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# Biopharmaceutical properties of liquid and tablet antacids: *in vivo* studies using the intragastric pH-measurement technique

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Three types of liquid and tablet antacids have been studied *in vitro* and *in vivo:* aluminium hydroxide, aluminium hydroxide-magnesium carbonate and hydrotalcite. The effects on gastric pH of antacid suspensions and antacid chewing tablets having identical active ingredients have been studied in 36 volunteers, the sequence of both forms of administration being randomized. Gastric acid secretion was continuously stimulated during the experiment by a pentagastrin infusion. Antacid chewing tablets gave inferior results when compared with the same antacid in liquid. Antacid suspensions are therefore preferred in the treatment of acid-peptic disease.

The *in vivo* effects of liquid and tablet antacids have been discussed by Sommer, Kasper & Herzberger (1973) and Ekeved & Walan (1975). In those studies the liquid and tablet antacids gave almost equal reduction in acidity and a duration of action from 10 to + 60 min. However, the chemical composition of the active ingredients of the liquid and tablet antacids differed leaving the findings unclear.

There are no studies in which the *in vitro* and *in vivo* effects of liquid and tablet antacids with the *same active ingredients*, both qualitative as quantitative, have been compared. We therefore have investigated three types of acid neutralizing substances in tablet and liquid form of administration: aluminium hydroxide, aluminium hydroxide - magnesium carbonate (F-MA 11), hydrotalcite (Ultacit = Altacite).

For pH measurement we used a modification of the steady intragastric pH measurement technique as described by Sommer & others (1973).

## MATERIALS AND METHODS

### In vitro *tests*

The total acid consuming capacity (ACC) was determined as recommended in the U.S.P. XIXth revision. The ACC was calculated from the test results for three tablets or the equivalent amount of antacid suspension. For additional simulation of the *in vivo* conditions, the products were tested by a modified Schaub-method (Brouwers, 1975). Before testing, the chewing tablets were crushed into three different sizes: 105, 210–300 and 1400–2800 $\mu$m. The dose recommended by the B.P. (1973) or by the manufacturer was tested: this is 2 tablets or the equivalent amount in 20 ml suspension.

### In vivo *tests*

All the experiments were with healthy volunteers in each of whom a stomach pH electrode, calibrated immediately before introduction, was passed after an overnight fast. The tip of the electrode was positioned fluoroscopically at the junction of the middle and lower thirds of the greater curvature (Hassan & Hobsley, 1970; Cleator, Stoller & others, 1972). Saliva was constantly aspirated to avoid contamination of the gastric contents. The subjects were semi-recumbent or resting in an armchair. Gastric acid secretion was stimulated by pentagastrin, 1 $\mu$g kg$^{-1}$ h$^{-1}$ (Nordgren, 1971), administered in 0·15 M NaCl as a continuous infusion at a rate of 30 ml h$^{-1}$. This gave a relatively stable low pH over a prolonged time. The tests were blind, the tablet and liquid antacids were coded. Volunteers were instructed to chew tablets thoroughly before swallowing with the same volume of water as in the equivalent amount of liquid antacid (30 ml except when noted in Fig. 1).

The active ingredients of the drugs are summarized in Table 1. The first test dose was given when the intragastric pH was stable and lower than pH 2 for at least 10 min. When after the administration of the first test preparation, the pH dropped again below 2 and remained stable for another 10 min, the second test preparation was administered. The experiment was stopped when the pH dropped again below 2 for another 10 min. When no effect at all was observed after the second test preparation, which occurred

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occasionally with the tablet forms, the volunteer was given a 50 ml 8% aqueous sodium bicarbonate solution to test the reactivity of the pH electrode *in situ*. The duration of action of the antacids was determined by measuring the length of time during which the pH remained above pH 2 or above pH 3.

*pH-measurement* in vitro *and* in vivo

The *in vitro* pH measurements were made with a pH glass-electrode (Philips, type CA 42) connected with a digital pH meter and potentiometric recorder (Philips-Netherlands). The intragastric pH-measurement was made with a combination microelectrode with capillary action reference (Beckman-Scotland/ type Cecar). The pH electrode was shielded by a rubber balloon head of light-bulb shape with vertical slits, the base slipping over the electrode (Brouwers & Tytgat, 1976). This prevented mucosal fold entrapment and ensured constant interaction with the bathing gastric fluid. The pH electrode was fixed to a pH meter with a potentiometric recorder (Electronic Instruments-England/Vitatron-Netherlands). For calibration of the pH electrode we used buffer solutions of pH 1·68, 4·0 and 7·0 (Electrofact-Danmark).

For statistical analysis of the *in vivo* results we used the Wilcoxon's rank sum test (Swinscow, 1976).

## RESULTS

In vitro *antacid potency*

The ACC was tested according to the U.S.P. XIX test. The volumes of 0·1 N HCl neutralized by the various dosage forms are shown in Table 1. The corresponding volumes of 0·1 N HCl neutralized by 1 g of these antacids were calculated. The liquid and tablet antacid formulations of aluminium hydroxide-magnesium carbonate gave almost the same ACC as hydrotalcite. Aluminium hydroxide tablets gave a much lower ACC compared with the same amount of aluminium hydroxide gel B.P. 1973 in liquid form.

With the modified Schaub test, the physiological conditions are mimicked because both gastric juice secretion and gastric juice loss through the pylorus are simulated. Artificial gastric juice was used in the test. Chewing was simulated *in vitro* by the use of different fragment sizes. With fragments of 1400–2800 $\mu$m a pH rise to 3 was not reached for any preparations and aluminium-hydroxide tablet fragments smaller than 150 $\mu$m and from 210–300 $\mu$m also failed to reach pH 3. All the liquid antacids had a rapid neutralizing effect and a duration of action longer than 1 h (Brouwers & Tytgat, 1976).

Table 1. *Active ingredients of the test preparations and acid consuming capacity (ACC) according to the U.S.P. XIXth test.*

| Active ingredients | Type | Unit dose | Admin. unit doses *in vivo* | ACC per 3 doses (ml) | ACC $g^{-1}$ (ml) |
|---|---|---|---|---|---|
| Aluminium hydroxide[1] | dried gel | 1 tablet = 600 mg | 3 | 455 | 253 |
| Aluminium hydroxide[1] | wet gel | 10 ml = 600 mg | 3 | 640 | 355 |
| Aluminium hydroxide magnesium carbonate[2] | co-dried-gel | 1 tablet = 450 mg | 3 | 387 | 287 |
| Aluminium hydroxide-magnesium carbonate[2] | wet gel | 10 ml = 450 mg | 3 | 380 | 281 |
| Hydrotalcite[3] | dried | 1 tablet = 500 mg | (2) 3 (4)* | 414 | 276 |
| Hydrotalcite[3] | suspension | 10 ml = 500 mg | (2) 3 (4) | 422 | 281 |

ACC: ml 0·1 N HCl ($S_x$ = 2 ml).

1. *Tablets.* Prepared acc. to the 'Formularium of Dutch Pharmacists' (abbrev. FNA) with dried aluminium hydroxide gel B.P. 1973 (Giulini Gmbh Ludwigshafen West Germany/ type A 211). ACC: 289 ml $g^{-1}$.
   *Liquid.* Aluminium hydroxide gel B.P. 1973, prepared with aluminium hydroxide compressed wet gel (Reheis Chem. Comp. Chicago-Illinois USA/ type F 1000).
2. *Tablets.* Regla pH (Union Chimique Belge-Belgium).
   *Liquid.* Prepared with aluminium hydroxide-magnesium carbonate compressed wet gel (Reheis Chem. Comp. Chicago-Illinois USA/ type F-MA 11).
3. *Tablets.* Ultacit (= Altacite/ Roussel UK).
   *Liquid.* Ultacit suspension dilution 1:1.

* One subject received 2, others 4 doses.

In vivo *antacid potency*

Thirty three of the subjects completed both phases of the randomized study. The results are shown in Fig. 1. and Table 2. In the aluminium hydroxide-magnesium carbonate group one subject showed a prolonged hypoacidity (pH >2,>120 min). Therefore we could not test the F-MA 11 liquid dosage

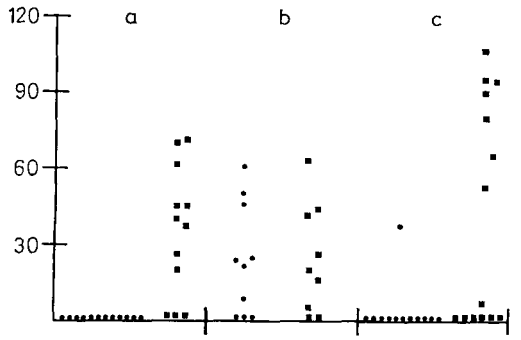


FIG. 1. Duration of action in min (pH > 3) for liquid (■) and tablet (●) antacids. Dose: 3 tablets or equivalent dose in liquid. Note: In the hydrotalcite group one volunteer received 2 tablets, and 5 volunteers received 4 tablets and equivalent dose in liquid.
(a)—Aluminium hydroxide ($P < 0.01$). (b)—F—MA 11, (N.S.). (c)—Hydrotalcite ($P < 0.05$). Ordinate: Duration of action in min (pH > 3).

form in the same experiment. In the hydrotalcite group two subjects were excluded because of nausea and vomiting.

Table 2. *pH values: mean ± s.e.m. (range).*

| | Aluminium hydroxide | Aluminium hydroxide-magnesium carbonate | Hydrotalcite |
|---|---|---|---|
| First base line pH | 1·2 ± 0·09 (0·9–1·9) | 1·1 ± 0·06 (0·8–1·4) | 1·1 ± 0·06 (0·8–1·7) |
| Second base line pH | 1·5 ± 0·11 (1·0–2·0) | 1·7 ± 0·06 (1·2–2·6) | 1·4 ± 0·15 (0·8–2·8) |
| pH max. Liquid | 3·7 ± 0·49 (2·6–5·0) | 3·3 ± 0·50 (1·6–6·0) | 3·5 ± 0·44 (1·3–6·8) |
| pH max. Tablet | 1·5 ± 0·13 (1·0–2·5) | 3·5 ± 0·53 (1·4–7·0) | 1·7 ± 0·20 (0·8–3·5) |

Fig. 1 shows the results in 12 subjects who received aluminium hydroxide in tablet and liquid form. Although the response to antacid therapy varied widely, there was a statistically significant difference in duration of action between the tablet and the liquid formula, measured by the interval of the pH rise above 2 as well as above 3 ($P<0·01$). Eleven of the volunteers did not show any effect after the administration of three aluminium hydroxide tablets. Aluminium hydroxide gel B.P. 1973 gave induced acid neutralization (pH>2) in all volunteers tested. This is in accordance with the *in vitro* results.

In the F-MA 11 group (Fig. 1) there was no significant difference between the liquid and tablet forms in duration of action (length of time pH>3 and pH>2). These results are also in agreement with those obtained in the *in vitro* study.

Hydrotalcite tablets (Fig. 1) failed to show any neutralizing effect. As well for the interval of pH increase above 3 and above 2, only in one subject could a short duration of action be demonstrated. The hydrotalcite suspension showed a great individual variation but the differences between the tablet and the liquid antacid were statistically significant: respectively $P<0·05$ for a rise above 3 and $P<0·01$ for a pH rise above 2.

## DISCUSSION

Opinions differ concerning the optimal intragastric pH for alleviation of epigastric distress due to acid-peptic agression. Many authors believe this to be in the pH 3–5 range. For that reason pH 3 was selected as optimal pH value for our *in vitro* experiments. The U.S.P. XIX *in vitro* test for measuring neutralizing properties, gives only information about the total acid consuming capacity within a fixed time interval for 1 h. It is however obvious that the *acid consuming rate* is of major importance for *in vivo* efficacy since the higher the neutralization rate, the less likely is the unconsumed antacid to be lost by gastric emptying, thereby lowering the overall *in vivo* acid neutralizing capacity. For this reason we also used the modified *in vitro* Schaub test, which simulates both gastric emptying and ongoing acid secretion. From these results it was obvious that an antacid with a high rate of neutralization has a much longer duration of action compared with one having a low neutralization rate (even with similar overall ACC). We were also able to demonstrate this *in vivo* (Brouwers & Klopper, 1976).

Aluminium hydroxide has some peculiar effects on gastric emptying, depending on its physicochemical properties. As shown by Hurwitz, Robinson & others (1976), aluminium hydroxide with a low rate of neutralization did not effect gastric emptying, whereas that with a high rate of neutralization, delayed gastric emptying in man, thus giving a longer duration of action. The aluminium hydroxide tablets used in the present study contained dried aluminium hydroxide B.P. 1973 with a moderately high *in vitro* rate of neutralization and ACC (ACC 289 ml $g^{-1}$). As previously shown (Brouwers & Tytgat, 1976) the degree of tablet compression affects both rate of neutralization and overall ACC. This may explain the lack of *in vivo* efficacy we found for aluminium hydroxide tablets compared with its suspension.

Aluminium hydroxide-magnesium carbonate (F-MA 11) has been extensively studied *in vitro* (Beekman, 1960; Playle & Llewellyn, 1974). The dried F-MA 11 has a high neutralization rate *in vitro* even after compression (Sjögren, 1965). Our study shows that clear differences in antacid properties between the liquid and tablet forms were observed *in vivo* confirming the *in vitro* data.

The *in vitro* neutralizing properties of hydrotalcite are comparable to those of F-MA 11. The main difference is the high carbonate content of F-MA 11, which amounts to 12% as $CO_2$. Despite similarity with *in vitro* results the *in vivo* data were different, showing an inferior neutralizing efficacy between the tablet and its liquid counterpart ($P<0·05$).

From a theoretical point of view there are two possible sources of error in our study: first there might be a variable and unknown vagal stimulation of acid secretion induced by the presence of the intragastric electrode. Second the response of the stomach upon submaximal pentagastrin infusion in our volunteers might be variable. We feel neither criticism invalidates our *in vivo* results for the follow-

ing reasons: Fordtran, Morawski & Richardson (1973) and Ekeved & Walan (1975) did not find any correlation between the basal acid output and maximum acid output and the duration of action of antacids. Their results suggest therefore, that gastric emptying is a major limiting factor of antacid therapy even in patients or volunteers with stimulated gastric acid secretion. In addition, the influence of gastric emptying time in this study was reduced because volunteers functioned as their own controls by taking the antacids in a randomized sequence in the same experiment. Moreover, continuous pentagastrin infusion was given to overcome any direct vagal stimulatory effect by superimposing a larger constant stimulus.

In conclusion, we have shown an obvious difference in the *in vivo* duration of action of antacids related to differences in the form of administration for two of the three preparations tested. It is particularly intriguing why F-MA 11 and hydrotalcite behave differently *in vivo* while showing almost the same *in vitro* neutralizing properties. Whether the carbonate content is important or whether the 'chewing factor' of the tablets is sufficient to explain the difference between the F-MA 11 and hydrotalcite forms of administration remains unclear. Incomplete chewing of the tablets has been proved *in vitro*, by artificial changes in particle change, to be important in explaining a failure of neutralizing capacity.

Recent studies show that histamine-$H_2$-receptor blockers will probably play a major role in the management of peptic ulcer disease. In many trials with cimetidine the patients are given a *tablet* antacid supplement (Bodemar & Walan, 1976; Gray, McKenzie & others, 1977). From the present study it would seem that antacids in liquid form are to be preferred because of the better *in vivo* efficacy.

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