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Antacids Revisited

A Review of Their Clinical Pharmacology and Recommended Therapeutic Use

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Contents

Abstract

Antacids are commonly used self-prescribed medications. They consist of calcium carbonate and magnesium and aluminum salts in various compounds or combinations. The effect of antacids on the stomach is due to partial neutralisation of gastric hydrochloric acid and inhibition of the proteolytic enzyme, pepsin. Each cation salt has its own pharmacological characteristics that are important for determination of which product can be used for certain indications. Antacids have been used for duodenal and gastric ulcers, stress gastritis, gastro-oesophageal

reflux disease, pancreatic insufficiency, non-ulcer dyspepsia, bile acid mediated diarrhoea, biliary reflux, constipation, osteoporosis, urinary alkalinisation and chronic renal failure as a dietary phosphate binder. The development of histamine H_2-receptor antagonists and proton pump inhibitors has significantly reduced usage for duodenal and gastric ulcers and gastro-oesophageal reflux disease. However, antacids can still be useful for stress gastritis and non-ulcer dyspepsia. The recent release of proprietary H_2 antagonists has likely further reduced antacid use for non-ulcer dyspepsia. Other indications are still valid but represent minor uses.

Antacid drug interactions are well noted, but can be avoided by rescheduling medication administration times. This can be inconvenient and discourage compliance with other medications. All antacids can produce drug interactions by changing gastric pH, thus altering drug dissolution of dosage forms, reduction of gastric acid hydrolysis of drugs, or alter drug elimination by changing urinary pH. Most antacids, except sodium bicarbonate, may decrease drug absorption by adsorption or chelation of other drugs.

Most adverse effects from antacids are minor with periodic use of small amounts. However, when large doses are taken for long periods of time, significant adverse effects may occur especially patients with underlying diseases such as chronic renal failure. These adverse effects can be reduced by monitoring of electrolyte status and avoiding aluminum-containing antacids to bind dietary phosphate in chronic renal failure.

Antacids, although effective for discussed indications of duodenal and gastric ulcer and gastro-oesophageal reflux disease, have been replaced by newer, more effective agents that are more palatable to patients. Antacids are likely to continue to be used for non-ulcer dyspepsia, minor episodes of heartburn (gastro-oesophageal reflux disease) and other clear indications. Although their widespread use may decline, these drugs will still be used, and clinicians should be aware of their potential drug interactions and adverse effects.

Antacids have been available for many years. However, their importance has declined since the development of histamine H_2 antagonists and more recently proton pump inhibitors. Although there are now drugs available that are much more effective than antacids at healing ulcers and relieving the symptoms of gastro-oesophageal reflux, many people buy antacids over-the-counter for symptomatic relief of gastrointestinal complaints and find them quite sufficient and satisfactory. Indeed, in the US the annual expenditure on antacids exceeds 2 billion dollars. Whether the consumption of antacids will fall with the availability of over-the-counter H_2 antagonists remains to be seen.

Among antacids there is a wide variability of chemical composition, acid neutralising capacity (ANC), adverse effects and drug interactions making this an area where rational use of antacids in particular circumstances is to be desired.

This article reviews the chemical composition of various available antacids, and their clinical pharmacology including drug interactions. It also discusses the use of antacids in a variety of gastrointestinal and other diseases. Because antacids are marketed under different names in different countries, proprietary names have not been used in this review. Agents often thought of as 'antacids', but without any significant ANC, such as Gaviscon®, sucralfate and bismuth compounds have not been included.

Antacids are salts of aluminum, calcium, magnesium or sodium or a combination of these (table I).

1. Clinical Pharmacology

1.1 Potency and Activity

Antacids are inorganic, relatively insoluble salts which when dissolved in the stomach partially neutralise gastric hydrochloric acid. Antacid potency is based on molar equivalency to neutralise a known amount of gastric acid. Calcium carbonate is the most potent on a weight basis followed by sodium bicarbonate, then magnesium salts and aluminum salts.

Antacid effects are due in part to the neutralisation of a portion of gastric acid, thus raising gastric pH.[5] Generally, large doses of antacids are needed to raise gastric pH significantly.[6,8] Both aluminum hydroxide and magnesium hydroxide also bind bile acids with magnesium hydroxide having a lesser degree of binding.[7-10] Antacid-induced increases in gastric pH inhibit pepsin activity; therefore, its proteolytic activity is reduced. Inhibition of pepsin activity is dependent upon the rise in gastric pH and is maximally inhibited at approximately pH4. Aluminum hydroxide and calcium carbonate have also been reported to directly absorb pepsin. Aluminum hydroxide and magnesium/aluminum hydroxides are also reported to have cytoprotective effects.[1,7-10,11] *In vitro* studies have indicated that cytoprotective effects are due to an increase in gastric bicarbonate secretion and both luminal and mucosal prostaglandin release. In addition, mucous secretion and microvascular blood flow are increased. Thus, antacid effects are both dependent on and independent of ANC.[11]

1.2 Calcium Carbonate

Calcium carbonate dissolves slowly in the stomach. It reacts with gastric hydrochloric acid to produce calcium chloride, carbon dioxide and water. About 90% of the calcium chloride produced is converted into insoluble calcium salts primarily calcium soaps in the small intestine and is not absorbed.[1,7-10] Calcium salts can cause constipation.

1.3 Sodium Bicarbonate

Sodium bicarbonate is the most rapidly acting antacid. It rapidly reacts with gastric hydrochloric acid to produce sodium chloride, carbon dioxide and water. Excess bicarbonate rapidly empties into the small intestine and is then absorbed. Since endogenous bicarbonate is not needed in the small intestine, a mild metabolic alkalosis with alkalinisation of the urine may be seen following doses of sodium bicarbonate. Sodium bicarbonate may produce gastric distention, belching and flatulence due to the rapid production of carbon dioxide. Because of the high sodium load associated with ingestion of

Table I. Chemical composition of currently available antacids[1-4]

Name	Chemical formula	Acid neutralising capacity (mEq/15mL of a commercially available product)
Aluminum hydroxide	$Al(OH)_3$	29
Aluminum carbonate	$Al_2(CO_3)_3$	36
Aluminum phosphate	$AlPO_4$	6
Calcium carbonate	$CaCO_3$	58
Dihydroxyaluminum aminoacetate	$NH_2CH_2COOAl(OH)_2$	17
Dihydroxyaluminum sodium carbonate	$(HO)_2AlOCO_2Na$	8.5/tablet
Magaldrate	$[Mg(OH)_2 + MgSO_4 + Al(OH)_3 + Al_2(SO_4)_3]$	33
Magnesium carbonate	$MgCO_3$	(Low – used in combination with other products)
Magnesium hydroxide	$Mg(OH)_2$	35
Magnesium oxide	MgO	8-20 mEq/g
Magnesium trisilicate	$Mg_2O_8Si_3$	Low
Magnesium and aluminum hydroxides	$Mg(OH)_2 + Al(OH)_3$	63[a]
Sodium bicarbonate	$NaHCO_3$	17

a From Maalox® (Drake and Hollander method).[4]

sodium bicarbonate, it is not commonly recommended as an antacid.[1,7-10]

1.4 Magnesium Salts

Magnesium hydroxide rapidly reacts with gastric hydrochloric acid. This chemical reaction produces magnesium chloride and water. When magnesium carbonate reacts with gastric acid, carbon dioxide is formed in addition to the other reaction products. Magnesium trisilicate dissolves slowly, and reaction products from gastric acid are magnesium chloride, silicon dioxide and water. Because of its slow dissolution it is not very effective in raising gastric pH. Magnesium chloride has a bioavailability of 15 to 30% and is excreted renally. Magnesium is retained in renal impairment depending upon the magnitude. Magnesium antacids can produce a cathartic effect.[1,7-10]

1.5 Aluminum Salts

Aluminum hydroxide and aluminum oxide dissolve slowly in the stomach. They react with gastric acid to produce aluminum chloride and water. Aluminum carbonate or dihydroxyaluminium sodium carbonate produces carbon dioxide plus aluminum chloride and water. Aluminum phosphate and gastric acid produce aluminum chloride and phosphoric acid. Aluminum chloride is 17 to 30% bioavailable in the small intestine and excreted renally. With impaired renal function, aluminum is retained. Uraemic aluminum overload has been associated with dementia.[1,7-10]

1.6 Phosphate Binding

Aluminum- and calcium-containing antacids combine with dietary phosphate to form insoluble aluminum or calcium phosphate. The phosphate binding may result in decreased phosphate absorption and cause hypophosphataemia and hypophosphaturia in patients with normal renal function. Aluminum hydroxide and calcium carbonate are used to bind dietary phosphate in patients with chronic renal failure. This reduces phosphate load and decreases the hyperphosphataemia seen in patients with chronic renal failure. Calcium carbonate is the preferred phosphate binder because of the dementia associated with aluminum salts. Aluminum salts and calcium carbonate commonly cause constipation.[1,7-10]

1.7 Duration of Action, Pepsin Absorption and Acid Rebound

With normally prescribed doses, antacids raise gastric pH significantly compared with placebo, but usually not above 4 or 5 except with massive doses. Antacids raise pH immediately and have a duration of action of up to 3 hours when given with or 1 hour after a meal.[12] When ingested on an empty stomach, the duration of action is 20 to 60 minutes. In addition to decreasing pepsin activity by raising gastric pH, aluminum and calcium antacids appear to adsorb pepsin and reduce its actions more than would be predicted by pH changes alone.[5] Calcium carbonate is reported to produce gastric acid hypersecretion and rebound due to a local effect on gastrin producing cells.[13] However, recent studies have questioned this finding because of the dose inequivalence when compared with the other antacids.[14] In a recent study using similar doses of antacids with and without calcium, no rebound was found.[14] When antacid dose plus the buffering capacity of food exceed gastric acid production, excess bicarbonate is reabsorbed from the duodenum stimulating more gastric acid production and subsequent acid rebound. In the US, all antacid products must neutralise at least 5 mEq of gastric acid per dose.[1]

2. Therapeutic Uses

2.1 Duodenal Ulcer

2.1.1 Antacids vs Placebo

A number of controlled studies have examined the effects of antacids versus placebo in healing duodenal ulcer.[15-20] All the studies compared magnesium/aluminum mixtures given usually as 6 to 7 doses per day but occasionally 4 doses per day.[19-20] All the studies lasted for 4 weeks except one.[20] In 5 of the studies, antacids were significantly supe-

rior to placebo for ulcer healing. This was true whether large doses of antacid were given (1000 mEq ANC/day[15]) or small doses (120 mEq ANC/day).[19] Healing rates for placebo varied from 24 to 45% in these studies and for antacid from 74 to 88%. The only study that failed to demonstrate superiority for antacids[20] had a placebo response rate of 76% with antacids, healing 92% and lasted for 6 weeks.

One study[20] attempted to identify the appropriate dose of antacid comparing 104, 207 and 414 mEq ANC/day with placebo. Healing rates of 46, 85 and 88% compared with the placebo rate of 24% were observed. Because the 414 mEq regime was associated with more diarrhoea, with no increased response rate, the authors concluded that 207 mEq ANC/day was the optimum dose.

The overall lack of a dose response to antacids is somewhat surprising as Hunt et al.,[21] have found in a meta-analysis that ulcer healing is related to the number of hours in the day that gastric pH is greater than 3. It may be that the antacid studies have not been sufficiently large to demonstrate any differences. However, none of the antacid regimens increase nocturnal pH,[21] an important determinant of ulcer healing with H_2 antagonists. Thus, it may be that daytime antacid regimens are able to heal only a percentage of ulcers no matter how well that daytime acidity is neutralised. Another possibility is that the action on ulcer healing by antacids is at least in part not related to their ability to act as antacids. In animal studies antacids have other effects including increasing tissue prostaglandins and other cytoprotective effects.[19,22,23] However, there are no data in clinical studies.

Interestingly, in these studies antacids were not significantly better than placebo for symptom relief. In the studies that examined this specifically, two[15,16] found no differences and one[18] found differences for 414 and 214 mEq ANC/day but no difference for 104 mEq ANC/day.

2.1.2 Antacids vs H_2 Antagonists

Numerous controlled trials have compared antacids with H_2 antagonists.[24-36] All these studies compared magnesium and aluminum mixtures to cimetidine 800, 1000 or 1200 mg/day or to ranitidine 300 mg/day.[30,35] Studies lasted 4 to 6 weeks or in one case 8 weeks.[36] As with the placebo studies ANC varied widely from 88 to 1008 mEq/day. One study found that the cimetidine 800 mg/day healing rate of 88% was better than the 44 mEq antacid twice daily healing rate of 62%.[36] In all the other studies healing rates for antacids were 52 to 96% and were not different from those for H_2 antagonists (59 to 100%). Again, there did not appear to be a dose-related healing response rate to antacids in these studies, but more diarrhoea was noted with higher doses.

In the 6 studies that addressed symptom response,[24,25,27,29,30,36] the same lack of difference between antacids and H_2 antagonist was noted.

In a single study comparing the ability of antacids and H_2 antagonists to prevent relapse of healed duodenal ulcer, Bardham[37] compared placebo to antacid 87 mEq ANC at night, 87 mEq twice daily and cimetidine 400mg at night. Relapse rates after 1 year were lowest with antacid b.i.d and cimetidine (23 and 25%, NS) and both were better than antacid at night (39%, $p < 0.05$) or placebo (59%, $p < 0.01$). Bianchi-Porro et al.,[38,39] in a small study found that antacid 100 mEq ANC/day was less effective than cimetidine 400mg at bedtime at preventing ulcer relapse both at 6 and 12 months (54 *vs* 41% relapse rate).

2.1.3 Conclusions

These studies demonstrate that antacids are more effective than placebo and as effective as H_2 antagonists at healing duodenal ulcer disease. However, like H_2 antagonists they are not consistently more effective than placebo at symptom relief. In general, low-dose antacid regimens have been shown to be as effective as high-dose regimens, although no such study has been undertaken in the US to establish whether that is true for that population.

None of the studies cited above controlled for the presence of *Helicobacter pylori*, and only some controlled for intake of nonsteroidal anti-inflammatory drugs (NSAIDs). These variables may well account for some of the differences in response rates seen in these studies. Certainly,

although antacids are effective in duodenal ulcer disease, they have been superseded by other approaches. For ulcers associated with *H. pylori*, antibacterial therapy with antisecretory therapy not only produces more effective and rapid healing but also cures the ulcer diathesis. For duodenal ulcers associated with NSAIDs, misoprostol, H_2 antagonists and proton pump inhibitors are the drugs of choice.

2.2 Gastric Ulcer

2.2.1 Antacids vs Placebo

There are fewer data comparing antacids versus placebo in patients with gastric ulcer than duodenal ulcer. Of the 4 studies[23,40-42] one[23] studied only 16 patients and judged healing (including partial healing) by barium studies. The others used more conventional, modern methods and criteria. Trial lengths lasted from 3 to 12 weeks and ANC, when given, varied from 120 to 320 mEq ANC/day. Of the 3 larger studies, only one[42] showed significantly more healing with antacids, and the only study that looked at symptoms suggested placebo was as good as antacid for symptom relief.

2.2.2 Antacids vs H_2 Antagonists

Five controlled trials have compared antacids with H_2 antagonists for healing of gastric ulcers.[29,41,43-45] These trials compared cimetidine 1000 to 1200 mg/day or ranitidine 300 mg/day[29] with aluminum and magnesium hydroxides in dosages of 100 to 328 mEq ANC/day and lasted between 4 and 8 weeks. Of the studies, all of which were of adequate size, two[41,45] showed H_2 antagonists to be superior to antacids while the other three showed no difference, although H_2 antagonists were numerically superior to antacids for healing in 2 studies.[29,44] Only one of these studies compared symptom relief and found H_2 antagonists to be superior,[29] but the antacid dose in this study was low (100 mEq ANC/day).

2.2.3 Conclusions

Although the data are not conclusive, antacids may well increase gastric ulcer healing rates, but probably not as much as H_2 antagonists. As with duodenal ulcer studies very few of these trials conrolled for NSAIDs and none controlled for the presence of *H. pylori*. More potent drugs have superseded antacids in this disease.

2.3 Stress Gastritis

Severely ill patients in intensive care units are at risk of developing multiple superficial lesions in the stomach, particularly the body and fundus, that can cause minor or major gastrointestinal bleeding. These lesions are the result of mucosal ischaemia that leads to intra-mucosal acidosis, loss of bicarbonate and mucus secretion and most importantly back diffusion of hydrogen ions.[46] Gastric mucosal injury occurs in nearly all patients in intensive care.[47] Most remain asymptomatic, up to 50% develop occult bleeding (positive guaic testing), 6 to 25% develop overt bleeding[48] and 1 to 2% develop clinically significant bleeding with a fall in haemoglobin or need for transfusion or both.[49]

Many factors have been proposed that increase the risk of stress gastritis. However, in a prospective study of more than 2000 patients the only independent factors were respiratory failure (odds ratio 15.6) and coagulopathy (odds ratio 4.3). Hypotension, renal failure, hepatic failure and sepsis apparently had no effect. Patients with head injury, extensive burns, organ transplants and a history of recent ulcers or gastrointestinal bleeding were excluded as they received prophylactic therapy.[50] In those patients with clinically significant bleeding the mortality was 48.5%, not usually due to the bleeding but because these patients were extremely ill. Therapy directed at raising gastric pH above 4.0 has resulted in reduction in occult and overt bleeding but results concerning clinically significant bleeding were less clear.

2.3.1 Antacids vs Placebo

Many studies have compared antacids with placebo or no treatment for prevention of bleeding in stress gastritis.[52-58] Studies used 85 to 360 mEq ANC/hour of antacid and in most cases aimed to keep pH above 4. The trials examined the effects on occult[52-54] or overt[51,55-58] bleeding. Six of the 8 studies found antacids to be significantly better

than placebo.[51-54,56-58] In a meta-analysis of such studies Schuman[48] found antacids to be superior to placebo for both occult (3.7 *vs* 27.3%) and overt (3.3 *vs* 15%) bleeding.

2.3.2 Antacids vs H_2 Antagonists

Numerous studies have compared antacids to H_2 antagonists in stress gastritis.[54-64] Antacids were given in doses of 27 to 612 mEq ANC/hr, usually to raise gastric pH to greater than 4. Cimetidine 800 to 2400 mg/day was given for comparison. Only one study demonstrated a significant difference between treatment arms. Priebe et al.[59] found antacids were significantly better than cimetidine. This study found that cimetidine was less effective than antacids at raising gastric pH as also occurred in other studies.[55,61,62] A meta-analysis of antacids versus H_2 antagonists by Schuman[48] found that overall antacids were significantly more effective than H_2 antagonists at preventing occult bleeding, but not at preventing overt bleeding.

2.3.3 Antacids vs Prostaglandins

In a single study in 46 patients, Skillman et al.[65] found that antacid was superior to a prostaglandin E_2 analogue in preventing occult bleeding. In the antacid group occult bleeding occurred in 14% of cases and in the prostaglandin group bleeding occurred in 50%.

2.3.4 Antacids vs Sucralfate

Several studies have compared antacids with sucralfate 1g every 6 hours in the prevention of stress gastritis bleeding.[66-71] Only one study showed a difference between the 2 treatments. Cannon et al.[69] found antacids were significantly better than sucralfate at preventing overt bleeding. The other studies found no differences for occult[66,67,71] or overt[68,70,71] bleeding.

2.3.5 Conclusions

In an attempt to reconcile the often conflicting data in various studies, some of those involved in these studies have undertaken a sophisticated meta-analysis of 63 randomised trials.[72] They concluded use of antacids led to a trend towards less overt bleeding and less clinically important bleeding than placebo, but these differences did not reach statistical significance. Antacids were less effective than H_2 antagonists, but probably more effective than sucralfate. However, sucralfate was associated with lower rates of nosocomial pneumonia and lower mortality rates than H_2 antagonists and antacids.[72] They concluded that further studies of sucralfate versus H_2 antagonists were warranted.

Whether patients in intensive care units should be given any prophylactic treatment to prevent bleeding has been examined in a large prospective Canadian study.[73] Their conclusion was that prophylactic therapy should be given only to those at high risk of bleeding.

2.4 Gastro-Oesophageal Reflux Disease

In the US, most antacids are taken because of heartburn. However, there have been few published studies of the use of antacids in this disease. In a Gallup poll 44% of the US population stated that they suffered from heartburn at least once per month, and 7% had heartburn at least once per week.[74] In a study of patients who took antacids, the majority did so for heartburn.[75] Although most people with mild heartburn self-medicate with antacids, few studies have been performed. Furthermore, such patients may not have mild disease and require other therapy. In a recent study of 155 patients who had never sought medical therapy 47 had erosive oesophagitis, 6 had Barrett's oesophagus and 1 patient had adenocarcinoma of the oesophagus.[76] Furthermore, it is well recognised that patients can present with strictures caused by reflux with no antecedent heartburn, and the same is true of patients with asthma, globus, pneumonia or dental erosions, in whom the underlying abnormality is that of gastro-oesophageal reflux.

It has been assumed that antacids work in reflux disease in the same way they work in diseases of the stomach and duodenum, that is by neutralising gastric acid. However, that may not be true. Efficacy of antacids in patients with heartburn does not seem to be related to their neutralising capacity, but to their ability to 'stick' within the oesophagus and provide local intra-oesophageal antacid.[83]

2.4.1 Antacids vs Placebo

Only 3 studies have compared antacids with placebo in patients with reflux disease.[77-80] These studies used 560 to 592 mEq ANC/day, and lasted 2 to 6 weeks. Two studies examined healing rates of oesophagitis and found no differences between antacids and placebo.[77,80] Two of the studies documented symptom response, both found antacids were superior[78,80] but in only one case was the difference significant.[84]

2.4.2 Antacids vs H_2 Antagonists

Data comparing antacids with H_2 antagonists are also sparse. These studies have compared cimetidine 1200 mg/day[81,82] or ranitidine 300 mg/day[79] with antacid (595 to 700 mEq ANC/day) for between 6 and 12 weeks. These studies found symptomatic response to be equal or better with H_2 antagonists but only in one case was the H_2 antagonist significantly better than antacid.[81] The same study was the only study to show a greater mucosal improvement (not necessarily healing) with H_2 antagonists over antacids.

In terms of symptom relief in gastro-oesophageal reflux, antacids and H_2 antagonists may well be complementary when taken on an as needed basis. In a crossover study in 25 volunteers using 24-hour monitoring, calcium carbonate when taken after a meal had an immediate effect on raising gastric pH that lasted about 1 hour. The H_2 antagonists had no effect in the first hour but then raised pH for more than 4 hours.[12]

2.4.3 Conclusions

Antacids have little effect on healing of erosive oesophagitis, but are probably as effective or nearly as effective as H_2 antagonists. For such patients proton pump inhibitors have been demonstrated to be much more effective.

For patients with milder disease antacids are probably better than placebo and are nearly as effective as H_2 antagonists. Because of the immediacy of their effect antacids will continue to be useful to patients with milder reflux disease, or for those with more severe disease who experience breakthrough symptoms on prescription drugs.

2.5 Pancreatic Insufficiency

In pancreatic insufficiency due to chronic pancreatitis, administration of pancreatic enzyme supplements can reduce steatorrhoea and protein malabsorption. However, lipase is inactivated at pH <4 and pepsin is inactivated at pH <3.5. Because of reduced pancreatic bicarbonate secretion in patients with chronic pancreatitis, the duodenum is more acidic than normal. This results in less than 10% of administered enzyme supplement being available to aid digestion and absorption. Administration of sodium hydroxide or aluminum hydroxide to such patients has been shown to reduce steatorrhoea.[77] Conversely, administration of calcium carbonate or magnesium hydroxide worsens the steatorrhoea.[77,84] These antacids cause precipitation of calcium or magnesium soaps and bile salts.[85,86] Currently, the activity of enzyme supplements can be protected and upper gastrointestinal pH controlled more effectively with either H_2 antagonists or proton pump inhibitors, thus rendering antacids second line drugs in this circumstance.

2.6 Non-Ulcer Dyspepsia

Many patients take antacids for dyspepsia that defies a definitive diagnosis and thus gets termed non-ulcer dyspepsia. Many patients apparently benefit from symptom relief with these agents. However, there are no studies that provide any firm data to support the use of antacids in this circumstance.

2.7 Bile Acid–Mediated Diarrhoea

Patients with a resection of the terminal ileum or ileal disease such as in Crohn's disease may develop diarrhoea due to loss of the ability to reabsorb conjugated bile acids. When bile acids are not reabsorbed in the terminal ileum and spill into the colon they cause water secretion and stimulate mucous secretion and colonic motility, resulting in watery diarrhoea. Often this diarrhoea is worse in the morning after the first meal of the day and improves as the day goes on. A similar pattern of

diarrhoea is sometimes seen after cholecystectomy or after a vagotomy.

Aluminum and magnesium salts can each bind bile acids *in vitro*.[87] However, aluminum salts bind bile acids more tightly. Aluminum hydroxide binds dihydroxy bile acids more avidly than trihydroxy bile acids. Glycine conjugates are more tightly bound than taurine conjugates.[88] Aluminum hydroxide 30ml immediately upon arising in the morning and at night has been shown to effectively reduce cholorrheic diarrhoea.[89] Nevertheless, bile acid binding resins such as cholestyramine and colestipol that were developed originally for hypercholesterolaemia bind all bile acids more avidly and are more effective than aluminum salts.

2.8 Biliary Reflux

Although gastro-oesophageal reflux of acid is generally regarded as the most important factor in reflux disease some authorities believe that reflux of bile acids into the oesophagus may also be important in certain circumstances. Furthermore, duodeno-gastric reflux of bile has been implicated in gastric damage after gastric operations that include a pyloroplasty. Aluminum salts and cholestyramine can be used in circumstances where bile acids are thought to be playing a role, but studies of efficacy have so far proven negative.[90]

2.9 Constipation

Of the antacids, calcium and aluminum salts are often thought to cause constipation. However, studies have shown no evidence for this.[91,92] Magnesium salts tend to cause diarrhoea.[93] The absorbable antacid sodium bicarbonate does not affect stool frequency. The side effects of antacids may be used to advantage in particular patients. If the patient has a tendency to constipation then a magnesium antacid might well be the best choice. In a patient with a tendency to loose stools then calcium or aluminum antacids would be preferable.

2.10 Osteoporosis

Current studies suggest that most adults ingest insufficient calcium, and that a diet supplemented with calcium salts has a small beneficial effect on the prevention or reduction of osteoporosis.[94] In a patient who also needs an antacid, both needs can be met by ingesting calcium carbonate.

2.11 Urinary Alkalinisation

In order to affect the acidity of urine the agent must be absorbed. Sodium bicarbonate causes urinary alkalinisation and a metabolic alkalosis. Although regarded as a nonsystemic antacid, ingestion of magnesium hydroxide also increases urinary pH, possibly through neutralisation of gastric acid,[95] and increased available duodenal bicarbonate and its absorption. Increased urinary pH increases urate solubility and reduces the risk of urate stones. However, allopurinol, which prevents the formation of urates from purines, has rendered this approach obsolete.

2.12 Chronic Renal Failure

Bone disease in chronic renal failure can be managed by controlling calcium and phosphate homeostasis. A diet low in phosphate combined with calcium carbonate 6 to 14 g/day taken with meals to bind dietary phosphates can control serum phosphate. Serum calcium can be maintained by oral calcium salts and vitamin D and can prevent the secondary hyperparathyroidism, and osteodystrophy seen in patients with chronic renal failure.[96]

3. Drug Interactions

Drug interactions involving antacids[97-103] occur through 3 mechanisms; antacid binding of another drug in the gastrointestinal tract, antacid induced changes in gastrointestinal pH and urinary pH. Antacids are thought to nonspecifically adsorb drugs to their surface; for example, aluminum and magnesium hydroxides impair the absorption of phenytoin. Antacids with divalent or trivalent cations may complex with certain drugs reducing absorption. For example, magnesium, aluminum, and

Table II. Antacid drug interactions

Drug	Interaction (effect on drug in column 1)	Mechanism
Allopurinol	Decreased activity	Unknown, adsorption suspected
Amphetamines	Prolonged effect with $NaHCO_3$	Decreased urinary elimination
ACE inhibitors	Decreased captopril bioavailability (by 35-40%)	Unknown, adsorption suspected
Oral anticoagulants (dicoumarol)	Increased absorption ($Mg(OH)_2$)	Chelation
Enteric-coated aspirin	Increased rate of absorption	Enhanced drug release from dosage form
Benzodiazepines (chlordiazepoxide clorazepate, diazepam, temazepam, triazolam)	Delayed rate but not extent of absorption (Mg and Al hydroxides)	Adsorption
β-Blockers:		
propranolol, atenolol	Decreased bioavailability and rate of absorption ($Al(OH)_3$ containing antacid)	Decreased rate of gastric emptying
atenolol	Decreased bioavailability and prolonged half-life (Ca-containing antacids)	Unknown
metoprolol	Increased bioavailability (Mg- and Al-containing antacids)	Unknown
Chloroquine	Decreased absorption (AUC decreased by 18% by Mg trisilicate)	Adsorption
H_2 antagonists (reported for cimetidine and raniditine, probably occurs with others)	Decreased absorption	Unknown, adsorption suspected
Corticosteroids (prednisone, dexamethasone)	Decreased absorption	Unknown, adsorption suspected
Diflunisal	Decreased absorption ($Al(OH)_3$ decreased bioavailability by 25-40%; (Mg and Al hydroxides decreased bioavailability by 15-20%)	Unknown, adsorption suspected
Digoxin	Decreased absorption of digoxin	Adsorption and faster gastric emptying
Erythromycin stearate	Increased half-life	Delayed absorption
Ethambutol	Decreased absorption with Al-containing antacids	Unknown, adsorption suspected
Indomethacin	Decreased bioavailability	Increased gastric pH resulting in increased ionised indomethacin and less absorption
Iron preparations	Mg trisilicate and carbonate antacids inhibit absorption	Chelation
Isoniazid	$Al(OH)_3$ and magaldrate decrease bioavailability	Chelation
Ketoconazole	Decreased bioavailability	Increased gastric pH resulting in decreased dissolution in the stomach
Levodopa	Decreased breakdown in the stomach, with increased absorption	Increased gastric emptying rate
Lithium	Decreased serum concentrations with $NaHCO_3$	Alkalinisation of the urine enhances renal clearance
Mecamylamine	Increased effect on lowering blood pressure with $NaHCO_3$	Alkalinisation of the urine decreased urinary elimination
Mefenamic acid	Increased absorption with $Mg(OH)_2$	Unknown
Methenamine	Decreased antibacterial activity with $NaHCO_3$	Alkalinisation of urine decreased formaldehyde production in urine
Methotrexate	Decreased effect with $NaHCO_3$	Alkalinisation of the urine increases renal clearance
Naladixic acid	Decreased absorption of naladixic acid	Increased pH resulting in ionisation of naladixic acid and decreased ability to be absorbed
Naproxen	Antacids delay absorption and may alter bioavailability (Mg and Al hydroxides decrease bioavailability, $NaHCO_3$ increases bioavailability	Unknown

Table II. Contd

Drug	Interaction (effect on drug in column 1)	Mechanism
Nitrofurantoin	Decreased absorption	Increased pH resulting in ionisation of nitrofurantion and decreased ability to be absorbed
Penicillamine	Decreased absorption and urinary recovery	Chelation
Penicillin	Increased and decreased absorption	Increased pH resulting in increased ionisation and decreased absorption. Also increased pH resulting in less gastric acid degradation and increased absorption
Phenothiazines	Decreased absorption on orally administered drug ($Al(OH)_3$ decreased urinary excretion of chlorpromazine by 10-48%, Mg trisilicate and $Al(OH)_3$ decreased serum concentrations of chlorpromazine)	Adsorption
Phenytoin	Decreased absorption in some patients	Unknown, adsorption suspected
Procainamide	May delay absorption in dogs with a reduced maximum serum concentration	Unknown
Quinidine	Increased urinary reabsorption with increased serum concentrations	Increased urinary pH increases unionised quinidine in the urine thus, increasing urinary reabsorption
Salicylates	Decreased serum concentrations due to decreased urinary reabsorption	Increased urinary pH decreased urinary reabsorption (less ionised)
Sodium polystyrene and sulfonate resin	Increased serum alkalinisation	Binds Mg and Ca preventing binding to HCO_3–, impairs neutralisation of gastric acid and increases serum HCO_3–
Sulphonamides	Decreased absorption	Increased gastric pH increases ionised sulphonamide, thus decreasing absorption
Sulphonylureas [glibenclamide (glyburide)]	Increased absorption with increased effect and possible hypoglycaemia with Mg antacids	Unknown
	Decreased effect with $NaHCO_3$	Increased urinary pH increased renal clearance
Sympathomimetics	Increased effect with $NaHCO_3$	Increased urinary pH decreased renal tubular reabsorption
Tetracycline	Decreased absorption of tetracycline (significant interaction)	Chelation by binding with di- and trivalent ions
	Decreased effect with $NaHCO_3$	Increased urinary pH, increased renal clearance
Valproic acid (sodium valproate)	Increased bioavailability and aluminum-magnesium hydroxide, calcium carbonate, and aluminum-magnesium trisilicate antacid	Decreased clearance via unknown mechanism

calcium antacids reduce the absorption of tetracycline. The only antacid which does not appear to bind to other drugs is sodium bicarbonate.

One overlooked, but commonly seen drug interaction, is antacid increase in gastric pH. This interaction can alter the degree of ionisation of the drug (weak acids are more ionised and less absorbed, weak bases are less ionised and more likely to be absorbed). Furthermore, changes in gastric pH can alter dissolution of drugs which are dependent upon a low gastric pH for absorption. For example, ketoconazole is dependent upon a low gastric pH for disintegration and dissolution. Increasing gastric pH significantly reduces the absorption of ketoconazole. This interaction involves all antacids.

Some drugs may demonstrate enhanced absorption due to changes in gastric pH. Penicillins are examples of drugs which are degraded by gastric acid. Antacids which raise gastric pH have been reported to increase the absorption of amoxicillin (table II).

Antacids can also alter gastric motility. Levodopa absorption is enhanced by antacids because of faster gastric emptying and less acid induced

degradation in the stomach. Drug dosage forms which are dependent upon pH for dissolution may have absorption altered by increased gastric pH. Enteric-coated aspirin can prematurely dissolve with resultant release of aspirin in the stomach instead of the duodenum.

Magnesium- and aluminum-containing antacids can raise urinary pH by one unit. This can alter the ionisation of drugs in the renal tubule either enhancing or diminishing reabsorption. Weak acids such as salicylates can become more ionised decreasing renal tubular reabsorption. Weak bases such as quinidine become less ionised increasing tubular reabsorption.

4. Adverse Effects

Considering the widespread nonprescription use of antacids, adverse effects[1,7,10,104-108] are minimal for individuals with normal renal function. This is probably because of the use of low doses and sporadic use by patients. Adverse effects are of greater significance with higher dosages and prolonged use. Adverse effects are related to the specific action.

Although questioned (see section 2.9) the most common adverse effect of aluminum-containing antacids is constipation. This may progress to include intestinal obstruction, faecal impaction and development of haemorrhoids and anal fissures. The formation of insoluble aluminum salts appears to produce the constipating effect. In addition, between 17 to 30% of the aluminum chloride produced from the reaction with gastric hydrochloric acid and aluminum hydroxide is systemically absorbed. In patients with normal renal function, the aluminum is rapidly eliminated; however, in patients with impaired renal function, aluminum can be retained in the brain and other tissues.

When aluminum hydroxide was used to bind excess phosphate in the gut of hyperphosphataemic renal failure patients, these patients were unable to clear the aluminum which resulted in hyperaluminiumaemia. The accumulation of aluminum in the brain produced neurotoxicity manifested as encephalopathy in patients on chronic haemodialysis. This was also known as 'dialysis dementia.' Because aluminum-containing antacids, except aluminum phosphate, bind phosphate in the intestine by forming insoluble phosphate salts, too much phosphate may be bound resulting in hypophosphataemia. The symptoms of phosphate depletion are nonspecific and include anorexia, malaise, and muscle weakness. Long term use of aluminum-containing antacids at high doses with resultant phosphate binding can lead to calcium resorption from bone with resultant osteomalacia, osteoporosis, and fractures.

Calcium-containing antacids have been noted to cause constipation, belching and flatulence. Constipation as an adverse drug reaction also has been questioned (see section 2.9). Belching and flatulence from calcium carbonate is due to the release of carbon dioxide as the result of the chemical reaction of calcium carbonate and gastric hydrochloric acid. Ingestion of calcium carbonate when combined with milk intake and vitamin D ingestion can lead to milk-alkali syndrome (discussed later). Prolonged ingestion of large doses of calcium carbonate >20 g/day may produce hypercalcaemia. In patients with impaired renal function, doses as low as 4g per day of calcium carbonate may lead to hypercalcaemia. This can be a concern since calcium carbonate is now used almost exclusively in the US to bind phosphate in renal failure patients receiving chronic haemodialysis.

The most frequent adverse effect of magnesium-containing antacids is diarrhoea. The diarrhoea produced by magnesium is thought to be caused by the poor absorption of the relatively insoluble magnesium salts and the subsequent osmotic effect in the bowel. It is dependent upon the dose and can be severe, producing fluid and electrolyte imbalances. Since 5 to 10% of the magnesium chloride produced from the reaction of magnesium hydroxide and gastric hydrochloric acid can be systemically absorbed, hypermagnesaemia may result in patients with impaired renal function. Significant hypermagnesaemia may depress the CNS and cause cardiac arrhythmias. In patients with creatinine clearances <30 ml/min, magnesium doses exceed-

ing 50 mEq per day should only be used with frequent electrolyte monitoring.

In the past, most antacids contained significant amounts of sodium as a contaminant, which could lead to sodium overload in susceptible patients causing congestive heart failure, ascites or renal impairment. Most currently marketed antacids contain less than 1mg (0.04 mEq) of sodium per 5ml. However, individual products should be evaluated for sodium content before use. With the use of sodium bicarbonate, sodium overload can be a significant factor in the aforementioned patient types. Sodium bicarbonate, because of its immediate effect and subsequent carbon dioxide production can also produce belching, gastric distention and flatulence. In addition, excessive sodium bicarbonate administration can cause systemic alkalosis and alkalinisation of the urine. Milk-alkali syndrome has also been seen with the use of sodium bicarbonate and milk products. Use of sodium bicarbonate as an antacid should be discouraged.

The milk-alkali syndrome has been related to previous therapy for peptic ulcer disease which used high doses of antacid combined with milk. The syndrome as described by McMillan and Freeman[105] includes the acute onset of irritability, distaste for milk, headache, occasional nausea and vomiting, muscle ache, weakness and malaise. Impairment of renal function including a decrease in creatinine clearance and urinary concentrating capacity has also been observed. The syndrome has a reported mortality of about 5%. It has been related to excess calcium absorption from calcium carbonate, but has been seen with other antacids combined with milk.

The mechanism for this syndrome is thought to be due to the development of hypercalcaemia with subsequent suppression of parathyroid hormone. Thus, phosphate retention occurs with resultant hyperphosphataemia. High levels of calcium and phosphate precipitate in the kidney tubules resulting in renal damage and the subsequent decline in creatinine clearance. With the current trends to advise increased calcium intake using calcium carbonate, patients should be advised to limit intake of calcium carbonate to about 1200 mg/day (approximately 2 Tums®). As an alternative, calcium supplementation can be made through adequate milk (skim milk) or milk product (low fat yogurt) intake. Adequate vitamin D intake is necessary to absorb calcium, especially in the elderly, who are likely to have low vitamin D levels.

Allergic reactions, including asthma, can be seen because of the tartrazine dye in some antacid products.

5. Conclusions

Although more effective drugs are available, antacids continue to be taken in substantial amounts. Considering their widespread use, antacids have proved to be very safe. Nevertheless, in particular patients the potential for adverse effects or drug interactions exists. Awareness of these possibilities is important as patients often fail to inform their physician about antacid use unless specifically asked.

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