatic effect and objective assessment is therefore different. It is in this field that randomised, controlled trials are most helpful, indeed vital\(^3\). Carbenoxolone\(^3\) and recently the \(H_2\)-receptor antagonists\(^4,5\) have been tested in this way and found to be effective in healing peptic ulcer. We feel a review of similar work on antacids is appropriate.

The use of antacids is based on the premise that gastric acid plays some part in the causation of peptic ulcer and also on the observation that symptoms are often relieved by antacid preparations. Schwarz’s dictum, ‘no acid—no ulcer’, is still valid, though the pattern of acid secretion is different in gastric and duodenal ulcer. Hypersecretion of acid is probably a more important factor in duodenal ulcer, though several aspects of the pathophysiology remain controversial\(^6\). Most patients with an ulcer in the body or fundus of the stomach have normal or low rates of acid secretion and changes in mucosal resistance are probably more important\(^7,8\). Reflux of bile into the stomach probably causes gastric mucosal damage which may play a part in the pathogenesis of gastric ulcer\(^9\). Antacids may not only neutralise gastric contents but in the case of aluminium hydroxide also bind bile acids\(^10\). Peptic activity is difficult to separate from acid secretion and its role is similarly ill-defined. A rise in gastric pH to 5 will inactivate pepsin; calcium carbonate has also been shown to produce a marked reduction in pepsin activity, while aluminium hydroxide, in spite of binding to pepsin, has little effect\(^11\).

The total cost of antacids in the United Kingdom during 1976 was about 20 million pounds, a figure which includes both Health Service prescriptions and over-the-counter sales. The so-called semi-ethical preparations are available on prescription or from a pharmacist but are not advertised to the general public. The cost to the Health Service of these preparations is about 12 million pounds per annum—7 million for plain antacids, 4 million for silicone-containing antacids, and 1 million pounds for antacids combined with antispasmodics or local anaesthetics. While the cost to the Health Service has grown considerably in recent years because of inflation, the number of prescriptions has remained constant at 9\(\frac{1}{2}\) million per annum. Liquid preparations are prescribed more often than tablets and silicone-containing antacids are increasingly prescribed in place of plain preparations.
Antacids and peptic ulcer—a reappraisal

There is comparatively little precise information available about over-the-counter sales of antacids, although the total market value of these products is about £4 million pounds per annum and these sales have tended to decline in recent years.

Most prescribed antacids contain a mixture of aluminium and magnesium salts, which minimises bowel disturbance. Precise methods of preparation and presentation are important because they influence the physicochemical properties and the therapeutic effect of antacids. For example, Littman\(^1\) has shown that the activity of a series of aluminium hydroxide gels \textit{in vitro} is related to the method of preparation which alters the solubility of the aluminium hydroxide in acid. Tablets, though more convenient, are less effective in lowering gastric acidity than liquid preparations\(^2\). Silicone is added to several antacid preparations as dimethicone (dimethylpolysiloxane), which belongs to a group of polymers of silicone and carbon widely used in industry because they lower surface tension and have an anti-foaming effect. \textit{In vivo}, dimethicone counters flatulence and in a clinical trial\(^3\) has been shown to relieve functional dyspeptic symptoms; this may account for some of the symptomatic relief from antacid preparations. Peppermint oil is commonly used to flavour antacid preparations and is a strong antispasmodic which reduces tone in the lower oesophageal sphincter\(^4,5\), this may not be desirable in patients with reflux oesophagitis\(^6\) but facilitates eructation of wind with some alleviation of discomfort. Alginates are hydrophilic compounds derived from polyuronic acid and obtained from a species of seaweed. They are soluble in alkaline hydroxides but precipitate on contact with gastric acid to form a sticky gel which tends to adhere to the mucosal surface. Their addition to antacids is intended to reduce damage from gastro-oesophageal reflux.

We wish to discuss the role of antacids in peptic ulcer and to consider several questions which are pertinent to an assessment of their effectiveness.

Do antacids reduce gastroduodenal acidity?

The interpretation of early antacid studies\(^7\) is difficult because they were often carried out on fasting subjects or in combination with frequent milk feeds. Piper and Fenton\(^8\) and, more recently, Fordtran and his colleagues\(^9,10\) have described methods for assessing the potency of antacids \textit{in vitro}. Details in the technique are important, particularly the mixing procedure and the titration end-point because they influence the \textit{in vitro} potency. Using Fordtran’s technique, several studies\(^11,12\) have shown that the \textit{in vitro} neutralising capacity of different antacids varies as much as thirty-fold. Tested in this way the \textit{in vitro} neutralising capacity of antacids correlates well with their activity \textit{in vivo} and the authors suggest that they should perhaps be prescribed as milliequivalents of alkali rather than as a number of tablets or simple volumes.

Fordtran and Collyns\(^13\) investigated the effect of two antacid regimens on gastric acidity in patients with duodenal ulcer eating a normal diet and found that 4 g calcium carbonate given one hour after a meal lowered gastric acidity for at least three hours compared with controls. The duration of action was only 20 to 40 minutes when the same dose of calcium carbonate was given on an empty stomach. Anticholinergics given before food did not influence the effect of antacid but larger doses of antacid prolonged the effect.
after food but not while fasting. Aluminium-magnesium hydroxide gave similar results but was less effective than calcium carbonate.

A recent paper from the Mayo Clinic\textsuperscript{28} compared the delivery of acid to the duodenum after food in patients with duodenal ulcer given the $\text{H}_3\text{R}$-receptor antagonist cimetidine, or aluminium-magnesium-hydroxide. It was found that 400 mg cimetidine with a meal decreased the four-hour delivery into the duodenum of titratable acid and hydrogen ion by 63\% and 86\% respectively ($p < 0.01$ versus control). The aluminium-magnesium-hydroxide regime (30 ml one hour and three hours after meals) lowered titratable acid and hydrogen ion concentration by 47\% and 74\% respectively ($p < 0.01$ versus control). The decrease in acid delivered to the duodenum was comparable in degree, though the results with antacid showed greater fluctuation than after cimetidine.

Another phenomenon of importance is rebound hyperacidity after antacid therapy\textsuperscript{24} which occurs with calcium carbonate specifically\textsuperscript{25} and not with other antacid preparations. This is due to the direct effect of calcium on gastrin release and gastric acid secretion\textsuperscript{24,27,28}.

The evidence currently available shows that antacids lower gastro-duodenal acidity for considerable periods when given after food, although the quantities used were large compared with British practice.

\section*{Do antacids accelerate healing in peptic ulcer?}

Doll and others\textsuperscript{29} examined the rate at which gastric ulcer healed in a group of inpatients who for four weeks were given a continuous intragastric milk drip alkalinised with sodium bicarbonate. There was no effect on the rate of healing compared with the control group. However, this regimen was similar to the one developed by Winkelstein \textit{et al.}\textsuperscript{30} and was subsequently shown to produce only a modest reduction in gastric acid\textsuperscript{31}. Doll's control group also received antacids for relief of symptoms\textsuperscript{32}. One cannot obtain from this study an answer regarding the efficacy of antacids in healing gastric ulcer; the study shows that a continuous intragastric milk drip together with prolonged but modest reduction in gastric acidity offers no further benefit to that obtained from bed-rest and symptomatic antacid therapy\textsuperscript{33}.

Hollander and Harlan\textsuperscript{34} in a double-blind controlled trial examined the effect of antacids on the rate of healing in outpatients with peptic ulcer. The antacid regimen was two-hourly calcium carbonate (420 mg) and proved more effective than placebo in healing gastric ulcer ($p = 0.04$) but showed no benefit in duodenal ulcer. In a similar trial\textsuperscript{35} hospitalised patients with gastric ulcer were given a liquid antacid containing aluminium-magnesium-hydroxide, 60 ml every two hours, and endoscopy was used to assess healing. There was no benefit from this regimen compared with placebo. The conflicting results from these studies suggest that antacids do not have a marked effect on healing rate in gastric ulcer. The greater potency of calcium carbonate both as an antacid and anti-pepsin compared with aluminium-magnesium-hydroxide may partly explain the results. Admission to hospital is known to accelerate healing in gastric ulcer and if the benefit obtained from antacid therapy is slight it could easily be lost during an inpatient trial. Thus, carbenoxolone is effective in healing gastric ulcer in outpatients\textsuperscript{3} but not in inpatients\textsuperscript{36}.

A major problem in the assessment of healing in duodenal ulcer has been
Antacids and peptic ulcer—a reappraisal

the limitation of radiology in demonstrating a measurable ulcer crater, particularly in a deformed duodenal cap. The introduction of fibreoptic endoscopy has partly solved this problem and, in most patients, allows one to measure the ulcer size.

A recent study from Dallas37 examined the effect of antacids in large doses on the healing rate of duodenal ulcer assessed endoscopically. Seventy-four patients with duodenal ulcer were treated for 28 days in a double-blind controlled trial. The ulcer healed completely in 28 of the 36 patients given antacids compared with 17 of the 38 patients given placebo (p < 0.005). Doses of 30 ml aluminium-magnesium-hydroxide were given seven times daily with a total in vitro neutralising capacity of 1008 mEq. This important study was the first to demonstrate the effectiveness of antacids in healing duodenal ulcer but the dosage of antacid required produced bowel disturbance in 30% of the subjects.

Ippoliti et al.38 have also compared intensive antacid therapy with cimetidine in duodenal ulcer. The study was a double-blind controlled comparison of cimetidine, 800 mg or 1200 mg daily, with aluminium-magnesium-hydroxide, 210 ml daily, on the rate of healing (assessed endoscopically) and on pain relief in duodenal ulcer. Ulcers healed in 21 of the 33 patients given cimetidine, 1200 mg daily, 19 of 32 given 800 mg cimetidine daily and 15 of 21 given antacid. Results from the three groups did not differ significantly, so that antacid appeared as effective as cimetidine in healing duodenal ulcer but with a higher incidence of side-effects, usually in the form of a bowel disturbance.

Acute peptic ulceration in seriously ill patients ('stress ulcers') may cause major problems from gastrointestinal haemorrhage or perforation. Patients with burns, severe trauma, renal or respiratory failure, or severe hepatic disease are most at risk and antacids have been tested in these situations in recent studies. A randomised controlled study of patients with severe burns39 showed that antacid therapy reduced the incidence of severe gastrointestinal bleeding from 25% to 4% (p < 0.05). A similar study carried out by the King's College Hospital group40 in patients with severe hepatic failure demonstrated benefit with H₂-receptor antagonists but not with antacid. Hastings et al.41 have recently tested a more intensive antacid regimen against placebo in a randomised trial in 100 seriously ill patients. Antacid (aluminium-magnesium-hydroxide with dimethicone) was administered hourly via a nasogastric tube and the dose was adjusted to keep gastric pH above 3.5. Two of the 51 patients who received antacid bled compared with 12 of the 49 controls (p < 0.005).

It would appear that antacids have little effect on the healing rate of gastric ulcer but in large doses accelerate healing in duodenal ulcer and reduce the risk of haemorrhage in patients with stress ulceration, although H₂-receptor antagonists may prove to be both more convenient and effective.

Do antacids relieve symptoms in peptic ulcer?

Although most clinicians accept that antacids relieve the pain of peptic ulcer, there are few studies which compare a single dose of antacid with placebo. Lawrence42, more than 25 years ago compared several liquid antacids with placebo (barium sulphate) for acute relief of spontaneous pain in peptic ulcer. The study was single-blind and showed that magnesium trisilicate and magnesium carbonate were more effective than placebo, but there was no
significant advantage for aluminium hydroxide. Sturdevant et al. reported two double-blind controlled randomised trials comparing single doses of aluminium-hydroxide-magnesium trisilicate with placebo in relieving spontaneous pain in 30 male patients with duodenal ulcer. There were no significant differences between antacid and placebo in the time of onset, degree or duration of pain relief. This surprising result led the authors to suggest that factors other than reduction of gastric acidity may be important in acute relief of spontaneous duodenal ulcer pain. Both the antacid and the placebo used in this work contained peppermint oil and the carminative effect of the latter may partly account for the failure to show a difference between the preparations.

However, Littman et al. reported studies with aluminum hydroxide gel in acute relief of pain in peptic ulcer. The analgesic effect of a single dose of antacid versus placebo was tested in two ways—in spontaneous ulcer pain and in pain provoked by instilling acid into the stomach. The trials which were randomised and double-blind were conducted at two hospitals. Patients reported spontaneous ulcer pain to a nurse who then gave either active or placebo gel. The result was recorded 20 minutes later and complete relief of pain was the only index of effectiveness. When pain was provoked by instillation of acid the preparation which contained either antacid or placebo was also instilled via the nasogastric tube and effectiveness was taken as complete relief of pain at 10 minutes. In one of the hospitals complete relief of pain was obtained with 15 ml aluminium-hydroxide-gel in 79% and with placebo in 45% (p < 0.05); 44 spontaneous episodes of pain were used in the assessment. In the other hospital, doses of 15 ml and 30 ml were tried but 38 identical trials revealed no significant difference between aluminium hydroxide and placebo. At neither hospital was there any significant advantage for aluminium hydroxide gel over placebo in relief of pain provoked by acid instillation.

The question of long-term relief of symptoms in peptic ulcer by antacids is also difficult to answer with any confidence. Relief of symptoms and healing need not go hand in hand. A surprising feature of the Dallas study was that, although the intensive antacid regimen accelerated healing in duodenal ulcer, no benefit on symptoms was demonstrated compared with controls.

Hollander and Harlan found calcium carbonate more effective than placebo in relieving symptoms of gastric ulcer in outpatients. Butler and Gersh, however, found no advantage for their liquid antacid regimen over placebo for inpatients with gastric ulcer.

The effectiveness of antacids in relieving pain in peptic ulcer is therefore still an open question and further studies are needed.

Are antacids safe and palatable?

In the United Kingdom serious complications from antacids are uncommon for two major reasons:

1. They are usually prescribed for relief of pain rather than given in large doses as part of an intensive regimen to reduce gastric acidity for long periods.

2. The most frequently used antacids are aluminium-magnesium salts
which are poorly absorbed and, as combined preparations in small doses, produce few bowel symptoms.

Well-absorbed antacids such as sodium bicarbonate are seldom prescribed these days but many proprietary antacid mixtures contain appreciable amounts of them, which may be important in patients on low sodium diets. Well-absorbed alkalis may also produce metabolic alkalosis and hypokalaemia.

Calcium carbonate is well known for its part in the milk-alkali syndrome. The features of this syndrome include metabolic alkalosis, hypercalcaemia, and hyperphosphataemia with hypokalaemia. Renal function deteriorates rapidly and the patients develop headache, irritability, weakness, nausea, and vomiting which accelerates the disorder. The initial event is thought to be suppression of parathyroid hormone secretion by hypercalcaemia consequent upon the greatly increased calcium intake. Repeated episodes may cause nephrocalcinosis and chronic renal failure. The syndrome does not occur in patients taking aluminium-magnesium antacids.

Recent evidence suggests that the ‘non-absorbable’ antacids are not without problems. Aluminium-magnesium hydroxides reduce the absorption of drugs such as digoxin, tetracycline, and chlorpromazine and alter the excretion of anticoagulants and salicylates by changing urinary pH. Aluminium hydroxide binds phosphate in the bowel and precipitates as insoluble aluminium phosphate. This is of value in patients with chronic renal failure and hyperphosphataemia but in other patients large quantities taken over long periods may produce phosphate depletion and osteomalacia. Aluminium hydroxide also binds bile salts in vitro and is as effective in this respect as cholestyramine. However, the importance of this in vivo is uncertain, as aluminium hydroxide rapidly precipitates as the phosphate in the small bowel. Small amounts of aluminium are absorbed as shown by increased levels in plasma and urine with the possibility of toxic effects. Reduction in gastric acidity may also increase susceptibility to intestinal pathogens. This old observation has recently been reviewed and, in a report given of people who drank Brucella-infected goat’s milk, only the two patients who were currently taking aluminium magnesium antacid developed brucellosis.

Palatability becomes an important factor when large dose regimens are used, particularly in patients who may already be nauseated. In a recent study commonly prescribed antacids were compared for their palatability and acid neutralising capacity. Sixty normal subjects took part in the study and were divided into groups of 12. Each group assessed four antacids over four days and compared them with a standard and listed their preference. Although most preparations were palatable, some were quite unacceptable.

Summary

Antacids can reduce gastroduodenal acidity for long periods if taken in substantial quantities after food. Their healing effect on gastric ulcer is minimal, if present at all, and easily overwhelmed by the benefit obtained from admission to hospital. Intensive antacid therapy appears effective in healing duodenal ulcer and preventing haemorrhage from stress ulcer, and is comparable in these respects with cimetidine but with a higher incidence of
side-effects. Clinical impression strongly suggests that antacids relieve pain in peptic ulcer but objective confirmation is lacking.

T. MORRIS AND J. RHODES
Department of Gastroenterology
University Hospital of Wales
Heath Park, Cardiff

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Antacids and peptic ulcer—a reappraisal

545

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