THE EVALUATION OF BUFFER ANTACIDS, WITH PARTICULAR REFERENCE TO PREPARATIONS OF ALUMINIUM

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The treatment of gastric hyperacidity by the administration of substances with antacid properties has engaged the attention of numerous workers in the clinical and related fields. The trend of medical opinion has been to move away from the idea of complete neutralisation of the gastric fluid with the straightforward antacids, and to turn to the use of buffer substances with the object of controlling the *p*H at a more physiologically desirable level. The endeavour has been to remove hyperacidity whilst avoiding the stimulation of acid rebound, or the risks of alkalosis, respectively associated with temporary or prolonged over-neutralisation.

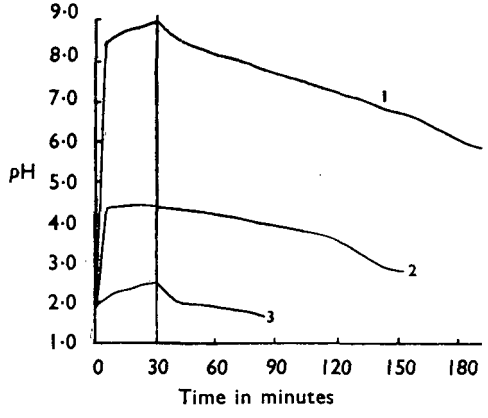

Fig. 1. Type of response when the described method is applied to:—

1. Light magnesium carbonate.
2. Aluminium glycinate.
3. Magnesium trisilicate.

From the pharmaceutical view-point it is a simple matter to ensure that the clinician is provided with sodium bicarbonate of a standard antacid quality, but to ensure a similar service in the case of buffer substances presents something of a problem. Of these buffer types of antacid it is probable that the aluminium preparations are among the most widely used and there can be little doubt that a determination of acid-neutralising capacity as laid down in the B.P.C. 1949 and U.S.P. XIV, for aluminium hydroxide gel, is an inadequate measure of the therapeutic value of the antacids in question, at least so far as the dried forms are concerned.

This type of test was criticised by Holbert, Noble and Grote[1,2] when assessing aluminium preparations and they suggested an alternative procedure based on a modification of a method designed by Johnson and Duncan[3] to simulate conditions in the stomach. These methods were dependent on measuring the rate of change of *p*H of an acid solution in the presence of the antacid in question, and thus took account of the time factor and the reactivity of the antacid under standard empirical conditions. Various procedures based on this principle have been employed by other workers (Mutch[4,5]; Hammarlund and Rising[6,7] and Murphey[8]) in comparing the status of antacids, mainly of the insoluble type.

The purpose of the present paper is to focus further attention upon this problem and to illustrate the use of a somewhat simplified procedure which experience has shown to be of considerable value in assessing antacid properties. Particular attention is directed to the desirability of reconsidering the standards for dried aluminium hydroxide gel.

Suggested Test Conditions

1·0 g. of sample, passing a 100 mesh B.S.S. screen, is added to 200 ml. of water and 3 ml. of N hydrochloric acid. The mixture is agitated continuously by mechanical stirrer to maintain a uniform suspension of the insoluble material. The *p*H of the mixture is determined at intervals of 5 minutes over a period of 30 minutes, the measurement being made electrometrically *via* electrodes remaining *in situ* in the liquid. Thereafter, 1 ml. of N hydrochloric acid is added at intervals of 10 minutes and the *p*H determined immediately prior to each successive addition. This procedure is continued for a period depending upon the rate at which the *p*H falls and the minimum target set for the particular antacid material under test. The whole operation is carried out at room temperature.

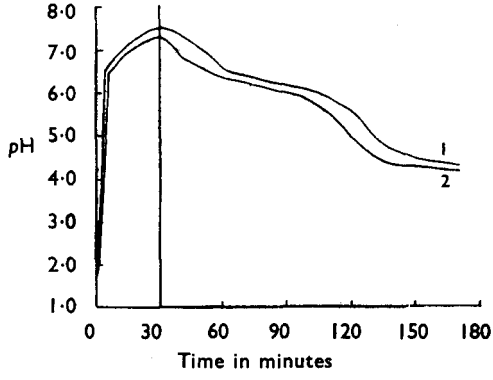

FIG. 2. Depressant tendency upon antacid activity of 1 per cent. of Karaya gum in a tablet containing magnesium carbonate, calcium carbonate and dried aluminium hydroxide gel.
1. Antacid mixture without gum.
2. Antacid mixture with gum.

During the first few minutes of the test the wettability of the powder is a potential factor. This, however, is not normally significant and is reduced to a minimum by rapidly levigating with a little of the test solution and rinsing the suspension into the vessel. It has been found unnecessary and indeed undesirable to use wetting agents.

Comments on the Suggested Conditions

Amongst other properties, the efficacy of an antacid depends upon the rate at which it can exert its effect on the gastric juice, the *p*H to which it will raise the juice when the antacid is present in excess, and its capacity to maintain the *p*H in the face of continued secretion of fresh juice. An attempt is made to assess the first two of these factors in the initial 30-minute period of the described test, whilst the subsequent part of the test takes into account the capacity factor.

The strength of the initial acid solution is such that the *p*H is approximately 1·8. This is chosen as a reasonable approximation of the order of values found in the untreated hyperacidic stomach as indicated by control measurements in fractional test meals[9]. The choice of volume of this

solution, and the strength and rate of addition of acid in the second part of the test, must obviously be on a much more speculative basis, but it is suggested that the chosen conditions have a practical bearing upon their *in vivo* counterparts. The interval between *p*H readings will obviously influence the sensitivity of the test in so far as the recorded points will generally not be equilibrium values. It is clear that the selectivity of the test will diminish as the interval between additions of acid is increased. The 10-minute interval was found to be about the minimum time consistent with expedience in adding acid, measuring the *p*H, and allowing reasonable accuracy in timing, upon which the reproducibility of the results very largely depends. The weight of sample taken should bear some relationship to customary dosage and the 1 g. quantity advocated is considered to be generally consistent with the preparations under discussion.

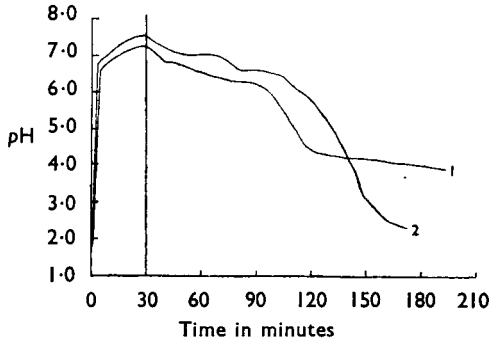

FIG. 3. Loss of buffer activity in the region of *p*H 4, in one of 2 antacid mixtures, due to an adverse condition in manufacture. The aluminium contents of the mixtures were of a similar order.

1. Mixture of magnesium carbonate, calcium carbonate and aluminium hydroxide.
2. Similar mixture to 1 in which the aluminium hydroxide is inactivated.

The suggested conditions do not demand any special elaboration in the laboratory, in that there is no elevated temperature control, and there are no intermittent withdrawals of the test liquid. These two conditions have been taken into account in methods previously described by other workers, with the object of closely simulating conditions in the stomach, but in our opinion the practical significance of these two factors is doubtful.

General Value of the Test

A graphical representation of the results of a test affords a very useful pictorial characterisation of an antacid, or mixture of antacids, in relation to probable clinical behaviour. For example, Figure 1 shows the curves obtained with light magnesium carbonate, dihydroxy aluminium aminoacetate, N.N.R. ("Aluminium Glycinate") and magnesium trisilicate.

The curves in Figure 1 for magnesium carbonate and aluminium glycinate illustrate the types of response when the described method is applied to a strong neutralising agent and a highly active buffer substance, respectively. From current concepts of antacid therapy it would be expected that any substance which gave a curve of the first type would tend to stimulate acid rebound and to have a comparatively brief antacid effect, whilst a substance giving the second type of curve should avoid these disadvantages. The third curve typifies the response obtained when

a slow acting weak buffer substance is submitted to the prescribed conditions. In the case of a mixture of the various classes of antacid, a composite curve is obtained which shows at a glance whether one or other type of action is likely to predominate.

A study of such curves has been found to be of great value in considering the formulation of antacid products, not only in respect of the selection of active components and assessing the promptness, type, and duration of action, but in providing a sensitive measure of the influence upon antacid activity of various factors during manufacture and storage. Figure 2, for example, shows the depressant tendency upon antacid activity of 1 per cent. of Karaya gum in a tablet containing magnesium carbonate, calcium carbonate and dried aluminium hydroxide gel. The curves reproduced in Figure 3, obtained from two antacid mixtures similar to that in Figure 2, show the loss of buffer activity in the region of *p*H 4 due to adverse conditions in manufacture. The aluminium contents of these two mixtures were of a similar order.

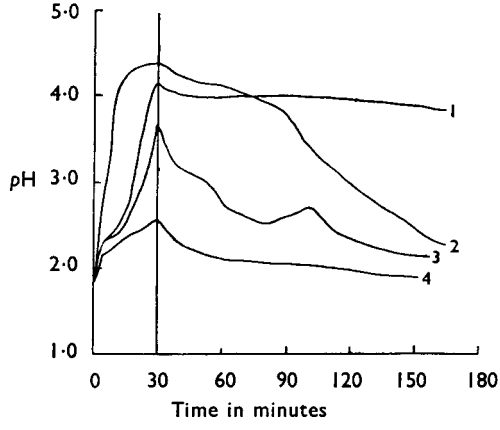

FIG. 4. Difference in reactivity and buffer capacity of 4 samples of B.P.C. dried aluminium hydroxide gel.

ALUMINIUM PREPARATIONS

It is proposed to confine attention to dried aluminium hydroxide gels and aluminium glycinate. The former are the subject of monographs in the B.P.C. 1949 and U.S.P. XIV, and a monograph is devoted to the latter antacid in New and Nonofficial Remedies 1952 (N.N.R.). In each case an evaluation of antacid activity is based on a measurement of the amount of acid absorbed under standard conditions by allowing the sample to stand in contact with an excess of acid for 1 hour at 37°C in the B.P.C. and U.S.P. tests, and for 10 minutes at room temperature in the N.N.R. test. In all cases the residual acid is measured by titration with alkali using bromophenol blue as indicator.

From the purely analytical aspect the end-point is ill-defined because of the strong buffer action of the aluminium salt present. It is suggested that if this type of test should be retained it would be preferable to specify an electrometric procedure.

In addition to the acid absorption test for aluminium glycinate the N.N.R. monograph describes a test designed to measure rate of reaction. This test specifies that the *p*H must exceed 3 when about 0·2 g. has been in contact with 25 ml. of 0·1N hydrochloric acid for 10 minutes, the suspension being shaken during the first 5 minutes. Disregarding for the moment any criticism of this test, the imposition of this additional standard implies

that the acid absorption type of test is not wholly adequate in assessing antacid value, and it would seem desirable that some form of test which specifically takes the rate of reaction into account should likewise be extended to the dried aluminium hydroxide gels.

It is instructive to consider the curves reproduced in Figure 4, which were obtained by the method described by us, when applied to 4 samples of dried aluminium hydroxide gel, all of which passed the B.P.C. neutralising capacity test. The actual acid absorptions of samples (1) to (4) determined by the B.P.C. procedure and expressed in terms of ml. of acid consumed per g. were 282, 266, 231 and 200, respectively. From an inspection of the curves in their entirety, it is evident that the antacid activities of these samples are very widely divergent. Sample (1) is clearly superior as an antacid buffer. Sample (4) is very poor both in regard to promptness of action, as indicated in the first part of the test, and capacity to sustain the *p*H at an effective level, as shown by the second stage of the test. Sample (3) approaches sample (1) in its promptness of action, but it is evidently much less effective in its buffering capacity. The curve for sample (2) indicates a high rate of reaction but a comparatively weak buffer capacity, and its general shape suggests the presence of residual sodium carbonate, for which the B.P.C. monograph does not impose any limit. The U.S.P. pays some attention to the presence of strong alkali by prescribing a limit for *p*H of the filtrate from an aqueous suspension of the sample.

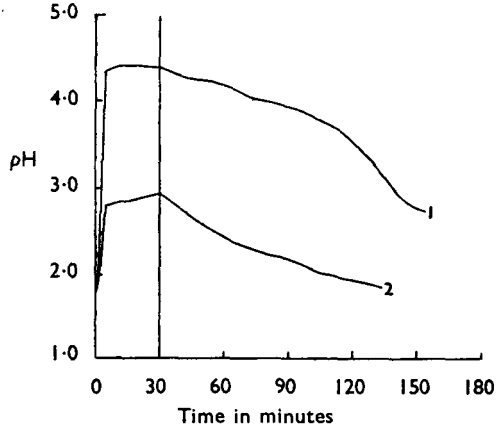

FIG. 5. Responses to the described test from samples of:—
1. Aluminium glycinate.
2. Dried aluminium hydroxide gel and glycine mixture of equivalent aluminium and nitrogen content to 1.

Figure 5 shows the responses to the described test from samples of aluminium glycinate and a mixture of dried aluminium hydroxide gel and glycine such that the aluminium and nitrogen contents were the same in both samples. These two curves show that the aluminium glycinate is a greatly superior antacid to the physical mixture of the parent components. These two samples were also subjected to the acid absorption tests as prescribed in the B.P.C. and N.N.R. monographs and to the N.N.R. reaction rate test. The results are shown in Table I.

The acid absorption figures in Table I illustrate the influence of conditions upon the degree of discrimination exhibited by this type of test. It is plain that the conditions prescribed in the N.N.R. monograph are much more stringent than those of the B.P.C. It is also evident that the reaction rate test is a useful criterion of activity.

Discussion

From data presented in this and other communications, it would seem desirable to consider whether the B.P.C. standard for antacid activity of dried aluminium hydroxide gel is adequate. It is tentatively suggested that if the B.P.C. test is to be retained in its present form, it might be well to consider raising the lower limit for acid absorption from 200 to 250 ml. of 0·1N hydrochloric acid per g. It would also seem desirable to adopt a test for reactivity on the lines of those used for aluminium glycinate or aluminium phosphate gel U.S.P.

Measurements of the properties mentioned above are integrated in the test at present described. So far as dried aluminium hydroxide gel is concerned it is suggested that reasonable standards would be *p*H of 3·5 to 4·5 after the initial 30 minutes and a total acid consumption of not less than 10 ml. of N hydrochloric acid before the *p*H falls below 3·5, corresponding to 100 minutes under the conditions of the test. In selecting the various critical conditions for this type of test, it is obvious that the possible variations are almost infinite. The choice of the actual conditions described was dictated by an attempt to compromise in order of importance between therapeutic significance and expedience in the laboratory.

TABLE I

SHOWING THE RESPONSES TO B.P.C. AND N.N.R. TESTS OF (1) A SAMPLE OF ALUMINIUM GLYCINATE AND (2) A MIXTURE OF GLYCINE AND DRIED ALUMINIUM HYDROXIDE GEL WITH THE SAME ALUMINIUM AND NITROGEN CONTENTS AS SAMPLE (1).

Sample	Acid absorption test ml. of 0·01N HCl/g.		*p*H obtained in N.N.R. reaction rate test
	B.P.C.	N.N.R.	
1	183	152	3·9
2	159	42	1·6

In considering any test for antacid activity such as the measurement of neutralising capacity as prescribed in the B.P.C., or the type at present described, it is important not to overlook the fact that such measurements are concerned solely with the ability of a substance to neutralise hydrochloric acid. No account is taken of the multiplicity of factors likely to arise in the stomach such as the influence of pepsin. It is merely submitted that the suggested procedure, in measuring both promptness and duration of buffer action, is more discriminating and informative than that used in the B.P.C. monograph in estimating the clinical potentialities of dried aluminium hydroxide gel.

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References

1. Holbert, Noble and Grote, *J. Amer. pharm. Ass. Sci. Ed.*, 1947, **36**, 149.
2. Holbert, Noble and Grote, *ibid.*, 1948, **37**, 292.
3. Johnson and Duncan, *Quart. J. Pharm. Pharmacol.*, 1945, **18**, 251.
4. Mutch, *ibid.*, 1946, **19**, 490.
5. Mutch, *Lancet*, 1949, **256**, 859.
6. Hammarlund and Rising, *J. Amer. pharm. Ass. Sci. Ed.*, 1949, **38**, 586.
7. Hammarlund and Rising, *ibid.*, 1952, **41**, 295.
8. Murphey, *ibid.*, 1952, **41**, 361.
9. Baron (*Personal Communication*), 1953.