Effect of Surfactants on Absorption through Membranes V: Concentration-Dependent Effect of a Bile Salt (Sodium Deoxycholate) on Absorption of a Poorly Absorbable Drug, Phenolsulfonphthalein, in Humans

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Abstract □ The effect of administration of 600- and 300-mg doses of sodium deoxycholate 1 hr before phenolsulfonphthalein solution is reported. The 600-mg dose caused a decrease in drug bioavailability as measured by the total amount excreted in 24 hr. The 300-mg dose caused an increase in the initial phenolsulfonphthalein absorption rate, suggesting a direct action of the bile salt on membrane permeability. The decrease in absorption upon administration of 600 mg was attributed to micellar entrapment of the drug molecule.

Keyphrases □ Sodium deoxycholate—effect of preadministration on absorption and excretion of phenolsulfonphthalein, humans □ Phenolsulfonphthalein—absorption and excretion, effect of preadministration of sodium deoxycholate, humans □ Absorption—phenolsulfonphthalein, effect of preadministration of sodium deoxycholate, humans □ Excretion—phenolsulfonphthalein, effect of preadministration of sodium deoxycholate, humans □ Bile salts—sodium deoxycholate, effect of preadministration on absorption and excretion of phenolsulfonphthalein, humans

Bile salts, an important class of surface-active agents, play a significant role in the intestinal absorption of lipids (1, 2) and lipid-soluble vitamins. Several reports (3–6) indicated that bile salts influence drug absorption. Most accumulated data were derived from animal studies. Data obtained from human studies are limited. An increase in the urinary recovery of riboflavin in humans was reported when a 600-mg dose of sodium deoxycholate was administered 0.5 hr prior to the oral ingestion of the vitamin (7).

Sodium deoxycholate enhanced the absorption of phenolsulfonphthalein, a poorly absorbable drug, in the rat (4). The aim of the present study was to determine if a similar effect occurs in humans.

EXPERIMENTAL

The study was designed in a crossover fashion. The urinary excretion of phenolsulfonphthalein was determined following the administration of Treatments A, B, and C (Table I). Ten healthy volunteers (capable of informed consent) participated in Treatments A and B, and seven of these volunteers participated in Treatment C. Doses were administered at weekly intervals to fasting subjects. Fluid and food intake, as well as the analysis of the urine samples, was carried out as previously described (8).

RESULTS AND DISCUSSION

Administration of 600 mg of sodium deoxycholate 1 hr before phenolsulfonphthalein solution did not result in a significant change in the amount of the dye excreted in 1 hr. However, the total amount excreted in 24 hr was significantly less than the control (Table II). Administration of 300 mg of the bile salt increased significantly the amount of phenolsulfonphthalein excreted in 1 hr, while the total amount of the dye excreted in 24 hr was not significantly different from the control. The time course of phenolsulfonphthalein excretion following the various treatments is shown in Fig. 1. The average data in the figure are a good reflection of the individual results.

The increase in the initial rate of absorption (1-hr urinary excretion data, Table II) following the administration of 300 mg of sodium deoxycholate suggests a direct action of the bile salt on the membrane permeability, in agreement with other studies in animals (4, 5) and humans (7). Data in Table II and Fig. 1 indicate that 600 mg of sodium deoxycholate did not significantly affect the initial phenolsulfonphthalein absorption rate. Previous studies with bile salts indicated that the change in membrane permeability did not increase with an increase in the surfactant concentration (9). A minimum concentration of bile salt was usually sufficient to produce a maximum effect on membrane permeability. Hence, the higher dose of sodium deoxycholate was expected to produce a similar, but not necessarily greater, effect on the initial phenolsulfonphthalein absorption rate as that of the lower dose.

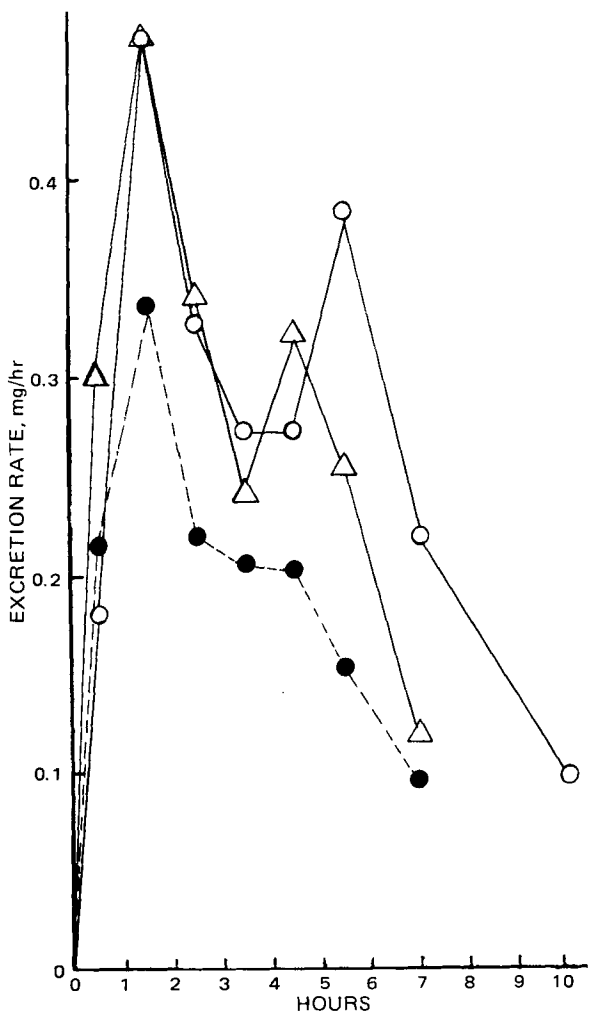

Figure 1—*Mean urinary excretion rates of phenolsulfonphthalein after oral administration of 20 mg in solution. Key: ○, control (average of 10 subjects); ●, pretreatment with 600 mg of sodium deoxycholate (average of 10 subjects); and △, pretreatment with 300 mg of sodium deoxycholate (average of seven subjects).*

Table I—Regimen of Treatments Administered to Human Volunteers

Hours	Treatment A	Treatment B	Treatment C
−1	100 ml of water	600 mg of sodium deoxycholate[a] with 100 ml of water	300 mg of sodium deoxycholate[a] with 100 ml of water
−0.5	100 ml of water in all treatments		
0	20 mg of phenolsulfonphthalein[b] dissolved in 50 ml of water[c] in all treatments		
1, 2, 3, 4, 5, 6, 8, 12, 24	Collection of urine in all treatments		

[a] Sodium deoxycholate (Mann Research Lab., New York, N.Y.) was administered in hard gelatin capsules, each containing 300 mg. [b] Nutritional Biochemical Corp., Cleveland, Ohio. [c] Contains 20 mg of sodium bicarbonate to aid the solubility of phenolsulfonphthalein.

The results obtained with Treatment B are not in agreement with this expectation and suggest that the direct effect of the bile salt on the membrane must have been masked by an opposing effect tending to decrease phenolsulfonphthalein absorption. The 24-hr urinary excretion data (Table II) give the same picture of two opposing effects of the bile salt on phenolsulfonphthalein absorption and provide evidence that the decrease in drug absorption becomes significant with the increase in the sodium deoxycholate concentration.

The decrease in the total excretion of phenolsulfonphthalein upon administration of 600 mg of the bile salt is believed to be the result of micellar solubilization. Entrapment of the dye in the micelles of sodium deoxycholate, with the resultant loss in thermodynamic activity, is expected to result in decreased absorption. Phenolsulfonphthalein was previously shown (5) to be a candidate for entrapment in the micelles of other bile salts. The concentration of bile salts in human intestinal content was reported (10) to be slightly above their critical micellar concentration. Therefore, it is expected that administration of both 300 and 600 mg of sodium deoxycholate will result in a micellar solution in the intestinal tract.

It seems that a direct membrane effect, resulting in potentiation of the initial rate of absorption, predominates at the lower dose, while more micelles entrap more drug at the higher dose, resulting in decreased absorption. The excretion pattern (Fig. 1) suggests this possibility. Higher concentrations of surfactants (3) including bile salts (11) decreased drug absorption. Although none of the volunteers reported experiencing a laxative effect, the possibility that the 600-mg dose of the bile salt resulted in an increased GI motility, and hence decreased absorption, cannot be ruled out. The delay in gastric emptying, suggested (7) as one possible explanation of the increased bioavailability of riboflavin after administration of a similar dose of the same bile salt, was not evident in the present study (Fig. 1).

The data of the present study and of Mayersohn *et al.* (7) suggest that, depending on the drug and its absorption mechanism, bile salts could decrease as well as increase drug absorption.

Table II—Effect of Sodium Deoxycholate on Phenolsulfonphthalein Absorption in Humans

Subject (Age, years; Weight, kg)	Amount of Phenolsulfonphthalein Excreted, mg: 1 hr A[a]	1 hr B	1 hr C	24 hr A	24 hr B	24 hr C
SK (41, 94)	0.122	0.148	0.378	3.430	1.210	2.280
OA (27, 90)	0.103	0.212	0.224	2.030	1.350	1.730
AH (50, 75)	0.218	0.179	0.231	2.150	1.480	1.940
SA (24, 71)	0.262	0.251	0.486	2.530	1.450	2.380
AR (31, 72)	0.181	0.254	0.196	1.750	1.630	1.840
MS (30, 61)	0.215	0.259	0.222	2.280	1.470	2.340
GM (29, 66)	0.167	0.120	0.349	1.860	1.490	2.660
WG (36, 72)	0.182	0.167		4.050	1.660	
ME (29, 63)	0.245	0.399		3.020	2.070	
AA (29, 69)	0.108	0.172		1.340	1.470	
Mean	0.180	0.216	0.298	2.444	1.528	2.167
RSD	31	37	36	34	15	16
Significance level[b]		N.S.	95.0%		99.0%	N.S.

[a] Treatment. [b] Paired *t* test *versus* Treatment A (same subjects).

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