Acceleration of Peritoneal Dialysis with Minimum Amounts of Dioctyl Sodium Sulfosuccinate

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Abstract □ Previous work had shown that dioctyl sodium sulfosuccinate accelerated peritoneal dialysis of urea. This study demonstrates the effectiveness of dioctyl sodium sulfosuccinate when used as a single, short-term lavage prior to dialysis with control fluid. Intermittent dialysis was used for evaluation. Urea and phosphate were removed at about twice the normal rate, while creatinine removal was not significantly affected.

Keyphrases □ Peritoneal dialysis—accelerated using dioctyl sodium sulfosuccinate □ Dialysis, peritoneal—short-term lavage with dioctyl sodium sulfosuccinate used to achieve increased urea and phosphate clearance rates □ Dioctyl sodium sulfosuccinate—short-term lavage prior to peritoneal dialysis, increased urea and phosphate clearance rates

In previous publications (1, 2), it was reported that peritoneal dialysis of urea could be accelerated by the addition of 0.01% dioctyl sodium sulfosuccinate to a standard dialysis fluid. Since absorption of dioctyl sodium sulfosuccinate from the peritoneum might be expected and little is known of its toxicity when administered in this manner, an effort was made to attain the beneficial effects of dioctyl sodium sulfosuccinate with minimum exposure. Results of this study are reported in this paper.

MATERIALS AND METHODS

Healthy mature male albino rabbits were used as the experimental animals. They were given 2 ml. of chlorpromazine injection, 25 mg./ml., intramuscularly about 30 min. prior to the experiment and were then injected intravenously with one of the compounds being studied—radiolabeled urea, creatinine, or phosphate. Thirty minutes was allowed in each case for the compound to be equilibrated in the tissues. At that time a blood sample was taken, and 60 ml./kg. of dialysis fluid was rapidly injected intraperitoneally *via* a pediatric-size catheter. At the end of the prescribed dwell time, the peritoneal fluid was drained by gravity through the same catheter into a graduated cylinder, a period of 10 min. being allowed for drainage in each case. At the end of drainage, another blood sample was taken and the next exchange of fluid was rapidly injected. The volume of return fluid was measured for each exchange, it was mixed thoroughly, and a sample of 0.5 ml. was taken for measurement. Plasma samples were measured in the same manner, pipeting 0.5 ml. directly into a counting vial, adding 10 ml. of scintillation fluid [1,4-bis-2-(5-phenyloxazolyl)benzene, 0.01%, and 2,5-diphenyloxazole, 0.4%, in a solvent of 33% nonionic wetting agent[1] and 67% toluene], and counting the vials in a liquid scintillation counter in the usual manner.

Counts were converted to disintegrations per minute by the channels ratio method and to micrograms per milliliter by comparison to a standard dilution of the appropriate injection counted at the same time. Results were expressed as clearances by multiplying the concentration in the dialysate by the dialysate volume, dividing by the time for each exchange (30 min.), and then dividing by the average plasma concentration for the samples taken at the beginning and end of the given exchange.

It was found in preliminary work that a single short-time exposure of the peritoneum to a 0.02% dioctyl sodium sulfosuccinate solution gave an accelerated dialysis effect which lasted throughout several subsequent exchanges with ordinary control fluid. A similar short-time exposure to control fluid had no significant effect on subsequent exchanges. On the basis of this finding, the test animals were subjected to a single intraperitoneal instillation of 0.02% dioctyl sodium sulfosuccinate fluid for a 5-min. dwell time and a 10-min. drainage; then five exchanges were run with control fluid, using 20-min. dwell periods and 10-min. drainage, giving 30-min. cycles. With urea tests, a group of test animals was run using five 30-min. exchanges with 0.01% dioctyl sodium sulfosuccinate fluid throughout. Controls were run in the same manner, except for elimination of the 15-min. exposure to dioctyl sodium sulfosuccinate fluid, thus using only control fluid for five exchanges.

The control fluid consisted of dextrose (1.5%), sodium lactate (0.5%), sodium chloride (0.56%), calcium chloride (0.026%), and magnesium chloride hexahydrate (0.015%) in water for injection. The dioctyl sodium sulfosuccinate fluids were prepared simply by dissolving the calculated amount of dioctyl sodium sulfosuccinate in the control fluid.

The radioactive compounds injected were ^{14}C-urea, 200 mg./ml., with 1.2 μc./ml., injected at a level of 200 mg./kg.; ^{14}C-creatinine, 50 mg./ml., with 0.6 μc./ml., injected at a level of 100 mg./kg.; and sodium ^{32}P-phosphate, 10 mg./ml., with 2 μc./ml., injected at a level of 20 mg./kg.

RESULTS

Results for urea, phosphate, and creatinine are summarized in Tables I–III, respectively. It is seen that 0.01% dioctyl sodium sulfosuccinate used throughout and control fluid following a 15-min. lavage with 0.02% dioctyl sodium sulfosuccinate gave urea clearances which were about equal, and both of these gave clearances nearly double that with controls. With phosphate, also, pretreatment with 0.02% dioctyl sodium sulfosuccinate gave about double that of controls. With creatinine the clearances varied appreciably from one animal to another in both control and test groups, as seen by the confidence limits, and the difference between test and control cannot be said to be significant, even though the group average for the test animals appeared to be higher.

DISCUSSION

The data clearly confirm the accelerating effect of dioctyl sodium sulfosuccinate on peritoneal dialysis of urea and demonstrate an equivalent acceleration of phosphate. Of particular importance is the finding that a single short-term lavage of dioctyl sodium sulfosuccinate fluid accelerates removal of urea and phosphate over at least five subsequent exchanges. This makes the amount of dioctyl sodium sulfosuccinate to which a patient might be exposed quite small (400 mg. in a single 2-l. lavage), and the time of exposure is short enough to minimize absorption into the general circulation. With these findings, the potential for use of dioctyl sodium sulfosuccinate as an accelerator for treatment of human uremia is greatly increased. Further work measuring the amounts absorbed is needed, however, before evaluation in humans.

The finding that creatinine dialysis is not accelerated by dioctyl sodium sulfosuccinate is disappointing and appears to be contrary to previous indications (1). Earlier work in which dialysis rate constants were estimated gave rate constants for creatinine nearly three times as great in the presence of the wetting agent, but dioctyl sodium sulfosuccinate was not tried at that time in intermittent dialysis. In the intermittent dialysis procedure, the amount removed or clearance is a function of the concentration gradients existing throughout the dwell period, and the effect of an accelerator may not be reflected if the dwell time is long enough to allow the system

[1] Triton X-100, Rohm & Haas, Philadelphia, Pa.

Table I—Peritoneal Urea Clearances[a] with Control Fluid, with 0.01% Dioctyl Sodium Sulfosuccinate, and with Control Fluid following a 15-min. Lavage with 0.02% Dioctyl Sodium Sulfosuccinate

Control Fluid		0.01% Dioctyl Sodium Sulfosuccinate		Control Fluid after 15-min. 0.02% Dioctyl Sodium Sulfosuccinate	
Animal Number	Average Clearance, ml./min.	Animal Number	Average Clearance, ml./min.	Animal Number	Average Clearance, ml./min.
O-33	1.46	141	2.82	O-28	2.16
140	1.29	143	2.96	O-29	2.74
142	1.79	145	2.30	O-30	2.23
144	1.13	146	3.04	O-31	3.27
D-15	1.71	147	2.41	O-32	3.73
Group mean and 95% confidence limits	1.48 ± 0.34		2.71 ± 0.41		2.83 ± 0.84

[a] Each average clearance represents an average of five clearances.

Table II—Peritoneal Phosphate Clearances[a] with Control Fluid and with Control Fluid following a 15-min. Lavage with 0.02% Dioctyl Sodium Sulfosuccinate

Control Fluid		Control Fluid after 15-min. 0.02% Dioctyl Sodium Sulfosuccinate Lavage	
Animal Number	Clearance, ml./min.	Animal Number	Clearance, ml./min.
C-11	0.60	C-12	1.27
C-13	0.44	C-14	0.70
C-16	0.44	C-15	1.14
		C-17	1.28
Group mean and 95% confidence limits	0.49 ± 0.53		1.10 ± 0.46

[a] See *Footnote* [a], Table I.

Table III—Peritoneal Creatinine[a] Clearances with Control Fluid and with Control Fluid following a 15-min. Lavage with 0.02% Dioctyl Sodium Sulfosuccinate

Control Fluid		Control Fluid after 15-min. 0.02% Dioctyl Sodium Sulfosuccinate Lavage	
Animal Number	Clearance, ml./min.	Animal Number	Clearance, ml./min.
C-2	0.96	C-1	1.82
C-3	0.91	C-4	3.51
C-5	2.66	C-7	4.70
C-6	3.71	C-9	3.72
C-8	1.87	C-10	2.47
Group mean and 95% confidence limits	2.02 ± 1.47		3.24 ± 1.39

[a] See *Footnote* [a], Table I.

to approach equilibrium in both test and control fluids. The high rate of excretion of creatinine in experimental animals causes the plasma level to drop rapidly and the plasma–dialysate system to reach equilibrium quickly. This appears to be the most likely reason for failure to obtain significantly higher clearances for creatinine in the presence of dioctyl sodium sulfosuccinate, recognizing that the difference must be large to be detected as significant. A rapid drop in plasma level *via* urinary excretion would not occur in the uremic patient; in such a case, dioctyl sodium sulfosuccinate may be found to accelerate the removal of creatinine. This possibility will be examined in the future by testing nephrectomized animals.

An increase in the rate of transfer of drugs across membranes has been reported by a number of workers, most of them concerned with membranes of the GI tract (3–7). Generally, the results were interpreted as physical effects of the wetting agents on the state of the drug to promote dissolution or dispersion. Davis *et al.* (8) found improved absorption of several antibiotics from a gastric pouch with certain wetting agents, and they demonstrated that the effect may persist for some time after removal of the wetting agent. They interpreted the hyperabsorption to the alteration of structure of the highly ordered membrane. The report of Mezei and Lee (9) is especially interesting in that they found surfactants to cause significant increases in turnover rates of phospholipids in epidermal membranes but little change in membrane composition. This finding indicated membrane damage resulting from contact with the surfactant. How widespread and how serious this damage may be is yet to be determined.

In this laboratory the dioctyl sodium sulfosuccinate dialysis fluid, after removal from the animal, was extracted with petroleum ether and with chloroform. The petroleum ether extract yielded no measurable residue upon evaporation, indicating the absence of neutral fats. The chloroform extract, on the other hand, yielded a residue of 3.7 mg. of solid. A sample of this solid was tested by the method of Keenan *et al.* (10) and was found to contain phosphatides. Further work is planned to identify the particular phosphatides present. This evidence agrees with the findings of Mezei and Lee (9) and strongly indicates that the wetting agent affects the structure of the mesentery membrane by removal of phospholipids.

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