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Pharmacokinetic Aspects of the Interaction of Sulfonamides with Ibuprofen or Mepirizole in Dogs[1)]

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Interactions between two sulfonamides and ibuprofen or mepirizole were investigated in dogs by pharmacokinetic analysis. When sulfamethizole was coadministered with an acidic non-steroidal anti-inflammatory agent, ibuprofen, the β-elimination half-life ($t_{1/2}$ (β)) for sulfamethizole was increased approximately 10 times compared to the control, whereas the coadministration of sulfamethizole with a basic agent, mepirizole, resulted in slightly prolonged or unchanged $t_{1/2}$ (β) compared to the control. In the case of sulfanilamide, the time course of plasma level was not altered by coadministration of either anti-inflammatory agent.

An attempt was made to elucidate the mechanism by which ibuprofen alters the pharmacokinetics of sulfamethizole. In renal clearance experiments, the clearance ratio of sulfamethizole was markedly decreased after ibuprofen infusion. No significant alteration of protein binding of sulfamethizole was found when ibuprofen was added to dog plasma. These results suggest that the increased terminal half-life of sulfamethizole caused by ibuprofen is mainly a result of competitive interactions between them at the renal secretory level.

Keywords——drug interaction; sulfamethizole; sulfanilamide; ibuprofen; mepirizole; pharmacokinetic parameters; renal excretion; protein binding; dog

Drug interactions have become an important problem in connection with therapeutic and toxic responses. For example, sulfonamides are clinically used in combination with anti-inflammatory agents in order to obtain an improved response. In previous studies,[2,3)] we investigated the interaction between several sulfonamides and non-steroidal anti-inflammatory agents such as 5-*n*-butyl-1-cyclohexyl-2,4,6-trioxoperhydropyridine (BCP) and sulfinpyrazone in dogs. The results indicated that the maintenance of an effective plasma level of sulfamethizole was prolonged by coadministration of these acidic anti-inflammatory agents.

The widely used new non-steroidal anti-inflammatory agents, ibuprofen[4)] and mepirizole,[5)] are a weak acid and a weak base, respectively, and it was felt worthwhile to compare their compatibility with sulfonamides.

Although several reports on sulfonamide-anti-inflammatory agent interactions have appeared,[6–8)] only limited pharmacokinetic information has been reported, and no information is available for ibuprofen and mepirizole.

This investigation was carried out to examine the pharmacokinetic aspects of the interaction between sulfonamides and ibuprofen or mepirizole; the two sulfonamides used in the experiment were sulfamethizole and sulfanilamide. The mechanism of interaction was also studied.

Experimental

Materials——Commercial sufanilamide and sulfamethizole were recrystallized from ethanol (mp 165—167°C and 207—208°C, respectively). Ibuprofen and mepirizole (mp 88—89°C) were purchased from Kakenyaku Kako Co., Ltd. and Daiichi Seiyaku Co., Ltd., respectively. Ibuprofen was recrystallized from acetone as the sodium salt (mp 194—196°C).

Plasma Level of Sulfonamides in Dogs[2,3)]——Male or female dogs, weighing 11—16 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 immediately after the administration of the sulfonamide.

Pharmacokinetic Analysis[9]——Pharmacokinetic parameters were calculated by standard graphical techniques.[10] A two-compartment open model was used to describe the blood concentrations of sulfonamides following the intravenous dose, as shown in Chart 1.

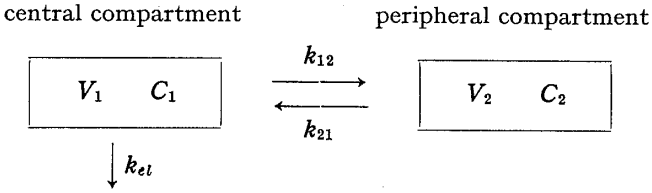

Chart 1. Two-Compartment Open Model of Drug Distribution

C: concentration in compartment.
V: distribution volume of compartment.
k: rate constant.

Protein Binding Experiment——The extent of binding of sulfonamides to dog plasma was determined by the equilibrium dialysis method, as described previously.[11] Percentage displacement of sulfonamides by ibuprofen or mepirizole was evaluated by the method of Anton.[12]

Renal Clearance Experiment——Renal clearance studies were made in two dogs by the standard procedures previously employed.[11] Each substance was given intravenously and infusion was continued throughout the experiments. In order to block the renal excretion of a sulfonamide, ibuprofen (40 mg/kg) was given initially through the cephalic vein after 3 control clearance experiments, and infusion of ibuprofen (0.9 mg/min) was continued at a rate of 3 ml/min. Drug clearance (C, ml/min) is calculated as $C=UV/P$, where U and P are the drug concentrations (mg/ml) in urine and plasma, respectively, and V is the urine flow rate (ml/min). In order to evaluate the fate of a 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 analyzed by diazotization[13] for sulfonamides or by a modification of the method described by Dische *et al.*[14] for inulin.

Results and Discussion

Pharmacokinteic Analysis of the Interaction of Sulfamethizole with Ibuprofen or Mepirizole in Dogs

The plasma levels of sulfamethizole after intravenous administration were studieed in three dogs in a cross-over fashion with and without anti-inflammatory agents. The plasma concentration profiles of sulfamethizole with and without ibuprofen and mepirizole are shown in Figs. 1 and 2, respectively. The pharmacokinetic parameters determined from these data are listed in Table I.

As shown in Figs. 1 and 2, sulfamethizole exhibited biexponential kinetics, with distribution and elimination phases. Thus, a two-compartment open model was chosen to describe the plasma sulfamethizole concentrations following the intravenous administration to dogs.

As shown in Table I, major differences in the values of the β-elimination half-life ($t_{1/2}(\beta)$) and the elimination rate constant (k_{el}) in the presence and absence of ibuprofen were noted throughout most of the investigation. When sulfamethizole was coadministered with ibuprofen, its β-elimination half-life ($t_{1/2}(\beta)$) was increased approximately 10 times compared to the control value in each dog. Thus, by simultaneous medication with ibuprofen, a high plasma level of sulfamethizole could be maintained for a long time, resulting in prolonged pharmacological effect. On the other hand, the administration of sulfamethizole with a basic agent, mepirizole, resulted in a slightly longer or unchanged terminal hlf-life compared to the control.

This investigation showed that ibuprofen can modify the elimination kinetics of sulfamethizole in dogs. On the other hand, a basic agent, mepirizole, did not have any significant effect on the elimination kinetics of sulfamethizole. These results suggested that acidic non-steroidal anti-inflammatory drugs have greater rate-retarding effects than basic agents. The difference between an acidic agent and a basic agent may be considered to depend on the nature of tubular secretion, as discussed later. The possible influence of other basic anti-inflammatory agents on the pharmacokinetic behavior of sulfonamides seems worthy of investigation.

From the standpoint of drug therapy, these findings indicate that care should be taken when sulfamethizole is clinically used in combination with ibuprofen, since lengthening of the sulfonamide half-life might enhance the therapeutic effect.

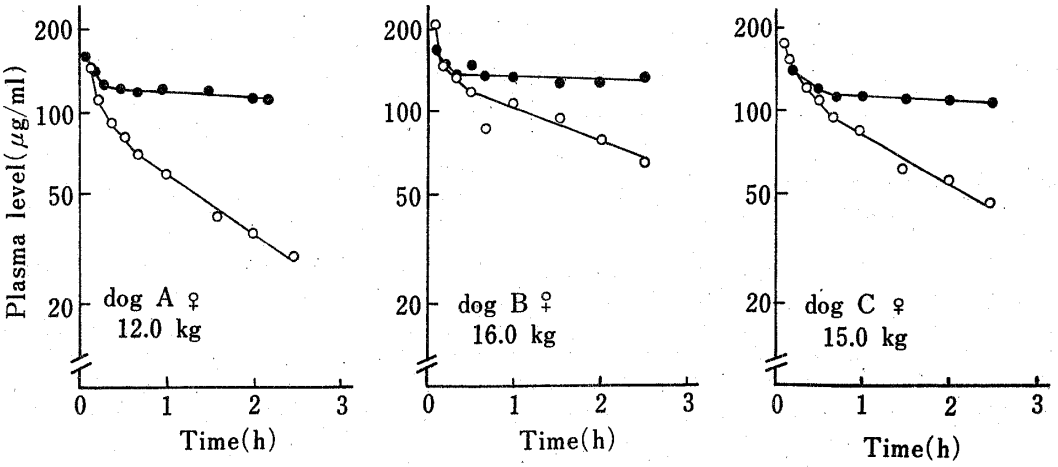

Fig. 1. Effect of Ibuprofen on the Plasma Level of Sulfamethizole in Dogs

○: sulfamethizole.
●: sulfamethizole with ibuprofen.

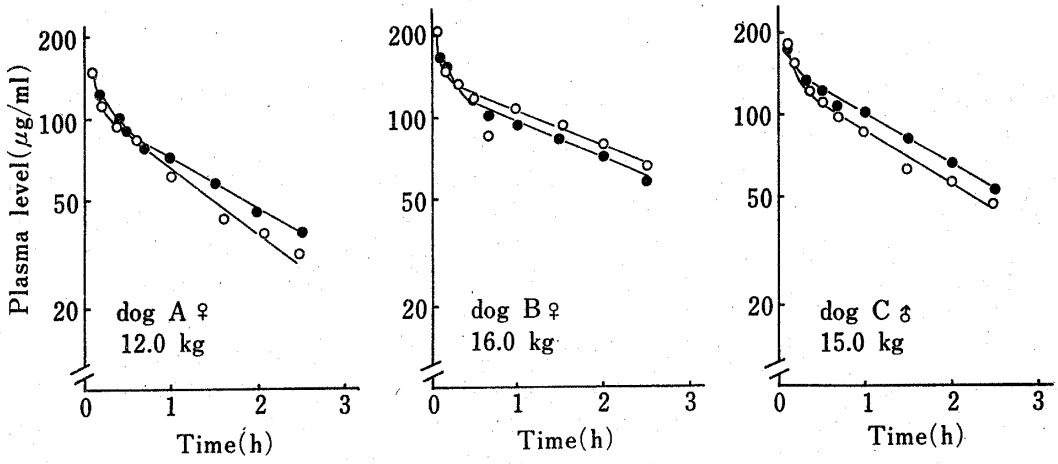

Fig. 2. Effect of Mepirizole on the Plasma Level of Sulfamethizole in Dogs

○: sulfamethizole.
●: sulfamethizole with mepirizole.

Pharmacokinetic Analysis of the Interaction of Sulfanilamide with Ibuprofen or Mepirizole in Dogs

In continuing our program of investigations involving the interactions of non-steroidal anti-inflammatory agents and sulfonamides in dogs, we have studied the combination of

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})	$t_{1/2}$ (β) (h)	V_1 (l)	V_2 (l)
A	SMZ[a]	2.88	0.898	2.33	1.51	1.78	1.43
	SMZ+IBP[b]	6.12	0.0750	3.39	14.3	1.77	0.980
	SMZ+MPZ[c]	3.25	0.718	2.23	1.72	1.92	1.32
B	SMZ	6.15	0.681	7.98	2.40	1.41	1.83
	SMZ+IBP	4.98	0.0380	2.61	27.9	2.34	1.23
	SMZ+MPZ	2.85	0.470	1.63	2.42	2.29	1.32
C	SMZ	3.55	0.700	2.12	1.66	1.93	1.15
	SMZ+IBP	4.53	0.0910	4.30	15.0	1.86	1.78
	SMZ+MPZ	5.22	0.322	1.77	2.40	2.34	0.798

a) Sulfamethizole.
b) Ibuprofen.
c) Mepirizole.

ibuprofen or mepirizole and sulfanilamide.

As shown in Figs. 3 and 4, the plasma concentration–time curves for sulfanilamide both with and without the anti-inflammatory agents declined biexponentially after intravenous administration. The results of the pharmacokinetic analysis are given in Table II. The time course of plasma levels of sulfanilamide was not altered by coadministration of ibuprofen (Fig. 3) or mepirizole (Fig. 4). Intravenous administration of sulfanilamide with ibuprofen or mepirizole resulted in slightly longer or unchanged $t_{1/2}$ (β) values compared to the control (Table II). This observation is in agreement with that reported previously[2,3] on the alteration of plasma levels of sulfanilamide by BCP and sulfinpyrazone.

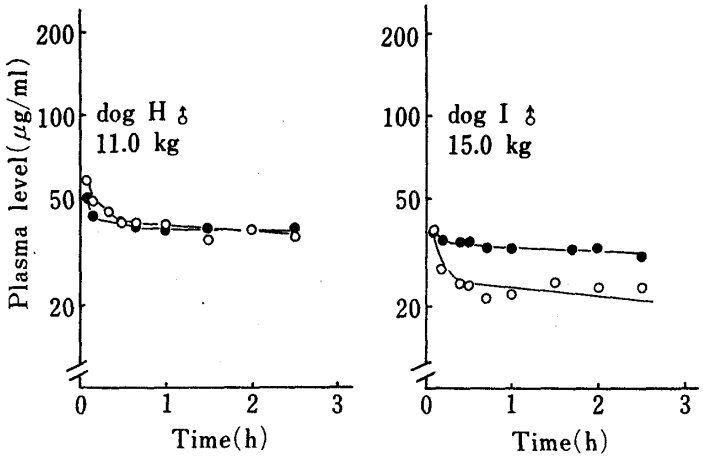

Fig. 3. Effect of Ibuprofen on the Plasma Level of Sulfanilamide in Dogs

○: sulfanilamide.
●: sulfanilamide with ibuprofen.

Mechanism of Sulfamethizole-Ibuprofen Interaction in Dogs

The results mentioned above demonstrate that ibuprofen retarded the elimination of sulfamethizole from dog plasma. We next attempted to elucidate the mechanism by which ibuprofen alters the pharmacokinetics of sulfamethizole.

Interactions at the level of excretion occur when two drugs compete for the same tubular transport system. In general, drugs that are weak acids or weak bases will compete with

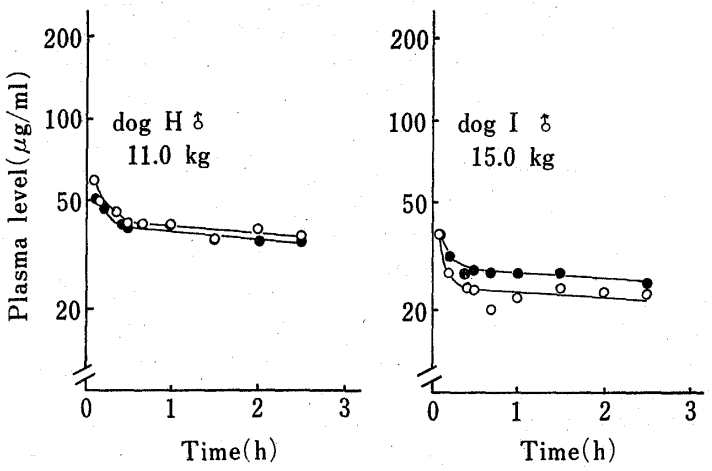

Fig. 4. Effect of Mepirizole on the Plasma Level of Sulfanilamide in Dogs

○: sulfanilamide.
●: sulfanilamide with mepirizole.

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})	$t_{1/2}(\beta)$ (h)	V_1 (l)	V_2 (l)
H	SA[a]	4.47	0.0993	3.87	13.1	4.57	3.95
	SA+IBP[b]	8.92	0.0740	7.47	17.3	4.26	3.57
	SA+MPZ[c]	4.25	0.0713	3.49	17.8	4.43	3.64
I	SA	6.32	0.0570	7.20	23.0	8.38	9.54
	SA+IBP	1.10	0.0240	0.182	34.1	10.1	1.67
	SA+MPZ	3.80	0.0460	2.02	23.1	8.09	4.31

a) Sulfanilamide.
b) Ibuprofen.
c) Mepirizole.

other agents of the same class. Thus, the urinary excretion of sulfamethizole, which involves active tubular secretion, is inhibited by BCP, sulfinpyrazone, and oxyphenbutazone, all these compounds being weak acids.[2,3] Our previous reports also demonstrate that sulfamethizole[15] is substantially secreted through renal proximal tubules by the *p*-aminohippurate mechanism, although sulfanilamide[16] is poorly secreted by this mechanism. Ibuprofen is a weak acid with a pK_a of 5.2.[17] However, no information has been obtained on the renal handling of ibuprofen.

Judging from our previous data[2,3,15,16] and the present observations, we consider that the prolonging effect of ibuprofen on sulfamethizole plasma levels may be closely correlated with competitive inhibition between the drugs at the renal level. Therefore, renal clearance experiments were performed to determine whether renal excretion of the sulfonamide could be inhibited by ibuprofen. The results are shown in Fig. 5. Typical data are given in Table III and IV.

There was a marked difference in the clearance ratio of sulfamethizole before and after ibuprofen. The marked effect of ibuprofen in suppressing the clearance ratio of sulfamethizole suggests that ibuprofen competitively interferes with the proximal tubular secretion of sulfamethizole. These results suggest that ibuprofen might be actively secreted by the same renal tubular transport mechanism as that proposed for the secretion of iodopyracet and other organic acids, and might compete with sulfamethizole in renal proximal tubular secretion.

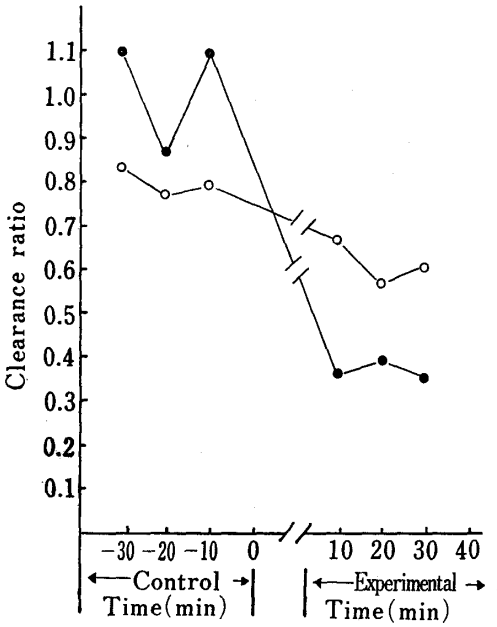

Fig. 5. Clearance Ratio of Sulfamethizole before and after Blockade of Renal Proximal Tubular Secretion by Ibuprofen

○: dog S, 11.0 kg ♂.
●: dog T, 11.5 kg ♂.

Although competition in renal tubular secretion may be the cause of the change of elimination kinetics in dogs, several other possibilities such as protein binding displacement and an effect of ibuprofen on the metabolism of sulfonamides can not be ruled out.

A number of acidic drugs are known to compete for the same limited number of protein binding sites.[18] Hence one acidic drug may be displaced by another, thereby increasing the concentration of unbound drug at target sites. Ibuprofen, an acidic drug, is known to displace warfarin from serum protein binding sites. A study in rats showed that ibuprofen increased the total clearance and the anticoagulant effect of warfarin.[19] However, human serum containing ibuprofen showed only a 10% increase in free warfarin.[20]

In our experiments, ibuprofen was examined for activity to displace bound sulfonamides from dog plasma protein by the method of Anton.[12] As shown in Table V, ibuprofen exhibits very little affinity for dog plasma proteins. As determined

Table III. The Effect of Ibuprofen on Renal Clearance of Sulfamethizole in Dog S[a]

	Time (min)	V^{c} (ml/min)	GFR^{d} (ml/min)	Sulfamethizole U^{e} (mg/ml)	P^{f} (mg/ml)	C^{g} (ml/min)	CR^{h}
Control	30—20	1.08	23.6	9.63	0.530	19.6	0.833
	20—10	1.12	24.4	8.55	0.512	18.7	0.766
	10— 0	1.12	24.4	8.25	0.478	19.4	0.794
Exptl.[b]	30—40	1.20	20.8	5.09	0.440	13.9	0.668
	40—50	1.04	21.3	5.23	0.448	12.1	0.569
	50—60	1.02	21.1	5.67	0.444	13.0	0.617

a) Dog S: 11.0 kg, ♂. d) Glomerular filtration rate. g) Drug clearance.
b) Experimental. e) Urine concentration. h) Clearance ratio.
c) Urine flow rate. f) Plasma concentration.

Table IV. The Effect of Ibuprofen on Renal Clearance of Sulfamethizole in Dog T[a]

	Time (min)	V^{c} (ml/min)	GFR^{d} (ml/min)	Sulfamethizole U^{e} (mg/ml)	P^{f} (mg/ml)	C^{g} (ml/min)	CR^{h}
Control	30—20	0.68	14.2	7.60	0.351	14.7	1.04
	20—10	1.05	23.8	6.84	0.347	20.7	0.870
	10— 0	0.90	15.2	7.48	0.406	16.6	1.09
Exptl.[b]	30—40	0.50	19.3	5.23	0.376	6.96	0.360
	40—50	0.45	20.5	6.79	0.374	8.17	0.397
	50—60	0.39	17.5	5.93	0.376	6.15	0.351

a) Dog T: 11.5 kg, ♂. d) Glomerular filtration rate. g) Drug clearance.
b) Experimental. e) Urine concentration. h) Clearance ratio.
c) Urine flow rate. f) Plasma concentration.

by equilibrium dialysis, the displacing activity of ibuprofen on bound sulfamethizole was 6.53 and 15.8% at concentrations of 50 and 100 μg/ml, respectively. No significant alteration of binding of sulfamethizole was found when mepirizole was added to the plasma.

Table V. Interference by Ibuprofen or Mepirizole with the Binding of Sulfamethizole to Dog Plasma Protein

Sulfamethizole concentration (μg/ml)	% Bound to dog plasma	Displacing activity *in vitro*[a]	
		Ibuprofen	Mepirizole
50	69.5	6.53	5.19
100	68.9	15.8	6.44

a) Displacing activity is defined as $DA_c=100-(a/b\cdot 100)$, where DA_i=displacing activity *in vitro*, a=% sulfamethizole bound in the presence of the anti-inflammatory agent, b=% sulfamethizole bound in the absence of the drug.

It has been suggested that non-steroidal anti-inflammatory agents such as phenylbutazone[21] and oxyphenbutazone[22] may act as inhibitors of drug-metabolizing enzymes in the liver. Thus, the possibility of an inhibitory action of ibuprofen on the enzyme system cannot be excluded. Since ibuprofen has an apparent inhibitory effect on drug-metabolizing enzymes,[23] the possibility remains that the increased terminal half-life was due to enzyme inhibition.

However, sulfamethizole is rapidly excreted almost unchanged in the urine in dogs, so its greatest area of clinical usefulness is in the treatment of urinary tract infection. Thus, the possibility of influence on drug-metabolizing enzymes is unlikely.

The present study suggests that the increased terminal half-life of sulfamethizole caused by coadministration with ibuprofen is mainly a result of competitive interactions between them at the renal secretory level.

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References and Notes

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