THE *IN VITRO* EVALUATION OF A SODIUM POLYHYDROXYALUMINIUM MONOCARBONATE HEXITOL COMPLEX AS A GASTRIC ANTACID

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Techniques for assessing antacid activity are discussed. The commonly used antacids have been evaluated using two complementary *in vitro* techniques and appraised using as criteria the properties considered to describe the ideal antacid. In confirmation with previous workers most of the substances tested were shown not to meet the optimum requirements. In particular the results confirmed the loss of activity of aluminium hydroxide gel preparations on drying and their variation in neutralising capacity. A new substance, a sodium polyhydroxyaluminium monocarbonate hexitol complex, which is a white tasteless odourless powder, compared favourably with the best of the established preparations tested—a liquid aluminium hydroxide gel and was the only solid meeting the suggested criteria.

IT has been recognised by many workers in this field that determination of merely the total neutralising value of an antacid is insufficient. Such a method[1] ignores certain important considerations, for example, the speed of action or the possibility of alkalisation with subsequent acid rebound. In our view, test methods should be capable of assessing each of the criteria required in the ideal antacid, and we consider these to be as follows. (i) It should show its maximum neutralising effect in the shortest possible time. (ii) It should neutralise an adequate amount of gastric hydrochloric acid and maintain its action during the normal period of gastric digestion. (iii) Any excess, however great, beyond the amount required to neutralise free gastric acid should not cause alkalisation. (iv) To be of value in ulcer therapy, it should raise the pH of the gastric contents to a level at which pepsin activity is significantly reduced but not totally inhibited. (v) Adequate and repeated doses should be palatable to the hyper-acid patient. Its use should not lead to laxative, constipating or other side effects, such as gastric irritation. Armstrong and Martin have pointed out that certain of these physiological properties can be determined "by theoretical consideration and known effects"[2].

The pH of gastric juice is normally quoted as 1·4–1·6[3,4] and the desirable value to be obtained by the use of an antacid is given variously as 3·5–4·0[5], 4·0–5·0[6], 4·0–5·0 +[7], 4·0–5·5 +[8], 4·0–6·0[4], and 4·0–8·0[9]. However acid rebound may occur if the pH of the gastric contents rises above 7·0[10]. In view of this risk, it seems desirable to raise the pH of the gastric contents only far enough to ensure adequate relief from hyperacidity, particularly if an ulcer site is present. A pH of 3·5–4·5 appears to attain this, and at the same time there is apparently sufficient residual pepsin activity to avoid secondary digestive disturbances[11].

In Vivo *and* In Vitro *Evaluation of Antacids*

Flexner and his various co-authors [12–14] compared results from the continuous recording of gastric pH *in situ* in dogs with those from *in vitro*

techniques and concluded that the latter gave adequately comparable values. Extension of their work to human subjects led them to draw similar conclusions.

This was generally confirmed by Brindle[15], who prepared an artificial gastric juice consisting of 0·05N hydrochloric acid containing 0·15 per cent each of pepsin, peptone and sodium chloride, and which had a pH (average) of 1·5 at 38°. A comparison of this with human gastric secretion by titration with 0·5N sodium hydroxide showed almost identical behaviour.

Clemow and Lowry[16] showed that 0·05N hydrochloric acid gave results strictly comparable with those for artificial gastric juice, and stated that this confirmed the work of Rossett and Flexner[17]. They also pointed out that *in vitro* experiments should be carried out at 37°. The omission of pepsin and other enzymes and buffers was, in their opinion, an advantage since differences in rates of reaction could be more readily detected.

For the *in vitro* evaluation of antacids two basic methods are available.

1. A therapeutic dose of the antacid is suspended in water and the volume of acid required to maintain an arbitrary pH is plotted against time. This curve is a function of the rate of neutralisation and neutralising capacity.

2. Simulated gastric juice is added continuously to an excess of the antacid, and the pH plotted against time. The resultant curve indicates duration of action (a function of the neutralising capacity), risk of acid rebound, probable degree of inhibition of pepsin activity and—to some extent—neutralisation rate. The detailed method, like that of most other workers, is essentially a modification of that of Rossett and Flexner[17], demonstrating the buffering ability of the antacid.

For a full *in vitro* evaluation of the efficiency of an antacid, both methods should be used, since the first indicates the rate at which neutralisation is achieved, and the second the duration of action at the desired pH.

Both approaches accordingly have been studied in the present work.

EXPERIMENTAL

1. *Acid Neutralised against Time (pH Constant)*

The antacid, if a tablet or powder, is reduced to a slurry with a little water in a mortar, and is transferred quantitatively to a 250 ml. jacketted glass reaction vessel. Liquid preparations (suspensions) are placed directly in the reaction vessel. Water at 37° is circulated through the jacket to bring the contents to normal body temperature. When temperature equilibrium has been attained, 0·1N hydrochloric acid is added to maintain the pH at the predetermined arbitrary level and the volume is plotted against time. The most important portion of the resultant curve is that covering the first 5–10 minutes.

2. *pH Against Time (Rate of Acid Addition Constant)*

The foregoing basic technique is used. 12·5 ml. of 0·2N hydrochloric acid are diluted with water to 75 ml. in the reaction vessel and the temperature brought to 37°. The antacid is added as a slurry in water, also

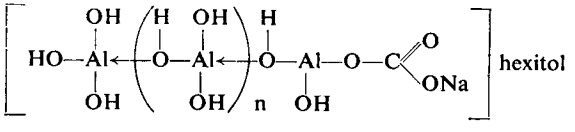
at 37°, followed after exactly one minute by the continuous addition of further 0·2N acid at the rate of 1·0 ml. per minute. This latter acid may be at room temperature without significantly affecting the temperature of the contents of the reaction vessel.

The variation between the rates of acid secretion in individuals is so great that an arbitrary rate of acid addition has to be adopted. Rossett and Flexner[17] suggested a secretion rate of 120 ml. of 0·1N hydrochloric acid per hour which is consistent with figures for the nocturnal secretion of patients with duodenal ulcer[18,19]. It is also similar to the rate generally employed by others[5].

To ensure a constant rate of addition of acid Schleif[20] used a large number of small increments delivered from an automatic pipette (cf. Armstrong and Martin[2]). We have preferred a burette so modified that air is fed to the head space at constant hydrostatic pressure. The pH of the mixture is recorded continuously. The end point occurs when sufficient acid has been added to cause the pH to fall below 3, that is, when the neutralising capacity of the antacid under these conditions is exhausted.

The methods described above were used to study the following, sodium bicarbonate, magnesium carbonate, magnesium trisilicate, Mixture of Magnesium Trisilicate, B.P.C., bismuth subnitrate plus antacids (magnesium carbonate and sodium bicarbonate), milk solids plus antacids, aluminium glycinate, aluminium phosphate, aluminium hydroxide gel, dried aluminium hydroxide gel, and a new compound, sodium polyhydroxyaluminium monocarbonate hexitol complex.

This last compound is a white tasteless and odourless powder, decomposing without melting when heated strongly. It is insoluble in water but readily and completely soluble in dilute acids. At normal temperatures it may be stored indefinitely with no apparent change in its physical or chemical properties, including reactivity with acids. It probably has the structure:



where n = O or an integer, controlled by the preparative conditions.

Results

The results of these various studies are shown in the accompanying Tables and enable the division of these various antacids into the following categories.

(*a*) *Preparations which may produce acid rebound.* Reference to Table I shows that most of the older, rapidly acting antacids, for example, sodium bicarbonate, and magnesium carbonate, cause large variation in pH with dose. By increasing the dose it is possible to raise the pH above 7·0, producing alkaline conditions and the probability of acid rebound[10].

(*b*) *Preparations which may unduly inhibit pepsin activity* (Table I). It is generally accepted[17] that pepsin is inactivated at pH values greater than 5·0. Such widely used products as Mixture of Magnesium Trisilicate, B.P.C., and preparations of bismuth subnitrate with magnesium carbonate and sodium bicarbonate fall into this group.

TABLE I

EFFECT ON pH OF VARYING THE QUANTITY OF ANTACID WITH CONSTANT ACID ADDITION RATE
(see also Table III)

Material and weight used (as total active ingredients)	pH at (minutes)					
	1	5	10	30	50	70
Magnesium trisilicate .. .. 0·5 g.	1·75	2·57	2·67	2·31	1·95	—
" " .. .. 1·0 g.	2·10	4·50	5·07	4·48	3·90	3·22
" " .. .. 2·0 g.	3·25	5·43	5·57	5·31	5·07	4·81
" " .. .. 3·0 g.	4·80	6·52	6·35	5·95	5·73	5·48
Sodium polyhydroxyaluminium monocarbonate hexitol complex. 0·5 g.	4·05	3·90	3·88	3·80	3·72	3·68
" " " " " " 1·0 g.	4·07	3·95	3·94	3·88	3·83	3·78
" " " " " " 2·0 g.	4·13	4·02	4·01	3·98	3·97	3·94
Mixture of Magnesium Trisilicate, B.P.C. .. .. 0·5 g.	4·02	6·15	6·12	2·97	—	—
" " " " .. .. 1·0 g.	4·75	6·92	7·08	6·24	5·22	4·04
" " " " .. .. 2·0 g.	6·61	7·32	7·29	7·13	6·97	6·81
Bismuth subnitrate with antacids .. .. .. 0·5 g.	5·97	7·22	7·19	6·70	6·18	5·66
" " " " .. .. .. 1·0 g.	7·18	7·40	7·41	7·28	7·16	7·02
" " " " .. .. .. 2·0 g.	7·67	8·04	8·01	7·89	7·78	7·63
Magnesium carbonate .. .. 0·5 g.	5·50	7·16	7·17	6·54	5·91	5·25
" " .. .. 1·0 g.	7·10	7·41	7·33	6·92	6·48	5·95
Sodium bicarbonate .. .. 0·5 g.	5·33	6·28	6·22	3·95	—	—
" " .. .. 1·0 g.	5·58	6·61	6·57	6·12	5·68	—
" " .. .. 2·0 g.	7·07	7·32	7·28	7·13	7·05	—
Calcium carbonate .. .. 1·0 g.	4·88	6·31	6·23	5·97	5·70	—
" " .. .. 2·0 g.	5·30	6·42	6·52	6·43	6·41	—
Aluminium glycinate .. .. 1·0 g.	2·90	4·24	4·16	4·00	3·81	3·62
" " .. .. 2·0 g.	3·94	4·48	4·34	4·20	4·12	4·03
" " .. .. 3·0 g.	4·04	5·64	5·66	4·57	4·37	4·18
Aluminium phosphate .. .. 1·0 g.	1·85	2·49	2·48	2·34	2·20	—
" " .. .. 2·0 g.	2·44	2·69	2·66	2·49	2·32	—
" " .. .. 3·0 g.	2·62	2·89	2·84	2·67	2·49	—
Milk solids with antacids .. .. 1·0 g.	5·25	6·56	5·96	4·45	3·16	—
" " .. .. 2·0 g.	7·10	8·02	8·28	7·73	6·70	5·65
" " .. .. 3·0 g.	7·44	8·13	8·38	7·97	7·37	6·75
Milk solids (alone) .. .. 1·0 g.	2·39	2·13	1·86	1·31	—	—
" " .. .. 2·0 g.	2·74	2·50	2·22	1·66	—	—

pH at zero time : 1·50

TABLE II

COMPARATIVE RATES OF ACID NEUTRALISATION TO pH 3·5 FOR VARIOUS ANTACID PREPARATIONS

Material	Ml. 0·1N hydrochloric acid neutralised at (minutes)					
Basis of comparison: 0·5 g. active ingredient	1	2	5	10	15	20
Aluminium hydroxide gel (best available grade)	12	18	41	100	131	155
Magnesium carbonate	29	60	102	105	106	107
Milk solids with antacids	21	45	90	102	107	112
Sodium polyhydroxyaluminium monocarbonate hexitol complex ..	12	22	46	75	96	113
Bismuth subnitrate with antacids	16	31	69	81	84	88
Calcium carbonate	19	37	65	77	80	83
Mixture of Magnesium Trisilicate, B.P.C.	16	29	61	76	79	81
Sodium bicarbonate	57	58	59	59	60	60
Aluminium glycinate	4	8	21	36	47	55
Aluminium hydroxide tablets (best available grade)	3	5	14	30	48	67
Magnesium trisilicate	3	6	15	26	34	41
Milk solids	12	14	14	14	14	14
Aluminium phosphate gel	1	1	2	2	3	3

(*c*) *Preparations which do not raise the pH adequately* (Tables I and III). Aluminium phosphate, and milk solids alone or combinations of the last

with antacids fall into this group; it is appreciated that this method does not necessarily evaluate fully milk solid preparations. Most samples of magnesium trisilicate are also classed here; this compound not only gives a widely ranging pH according to dosage (Table I) but also differs in effect and effectiveness from one source to another[21,22], this accounting for the variable results reported in the literature.

TABLE III

VARYING EFFECT ON pH FOR ALUMINIUM HYDROXIDE PREPARATIONS FROM VARIOUS SOURCES

(Sodium polyhydroxyaluminium monocarbonate hexitol complex included as a reference substance)

Material Basis: Al content equivalent to 0·5 g. $Al(OH)_3$ (0·327 g. Al_2O_3)	Source of Sample	pH at (minutes)					
		1	5	10	60	80	90
Sodium polyhydroxyaluminium monocarbonate hexitol complex.	–	4·10	4·17	4·10	4·07	4·03	3·97
Aluminium hydroxide gel*	A	2·75	4·02	4·02	3·75	3·50	2·80
" " " *	B	3·50	4·12	4·04	3·84	3·56	3·14
Dried aluminium hydroxide gel*	C	2·20	3·25	4·07	3·90	3·69	3·17
" " " " *	D	2·02	2·87	3·94	3·72	3·28	2·60
" " " " *	E	2·83	4·05	4·02	3·77	3·09	2·50
" " " " *	F	2·32	3·35	3·68	3·18	2·56	—
" " "	G	1·78	1·96	1·96	1·70	—	—
Aluminium Hydroxide, B.P.C. 1934	H	1·74	1·84	1·86	1·70	—	—
Aluminium hydroxide tablets*	A	2·03	3·54	3·62	3·43	3·28	2·74

* Described as complying with the B.P.C. (1954)
pH at zero time : 1·50

(*d*) *Preparations which are slow in action.* Certain of the preparations studied, aluminium glycinate, aluminium phosphate, and some samples of magnesium trisilicate, although raising the pH to the ideal range with adequate dosage, nevertheless have a delayed onset of action. This is particularly true for preparations of dried aluminium hydroxide gel. The marked loss of activity on drying aluminium hydroxide gels has previously been noticed (e.g.,[19]), and Tables III and IV illustrate the remarkably wide variations in reactivity of aluminium hydroxide preparations commercially available in this country.

TABLE IV

VARIATION IN SPEED OF ACID NEUTRALISATION TO pH 3·5 FOR ALUMINIUM HYDROXIDE PREPARATIONS FROM VARIOUS SOURCES

(Sodium polyhydroxyaluminium monocarbonate hexitol complex included as a reference substance)

Material Basis: Al content equivalent to 0·5 g. $Al(OH)_3$ (0·327 g. Al_2O_3)	Source of sample	Ml. 0·1N hydrochloric acid neutralised at (minutes)					
		1	2	5	10	15	20
Sodium polyhydroxyaluminium monocarbonate hexitol complex.	—	22	35	63	98	125	144
Aluminium hydroxide gel*	A	12	20	40	100	131	155
" " " *	B	14	22	42	65	83	100
Dried aluminium hydroxide gel*	C	10	16	28	47	66	85
" " " *	D	9	14	22	40	55	69
" " " *	E	9	14	25	39	50	55
" " " *	F	8	15	24	32	40	47
" " "	G	<1	<1	<1	<1	1	1½
Alumium Hydroxide, B.P.C. 1934	H	<1	<1	<1	<1	<1	<1
Aluminium hydroxide tablets*	A	3	5	14	30	48	67

* Described as complying with the B.P.C. (1954)

(*e*) *Preparations meeting the criteria of the ideal antacid.* Of the range of solid preparations tested, the only product fulfilling all requirements was sodium polyhydroxyaluminium monocarbonate hexitol complex. Of liquid preparations, only certain better grades of aluminium hydroxide gel gave a comparable performance.

Discussion

Using techniques similar to other workers our results in general agree with previous evaluations. In addition to established preparations, a new substance, a sodium polyhydroxyaluminium monocarbonate hexitol complex, has been tested. From the results it compares well with the best preparation examined—a liquid aluminium hydroxide gel—in rate and amount of acid neutralised and in maintenance of the pH at the optimum range of 3·5–4·5. In particular, its superiority over dried aluminium hydroxide gels is apparent. The loss of activity that may accompany drying and tabletting of these gels is well-known, and the results show the new compound to be at least twice as rapid in action as the best dried gel tested and to have superior powers of neutralisation and pH maintenance, which suggests that it might prove a clinically efficacious substance in the convenient form of tablets.

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