SCIENCE PAPERS AND DISCUSSIONS

AN *IN VITRO* EVALUATION OF COMMONLY USED ANTACIDS WITH SPECIAL REFERENCE TO ALUMINIUM HYDROXIDE GEL AND DRIED ALUMINIUM HYDROXIDE GEL

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Received July 13, 1953

BECAUSE of the difficulties of comparing antacids by clinical methods the use of *in vitro* methods has been investigated by several workers for assessing the relative efficiencies of antacids.

It has been demonstrated by Rossett and Flexner[1] that the effect of an antacid could be measured by an *in vitro* test and correlated with the effect of the same antacid in the human stomach. They were able to show exact duplication of *p*H changes in man and *in vitro* when a given dose of the antacid was administered. Other workers[2,3] have based their methods of evaluating antacids *in vitro* using modifications of the method of Rossett and Flexner, which measured the *p*H changes which occurred with time when the antacid was added to 100 ml. of hydrochloric acid solution of *p*H 1·4 to which 0·1N hydrochloric acid is added at the rate of 120 ml. per hour. The results obtained show that the method is capable of demonstrating both the extent of the *p*H change and the time during which neutralisation or buffering is effective. Johnson and Duncan[2], Holbert *et al.*[3], Murphy[4], and other workers have expressed the view that the method is of greater value in assessing the efficacy of an antacid than is the acid neutralising test of the B.P.C. and U.S.P. With these workers we agree.

To assess the merits of any method for evaluating materials described as antacids it is necessary to consider the purpose and requirements of antacid therapy.

An ideal antacid should:—(*a*) not be absorbed from the alimentary system, (*b*) be without undesirable laxative or constipating effect, (*c*) be of high neutralising capacity and at the same time rapid in showing initial effect, (*d*) maintain its effect over a prolonged period, (*e*) be non-eructating, (*f*) not cause "acid-rebound."

Acid rebound is caused by the compensatory secretion of parietal hydrochloric acid which occurs when the *p*H of the gastric contents becomes even slightly alkaline[5] and the acid so produced may exceed the original hyperacidity present. Apart from acid-rebound if the gastric contents become alkaline there is a possibility that the mucous membrane of the stomach may be subjected to the strong digestive action of the enzymes, trypsin and erepsin which may enter the stomach by regurgitation from the duodenum[1]. The degree to which gastric acidity should be reduced is an important question on which no general agreement has been reached. It is accepted that except in the presence of pepsin, ulceration of the stomach is not produced by any physiological concentration of acid.

It is known that pepsin is inactive at *p*H values above 3·0. Johnson and Duncan[2] summarised authoritative opinions and concluded that an ideal antacid should buffer at a *p*H within the range of 3·5 to 4 even when the antacid is taken in excess dosage. The *in vitro* method by measuring the *p*H changes which occur under conditions simulating those occuring in the stomach, determines the neutralising or buffering capacity of an antacid in relation to its rate of action and duration of effectiveness and is therefore capable of predicting antacid efficiency within the concept of an ideal antacid. The properties of an antacid in relation to absorption from the alimentary tract, eructation, and effect on the bowel can be determined by theoretical consideration and known effects.

The *in vitro* method we have used in this investigation is essentially a modification of that used by Johnson and Duncan[2] which was described in a paper read before this Conference in 1945. A sample of the antacid in the appropriate dose is added to 150 ml. of artificial gastric juice consisting of hydrochloric acid (0·05N approx.) adjusted to *p*H 1·5 with water and with the addition of 2·0 g. of pepsin per l. This solution corresponds to what would be a hyperchlorhydric level (*p*H 1·0 to 1·5) in the human stomach. The mixture is maintained at 37° C. and continuously stirred. The *p*H is recorded electrometrically, using a glass electrode, after 30 seconds and then at 2, 4, 6, 8 and 10 minutes. 20 ml. of the mixture, representing the physiological loss from the stomach, is then withdrawn and 20 ml. of artificial gastric juice, is added. This procedure is repeated at the end of each 10-minute period. The test is continued until the *p*H readings indicate that the antacid has been neutralised or is no longer effective. The various modifications of this type of test which have been described are, in the main, concerned with the choice of the testing solution and the rate of addition and withdrawal, and there exists a need for a standardised procedure. The addition of pepsin to the artificial gastric juice is important and we have confirmed the observation of Murphy[4] that the antacid effect of the aluminium hydroxide preparations is inhibited to some extent by pepsin.

The method may be used in conjunction with clinical tests to eliminate material and formulations of low antacid activity. It does not give any indication of clinical response to factors other than the antacid effect. For example, it does not indicate protective effect due to coating of the gastric mucosa.

The antacids considered in this investigation have been confined to the non-systemic and non-eructating antacids. The dosage used in each case was the quantity which would maintain a buffering effect for approximately 1 hour under the condition of the test. In the case of the official substances it was found that this dosage was within the limits of the official dosage with the exception of dried aluminium hydroxide gel, the amount of which had to be increased from 0·6 g. to 1·5 g., to obtain the desired effect. The antacids and dosages considered in this investigation are listed in Table I.

Typical results obtained are represented graphically in Figures 1 and 2 and are tabulated in Table II. The curves show maxima and minima for

*p*H with each 10-minute period. For comparison purposes the maxima have been used in compiling the curves shown in Figures 3 to 7.

Examination of the curves in Figures 3 and 4 show that aluminium hydroxide gel B.P.C. (8 ml. dose), dried aluminium hydroxide gel B.P.C. (1·5 g. dose), dihydroxy aluminium aminoacetate (1·5 g. dose) and calcium phosphate B.P. (1·5 g. dose) buffer within the desired clinical range 3·5 to 4 for approximately 60 minutes. Of the other antacids considered aluminium phosphate gel (8 ml. dose), dried aluminium hydroxide gel

TABLE I

THE ANTACIDS AND DOSES CONSIDERED IN THE INVESTIGATIONS

Substance	Dose
Magnesium oxide, light B.P.	0·25 g. and 0·5 g.
Magnesium trisilicate B.P	1·5 g.
Calcium phosphate B.P.	1·5 g.
Aluminium hydroxide gel B.P.C.	120 minims
Dried aluminium hydroxide gel B.P.C.	0·6 g. and 1·5 g.
Dihydroxy aluminium aminoacetate	1·5 g.
Aluminium phosphate gel	120 minims
Bismuth carbonate	1·8 g. and 30 g.
Ion exchange resin A	15 .g
Ion exchange resin B	8 g.
Ion exchange resin C	1 g.

• Ion exchange resin A consists of the mixed potassium and ammonium form of cross-linked polyacrylic (cation) exchange resin.

Ion exchange resin B consists of:—

Alkylene polyamine resin	12 per cent.
Potassium salt of carboxylic resin	29 „ „
Carboxylic resin	59 „ „

Ion exchange resin C consists of:—

Polyamine-methylene resin.

TABLE II

*p*H READINGS WITH LIGHT MAGNESIUM OXIDE AND MAGNESIUM TRISILICATE

Readings obtained by adding 20 ml. of artificial gastric juice and withdrawing 20 ml. of the mixture at 10-minute intervals (*see* Fig. 1)

Period	Magnesium oxide, light B.P. 0·5 g.								
	0–10	10–20	20–30	30–40	40–50	50–60	70–80	80–90	90–100
½ minute	9·16	9·24	9·1	9·06	8·9	8·48	7·7	6·16	2·78
2 minutes	9·61	9·66	9·54	9·54	9·39	9·14	8·88	7·62	2·81
4 minutes	9·66	9·72	9·69	9·69	9·48	9·32	9·07	8·2	2·82
6 minutes	9·7	9·7	9·73	9·73	9·58	9·42	9·18	8·38	2·83
8 minutes	9·7	9·7	9·71	9·71	9·66	9·48	9·24	8·5	2·83
10 minutes	9·7	9·7	9·71	9·71	9·68	9·53	9·3	8·57	2·83
	Magnesium trisilicate, B.P. dose 1·5 g.								
½ minute	1·88	5·37	4·57	3·29	2·81	2·52	2·33		
2 minutes	4·84	6·18	6·0	5·51	3·75	2·70	2·35		
4 minutes	6·38	6·49	6·34	6·15	5·38	2·84	2·38		
6 minutes	6·68	6·64	6·51	6·27	5·95	3·07	2·4		
8 minutes	6·8	6·74	6·62	6·49	6·16	3·26	2·43		
10 minutes	6·88	6·8	6·69	6·58	6·29	3·49	2·46		

B.P.C. (0·6 g. dose), ion exchange resin C (1 g. dose) and bismuth carbonate (1·8 g. and 30 g. dose), fail to raise the *p*H to 3·5. Magnesium trisilicate B.P. (1·5 g. dose), and ion exchange resin A (15 g. dose) and B (8 g. dose) raised the *p*H above 4 but not greater than 7. Light magnesium oxide B.P. (0·25 g. and 0·5 g.) caused an immediate rise to a *p*H approaching 10.

The following observations can be made on these results. Aluminium hydroxide gel B.P.C. (8 ml. dose) is rapid in initial effect and buffers at a *p*H level of 4, maintaining its effect for approximately 60 minutes. Dried aluminium hydroxide gel at the official maximum dose (0·6 g.) is very slow in exerting its effect and the maximum *p*H attained is 2·2 after

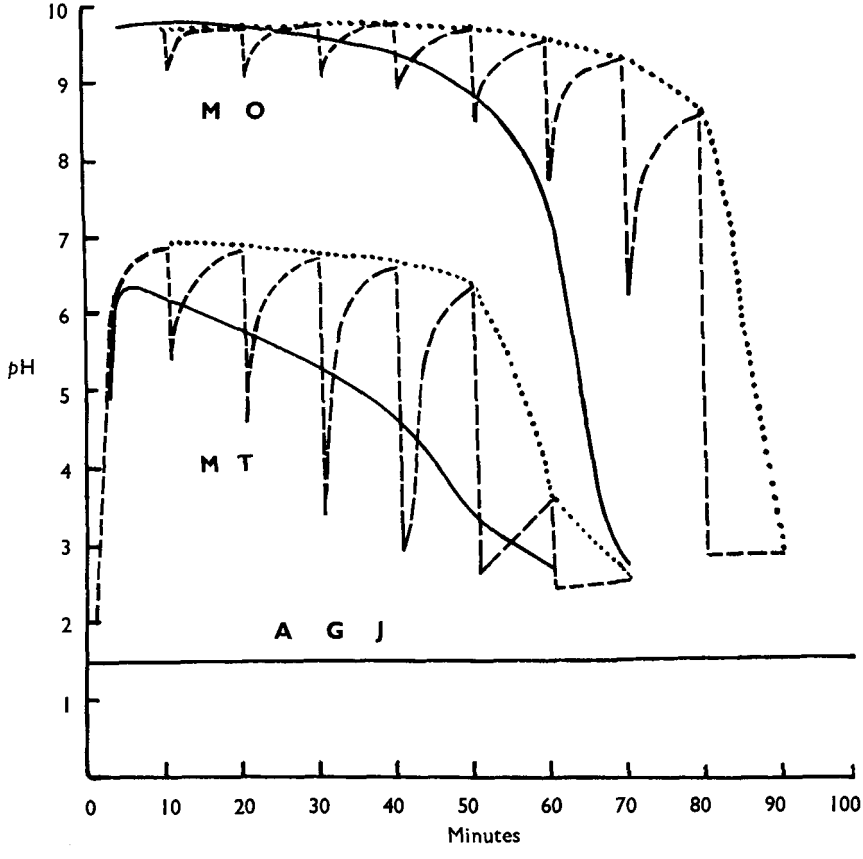

FIG. 1. Curves of light magnesium oxide (MO) B.P. (0·5 g.) and magnesium trisilicate (MT) B.P. (1·5 g.) showing the effect of periodic and continuous addition of artificial gastric juice.

———— Continuous addition (0·5 ml. every 15 seconds).
— — — Periodic addition (20 ml. every 10 minutes).
. . . . . Peak curve.
A G J. *p*H of artificial gastric juice (*p*H 1·5).

40 minutes. Increasing the dosage to 1·5 g. serves to raise the *p*H level to 3·5 and increases the time of effectiveness. With the higher dosage the speed of the initial effect is slightly increased, the maximum *p*H being obtained after 20 minutes, but the dried gel is not comparable with the liquid preparation in this respect. This difference was confirmed with several samples of aluminium hydroxide preparations obtained from various sources. All were found to comply with the B.P.C. requirements.

On examination by the *in vitro* method all gave the typical results shown in Figure 3. The differences between aluminium hydroxide gel and the dried aluminium hydroxide gel is discussed in detail later. Dihydroxy aluminium aminoacetate buffers at the same level as the dried aluminium hydroxide gel at equal dosage (1·5 g.) but is markedly more rapid in

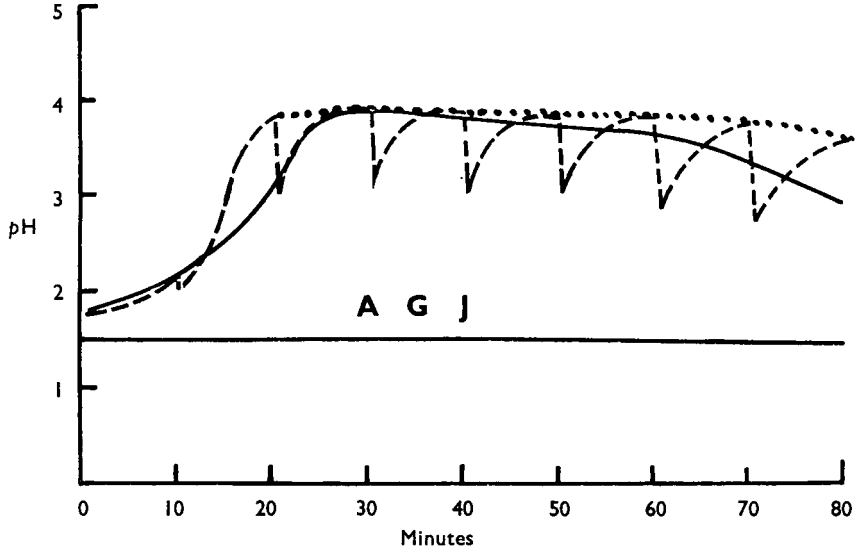

FIG. 2. Curves of aluminium hydroxide gel B.P.C. (1·5 g.) showing the effect of periodic and continuous addition of artificial gastric juice.

———— Continuous addition (0·5 ml. every 15 seconds).
— — — Periodic addition (20 ml. every 10 minutes).
..... Peak curve.
A G J. *p*H of artificial gastric juice (*p*H 1·5).

initial effect than the latter, and approaches the speed of aluminium hydroxide gel in this respect. This is due to the availability of the amino grouping for immediate neutralisation, the hydroxy groups reacting slowly as in aluminium hydroxide. Aluminium phosphate gel (8 ml. dose) is rapid in initial effect but fails to raise the *p*H above 2·5. Ion exchange resin C, distributed in the U.S.A. as an antacid, was used at the recommended dosage (1 g.). At this concentration it is low in buffering capacity and has little sustaining power. Bismuth carbonate cannot be regarded as an antacid. The normal dose (1·8 g.) fails to raise the *p*H of the testing solution and high dosage (30 g.) fails to raise the *p*H above 2. Magnesium trisilicate B.P. (1·5 g. dose) is rapid in initial effect and taking the peak curve, buffers at a *p*H level of 6 to 7 for 60 minutes after which time it rapidly loses effect. Although this buffering level is higher than is considered essential, magnesium trisilicate in use would not be likely to cause acid-rebound and may be classed as a good and effective antacid. The ion exchange resins A and B are used therapeutically to correct the electrolyte balance, but they do have an antacid effect and were

accordingly included in this survey. Resin A at the high recommended dosage (15 g.) has a prolonged buffering effect in the region of *p*H 7 and resin B at the recommended dosage of 8 g. buffers at *p*H 5 for approximately 40 minutes. Resin A at smaller dosages buffers at lower *p*H levels and is correspondingly effective for shorter periods. (See Fig. 4.) Magnesium oxide exerts its effect immediately and if in excess raises the *p*H to almost 10. It has little buffering action and achieves its effect

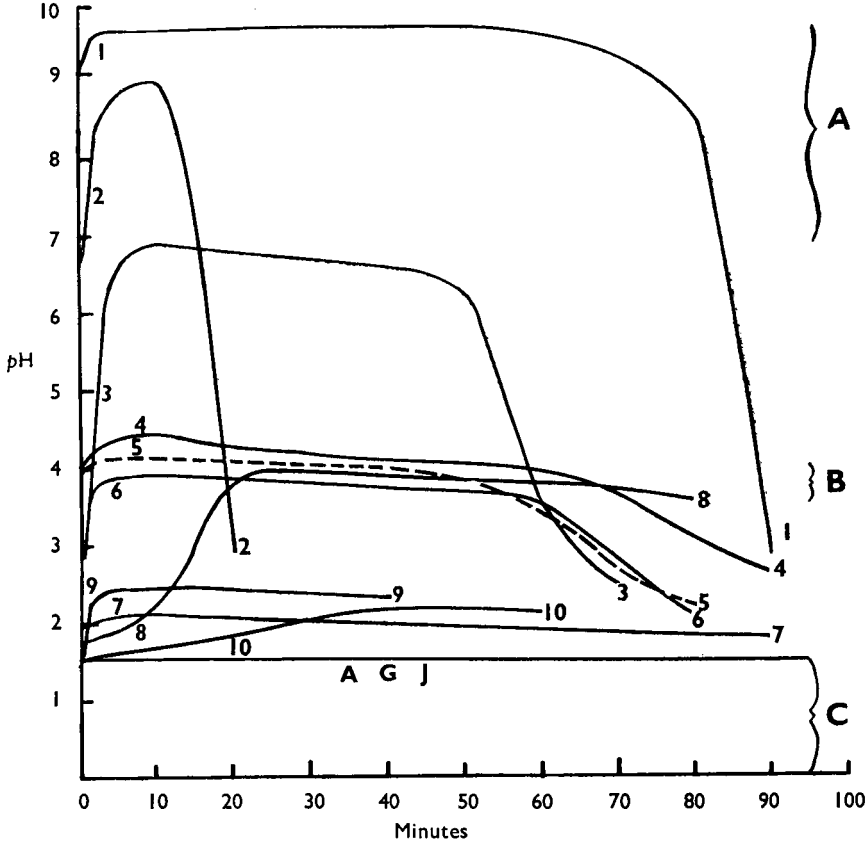

FIG. 3. A comparison of the antacid effect of some commonly used antacids.

1. Light magnesium oxide B.P. (0·5 g.).
2. Light magnesium oxide B.P. (0·25 g.).
3. Magnesium trisilicate B.P. (1·5 g.).
4. Calcium phosphate B.P. (1·5 g.).
5. Aluminium hydroxide gel B.P.C. (8 ml.).
6. Dihydroxy aluminium aminoacetate (1·5 g.).
7. Bismuth carbonate (30 g.).
8. Dried aluminium hydroxide gel (1·5 g.).
9. Aluminium phosphate gel (8 ml.).
10. Aluminium hydroxide dried gel (0·6 g.).

A. Region of acid rebound (*p*H 7 and above).
B. Region of ideal antacid neutralisation (*p*H 3·5 to 4).
C. Hyperchlorhydric region (*p*H below 1·5).
A G J. *p*H of artificial gastric juice (*p*H 1·5).

almost entirely by chemical neutralisation. The duration of effect depends on the amount used. Magnesium oxide when used at a dosage greater than 0·25 g. is an alkalising agent and will cause acid-rebound, and it could be argued that in peptic ulcer therapy even the lower B.P. dose is higher than desirable. It was established that, with the exception

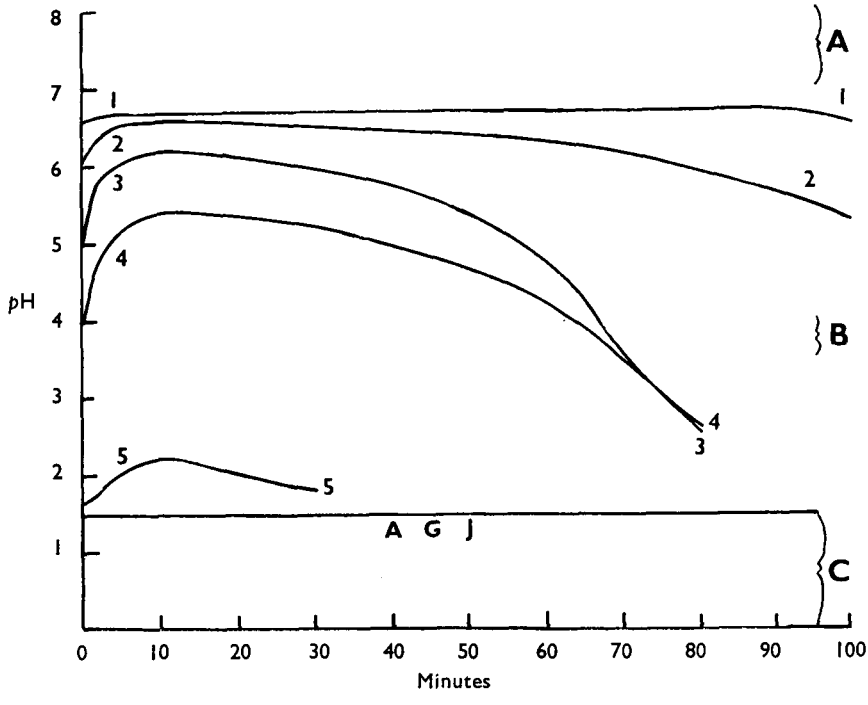

FIG. 4. The antacid effect of some ion exchange resins.

1. Ion exchange resin A (15 g.).
2. Ion exchange resin A (7·5 g.).
3. Ion exchange resin A (3·75 g.).
4. Ion exchange resin B (8 g.).
5. Ion exchange resin C (1 g.).

A. Region of acid rebound (*p*H 7 and above).
B. Region of ideal antacid neutralisation (*p*H 3·5 to 4).
C. Hyperchlorhydric region (*p*H below 1·5).
A G J. *p*H of artificial gastric juice (*p*H 1·5).

of the ion exchange resin and the dried aluminium hydroxide gel (0·6 g. dose), increased dosage prolonged the period of effectiveness without affecting the *p*H level attained.

In conjunction with Figure 3 it is of interest to consider some of the typical curves obtained by plotting the *p*H readings taken at 2-minute intervals. The selected curves are shown in Figures 1 and 2 and contrast the immediately effective or stoichiometric type of antacid as represented by magnesium oxide (Fig. 1) and the buffering type of antacid represented by magnesium trisilicate (Fig. 1) and aluminium hydroxide (Fig. 2). The curve for magnesium oxide shows that further addition of artificial

gastric juice does not appreciably affect the high *p*H level attained indicating that the acid is immediately neutralised. When the excess of magnesium oxide has been used up the curve exhibits a steep decline. The curves for magnesium trisilicate and aluminium hydroxide show that these substances, which act partially by neutralisation and partially by adsorbing hydrogen ions, are more appreciably affected by the further additions of artificial gastric juice but until the antacids are used up they are capable of recovery to the equilibrium *p*H level on each occasion the acid is added. The curves also show that compared with aluminium hydroxide, magnesium trisilicate attains a higher *p*H level, is more

TABLE III

*p*H READINGS WITH ALUMINIUM HYDROXIDE GEL (SEE FIG. 2)

A. Readings obtained by adding 20 ml. of artificial gastric juice and withdrawing 20 ml. of the mixture at 10-minute intervals

Period	Dried aluminium hydroxide gel, B.P.C. 1·5 g.							
	0–10	10–20	20–30	30–40	40–50	50–60	60–70	70–80
½ minute	1·75	2·04	3·01	3·05	3·03	3·03	2·78	2·75
2 minutes	1·8	2·2	3·47	3·45	3·45	3·41	3·25	2·85
4 minutes	1·85	2·51	3·76	3·75	3·75	3·72	3·48	3·21
6 minutes	1·92	—	3·83	3·81	3·78	3·76	3·51	3·39
8 minutes	2·0	3·68	3·86	3·82	3·80	3·76	3·73	3·51
10 minutes	2·16	3·82	3·87	3·82	3·82	3·77	3·74	3·59

B. Readings obtained by adding 0·5 ml. of artificial gastric juice and withdrawing 1 ml. of mixture at 15 seconds and 30 seconds respectively

	Dried aluminium hydroxide gel, B.P.C. 1·5 g.							
2 minutes	1·82	2·26	3·46	3·89	3·84	3·74	3·65	3·27
4 minutes	1·89	2·42	3·71	3·88	3·83	3·72	3·60	3·20
6 minutes	1·97	2·61	3·83	3·85	3·82	3·70	3·52	3·18
8 minutes	2·04	2·82	3·89	3·85	3·78	3·69	3·46	3·03
10 minutes	2·14	—	3·89	3·85	3·76	3·67	3·38	3·01

appreciably affected by the additions of the artificial gastric juice and exhibits a steep decline of the *p*H level at the end of the period of effectiveness. This indicates that magnesium trisilicate is more dependent for its antacid effect on its neutralising capacity, due to the magnesium oxide content of the complex, than on its ability to adsorb hydrogen ions.

Figures 1 and 2 also show the effect on these antacids of a more or less continuous addition of artificial gastric juice and continuous withdrawals of the mixture. This more closely simulates the conditions occurring in the stomach. In this modification of the original method used in this investigation, 0·5 ml. of the artificial gastric juice was added every 15 seconds and 1 ml. of the mixture was withdrawn every 30 seconds, the *p*H being recorded at 2-minute intervals. This modified method approximates to the method of Rossett and Flexner[1] which requires a more elaborate technique or apparatus than the original method used in this investigation. The curves obtained from the results of the modified method are superimposed in Figures 1 and 2 on the curves obtained by our original method. As would be expected the curves for *p*H levels lies between the maxima and minima lines of the original curves. The modified curve of magnesium oxide when compared to the "peak curve"

is initially identical but gradually shows an increasingly steeper slope as the reaction proceeds, differing appreciably in *p*H level towards the end of the reaction. The modified curve obtained by the drip method for magnesium trisilicate differs appreciably both in *p*H level and in slope throughout the reaction period, and approximates to what would be the mean curve of the maxima and minima lines obtained by our original method.

TABLE IV

*p*H READINGS WITH VARIOUS ANTACIDS

Period	*Antacid									
	1	2	3	4	5	6	7	8	9	10
½ minute	9·16	6·8	1·88	4·05	3·9	2·8	1·92	1·75	1·61	1·55
2 minutes	9·61	8·37	4·84	4·25	4·08	3·73	1·98	1·8	2·34	1·56
4 minutes	9·66	8·72	6·38	4·33	4·08	3·86	2·02	1·85	2·42	1·58
6 minutes	9·7	8·86	6·68	4·38	4·08	3·89	2·02	1·92	2·42	1·61
8 minutes	9·7	8·94	6·8	4·4	4·09	3·9	2·05	2·0	2·42	1·64
10 minutes	9·71	9·01	6·88	4·42	4·09	3·9	2·08	2·16	2·42	1·68
20 minutes	9·7	2·84	6·8	4·26	4·08	3·82	2·04	3·82	2·36	1·83
30 minutes	9·71	—	6·69	4·18	4·01	3·80	2·01	3·87	2·3	2·06
40 minutes	9·72	—	6·58	4·08	3·98	3·76	1·96	3·82	—	2·2
50 minutes	9·68	—	6·29	4·03	3·83	3·69	1·91	3·82	—	2·18
60 minutes	9·53	—	3·49	3·93	3·41	3·55	1·88	3·77	—	2·11
70 minutes	9·3	—	2·46	3·69	2·67	2·87	1·82	3·74	—	—
80 minutes	8·57	—	—	3·07	2·25	2·61	1·83	3·59	—	—
90 minutes	2·83	—	—	2·61	—	—	1·8	—	—	—

* See Figure 3 for names and quantities of antacids. Bismuth carbonate 1·8 g. did not raise the *p*H of the testing solution.

TABLE V

*p*H READINGS FOR ION EXCHANGE RESINS

Period	*Ion exchange resin				
	1	2	3	4	5
½ minute	6·6	6·06	5·08	4·0	1·68
2 minutes	6·68	6·35	5·8	4·82	1·75
4 minutes	6·68	6·46	6·0	4·92	1·96
6 minutes	6·68	6·52	6·08	5·04	2·09
8 minutes	6·69	6·53	6·14	5·04	2·15
10 minutes	6·7	6·57	6·18	5·4	2·2
20 minutes	6·72	6·54	6·1	5·34	2·0
30 minutes	6·68	6·51	5·94	5·18	1·82
40 minutes	6·66	6·45	5·74	4·96	—
50 minutes	6·68	6·37	5·35	4·64	—
60 minutes	6·68	6·28	4·8	4·19	—
70 minutes	6·66	6·09	3·54	3·48	—
80 minutes	6·66	5·9	2·52	2·57	—
90 minutes	6·64	5·64	—	—	—
100 minutes	6·52	5·26	—	—	—

* See Figure 4 for names and quantities of ion exchange resins.

The "drip" curve for dried aluminium hydroxide gel (1·5 g. dose) is almost identical with the "peak curve" differing in a slightly more gradual initial effect and a slightly steeper curve at the end of the period of effectiveness. While no generalisation can be made on these results in relation to the other antacids considered it is felt that the modified method will more closely predict the effect of magnesium trisilicate in actual use and indicates that it would buffer within the region of *p*H 6 to 3·5 for 40 minutes so long as active secretion and withdrawal of gastric juice is taking place.

It is apparent from the results obtained that based on the equivalent aluminium oxide content, dried aluminium hydroxide gel B.P.C. is less

effective than the aluminium hydroxide gel B.P.C. This feature has been previously observed by Adams *et al.*[6] and Johnson and Duncan[2]. Figure 5 shows in detail that at the maximum recommended dose of 0·6 g. dried aluminium hydroxide gel (Al_2O_3 content 0·33 g.) is almost devoid of antacid property contrasting markedly with the efficient antacid properties of the aluminium hydroxide gel B.P.C. at the B.P.C. equivalent dosage of 8 ml. (Al_2O_3 content 0·37 g.). To obtain a similar antacid effect to that produced by 8 ml. of the liquid gel 1·5 g. of the dried gel was required.

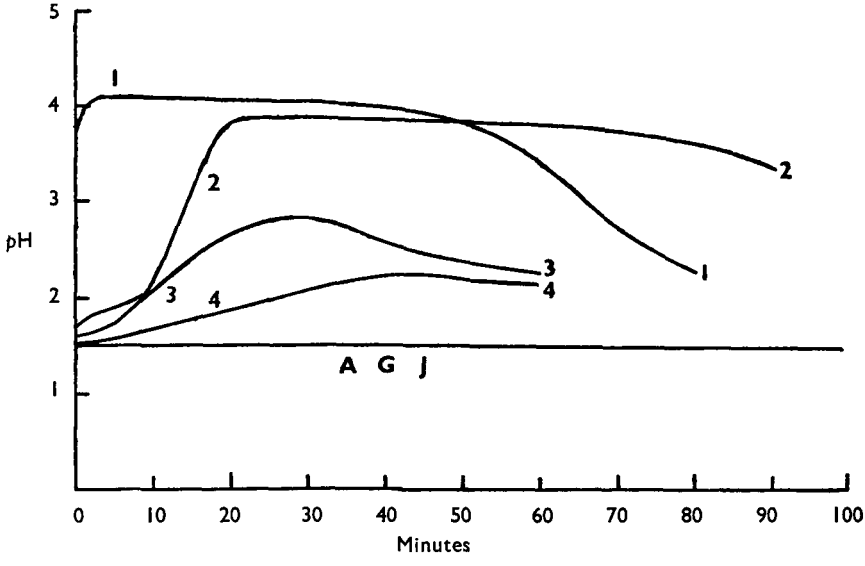

FIG. 5. The difference in antacid effect between aluminium hydroxide gel B.P.C. and dried aluminium hydroxide gel B.P.C.

1. Aluminium hydroxide gel B.P.C. 8 ml. ≡ 0·37 g. Al_2O_3.
2. Dried aluminium hydroxide gel B.P.C. 1·5 g. ≡ 0·825 g. Al_2O_3.
3. Dried aluminium hydroxide gel B.P.C. 0·6 g. + 7·75 ml. of water and heated at 70° C. for 5 minutes.
4. Dried aluminium hydroxide gel B.P.C. 0·6 g. ≡ 0·33 g. Al_2O_3.

A G J. *p*H of artificial gastric juice (*p*H 1·5).

At this increased dosage the dried gel requires 20 minutes to obtain approximately the same *p*H level, as that which is produced almost at once by the liquid gel.

These two samples were subjected to the B.P.C. neutralising capacity test at equivalent amounts, based on the aluminium oxide content. 5·65 g. (required 5·647 g.) of aluminium hydroxide gel B.P.C. and 0·5 g. of dried aluminium hydroxide gel B.P.C. respectively, were added to 150 ml. of 0·1N hydrochloric acid. The mixture was stirred continuously and maintained at 37° C. for 1 hour. After cooling the amount of acid neutralised was determined by titration with 0·1N sodium hydroxide using bromophenol blue as the indicator. In addition to the B.P.C. test the *p*H of the reaction mixture was recorded at 2-minute intervals during the period of the test. The *p*H readings obtained are shown graphically

in Figure 6. The aluminium hydroxide gel (5·65 g.) neutralised 136 ml. of 0·1N hydrochloric acid and the dried aluminium hydroxide gel B.P.C. (0·5 g.) neutralised 127 ml. of 0·1N of hydrochloric acid under the conditions of the B.P.C. test. In both cases the B.P.C. requires the neutralisation of not less than 100 ml. of hydrochloric acid. (The B.P.C. directs that 5 g. of the liquid gel be taken for the acid neutralisation test.)

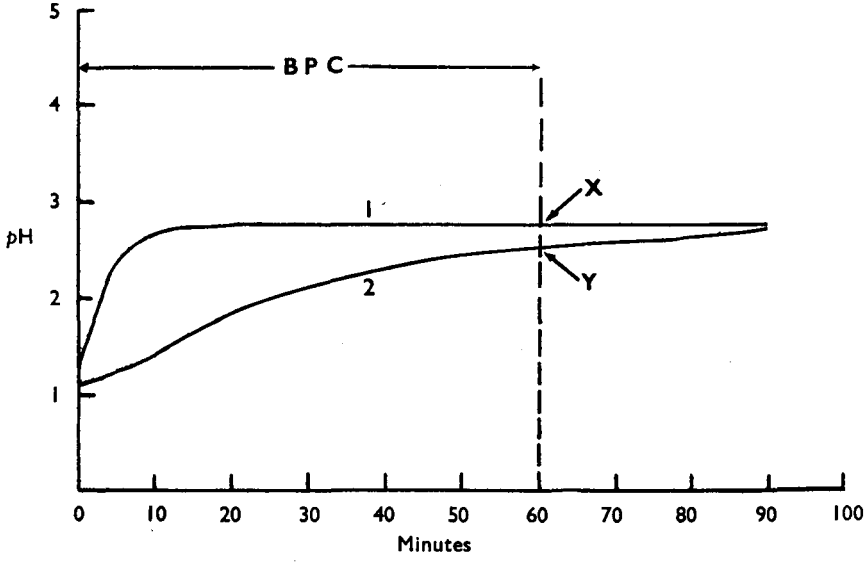

FIG. 6. *p*H changes occuring during the period of the acid neutralising test of the B.P.C. in the case of aluminium hydroxide gel B.P.C. and the dried gel.

1. Aluminium hydroxide gel B.P.C. 5·65 g. ≡ 0·261 g. Al_2O_3.
2. Dried aluminium hydroxide gel B.P.C. 0·5 g. ≡ 0·26 g. Al_2O_3.

X. 136 ml. of 0·1N hydrochloric acid neutralized.
Y. 127 ml. of 0·1N hydrochloric acid neutralized.
B.P.C. Period of B.P.C. test.

The acid neutralising capacities of the two preparations at equivalent amounts should be identical but as indicated by the B.P.C. test there is a difference in acid neutralising capacity. Examination of the *p*H curves in Figure 6 show that this is due to dried gel requiring more than 1 hour for neutralisation, whereas the liquid gel requires 20 minutes for complete neutralisation. A repeat experiment showed that the dried gel required 90 minutes for complete neutralisation. This curve is represented in Figure 6. The marked difference in the low *p*H level attained by the dried gel, as shown by the *in vitro* test, is due to the progressive loss of unreacted dried aluminium hydroxide gel in the repeated withdrawals of the reaction mixture. These withdrawals, however, represent physiological loss from the stomach.

It was thought that a difference in effectiveness, in relation to the speed of action, may be due to a difference in particle size associated with the degree of hydration and surface properties. Particle size determination by a microscopic technique was found to be unsatisfactory, the particle

size being beyond the size of resolution. Electron micrographs revealed that in the dried gel the particles were aggregated and that the individual particle size would be of the order of 0·1 μ. The use of agents such as sodium tartrate, wetting agents, etc., did not cause any appreciable deflocculation. It is not of course possible to examine the liquid gel by electron microscope without altering its character.

Consideration was given to the affect of wetting and hydration of the dried gel but treatment of 0·6 g. of the dried gel by stirring with water for 1 hour in the cold did not appreciably affect the curve for antacid effect.

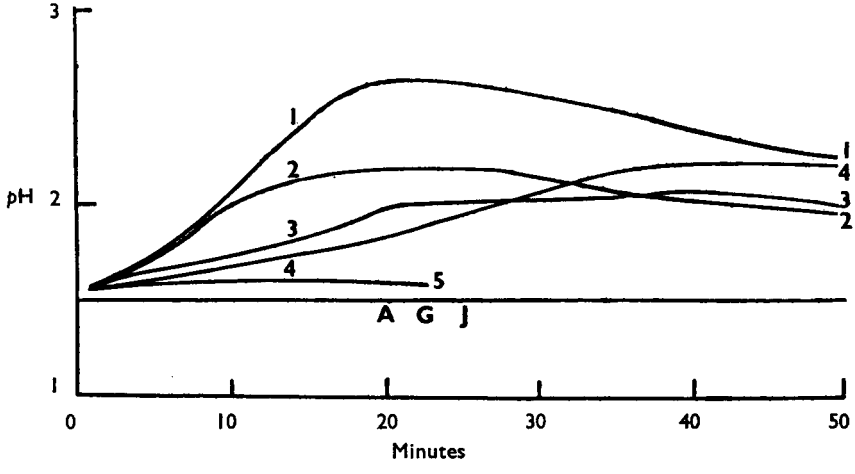

FIG. 7. A comparison of the antacid efficiency of dried aluminium hydroxide gel when hydrated at various temperatures. In each case 0·6 g. of the dried gel was heated with 7·75 ml. of water for the period indicated prior to testing.

1. 70° C. for 5 minutes.
2. 70° C. for 1 hour (*a*) and 90° C. for 5 minutes (*b*).
3. 50° C. for 5 minutes.
4. Material at room temperature.
5. 90° C. for 30 minutes (*a*) and 1 hour (*b*).

A G J. *p*H of artificial gastric juice (*p*H 1·5).

By heating dried aluminium hydroxide gel with water partial hydration can be effected with increased antacid efficiency. The amount of heat applied, governed by volume, time and temperature, is critical, as overheating may cause the deterioration or even complete loss of antacid efficiency. This effect is shown graphically in Figure 7, and the curve showing optimum efficiency achieved by hydration is shown for comparative purpose in Figure 5.

SUMMARY

Conclusions

1. An *in vitro* method has been used to compare the relative efficiencies of antacids in respect of the *p*H changes, rate and time of effectiveness when tested under conditions simulating those occurring in the stomach. Further work is indicated to establish a standardised procedure.

2. Of the antacids considered aluminium hydroxide gel B.P.C., dried

aluminium hydroxide gel B.P.C., dihydroxy aluminium aminoacetate, and calcium phosphate B.P. at appropriate dosage buffer at the desired clinical range of *p*H 3·5 to 4.

TABLE VI

*p*H READINGS FOR ALUMINIUM HYDROXIDE PREPARATIONS

Period	*Preparation 1	2	3	4
½ minute	3·9	1·75	1·55	1·55
2 minutes	4·08	1·8	1·6	1·56
4 minutes	4·08	1·85	1·68	1·55
6 minutes	4·08	1·92	1·79	1·61
8 minutes	4·09	2·0	1·92	1·64
10 minutes	4·09	2·16	2·06	1·68
20 minutes	4·08	3·82	2·64	1·83
30 minutes	4·01	3·87	2·84	2·06
40 minutes	3·98	3·82	2·57	2·22
50 minutes	3·83	3·82	2·36	2·18
60 minutes	3·41	3·77	2·25	2·11
70 minutes	2·67	3·74	—	—
80 minutes	2·25	3·59	—	—
90 minutes	—	3·36	—	—

*See Figure 5 for the quantities of aluminium hydroxide preparations used.

TABLE VII

*p*H READINGS OBTAINED DURING THE B.P.C. ACID NEUTRALISING TEST

(*see* Fig. 6)

Period	Dried aluminium hydroxide gel, B.P.C. 0·5 g. 0–10	10–20	20–30	30–40	40–50	50–60	60–70	70–80	80–90
2 minutes	1·13	1·5	1·88	2·1	—	2·45	—	—	—
4 minutes	1·18	1·57	1·96	2·2	2·34	2·46	—	—	—
6 minutes	1·24	1·68	2·0	2·24	2·36	2·46	—	—	—
8 minutes	1·31	1·74	2·04	2·28	2·4	2·49	—	—	—
10 minutes	1·4	1·84	2·08	2·29	2·42	2·50	2·58	2·64	2·72

Period	Aluminium hydroxide gel, B.P.C. 5·65 g. 0–10	10–20	20–30	30–40	40–50	50–60	60–70	70–80	80–90
2 minutes	1·71	2·71	2·78	—	—	—	—	—	—
4 minutes	2·2	2·74	2·78	—	—	—	—	—	—
6 minutes	2·43	2·76	2·78	—	—	—	—	—	—
8 minutes	2·58	2·76	2·78	—	—	—	—	—	—
10 minutes	2·66	2·78	2·78	2·78	2·78	2·78	2·78	2·78	2·78

TABLE VIII

*p*H READINGS FOR DRIED ALUMINIUM HYDROXIDE GEL

Period	*Preparation 1	2 (*a*)	2 (*b*)	3	5 (*a*)	5 (*b*)
½ minute	1·55	1·61	1·58	1·59	1·58	1·56
2 minutes	1·6	1·66	1·75	1·6	1·6	1·58
4 minutes	1·68	1·74	1·83	1·63	1·6	1·57
6 minutes	1·79	1·82	1·90	1·68	1·6	1·57
8 minutes	1·92	1·91	1·98	1·72	1·6	—
10 minutes	2·06	2·0	2·03	1·78	1·6	—
20 minutes	2·64	2·17	2·18	2·0	1·57	—
30 minutes	2·84	2·12	2·15	2·07	—	—
40 minutes	2·57	2·02	2·08	2·06	—	—
50 minutes	2·36	1·93	2·0	2·0	—	—
60 minutes	2·25	1·84	—	1·98	—	—

*See Figure 7 for quantities and treatment of aluminium hydroxide.

3. Magnesium trisilicate B.P. is an effective antacid buffering at a slightly higher *p*H level of 6 to 3·5.

4. Bismuth carbonate cannot be considered an antacid.

5. Magnesium oxide B.P.C. at the lower B.P. dosage (0·5 g.) is an alkalising agent and in use is likely to cause acid re-bound.

6. A difference in antacid effectiveness between aluminium hydroxide gel B.P.C. and the dried gel at equivalent dosage has been demonstrated.

7. The B.P.C. acid neutralising test does not indicate the difference in antacid effectiveness of the aluminium hydroxide preparations.

In conclusion we wish to thank Mr. A. W. Bull and Mr. C. A. Hill for helpful suggestions and advice, and the Directors of Boots Pure Drug Co. Ltd., for permission to publish this paper.

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