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APPLICATION OF THE PERISTALTIC IN VITRO ASSEMBLY TO GASTRIC ACID NEUTRALIZATION BY LIQUID ANTACIDS: A PRELIMINARY REPORT

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ABSTRACT

The utility of the peristaltic in vitro assembly is further demonstrated in a gastric acid neutralization study involving a liquid antacid formulation, a placebo and a group of hypersecretory subjects. By adding an acid delivery system to the assembly to simulate gastric acid secretion and using dilute hydrochloric acid as the reaction medium, hydrogen ion concentration-time plots were obtained which were comparable to their in vivo counterparts.

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INTRODUCTION

The predictive in vivo capability of the peristaltic in vitro assembly has been demonstrated in a series of drug dissolution and absorption correlation studies conducted on formulation variables and their effect on drug release performance from tablets or capsules. Drugs for which excellent in vitro in vivo correlations have been obtained to date are: tolbutamide (1,2), meprobamate (3), prednisone (4), ibuprofen (5), allopurinol (5), furosemide (6), carisoprodol (6), chlorpropamide (6), haloperidol (6) and flurazepam (6).

The purpose of the present study was to broaden the scope of the peristaltic in vitro assembly and extend the in vitro in vivo correlations to include alumina and magnesia oral suspensions whose in vivo response, i.e., effect on gastric acidity, is measurable directly in the stomach. Hydrogen ion concentrations [H^+] expressed as milliequivalents per liter (meq/L) following placebo and antacid administration were compared at fifteen minute intervals during a two hour time period in a modified peristaltic assembly and in a combined group of hypersecretory duodenal ulcer patients and normal volunteers.

EXPERIMENTAL

In Vivo Study[1]:

Five duodenal ulcer patients and three normal volunteers who had a peak output in response to pentagastrin of greater than

[1]This study was performed by Dr. John S. Fordtran, Baylor School of Medicine, Dallas, Texas (see reference 8).

30 meq/L were selected for the study. No gastric antisecretory drugs were ingested for at least one week prior to the study. Informed consent was obtained from each subject.

After a fast of 10 hours, the subjects were fed a standard meal consisting of five ounces of cooked ground steak, one piece of toast and butter and ten ounces of water. Each subject received on different test days either 30 mL of an antacid suspension formulation (200 mg each of aluminum and magnesium hydroxides and 25 mg of simethicone per 5 mL) or 10 ounces of water as placebo and adhered to the following regimen. The meal was consumed between 8 and 8:20 am. At 8:30, a nasogastric tube was inserted into the stomach under fluoroscopic control. At 8:59, a sample of gastric contents was removed, the pH determined and the sample returned to the stomach. At 9 am or approximately one hour after the start of the meal, the medication was administered. Each gastric sample was analyzed immediately for pH and then returned to the stomach via the nasogastric tube. pH values for each sample were transformed to $[H^+]$ according to the method of Moore and Scarlata (7). Results are presented graphically in Figure 1.

In Vitro Study

Equipment and Materials

1. Peristaltic in vitro assembly (1)
2. Two-speed proportioning pump[2] (AA/I autoanalyzer).
3. SMA flow rated tygon pump tubings[2], delivery rate 1.0 mL/min. - P/N 116-0549-P11.

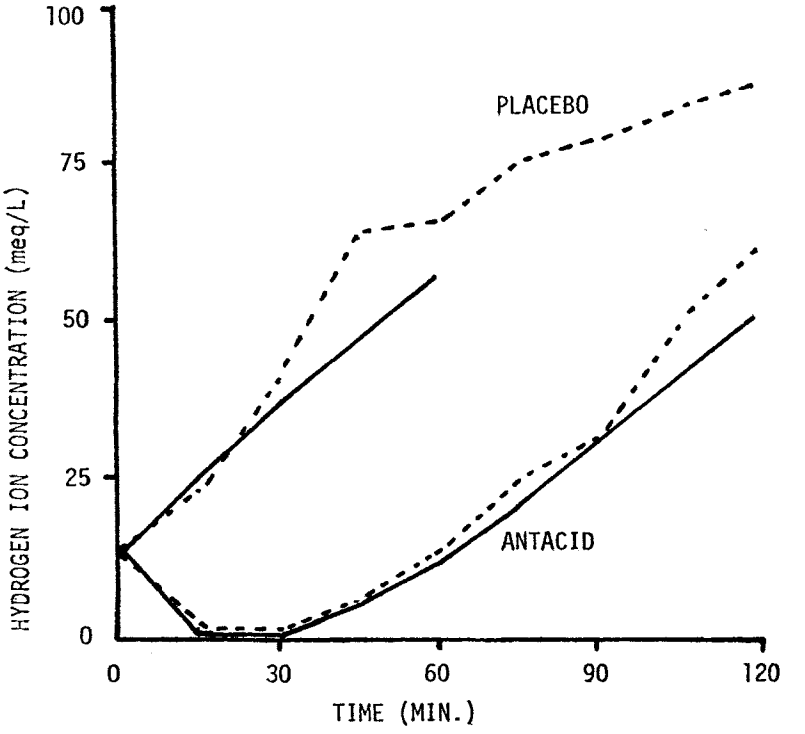

Figure I: Hydrogen ion concentration versus time plots for placebo and antacid: —— in vitro, --- in vivo

4. Tygon transmission tubing[2], P/N 116-0528-P01.
5. Polyethylene plastic nipples[2], double end, N9, P/N 116-0010-P01.
6. Accumet pH meter[3], model 291.
7. Laboratory combination pH electrode[4], Futura style # 39503.
8. Disposable 50 lambda pipets[3].

[2] Technicon Instruments Corporation, Terrytown, NY 10591
[3] Fisher Scientific Co. Ltd., Montreal, Quebec, H4P 2L4
[4] Beckman Instruments Inc., Fullerton, CA 92634

9. Stopwatch.

10. Acculute[5], concentrated hydrochloric acid for dilution.

Assembly

The peristaltic in vitro assembly is operated under the same conditions described previously (1) except that the reaction medium is hydrochloric acid (0.01N, 800 mL). To the proportioning pump, two flow rated pump tubings are secured into the central channels of the proportioning pump manifold. Each pump tubing is extended via nipple connectors with an inlet (54 cm) and an outlet (45 cm) transmission tubing. Lambda pipets are inserted at the exit points of the outlet tubings. The ends of the two inlet tubings are immersed in graduate cylinders (100 mL) containing 1N and 0.5 N hydrochloric acid. Flow rates (0.95 mL/min.) were determined prior to each run. An acid delivery solution which is not being used during the in vitro procedure is simply recycled back to its container. The electrode is placed in the reaction medium so that it is positioned 6.5 cm from the bottom of the beaker and approximately 5 cm removed from the delivery pipet. The latter is secured vertically to the glass U-tube of the peristaltic apparatus with the tip approximately 4.5 cm from the surface of the medium.

Procedure

After the reaction medium (0.01N hydrochloric acid, 800 mL) and acid delivery solutions (0.5 N and 1.0 N) are equilibrated to

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[5] Anachemia Chemicals Ltd., Montreal, Quebec, H8S 2T2

37°C, the electrode is positioned in the medium and the pH meter and peristaltic assembly are switched on. The system is allowed to stabilize for a few minutes and the pH recorded. Thirty milliliters of the antacid formulation was added to the reaction medium and the proportioning pump turned on immediately in order to initiate the 1 N acid delivery solution. After forty minutes, the acid delivery solution is changed to 0.5 N hydrochloric acid for the duration of the experiment. The same procedure was utilized in the absence of antacid (e.g., placebo) except that 0.5 N acid delivery solution was used throughout the experiment and differed from the in vivo study in that ten ounces of water was not added to the reaction medium. pH was recorded at appropriate time intervals and transformed by a logarithmic equation to $[H^+]$. Results are presented graphically in Figure I.

RESULTS

In Vitro In Vivo Correlation:

In vitro and in vivo results are presented graphically in Figure I. The placebo in vivo response revealed an increase in $[H^+]$ from 13.8 to 87.2 meq/L during the two hours after water administration or an approximate gastric acid secretion rate of 0.5 meq per minute. In vitro simulation was easily achieved by using 0.01 N hydrochloric acid at 37°C as reaction medium and the 0.5 N acid delivery solution operating at a flow rate of approximately 1 milliliter per minute. The procedure was terminated at 60 minutes. Linear regression analysis of the combined data (Table I) at corresponding 15 minute intervals to

TABLE I

A COMPARISON OF IN VITRO IN VIVO DATA FOR PLACEBO AND ANTACID

	HYDROGEN ION CONCENTRATION (meq/L)			
TIME	PLACEBO		ANTACID	
(mins)	IN VITRO*	IN VIVO+	IN VITRO*	IN VIVO+
0	12.31	13.85		
15	25.32	24.20		
30	37.16	40.73	0.34	1.53
45	47.13	62.63	5.07	6.19
60	57.54	65.44	12.15	13.29
75			21.24	24.70
90			31.15	30.88
105			41.24	49.75
120			50.93	60.60

*Average of 3 runs

+Average from 8 subjects

60 minutes demonstrated a good fit with a correlation coefficient of 0.979.

In vivo results for the antacid formulation revealed an immediate decrease in $[H^+]$. This effect was maintained for approximately 30 minutes at which time the $[H^+]$ increased at a rate corresponding to that obtained with the placebo. Attempts

to duplicate these results in vitro with the 0.5 N acid delivery solution were unsuccessful. In order to simulate the in vivo response, it was necessary to employ the 1 N delivery solution for 40 minutes and then change to 0.5 N for the duration of the experiment. Statistical treatment was confined to linear regression analysis of the combined data (Table I) from 30 to 120 minutes or the time period corresponding to duration of antacid activity and again a good fit ($r = 0.992$) was demonstrated.

In Vitro Evaluation of Commercial Antacid Suspensions

Six antacid suspensions containing amounts of aluminum and magnesium hydroxides equivalent to the antacid formulation used in the correlation study were purchased on the Canadian market and treated to the in vitro procedure described above. $[H^+]$ values at 120 minutes are recorded in Table II. Of particular interest was A because of published in vivo data on the simethicone-free product. In a dose-response study performed on Maalox in hypersecretory duodenal ulcer patients, Fordtran (8) observed $[H^+]$ values of 37, 24 and 12* meq/L at 120 minutes after administration of 15, 30 and 60 mL, respectively. In vitro values of 39.8, 22.8 and 0.4 meq/L were obtained at the same time period for similar volumes of A by utilizing the appropriate acid delivery solutions.

Some interproduct differences were observed in this limited in vitro study. Product F settled to the bottom of the beaker as

* In a separate experiment, the author found a value of ~3 meq/L at 2 hours for 60 mL of this antacid.

TABLE II

IN VITRO COMPARISON OF COMMERCIAL ALUMINA AND MAGNESIA ORAL SUSPENSIONS[a]

PRODUCT	MG/AL HYDROXIDES PER 5 mL (mg)	VOLUME (mL)	TOTAL ANTACIDS (mg)	OPERATING TIME FOR ACID DELIVERY SOLUTIONS (min) 1 N	0.5 N	$[H^+]$ AT 120 MIN. (meq/L)[b]
A	200/228	15	1284	0	120	39.8 (38.9-40.7)
		30	2568	40	80	22.8 (20.4-24.0)
		60	5136	120	0	0.4
B	200/200	30	2400	40	80	14.8 (13.8-15.8)
C	200/200	30	2400	40	80	36.1 (32.3-39.8)
D	400/400	15	2400	40	80	32.9 (31.6-33.9)
E	400/450	15	2550	40	80	24.0
F	400/400	15	2400	40	--	40.7

a - Products and lot numbers (manufacturer): A, Maalox Plus 22398 (Rorer), B, Diovol, 9I 112 (Horner); C, Mylanta, HL 115 (Parke Davis); D, Mylanta-2 JM 156 (Parke Davis; E, Hycon MA 0892T (ICI); F, Gelusil - 400, KA 119 (Parke Davis)

b - Average of 3 runs with ranges or single runs

an intact mass and failed to disperse through the reaction medium. Testing was terminated at 40 minutes when the $[H^+]$ had already reached 40 meq/L.

DISCUSSON

The results obtained in this study has provided additional assurance for the impression that the hydrodynamic conditions existing in the peristaltic in vitro assembly are similar to those generated by the gastro-intestinal musculature. This impression evolved from results of drug dissolution and absorption correlation studies conducted on solid oral dosage forms (1-6). Both beagle dogs and human volunteers served as in vivo models. In each study, a direct relationship existed between percent dissolved plots at t minute intervals and plasma or serum drug concentration-profiles at 3t minute intervals. The larger time factor for determining the in vivo response is accounted for by the delay due to the drug absorption and distribution processes occurring after in vivo dissolution.

The opportunity to test an oral medication which could result in an in vitro in vivo correlation at identical time intervals was made possible several years ago. An antacid suspension containing aluminum and magnesium hydroxides was formulated as a potential product candidate and submitted to Dr. Fordtran for an in vivo evaluation versus placebo (water). The antacid performance was disappointing especially when the results were compared with published in vivo data (8) on a chemically similar marketed product. These findings plus the inability of

an official acid neutralizing capacity test (9) to differentiate between formulation variables of antacid liquids posed a serious problem for the product development program. An evaluation of other published neutralization procedures was beyond the scope of this report. With its successful application in drug dissolution and absorption correlation experiments established, a decision was made to investigate the applicability of the peristaltic in vitro assembly to the acid neutralization field. Since $[H^+]$ versus time plots were available from the in vivo study for the placebo and antacid, it required a simple modification of the assembly in order to simulate the gastric environment and obtain corresponding in vitro plots. An extension of the work to Maalox and other similar liquid antacids on the Canadian market reaffirmed the validity and discriminatory feature of the in vitro method. These results enhanced the status of the assembly for future optimization studies of antacid formulations.

The controlled in vitro procedure described in this report was adopted from a single in vivo study and is applicable to a group of subjects who display rapid gastric acid secretion rates. Obviously such a group is desirable for comparative evaluation of antacid products.

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