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EVALUATION OF ANTACIDS IN MAN USING THE HEIDELBERG CAPSULE

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ABSTRACT

Thirteen commercially available antacids in tablet form were tested in healthy young volunteers using a transistorized miniature telemetric device (Heidelberg Capsule). After the radio transmitter capsule was swallowed, an alkali response test was performed, and two tablets of the antacid to be tested then administered. The recorded pH *versus* time curves were evaluated for onset of action defined as increase of pH to a value above 3, the maximum pH obtained, and the area under the pH *versus* time curve after the alkali response test and after administration of the antacid. For the latter one two areas were determined, the one above the base line and that above pH 5.5. It has been determined that to be effective in ulcer patients an antacid should bring the gastric pH to a value of 5.5 or above at which point the proteolytic enzymes are inactive. Only 9 of the 13 preparations

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resulted in pH above 5.5. Dividing the areas under the curve above the base line after administration of the antacid by the area under the curve obtained after the alkali test the extent of antacid capacity (E.A.C.) or "potency" of the preparation is obtained. Only four of 13 antacids resulted in an E.A.C. of more than twice that found during the alkali test.

INTRODUCTION AND PURPOSE OF STUDY

Antacids comprise a group of preparations extremely widely used: in 1971 $41.1 million in tablets were purchased (1), and, because of being a non-prescription item, were much advertised. Antacids are drugs expected to lower the hydrogen ion concentration of the gastric content, thus increasing the gastric pH. The pepsin activity in stomach fluid is optimal at pH 2-3. Since it is desirable for ulcer patients to control both pH and proteolytic activity, antacids should be able to increase the pH to at least about 3.

The human stomach produces approximately 3 ml of a 0.05 N-hydrochloric acid per min. during the hours of being awake (2) with a total production of about 1.5 l per day. However, the production and secretion of hydrochloric acid underlies large intersubject variation and varies even in the same individual under varying conditions (3). Due to these differences, opinions on evaluation of antacids vary widely among investigators. A large number of methods for the determination of gastric secretion (4-8) and evaluation of antacids using various *in vitro* and *in vivo* methods (3, 9-25) are reported in the literature.

The purpose of this investigation was to study with the use of the Heidelberg Capsule the pH *versus*

time profile upon P.O. administration of different antacids in man. The Heidelberg Capsule has been evaluated *in vitro* (26) and *in vivo* (21) for applicability of testing antacids and has been used in evaluation of such preparations (22, 23, 25). The Heidelberg Capsule is a high frequency transmitter encased in an indigestible polyacrylic capsule and designed to be swallowed. It operates at an average frequency of 1.9 MHz. The transmitted signal is picked up by a belt antenna, passed on to a receiver, and after amplification and transformation, recorded by a strip chart recorder.

EXPERIMENTAL

Thirteen antacid preparations in tablet form, purchased from pharmacies, were evaluated in the study. The study was carried out as a teaching experiment in which 34 healthy students (8 females, 26 males) participated. Any previous or present gastrointestinal disorder, hypo-or hyperacidity were exclusion parameters. No solid food or alcoholic beverages were allowed during the 2 hrs prior to the experiment. After activation of the Heidelberg Capsule with 0.9% sodium chloride solution and calibration in buffer solution at pH 1 and pH 7 at 37°C, the capsule, to which a silk thread* was attached, was swallowed with 50 ml of water by the fasted subject. The receiving antenna was tied around the belly. The impulses received by the antenna were fed to the Heidelberg unit**, decoded and recorded

*Deknatel Green Braided Tevdex, 79-413, Queens Village, N.Y.

**Telefunken, distributor: Electromedical Devices, Inc., Atlanta, Georgia

as pH versus time at a chart speed of 72 mm/hr. As soon as the capsule reached the stomach, the capsule was positioned by fixing the thread to the cheek using an adhesive tape to prevent loss of the capsule due to stomach emptying. The subjects were in a standing position throughout the experiment. As soon as a constant baseline of gastric pH was obtained the alkali response test was performed according to the method for antacid testing described by Nöller (27,28). For the alkali test 5 ml of a saturated solution of sodium bicarbonate was given P.O. followed by 50 ml of water at room temperature. The time needed for the pH curve to return to the baseline was observed. Subjects in which the baseline was reached in less than 5 min. or more than 20 min. were excluded from continuing in the experiment. For antacid testing two tablets of a given preparation were administered. The tablets were properly masticated and then swallowed followed by rinsing with 50 ml of water. The pH curve was recorded until it returned to the baseline. At the end of the experiment the thread was swallowed and the capsule excreted with the feces. Although a crossover design would have been desirable, this was not feasible for technical reasons. The preparations tested and their composition are listed in Table I (from 1).

RESULTS AND DISCUSSION

The individual pH versus time curves, of which a representative sample is shown in Fig. 1, were evaluated for time needed for the pH to rise from the baseline to pH 3, and for maximum pH obtained. The areas under the pH versus time curve from 0 to ∞ were determined for the curve obtained after the alkali test, for the curve obtained upon administration of

TABLE 1: Composition of Antacids Tested (1) mg per Tablet

Product	Calcium Carbonate	Aluminum Hydroxide	Magnesium Oxide or Hydroxide	Magnesium Trisilicate	Other	Sodium (29)
Aludrox		500				<5
Amphojel		600				<5
Basaljel		654				<5
BiSoDol	X		X	X	peppermint	0.036
Dicarbosil	489			6	magn.carb. 11, oil of peppermint	2.7
DiGel		X	X		magn.carb. X Simethi-cone 25	7
Gelusil		250		500	mint flavor alginates	5.1
Gelusil M		X	X	X	mannitol	6.1
Kolantyl		180	170			10
Maalox #1		+	+			1
Maalox #2		XX	XX			2
Mylanta		200	200		Simethicone 20	0.79
Rolaids					dihydroxy alum. Na carbonate 330	53

X Quantitative statement not provided
\+ Amounts listed as 400 mg combined hydroxides of magnesium and aluminum
XX Amounts listed as 800 mg combined hydroxides of magnesium and aluminum

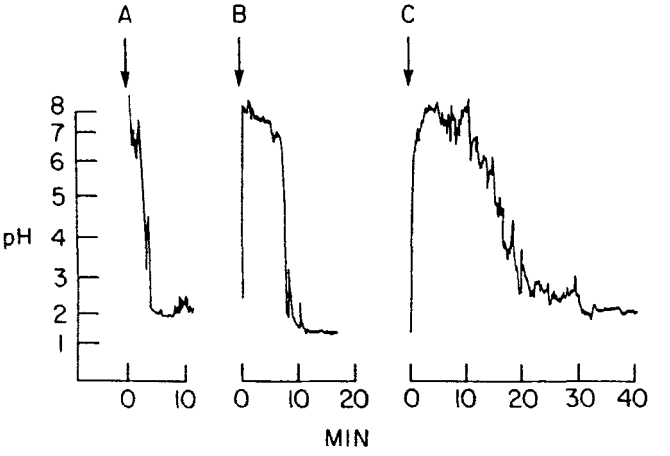

Fig. 1: Typical chart strip for Heidelberg Capsule pH versus time recording.
A = Heidelberg Capsule swallowed
B = Alkali test, administration of 5 ml of saturated $NaHCO_3$ solution
C = Administration of 2 tablets Kolantyl

the antacid for the portion above the baseline and for that portion of the curve above pH 5.5 using the trapezoidal rule. The data are listed in Table 2.

The opinions concerning which pH range comprises an optimal antacid effectiveness vary widely between investigators. In Table 3 the desirable pH ranges according to various investigators are listed. Since antacids are used to a large extent by ulcer patients, it is not only important to increase the pH to a value above that of the gastric fluid but to consider the activity of pepsin and cathepsin. The optimum for activity of pepsin is at pH 2-3 (13, 31). At a pH above 3 pepsin is practically inactive. The proteolytic enzyme cathepsin has its activity optimum at pH 3

to 4 (39). There is an overlapping of the activity curves of pepsin and cathepsin, hence, it has to be assumed that the gastric fluid has proteolytic activity between pH 1-5. Mutch (30), Henning (37) and Spegg (38) reported that the proteolytic enzymes are inactive only above pH 5 to 5.5, respectively. For this reason we determined the area under the pH versus time curve for that portion of the curve above pH 5.5. In order to obtain a relative measurement correlated for individual variation we calculated the extent of antacid capacity, E.A.C. for each preparation, according to equation 1.

$$EAC = \frac{AUC_{drug\ above\ baseline}^{o\to\infty}}{AUC_{alkali\ test}^{o\to\infty}} \qquad \text{Eq. 1.}$$

From the results listed in Table 2 it can be concluded that for all preparations but one, the time for onset of antacid effectiveness (time to reach pH of 3 upon P.O. administration of 2 tablets) is rather short being less than 1 min. up to 1.5 min. The total period of time above the baseline varies between 18 and 55.5 min. with maximum pH values ranging from pH 3.75 to 8.4. These results coincide well with the literature data that stomach acidity is reduced by antacids for a period of 20-40 min. (17). It would be of interest for further studies to follow the recommendation of Fordtran et al. (17) to administer the antacid one hour after a meal in order to prolong the duration of antacid activity. However, this was not feasible in our experimental design, because of the requirement for a standardized meal.

Only one preparation reached a pH of 8 while 9 of the 13 preparations resulted in a pH above 5.5. Since

TABLE 2: Effectiveness of Antacid Preparations Tested

Product	N	Alkali Test $AUC^{0\to\infty}$ ± S.D.	Onset [Min.]	time above Baseline [Min.] ± S.D.	Max. pH ± S.D.	$AUC^{0\to\infty}$ above Baseline [pH•Min.] ± S.D.	$AUC^{0\to\infty}$ pH>5.5 [pH•Min.] ± S.D.	Extent of Antacid Capacity
Aludrox	3	22.5 ± 10.5	5.8 ± 6.33	36.0 ± 11.3	3.75 ± 1.0	21.875 ± 5.0	0	0.97
Amphojel	2	45.0 ± 29.8	<1	40.0 ± 8.2	5.0 ± 0.3	78.5 ± 15.5	0	1.744
Basaljel	3	71.41 ± 29.1	<1	46.3 ± 9.0	5.8 ± 0.7	65.58 ± 36.6	0.33 ± 0.28	0.918
BiSoDol	2	60.0 ± 10.0	<1	18.0 ± 3.5	6.5 ± 0.1	75.46 ± 14.3	9.25 ± 0.35	1.25
Dicarbosil	5	46.56 ± 33.4	<1	44.4 ± 13.75	5.8 ± 0.5	99.275 ± 19.9	1.1 ± 1.59	2.132
DiGel	3	48.75 ± 15.9	<1	26.8 ± 15.0	6.75 ± 0.37	91.166 ± 32.5	13.75 ± 5.72	1.87
Gelusil	3	88.75 ± 8.8	<1	39.0 ± 10.4	6.75 ± 1.1	90.125 ± 17.75	8.33 ± 10.58	1.015
Gelusil M	5	40.8 ± 29.6	<1	30.0 ± 10.0	7.1 ± 0.85	92.5 ± 33.6	12.375 ± 9.12	2.267
Kolantyl	4	51.58 ± 21.2	<1	41.0 ± 10.0	8.0 ± 0.5	142.8 ± 31.3	20.375 ± 10.5	2.768
Maalox #1	3	72.33 ± 6.7	<1	36.6 ± 17.9	7.4 ± 0.57	109.83 ± 47.7	11.5 ± 8.04	1.518

Maalox #2	3	36.25 ± 5.3	<1	55.5 ± 5.5	7.3 ± 0.36	148.98 ± 31.38	24.166 ± 16.0	4.109
Mylanta	3	50.0 ± 35	1.5	22.3 ± 5.65	5.2 ± 0.29	29.58 ± 6.8	0	0.59
Rolaids	3	53.75 ± 44.1	<1	21.6 ± 5.2	5.8 ± 0.76	26.73 ± 11.5	1.0	0.49

TABLE 3: Desirable pH Ranges for Antacids According to Various Investigators

Desirable pH Range	References	
2-4	Mutch	30
2.5-4.5	Rosett et al.	9
3.5-4	Gill et al.	31
3.5-4	Johnson et al.	12
3.5-4	Holbert et al.	32
3-5	Fuchs	3
4-5.5	Kirsner et al.	33
4-6	Naimark	34
3-5.5	Packman et al.	35
4-4.5	vanArkel	36
3-5	Beekman	15
>5	Henning	37
2-5	Berg et al.	18
>3	Kutter et al.	23
2.5-4.5	Fürst et al.	20
>3	Fordtran et al.	17
>5.5	Spegg	38
>3.5	Federal Register	43

the integration of the pH versus time curve, expressed as area under the time curve, is a measurement of extent of antacid effectiveness, it allows an overall evaluation of a given preparation. Based on our limited number of subjects for each preparation, the products with the highest E.A.C.'s were Maalox #2®, followed by Kolantyl®, Gelusil M® and Dicarbosil®. These preparations should not only be effective as antacids but also as antiproteolytic agents. This study carried out in healthy volunteers constitutes a bioavailability study.

However, other factors than E.A.C. have to be considered, too, in the choice of an antacid. Fordtran et al. (24) state that cost, taste, salt content, bowel habit, underlying deseases, other than peptic

ulcer, and side effects are also important. Capper et al. (40) found wide variation in the pH fields of the gastric mucosa between patients suffering from pyloric stenosis and chronic gastric ulcers. Often anticholinergic agents are used together with antacids. Atropine inhibits only the extraganglionic hypersecretion (41). In the presence of inflammatory processes of the gastric submucosa atropine may enhance secretion. Therefore, gastric secretion is inhibited in a normal peptic ulcer, whereas secretion is increased in the acute peptic ulcer. Also not considered in our study was the possibility of acidic rebound which may be caused by different preparations. In this respect preparations containing magnesium trisilicate may be superior to salts containing carbonates (42).

However, the study indicates that there are not only individual variations of the response of antacids but that there are also large differences between the products tested.

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