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IN-VITRO ADSORPTION OF CHOLATE ANION AT pH 7.5 BY ALUMINUM HYDROXIDE

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ABSTRACT

The in-vitro adsorptive capacities of aluminum hydroxide gel, dried aluminum hydroxide gel, and boehmite for cholate anion were determined at pH 7.5, 37°C and compared to cholestyramine. The adsorptive capacity of aluminum hydroxide gel was similar to cholestyramine. However, spray drying reduced the adsorptive capacity by approximately 50%. Boehmite, a crystalline aluminum oxyhydroxide, had an adsorptive capacity similar to dried aluminum hydroxide gel. The results support the hypothesis that adsorption of bile salts contributes to the constipation which is sometimes associated with aluminum hydroxide therapy.

INTRODUCTION

Constipation is the only significant side effect which is associated with the use of aluminum hydroxide as an antacid (1). Its cause has not been fully established although the adsorption of bile salts in the small intestine has been suggested. When adsorbed, bile salts are not able to exert their usual function, which may lead to constipation. The contribution of bile salts in promoting regular defecation is illustrated by the presence of constipation in individuals having a congenital absence of bile salts (2). Furthermore, choleraic diarrhea is frequently treated with cholestyramine, an anion-exchange resin which is used to treat hypercholesterolemia by adsorbing bile salts in the intestine (3). Aluminum hydroxide has been found to increase the fecal bile salt concentration in normal subjects (4). When patients with severe choleraic diarrhea were treated with aluminum hydroxide, bowel motion became less frequent and daily fecal weight decreased (4).

The adsorption of bile salts by aluminum hydroxide has been noted in many studies. Wenger and Heymsfield (5) found that aluminum hydroxide adsorbed bile salts and suggested that it would be useful for preventing bile reflux gastritis. In these in-vitro studies, doses of aluminum hydroxide gel were exposed to two

concentrations of bile. Another study, also directed at duodenal-gastric reflux of bile salts, demonstrated the bile salt binding properties of aluminum hydroxide and hydrotalcite when 30 mg of antacid were exposed to either 10 or 20 μmole of bile salts (6).

Clain, et al (7) compared the binding properties of various commercial antacids for bile salts and found that aluminum hydroxide had the greatest binding capacity and was similar to cholestyramine. Normal doses of antacids were exposed to several concentrations of bile salts up to 10 mM. Aluminum hydroxide was the only antacid which did not exhibit saturation.

In contrast, Cousar and Gadacz (8) found that aluminum hydroxide did not adsorb as much bile salt as cholestyramine when exposed to 5 mM. A recent study (9) found that aluminum hydroxide and cholestyramine adsorbed a similar quantity of bile salts when exposed to 2.5 mM.

The in-vitro studies of bile salt adsorption by aluminum hydroxide do not fully characterize the ability of aluminum hydroxide to adsorb bile salts in the intestine because only one or two concentrations of bile salts were used and the pH conditions varied from 2 to 7.5. Characterization of the adsorption isotherm of aluminum hydroxide for bile salts at pH 7.5 is

needed to predict the in-vivo adsorption as this is the pH at the distal portion of the ileum where bile salt absorption is believed to occur (10).

Furthermore, the published studies do not consider the various forms of aluminum hydroxide which may be present as the adsorbent in the small intestine. The most amorphous forms of aluminum hydroxide are capable of dissolving almost completely in gastric fluid during the normal gastric residence time (11). The soluble aluminum cation, formed in gastric fluid, is reprecipitated in the small intestine when the pH reaches 4.5 or higher. A perfused rat gut experiment recently demonstrated that a high surface area amorphous aluminum hydroxide was precipitated in the intestine when an aluminum chloride solution was perfused (12). Other more highly ordered forms of aluminum hydroxide, such as those produced by drying, may only partially dissolve during the gastric residence period and reach the small intestine largely in their original state. Thus, the adsorptive capacities of several forms of aluminum hydroxide were studied including amorphous aluminum hydroxide gel which is believed to be similar in surface area to the aluminum hydroxide reprecipitated in the small intestine following oral administration of a highly reactive aluminum hydroxide-containing antacid. A

commercially spray-dried aluminum hydroxide gel was studied to represent the situation in which the aluminum hydroxide did not dissolve completely during the gastric residence time.

Boehmite, a crystalline aluminum oxyhydroxide (AlO(OH)), which is virtually nonreactive in gastric acid (13), was used to represent a form of aluminum hydroxide which would pass through the stomach unchanged.

Thus, this study was undertaken to determine the adsorption isotherm for cholate anion at pH 7.5, 37°C by different forms of aluminum hydroxide. Cholate anion was chosen as it is frequently used as a model bile salt.

MATERIALS AND METHODS

Aluminum hydroxide gel (Barcroft), dried aluminum hydroxide gel (Chattem) and boehmite (SPCA) were obtained commercially.

pH-stat titration at pH 3, 37°C (14) (Radiometer) was used to determine the fraction which dissolved during the estimated gastric residence time for antacids of 15 to 60 min. (15).

Adsorption isotherms were constructed by exposing a sample equivalent to 100 mg Al_2O_3 to 100 ml of sodium cholate solutions (2, 5.5, 7, 9, 12.5, 16, 19.5, 23 or 26.5 mM) adjusted to pH 7.5 with 0.05 N NaOH at 37°C.

The pH was maintained at 7.5 during a 20 min. equilibration period by use of a pH-stat titrator (Radiometer) using 0.05 N HCl. The volumes of 0.05 N HCl required to maintain the pH were very small (<0.1 ml) and were included in the calculations. Preliminary experiments indicated that equilibration occurred in less than 20 min. The supernatant solution was collected by centrifugation followed by filtration through a 0.2 μ membrane filter which was tested and found not to adsorb cholate anion. The cholate anion concentration of the supernatant solution was assayed by a high pressure liquid chromatographic technique using methylparaben as the internal standard (16). The cholate anion and methyl paraben peaks appeared at 7.2 and 4.6 min., respectively. All standard curves had an R^2 of 0.99 or greater.

The plateau of the adsorption isotherm was taken as the adsorptive capacity.

RESULTS AND DISCUSSION

The rate of acid neutralization by antacids at pH 3, 37°C has been correlated with in-vivo acid neutralization (17). Therefore, pH-stat titration at pH 3, 37°C was used to evaluate the rates of acid neutralization of the 3 forms of aluminum hydroxide. As seen in Figure 1, aluminum hydroxide gel was 65% neutralized in 15 min. and completely neutralized in

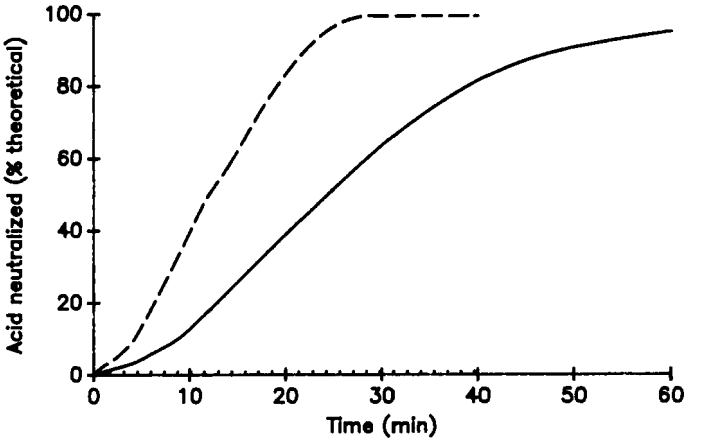

Figure 1 - Rate of acid neutralization at pH 3, 37°C. Key: dashed line, aluminum hydroxide gel; solid line, dried aluminum hydroxide gel; dotted line, boehmite.

approximately one half hour. As expected, spray drying caused a substantial reduction in the rate of acid neutralization as 25 and 65% were neutralized in 15 and 30 min., respectively. Boehmite was virtually nonreactive under simulated gastric conditions. Thus, the aluminum hydroxide gel represents the best case for adsorption of bile salts in which a high surface area aluminum hydroxide is present at the distal end of the ileum.

The adsorption isotherms for the 3 forms of aluminum hydroxide are shown in Figure 2. The adsorptive capacities are compared to cholestyramine in Table I. The adsorptive capacity of aluminum hydroxide gel is similar to cholestyramine which agrees with

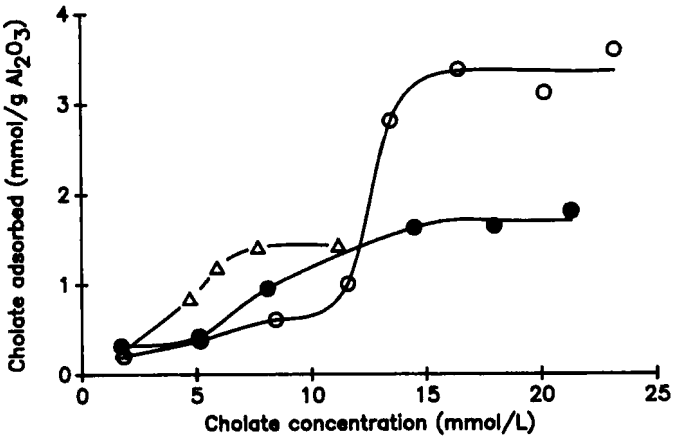

Figure 2 - Adsorption isotherm of cholate anion at pH 7.5, 37°C. Key: O, aluminum hydroxide gel; ●, dried aluminum hydroxide gel; Δ, boehmite.

TABLE 1

Adsorptive Capacity of Aluminum Hydroxide and Boehmite for Cholate Anion at pH 7.5, 37°C

Adsorbent	% Equivalent Al_2O_3	Adsorptive Capacity at pH 7.5, 37°C mmole/g Al_2O_3
Cholestyramine[a]	-	3.5[b]
Aluminum Hydroxide Gel	12.9	3.4
Spray Dried Aluminum Hydroxide Gel	51.8	1.7
Boehmite	67.0	1.4

[a]From ref. 18

[b]mmole/g cholestyramine

references 8 and 10. The adsorptive capacity of dried aluminum hydroxide and boehmite are less than half of cholestyramine, which agrees with reference 9. Thus, the conflicting results in the literature may be related to the form of aluminum hydroxide which was studied.

It is interesting to note that drying of amorphous aluminum hydroxide gel caused a large decrease in the adsorptive capacity probably because of the development of order and the concommitant decrease in surface area.

Since cholestyramine causes constipation because of the adsorption of bile salts (2) and the adsorptive capacity of aluminum hydroxide gel is similar to cholestyramine, the results suggest that aluminum hydroxide may also lower the bile salt concentration of intestinal fluid enough in certain individuals to produce constipation.

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