SOME *IN VITRO* TESTS ON SODIUM GLUCONATODIHYDROXO-ALUMINATE III: A SOLUBLE BUFFER ANTACID

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The properties of a new buffer antacid, the active substance of which is a 40 per cent w/v aqueous solution of a complex considered to be sodium gluconatodihydroxoaluminate III, have been compared with those of some existing antacid preparations. The unit dose (4 ml.) of this preparation has high acid neutralising capacity, speed of action and buffering power.

Various compositions have been used as liquid buffer antacids, for example, aluminium hydroxide gel preparations, aluminium phosphate gel and magnesium trisilicate gel, alone or as mixtures. Such preparations are suspensions of insoluble substances generally of unattractive flavour and texture. Aluminium hydroxide gel is frequently astringent to the oral mucosa and has a flocculent texture.

A soluble buffer antacid of acceptable flavour would represent an advance on the existing preparations. The minimum requirements include palatability, and solubility associated with a good acid consuming capacity to permit an effective dose in a reasonable bulk desirably buffering in the physiological pH range of 5 to 3. Hitherto, no compound has been available which met these requirements, but a new preparation based on a complex derived from sodium aluminate, aluminium hydroxide and glucono delta lactone, appears to do so. The complex has a composition corresponding to sodium gluconatodihydroxoaluminate III. The formula is considered to be

$$Na[Al(OH)_2(C_6H_{10}O_7)]$$

Molecular weight = 278·16

Content of Al 9·70 per cent (dry basis)

Content of Na 8·27 per cent (dry basis).

Properties

The complex is an odourless, off-white, non-crystalline solid of bland flavour. Its solubility in water at 25° is over 80 per cent w/v. It is insoluble in dehydrated ethanol, ether and chloroform. A 30 per cent w/v solution has a pH of 8·5. Acid neutralising capacity: when 1 g. is digested with 10 ml. N hydrochloric acid on a water bath for 1 hr., the pH is raised to 3.

Antacid Properties

The desirable characteristics of an antacid may be defined as: (1) high acid neutralising capacity; (2) rapid action; (3) not alkaline, even in conditions of overdosage; (4) without significant systemic effects; (5) not flocculent or astringent to the oral mucosa; (6) neither constipating nor

excessively laxative; (7) pepsin inhibiting, but not inactivated by pepsin or peptones; (8) palatability.

To investigate points 1, 2 and 3, four tests were selected and the new complex was compared with five liquid suspension antacids and two antacid tablets of the quick-acting buffer type. Table I lists the preparations and the active ingredients tested. With one exception the comparisons were made with a unit dose of the preparation (4 ml. or one tablet). This was regarded as appropriate since, if the unit dose has a low content of active substance, there are other limiting factors such as viscosity, the thixotropic character or the stability of a liquid suspension, or the size of a tablet.

TABLE I

COMPOSITION OF PREPARATIONS TESTED

Preparation	Content of active agent
40 per cent w/v aqueous solution of sodium gluconato-dihydroxoaluminate III	4 ml. contains 1·6 g. of the complex
Mixture of magnesium carbonate B.P.C.	½ fluid oz. contains: light magnesium carbonate 0·343 g. sodium bicarbonate 0·515 g.
Aluminium hydroxide gel B.P.	4 ml. contains: aluminium hydroxide 0·224 g.
Aluminium hydroxide/magnesium trisilicate gel	4 ml. contains: aluminium hydroxide 0·25 g. magnesium trisilicate 0·50 g.
Magnesium hydroxide gel	4 ml. contains: magnesium hydroxide 0·357 g.
Aluminium phosphate gel	4 ml. contains: aluminium phosphate 0·327 g.
Aluminium hydroxide-magnesium carbonate co-dried gel (Tablet)	Each tablet contains: co-dried gel 0·375 g.
Sodium polyhydroxy-aluminium monocarbonate hexitol complex (Tablet)	Each tablet contains: complex 0·360 g.

An exception to the unit dose basis was made for the B.P.C. mixture of magnesium carbonate, where half the minimum B.P.C. dose of ½ fluid oz. was taken as this was a more appropriate quantity for the tests.

The tabletted products were powdered and prepared as a slurry.

To investigate the inhibition of antacid activity by pepsin and peptone, the test complex was compared with the aluminium hydroxide gel B.P., the sodium polyhydroxyaluminium monocarbonate hexitol complex tablets and the aluminium hydroxide-magnesium carbonate co-dried gel tablets.

EXPERIMENTAL

Antacid Activity Test

This is the test of Gore, Martin and Taylor (1953) modified to use the unit dose, or other quantity, as defined. The dose of antacid is introduced into a 200 ml. pool containing 3 m-equiv. of hydrochloric acid giving the solution a normality of 0·015N. The pool of acid is contained in a beaker

holding a saturated calomel and wide range glass electrode assembly and stirrer connected to a direct reading Cambridge pH meter and recorder. The pH is recorded for 30 min. and further hydrochloric acid is then injected by a motor and worm driven syringe at the rate of 6 m-equiv./hr. to an end-point of pH 3, the rate of change of pH with time being automatically recorded throughout. The test gives information about the speed of neutralisation, the pH reaction to overdosing, acid neutralising capacity and buffering capacity.

Acid-consuming Capacity Test

This is a modification of the U.S.P. test (1960). It measures the amount of 0·1N hydrochloric acid neutralised or absorbed by the antacid when it is digested with excess of acid at 37° for 1 hr. The excess is titrated with sodium hydroxide to pH 3.

Speed of Neutralisation Test

In this test the unit dose of antacid is introduced into 200 ml. pools at 37° containing 0·1N hydrochloric acid in progressively larger amounts, and the time necessary for pH 3 to be attained in each of the pools is recorded. When the acidity of the pool exceeds the capacity of a unit dose of antacid, the pH never attains 3; then, using a pool not more than 5 ml. 0·1N hydrochloric acid in excess of that last giving pH 3, the value of the pH after 40 min. is determined and recorded as the final observation.

Speed and Buffering Capacity Test

The amount of N hydrochloric acid necessary to give a "weak" and a "strong" 200 ml. pool at 37°, of a strength such that when a unit dose of antacid was introduced the pH reached after 5 min. was at least 3·0 and after 30 min. was not greater than 5·0, was ascertained.

Inhibition of Antacid Activity by Pepsin and Peptone

The B.P. neutralising test was employed in the first instance as specified in the B.P. (1958) and then repeated substituting the artificial gastric juice described by Brindle (1953) for the hydrochloric acid. With aluminium hydroxide gel B.P. the amount specified in the B.P. test was used (5 g. ≡ 4·8 ml.), while the unit dose of 4 ml. of test complex and two tablets of sodium polyhydroxyaluminium monocarbonate hexitol complex and aluminium hydroxide-magnesium carbonate co-dried gel were taken.

RESULTS

Antacid Activity Test

The results obtained in the antacid activity test are as shown graphically in Fig. 1.

With the complex the pH rose almost instantly to a value of 4, and reached its maximum value of pH about 5 after 10 min. and remained

at about 5 for the next 20 min. during which no acid was injected. This indicated that the pH reaction to over-dosing *in vivo* might be expected not to rise above pH 5. When further acid was injected, the pH did not fall below 3 until approximately a total of 15 m-equiv. of hydrochloric acid had been injected.

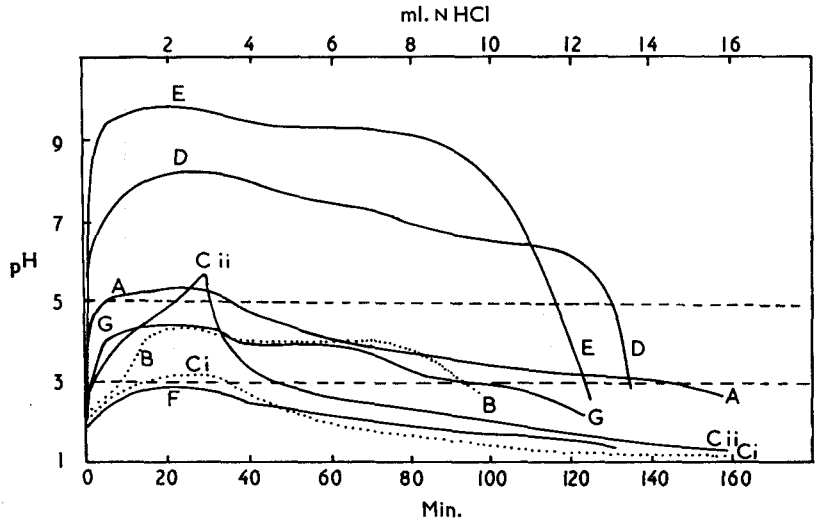

FIG. 1. Antacid activity test (Method of Gore, Martin and Taylor, 1953).

A, 40 per cent w/v aqueous solution of sodium gluconatodihydroxoaluminate III, 4 ml. B, Aluminium hydroxide gel B.P., 4 ml. C, Aluminium hydroxide/magnesium trisilicate gel, 4 ml. (i) Sample 1. (ii) Sample 2. D, Mixture of magnesium carbonate B.P.C., ¼ fl. oz. E, Magnesium hydroxide gel, 4 ml. F, Aluminium phosphate gel, 4 ml. G, Aluminium hydroxide/magnesium carbonate co-dried gel, 1 tablet.

The other antacids tested were less rapid in their action and gave curves resembling those previously published for similar types of tests, for example, Beekman (1960). It is also noteworthy that some of the preparations (magnesium hydroxide gel and mixture of magnesium carbonate B.P.C.) took the pH into the acid rebound range and would not show up any better in this test if a different quantity of active substance were taken. Other preparations (aluminium hydroxide/magnesium trisilicate gel and aluminium phosphate gel) could not be expected to give a significantly improved performance unless a multi-dose quantity was taken. With the aluminium hydroxide/magnesium trisilicate gel a second sample of the preparation from the same source was found to be markedly more reactive, although the acid consuming capacities were the same for the two samples.

The aluminium hydroxide/magnesium carbonate co-dried gel tablets had a good neutralising capacity within the pH range 3–5 and had a superior speed of action to the aluminium hydroxide gel.

Acid Consuming Capacity Test

The results obtained from the acid consuming capacity test are shown in Table II. The unit dose of the test substance can be seen to have neutralised more acid than unit doses of the other preparations examined.

TABLE II

ACID CONSUMING CAPACITY TEST (U.S.P. MODIFIED)

Product	Quantity	ml. 0·1N HCl neutralised
Sodium gluconatodihydroxoaluminate III in 40 per cent w/v aqueous solution	4 ml.	160 ml.
Magnesium hydroxide gel	4 ml.	125 ml.
Aluminium hydroxide gel B.P.	4 ml.	115 ml.
Aluminium hydroxide-magnesium carbonate co-dried gel	1 tablet	103 ml.
Sodium polyhydroxyaluminium monocarbonate hexitol complex	1 tablet	88 ml.
Aluminium hydroxide/magnesium trisilicate gel	4 ml.	79 ml.
Aluminium phosphate gel	4 ml.	18 ml.

Speed of Neutralisation Test

The results obtained from the speed of neutralisation test are depicted in Fig. 2.

With most antacids the speed of neutralising acid in this test varies markedly with the acidity of the pool to be neutralised. This is not true of the test complex and also of magnesium hydroxide gel which responded almost instantaneously, irrespective of the acidity of the pool up to about 12 m-equiv. of hydrochloric acid, which is about 75 per cent of the total neutralising capacity of the dose of the complex and over 90 per cent of the dose of the gel.

Speed and Buffering Capacity Test

The results of the speed and buffering capacity test are given in Table III.

TABLE III

SPEED AND BUFFERING CAPACITY

Product	Quantity	ml. 1·0N HCl buffered in the pH range 3–5 between 5 and 30 min.	
		Minimum	Maximum
Sodium gluconatodihydroxoaluminate III in 40 per cent w/v aqueous solution	4 ml.	3·5	12·0
Aluminium hydroxide gel B.P.	4 ml.	0·4	8·7
Sodium polyhydroxyaluminium monocarbonate hexitol complex	1 tablet	0·7	7·0
Aluminium hydroxide-magnesium carbonate co-dried gel	1 tablet	1·1	8·1
Magnesium hydroxide gel	4 ml.	11·6	11·7
Mixture of magnesium carbonate B.P.C.	½ fluid oz.	6·8	7·3
Aluminium hydroxide/magnesium trisilicate gel	4 ml.	4·7	5·0
Aluminium phosphate gel	4 ml.	0·1	0·7

For rapid buffering, the test complex covers a wider range of acidities (8·5 ml. 1·0N HCl) than the other antacids. Aluminium hydroxide gel B.P., sodium polyhydroxyaluminium monocarbonate hexitol complex and

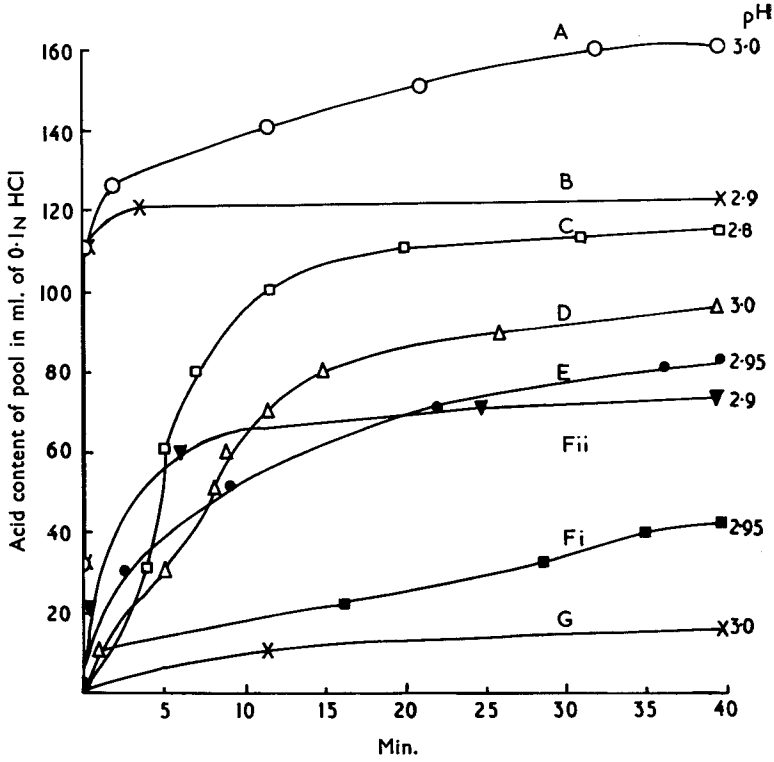

FIG. 2. Speed of neutralisation test. Each experimental observation was obtained by adding a dose of antacid to a 200 ml. acid pool at 37°. The points mark the acidity of the pools and the times to reach pH 3, except for the 40 min. points where the pH attained is shown.

A	40 per cent w/v aqueous solution of sodium gluconato-dihydroxoaluminate III	4 ml.
B	Magnesium hydroxide gel	4 ml.
C	Aluminium hydroxide gel B.P.	4 ml.
D	Aluminium hydroxide/magnesium carbonate co-dried gel	one tablet
E	Sodium polyhydroxyaluminium monocarbonate hexitol complex	one tablet
F	Aluminium hydroxide/magnesium trisilicate gel .. .. (i) Sample 1 (ii) Sample 2	4 ml.
G	Aluminium phosphate gel	4 ml.

the aluminium hydroxide-magnesium carbonate co-dried gel nearly equal this buffering range, for while their maximum capacities are lower, they are able to deal with smaller amounts of acid without exceeding pH 5·0. No disadvantage is considered to be associated with the test complex minimum of 3·5 ml. of N hydrochloric acid, however, as this ratio of antacid to acid corresponds to a considerable degree of over-dosing *in vivo*.

The remaining antacids examined are shown in this test to have limited buffering capacities.

Inhibition of Antacid Activity by Pepsin and Peptone

The results of the tests for the inhibition of antacid activity by pepsin and peptone for the three preparations tested are given in Table IV and graphically for two of the antacids in Fig. 3.

TABLE IV

INHIBITION OF ANTACID ACTIVITY BY PEPSIN AND PEPTONE

B.P. Neutralising Capacity Test (*a*) with HCl, and (*b*) with artificial gastric juice (Brindle, 1953)

	Initial pH	pH after 10 min.	pH after 15 min.	pH after 20 min.	Back titration 0·1N NaOH
B.P. Standard—not less than	—	1·8	2·3	3·0	Not more than 50 ml.
Sodium gluconatodihydroxoaluminate III in 40 per cent w/v aqueous solution (4 ml.)—					
0·05N HCl	1·35	3·5	3·55	3·6	23 ml.
Gastric juice	1·45	3·4	3·45	3·5	28 ml.
Aluminium hydroxide gel B.P. (5 g. = 4·8 ml.)—					
0·05N HCl	1·35	3·65	3·70	3·73	38·6 ml.
Gastric juice	1·45	2·44	2·78	2·98	44·8 ml.
Sodium polyhydroxyaluminium monocarbonate hexitol complex (2 tablets)—					
0·05N HCl	1·35	3·85	3·9	3·95	not
Gastric juice	1·45	2·6	2·78	2·9	applicable
Aluminium hydroxide-magnesium carbonate co-dried gel (2 tablets)—					
0·05N HCl	1·35	4·0	4·05	4·05	not
Gastric juice	1·45	3·4	3·55	3·65	applicable

The inhibiting effect on the activity of the sodium gluconatodihydroxoaluminate III complex is insignificant, while it is appreciable for the aluminium hydroxide-magnesium carbonate co-dried gel and considerable for the aluminium hydroxide gel B.P. and for the sodium polyhydroxyaluminium monocarbonate hexitol complex. As the extent of loss of activity is similar in both instances only one is compared with the test complex in Fig. 3.

DISCUSSION

The tests described suggest that sodium gluconatodihydroxoaluminate III would be an effective soluble buffer antacid compound. The preparation compares favourably with similar doses of other antacids for acid consuming capacity, speed of neutralisation and buffering power. The tests also suggest that acid rebound would be unlikely *in vivo*.

Unlike aluminium hydroxide gel B.P. and some other preparations containing it, the antacid activity of sodium gluconatodihydroxoaluminate III is not significantly depressed by pepsin and peptone. Newey (1962) has drawn attention to the fact that the effect of peptone on antacid activity is more significant than that of pepsin. Peptones are among the intermediate soluble breakdown products of proteins, the disruption being accelerated by enzyme action. Pepsin and peptones may therefore be expected to be present in the stomach after meals and it is relevant to consider their interaction with antacids. It is obviously desirable to

avoid inactivating the antacid: in addition, reduction of the proteolytic activity of pepsin to safeguard against the auto-digestion of impaired mucosal tissue, without complete inhibition which would stop normal digestion, is desirable. The proteolytic action of pepsin diminishes with increasing pH, losing about 80 per cent of its power at pH 4 (Douthwaite, 1958).

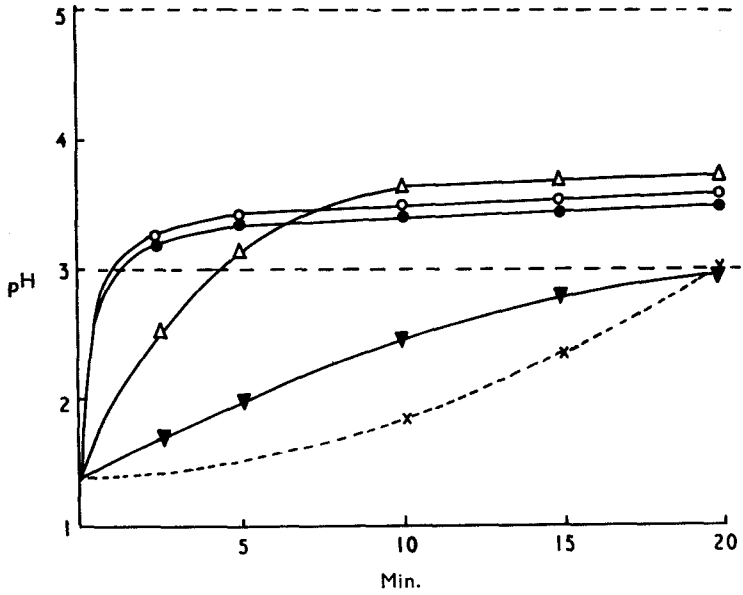

FIG. 3. Inhibition of antacid activity by pepsin and peptone. The B.P. neutralising capacity test for aluminium hydroxide gel was carried out and then repeated using artificial gastric juice containing 0·15 per cent each NaCl, pepsin and peptone in 0·05N HCl.

○—○ 4 ml. sodium gluconatodihydroxoaluminate III (40 per cent w/v aqueous solution) in HCl.
●—● 4 ml. sodium gluconatodihydroxoaluminate III in artificial gastric juice.
△—△ 5 g. (4·8 ml.) of aluminium hydroxide gel B.P. in HCl.
▼—▼ 5 g. (4·8 ml.) of aluminium hydroxide gel B.P. in artificial gastric juice.
X--X B.P. test minimum pH values.

Sodium gluconatodihydroxoaluminate III, therefore, would be expected to permit a reduced amount of peptic digestion to proceed except under conditions of over-dosage. It is often stated (for example, Almy and Steinberg, 1958–59) that aluminium hydroxide possesses a specific pepsin inhibiting action independent of pH. This aspect has not been investigated in the present study but such an effect, and also the reduction of the antacid action of aluminium hydroxide by peptone would be consistent with a precipitating action of aluminium hydroxide on proteins.

We have found that sodium gluconatodihydroxoaluminate III does not precipitate proteins, for example, when it is added to a solution of casein.

There is probably a connection between this latter fact and the finding that the complex is not astringent to the oral mucosa.

Histological and biochemical studies, and chronic toxicity tests on dogs have so far shown (Mr. D. M. Brown, personal communication) the complex to be non-toxic.

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