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Efficacy of Hemodialysis and the Effects of Certain Displacing Agents on Plasma Protein Binding of Sulfamethoxazole and Sulfaphenazole in Patients with Chronic Renal Failure

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The binding of sulfamethoxazole and sulfaphenazole to the plasma protein of 7 patients with chronic renal failure, undergoing chronic hemodialysis, was studied by the equilibrium dialysis method and the results were compared with those for 12 normal subjects.

The binding percentages of the two sulfonamides were found to be impared in the patients' plasma as compared with normal plasma. The binding percentages increased in the patients' plasma after hemodialysis except in the cases of 2 patients for sulfamethoxazole (SMX) and 1 patient for sulfaphenanzole (SPH).

The effect of hemodialysis on drug protein binding was examined by calculating the percentage displacement of bound sulfonamides by oxyphenbutazone and sulfinpyrazone. Percentage displacements were higher in the patients' plasma than in normal plasma. The percentage displacement decreased in the patients' plasma after hemodialysis, except in the cases of 1 patient for SMX and 1 patient for SPH.

Such a decrease in the percentage displacement after hemodialysis suggests that the drug binding activity of plasma albumin can be improved through hemodialysis for patients with chronic renal failure.

Keywords——chronic renal failure; hemodialysis; equilibrium dialysis; sulfonamides; displacing activity; percentage of displacement; Scatchard's plots; protein binding

It is well known that drug protein binding can appreciably influence the free concentration of many drugs and affect their pharmacokinetic properties and pharmacological activities.

The degree of drug binding to plasma protein may be influenced by many factors, such as the physicochemical properties of the drug, the plasma protein concentration, the presence of other drugs or endogenous substances, and disease states.[2—7]

Many reports have been published on the effects of various disease states on the binding of drugs to plasma protein.

In the present investigation, the protein binding of sulfamethoxazole (SMX) and sulfaphenazole (SPH) in the plasma of patients with chronic renal failure, undergoing chronic therapeutic hemodialysis, was studied by the equilibrium dialysis method and the results were compared with those observed in normal plasma.

Furthermore, the displacing effects of oxyphenbutazone (OPB) and sulfinpyrazone (SPZ) on the binding of SMX and SPH to plasma protein were compared in these patients and

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2) J. Rieder, *Arzneim.-Forsch.*, **13**, 84 (1963).
3) W. Scholtan, *Arzneim.-Forsch.*, **14**, 348 (1964).
4) M. Nakagaki, N. Koga, and H. Terada *Yakugaku Zasshi*, **83**, 586 (1963).
5) M.C. Meyer and D.E. Guttman, *J. Pharm. Sci.*, **57**, 895 (1968).
6) J.J. Vallner and L. Chen., *J. Pharm. Sci.*, **66**, 447 (1977).
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in normal subjects, in order to develop an appropriate method for evaluating the binding activity of plasma of patients with chronic renal failure.

Experimental

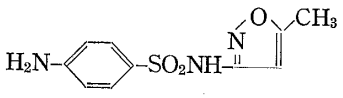
Materials——Human albumin (HA) (fraction V, Sigma Chemical Co., U.S.A.) was used; its molecular weight was assumed to be 69000.

Reagent grade KH_2PO_4, Na_2HPO_4 and NaCl were used to prepare 0.1 M isotonic phosphate buffer solution.

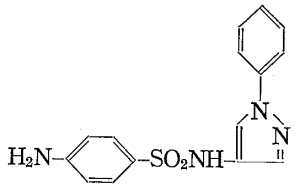
All other substances were purchased from commercial sources.

Sulfamethoxazole, sulfaphenazole, oxyphenbutazone and sulfinpyrazone were recrystallized before use.

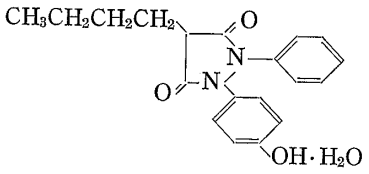
Sulfamethoxazole	(SMX)	mp 168—171°
Sulfaphenazole	(SPH)	mp 180—182°
Oxyphenbutazone	(OPB)	mp 93°
Sulfinpyrazone	(SPZ)	mp 131—132°



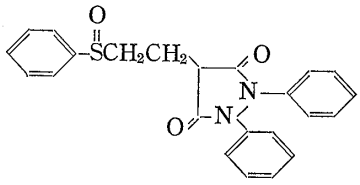
sulfamethoxazole (SMX)



sulfaphenazole (SPH)



oxyphenbutazone (OPB)



sulfinpyrazone (SPZ)

Chart 1. Drugs used in This Study

Patients and Normal Subjects——Seven patients with chronic renal failure and 12 normal subjects participated in this study.

All the patients were undergoing chronic therapeutic hemodialysis 1—3 times a week at the Renal Unit, National Sanatorium of Nishi-Sapporo Hospital in Sapporo. Hemodialysis was usually carried out for 6 hours.

The diagnosis, BUN values and drugs given to the patients are listed in Table I. All clinical laboratory test data shown in Table I were supplied by the Clinical Pathological Unit, National Sanatorium of Nishi-Sapporo Hospital.

The normal subjects were 12 healthy adults aged from 19 to 46 years, consisting of student nurses at the National Sanatorium of Nishi-Sapporo Hospital, and students and members of the staff at Higashi-Nippon Gakuen University.

Plasma——In all plasma samples studied, only heparin was used as an anticoagulant. Blood samples were collected just before the start of hemodialysis, and also just before the termination of hemodialysis, through a needle puncture of the cellophan dialysis coil.

The plasma samples from the patients and normal subjects were obtained by centrifugation of blood samples and were used for drug protein binding experiments. All plasma samples were stored at 4° and were used within one week. Protein and albumin contents in plasma were determined by electrophoresis using a Densitron 20 M (Joko Co., Japan).

Binding Experiment——The extent of binding of drugs to plasma was determined by the equilibrium dialysis method as described previously.[8] The medium used was 0.1 M isotonic phosphate buffer, pH 7.4. The osmotic pressure of the buffer was determined with a Knauer semimicro osmometer.

The outer compartment contained the isotonic phosphate buffer together with a drug at a concentration of 100 μg/ml in a total volume of 2 ml. The inner compartment (seamless cellulose tubing; Visking Co.) contained 0.5 ml of plasma. Incubation was carried out for 24 hours at 37° with constant mild shaking.

8) T. Arita, R. Hori, M. Takada and A. Misawa, *Chem. Pharm. Bull.*, **19**, 930 (1971).

Table I. Clinical Data for Patients with Chronic Renal Failure[a] and Normal Subjects

	Sex	Age	Diagnosis	BUN (mg/dl) Hemodialysis[b] before	BUN (mg/dl) Hemodialysis[b] after	Drugs[c]
Patients						
No. 1	Male	55	Nephrectomy	95.8	49.2	Alumigel 3.0 g/day
No. 2	Male	43	Malignant hypertension	121.5	65.8	Alumigel 3.0 g/day
No. 3	Male	52	Chronic nephritis	75.4	41.2	Alumigel 3.0 g/day, Festal 3T, and Mg. ust 1.0 g/day
No. 4	Male	18	Chronic nephritis	83.8	37.3	Alumigel 3.0 g/day
No. 5	Female	16	Chronic nephritis	92.7	43.1	Alumigel 3.0 g/day
No. 6	Female	15	Chronic nephritis	85.0	23.1	Alumigel 3.0 g/day
No. 7	Female	15	Chronic nephritis	94.6	27.7	Alumigel 3.0 g/day

	Sex	Age		Sex	Age
Normal Subjects					
No. 1	Male	46	No. 7	Female	19
No. 2	Male	22	No. 8	Female	19
No. 3	Male	23	No. 9	Female	20
No. 4	Female	26	No. 10	Female	19
No. 5	Female	26	No. 11	Female	20
No. 6	Female	19	No. 12	Female	19

a) These patients were being treated by chronic intermittent hemodialysis.
b) Blood samples were obtained as described in "Experimental."
c) Drugs administered for treatment.

Upon attainment of equilibrium, the contents of the outer compartment were separated. The sulfonamides were analyzed by diazotization.[9]

Method of Evaluating the Sulfonamide-Displacing Activity of a Drug——Two pyrazolone derivatives, OPB and SPZ, were used, and their ability to interfere with the binding of sulfonamides to plasma proteins was compared in patients with chronic renal failure and in normal subjects.

The parameter used is referred to as "percentage displacement" and is defined as follows:[10]

$$\beta = \frac{B - B_i}{B} \times 100\ (\%)$$

where β is the percentage displacement *in vitro*; B is the percentage of SMX or SPH bound in the absence of a competing drug; B_i is the percentage of SMX or SPH bound in the presence of a competing drug. All drugs were used at a level of 100 μg/ml in this work.

Results

Binding of Sulfonamides to HA

The binding of SMX and SPH to crystalline HA was evaluated by the equilibrium dialysis method. Scatchard plots of the data indicate the presence of two classes of binding sites for SMX and SPH (Figs. 1 and 2).

The association constant for binding (K, M^{-1}) and the number of binding sites (n) were estimated by graphic analysis.

The data for SMX obtained from the Scatchard plots are as follows: $n_1=0.515$, $K_1=1.60\times10^4\,M^{-1}$, $n_2=5.56$, $K_2=2.16\times10^2\,M^{-1}$. Those for SPH are as follows: $n_1=1.14$, $K_1=9.61\times10^4\,M^{-1}$, $n_2=5.41$, $K_2=5.34\times10^2\,M^{-1}$.

Judging from these results, it is evident that SPH possesses a considerably higher affinity for HA than does SMX. The results of this investigation are consistent with the data reported by Kaneo[10] and Rieder.[2]

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10) Y. Kaneo, A. Nishikawa, Y. Kato and S. Kiryu, *Yakugaku Zasshi*, **98**, 1452 (1978).

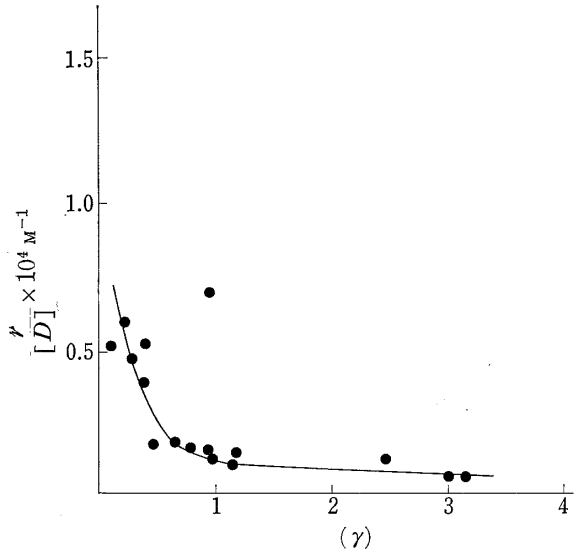

Fig. 1. Scatchard Plots of SMX binding to HA (4 g per 100 ml)

(r), number of mol of SMX bound per mol of HA.
[D], molar concentration of free SMX.

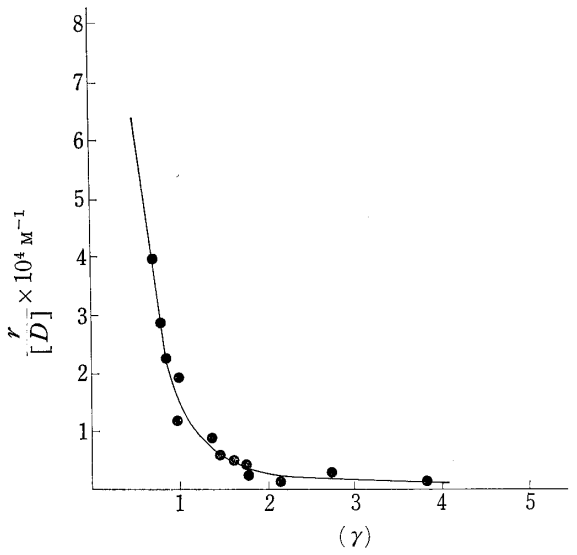

Fig. 2. Scatchard Plots of SPH binding to HA (4 g per 100 ml)

(r), number of mol of SPH bound per mol of HA.
[D], molar concentration of free SPH.

Plasma Binding of Sulfonamides in Patients with Chronic Renal Failure before and after Hemodialysis and in Normal Subjects

The protein binding of SMX and SPH in the plasma of 7 patients with chronic renal failure before and after hemodialysis, and in the plasma of 5 normal subjects was investigated in 0.1 M isotonic phosphate buffer, pH 7.4.

Calculations of the binding were based on a sulfonamide concentration of 100 μg/ml, and the results were expressed as percentages of the drugs bound.

TABLE II. Drug Protein Binding in Patients with Chronic Renal Failure[a] before and after Hemodialysis, and in Normal Subjects

	Total protein (g/dl)		Albumin Conc. (g/dl)		Binding of drugs (% bound)[b] SMX		SPH	
	before	after	before	after	before	after	before	after
Patients								
No. 1	6.4	6.7	4.6	5.0	40.8	43.7	77.3	77.5
No. 2	6.6	6.8	4.3	4.3	40.8	28.9	73.3	73.1
No. 3	7.4	8.4	4.8	4.9	34.1	46.5	79.6	85.4
No. 4	6.7	7.2	4.8	5.1	28.2	45.2	78.9	82.2
No. 5	7.0	7.2	4.6	4.9	28.2	17.6	69.4	76.8
No. 6	7.1	8.4	4.9	5.5	14.2	45.2	54.5	85.0
No. 7	6.9	7.2	4.9	5.1	35.8	59.0	77.3	86.2
Mean±S.D.	6.9±0.3	7.4±0.7	4.7±0.2	5.0±0.4	31.7±9.3	40.9±13.5	72.9±8.9	80.9±5.1
Normal subjects								
No. 1	7.7		5.1		64.6		87.9	
No. 2	8.6		5.7		72.6		92.2	
No. 3	8.5		5.6		69.2		90.2	
No. 4	9.3		6.0		69.0		90.5	
No. 5	9.1		5.6		69.7		91.2	
Mean±S.D.	8.6±0.6		5.6±0.3		69.0±2.9		90.4±1.6	

a) Drug protein binding in the patients was determined before and after hemodialysis.
b) Protein binding was determined at 100 μg/ml of each sulfonamide.

The data are listed in Table II.

The total protein and albumin concentrations of each patient appeared to be at a normal level, and the differences of concentration before and after hemodialysis did not show any particular pattern that could be associated with altered binding.

The five normal subjects showed a remarkable consistency in binding to plasma protein for SMX; 69.0±2.6% of SMX was bound to the plasma protein. In contrast, the 7 patients with chronic renal failure showed marked interindividual variability; the binding of SMX to plasma in the patients was less than that in normal plasma (31.7±8.6% before hemodialysis and 40.9±12.5% after hemodialysis). It is interesting that the percentage binding unexpectedly decreased after hemodialysis in 2 patients (Patients 2 and 5 in Table II).

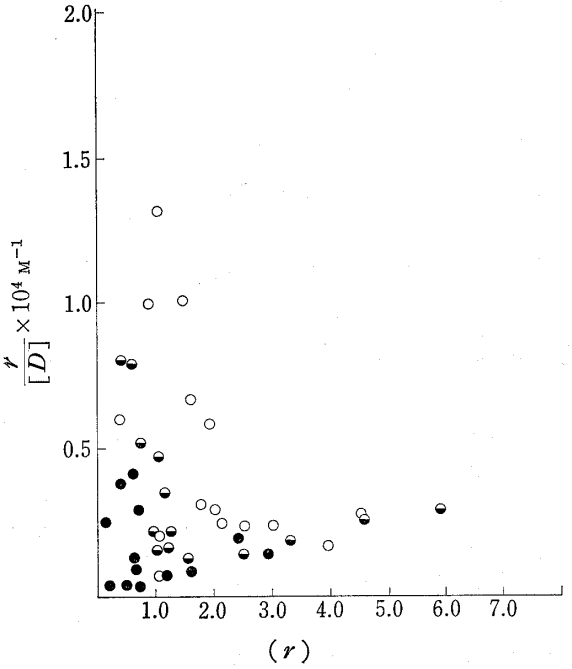

Fig. 3. Scatchard Plots of the Binding of Sulfaphenazole to Normal Plasma (○) and the Patients' Plasma before Hemodialysis (●) and to the Patients' Plasma after Hemodialysis (◒)

Plasma was pooled from 7 normal subjects, from 7 patients before hemodialysis, and from the same patients after hemodialysis for these experiments.

In the case of SPH, as shown in Table II, the 5 normal subjects showed great consistency in the plasma protein binding of SPH; 90.4±1.4% of SPH was bound to plasma protein. In contrast, the 7 patients with chronic renal failure showed moderate interindividual variability in the plasma protein binding of SPH; in addition, the binding was less than that of normal plasma (72.9±8.2% before hemodialysis and 80.9±4.7% after hemodialysis). It is noteworthy that the degree of binding before and after hemodialysis remained almost the same in 2 patients (Patients 1 and 2 in Table II).

Table II indicates that the binding percentages of sulfonamides (both SMX and SPH) in most of the patients increased after hemodialysis as compared with the values before hemodialysis, and approached those recorded for normal subjects.

Plasma from 7 patients and from 7 normal subjects (Nos. 6—12) were each pooled and used for binding experiments with SPH. The results were analyzed by Scatchard's method.

Typical Scatchard plots for SPH binding are shown in Fig. 3. It is clear that the protein binding of SPH in the patients' plasma is lower than that in normal plasma.

Figure 3 also indicates that the binding activity of the patients' plasma approached that of normal plasma after hemodialysis.

The Displacing Effects of OPB and SPZ on the Binding of Sulfonamides to Plasma of Patients with Chronic Renal Failure and Normal Subjects

It is well known that plasma albumin binds OPB and SPZ strongly, and OPB and SPZ readily displace certain acidic drugs.[11] In this experiment, OPB and SPZ were used to assess the binding characteristics of plasma of patients with chronic renal failure.

Although OPB and SPZ were both used to displace plasma-bound SPH, only SPZ was used in the case of SMX binding.

The results are shown in Table III—V.

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TABLE III. Displacing Effect of Sulfinpyrazone on the Protein Binding of Sulfamethoxazole in Patients with Chronic Renal Failure before and after Hemodialysis, and in Normal Subjects[a]

	Binding without SPZ (%)		Binding with SPZ (%)		Percentage displacement[b] (%)	
	before	after	before	after	before	after
Patients						
No. 1	40.8	43.7	13.5	15.4	66.9	64.8
No. 2	40.8	28.9	20.4	1.2	50.1	95.8
No. 3	34.1	46.5	5.5	18.8	83.8	59.6
No. 4	28.2	45.2	3.5	22.8	87.6	49.5
No. 5	28.2	17.6	9.7	9.7	65.5	44.5
No. 6	14.2	45.2	—	—	—	—
No. 7	35.8	59.0	8.7	42.7	75.6	27.6
Mean±S.D.	31.7±9.3	40.9±13.5	10.2±6.1	18.4±14.1	71.6±13.7	57.0±23.0
Normal subjects						
No. 1	64.6		33.9		47.5	
No. 2	72.6		55.8		23.2	
No. 3	69.2		57.2		17.4	
No. 4	69.0		54.7		20.8	
No. 5	69.7		55.1		21.0	
Mean±S.D.	69.0±2.9		51.3±9.8		26.0±12.2	

a) Drug protein binding and the displacement by sulfinpyrazone were determined before and after hemodialysis.
b) Percentage displacement=$[(B-B_i)/B]\times 100$ (%), where B is the binding percentage of sulfaphenazole alone, and B_i is that in the presence of the displacing agent.

TABLE IV. Displacing Effect of Oxyphenbutazone on the Protein Binding of Sulfaphenazole in Patients with Chronic Renal Failure before and after Hemodialysis, and in Normal Subjects[a]

	Binding without OPB (%)		Binding with OPB (%)		Percentage displacement[b] (%)	
	before	after	before	after	before	after
Patients						
No. 1	77.3	77.5	68.5	74.2	11.4	4.3
No. 2	73.3	73.1	64.2	68.2	12.4	6.8
No. 3	79.6	85.4	69.8	77.2	12.3	9.5
No. 4	78.9	82.2	71.0	78.2	10.0	5.0
No. 5	69.4	76.8	60.6	71.6	12.8	6.8
No. 6	54.5	85.0	48.8	79.4	10.4	6.4
No. 7	77.3	86.2	—	—	—	—
Mean±S.D.	72.9±8.9	80.9±5.1	63.8±8.3	74.8±4.3	11.6±1.1	6.4±1.7
Normal subjects						
No. 1	87.9		82.6		6.0	
No. 2	92.2		84.9		7.9	
No. 3	90.2		85.8		5.0	
No. 4	90.5		87.3		3.6	
No. 5	91.2		84.8		7.1	
Mean±S.D.	90.4±1.6		85.1±1.7		5.9±1.7	

a) Drug protein binding and the displacement by oxyphenbutazone were determined before and after hemodialysis.
b) Percentage displacement=$[(B-B_i)/B]\times 100$ (%), where B is the binding percentage of sulfaphenazole alone, and B_i is that in the presence of the displacing agent.

As shown in Table III, SPZ shows strong displacing activity towards protein-bound SMX in the patients' plasma (71.6±13.7% before hemodialysis, 57.0±23.0% after hemodialysis). It is noteworthy that, in patient No. 7, the percentage displacement after hemodialysis decreased by about one-third compared with that before hemodialysis. It is also noteworthy that in patient No. 2 the percentage displacement after hemodialysis greatly exceeds that before hemodialysis.

Table V. Displacing Effects of Sulfinpyrazone on the Protein Binding of Sulfaphenazole in Patients with Chronic Renal Failure before and after Hemodialysis, and in Normal Subjects[a]

	Binding without SPZ (%)		Binding with SPZ (%)		Percentage displacement[b] (%)	
	before	after	before	after	before	after
Patients						
No. 1	77.3	77.5	62.9	72.1	18.6	7.0
No. 2	73.3	73.1	64.1	62.2	12.5	15.0
No. 3	79.6	85.4	64.0	75.3	19.1	11.9
No. 4	78.9	82.2	70.3	75.3	10.9	8.4
No. 5	69.4	76.8	55.4	69.7	19.9	9.3
No. 6	54.5	85.0	50.6	79.5	7.1	6.4
No. 7	77.3	86.2	65.2	81.7	12.1	5.2
Mean±S.D.	72.9±8.9	80.9±5.1	61.8±6.6	73.7±6.5	14.3±4.9	9.0±3.4
Normal subjects						
No. 1	87.9		82.5		6.2	
No. 2	92.2		87.0		5.6	
No. 3	90.2		85.8		5.0	
No. 4	90.5		87.3		3.6	
No. 5	91.2		86.5		5.2	
Mean±S.D.	90.4±1.6		85.8±1.9		5.1±1.0	

a) Drug protein binding and the displacement by sulfinpyrazone were determined before and after hemodialysis.
b) Percentage displacement=$[(B-B_1)/B]\times 100$ (%), where B is the binding percentage of sulfaphenazole alone, and B_1 is that in the presence of the displacing agent.

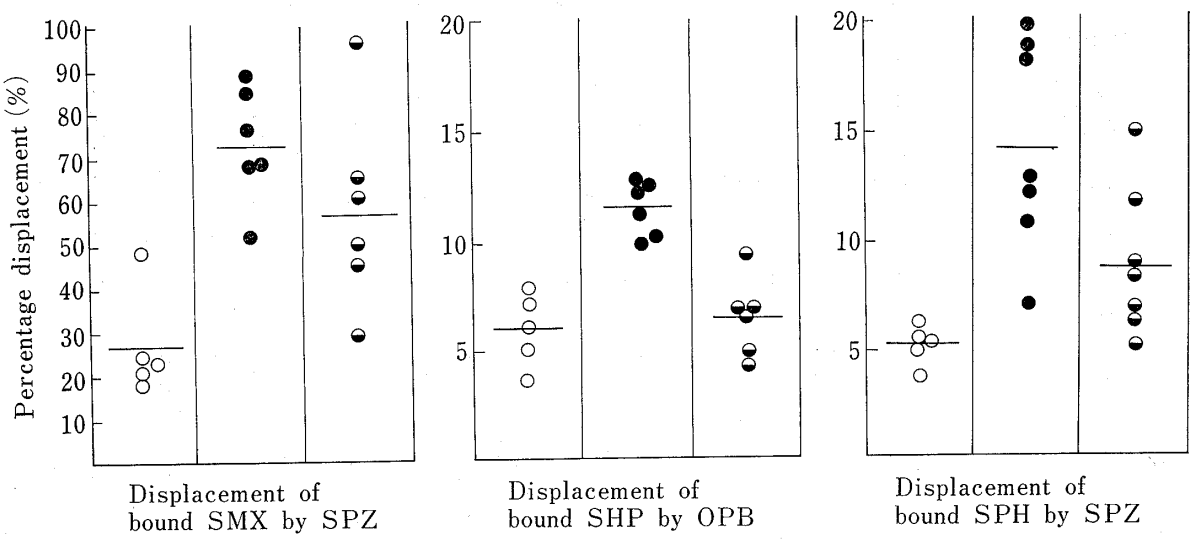

Fig. 4. Effect of Hemodialysis on the Percentage Displacement of bound Sulfonamides by SPZ and OPB

○, normal plasma. ●, plasma before hemodialysis. ◒, plasma after hemodialysis. The solid horizontal lines represent the mean percentage displacement for each group.

In normal plasma, the percentage displacement of bound SMX was considerably lower than in the patients' plasma (26.0±10.9%).

Tables IV—V indicate that both OPB and SPZ effectively displace protein-bound SPH, but the percentage displacements of bound SPH by both agents are much smaller than those of bound SMX.

Percentage displacements by OPB of bound SPH in the patients' plasma were 11.6 ±1.0% before hemodialyis and 6.4±1.5% after hemodialysis, while that in normal plasma was 5.9±1.5% (Table IV). Thus, the percentage displacement of bound SPH in the patients' plasma decreased after hemodialysis and approached that of normal plasma.

The percentage displacements by SPZ of bound SPH in the patients' plasma were 14.3 ±4.5% before hemodialysis and 9.0±3.2% after hemodialysis, while that in normal plasma was only 5.1±0.9% (Table V). It is noteworthy that, in patient No. 2, the percentage displacement of bound SPH after hemodialysis exceeded that before hemodialysis, as seen in the SMX displacing experiment.

The effects of hemodialysis on drug displacement are illustrated in Fig. 4.

After hemodialysis, the percentage displacements of both bound SMX and SPH in the patients' plasma decreased and approached those of normal plasma, except in 1 patient (No. 2).

Discussion

In view of its clinical importance and pharmacological interest, many investigations[12-21] on drug binding to plasma protein in cases of chronic renal failure have been undertaken.

It is generally believed that decreased binding in cases of chronic renal failure may be due to a defect in albumin itself or to the accumulation in the plasma of endogenous substances which competitively inhibit drug binding to albumin.

However, the mechanisms which cause such decreased protein binding remain to be elucidated.

In this work, the protein binding of SMX and SPH in the plasma of 7 patients with chronic renal failure was examined and compared with the protein binding in normal plasma. Reduced protein binding of SMX and SPH in the plasma of patients with chronic renal failure was observed. This was not due to hypoalbuminemia, because the total protein and albumin concentrations of patients with chronic renal failure in our experiments were at the normal level, as shown in Table II.

The binding percentages of the two sulfonamides in the patients' plasma increased after hemodialysis as compared with those before hemodialysis, except for SMX binding in two patients (Table II).

Judging from the reduced binding of sulfonamides in the plasma in cases of chronic renal failure and the increased binding after hemodialysis in the most cases, the decreased binding of sulfonamides in the patients' plasma before hemodialysis may be due to an accumulation of certain endogenous substances which inhibit drug protein binding. The increased binding after hemodialysis would then be ascribable to the removal of endogenous substances during hemodialysis.

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One of the major indicators of efficacy of hemodialysis is the removal of endogenous waste products which accumulate in patients with chronic renal failure. The differences of binding percentage before and after hemodialysis in our experiments may be thus considered to indicate the efficacy of hemodialysis.

However, other factors clearly cannot be neglected, since hemodialysis had little effect on protein binding in 2 patients in spite of a marked decrease of BUN during hemodialysis.

Andreason[15,16] suggested that some dialyzable endogenous substances may compete at drug binding sites, and Sjöholm[19] reported evidence for the presence of nondialyzable strong inhibitors in uremic plasma; these could be removed by charcoal treatment.

It is well known that the binding of acidic drugs to albumin may be influenced by the presence of other drugs which also bind to albumin.[10,11,13,15,16,21] Therefore, it should be possible to use displacing agents as a tool to assess the binding characteristics of drugs to plasma albumin in disease states. OPB and SPZ used in this study are widely recognized as strong displacing agents for protein bound sulfonamides.[11]

SPZ exhibited pronounced displacing effects on bound SMX and SPH in the plasma in cases of chronic renal failure as compared with those in normal plasma. OPB also had a moderate displacing effect on bound SPH. Clear differences in the percentage displacements of bound sulfonamides between the patients' plasma and normal plasma were observed.

Judging from the small percentage displacements for normal plasma and the large percentage displacements for the patients' plasma, these data appear to reflect well the inferior ability of the patients' plasma albumin to bind acidic drugs.

The decrease in the percentage displacements of bound sulfonamides by OPB and SPZ was more pronounced in the patients' plasma after hemodialysis than before, except in the cases of two patients (in one case for SMX, and in the other for SPH). Such a decrease may be caused by the removal of substances capable of inhibiting the normal binding of sulfonamides, and presumably reflects the improvement in the drug binding ability of the patients' plasma albumin.

Protein binding of certain drugs is thought to play an important role in controlling the tissue distribution, biotransformation and renal excretion of drugs.[11,22,23] Therefore, more detailed studies seem desirable regarding the influence of altered protein binding on the pharmacokinetic behavior of drugs in cases of chronic renal failure.

22) G. Levy and A. Yacobi, *J. Pharm. Sci.*, **63**, 805 (1974).
23) S. ϕie and G. Levy, *J. Pharm. Sci.*, **68**, 1 (1979).