Drug Treatment of Disease

ANTACIDS AND ALLIED DRUGS

BY

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It is difficult for a doctor to appreciate how many tons of antacids are taken yearly by the public, for great numbers of patients complaining of indigestion buy themselves some form of alkaline powder privately and do not go near a doctor at all. The layman has a traditional and long-accepted belief that dyspepsia is due to acidity and that certain foods are more acid than others. In choosing his antacid he is much influenced by its taste, colour, price, the way it is presented, its advertisements, and its reputation. In judging its efficiency he relies entirely upon its action in relieving symptoms, whether these be heartburn, pain, nausea, vomiting, or flatulence.

General Observations

The physician must view the use of antacids more critically, and attempt, even if unsuccessfully, to appreciate the scientific reasons for their actions in the body and their chemical behaviour. For this reason certain brief general observations may be apposite:

(1) Though acid excites pain in cases of peptic ulcer, there is no constant relationship between the pain of ulceration and the level of gastric acidity.

(2) High acid secretion—with nocturnal hypersecretion—is usual in patients with duodenal ulcer, but all levels of acid secretion occur in gastric ulcer—high, normal, or low.

(3) Fractional test meal examinations play no significant part in the practical management of ulcer patients, and almost no part in the diagnosis.

(4) Men secrete more acid and pepsin than women, mainly because they have a larger number of acid-secreting parietal cells in their stomachs.

(5) Acid secretion varies greatly in the same individual at different times, even with the same stimulus.

(6) Active stimulants of acid secretion are alcohol, caffeine, histamine, insulin, and some corticoids.

(7) Gastric acidity is normally lowered both by dilution with saliva, food, and drinks, and by neutralization with mucin, pepsin, neutral chlorides, mineral bases, bicarbonates, and slightly by duodenal regurgitation.

(8) Heartburn may be, but it not always, due to the presence of acid gastric juice in the oesophagus.

(9) An acid or bitter taste in the mouth is not necessarily related to gastric acidity.

(10) Changes in motility—especially spasm—of the stomach may be as important in causing symptoms as changes in secretory activity.

(11) Experiments *in vitro* with antacids do not necessarily correspond with their biological behaviour in the human body.

(12) Though histamine may perhaps be the substance by which gastric secretion is ultimately stimulated, either by chemical or nervous means, antihistamines do not antagonize this action, or only do, so by causing toxic effects locally on the mucosa.

With such considerations as these in mind, the use of antacids and allied drugs may be reviewed from the point of view of their chemical activity, their effect in relieving symptoms, and their action, if any, in promoting healing or cure of disease processes, such as peptic ulcer.

True antacids act either as chemical neutralizers or as physical adsorbents or as both. Other drugs producing similar clinical effects act through the nervous system as

inhibitors of acid secretion or motility or both by depressing or blocking the vagus nerve. Atropine and anticholinergic drugs act in this way and produce results comparable to the surgical operation of vagotomy.

Foods

Food acts as a stimulus to the stomach by both nervous and chemical pathways. The thought, smell, and taste of food or of cooking normally increases gastric secretion, which is inhibited by fear, depression, extreme fatigue, or sensations such as nausea and the dislike of food. Pleasant anticipation of food produces a flow of acid, which is diluted at once when food enters the stomach. Acid-tasting fruits such as lemon have no greater true acidity than runner beans, carrots, or boiled beetroot, rather less than sultanas or prunes, and exercise no greater effect on gastric secretion. Milk and cream act poorly as antacids, and hourly milk and cream feeds reduce acidity no more than do three meals a day of a general diet. Uncooked fats lessen gastric secretion while cooked fats increase it: the longer a fat is heated the lower its iodine value and the more stimulant it becomes to acid secretion.

CHEMICAL NEUTRALIZERS

Most chemical antacids have only a transient action in the stomach, and even in big doses do not lower acidity for more than 20 to 60 minutes at most. Their effect in relieving the pain of an ulcer does not usually begin for five to ten minutes after being swallowed. To obtain their maximum benefit, therefore, they should be given when the acid concentration in the stomach is high and the contents are not already diluted by food or fluids. They should be in a form that can mix well with the stomach contents and not act only in a small area. They are likely for this reason to be more effective as neutralizers when the stomach is active than when it is atonic, with poor motility. Tablets must be chewed or sucked in the mouth and not swallowed whole.

As judged by the rate of healing or by the incidence of relapses, the evidence that alkalis are of value in the treatment of patients with peptic ulcer is unconvincing, though symptomatic relief from their use is undoubted. To obtain the best symptomatic effect on ulcer pain, antacids should be given at the earliest moment that the pain begins; if pain has lasted for some time it is much less likely to be controlled. For this reason alkalis should be ready to hand at very short notice, and carried about in the pocket ready to be taken at any time. If there are no symptoms, it is doubtful if alkalis are indicated at all in the treatment of ulcer, and their routine administration after food in asymptomatic cases has no proved therapeutic value.

Sodium Bicarbonate

A 9% solution of sodium bicarbonate introduced into the stomach was shown by Smith (1955) to relieve the pain of peptic ulcer. It causes some gaseous distension on account of the carbon dioxide evolved in its reaction with hydrochloric acid, and this may bring about

eructation of gas with relief of discomfort. It is slightly solvent of mucin. Contrary to popular belief, it causes no significant "rebound" effect upon acidity, but its neutralizing action is very short-lived. Large doses of sodium bicarbonate may be needed to raise the pH of the stomach contents to any important extent, and even when added in amounts up to 4 oz. (120 g.) a day to a milk drip of 6 litres a day the effect on gastric acid was not always sufficient to keep the pH above 4, above which level pepsin is almost inactivated (Doll *et al.*, 1956).

Sodium bicarbonate may cause alkalosis, but only if given in large doses; the risk is greater if there is pyloric stenosis, renal failure, or severe constipation.

Its transitory effect and the risk of causing alkalosis make it an alkali of limited use, but it is often particularly helpful in relieving the heartburn which may occur with hiatus hernia, and in relieving gastric discomfort by producing distension and eructation of gas. The popular "soda mint" tablet (tab. sod. bicarb. co. *B.N.F.*) containing 5 gr. (300 mg.) of sodium bicarbonate and 1/15m. (0.004 ml.) of peppermint oil sucked in the mouth is for this reason often helpful in mild postprandial discomforts, but of little value in more serious conditions such as peptic ulcer. Sodium bicarbonate is often given with aspirin, and sometimes with citric acid as well to cause effervescence, with the idea of lessening gastric irritation; the combination is much vaunted as a cure for a "hangover" after alcoholic excess, and for the headache and vomiting of mild attacks of migraine.

Magnesium Preparations

Most magnesium preparations are mildly laxative, the carbonate and hydroxide acting as fairly efficient neutralizers; the magnesium chloride which is formed in the stomach has some action in retaining water and so causing loose bowel actions. The hydroxide does not lead to production of carbon dioxide, and is often given as "cream" or "milk" of magnesia to infants for its aperient action.

The carbonate is the main ingredient in many proprietary antacids, most of which have a composition similar to the old pulv. antacid. *N.F.*, 1939, or pulv. mag. carb. co. *B.N.F.*, 1957, which is:

Heavy mag. carb.	...	...	320 gr. (20 g.)
Calc. carb.	...	...	320 gr. (20 g.)
Sod. bicarb.	...	...	240 gr. (15 g.)
Light kaolin	...	...	80 gr. (5 g.)

The dose recommended is $\frac{1}{2}$ dr. (2 g.) in water, which contains only sufficient alkali for a very transitory antacid effect.

These powders may cause alkalosis, and though the risk with ordinary dosage is small it must not be forgotten. For this reason magnesium trisilicate is more often used, as it has no such danger. It is insoluble in water, and though it acts only as a slow neutralizer it is an efficient adsorbent of acid. It is non-toxic but is often too laxative in its action. It is a tasteless powder and by itself is often less effective in relieving symptoms than when combined with more rapid acting neutralizers, as in the very useful pulv. mag. trisil. co. *B.N.F.*, which is made up of equal parts of mag. trisil., mag. carb., chalk, and sod. bicarb. Mixed powders such as this are found in many proprietary preparations, and in "nulacin" tablets these alkalis are prepared with milk, dextrin, and maltose, to be slowly sucked in the mouth

with the purpose of giving a continuous action comparable to an alkaline milk drip.

Aluminium Preparations

Kaolin is pure aluminium silicate. It is insoluble and has no value as a neutralizer or adsorbent of acid. Aluminium hydroxide, however, does act as an antacid and carries no risks of alkalosis. Its action is slow and moderately efficient, but it is liable to cause constipation. The colloidal aluminium hydroxide gel is amphoteric and may have some action in precipitating mucin over an ulcer surface. It may very conveniently be ordered combined with mag. trisilicate, as in the tab. mag. trisil. co., and in proprietary preparations such as "gelusil."

Aluminium Glycinate

Aluminium hydroxide may be combined with the amino-acid glycine; the resulting product has a valuable buffering action and carries no danger of alkalosis. One useful tablet called "prodexin" is made of mag. carbonate 0.1 g. added to 0.9 g. of aluminium glycinate, and can be sucked freely as required. A recent product, "actal," is a sod. polyhydroxyaluminium monocarbonate hexitol complex, which is also effective in reducing acidity and is a pleasant-tasting tablet which dissolves readily in the mouth.

Bismuth

Bismuth preparations are very expensive. Moreover, the belief that they coat a gastric ulcer mechanically and thus promote healing is probably incorrect, and certainly untrue in the case of duodenal ulcers. In spite of this, patients often seem to find striking relief from bismuth compounds, though even the carbonate has minimal neutralizing effects. No bismuth preparations for digestive purposes are included in the *National Formulary*. One proprietary tablet, "Roter," contains 35% of bism. subnitrate. Many other proprietary preparations contain bismuth carbonate in small amounts. The subnitrate carries a small risk of poisoning, mainly in infants, owing to the possible conversion of the nitrate to nitrite by intestinal organisms and the production of methaemoglobinemia. Bismuth discolours the stools, giving a grey, muddy appearance. As Hamilton (1955) points out, roter tablets combine the psychological advantages of expensiveness, taste, and colour with a notable effect upon the stools. He comments favourably upon their use in general practice.

INTESTINAL EXTRACTS

Since Ivy and his co-workers isolated extracts from the intestine and from urine—enterogastrone and urogastrone—which depressed gastric secretion and motility in dogs, many attempts to apply this form of treatment in man have been made. "Robaden" is a Swiss preparation extracted from the stomach and small intestine of animals. It is free from lipoids and proteins and not identical with enterogastrone. Robaden has been widely used for many years as an out-patient treatment, but, though reports in the Continental literature rate it highly, controlled trials both in Great Britain and abroad have shown no significant difference in results when this preparation is compared with similar but inert tablets and injections, or a placebo (Stolte, 1950; Evans, 1954).

Oral preparations of gastric inhibitory hormones are almost without effect on acidity in man.

Mucin

It is known that natural mucin plays an important part in the control of gastric acidity, but efforts to produce an artificial mucin with equal effect have not proved successful. Methyl cellulose is a useful demulcent and is given with the hope of forming a protective coating over ulcerated surfaces. It may be of value in some forms of colitis, but is of doubtful advantage in nervous dyspepsias or peptic ulcers.

DRUGS ACTING ON NERVOUS SYSTEM

Many drugs are available which act in principle by blocking vagal nerve junctions and thus depressing gastric motility and secretion. Like atropine and belladonna, they may produce troublesome side-effects, and it is unfortunately often the case that the dose needed to affect the stomach appreciably is very close to the toxic level. Of these side-effects the most important are: dry mouth, blurred vision, constipation, headache, drowsiness, and difficulty with micturition.

Atropine

The action of atropine and atropine-like preparations on gastric section is inconstant and unpredictable, and seems to depend much upon the patient's sensitivity, which varies from time to time under different circumstances.

Belladonna is used in many proprietary preparations combined with alkalis or sedatives, but most of these contain only about 0.25 mg. of the total belladonna alkaloids per tablet, and much of their good effect is probably due to the sedative—such as phenobarbitone—which many contain. The *B.N.F.* preparation of tab. bellad. et phenobarb. contains 2/5 gr. (26 mg.) of dried extract of belladonna with 3/4 gr. (50 mg.) of phenobarbitone. In comparison with most similar proprietary preparations it contains rather more sedative, so that if given three times a day the depressant and dulling effect of this may be troublesome. Its cost is approximately one-twelfth that of similar proprietary tablets.

Methanthelinium

Methanthelinium bromide ("banthine") has no constant effect upon gastric acidity, though it strongly depresses gastric tone and peristalsis. The usual dosage is 50 mg. six-hourly up to 100 mg. six-hourly. Controlled studies have not shown any direct action on the healing of ulcers.

Propantheline bromide ("pro-banthine") is about three times as powerful as banthine, but causes relatively fewer side-effects. The dose is 15 mg. three times a day before meals, with 30 mg. at night before retiring. This drug is certainly effective in reducing hypermotility of the stomach, and is best used in association with more conventional chemical antacids. If the dosage is increased sufficiently to reduce acidity, side-effects may be most uncomfortable, and these drugs should be prescribed essentially for their effect on motility, which probably accounts for their often excellent effect in the symptomatic relief of pain. In spite of reports that single doses of 30 to 50 mg. of pro-banthine may cause achlorhydria for several hours (Kirsner *et al.*, 1954), it is doubtful if the effect of these drugs in general on acidity in contrast to motility is of real therapeutic importance. Ihre (1958) indeed reports a blind trial of

two new anticholinergic drugs in which he found no difference either in alleviation of subjective symptoms or in radiographic healing of duodenal and gastric ulcers as between the active drugs and an inert control preparation.

Other Antispasmodic Drugs

Other drugs acting similarly to banthine and pro-banthine are preparations of dicyclomine hydrochloride, which have useful antispasmodic action and are given in a dosage of 10 mg. Such are "wyovin," which is about one-quarter the price of pro-banthine, "merbentyl," and "kolantyl." Tricyclamol ("elorine") is given in a dose of 100 mg. three times a day, with 200 mg. at night with the purpose of reducing nocturnal secretion of acid. Among other recent anticholinergic drugs are hexocyclium ("tral"), a quaternary ammonium salt, and "nacton," a drug with the formula (1-methyl-2-pyrrolidyl) methyl benzilate methyl methosulphate, which is stated to depress acidity for long periods without side-effects. The dose is 2 to 4 mg. three times a day; it has been well spoken of by Douthwaite (1958).

When prescribing anticholinergic drugs, especial care must be taken if they are ordered for patients suffering from coronary artery disease, prostatic obstruction, or pyloric stenosis, while they are contraindicated for patients suffering from glaucoma.

The best use of anticholinergic drugs in the treatment of ulcer is obtained by adjusting the dose individually, and by prescribing antacids and a special diet with them. Though such a combination is successful in the relief of symptoms, several carefully studied series of patients so treated have shown no significantly better results than in cases treated with phenobarbitone or other simple measures (Friedlander, 1954; Doll and Pygott, 1952; Rowlands, 1952).

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Since the proportion of old people in the population will increase in the coming years, the numbers in mental hospitals are likely to do so. Dr. C. P. BLACKER has therefore written a memorandum "to suggest a means of reducing the numbers of persons aged 65 plus who find their way into mental hospitals and stay there." Copies are obtainable (2s. net) from the Secretary, Maudsley Hospital, Denmark Hill, London, S.E.5. The author emphasizes that the people concerned with solving these problems must meet and discuss them, and that someone must be designated as responsible for convening the meetings. In order to help such groups in their discussions, he lists 21 questions on the arrangements needed to care for elderly people.