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Further Investigation on the Interaction of Sulfonamides with Non-steroidal Anti-inflammatory Agents in Dogs

Masahiko Takada,*,[a] Shozo Miyazaki,[a] Kazumoto Chiba,[a] Mieko Sakamoto,[a] Megumi Ito,[a] Naomi Yagi,[a] Hitoshi Sekikawa,[a] Takaichi Arita,[b] and Ryohei Hori[c]

Faculty of Pharmaceutical Sciences, Higashi Nippon Gakuen University,[a] Ishikari-Tohbetsu, 061-02, Japan, Department of Pharmacy, Hokkaido University Hospital,[b] Kita-ku, Sapporo, Japan, and Department of Pharmacy, Kyoto University Hospital,[c] Sakyo-ku, Kyoto, 606, Japan

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An interaction study between sulfonamides and non-steroidal anti-inflammatory agents similar to that described in the previous paper was repeated in dogs to confirm the previous findings and conclusions. Pharmacokinetic parameters were calculated from the plasma levels after intravenous administration using a two-compartment open model. The data are presented and compared with those given in previous reports.

Keywords——drug interaction; pharmacokinetic parameter; dog; sulfonamides; non-steroidal anti-inflammatory agents

In the previous papers,[1,2] interactions between several sulfonamides and acidic non-steroidal anti-inflammatory agents such as 5-*n*-butyl-1-cyclohexyl-2,4,6-trioxoperhydropyrimidine (BCP), sulfinpyrazone, and oxyphenbutazone were investigated in dogs. The results indicated that the maintenance of an effective plasma level of sulfamethizole was considerably prolonged by coadministration of these anti-inflammatory agents. Simultaneous administration of BCP and sulfamethoxazole caused a small sudden drop of the sulfamethoxazole plasma level. No alteration was observed in the plasma level patterns of sulfanilamide on combined administration.

Although we investigated the effect of coadministration of the anti-inflammatory agents on plasma levels of sulfonamides in dogs, only a limited number of experiments was performed in most of the interaction studies, and no pharmacokinetic information was reported. An investigation similar to the previous ones[1,2] was therefore carried out to confirm the previous results and conclusions, and to investigate the kinetic interaction between sulfonamides and non-steroidal anti-inflammatory agents.

Experimental

Materials——Commercial sulfamethizole, sulfanilamide, and sulfamethoxazole were recrystallized from ethanol. 5-*n*-Butyl-1-cyclohexyl-2,4,6-trioxoperhydropyrimidine (BCP, Takeda Chemical Industries) was recrystallized from *n*-hexane. Sulfinpyrazone and oxyphenbutazone (Fujisawa Pharmaceutical Co.) were used as received.

Plasma Levels of Sulfonamides in Dogs——Male or female dogs, weighing 11—18 kg, were used in this study. They were anesthetized with pentobarbital sodium (30 mg/kg). A sulfonamide at a dose of 30 mg/kg was administered to dogs through the cephalic vein. An anti-inflammatory agent at a dose of 30 mg/kg was also administered through the cephalic vein at the same time as or after the administration of the sulfonamide. Plasma samples were deproteinized with 10% trichloroacetic acid, and analyzed by diazotization[3] for sulfonamides. The procedure was described in detail in the previous report.[1,2]

Pharmacokinetic Analysis——Pharmacokinetic parameters were calculated from the plasma levels after intravenous administration using equations based on the two-compartment open model.[4] The calculations were carried out according to standard graphical procedures.[5]

Results and Discussion

The sulfonamides used for this study were sulfamethizole, sulfanilamide, and sulfamethoxazole, which are typical sulfonamides with short, intermediate, and long half-lives, respectively.

Plasma levels of intravenous sulfonamides were studied in dogs in a cross-over fashion with and without anti-inflammatory agents. The plasma concentration-time curves for sulfonamides declined biexponentially in general, so the data were analyzed by a two-compartment open model. In the pharmacokinetic analysis, two major parameters, elimination rate constant (k_{el}) and β-elimination half-life ($t_{1/2}(\beta)$), were utilized because they are key factors in explaining the elimination patterns of sulfonamides in dogs.

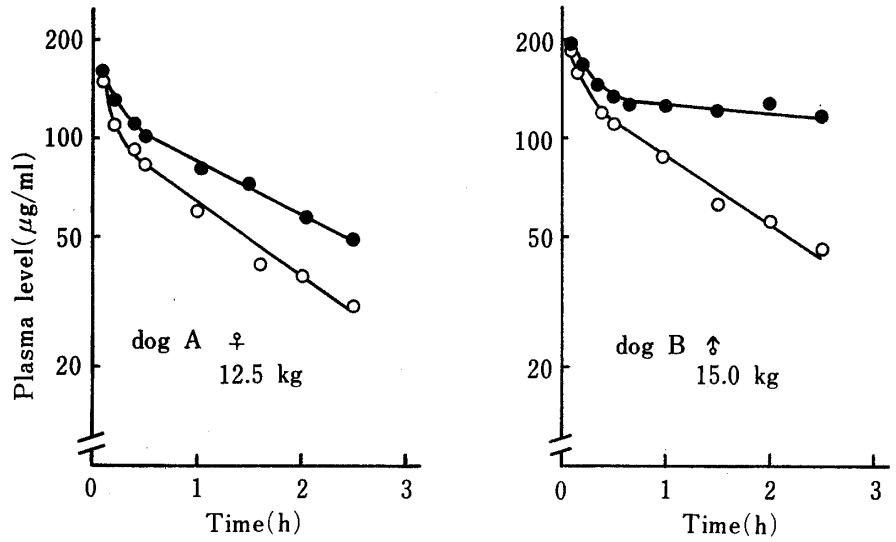

Fig. 1. Effect of BCP on the Plasma Level of Sulfamethizole in Dogs

—○—: sulfamethizole.
—●—: sulfamethizole with BCP.

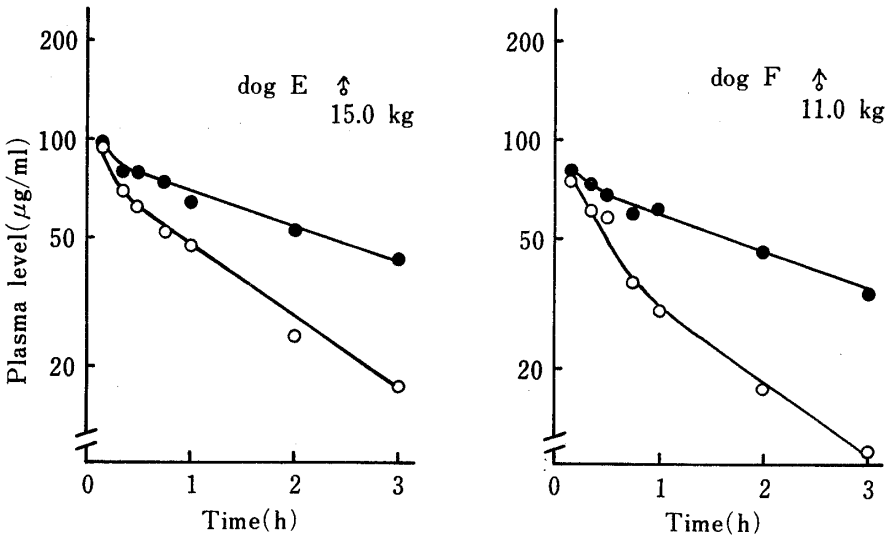

Fig. 2. Effect of Sulfinpyrazone on the Plasma Level of Sulfamethizole in Dogs

—○—: sulfamethizole.
—●—: sulfamethizole with sulfinpyrazone.

Pharmacokinetic Interaction of Sulfamethizole with Anti-inflammatory Agents

The plasma concentration profiles of sulfamethizole with and without BCP, sulfinpyrazone, and oxyphenbutazone are shown in Figs. 1, 2, and 3, respectively; they are clearly biphasic. As shown in the figures, the plasma levels of sulfamethizole declined more slowly in dogs given simultaneous administration of these acidic anti-inflammatory agents than in the controls.

The pharmacokinetic parameters estimated from these data are listed in Table I. The table also includes the kinetic parameters calculated from the previous data.[1,2] Distinct

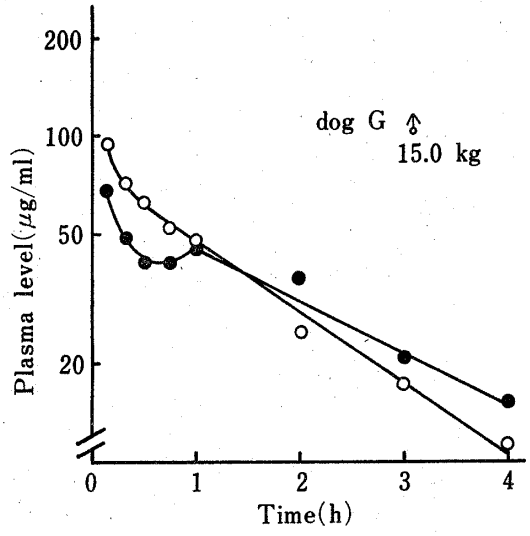

Fig. 3. Effect of Oxyphenbutazone on the Plasma Level of Sulfamethizole in Dogs

—○—: sulfamethizole
—●—: sulfamethizole with oxyphenbutazone.

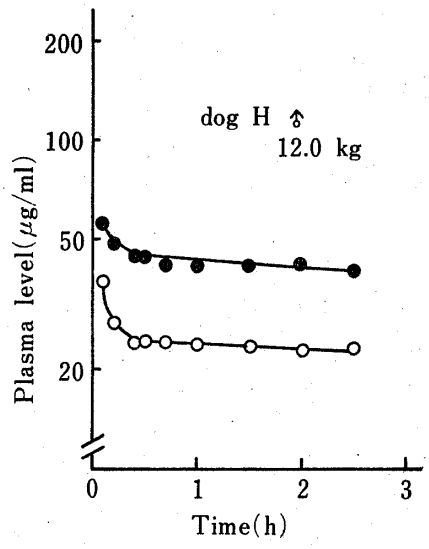

Fig. 4. Effect of BCP on the Plasma Level of Sulfanilamide in Dogs

—○—: sulfanilamide.
—●—: sulfanilamide with BCP.

TABLE I. Pharmacokinetic Parameters for Sulfamethizole following Intravenous Administration to Dogs

Dog	Coadministration	k_{21} (h^{-1})	k_{el} (h^{-1})	k_{12} (h^{-1})	$t_{1/2}(\beta)$ (h)	V_1 (l)	V_2 (l)
A	SMZ[a]	3.78	0.941	2.63	1.33	1.79	1.25
	SMZ+BCP[b]	4.40	0.630	2.73	1.85	1.75	1.04
B	SMZ	3.56	0.700	1.32	1.41	2.09	0.771
	SMZ+BCP	3.63	0.498	2.10	8.55	1.90	1.10
C[c]	SMZ	3.95	0.965	2.39	1.23	1.71	1.04
	SMZ+BCP	3.34	0.581	3.10	2.41	2.10	1.95
D[c]	SMZ	5.26	1.03	1.78	0.937	2.78	0.943
	SMZ+SPZ[d]	7.41	0.207	1.48	4.02	3.80	0.758
E	SMZ	4.09	0.786	2.02	1.38	3.38	1.67
	SMZ+SPZ	6.41	0.338	2.29	2.81	3.59	1.28
F	SMZ	1.47	0.825	0.478	1.27	3.49	0.198
	SMZ+SPZ	5.97	0.345	1.68	2.60	3.26	0.917
G	SMZ	3.94	0.846	2.30	1.37	3.16	1.84
	SMZ+OPB[e]	—	—	—	(1.91)[f]	—	—

a) Sulfamethizole.
b) 5-*n*-Butyl-1-cyclohexyl-2,4,6-trioxoperhydropyrimidine.
c) Calculated from the data in refs. 1 and 2.
d) Sulfinpyrazone.
e) Oxyphenbutazone.
f) The half-life was obtained from the slope of the linear portion.

differences in the values of k_{el} and $t_{1/2}$ (β) obtained in the presence and absence of the anti-inflammatory agents were noted in most cases; simultaneous medications resulted in larger $t_{1/2}$ (β) values of sulfamethizole than single administration. When coadministered with BCP, in particular, the $t_{1/2}$ (β) for sulfamethizole was increased approximately 6 times compared to the control value in dog B. The present finding that significant prolongation of the half-life of sulfamethizole was observed when anti-inflammatory agents were administered, is in agreement with that of the previous work.[1,2] Thus, this quantitative investigation showed that acidic anti-inflammatory agents can modify the elimination kinetics of sulfamethizole in dogs. No consistent change in the volumes of the compartments (V_1, V_2) or in the intercompartmental transfer rate constants (k_{12}, k_{21}) occurred when anti-inflammatory agents were given to the dogs.

Pharmacokinetic Interaction of Sulfanilamide with Anti-inflammatory Agents

As shown in Fig. 4, the plasma concentration-time curves for sulfanilamide both with and without BCP declined biexponentially after intravenous administration. The results of the pharmacokinetic analysis are given in Table II.

The time course of sulfanilamide plasma levels was not altered by coadministration with BCP (Fig. 4). Intravenous administration of sulfanilamide with BCP, sulfinpyrazone, and

Table II. Pharmacokinetic Parameters for Sulfanilamide following Intravenous Administration to Dogs

Dog	Coadministration	k_{21} (h^{-1})	k_{el} (h^{-1})	k_{12} (h^{-1})	$t_{1/2}$ (β) (h)	V_1 (l)	V_2 (l)
H	SA[a]	4.42	0.121	5.63	13.1	6.18	7.87
	SA+BCP[b]	4.73	0.0893	2.88	12.5	4.77	2.90
I[c]	SA	2.44	0.122	1.07	8.26	9.64	4.22
	SA+SPZ[d]	4.00	0.139	1.22	6.55	10.6	3.23
	SA+OPB[e]	3.00	0.124	0.616	6.80	10.4	2.13

a) Sulfanilamide.
b) 5-*n*-Butyl-1-cyclohexyl-2,4,6-trioxoperhydropyrimidine.
c) Calculated from the data in refs 1 and 2.
d) Sulfinpyrazone.
e) Oxyphenbutazone.

oxyphenbutazone resulted in slightly shorter or unchanged $t_{1/2}$ (β) values compared to the control values (Table II).

Pharmacokinetic Interaction of Sulfamethoxazole with Anti-inflammatory Agents

The plasma levels of sulfamethoxazole with and without the anti-inflammatory agents were also determined. The results of pharmacokinetic analysis of the plasma concentration data obtained from dogs given 30 mg of sulfamethoxazole/kg *i.v.* followed by 30 and 100 mg of BCP/kg are depicted in Figs. 5 and 6, respectively.

Sulfamethoxazole, which is a moderately long-acting sulfonamide, showed behavior quite different from that of sulfamethizole (Fig. 1) when BCP was coadministered. As shown in

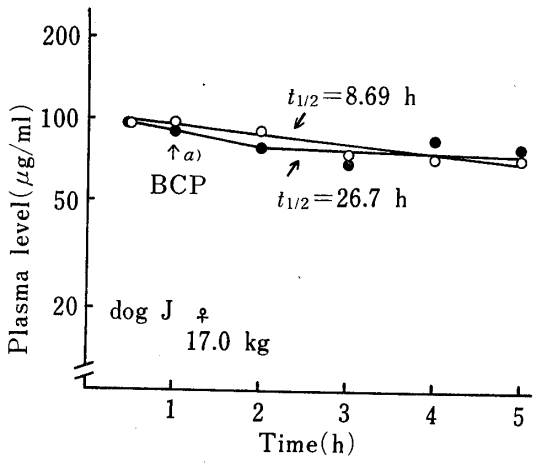

Fig. 5. Effect of BCP on the Plasma Level of Sulfamethoxazole in Dogs

—○—: sulfamethoxazole.
—●—: sulfamethoxazole with BCP (30 mg/kg).
a) This arrow indicates the administration of BCP.

Figs. 5 and 6, BCP caused a sudden drop in the plasma level of sulfamethoxazole. After the initial drop, the plasma level of sulfamethoxazole declined more slowly than in the control. For this study, the elimination half-life was estimated from the slope of the terminal linear portion of the curve of the logarithm of the plasma level-time relationship. The change in $t_{1/2}$ values shows that coadministration of BCP decreased the rate of elimination of the sulfonamide by 3- to 4-fold.

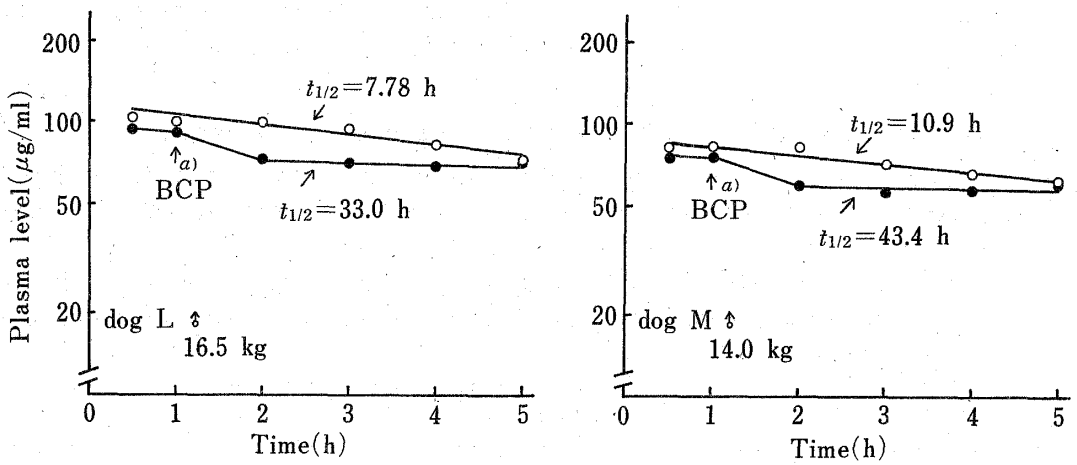

Fig. 6. Effect of BCP on the Plasma Level of Sulfamethoxazole in Dogs

—○—: sulfamethoxazole.
—●—: sulfamethoxazole with BCP (100 mg/kg).
a) These arrows indicate the administration of BCP.

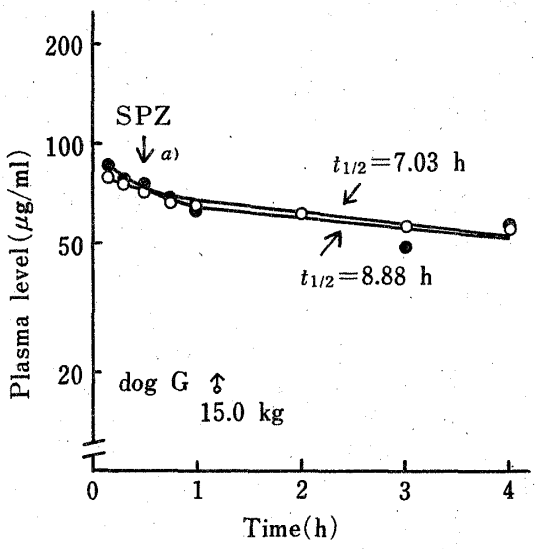

Fig. 7. Effect of Sulfinpyrazone on the Plasma Level of Sulfamethoxazole in Dogs

—○—: sulfamethoxazole.
—●—: sulfamethoxazole with sulfinpyrazone.
a) This arrow indicates the administration of SPZ.

BCP significantly alters the binding of sulfamethoxazole to dog plasma proteins and possesses a strong displacing activity.[2] This result may be related to the phenomenon observed in Figs. 5 and 6, *i.e.*, that BCP caused a sudden drop in the plasma level of sulfamethoxazole. As the result of the increase of unbound drug, the equilibrium of unbound drug between plasma and tissues would be disturbed and the redistribution of unbound drug from the plasma to tissues would produce the decrease in the plasma concentration. Similar phenomena in the time course of plasma levels of sulfonamides have been reported by Anton.[6]

Judging from the previous observations,[1,7] we consider that the prolonging effect of BCP on sulfamethoxazole plasma levels can be correlated with competitive inhibition between the drugs at the renal level.

The results of coadministration of BCP in the dog indicate an interaction involving not only displacement of the sulfonamide from protein binding sites, but also inhibition of its renal excretion.

In contrast, the time course of sulfamethoxazole plasma levels was not altered by coadministration of sulfinpyrazone or oxyphenbutazone, as shown in Fig. 7 and Table III.

TABLE III. Pharmacokinetic Parameters for Sulfamethoxazole following Intravenous Administration to Dogs

Dog	Coadministration	k_{21} (h^{-1})	k_{el} (h^{-1})	k_{12} (h^{-1})	$t_{1/2}$ (β) (h)	V_1 (l)	V_2 (l)
G	SMX[a]	3.94	0.116	0.389	7.03	5.00	0.875
	SMX+SPZ[b]	2.13	0.107	0.750	8.88	4.60	1.62
N[c]	SMX	4.10	0.0584	1.54	16.4	5.86	2.20
	SMX+SPZ	2.99	0.116	1.28	8.57	5.66	2.42
	SMX+OPB[d]	5.78	0.0690	2.41	14.3	5.36	2.23

a) Sulfamethoxazole.
b) Sulfinpyrazone.
c) Calculated from the data in refs. 1 and 2.
d) Oxyphenbutazone.

References and Notes

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