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Technical Note

In Vitro and *In Vivo* Interactions of Furosemide and Sucralfate

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INTRODUCTION

Sucralfate is a basic complex salt of polyaluminum hydroxide with a sulfate disaccharide skeleton (1); it is indicated for the short-term treatment of duodenal peptic ulcers. Its antiulcer mechanism of action is rather unique since it forms a viscous adhesive barrier on the surface of ulcerated and, to a lesser extent, intact mucosa of the stomach and duodenum. This barrier inhibits the diffusion of acid across the mucosal surface. *In vitro* sucralfate has been shown to bind to bile salts, pepsin, and proteins found at the ulcer crater (2). The barrier to diffusion and the potential for binding have led to the speculation that sucralfate could alter the absorption of concurrently administered drugs. This speculation was supported by recent reports of decreased absorption of warfarin (2), cimetidine (3), and sulpride (4). The present study has been conducted to investigate the *in vitro* binding of furosemide to sucralfate and its effect on the bioavailability and the diuretic effect of furosemide in the rat.

MATERIALS AND METHODS

Sucralfate [Carafate tablets, 1 g (average total weight, 1.22 g), Marion Laboratories, Kansas City, Missouri] was obtained commercially. All other chemicals were analytical grade; solvents used in high-performance liquid chromatographic (HPLC) analysis were chromatographic grade.

Adsorption Studies. A series of solutions containing furosemide 1–25 μg/ml and ranging from pH 1 to pH 6 was prepared. Twenty-five milliliters of each solution was transferred to a 50-ml flask, and 250 mg of powdered sucralfate tablet was added. The flasks were placed in a shaking water bath at 25°C and shaken at 50 rpm for 30 min. A 10-ml aliquot of each solution was withdrawn, centrifuged, and assayed as described below.

In Vivo *Studies.* Ten male Sprague Dawley rats weighing 317–363 g were fasted overnight, water being allowed *ad lib.* At −1 hr all rats received an oral water load equal to 3% of their body weight, and at 0 hr they received orally 5 mg/kg of furosemide dissolved in phosphate buffer. Five rats also received a suspension of 50 mg of sucralfate in 0.5 ml of distilled water, while the others received only 0.5 ml of distilled water. At 1.75 hr the rats were given a second water load equal to 2% of their body weight. The rats were housed in metabolism cages for urine collection.

Urine Analysis. Furosemide was assayed by HPLC using a μBondapak C18 column with a C18 guard column, a Model 420 fluorescence detector, a 254-nm excitation filter, and a 400-nm emission filter. The mobile phase was 35% acetonitrile in 0.015 *M* phosphoric acid. Urine was filtered through a 0.45-μm membrane filter and injected. Sodium and potassium were determined in urine by flame photometry. The *t* test for paired values was used to assess the significance of differences between observations.

RESULTS AND DISCUSSION

Figure 1 shows the amount of furosemide bound at various pH values. Adsorption reaches its highest level at pH 3 and decreases rapidly as the pH increases. This is in line with previously observed binding of sucralfate with bile acids, which was also greatest below pH 4 (1). The fact that

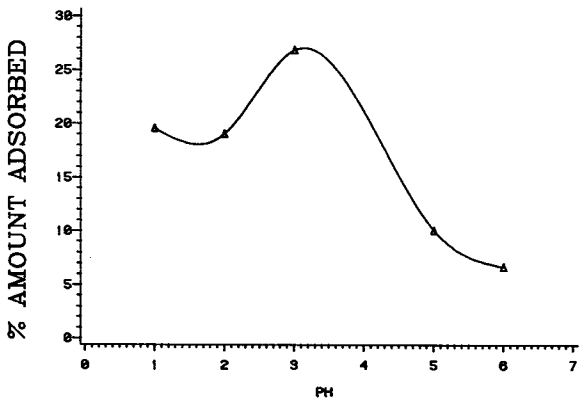

Fig. 1. pH profile of the percentage furosemide bound to sucralfate.

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Table I. Urinary Excretion of Furosemide, Sodium, and Potassium in Rats Following Administration of Furosemide Alone (Control) or Furosemide and Sucralfate (Test)[a]

	μg furosemide		μEq sodium		μEq potassium	
Time (hr)	Control	Test	Control	Test	Control	Test
0.0	00.00	00.00	0.000	0.000	0.000	0.000
0.5	1.95 ± 1.46	1.89 ± 1.48	0.045 ± 0.005	0.046 ± 0.013	0.056 ± 0.007	0.055 ± 0.044
1.0	5.85 ± 3.32	6.54 ± 2.72	0.083 ± 0.017	0.085 ± 0.021	0.102 ± 0.016	0.106 ± 0.012
2.0	9.46 ± 2.63	14.23 ± 2.31	0.113 ± 0.006	0.129 ± 0.034	0.158 ± 0.035	0.175 ± 0.033
4.0	15.52 ± 3.90	22.86 ± 7.48	0.143 ± 0.023	0.217 ± 0.096	0.228 ± 0.060	0.312 ± 0.102
24.0	76.81 ± 45.20	70.32 ± 58.10	0.474 ± 0.114	0.488 ± 0.068	0.933 ± 0.184	0.931 ± 0.136

[a] Mean ± SD of five animals.

binding decreased at pH values below 3 may indicate binding of sucralfate with the partially ionized furosemide, which has a pK_a of 3.9. At higher pH values, both furosemide and sucralfate are negatively charged; therefore, very low electrostatic attraction would exist between them.

Adsorption data also indicate that the maximum capacity of sucralfate for binding furosemide is approximately 0.4 mg/g. Considering the usual therapeutic doses of furosemide, 40 mg, and sucralfate, 1 g, there should be no therapeutic consequences of the combination of the two agents.

Our *in vivo* data show that the total amount of furosemide excreted in the urine in 24 hr (Table I) was not significantly ($P > 0.05$) altered as a result of sucralfate coadministration. The amount excreted (per 100 g body weight) was 76.8 ± 45.2 μg for furosemide alone vs 70.3 ± 58.1 μg with sucralfate. Furthermore, Table I also indicates that the cumulative excretion of sodium and potassium did not change significantly ($P > 0.05$). Sodium excretion (per 100 g body weight) was 0.474 ± 0.114 μEq without sucralfate and 0.488 ± 0.068 μEq with sucralfate. Potassium excretion (per 100 g body weight) was 0.933 ± 0.184 μEq in the absence of sucralfate and 0.931 ± 0.136 μEq in the presence of sucralfate.

In conclusion, it has been demonstrated through *in vitro* and *in vivo* experiments that the coadministration of sucralfate and furosemide is not likely to influence the therapeutic performance of the latter.

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