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Study of Interactions between Ibuprofen and Sulfonamides, and between Bucolome and Sulfonamides in Rats

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In this study, the effects of two non-steroidal anti-inflammatory drugs, ibuprofen and bucolome, on plasma levels of sulfonamides (sulfamethizole and sulfanilamide) were investigated in rats. The persistence of sulfamethizole in plasma was prolonged by coadministration of ibuprofen, while it was hardly affected (though the plasma level was slightly lowered) by coadministration of bucolome. No alteration was observed in the persistence or plasma level of sulfanilamide on coadministration of ibuprofen or bucolome. In experiments to investigate the renal excretion of sulfonamides, the clearance ratio of sulfamethizole was markedly decreased after ibuprofen infusion, while bucolome had little effect. From these results, it is speculated that prolongation of the persistence of sulfamethizole in plasma by ibuprofen is mainly caused by competitive interaction between sulfamethizole and ibuprofen at the renal secretory level.

In protein binding experiments, ibuprofen and bucolome were found to displace sulfamethizole bound to rat plasma protein. The displacing activity of bucolome was much stronger than that of ibuprofen. This activity of bucolome may increase the tissue distribution and glomerular filtration of sulfamethizole, and thus influence the plasma level and net renal handling of sulfamethizole.

Keywords——drug interaction; ibuprofen; bucolome; sulfamethizole; sulfanilamide; pharmacokinetic parameter; proximal tubular secretion; renal excretion; displacing activity; rat

Introduction

Administration of more than one drug at the same time is common in current clinical practice, and studies of interactions among drugs have become important in relation to drug therapy in order to enhance pharmacological effects or diminish toxicological effects.[1)]

Previously, we have reported studies on the interactions between sulfonamides and several non-steroidal anti-inflammatory drugs in dogs.[2-5)] In this work, we investigated interactions between sulfonamides and non-steroidal anti-inflammatory drugs by means of the pharmacokinetic analysis of plasma levels, and determinations of plasma protein binding and renal clearance in rats in order to clarify interspecies variation in the drug interactions. Though several reports have been published on interactions between ibuprofen and other drugs, and between bucolome and other drugs,[2,4-9)] more extensive and detailed study is desirable because of the pharmacological and pharmacokinetic importance of the drugs.

Experimental

Materials——Bucolome (BCP): commercially available BCP was recrystallized from *n*-hexane, mp 80—84 °C. Ibuprofen (IBP): commercially available IBP was recrystallized from acetone as the sodium salt, mp 194—196 °C. Sulfonamides: commercially available sulfanilamide (SA) and sulfamethizole (SMZ) were recrystallized from EtOH (mp 165—167 and 207—208 °C, respectively). All other chemicals were of reagent grade and were used without further purification.

Plasma Level of Sulfonamides in Rats——Male Wistar rats weighing 250—300 g were used in this study. They were anesthetized with pentobarbital sodium (30 mg/kg body weight), and were intubated to allow free respiration. After the incubation, the left femoral vein and right femoral artery were separately catheterized with polyethylene tubing (PE-50). Sulfonamide at a dose of 30 mg/kg was administered to rats through the left femoral vein. In coadministration experiments, an anti-inflammatory agent at a dose of 30 mg/kg was also administered through the left femoral vein immediately after administration of the sulfonamide. At each sampling time, about 0.2 ml of blood was withdrawn through the right femoral artery, and the plasma was obtained by centrifugation.

Pharmacokinetic Analysis——Estimation of pharmacokinetic parameters was carried out according to the two-compartment open model by least-squares fitting of the plasma levels using a microcomputer (NEC PC-8801).

Protein Binding Experiment——The extent of binding of SMZ to rat plasma was determined by the equilibrium dialysis method, as described previously.[10] Percentage displacement of SMZ by IBP or BCP was evaluated by the method of Anton.[11]

Renal Clearance Experiment——The retro-peritoneal approach procedure described by Sudo *et al.*[12] was employed for renal clearance studies in rats. After intubation, and catheterization of the left femoral vein and right femoral artery, the left ureter was catheterized with polyethylene tubing (PE-10) by the retro-peritoneal approach procedure. The rats were primed with sulfonamides (20 mg/body) and inulin (40 mg/body) through the left femoral vein, and a sustained infusion of sulfonamides (0.35 mg/min) and inulin (0.2 mg/min) in saline was continued throughout the whole experiment. For blockade of proximal tubular secretion of sulfonamides, IBP or BCP (2 mg/body) was primed through the femoral vein after two or three control clearance periods, and a sustained infusion of the anti-inflammatory agents (0.35 mg/min) was continued until the experiments were performed. Drug clearance (C) in ml/min was calculated as $C = UV/P$, where U and P, and V indicate urine and plasma concentrations of the drug in mg/ml, and urine flow rate in ml/min, respectively. To estimate the renal handling of the drug, clearance ratio (CR) has been conventionally used and was expressed as $CR = C/GFR$, where GFR represents glomerular filtration rate in ml/min.

Analytical Method——For the determination of sulfonamides, a high-performance liquid chromatograph (Shimadzu LC-5A) equipped with an ultraviolet (UV) detector (245 nm, Shimadzu SPD-2A) was used with a stationary phase of Zorbax C_8 (5—6 μm particle diameter) packed in 25 cm × 4.6 mm i.d. stainless-steel tubing. The mobile phase was 0.2 M sodium phosphate (monobasic, pH = 5.6) mixed with acetonitrile at a volume ratio of 3/2, and the flow rate was maintained at 0.5 ml/min. Inulin was determined by a modification of the method described by Dische and Borenfreund.[13]

Results

Elimination Profiles of SMZ and SA with or without IBP from Plasma

The plasma levels of SMZ and SA after administration with or without IBP were studied in rats. The two sulfonamides were eliminated biexponentially either in the presence or in the absence of IBP, as shown in Fig. 1. The values of elimination half-life ($t_{1/2\beta}$) and the other pharmacokinetic parameters of SMZ in the presence or in the absence of IBP are listed in Table I. When SMZ was coadministered with IBP, its elimination half-life ($t_{1/2\beta}$) was 15.2 h and this value was approximately 4.5 times the control value (3.38 h). V_1 and V_2 for SMZ with IBP were increased as compared with those for SMZ alone, as shown in Table I. The plasma elimination profile of SA was not altered by coadministration of IBP.

Elimination Profiles of SMZ and SA with or without BCP from Plasma

The plasma levels of SMZ and SA after intravenous administration with or without BCP

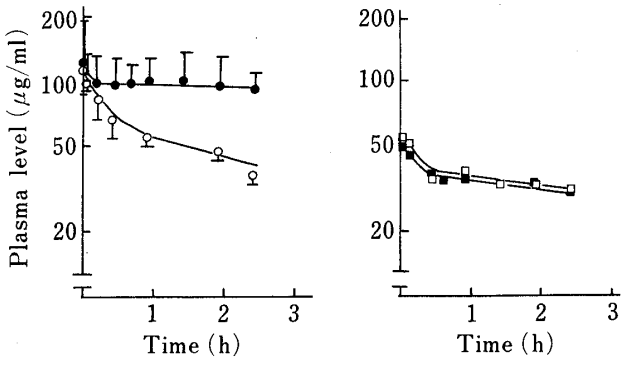

Fig. 1. Effect of IBP on the Plasma Levels of SMZ and SA in Rats

○, SMZ alone ($n=3$); ●, SMZ with IBP ($n=5$); □, SA alone ($n=1$); ■, SA with IBP ($n=1$). The S.D. is indicated by a bar (where more than one rat was used).

TABLE I. Pharmacokinetic Parameters for SMZ with or without Coadministration of IBP or BCP in Rats

Drug	K_{21} (h^{-1})	K_{12} (h^{-1})	K_{el} (h^{-1})	$t_{1/2\beta}$ (h)	V_1 (l)	V_2 (l)
SMZ ($n=3$)	1.79±0.699	2.52± 1.47	0.395±0.0810	3.38±0.206	0.149±0.0430	0.128±0.0390
SMZ+IBP ($n=5$)	7.32±5.87	7.08± 2.89	0.120±0.0498	15.2 ±0.573	0.231±0.0410	0.199±0.0680
SMZ+BCP ($n=3$)	6.63±6.99	13.2 ±18.2	0.379±0.189	4.08±0.743	0.268±0.157	0.210±0.159

Each values is the mean±S.D.

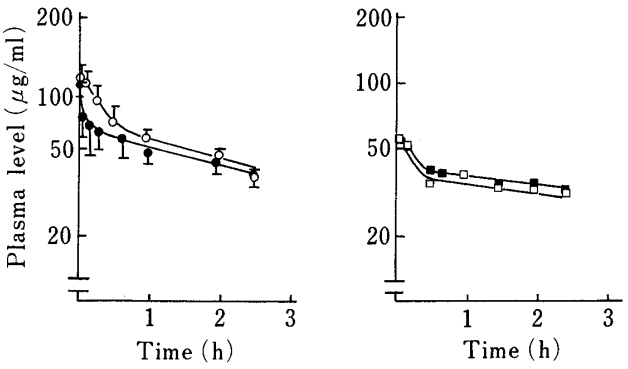

Fig. 2. Effect of BCP on the Plasma Levels of SMZ and SA in Rats

○, SMZ alone ($n=3$); ●, SMZ with BCP ($n=3$); □, SA alone ($n=1$); ■, SA with BCP ($n=1$). The S.D. is indicated by a bar (where more than one rat was used).

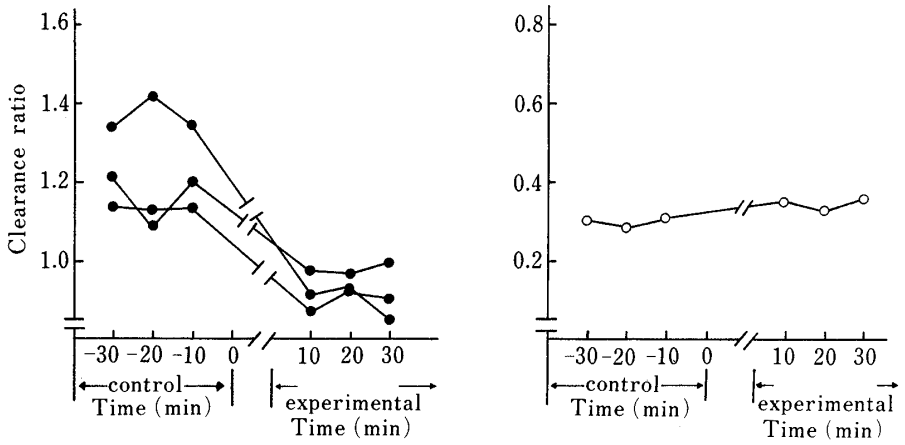

Fig. 3. Clearance Ratio of SMZ and SA before and after Blockade of Proximal Tubular Secretion by IBP in Rats

●, SMZ; ○, SA.

were studied in rats. The results are shown in Fig. 2. The values of elimination half-life ($t_{1/2\beta}$) and the other pharmacokinetic parameters of SMZ in the presence or in the absence of BCP are also listed in Table I. As shown in Fig. 2, SMZ was biexponentially eliminated from the plasma in the presence of BCP, and the plasma elimination patterns of SMZ hardly changed in the presence or in the absence of BCP. The plasma SMZ level was slightly lowered by concurrent administration of BCP, as shown in Fig. 2. V_1 and V_2 for SMZ with BCP were increased as compared with those for SMZ alone, as shown in Table I. The degree of increase of V_1 and V_2 for SMZ with BCP exceeded those for SMZ with IBP.

The elimination profile of SA was unchanged when it was coadministered with BCP, as

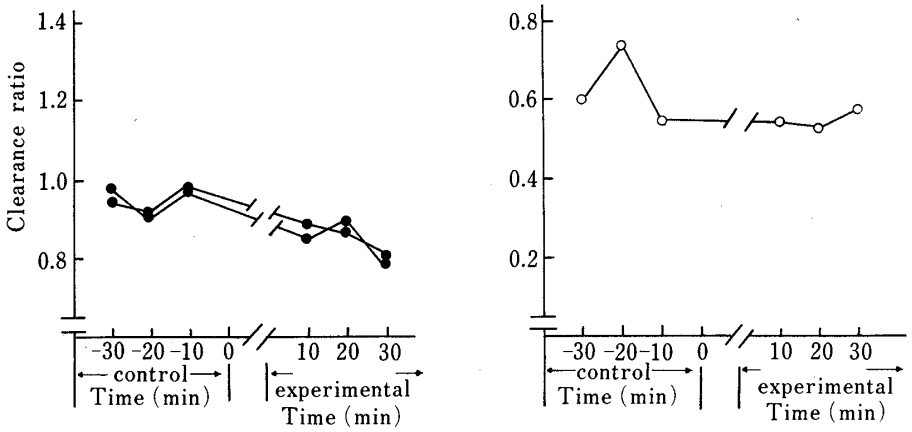

Fig. 4. Clearance Ratio of SMZ and SA before and after Blockade of Proximal Tubular Secretion by BCP in Rats

●, SMZ; ○, SA.

TABLE II. The Effect of IBP on Renal Clearance of SMZ in a Rat[a]

				SMZ			
	Time (min)	$V^{c)}$ (ml/min)	$GFR^{d)}$ (ml/min)	$U^{e)}$ (mg/ml)	$P^{f)}$ (mg/ml)	$C^{g)}$ (ml/min)	$CR^{h)}$
Control	30—20	2.94	10.1	0.876	0.223	11.6	1.15
	20—10	2.52	9.33	0.942	0.228	10.4	1.11
	10— 0	3.06	12.0	0.872	0.195	13.7	1.14
Exptl[b]	30—40	2.56	11.0	0.846	0.223	9.73	0.885
	40—50	2.20	9.00	0.917	0.243	8.31	0.923
	50—60	2.04	9.01	1.01	0.250	8.24	0.915

a) Body weight: 250 g. *b*) Experimental. *c*) Urine flow rate. *d*) Glomerular filtration rate. *e*) Urine concentration. *f*) Plasma concentration. *g*) Drug clearance. *h*) Clearance ratio.

TABLE III. The Effect of IBP on Renal Clearance of SA in a Rat[a]

				SMZ			
	Time (min)	$V^{c)}$ (ml/min)	$GFR^{d)}$ (ml/min)	$U^{e)}$ (mg/ml)	$P^{f)}$ (mg/ml)	$C^{g)}$ (ml/min)	$CR^{h)}$
Control	30—20	3.66	15.0	0.155	0.122	4.65	0.309
	20—10	5.04	18.1	0.115	0.111	5.23	0.288
	10— 0	4.96	16.0	0.120	0.120	4.96	0.311
Exptl[b]	30—40	4.40	18.5	0.178	0.119	6.58	0.355
	40—50	4.30	20.8	0.190	0.116	7.04	0.338
	50—60	4.32	17.8	0.189	0.126	6.48	0.363

a) Body weight: 250 g. *b*) Experimental. *c*) Urine flow rate. *d*) Glomerular filtration rate. *e*) Urine concentration. *f*) Plasma concentration. *g*) Drug clearance. *h*) Clearance ratio.

shown in Fig. 2.

Interactions between the Two Sulfonamides and IBP or BCP at the Renal Level

For renal clearance experiments, seven rats were used to determine whether the renal excretion of SMZ and SA could be altered by IBP or BCP infusion. The results are shown in

TABLE IV. The Effect of BCP on Renal Clearance of SMZ in a Rat[a]

	Time (min)	V[c] (ml/min)	GFR[d] (ml/min)	SMZ U[e] (mg/ml)	SMZ P[f] (mg/ml)	SMZ C[g] (ml/min)	SMZ CR[h]
Control	30—20	2.42	10.4	1.65	0.394	10.1	0.976
	20—10	2.44	12.6	1.66	0.394	11.4	0.906
	10— 0	2.72	11.5	1.54	0.375	11.2	0.969
Exptl[b]	30—40	3.18	11.5	1.04	0.350	9.83	0.852
	40—50	3.20	10.2	1.09	0.382	9.14	0.895
	50—60	2.72	10.5	1.05	0.347	8.25	0.787

a) Body weight: 290 g. *b*) Experimental. *c*) Urine flow rate. *d*) Glomerular filtration rate. *e*) Urine concentration. *f*) Plasma concentration. *g*) Drug clearance. *h*) Clearance ratio.

TABLE V. The Effect of BCP on Renal Clearance of SA in a Rat[a]

	Time (min)	V[c] (ml/min)	GFR[d] (ml/min)	SMZ U[e] (mg/ml)	SMZ P[f] (mg/ml)	SMZ C[g] (ml/min)	SMZ CR[h]
Control	30—20	3.64	15.7	0.225	0.0860	9.49	0.605
	20—10	3.74	17.0	0.299	0.0890	12.5	0.735
	10— 0	3.76	14.3	0.272	0.130	7.86	0.549
Exptl[b]	30—40	4.78	19.3	0.225	0.103	10.48	0.544
	40—50	4.52	18.9	0.232	0.105	9.96	0.528
	50—60	3.98	16.3	0.244	0.103	9.38	0.577

a) Body weight: 250 g. *b*) Experimental. *c*) Urine flow rate. *d*) Glomerular filtration rate. *e*) Urine concentration. *f*) Plasma concentration. *g*) Drug clearance. *h*) Clearance ratio.

TABLE VI. Interference by IBP or BCP with the Binding of SMZ to Rat Plasma Protein

SMZ concentration (μg/ml)	% bound in rat plasma	Displacing activity *in vitro*[a] IBP[b]	Displacing activity *in vitro*[a] BCP[b]
50	58.6	31.2	67.4
100	56.7	47.0	77.6

a) Displacing activity is defined as $DAc = 100 - (a/b \cdot 100)$, where DAc = displacing activity *in vitro*, a = %SMZ bound in the presence of the anti-inflammatory agent, b = %SMZ bound in the absence of the drug. *b*) IBP or BCP was used at the same concentration as SMZ respectively.

Figs. 3 and 4. The data obtained in individual rats in four typical renal clearance experiments are given in Tables II—V.

As shown in Fig. 3, a marked decline in the clearance ratio of SMZ after IBP infusion was observed. On the other hand, as shown in Fig. 4, the effect of BCP on the clearance ratio of SMZ was slight as compared with that of IBP.

SA excretion was not affected by either IBP or BCP, as shown in Figs. 3 and 4.

Effects of IBP and BCP on Plasma Protein Binding of SMZ

IBP and BCP were examined for ability to displace SMZ from the binding plasma

protein. As shown in Table VI, the displacement of bound SMZ by IBP amounted to 31.2 and 47.0% at equal concentration of the two drugs of 50 and 100 μg/ml, respectively. The displacement of bound SMZ by BCP was greater than that by IBP, amounting to 67.4 and 77.6% at concentrations of both drugs of 50 and 100 μg/ml, respectively.

Discussion

Generally, the pharmacokinetic behavior of a drug may be modified by the prior or concurrent administration of another drug.[1,14] For this reason, the possibility of drug interactions must be taken into consideration in every patient receiving multiple-drug administration. Many studies on drug interactions have been undertaken, but the mechanisms whereby drugs interact are not yet well understood. The aim of the present study was to investigate the effects of two non-steroidal anti-inflammatory agents on the persistence in plasma and the renal excretion of sulfonamides in rats, and to compare the results with the data previously obtained in dogs.[2,4]

Since marked prolongation of the persistence of SMZ in plasma by coadministration of IBP was observed, as shown in Fig. 1, and SMZ is well known to be mostly excreted unchanged, it seems likely that IBP exerts its effect on SMZ plasma level by altering SMZ excretion. SMZ is known to be secreted through the renal proximal tubules in dogs.[15] There was a marked difference in clearance ratio of SMZ before and after IBP infusion in rats as shown in Fig. 3 and Table II. These results suggest that IBP competitively interferes with the proximal tubular secretion of SMZ. Some organic acids are known to be secreted through renal proximal tubules by the *p*-aminohippuric acid (PAH) transport mechanism, and competition for tubular transport of such organic acids is well established as the mechanism underlying the depression of the secretion of one compound by another.[16] IBP is a weak organic acid and might be actively secreted by the same tubular transport mechanism as that proposed for the secretion of PAH and some other organic acids; further, it might compete with SMZ in renal proximal tubular secretion. These considerations are consistent with the previous data obtained in dogs.[4]

On the other hand, the persistence of SMZ in plasma was hardly affected by the coadministration of BCP, as shown in Fig. 2. It is interesting that coadministered BCP shows a tendency to lower the SMZ plasma level slightly in comparison to the control SMZ plasma level. This result is different from that obtained in dogs,[4] where the decline of SMZ plasma level was considerably retarded by simultaneous administration of BCP.[2] In dogs, the clearance ratio of SMZ was considerably decreased after BCP infusion.[2] However, in rats, as shown in Fig. 4, interaction between SMZ and BCP at the renal level seems to be slight, different from the result obtained in dogs.[2] It is well known that IBP binds to plasma protein of several animal species[17,18] and that BCP also binds to rat or dog plasma protein.[2,6] In the rat, IBP and BCP possess strong displacing activity, as shown in Table VI. The abilities of the two drugs to displace SMZ at 100 μg/ml in rats (47.0% for IBP and 77.6% for BCP) greatly exceed those in dogs (15.8% for IBP and 14.1% for BCP).[2,6] Judging from the data on displacing activity and pharmacokinetic data on volume of distribution (V_1 and V_2), it is presumed that coadministered IBP or BCP increases the free SMZ plasma level, influencing glomerular filtration and the tissue distribution of SMZ in rats. Anton[11] reported that the effect of a displacing agent *in vivo* was to decrease the plasma concentration of a drug and to increase the unbound fraction, resulting in an increased concentration of the drug in tissues. In rats markedly, BCP possesses very strong displacing activity, which exceeds that of IBP, towards bound SMZ. This correlate characteristic of BCP seems to with the changes observed in SMZ plasma elimination profile and net renal handling upon coadministration of BCP, as shown in Fig. 2. Similar phenomena were observed in the interaction between sulfametho-

xazole and BCP in dogs.[5] SA is well known not to be secreted by renal proximal tubules and to bind to plasma protein only to a small extent in dogs.[19] The pharmacokinetic behavior of SA in rats was quite similar to that in dogs. SA seems not to interact with IBP or BCP in rats, as shown in Figs. 3 and 4, and thus the results obtained in this study are not surprising.

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