Kidney International, Vol. 20 (1981), pp. 563–568

Enhancement of peritoneal dialysis clearance with docusate sodium

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Enhancement of peritoneal dialysis clearance with docusate sodium. A study was done in rabbits to determine the effect of docusate sodium (DSS) on the peritoneal clearance of creatinine and urea. Following a series of control exchanges with a commercially available peritoneal dialysis solution, three animals in each of four groups received DSS (0.005%, 0.01%, 0.02%, or 0.04%) in a single exchange, followed by 10 subsequent exchanges of control fluid. Creatinine and urea clearances were measured for each exchange. Comparison of post-DSS clearances (exchanges 5 through 15) with pre-DSS baseline values (exchanges 1 through 4) showed a mean percent increase in creatinine clearance that was proportional to the concentration and ranged from 74 to 244% above baseline. Similarly, urea clearance increased by 79 to 166%. The effect on both creatinine and urea clearance persisted through the completion of the dialysis procedure. No animals showed signs of toxicity from DSS. The mechanism of the DSS effect on clearance is unknown. Although studies are needed to delineate the mechanism of the effect and to identify potential toxic effects, the results of this study indicate that DSS has a significant effect on clearance of both creatinine and urea.

Augmentation de la clearance de dialyse péritonéale par le docusate de sodium. Une étude a été faite chez le lapin afin d'évaluer l'effet du docusate de sodium (DSS) sur la clearance péritonéale de la créatinine et de l'urée. Après une série d'échanges témoins avec une solution commerciale de dialyse péritonéale trois animaux dans chacun des quatre groupes a reçu du DSS (0,005%, 0,01%, 0,02%, ou 0,04%) dans un seul échange précédant 10 autres échanges avec du liquide contrôle. Les clearances de l'urée et de la créatinine ont été mesurées pour chaque échange. La comparison des clearances post-DSS (échanges 5 à 15) avec les valeurs pré-DSS (échanges 1 à 4) a montré un pourcentage moyen d'augmentation de la clearance de la créatinine proportionnel à la concentration de DSS et allant de 74 à 244% des valeurs basales. De la même façon la clearance de l'urée a augmenté de 79 à 166%. L'effet sur les clearances de la créatinine et de l'urée persiste jusqu'à la fin de la dialyse. Il n'a pas été observé de signe de toxicité du DSS. Le mécanisme de l'effet du DSS sur la clearance n'est pas connu. Bien qu'il soit nécessaire d'étudier le mécanisme de cet effet et d'identifier d'éventuels effets toxiques les résultats indiquent que le DSS a un effet significatif sur les clearances de la créatinine et de l'urée.

Peritoneal dialysis (PD) has become a recognized form of therapy for patients with acute and chronic renal failure [1–4] but so far its use remains limited. PD clearances are inadequate in some patients due to underlying vascular disease [5–7] and in others may decline over time for reasons that have not been defined [8]. The inherent limitation to the use of PD even under the best of circumstances is its inefficiency in the clearance of low molecular weight solutes compared with hemodialysis [9, 10]. As a consequence, long treatment times are required for control of uremic symptoms in patients receiving intermittent peritoneal dialysis (IPD). This problem is lessened to a certain extent with continuous ambulatory peritoneal dialysis (CAPD) [11, 12], but low clearances of urea and other small molecular weight solutes, which continue to be implicated in the pathogenesis of uremic toxicity, remain a stumbling block to the more widespread application of both IPD and CAPD.

A number of approaches have been explored in an attempt to augment peritoneal solute clearance. These include (*1*) altering dialysate dwell time, volume, or flow rate [13–16], (*2*) heating the dialysate solutions to body temperature [16], (*3*) using hypertonic dialysate solutions [17–20]; and (*4*) adding vasoactive agents [7, 20–29], diuretics [30] and surface active agents [31] to the dialysate solutions.

One promising area of research has involved the intraperitoneal administration of pharmacologic agents for the enhancement of clearance. In general, percentage increases in peritoneal clearance of creatinine seen with intraperitoneal accelerators range between 5 and 30% [24, 26, 28], although clearances as high as 50 to 55% above baseline have been reported [23]. Increases in urea clearances have been generally within the range of 5 to 20% [20, 27, 28], although, as in the case of creatinine, increases as high as 50% have been seen [23]. With the intraperitoneal administration of most accelerators tested, the effect on clearance rapidly disappears when the agent is removed from the dialysate solution [5, 23, 24, 26].

An earlier study in rabbits demonstrated an increase in the peritoneal clearance of radioactive urea and phosphate when docusate sodium (DSS) was added to the dialysate solution. Results regarding its effect on the peritoneal clearance of creatinine were, however, equivocal [31]. The present study was undertaken to examine further the potential value of the addition of DSS to the dialysis solution during peritoneal dialysis on the clearance of endogenous creatinine and urea. In addition, four separate concentrations of DSS (0.005%, 0.01%, 0.02%, and 0.04%) were studied to determine whether there is a dose-response relationship to increasing DSS concentrations.

Methods

Peritoneal dialysis was performed in 12 male New Zealand white rabbits with normal renal function. To prevent agitation,

Received for publication October 1, 1980
and in revised form February 13, 1981

0085-2538/81/0020-0563 $01.20

we gave each animal 50 mg of chlorpromazine hydrochloride i.m. prior to the dialysis procedure and subsequently restrained them. One animal required an additional dose of chlorpromazine during the dialysis procedure due to agitation.

An area in the anterior midline selected for catheter insertion was shaved and anesthetized. A pediatric peritoneal dialysis catheter was inserted and sutured into place. The external end of the catheter was fitted with polyethylene tubing extending into a 100-ml graduated cylinder placed for collection and measurement of dialysate drainage fluid.

Of the 12 animals studied, 10 animals received 15 peritoneal dialysis exchanges in the following sequence: 4 exchanges of control fluid, 1 exchange of control fluid to which DSS was added, and 10 additional exchanges of control fluid. Two animals received one extra exchange during the initial control period because of low drainage volume during the first exchange. These two animals received DSS in the 6th dialysis exchange, and received only 9 exchanges of control fluid following DSS administration.

Control cycles consisted of a commercially available solution containing: 1.5% dextrose, 141 mEq/liter sodium, 101 mEq/liter chloride, 45 mEq/liter lactate, 3.5 mEq/liter calcium, and 1.5 mEq/liter magnesium (Dianeal® Peritoneal Dialysis Solution with Dextrose, Travenol Laboratories, Deerfield, Illinois). The DSS exchange contained DSS in a concentration of 0.005%, 0.01%, 0.02%, or 0.04%, prepared by dissolving DSS (docusate sodium, USP, American Cyanamid Company, Pearl River, New York) in the standard Dianeal® solution. Three animals were dialyzed at each of the four DSS concentrations.

The dialysate exchange volume for each animal was 25 ml/kg of body wt. The dialysate was warmed to 37° C and instilled into the peritoneal cavity over 1 min via sterile syringe. A dwell time of 19 min and a drainage time of 10 min completed the total dialysis cycle time of 30 min.

Blood samples were obtained from the marginal ear vein of each animal prior to the beginning of dialysis, at the end of the control period, and at the completion of dialysis. The samples were centrifuged, and the plasma was removed. An equal volume of 0.2 M citrate buffer (pH, 6.25) was added to the plasma, which was then filtered through a 0.22-μ filter. At the end of each dialysis exchange, a 10-ml aliquot of the fluid was obtained and filtered undiluted through a 0.22-μ filter. All plasma and dialysate samples were then either analyzed within 3 hours for urea and creatinine or frozen at −20° C until the time of assay.

Creatinine concentration in plasma and dialysate samples was measured by high-performance liquid chromatography (HPLC) by a modification of the Jaffe reaction [32] that eliminated noncreatinine chromogens. A stainless-steel column of 4.6 mm in I.D. and 25 cm in length was packed with a strong cation exchange resin (Aminex A-4®, Bio-Rad Company, Richmond, California). Citrate buffer (0.2 M; pH, 6.25) was pumped through the column continuously at a rate of 0.5 ml/min. The apparatus was fitted with a loop injector to accept samples of up to 0.5 ml. A solution of sodium picrate (90 ml of saturated solution of picric acid plus 10 ml of 0.5 N sodium hydroxide) was added continuously to the column effluent. Solutions were pumped at a constant rate via an HPLC Pumping System (Glenco Scientific Company, Houston, Texas). The combined solutions were passed through a flow-type colorimeter (Altex Model 150B with 510 nm detector, Altex Scientific Corporation, Berkeley, California). The signal was recorded on a laboratory recorder (Strip Chart Recorder, No. 7123A, Hewlett-Packard, San Diego, California).

Creatinine content of the samples was calculated by comparison of peak areas to the peak area of a creatinine standard. DSS did not interfere with the determination of creatinine by this method.

Urea concentration in plasma and dialysate was analyzed with a commercially available Urea Nitrogen (BUN) Rapid Stat® Kit (Pierce Chemical Company, Rockford, Illinois). Absorbance of the colored reaction product was measured on a spectrophotometer (Hitachi-Perkin Elmer 139 UV-VIS Spectrophotometer, Perkin Elmer Corporation, Newark, Delaware) at a wavelength of 525 nm. Urea nitrogen concentration in each sample was calculated by comparison of its absorbance with that of a urea nitrogen standard. DSS did not interfere with the determination of urea nitrogen by this method.

Mean solute clearances were calculated for each dialysis exchange according to the following equation:

$$\text{Clearance} = \frac{(V_D)\,(C_D)}{(C_P)\,(t)} \qquad (1)$$

where V_D is the dialysate drainage volume; C_D, the dialysate solute concentration; C_P, the mean plasma solute concentration during dialysis; and t, the total dialysis cycle time.

The plasma concentrations represent the mean of the three measured values in each animal, obtained at the previously described sampling times. Prior to statistical analysis, all clearance values (ml/min) were adjusted for differences in animal weight and expressed as ml/min/kg.

Analysis of variance (ANOVA) and Duncan's Multiple Comparison Tests were performed with the statistical package "Statistical Analysis System" (SAS) available at the Triangle Universities Computation Center (TUCC), Research Triangle Park, North Carolina. A P value of less than 0.05 was considered significant.

Results

Individual clearances of creatinine and urea before and after DSS administration are shown for each animal in Table 1. Mean clearances of creatinine and urea for all 12 rabbits are shown for each dialysis exchange in Fig. 1. The mean creatinine clearance before DSS was 0.14 ± 0.01 ml/min/kg. Following DSS administration during the 5th dialysis exchange, the clearance of creatinine increased and remained elevated with a mean post-DSS clearance of 0.34 ± 0.01 ml/min/kg. The corresponding changes in urea clearance were 0.18 ± 0.12 ml/min/kg before DSS, and 0.37 ± 0.02 ml/min/kg after DSS. The increases in clearance resulting from the addition of DSS to a single dialysis exchange persisted throughout the remaining exchanges.

Table 2 shows mean creatinine and urea clearances grouped according to the DSS concentration utilized. The rank order increase in mean clearance values for both solutes is apparent. During the control period, however, mean clearances of individual animals (Table 1) of creatinine and urea ranged from 0.09 to 0.22 and from 0.06 to 0.33 ml/min/kg, respectively. This wide range in clearance for both solutes during the control period necessitated normalization for differences in means among the

Table 1. Mean control and post-DSS clearance of creatinine and urea[a]

Animal no.	Wt *kg*	DSS concentration %	C_{Cr} *ml/min/kg* Control (Exchanges 1–4)	C_{Cr} *ml/min/kg* Post-DSS (Exchanges 5–15)	C_{Urea} *ml/min/kg* Control (Exchanges 1–4)	C_{Urea} *ml/min/kg* Post-DSS (Exchanges 5–15)
1	2.33	0.005	0.19 ±0.05	0.25 ±0.10	0.15 ±0.04	0.26 ±0.07
2	2.65	0.005	0.14[b] ±0.06	0.20 ±0.04	0.19 ±0.07	0.21 ±0.05
3	2.55	0.005	0.09 ±0.01	0.22 ±0.06	0.06 ±0.02	0.15 ±0.07
4	4.33	0.01	0.17 ±0.05	0.41 ±0.09	0.08 ±0.04	0.18 ±0.06
5	2.84	0.01	0.11 ±0.01	0.26 ±0.05	0.33 ±0.03	0.46 ±0.13
6	2.69	0.01	0.10 ±0.02	0.22 ±0.06	0.25 ±0.07	0.52 ±0.10
7	4.19	0.02	0.10[b] ±0.02	0.32 ±0.05	0.14 ±0.03	0.53 ±0.03
8	2.17	0.02	0.22 ±0.08	0.42 ±0.10	0.16 ±0.05	0.29 ±0.08
9	2.92	0.02	0.14 ±0.02	0.29 ±0.07	0.19 ±0.04	0.37 ±0.08
10	2.03	0.04	0.20 ±0.04	0.65 ±0.15	0.27 ±0.02	0.70 ±0.15
11	4.01	0.04	0.11 ±0.03	0.32 ±0.13	0.20 ±0.06	0.58 ±0.19
12	2.82	0.04	0.11 ±0.02	0.46 ±0.20	0.10 ±0.02	0.25 ±0.05

[a]Clearances are the means ± SD.
[b]Received an extra control exchange and one less post-DSS exchange

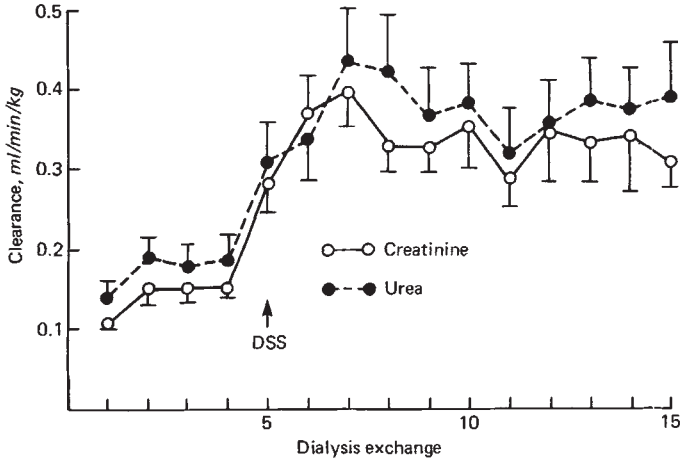

Fig. 1. *Influence of DSS on creatinine and urea clearance.*

various concentrations prior to statistical analysis. Accordingly, the clearances of creatinine and urea during the control period (exchanges 1 through 4) were used to calculate a mean baseline for each rabbit. This value was then used to determine the percent change in creatinine and urea clearances following addition of DSS to the dialysate (post-DSS). Percent change in clearance was thus defined as follows:

$$\% \text{ change} = \frac{(\text{post-DSS clearance}) - (\text{pre-DSS clearance})}{(\text{pre-DSS clearance})} \times 100\% \quad (2)$$

Percent changes in creatinine and urea clearances were computed for individual dialysis exchanges for each rabbit. Mean percent changes in creatinine and urea clearance were subsequently grouped according to concentration for determination of the influence of DSS concentration on clearance. Figures 2 and 3 show mean percent change for clearances of creatinine and urea, respectively, at each of the four concentrations of DSS. As can be seen from these figures, there were substantial increases in clearance throughout exchanges 5 through 15, which were proportional to concentration.

The bar graph in Fig. 4 illustrates the average post-DSS change in creatinine and urea clearances at each concentration. Even at a concentration of 0.005% DSS, there was approximately a 75% increase in both creatinine clearance ($P < 0.001$)[1] and urea clearance ($P < 0.001$). Clearance of creatinine continued to show statistically significant increases even at the 0.04% concentration ($P < 0.05$) over the 0.02% concentration. In contrast, the clearance of urea appeared to plateau with the 0.02% concentration at a mean percent change of approximately 150% relative to control clearance values.

Because only three rabbits were studied at each concentration, the relative influence of DSS concentration on clearances was also determined by median data. Nonparametric analysis of variance (Wilcoxon Rank Sum Test) also showed percent increase in clearance grouped by concentration to be statistically significant ($P < 0.001$).

[1]ANOVA for paired samples (crossover design)

Table 2. Effect of DSS concentration on creatinine and urea clearances[a]

DSS concentration %	No. of rabbits	C_{Cr} *ml/min/kg*	C_{Urea} *ml/min/kg*
0.005	3	0.23 ± 0.01	0.21 ± 0.01
0.01	3	0.30 ± 0.02	0.39 ± 0.03
0.02	3	0.34 ± 0.02	0.39 ± 0.02
0.04	3	0.48 ± 0.04	0.51 ± 0.04

[a]Baseline creatinine and urea clearances for all 12 rabbits prior to administration of DSS were 0.14 ± 0.01 ml/min/kg and 0.18 ± 0.01 ml/min/kg, respectively. Clearances are the means ± SEM.

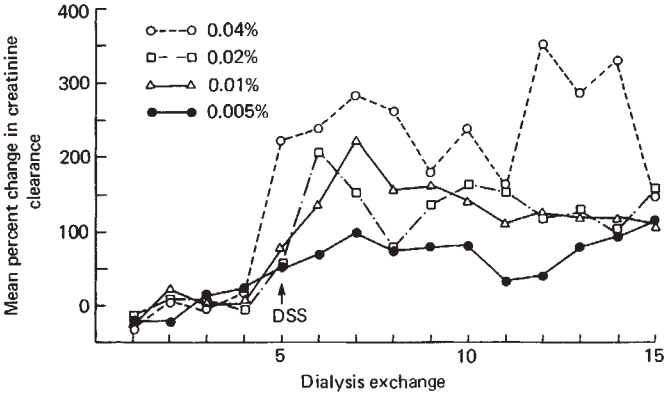

Fig. 2. *Influence of DSS on the clearance of creatinine.*

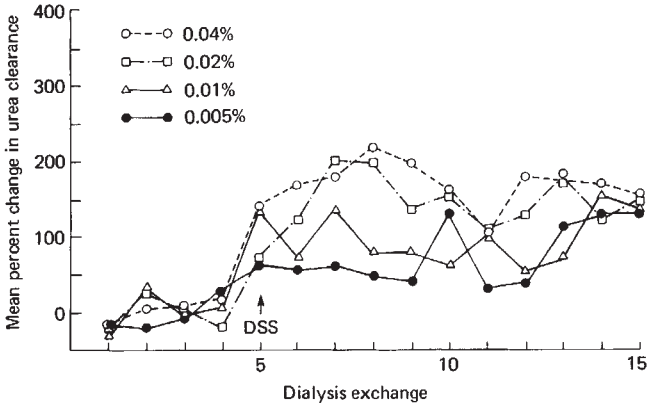

Fig. 3. *Influence of DSS on the clearance of urea.*

The hydration state of the animals remained constant throughout the procedure. Although we anticipated that the wetting properties of DSS might promote an increased drainage of dialysate fluid, analysis of the drainage volumes of all animals revealed no significant change following DSS administration. On the other hand, increases in dialysate creatinine and urea concentrations essentially paralleled the changes in clearance.

No changes in animal behavior were noted during cycles with dialysis fluid containing DSS as compared with control fluid alone. But some fibrinous material was noted in the dialysate

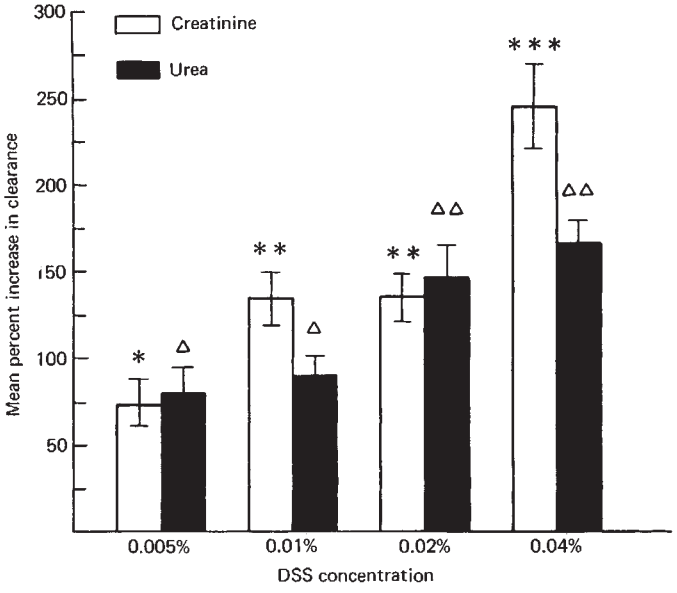

Fig. 4. *Change in creatinine and urea clearance following DSS addition to dialysate.* Each bar represents the mean response for all post-DSS exchanges in 3 rabbits. Bars with different symbol numbers are significantly different ($P < 0.05$).

drainage fluid of two animals receiving 0.04% DSS. Only trace amounts were observed in the fluid from the other animals, and no increase was noted in the post-DSS exchanges relative to the initial control exchanges.

Discussion

Based on the results obtained from this study, it is evident that DSS produces a significant increase in urea and creatinine clearance. Following the addition of DSS to a single dialysis exchange, the percent increase in creatinine clearance relative to baseline values ranged from 74 to 244%, and urea clearance increased by 79 to 166%. In addition to the overall increase in solute clearance, the magnitude of the effect correlated with increasing DSS concentrations, particularly so in the case of creatinine. Furthermore, the addition of DSS to a single dialysate exchange resulted in an increase in clearance that persisted for the duration of the dialysis procedure without a return toward baseline. Thus, the results of this study appear superior to those produced by other accelerators with respect to both the magnitude and the duration of the observed effect on clearance.

The mechanism of the DSS effect on promoting increases in peritoneal solute clearance is unknown. Based on earlier work exploring the potential of DSS as an accelerator, it was postulated that the effect of DSS might be related to an alteration in the structure of the peritoneal membrane due to the removal of phospholipids. This proposal was based upon the recovery of a significant quantity of phosphatides from dialysate return fluid [31]. Further work is currently underway in this laboratory with regard to the effect of DSS on membrane phospholipids.

The notable increases effected by DSS on urea clearance lead to further speculation on the effects of DSS. Nolph and Sorkin [33] recently proposed that the main limitations to urea clearance are due to peritoneal interstitial resistance and stagnant or unstirred dialysate fluid films. The ability of DSS to effect a

marked increase in urea clearance may result in part from an effect on interstitial resistance or on the unstirred layers, possibly through its surfactant properties.

Of particular significance is the finding that the increased clearances of urea and creatinine persisted throughout the duration of the dialysis procedure following a single exposure to DSS. The value of an accelerating agent that could effect a prolonged increase in clearance with a single exposure is unquestionable. Although the mechanism by which this effect occurs also remains unclear, several possible explanations for this observation are feasible. One is that DSS reversibly affects membrane phospholipids, resulting in a prolonged increase in clearance, but with eventual regeneration of the phospholipid component and return of peritoneal clearances to their baseline values. Alternatively, the continued clearance increase could reflect a permanent change in the membrane. Finally, the extended effect may relate to partitioning of DSS into the membrane, with the duration of its effect dependent on the kinetics of DSS removal from the membrane. Confirmation of the mechanism of DSS on increasing clearance as well as the nature of its persistent effect on clearance will require further investigation.

The contributing effect of continual dialysis on clearance increases might be questioned, because no animals in this study received only control fluid for the entire dialysis procedure. In our study, 4 to 5 control exchanges were performed in each animal prior to the administration of DSS. As can be clearly seen from Fig. 1, clearance values for both urea and creatinine stabilized during the baseline exchanges. Statistical analysis revealed no significant difference in control clearances of either solute during the 3rd and 4th exchanges. In addition, the highly significant concentration-related effect of DSS on clearance (not demonstrable during baseline) strongly argues against the increase resulting from continual dialysis.

The fibrinous material noted in the dialysate return fluid from two animals following the administration of 0.04% DSS is of interest. Fibrin clots and other debris are commonly seen in the dialysate drainage fluid of patients receiving PD, and the presence of fibrin in the dialysate is often increased in patients with peritonitis. Whether the increased formation of fibrin clots in these two study animals is indicative of peritoneal inflammation with the higher concentration of DSS is unknown, because the animals were not sacrificed for pathologic examination. Also white blood cell counts were not obtained on dialysate drainage fluid as an index of inflammation; this finding, however, is being evaluated in current studies of DSS in this laboratory.

The results of this study, although preliminary in nature, are very promising, as the magnitude and duration of the clearance increases with docusate sodium exceed those seen with other accelerators. Should ongoing animal studies fail to demonstrate toxicity associated with its use, further study will be clearly warranted to investigate the clinical value of DSS in improving peritoneal dialysis clearance.

Acknowledgments

The authors wish to thank Dr. W. D. Mattern for his advice and suggestions in preparation of this manuscript.

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