of KCNS would indicate the presence of forces other than those responsible for aggregation to account for increases in molecular weight.

In our next and final paper in this series we will show experimental data which indicate that molecular weight changes in the two fractions studied occur through a free radical mechanism.

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Antacid Properties of Calcium, Magnesium, and Aluminum Salts of Water-Insoluble Aliphatic Acids

By STUART P. ERIKSEN†, GEORGE M. IRWIN, and JOSEPH V. SWINTOSKY

The antacid properties of several calcium, magnesium, and aluminum salts of aliphatic acids were studied. A number of the salts showed potential antacid properties *in vitro*. Of this group calcium laurate also showed promising results by *in vivo* tests in dogs and humans. Along with their acid-neutralizing capacity, higher molecular weight metal salts have several interesting physical properties, for example, their insolubility in aqueous fluids above approximately pH 5, and their neutralizing properties below this pH. They tend to float on the surface of solutions and cling to the walls of a container before they react with acidic solutions. Following reaction with hydrochloric acid, salts of higher molecular weight aliphatic acids form insoluble aliphatic acids which are reputed to retard emptying of stomach fluids. A possible drawback to the higher molecular weight salts is a lower weight-to-weight antacid capacity when compared to antacids such as calcium carbonate and aluminum hydroxide.

ALKALI AND ALKALINE earth metal salts such as carbonates, bicarbonates, and glycinates have been of considerable use over the years as antacids. They possess the ability to neutralize the acid of the stomach efficiently but in some cases replace it with a considerable concentration of hydroxide ion. Recently, the authors have investigated the antacid properties of a series of metal-organic acid salts. It appeared from consideration of their physical properties that these substances might be useful antacids with interesting "secondary" properties. The *in vitro* and *in vivo* studies of these metal salts are reported in this paper.

The calcium, magnesium, and aluminum salts of long chain aliphatic acids possess several interesting properties which might counterbalance their high equivalent weight (low acid-combining power). Since they are essentially non-wetted, they tend to float on aqueous solutions, coat wet surfaces, and offer the possibility of good protective action. They react with acid only below a characteristic pH, depending on the compound. Because the acid product of the neutralization reaction is poorly dissociated and is often relatively water-insoluble, we may consider these metal salts as hydrogen ion-exchange compounds—hydrogen and metal ions being in equilibrium with the two solid forms according to the equation

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TABLE I.—ANALYSIS AND SOURCES OF ANTACID MATERIALS STUDIED

Compound[a]	Manufacturer	Analysis[b] Metal, %	Acid, %	Solvent, %
A. Commercial Compounds				
1. Calcium stearate	Matheson Coleman and Bell	100.5	95.5	2.8
2. Calcium 12-hydroxy stearate	Baker Castor Oil Co.	102.5	93.5	0.8
3. Aluminum mono-12-hydroxy-stearate	" " " "	[c]	74.2	3.7
4. Aluminum di-12-hydroxystearate	" " " "	[c]	89.6	2.6
5. Aluminum tri-12-hydroxystearate	" " " "	90.8	98.2	1.7
6. Magnesium 12-hydroxystearate	" " " "	66.6	92.8	2.7
B. Synthesized Compounds				
7. Calcium pelargonate		96.0	81.8	4.5
8. Calcium caprate		94.8	89.8	3.9
9. Calcium laurate		90.5	90.6	3.7
10. Calcium myristate		85.7	86.0	2.6
11. Calcium palmitate		92.3	91.1	3.3
12. Magnesium laurate		99.3	78.6	[d]
13. Magnesium myristate		84.6	86.3	[d]
14. Aluminum laurate		92.4	88.3	[d]
15. Calcium azelate		86.5	92.0	2.0
16. Calcium sebacate		88.4	92.9	3.0

[a] Compounds 1–6 were purchased from the manufacturers and used without purification. Compounds 7–16 were synthesized by mixing aqueous solutions of the metal chlorides and the sodium aliphatic acid soaps. The precipitated products were then washed with water and air-dried. The free acids were obtained from the following manufacturers: pelargonic, Emery Ind., Inc.; myristic, Foremost Food and Chemical; all others from Matheson Coleman and Bell. Seven other compounds were studied—aluminum hydroxide, calcium hydroxide, calcium carbonate, calcium citrate, magnesium oxide, magnesium trisilicate, and magnesium stearate. These were obtained as U.S.P. grade materials and used without further purification or analysis. [b] Solvent was calculated as per cent weight loss on drying 5 hours at 110° C. Metal determinations were done by standard EDTA titration. Acid determinations were made by titration of acid-ether extraction residue. [c] Other metals than aluminum also present. [d] Solvent not determined.

$$H^+ + \text{metal salt (solid)} \rightleftarrows \text{metal ion} + \text{organic acid (solid)}$$

The pH at which some of these salts exert their buffering effect is in the optimum range (below pH 4 to 5) for effective antacid action (1). They are essentially odorless, tasteless, and innocuous; many of the aliphatic acids are natural constituents of foodstuffs (2). Finally, the low density and poor wettability of some of these salts might decrease the efficiency with which they are emptied from the stomach (through floating and adhering to the moist stomach lining), which would result in a prolongation of antacid action.

It was our intention to study the relative reaction rates of various of these metal-aliphatic acid salts in dilute hydrochloric acid as a function of the metal ion and the chain length of the aliphatic acid used in an effort to find a candidate of sufficient potential to warrant an *in vivo* test of the ideas suggested above.

EXPERIMENTAL

Materials Used.—Pertinent data concerning the analysis and source of the compounds studied are tabulated in Table I.

pH Recording Systems.—All pH measurements were made with a Photovolt line operated pH meter, model 110, altered to permit recording on a 10 mv. Brown potentiometric recorder. The span of the recorder was adjusted to match the meter scale.

Studies in Vitro.—Studies were carried out in a 100-ml. beaker stirred at about 150 r.p.m. with a magnetic stirrer. Acid was added with a screw-driven 5-ml. hypodermic syringe at a rate of 0.23 ml. of 1.75 *N* HCl per minute (equivalent to 4 ml. 0.1 *N* HCl per minute[1]). The steps in the *in vitro* testing procedure were

1. Fifty ml. of 0.1 *N* HCl were put in the beaker and pH recording begun.
2. Five Gm. of antacid was added to the stirring acid[2] as either a powder or a glycerin-wetted suspension.
3. The pH was allowed to rise to equilibrium.
4. Acid addition was begun and continued (never longer than 30 minutes) until a trend was established.
5. The curve was evaluated using the following performance factors: (*a*) delay time, (*b*) static equilibrium pH, (*c*) dynamic equilibrium pH. The definitions of these performance factors and the methods for obtaining them are illustrated in Fig. 1.

Studies in Vivo.—Beckman glass stomach electrodes (type x800-22) were modified and used to record gastric pH and the changes caused by ingested antacid in humans and dogs. A polyethylene shield (as suggested by Harrisson, *et al.* (3),) was added to protect the tip of the glass electrode. The calomel half-cell made contact with the stomach contents through a saturated KCl-soaked thread held alongside the glass electrode lead. A fine polyethylene tube[3] (containing the KCl-soaked thread together with glass-electrode lead) was pulled through a larger polyethylene tube,[3] and the end of the thread allowed to hang out of this outer tube just above where the latter was seated on the glass electrode tip. The end of the thread and tube external to the patient was held in the side arm of a standard saturated-calomel half-cell with a small

[1] It was observed that 0.1 *N* HCl and U.S.P. simulated gastric fluid (1) gave the same results, so that for simplicity we chose to use 0.1 *N* HCl.

[2] The exact amount added is not important, provided an excess is present; however, it must be in an immediately dispersable form. (See *in vivo Studies* for powder information.)

[3] Adams Intramedic tubing, PE No. 160 and No. 340.

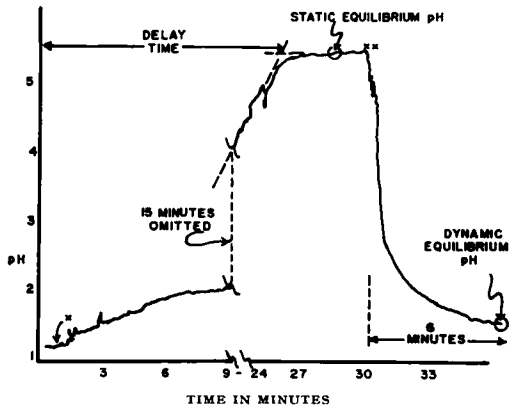

Fig. 1.—Antacid evaluation curve for magnesium stearate showing the points used to estimate the three antacid performance factors described in the text. ×, Time at which more than sufficient antacid was added to react with all of the HCl in the beaker. ××, Time at which HCl was added to stirred contents of beaker at a rate equivalent to 4 ml. 0.1 *N* HCl per minute.

cork stopper. Figure 3 is a drawing of the complete electrode system.

In vivo studies were carried out on human volunteers and anesthetized dogs. The measurement procedure used was essentially that described by Harrisson, *et al.* (3), where each subject served as his own control. Stomach pH was measured after 8 hours of fasting. (Water was given if needed.) Then the pH effects of a swallowed or intubated dose of antacid were recorded. The following suspension formula was used for all studies of powdered antacids: metal salt (5.0 Gm.), glycerin (7.0 ml.),[4] and water (30.0 ml.).

RESULTS AND DISCUSSION

The speed of response to added acid is essentially a measure of the rate of reaction with acid. If potentially longer-acting antacids are to be tested it is important that such rate of reaction studies not be done with concurrent removal of sample (simulated stomach emptying), *i.e.*, any antacid intended for prolonged action must be maintained in the stomach for the duration of its effect, either by some physical property of its own, or through special formulation.

The *in vitro* test used in this study is limited to the determination of reaction rates under two pH stresses, *i.e.*, "maximum stress" (pH 1) and "maximum rate of acid flow" (4 ml. of 0.1 *N* HCl per minue (4)). If reasonable stresses were used, it was expected that limits of response for each antacid could be observed *in vitro*, which would then correlate well with *in vivo* pH's as measured with the swallowed gastric glass electrode and would be true indications of the antacid utility of the compounds studied.

Figures 1 and 2 are tracings of pH *vs.* time records for aluminum hydroxide, calcium pelargonate, and magnesium stearate, showing the general shapes of the tracings and how the performance factors were determined. Using the performance factors shown in Fig. 1, 24 compounds were evaluated—six "simple" metal salts and hydroxides, and 18 aluminum, calcium, and magnesium salts of mono- and dicarboxylic acids of various chain lengths. The results of these *in vitro* studies are tabulated in Table II. The compounds studied show widely varying rates of reaction in acid of pH 1, the delay time for attaining static equilibrium ranging from several seconds to periods in excess of 30 minutes. The aluminum salts showed much slower rates of reaction than those of magnesium and calcium. The appearance of some rapid neutralizing effect by aluminum mono-12-hydroxystearate must be considered in the light of the presence of some other metal than aluminum (see Table I). Calcium and magnesium salts show much higher and more useful rates of reaction in acid, although the stearates in both cases seem to react slowly. All the so-called "simple" substances (hydroxide, carbonate, citrate, and trisilicate) show rapid rates of reaction. As one might expect, increase in the acid chain length slows reaction rates, though not always markedly. Dicarboxylic salts up to ten carbons show essentially the same reaction rate as the mono-basic acids.

Delay times are affected to some degree by factors such as rate of stirring, particle size, water solubility of the antacid, and degree of wetting. Although particle size may have been somewhat variable among these compounds, an effort was made to keep the rate of stirring constant and to wet the

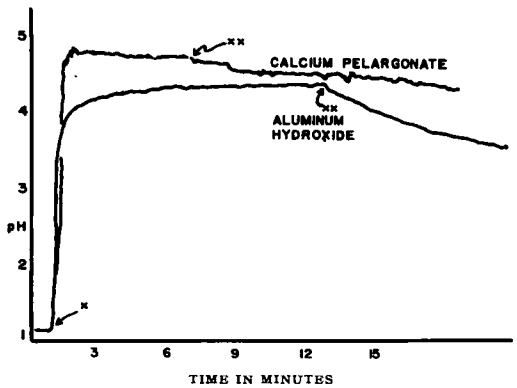

Fig. 2.—Antacid evaluation curves for aluminum hydroxide and calcium perlargonate. ×, Point of antacid addition. ××, Point at which acid input was started.

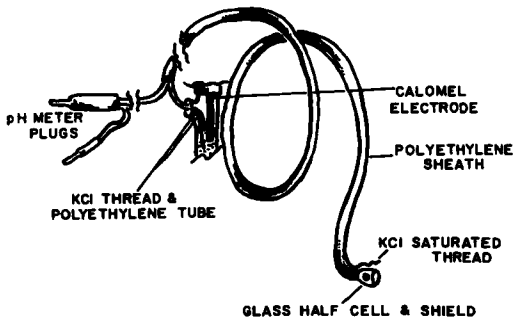

Fig. 3.—Diagram of the modified *in vivo* gastric electrode.

[4] Twenty-one ml. of glycerin was required for calcium stearate.

TABLE II.—*In Vitro* PERFORMANCE FACTORS FOR VARIOUS ANTACID SUBSTANCES

Antacid	Delay Time, Min.	Static Equilibrium, pH	Dynamic Equilibrium, pH	Dose in Gm. Calcd., 100 Min. Effect[a] 4 ml./min.	1 ml./min.
Aluminum hydroxide	<1	4.5	3.8	1.2	0.4
Calcium hydroxide	<1	12.6	12.6	1.7	0.6
Calcium carbonate	<1	5.7	5.3	2.3	0.8
Calcium citrate	<1	3.5	3.3	4.3	1.4
Magnesium oxide	<1	10.1	9.9	0.9	0.3
Magnesium trisilicate	<1	6.4	4.9	7.9	2.6
Calcium pelargonate	<1	4.8	4.6	8.0	2.7
Calcium caprate	<1	4.8	4.6	8.6	2.9
Calcium laurate	<1	4.8	4.5	9.9	3.3
Calcium myristate	1.0	4.8	4.5	11.1	3.7
Calcium palmitate	1.2	4.8	4.4	12.4	4.1
Calcium stearate	5.7	4.7	4.4	13.6	4.5
Calcium 12-hydroxystearate	2.3	5.0	4.5	14.3	4.8
Aluminum laurate	>30	...	...	9.4	3.1
Aluminum myristate	>30	...	...	10.6	3.5
Aluminum mono-12-hydroxystearate	26	3.0	1.8	5.4	1.8
Aluminum di-12-hydroxystearate	>30	...	...	9.6	3.2
Aluminum tri-12-hydroxystearate	>30	...	...	13.9	4.6
Magnesium laurate	<1	5.6	5.4	9.5	3.2
Magnesium myristate	<1	5.7	5.5	10.8	3.6
Magnesium stearate	26	5.5	1.4	13.3	4.4
Magnesium 12-hydroxystearate	4	6.1	2.5	14.0	4.7
Calcium azelate	<1	4.6	4.4	5.1	1.7
Calcium sebacate	<1	5.0	4.8	5.4	1.8

[a] Calculated on the basis of 50 ml. 0.1 *N* HCl residual acid plus 1 or 4 ml. of 0.1 *N* HCl secretion per minute for 100 minutes.

powders uniformly before determining the pH *vs.* time records.

The static equilibrium pH's reflect the pKa of the acid and the properties of the metal ion produced by neutralization. For aluminum salts the static pH's are about 3, for calcium 4.8, and for magnesium 5.5. The dynamic equilibrium pH's follow the delay times as expected; *i.e.*, where there are long delay times dynamic pH values are also low, which indicates slow response of the compound to added acid. The static pH values indicate the maximum pH's that the antacid is able to create in the stomach, while the dynamic values give an indication of the ability of an antacid to respond to stomach secretions—essentially its ability to maintain pH under high rates of acid secretion. While varying with stirring, wetting, and particle size, the dynamic equilibrium pH's are also functions of the rate of acid addition chosen. The maximum rate currently suggested (4) was selected to set a lower limit on antacid capability. The dynamic equilibrium value desired in these studies was that pH at which the rate of acid neutralization equals the rate of acid addition under a standard set of conditions. For practical reasons (sticking, clumping, etc.) this point is difficult to observe, and the pH after 6 minutes of acid addition was selected as the dynamic equilibrium value. This is recorded in Table II to permit ranking of compounds.

The final two columns of Table II are included to give an idea of the relative dose sizes of these compounds required to maintain pH at a value greater than 2 for 100 minutes under two extremes of acid production or addition (1 and 4 ml./min.).

Current opinion (1) suggests that an effective antacid should be capable of maintaining the stomach pH between 2–5. One might then conclude that compounds yielding static equilibrium and dynamic equilibrium pH's outside this range would be inferior antacids; calcium hydroxide and carbonate, magnesium oxide, tri-silicate, laurate, and 12-hydroxystearate have static pH's that fall outside this range by our test procedure.

From the table one would select calcium pelargonate, azelate, or sebacate as having optimum characteristics, *i.e.*, relatively low dose, fast onset, rapid response, and low static pH (to prevent the possibility of "acid rebound").[5] In selecting the acid moiety to be used in conjunction with the metal, an acid of low toxicity and volatility and of moderately short chain length is desirable.[6] Minimal volatility is desirable to avoid taste and odor from the free acid formed during the *in vivo* neutralization reaction. Aliphatic acids of less than 12 carbon atoms are liquid at body temperature and have disagreeable odors. The 12-carbon lauric acid is solid at body temperature and is virtually free of odor, and its calcium salt is an antacid with properties making it a potentially useful antacid. Thus, calcium laurate was selected for *in vivo* studies with calcium carbonate as the control.

In order to circumvent any membrane potential error, which the authors and others (6, 7) have observed to amount to about 30 mv. or $^1/_2$ pH unit, *in vivo* studies were not done with the calomel cell on the arm (3) or in the mouth. Direct calomel contact with the gastric contents, even by such elementary means as we have described, permits true pH values to be obtained inside or outside the body.

A summary of the data obtained from *in vivo* studies on three dogs and three humans is shown in Table III. Two conclusions may be drawn from these *in vivo* tests: (*a*) calcium laurate is an effective antacid, and (*b*), though its duration appears to be

[5] We could not demonstrate "rebound" in any of our studies on dogs and humans.

[6] Though the toxicity of azelaic and sebacic acids is not well understood, they have been reported to be *nephrotoxic* in animals (5) and therefore were not considered for the *in vivo* test.

TABLE III.—SUMMARY OF ANTACID DATA OBTAINED FROM SEVERAL ANTACIDS BY THE *in Vivo* ELECTRODE RECORDING TECHNIQUE, USING DOGS AND HUMANS

	Calcium Laurate			Control			
	Dose, Gm.	Max. pH	Duration,[a] min.		Dose, Gm.	Max. pH	Duration,[a] min.
Dog 1	0.5	7.0	70	Na_2CO_3	0.02	8.2	60
Dog 2	2.5	5.0	[b]	$CaCO_3$	0.19	6.0	65
Dog 3	2.5	4.8	>60[c]	$Mg(OH)_2$	0.10	7.7	30
Patient 1	3	4.6	65	...	...	...	...
Patient 2	2.5	4.8	80	...	...	...	...
Patient 3	5.0	5.1	100–130	$CaCO_3$	1.14	6.2	80

[a] Minutes after ingestion until gastric pH reached two. [b] Defective operation of pH meter. [c] Recording was stopped after 60 minutes.

longer in a human than an equivalent amount of calcium carbonate control, the difference is probably not significant. One might extrapolate this to mean that the principle of "floating" or adhering through poor wetting does not enhance stomach retention time markedly, although considerable more controlled *in vivo* work would be required to prove this conclusively.

SUMMARY

1. The following compounds were evaluated *in vitro* for antacid activity: aluminum hydroxide, aluminum laurate, aluminum myristate, aluminum mono-12-hydroxystearate, aluminum di-12-hydroxystearate, calcium hydroxide, calcium pelargonate, calcium citrate, calcium carbonate, calcium caprate, calcium laurate, calcium myristate, calcium palmitate, calcium stearate, calcium 12-hydroxystearate, calcium azelate, calcium sebacate, magnesium oxide, magnesium trisilicate, magnesium laurate, magnesium myristate, magnesium stearate, and magnesium 12-hydroxystearate.

2. In the *in vitro* studies, pH *vs.* time recordings were made under conditions which allowed evaluation of performance. Performance factors were designated (a) *delay time*, (b) *static equilibrium pH*, and (c) *dynamic equilibrium pH*. These factors indicated under the experimental conditions employed (*a*) the time required for an excess of the antacid to raise the pH of a 0.1 *N* HCl solution to an equilibrium value, (*b*) the equilibrium pH value when no further HCl was added to the system, and (*c*) the approximate equilibrium pH resulting (under conditions of excess antacid) when acid was added continuously at a rate equivalent to 4 ml. 0.1 *N* HCl per minute.

3. Most of the salts of carboxylic acids used in these studies have not been reported previously to be antacid substances, yet they all appear to possess this property. Their antacid properties result from their ability to react with HCl and form the free carboxylic acids. These free acids are poorly dissociated and many are insoluble in aqueous fluids. Thus their formation results in removal of hydrogen ions from solution.

4. The pH's below which these salts exert antacid action are influenced in part by the pKa of the carboxylic acid and the nature of the metal cation. For the aluminum, calcium, and magnesium salts studied, effective antacid actions were exerted at pH's near 4, 4.8, and 5.5, respectively.

5. Rate of acid neutralization *in vitro* appears to be influenced by factors such as rate of stirring, particle size of the antacid, its water solubility, and its wettability. Rates of acid neutralization cannot be predicted beforehand; however, in general, for salts derived from a given metal, the lower equivalent weight salts reacted more rapidly than those of higher equivalent weight. For example, calcium pelargonate or calcium azelate neutralized HCl much more rapidly than did calcium stearate.

6. Limited studies were performed in anesthetized dogs and in humans using a stomach electrode. Calcium laurate (a typical salt of a carboxylic acid) was shown to possess antacid properties *in vivo*.

7. One can infer from these studies that many salts of carboxylic acids possess antacid properties; however, none of the salts studied appeared to offer general advantage over some commonly used antacids. The principal drawback of the salts derived from the higher molecular weight carboxylic acids is the relatively high doses that would be required in practical therapy.

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