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## Study of the Interactions between Sulfamethizole and Three Anti-inflammatory Propionic Acid Derivatives at the Renal Level in Rats

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The effects of three anti-inflammatory propionic acid derivatives (ketoprofen, fenbufen and flurbiprofen) on renal excretion of sulfamethizole were investigated in rats, in order to clarify the mechanisms involved. The clearance ratio of sulfamethizole was markedly decreased after ketoprofen or fenbufen infusion, while flurbiprofen had no effect on sulfamethizole excretion.

From these results, it is speculated that the decrease of renal excretion of sulfamethizole caused by ketoprofen or fenbufen is mainly due to competitive interaction between sulfamethizole and ketoprofen or fenbufen at the renal secretory level.

**Keywords**—drug interaction; ketoprofen; fenbufen; flurbiprofen; sulfamethizole; proximal tubular secretion; renal excretion; rat

Patients are frequently given more than one drug simultaneously in current clinical practice. In cases of such multiple drug administrations, one drug can alter the pharmacokinetic behavior of or the pharmacological response to another drug.<sup>1,2)</sup> Many studies on the mechanisms of drug interactions have been undertaken, but the detailed mechanisms involved still remain to be elucidated.

Anti-inflammatory propionic acid derivatives represent a new group of effective, useful non-steroidal anti-inflammatory agents, and are frequently used in clinical practice.<sup>3)</sup> We previously reported studies on the interactions between sulfonamides and ibuprofen, which is one of the anti-inflammatory propionic acid derivatives.<sup>4,5)</sup>

In the present study, we took up ketoprofen, fenbufen and flurbiprofen as examples of anti-inflammatory propionic acid derivatives, and investigated the interactions between sulfamethizole and these three anti-inflammatory propionic acid derivatives by means of the renal clearance technique in rats.

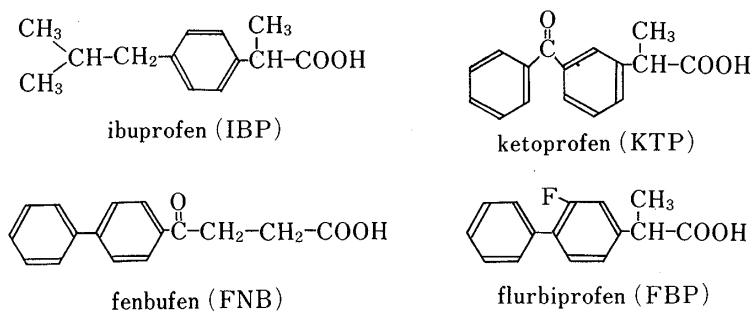


Chart 1

### Experimental

**Materials**—Anti-inflammatory Agents: Ketoprofen (KTP), fenbufen (FNB) and flurbiprofen (FBP) were purchased from commercial sources (mp 93—96 °C, 187 °C and 114.5—115.5 °C respectively).

**Sulfonamide:** Sulfamethizole (SMZ) was recrystallized from EtOH (mp 207—208 °C). All other chemicals were of reagent grade and were used without further purification.

**Renal Clearance Experiment**—The retro-peritoneal approach procedure described by Sudo *et al.*<sup>6)</sup> was employed for renal clearance studies in rats. Male Wistar rats weighing 250—300 g were used in this study. 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 SMZ (20 mg/body) and inulin (40 mg/body) through the left femoral vein, and a sustained infusion of SMZ (1 mg/min) and inulin (0.6 mg/min) in saline was continued throughout the experiment.

For blockade of proximal tubular secretion of SMZ, KTP, FNB or FBP (2 mg/body) was primed through the femoral vein after two or three control clearance periods, and a sustained infusion of the anti-inflammatory agent (1 mg/min) was continued until the experiments were performed.

Drug clearance ( $C$ ) in ml/min is calculated as  $C = UV/P$ , where  $U$ ,  $P$  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 ( $CR$ ) is conventionally used and is expressed as  $CR = C/GFR$ , where  $GFR$  represents glomerular filtration rate in ml/min calculated as inulin clearance.

**Analytical Methods**—For the determination of SMZ, 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  $\mu$ m particle diameter) packed in 25 cm  $\times$  4.6 mm i.d. stainless steel tubing and a mobile phase of 0.2 M sodium phosphate (monobasic, pH = 5.6) mixed with acetonitrile at a volume ratio of 3/2, whose flow rate was maintained at 0.5 ml/min. Inulin was determined by a modification of the method described by Dische and Borenfreund.<sup>7)</sup>

### Results and Discussion

Interactions between SMZ and KTP, FNB or FBP at the renal level were investigated. Nine rat renal clearance experiments were carried out to determine whether the renal excretion of SMZ could be altered by KTP, FNB or FBP infusion. The results are shown in Figs. 1—3, respectively. The individual data in three renal clearance experiments are given in Tables I—III.

As shown in Figs. 1, 2 and Tables I, II, a marked decrease in the clearance ratio of SMZ

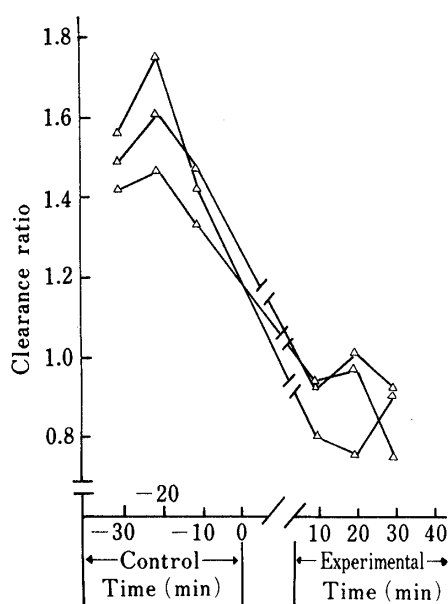


Fig. 1. Clearance Ratio of SMZ before and after Blockade of Proximal Tubular Secretion by KTP in Rats

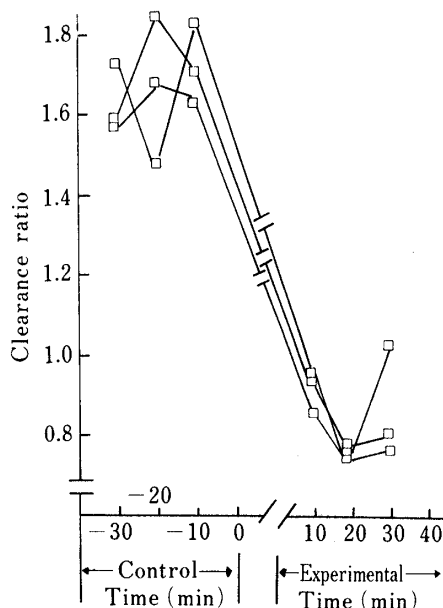


Fig. 2. Clearance Ratio of SMZ before and after Blockade of Proximal Tubular Secretion by FNB in Rats

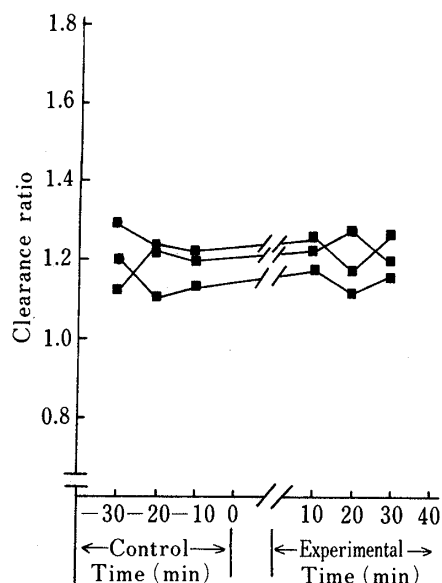


Fig. 3. Clearance Ratio of SMZ before and after Blockade of Proximal Tubular Secretion by FBP in Rats

TABLE I. The Effect of KTP on Renal Clearance of SMZ in a Rat<sup>a)</sup>

	Time (min)	SMZ					
		$V^c$ (ml/min)	$GFR^d$ (ml/min)	$U^e$ (mg/ml)	$P^f$ (mg/ml)	$C^g$ (ml/min)	$CR^h$
Control	30—20	2.43	7.96	0.802	0.164	11.9	1.49
	20—10	1.82	5.78	0.944	0.184	9.32	1.61
	10—0	1.87	5.42	0.965	0.225	8.02	1.48
Exptl <sup>b)</sup>	30—40	2.13	6.98	0.539	0.186	6.17	0.885
	40—50	1.58	6.64	0.729	0.162	7.09	1.07
	50—60	1.32	7.15	0.756	0.155	6.45	0.901

a) Rat: 260 g. b) Experimental. c) Urine flow rate. d) Glomerular filtration rate. e) Urine concentration. f) Plasma concentration. g) Drug clearance. h) Clearance ratio.

TABLE II. The Effect of FNB on Renal Clearance of SMZ in a Rat<sup>a)</sup>

	Time (min)	SMZ					
		$V^c$ (ml/min)	$GFR^d$ (ml/min)	$U^e$ (mg/ml)	$P^f$ (mg/ml)	$C^g$ (ml/min)	$CR^h$
Control	30—20	2.54	16.1	1.59	0.159	25.4	1.57
	20—10	3.30	15.7	1.18	0.148	26.5	1.68
	10—0	3.74	15.0	1.04	0.158	24.4	1.63
Exptl <sup>b)</sup>	30—40	3.88	23.9	0.754	0.142	20.6	0.865
	40—50	2.92	24.7	0.986	0.154	18.7	0.757
	50—60	2.22	21.3	1.40	0.192	16.2	0.760

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

was observed after KTP or FNB infusion. However, SMZ excretion was not affected by FBP at the dosage level of this experiment.

Ibuprofen was the first of the anti-inflammatory propionic acid derivatives to come into

TABLE III. The Effect of FBP on Renal Clearance of SMZ in a Rat<sup>a)</sup>

	Time (min)	$V^c)$ (ml/min)	$GFR^d)$ (ml/min)	SMZ			
				$U^e)$ (mg/ml)	$P^f)$ (mg/ml)	$C^g)$ (ml/min)	$CR^h)$
Control	30—20	0.480	12.6	4.18	0.141	14.2	1.13
	20—10	0.460	11.4	5.17	0.168	14.2	1.25
	10—0	0.520	10.3	3.81	0.158	12.5	1.21
Exptl <sup>b)</sup>	30—40	0.800	13.4	2.80	0.133	16.8	1.25
	40—50	0.820	11.8	2.47	0.145	14.0	1.19
	50—60	0.700	10.0	2.20	0.122	12.6	1.26

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

general use. Concerning the interactions of ibuprofen with other drugs, several studies have been undertaken in clinical practice from the viewpoint of therapeutic responses.<sup>8-10)</sup> We also reported the interactions between ibuprofen and sulfonamides in dogs and rats.<sup>4,5)</sup> In those studies, we confirmed that ibuprofen competitively inhibits renal proximal tubular secretion of sulfamethizole in both dogs and rats. Some studies concerning the interactions between KTP, FBP or FNB and other drugs have been also undertaken mainly from the viewpoint of clinical therapy.<sup>11-18)</sup> However, considering the complexity of the mechanisms of drug interactions, further studies are required to establish the detailed mechanisms of the interactions between these anti-inflammatory agents and other drugs.

We focused our attention on the interactions between the drugs at the renal level. The results of the renal clearance experiments showed a marked difference in the clearance ratio of SMZ before and after KTP or FNB infusion. It is generally accepted that some organic acids are secreted through the proximal tubules by *p*-aminohippuric acid (PAH) transport mechanisms, and competition for tubular transport of such organic acids is established as the mechanism underlying the depression of the secretion of one compound by another.<sup>19)</sup> Upton *et al.*,<sup>12)</sup> reported that KTP and its conjugates interact with probenecid at the renal level. Probenecid is well known to be secreted through renal proximal tubules by the PAH transport mechanism.<sup>20)</sup> KTP and FNB are weak organic acids and might be secreted by the same tubular transport mechanism as proposed for the secretion of *p*-aminohippuric acid and certain other organic acids, and might compete with SMZ in renal proximal tubular secretion.

From these results, we wish to emphasize that the plasma level of a drug which is secreted through renal proximal tubules by the PAH mechanism might be modified by coadministration of certain anti-inflammatory propionic acid derivatives such as ibuprofen, KTP and FNB.

The reason why SMZ excretion was not affected by FBP is obscure. FBP is the only compound containing fluorine in the molecular structure among the four examined propionic acid derivatives.<sup>5)</sup> Thus, the fluorination of the propionic acid derivatives might affect the renal handling. The correlation between the molecular features and the renal handling of propionic acid derivatives requires extensive study.

Further studies concerning other pharmacokinetic factors such as drug plasma elimination pattern and protein binding will be necessary to clarify the mechanisms of the interactions in detail.

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