Effect of Surfactants on Absorption through Membranes IV: Effects of Dioctyl Sodium Sulfosuccinate on Absorption of a Poorly Absorbable Drug, Phenolsulfonphthalein, in Humans

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Abstract □ To explore the effect of dioctyl sodium sulfosuccinate on drug absorption in humans, the urinary excretion of a poorly absorbable drug, phenolsulfonphthalein, administered in solution with and without the surfactant was determined. Coadministration of a therapeutic dose of the surfactant with the drug solution resulted in a significant increase in the initial rate of absorption. A small increase in the extent of absorption was also observed. Pretreatment with the surfactant for 6 nights, followed by administration of the drug on the 7th day, did not significantly change the rate or extent of absorption. The surfactant is thought to have a direct effect on the GI membrane, resulting in a temporary change in its permeability. This effect appears to be reversible after a few hours.

Keyphrases □ Dioctyl sodium sulfosuccinate—effect on phenolsulfonphthalein absorption, humans □ Phenolsulfonphthalein absorption—dioctyl sodium sulfosuccinate effect, humans □ Surfactant effect—dioctyl sodium sulfosuccinate on phenolsulfonphthalein absorption, humans □ Absorption, drug—effect of surfactant (dioctyl sodium sulfosuccinate) on phenolsulfonphthalein, humans

Hepatic drug reactions are not uncommon. Various drugs were reported to cause such reactions, yet involvement of a laxative preparation in jaundice manifestations is a novelty (1). Recently, clinical observations describing hepatitis with jaundice manifestations in humans, during long-term administration of a widely used and generally assumed innocent laxative combination, were reported (1–3). This laxative product incorporates dioctyl sodium sulfosuccinate (I) as a wetting agent and a stool softener together with sodium carboxymethylcellulose and the cathartic oxyphenisatin acetate. A hypersensitivity to oxyphenisatin was suggested as the probable cause of hepatitis (3). These reports have drawn attention to the possibility of I being indirectly responsible for causing jaundice. The surfactant was suspected of producing a hyperabsorptive state by a direct action on the biological membrane, resulting in the absorption of toxic amounts of oxyphenisatin (4). Similarly, toxicity in rats (5) after oral administration of subtoxic doses of danthron (1,8-dihydroxyanthraquinone) with I was attributed to increased absorption of the former in the presence of the surfactant. Clinical data in humans (6) also support the observed toxicity in rats. Consequently, warning notes have appeared in the literature concerning the hazards of drug combinations containing I (4, 7).

A systematic study of the effect of I on drug absorption through biological membranes of varying complexities was undertaken. The purpose of such a study is to determine whether this seemingly inert surfactant (8) changes the absorption profile of representative drugs when both are given concomitantly. A previous report (9) showed that I enhances the absorption of pentobarbital, a readily absorbable drug, in the goldfish. Dioctyl sodium sulfosuccinate also enhanced the absorption of a poorly absorbable drug, phenolsulfonphthalein, in the rat (10). Since animal studies may only indicate similar effects in humans, a study of the effect of this surfactant on drug absorption in human volunteers was deemed appropriate. The effect of coadministration of the drug and the surfactant in solution on drug absorption under experimentally controlled conditions was examined. In addition, the effect of I on the absorption of the drug under clinically oriented conditions was determined.

EXPERIMENTAL

Twelve healthy male volunteers participated in the present study (Table I). The study was designed in a crossover fashion. The urinary excretion of orally administered phenolsulfonphthalein was determined subsequent to the administration of each of the following treatments:

A. 20 mg of phenolsulfonphthalein[1] (12 subjects).

B. 20 mg of phenolsulfonphthalein and 250 mg of dioctyl sodium sulfosuccinate[2] (11 subjects).

C. 20 mg of phenolsulfonphthalein and 500 mg of I (four subjects).

D. 20 mg of phenolsulfonphthalein alone on the morning of the 7th day following the daily administration of 200 mg of I, in the form of 50-mg capsules[3], taken after supper for 6 successive days (six subjects).

At least 1 week elapsed between two successive treatments in any one subject. Each dose was dissolved in 50 ml of water, and 20 mg of sodium bicarbonate was added to aid the solubility of phenolsulfonphthalein. Solutions containing the doses were administered to subjects in the morning on an empty stomach. No food was allowed for the next 4 hr. Fluid intake was regulated to permit hourly collection of urine, and no other drug was permitted throughout the experimental period. Doses containing the surfactant, when administered, produced temporary throat irritation, which explains the reduced number of volunteers in Treatment C.

Subsequent to dose administration, urine was collected hourly for 7–9 hr and then every 2–3 hr until the drug could no longer be detected in the urine. All urine samples were stored in a refrigerator and assayed within 24 hr according to McLeod *et al.* (11). The buffer solution, suggested by Ashley and Levy (12) to avoid underestimation of phenolsulfonphthalein particularly in acidic urine, was used to dilute the urine samples. Diluted urine was centrifuged, and the supernate absorbance was determined at 560 nm spectrophotometrically[4]. Necessary blanks were prepared using urine diluted with 0.1 *N* acetic acid.

[1] Phenolsulfonphthalein, Nutritional Biochemical Corp., Cleveland, Ohio.
[2] Aerosol O.T. 100%, Sargent-Welch Scientific Co.
[3] Colace capsules, supplied by Mead Johnson Laboratories, Evansville, IN 47721
[4] Unicam SP 500 spectrophotometer.

Table I—Effect of Dioctyl Sodium Sulfosuccinate on Phenolsulfonphthalein Absorption in Humans

Subject	Age, years	Weight, kg	1 hr Treatments A	B	C	D	24 hr Treatments A	B	C	D
			Amount of Phenolsulfonphthalein Excreted, mg							
GM	28	66	0.16	0.69	0.60	0.42	1.5	3.9	3.5	3.4
NK	31	55	0.22	0.69	0.47	0.48	1.8	2.7	3.2	1.9
SK	40	95	0.14	0.91	0.45	—[a]	4.1	4.2	3.3	—[a]
OA	26	90	0.30	—[a]	0.36	0.23	3.1	—[a]	2.3	1.8
SA	24	71	0.42	0.58	—[a]	0.53	2.3	2.1	—[a]	3.2
AE	24	67	0.20	0.50	—	0.19	1.8	2.0	—	2.2
AR	30	71	0.22	0.53	—	0.30	1.6	3.0	—	2.3
AN	23	85	0.46	0.32	—	—	2.0	1.6	—	—
AA	32	79	0.30	0.81	—	—	1.1	1.4	—	—
MM	27	86	0.40	0.48	—	—	3.0	3.5	—	—
WG	35	72	0.10	0.71	—	—	2.6	3.4	—	—
HE	31	80	0.45	0.45	—	—	2.1	2.0	—	—
Mean			0.28	0.61	0.47	0.36	2.3	2.7	3.1	2.5
RSD			45	29	21	23	37	35	17	27
Statistical significance[b]				$p < 0.005$	$p < 0.01$	N.S.		$p < 0.1$	N.S.	N.S.

[a] Subjects did not participate in this treatment. [b] Paired *t* test *versus* Treatment A (same subjects).

RESULTS AND DISCUSSION

The amounts of phenolsulfonphthalein excreted 1 and 24 hr following Treatments A–D are given in Table I. The two excretion parameters reported were chosen to reflect the rate and extent of phenolsulfonphthalein absorption. Plots of the time course of drug excretion following the treatments are shown in Fig. 1.

The average amounts of phenolsulfonphthalein excreted in 1 and 24 hr in the control treatment (Treatment A) were 1.4 and 11.3% of the dose, respectively. These values are in close agreement with those reported by other investigators (12). The urinary excretion pattern observed with the majority of subjects in the control study exhibited two excretion peaks at approximately 2 and 5 hr. Ashley and Levy (12) reported similar excretion patterns in humans following the same dose of phenolsulfonphthalein as a solution. The secondary excretion rate peak, after food ingestion, was attributed to transfer of residual drug from the stomach to the intestine or enhanced absorption due to discharge of bile into the intestinal lumen.

The urinary excretion data reported in Table I were statistically analyzed. Each set of data was compared with the control data from the same subjects using a paired *t* test (Table I). It can be observed from the 1-hr urinary excretion data that coadministration of 250 mg of the surfactant and the drug (Treatment B) resulted in a significant increase in the rate of phenolsulfonphthalein absorption. In the presence of the surfactant, 3% of the administered dose was excreted within 1 hr (Treatment B, average of 11 subjects) compared to a value of 1.4% of the dose in the absence of the surfactant (Treatment A, average of the same subjects). The dose of I administered in Treatment B, which resulted in the hyperabsorptive state, was within the usual prescribed oral dose [100–400 mg daily (13)]. Criticism has been raised against *in situ* data reporting surfactant effects on drug absorption. Such data are sometimes obtained under nonphysiological conditions, such as using high surfactant concentration (14), which prevents extrapolation of results to human therapy.

Coadministration of the drug and 500 mg of the surfactant resulted in a similar significant increase in the rate of absorption. Inspection of the 1-hr urinary excretion data following Treatment C suggests that doubling the dose of the surfactant did not increase the rate of drug absorption over what was observed following Treatment B. On the contrary, there seemed to be a lesser increase in the absorption rate at the higher surfactant dose. This concentration-dependent effect of the surfactant was also observed in similar studies in the rat (10). The 500-mg dose of the surfactant corresponds to an approximately 1% concentration in the administered solution. Previous studies (10) showed that such a concentration results in micellar entrapment of the drug molecules and, hence, the observed smaller increase in the absorption rate. The number of volunteers participating in both Treatments B and C was too small to permit statistical analysis of the difference between the two sets of data.

In Treatment D, where there was premedication with capsules containing 200 mg of the surfactant for 1 week, experimental conditions were selected to simulate a possible clinical situation where this stool softener surfactant is administered for some time and a poorly absorbable drug is administered during the same period. Such a clinical situation is very likely. Treatments B and C simulate another possible situation where patients may take the two drugs at the same time or where patients receive a combination dosage form containing the two drugs. It was a combination dosage form of I and the nonabsorbable oxyphenisatin acetate that resulted in hepatic toxicity (1–3).

The 1-hr urinary excretion data obtained following Treatment D indicates a small increase in the rate of absorption. The amount of phenolsulfonphthalein excreted increased from 1.3% (average of six subjects) to 1.8% of the dose (average of the same subjects). Statistical analysis of the data indicates that the difference between the two means is not significant. This result could be due to a decline in the surfactant effect during the time (overnight) that elapsed before drug administration. The effect of this surfactant (9, 10) and others (15, 16) on animal membranes was found to be reversible; membranes regained normal behavior after some time.

In the present study, the hyperabsorptive state described by the 1-hr urinary excretion data following Treatments B and C was most probably due to a direct action of the surfactant on the membrane. A similar mode of action was suggested in animal studies using phenolsulfonphthalein with I (10). The latter was also shown to accelerate peritoneal dialysis of urea and phosphates in rabbits (17). Various investigators attributed promotion of drug absorption in the presence of surfactants to a similar mechanism (15, 16, 18–20).

The exact mechanism of the surfactant-induced change in the membrane permeability is still unknown. The possibility of removal of phospholipids from the membrane by surfactants was suggested (17), as was alteration of the highly ordered barrier by such agents (21). Recently, Dujvone and Shoeman (22) reported that patients given therapeutic doses of dioctyl sodium sulfosuccinate excreted considerable amounts in the bile; therefore, the previous belief that this surfactant is not absorbed from the GI tract was invalidated.

It is likely that some of the surfactant molecules, in passing through the biomembrane, remain dissolved in the lipoidal cell wall. Plasticization results from the dissolution of low molecular weight compounds in high molecular weight materials. Physical properties, including permeability, undergo substantial changes. In the present study, dissolution of I in the lipoidal cell wall and a resultant permeability increase due to plasticization of the membrane was probably responsible for the observed increase in the rate of absorption of phenolsulfonphthalein. Lovering and Black (23) suggested a similar mechanism to explain the enhancement of permeation of phenylbutazone through everted rat intestines.

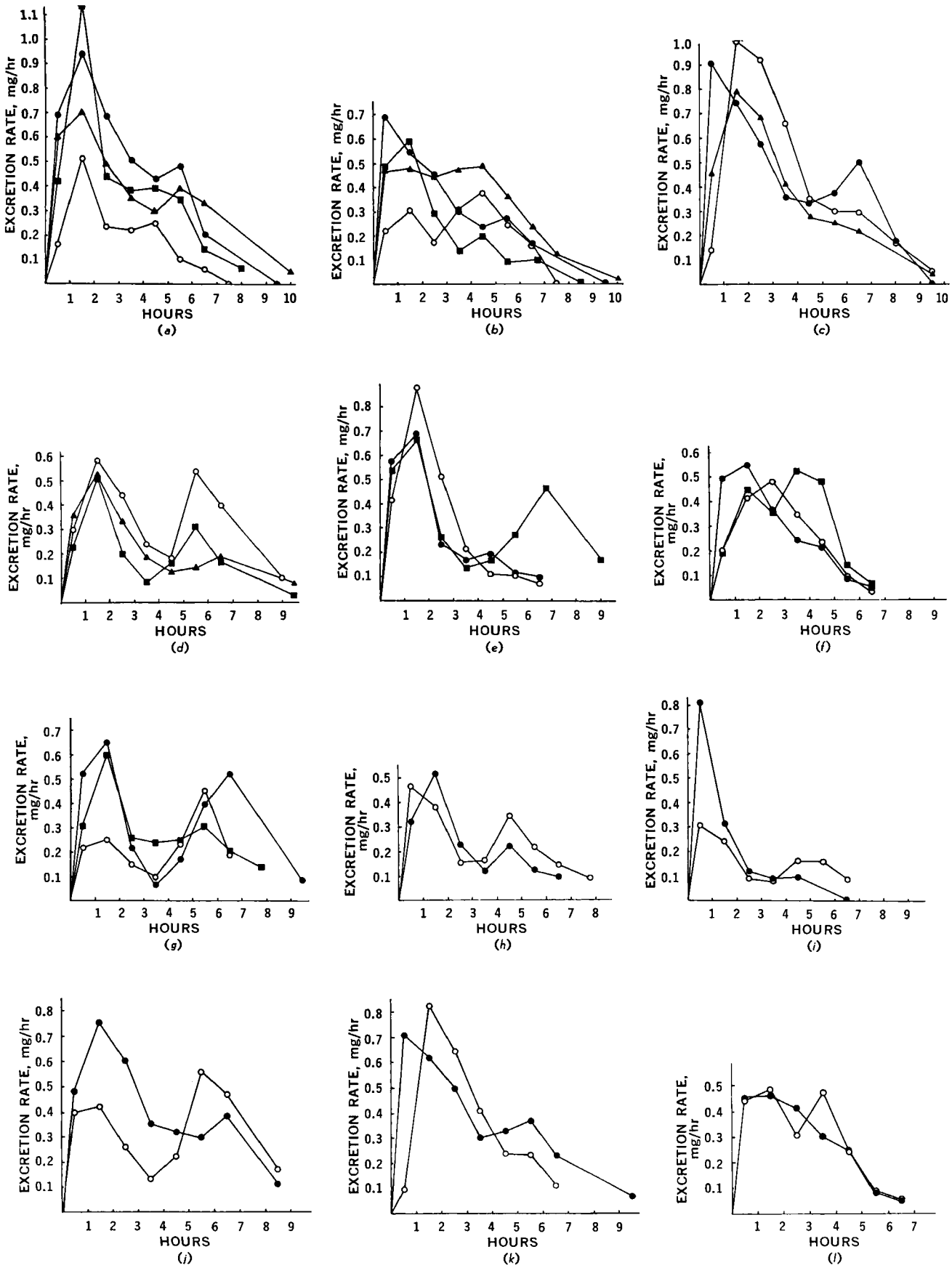

Figure 1—*Urinary excretion rates of orally administered phenolsulfonphthalein in human volunteers:* (a) *Subject GM,* (b) *Subject NK,* (c) *Subject SK,* (d) *Subject OA,* (e) *Subject SA,* (f) *Subject AE,* (g) *Subject AR,* (h) *Subject AN,* (i) *Subject AA,* (j) *Subject MM,* (k) *Subject WG, and* (l), *Subject HE. Key:* ○, *Treatment A;* ●, *Treatment B;* ▲, *Treatment C; and* ■, *Treatment D.*

Whatever the exact nature of this hyperabsorptiveness may be, it is generally agreed that it is reversible (9, 10, 15, 16). The membrane regains normal behavior toward drug permeation after some time, in contrast to the persistent hyperpermeability caused by fatty acids and aspirin (24).

Administration of 250 mg of the surfactant in phenolsulfonphthalein solution increased the total recovery of phenolsulfonphthalein from 10.9 to 13.5% (average of 11 subjects that participated in both Treatments A and B). This small increase was of borderline significance ($0.05 < p < 0.1$). Coadministration of 500 mg of the surfactant and premedication with capsules containing 200 mg of I did not significantly change the extent of absorption of phenolsulfonphthalein (Treatments C and D, Table I). Unavailability of the drug molecules for absorption due to micellar entrapment (10) could be the reason why a 500-mg dose of the surfactant did not increase the extent of absorption. The regaining of normal permeability characteristics by the membrane is probably responsible for the lack of increase in the extent of absorption following premedication with the surfactant capsules.

Two other factors should be considered for their possible implications on the results obtained in this study. The first factor is the mechanism of absorption of phenolsulfonphthalein. The drug is reported to be absorbed in animals and humans by both passive and specialized mechanisms (11, 25, 26). The latter has been described as a low capacity active transport process. Surfactants *have sometimes* been shown to retard the net absorption of drugs absorbed mainly by active mechanisms, in spite of the absence of drug micelle interactions (27–29). In the present investigation, although the coadministration of 250 mg of the surfactant and phenolsulfonphthalein resulted in an increase in net absorption, the increase was not as high as anticipated. Therefore, the mechanism of absorption of phenolsulfonphthalein could have exerted a damping effect on the increase in net absorption.

The second factor is that I has been reported to exert a pharmacological effect in animals that is not shared by other surfactants. It retards gastric emptying rate and inhibits gastric secretion in rats (30). These effects were only demonstrated at relatively high doses of the surfactant. Lish (30) reported retardation of gastric and intestinal motility using 100–1600 mg of I/kg in rats, while effects on gastric secretion were observed with 20–100 mg/kg in rats. In the present study, the hyperabsorptiveness was achieved with an average dose as low as 4 mg/kg in humans. Furthermore, the excretion pattern observed in Treatment B (Fig. 1) strongly suggests a direct action of I on the biomembrane and does not favor any of the previously discussed pharmacological effects of the surfactant. The sudden rise in urinary excretion rate of phenolsulfonphthalein during the 1st hr, with no apparent delay in peak excretion rate and no significant prolongation of absorption time, support the suggestion that the observed increase in absorption is due to a temporary change in membrane permeability.

In conclusion, the results of this study show that the initial rate of absorption of a poorly absorbable drug, phenolsulfonphthalein, from solution can be increased by the coadministration of a widely used medicinal surfactant, dioctyl sodium sulfosuccinate. The extent of absorption was only slightly increased. The results obtained also indicate that inclusion of this surfactant with the nonabsorbable laxative, oxyphenisatin acetate, could be one reason for the observed hepatic toxicity of the combination dosage form (4).

Therefore, it is imperative, as suggested by Tucker (31), that the possible effects of this and other surfactants on the absorption of each drug with which they are to be used be fully assessed. The drastic rise in excretion rate of phenolsulfonphthalein during the 1st hr (Subject WG, Treatment B, Table I) is strong proof of the possible hazards that may result from a sudden unintentional rise of the blood level of a potentially dangerous drug.

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