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Transformation and Excretion of Drugs in Biological Systems. IX.[1] Interactions between Sulfinpyrazone and Sulfonamides, and between Oxyphenbutazone and Sulfonamides in Dogs

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Interactions between sulfinpyrazone and sulfonamides, and between oxyphenbutazone and sulfonamides, were investigated in dogs.

The plasma level of sulfamethizole, sulfamethizole-N^4-acetate and sulfisomezole-N^4-acetate were prolonged by coadministration of sulfinpyrazone or oxyphenbutazone. But no alteration was observed in plasma level patterns of sulfisomezole and sulfanilamide.

Sulfinpyrazone and oxyphenbutazone possess some displacing activity towards sulfonamides bound to dog plasma proteins.

In renal clearance experiments, the clearance ratios of sulfamethizole, sulfamethizole-N^4-acetate, and sulfisomezole-N^4-acetate were markedly decreased after sulfinpyrazone infusion. The effect of oxyphenbutazone on sulfonamide excretion was relatively small compared with that of sulfinpyrazone, and oxyphenbutazone remarkably decreased the clearance ratio of sulfamethizole only. It became clear that prolongations of plasma levels of the certain sulfonamides by SPZ or OPB, are mainly caused by competitive interactions between the certain sulfonamides and the two anti-inflammatory drugs at renal secretory level.

Previously, we have reported[1] our studies on the mutual interaction between 5-*n*-butyl-1-cyclohexyl-2,4,6-trioxoperhydropyrimidine (BCP), a non-steroidal anti-inflammatory agent, and several sulfonamides in dogs. In continuing our program of investigation involving the interactions between non-steroidal anti-inflammatory agents and sulfonamides in dogs, it became necessary to investigate the effect of sulfinpyrazone and oxyphenbutazone on the plasma level, protein binding, and renal excretion of sulfonamides. Although several investigations[3–8] concerning the pharmacological and biopharmaceutical characteristics of sulfinpyrazone and oxyphenbutazone have been undertaken, the details of interactions between these two agents and sulfonamides still remain to be elucidated.

In the present study, the factors involved in the interactions between sulfinpyrazone and sulfonamides, and between oxyphenbutazone and sulfonamides, were extensively studied.

1) Part VIII: M. Takada, S. Akuzu, A. Misawa, R. Hori, and T. Arita, *Chem. Pharm. Bull.* (Tokyo), **22**, 542 (1974).
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3) J.J. Burns, T.F. Yü, A. Ritterband, J.M. Perel, A.B. Gutman, and B.B. Brodie, *J. Pharmacol. Exptl. Therap.*, **119**, 418 (1957).
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Experimental

Preparation of Materials——Sulfinpyrazone (SPZ) and oxyphenbutazone (OPB): Used as received (Fujisawa Pharmaceutical Co., Ltd.).

Sulfanilamide (SA): Recrystallized from EtOH. mp 165—167°.

Sulfamethizole (SMZ): Recrystallized from EtOH. mp 207—208°.

Sulfamethizole-N^4-acetate (SMZ-N^4-Ac): Synthesized by acetylation of sulfamethizole.[9] mp 234—237°.

Sulfisomezole (SIMZ): Recrystallized from EtOH. mp 168—171°.

Sulfisomezole-N^4-acetate (SIMZ-N^4-Ac): Synthesized by acetylation of sulfisomezole.[10] mp 223—224°.

Method of Drug Administration——A sulfonamide in dose of 30 mg/kg was administered to dogs through the cephalic vein. SPZ or OPB in dose of 30 mg/kg was also administered through the cephalic vein with or after the administration of sulfonamides. The detailed procedure was described in the previous report.[1]

Binding Experiments——The extent of binding of sulfonamides to dog plasma was determined by the method of equilibrium dialysis as described previously.[11] Interference by SPZ or OPB with the binding of various sulfonamides to dog plasma proteins was evaluated by the method of Anton.[4] Each sulfonamide was initially added to the external compartment to give a concentration of 100 μg/ml. SPZ or OPB was also present at the same concentration in the external compartment.

Method of Evaluating the Sulfonamide-displacing Activity of SPZ or OPB——The method described by Anton[4] was employed in our experiments. Drugs were compared for activity (at equal concentration by weight) in interfering with the binding of a sulfonamide to dog plasma proteins. The detailed procedure was described in the previous report.[1]

Renal Clearance Experiment——Renal clearance stdiues were made in dogs by the standard procedures previously employed.[11] All experiments were carried out in anesthetized (pentobarbital sodium) dogs. Male and female dogs weighing 8.5—14.5 kg were used in these experiments. Each substance was given intravenously and successive infusion was continued throughout the experiments. In order to block the renal excretion of sulfonamides, SPZ (30 mg/kg) or OPB (30—60 mg/kg) was given initially through the cephalic vein after 3 control clearance experiments, and a sustaining infusion of SPZ (0.9 mg/min) or OPB (0.9 mg/min) was continued at a rate of 3 ml/min, until the clearance experiment was completed. The detailed procedure has been described in the previous report.[1] Drug clearance (C) in ml/min is calculated as $C=UV/P$, where U and P, indicate the urine and plasma concentrations of the drug in mg/ml respectively, and V is urine flow rate in ml/min. In order to evaluate the fate of the drug in the kidney, clearance ratio (CR) has been conventionally used and is expressed as $CR=C/GFR$, where GFR represents glomerular filtration rate in ml/min calculated as inulin clearance.

Analytical Method——Plasma and urine samples were deproteinized with 10% trichloroacetic acid, and then analyzed as follows; sulfonamides by diazotization,[12] inulin by a modification of the method described by Dische *et al.*[13,14] A Hitachi-Horiba model F-4 pH meter with a glass electrode was used to determine the pH of urine.

Result

Alteration of Plasma Levels of Sulfonamides by SPZ or OPB

The time course of plasma levels of each sulfonamide in dogs with and without SPZ or OPB was determined under carefully controlled experimental conditions. The representative examples of the time course of each sulfonamide are illustrated in Fig. 1—5. As shown in Fig. 2, 4 and 5, with coadministration of SPZ, the plasma levels of SMZ, SMZ-N^4-Ac and SIMZ-N^4-Ac declined much slower than those of the control experiments. This effect was most predominant in the case of SMZ. On the other hand, SPZ did not significantly influence SIMZ and SA plasma levels as shown in Fig. 1 and 3, respectively.

Although OPB also demonstrated effects similar to those of SPZ as shown in Fig. 1—5, the effects on SMZ, SMZ-N^4-Ac, and SIMZ-N^4-Ac were somewhat less than those of SPZ.

9) T. Uno and M. Kataoka, *Yakugaku Zasshi*, **80**, 1785 (1960).
10) H. Kano and K. Ogata, *Ann. Rept. Shionogi Res. Lab.*, **7**, 301 (1957).
11) T. Arita, R. Hori, M. Takada, and A. Misawa, *Chem. Pharm. Bull.* (Tokyo), **19**, 930 (1971).
12) T. Koizumi, T. Arita, and K. Kakemi, *Chem. Pharm. Bull.* (Tokyo), **12**, 413 (1964).
13) Z. Dische and E. Borenfreund, *J. Biol. Chem.*, **192**, 583 (1951).
14) T. Arita, R. Hori, M. Takada, S. Akuzu, and A. Misawa, *Chem. Pharm. Bull.* (Tokyo), **20**, 570 (1972).

It is noteworthy that the time course of SIMZ plasma levels were not altered by coadministration of SPZ or OPB, in spite of the previous observation that BCP causes a small sudden drop in SIMZ plasma levels immediately after the medication.[1)]

Displacement of Sulfonamides bound to Dog Plasma Protein by SPZ or OPB

SPZ or OPB was examined for its activity in displacing bound sulfonamides to dog plasma protein *in vitro* by the method of Anton.[4)] Furthermore, the displacing activity of the two agents was also compared with that of BCP.[1)] The detailed data are shown in Table I.

As shown in Table I, SPZ or OPB possesses a moderate displacing activity and alters the protein binding of sulfonamides to dog plasma proteins. However, the magnitudes of the displacing activity of SPZ or OPB appear to be smaller than that of BCP and this difference in displacing activity clearly demonstrates their behaviors to bound SIMZ.

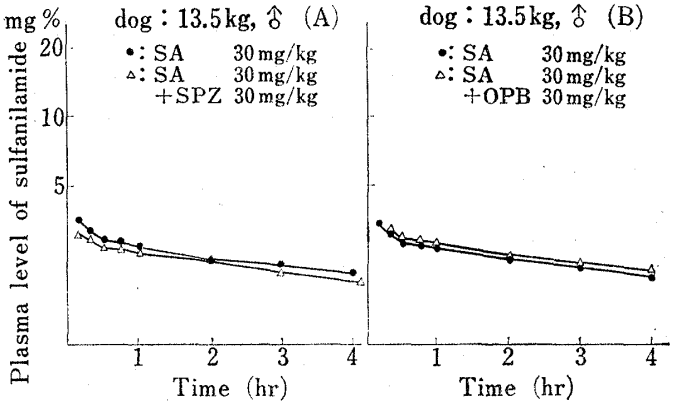

Fig. 1. Effect of Sulfinpyrazone and Oxyphenbutazone on the Plasma Levels of Sulfanilamide in Dogs

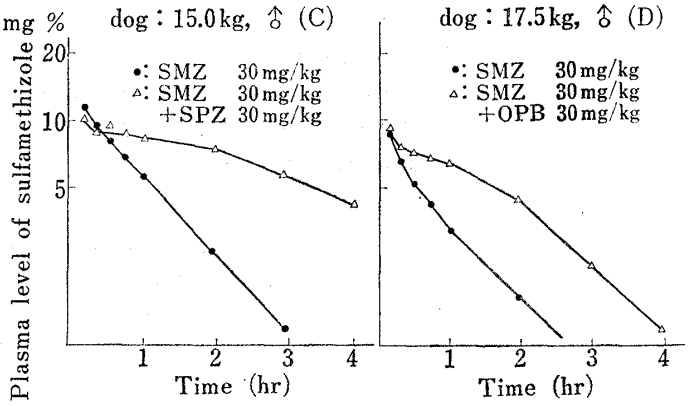

Fig. 2. Effect of Sulfinpyrazone and Oxyphenbutazone on the Plasma Level of Sulfamethizole in Dogs

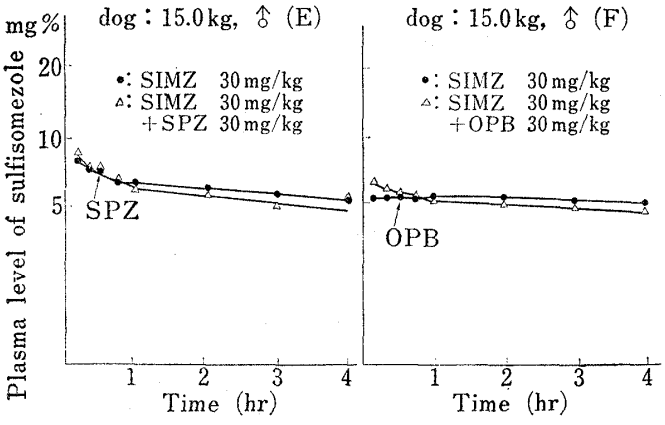

Fig. 3. Effect of Sulfinpyrazone and Oxyphenbutazone on the Plasma Levels of Sulfisomezole in Dogs

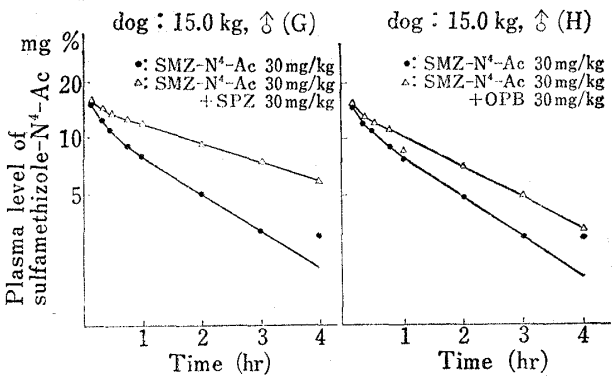

Fig. 4. Effect of Sulfinpyrazone and Oxyphenbetazone on the Plasma Levels of Sulfamethizole-N⁴-acetate in Dogs

Mutual Suppression between Sulfonamides and SPZ, or between Sulfonamides and OPB at Renal Level

Seven dog renal clearance experiments were performed to determine whether the renal excretion of the sulfonamides could be altered by SPZ or OPB infusion. The results are shown in Fig. 6 and Fig. 7. A detailed data of each compound are also presented in Tables II—VII.

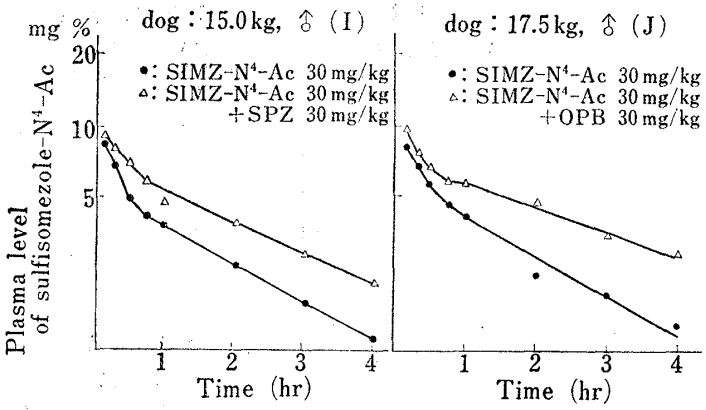

Fig. 5. Effect of Sulfinpyrazone and Oxyphenbutazone on the Plasma Level of Sulfisomezole-N⁴-acetate in Dogs

Inhibition of renal excretion between the three sulfonamides (SMZ, SIMZ, SIMZ-N⁴-Ac) and SPZ was demonstrated first. As shown in Fig. 6, the remarkable alteration in clearance ratio of SMZ before and after SPZ infusion was observed. On the contrary, the clearance ratios of SIMZ were not altered before and after SPZ infusion. The clearance ratio of SIMZ-N⁴-Ac, which is a major metabolite of SIMZ, is greatly decreased after SPZ infusion. Inhibitory behavior of OPB on the three sulfonamides was also examined. As shown in Fig. 7, alteration was observed in the clearance ratios of SMZ before and after OPB infusion, but the decreasing effect of OPB on clearance ratio of SMZ seemed to be moderately small in comparison with the effect of SPZ. SIMZ excretion was not affected by OPB at the dosage level of this experiment.

Table I. Intereference by SPZ or OPB, or BCP with the binding of Various Sulfonamides to Dog Plasma Protein

Sulfonamide	pK_a	% bound to dog plasma at 100 μg/ml	Displacing activity *in vitro* (%)		
			SPZ	OPB	BCP
Sulfanilamide	10.08	9.7	7.5		44.0
Sulfamethizole	5.45	62.9	20.6	12.9	14.1
Sulfisomezole	6.05	39.0	9.5	10.3	34.6
Sulfamethizole-N⁴-acetate		68.6		8.1	7.9
Sulfisomezole-N⁴-acetate	5.54	43.7	12.0	16.6	12.8

The displacing activity (at 100 μg/ml) was determined *in vitro* by equilibrum dialysis. Method of evaluating the sulfonamide-displacing activity of the three drugs was described under experimental.
Data of BCP was obtained from the preceding report.[1]
The pK_a were obtained also from the literatures.[15,16]

Table II. The Effect of SPZ on Renal Clearance of Sulfamethizole

	Time (min)	V (ml/min)	Urine pH	GFR (ml/min)	Sulfamethizole			
					U (mg/ml)	P (mg/ml)	C (ml/min)	CR
Control	30—20	2.16	7.20	46.4	0.470	0.0272	37.3	0.8039
	20—10	2.24	—	46.6	0.432	0.0246	39.3	0.8433
	10— 0	2.22	—	41.9	0.408	0.0234	38.7	0.9236
Exptl.[a]	15—25	1.96	7.25	36.2	0.129	0.0214	11.8	0.3260
	25—35	1.76	—	43.9	0.172	0.0228	13.3	0.3030
	35—45	2.12	—	43.2	0.170	0.0260	13.9	0.3218

dog: ♀ 8.5 kg (dog K in Fig. 6)
a) SPZ: 255 mg *i.v.*, 0.9 mg/min infusion

15) A.H. Anton and J.J. Boyle, *Canad. J. Physiol. Pharmacol.*, 42, 809 (1964).
16) J. Rieder, *Arzneimittel Forschung*, 13, 81 (1963).

Table III. The Effect of SPZ on Renal Clearance on Sulfisomezole

	Time (min)	V (ml/min)	Urine pH	GFR (ml/min)	Sulfisomezole U (mg/ml)	P (mg/ml)	C (ml/min)	CR
Control	30—20	4.30	7.02	42.7	0.0921	0.0424	9.34	0.2187
	20—10	4.50	—	46.1	0.0996	0.0433	10.4	0.2256
	10— 0	5.00	—	43.5	0.0958	0.0413	11.6	0.2667
Exptl.a)	15—25	5.66	7.00	43.5	0.0913	0.0445	11.6	0.2667
	25—35	5.84	—	45.8	0.0950	0.0463	12.0	0.2620
	35—45	5.20	—	40.1	0.1100	0.0487	11.7	0.2917

dog: ♂ 10.5 kg (dog L in Fig. 6)
a) SPZ: 315 mg *i.v.*, 0.9 mg/min infusion

Table IV. The Effect of SPZ on Renal Clearance on Sulfisomezole-N^4-acetate

	Time (min)	V (ml/min)	Urine pH	GFR (ml/min)	Sulfisomezole-N^4-acetate U (mg/ml)	P (mg/ml)	C (ml/min)	CR
Control	30—20	6.50	7.11	49.5	0.174	0.0291	38.7	0.7859
	20—10	8.40	—	49.7	0.129	0.0291	37.2	0.7485
	10— 0	9.12	—	43.2	0.113	0.0294	35.1	0.8144
Exptl.a)	15—25	7.92	7.05	39.8	0.0970	0.0392	19.6	0.4925
	25—35	7.08	—	41.9	0.106	0.0390	19.2	0.4582
	35—45	7.32	—	38.8	0.106	0.0399	19.4	0.5000

dog: ♂ 9.8 kg (dog M in Fig. 6)
a) SPZ: 294 mg *i.v.*, 0.9 mg/min infusion

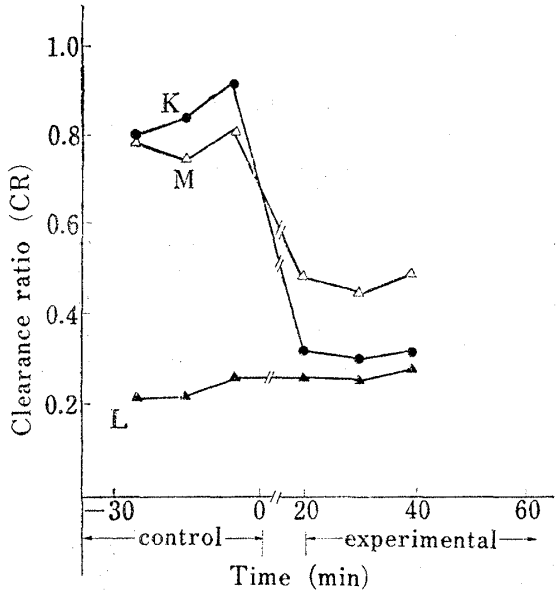

Fig. 6. Clearance Ratio of Sulfamethizole, Sulfisomezole and Sulfisomezole-N^4-acetate before and after Blockade of Proximal Tubular Secretion by Sulfinpyrazone

The lines connect the values for each dog.
K: dog ♀ 8.5 kg L: dog ♂ 10.5 kg M: dog ♂ 9.8 kg
●: sulfamethizole
▲: sulfisomezole
△: sulfisomezole-N^4-acetate

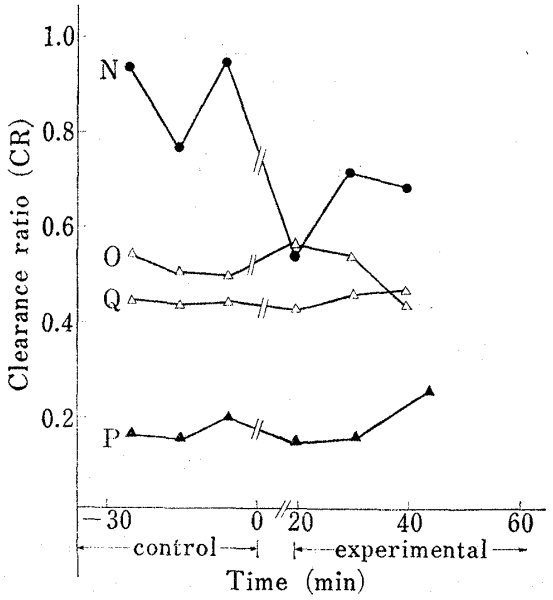

Fig. 7. Clearance Ratio of Sulfamethizole, Sulfisomezole and Sulfisomezole-N^4-acetate before and after Blockade of Proximal Tubular Secretion by Oxyphenbutazone

The lines connect the values for each dog.
N: dog ♂ 10.0 kg P: dog ♂ 14.5 kg
O: dog ♀ 11.0 kg Q: dog ♂ 12.0 kg
●: sulfamethizole
▲: sulfisomezole
△: sulfisomezole-N^4-acetate

Table V. The Effect of OPB on Renal Clearance of Sulfamethizole

	Time (min)	V (ml/min)	Urine pH	GFR (ml/min)	Sulfamethizole U (mg/ml)	P (mg/ml)	C (ml/min)	CR
Control	30—20	3.93	7.01	19.1	0.240	0.0525	18.0	0.9424
	20—10	4.23	—	22.3	0.214	0.0537	16.9	0.7578
	10— 0	4.45	—	19.3	0.208	0.0502	18.4	0.9534
Exptl.[a]	15—25	5.21	7.09	26.5	0.135	0.0488	14.4	0.5434
	25—35	4.85	—	19.9	0.151	0.0522	14.0	0.7035
	35—45	4.50	—	23.4	0.174	0.0500	15.7	0.6709

dog: ♂ 10.0 kg (dog N in Fig. 7)
a) OPB: 300 mg *i.v.*, 0.9 mg/min infusion

Table VI. The Effect of OPB on Renal Clearance of Sulfisomezole-N⁴-acetate

	Time (min)	V (ml/min)	Urine pH	GFR (ml/min)	Sulfisomezole-N⁴-acetate U (mg/ml)	P (mg/ml)	C (ml/min)	CR
Control	30—20	5.10	7.30	42.5	0.130	0.0268	24.7	0.5582
	20—10	5.00	—	47.4	0.140	0.0289	24.2	0.5105
	10— 0	4.90	—	46.4	0.149	0.0310	23.6	0.5086
Exptl.[a]	15—25	6.00	7.28	41.0	0.120	0.0305	23.6	0.5756
	25—35	5.46	—	41.8	0.124	0.0295	23.0	0.5502
	35—45	4.84	—	47.4	0.134	0.0310	20.9	0.4409

dog: ♀ 11.0 kg (dog O in Fig. 7)
a) OPB: 330 mg *i.v.*, 0.9 mg/min infusion

Table VII. The Effect of OPB on Renal Clearance of Sulfisomezole

	Time (min)	V (ml/min)	Urine pH	GFR (ml/min)	Sulfisomezole U (mg/min)	P (mg/ml)	C (ml/min)	CR
Control	30—20	4.80	6.88	29.6	0.0311	0.0301	4.96	0.1676
	20—10	5.44	—	31.1	0.0279	0.0321	4.73	0.1521
	10— 0	5.10	—	25.7	0.0337	0.0321	5.35	0.2082
Exptl.[a]	15—25	3.92	6.86	34.1	0.0428	0.0327	5.13	0.1504
	25—35	4.34	—	33.8	0.0431	0.0345	5.42	0.1607
	35—45	3.56	—	18.5	0.0506	0.0363	4.96	0.2681

dog: ♂ 14.5 kg (dog P in Fig. 7)
a) OPB: 435 mg *i.v.*, 0.9 mg/min infusion

It is noteworthy that, the clearance ratios of SIMZ-N⁴-Ac which were greatly decreased by SPZ infusion, were not altered after OPB infusion, even when OPB (60 mg/kg) was given initially.

Discussion

In clinical practice, patients frequently receive more than one drug concurrently. Such multiple-drug therapy may be effective if it provides greater efficacy, greater margin of safety, or longer duration of effect than can be achieved with single drug therapy. In multiple-drug therapy, the physiological behavior of a drug may be modified by the prior or coadministra-

tion of another drug. Thus, the possibilities of expected or unexpected drug interactions *in vivo* must be considered. Much works on the problems of interactions among drugs have been undertaken. However, mainly due to the complexity of interactions among drugs, the detailed mechanisms whereby drugs interact, still remain to be revealed.

As mentioned previously in this report, it is evident that plasma levels of SMZ, SMZ-N^4-Ac and SIMZ-N^4-Ac decline considerable slowly by coadministration of SPZ or OPB. Particularly, the prolonged effect of SMZ plasma levels by SPZ is remarkable and worthy of special attention (Fig. 2). On the contrary, the plasma level decay patterns of SA and SIMZ show no alterations with SPZ or OPB. It is noticeable that, plasma level of SMZ-N^4-Ac and SIMZ-N^4-Ac, which are the main metabolites of the parent sulfonamides, are distinctly prolonged by coadministration of SPZ or OPB (Fig. 4 and 5). Such retarded disappearance of SMZ-N^4-Ac and SIMZ-N^4-Ac from dog plasma by SPZ or OPB would suggest the possibility of occurrence of undesirable side effects being attributable to the accumulation of the pharmacologically inactive metabolites of sulfonamides *in vivo*. A similar possibility has already been reported following the coadministration of BCP.[1)]

Our previous reports[14,17)] demonstrate that, SMZ, SMZ-N^4-Ac and SIMZ-N^4-Ac are remarkably secreted through renal proximal tubules, although SIMZ and SA are insufficiently or very slightly secreted. Judging from the information and the present observation, it is presumed that such prolongations of the certain sulfonamide plasma level by SPZ or OPB can be closely correlated with competitive inhibition among the drugs at renal level. The prolonging effect of SPZ on the sulfonamides is greater than that of OPB, and this variation of the effect might be partially attributable to the differences of physiological behaviors between SPZ and OPB in dogs as mentioned below.

As one of possible mechanisms of interactions among drugs, it has been demonstrated[4,8,18)] that the pharmacological response to a drug can be diminished or increased as a result of interaction to form non-diffusable protein complexes, because the response to a drug is primarily determined by the concentration of unbound drug in plasma. A protein bound drug may be activated or inactivated by the addition of another drug to the system and this point deserves a special consideration, and attempts to evaluate such possibilities *in vitro* and *in vivo* have been reported.[1,4,8,19)] A number of acidic drugs are known to compete for the limited number of protein binding sites.[8)] Hence one acidic drug may be displaced by another, thereby increasing the concentration of unbound drug at target sites.

Concerning the displacing activity of SPZ or OPB in protein binding of sulfonamides, several reports have been published[4,8,20)] and they have indicated that SPZ or OPB possesses strong displacing activity to bound sulfonamides in man.

In our *in vitro* experiments the results of which are shown in Table I, SPZ and OPB have shown to possesses displacing activity in protein binding of several sulfonamides in dogs to some extent. It is well recognized[5)] that in dogs the affinity of SPZ and OPB to plasma protein is considerably low as compared with that of SPZ and OPB in man. Such a decreased affinity of SPZ and OPB to dog plasma protein might be correlated with relatively weak displacing activity to bound sulfonamides in dogs.

Judging from the data of the displacing experiments, it is quite probable that the remarkable prolongation of certain sulfonamide plasma levels is hardly affected by the comparatively small displacement of the sulfonamides from binding sites by SPZ or OPB. Thus, possibility of other mechanisms must be suggested.

As mentioned previously, it is strongly suggested that there is the possibility of competitive inhibition of tubular secretion between sulfonamides and the two anti-inflammatory

17) T. Arita, R. Hori, M. Takada, S. Akuzu, and A. Misawa, *Chem. Pharm. Bull.* (Tokyo), **19**, 937 (1971).
18) M.C. Meyer and D.E. Guttman, *J. Pharm. Sci.*, **57**, 895 (1968).
19) K. Kakemi, H. Sezaki, T. Komuro, K. Ikeda, and H. Kishi, *Chem. Pharm. Bull.* (Tokyo), **18**, 2386 (1970).
20) A.H. Anton, *J. Pharmacol. Exptl. Therap.*, **129**, 282 (1960).

agents. As for the renal excretion of sulfonamides, many reports have been published. Sulfonamides excretion is particularly complicated because in man extensive but variable biotransformation of the compounds takes place by the hepatic enzymes. Furthermore, the physicochemical properties of the individual sulfonamide vary extensively and the experimental data concerning their physiological behaviors are extremely complicated. According to several available evidences, renal tubules in both man and dog are known to actively secrete a variety of weak organic acids including sulfonamides, and the tubular secretion of these compounds appears to be competitive.[11,14,17,21–25]

As shown in Fig. 6 and 7, the nature of the interactions between sulfonamides and SPZ, and between sulfonamides and OPB at renal level, is evidently demonstrated by the renal clearance technique. SPZ interference with the renal excretion of certain sulfonamides becomes apparent only when the sulfonamide is markedly secreted through the proximal tubule. On the contrary, SPZ has no effect on the renal secretion of SIMZ, which is very slightly secreted through the proximal tubule. Interference efficacy of OPB on sulfonamide excretion is rather incomplete in comparison with that of SPZ, and clearance ratio of SMZ was only slightly decreased by OPB infusion (Fig. 7).

The renal behavior of SPZ and OPB has been studied and several reports[3,7,26] have been published. It is demonstrated that SPZ and OPB might be transported and they interfere renal tubular secretion of other anionic compounds. Similar alterations of sulfonamide excretion behaviors by BCP infusion has already been demonstrated.[1] From these evidences, it is strongly implied that the competitive inhibition of proximal tubular secretion between SPZ and certain sulfonamides or between OPB and certain sulfonamides, must be occurring in dogs.

The present finding, *i.e.* both SPZ and OPB might block the proximal tubular secretion of certain sulfonamides and cause prolongation of plasma level of the drugs, led our interest to the possibility that one of simultaneously administered anionic drugs might often provide prolongation of plasma level of the other drug which is considerably secreted through renal tubule, and thus achieve significant duration of the pharmacological effects. However, a great care must be exercised in selecting anionic drugs such as SPZ and OPB, as they also block the proximal tubular secretion of N^4-acetylated products of the sulfonamides. From this point of view, we must be concerned extensively with the possibility of competitive inhibition of renal excretion of the toxic metabolites of drugs at the time of multiple-drug therapy, in order to avoid untoward side effects.

Throughout our experiments, it was observed that the interaction between OPB and sulfonamides at renal level is relatively small as compared with that between SPZ and sulfonamides. Such a diminished response of OPB on sulfonamide disposition, might be due, in part, to the short biological half-life of OPB in dogs. In fact, the biological half-life of OPB is only 0.5 hr in dogs, and that in man is 72 hr.[5] Such a striking short half-life of OPB in dogs might be correlated with the weak effect of OPB on sulfonamide disposition shown in dogs.

Further, a possible induction of drug-metabolizing enzymes should be taken into consideration.[27] However, throughout the present experiments, each dog was studied only every two or three weeks in order to avoid such possibility of the enzyme induction. Fur-

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thermore, SMZ, the high plasma level of which was prolonged remarkably by coadministration of SPZ or OPB, is excreted almost unchanged in urine in dogs. This biotransformation pattern admits no compromise concerning the participation of induction of drug-metabolizing enzymes to the above mentioned drug interaction. It is also clear that, N^4-acetylated products of sulfonamides is the already biotransformed form and is excreted unchanged in urine. Thus, the possibility of influence of induction of drug-metabolizing enzyme on sulfonamide disposition would be eliminated.

Although several factors concerning the interactions between sulfonamides and few non-steroidal anti-inflammatory agents were discussed in the previous report[1] and present investigation, detailed mechanisms of interactions among the drugs still remain to be elucidated and this will continue to be an interesting subject for active research.