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Differential effects of ketoprofen on the pharmacokinetics of sulphadimethoxine in fast and slow acetylator rabbits

YORISHIGE IMAMURA, HIROYUKI MORI, MASAKI OTAGIRI, *Faculty of Pharmaceutical Sciences, Kumamoto University, 5-1 Oe-honmachi, Kumamoto 862, Japan*

Abstract—Intravenously co-administered ketoprofen decreased the plasma concentration of sulpha-dimethoxine (SDM) after intravenous bolus administration to fast acetylator rabbits, and significantly increased the total body clearance (CL_{tot}) and steady-state volume of distribution (Vd_{ss}) of SDM. On the other hand, ketoprofen had little effect on the plasma concentration of SDM in slow acetylator rabbits. When SDM was intravenously administered in combination with ketoprofen, an increase in the plasma concentration of N^4-acetylsulphadimethoxine, a major metabolite of SDM that strongly displaces SDM from its binding sites, was observed in all rabbits, but the increase was much larger in fast acetylators. We conclude that the acetylation capacity for SDM is a factor determining the pharmacokinetic interaction between SDM and ketoprofen in rabbits.

Genetic polymorphism in acetylation of drugs such as sulphonamides and isoniazid has been shown to be a determinant of their pharmacokinetic behaviour (Weber et al 1976; du Souich et al 1978; Vree et al 1980). However, little is known about the involvement of acetylation polymorphism in the pharmacokinetic interaction between two drugs. Our previous paper (Imamura et al 1987) demonstrated that, in the rabbit, ketoprofen indirectly reduces the serum protein binding of sulphadimethoxine (SDM), by causing a marked increase in the plasma concentration of N^4-acetylsulphadimethoxine (N^4-AcSDM), a major metabolite of SDM (Bridges et al 1968), that strongly displaces SDM from its binding sites (Imamura et al 1983), and significantly increases the total body clearance (CL_{tot}) and steady-state volume of distribution (Vd_{ss}) of SDM. These observations suggest that the difference in acetylation capacity for SDM may produce the individual variability in pharmacokinetic interaction of SDM with ketoprofen in the rabbit. The purpose of the present study is to elucidate the differential effects of ketoprofen on the pharmacokinetic behaviour of SDM in fast and slow acetylator rabbits.

Materials and methods

Chemicals. SDM was purchased from Daiichi Pharmaceutical Co. Ltd (Tokyo, Japan). Ketoprofen was supplied by Kaken Pharmaceutical Co. Ltd (Tokyo, Japan). All other chemicals were of reagent grade.

Animal experiments. Male rabbits (Japanese white, 2·5–3·2 kg) were used in a cross-over design. An interval of at least 10 days was taken to minimize the residual or cumulative effect of the preceding dose. The injections were prepared by dissolving the drugs in saline containing the same molar amount of NaOH. Both SDM (50 mg kg^{-1}) and ketoprofen (25 mg kg^{-1}) were administered intravenously as a bolus, the ketoprofen immediately after the SDM; control rabbits received an equivalent volume of 0·9% NaCl (saline) adjusted to pH 9 in place of the ketoprofen. Blood samples were collected from the ear vein at times after the SDM bolus, and plasma taken for analysis.

Correspondence to: Y. Imamura, Faculty of Pharmaceutical Sciences, Kumamoto University, 5-1 Oe-honmachi, Kumamoto 862, Japan.

Determination of acetylator phenotype. The acetylator phenotype of the rabbits was determined from the percentage acetylation of SDM in 2 h in plasma as described by Imamura et al (1988). The acetylation capacities for SDM of slow and fast acetylator rabbits used were $16·1 \pm 2·3$ and $42·9 \pm 3·2$% (mean ± s.e., n = 4), respectively.

Pharmacokinetic analysis. The data of plasma SDM concentration were analysed by statistical moment analysis to obtain values for the CL_{tot} and Vd_{ss} of SDM according to the equations $CL_{tot} = D/AUC$ and $Vd_{ss} = D \cdot MRT/AUC$, where D is the dose, AUC is the area under the plasma SDM concentration-time curve from zero to infinity and MRT is the mean residence time (Benet & Galeazzi 1979). AUC was determined by the trapezoid rule until the last point (C_t) with the area to infinity being calculated by adding the term C_t/β. The elimination rate constant (β) was obtained from the log-linear regression line of SDM concentrations at 3, 4, 5 and 6 h.

Analytical methods. SDM concentration in plasma was measured by the method of Bratton & Marshall (1939). Total SDM (SDM + metabolites) concentration in plasma was measured by the same method after acid hydrolysis (0·5 M HCl, 100°C) for 1 h. N^4-AcSDM concentration in plasma was estimated by subtracting SDM from total SDM concentration, since no metabolite other than N^4-AcSDM was detected in plasma by the extraction method of Rieder (1972).

Statistics. The results were analysed statistically with the paired Student's *t*-test. A *P*-value of 0·05 or less was considered to be significant.

Results and discussion

The rabbit is much used as a model of acetylation polymorphism (Gordon et al 1973). Since the pattern of frequency distribution of percentage acetylation of SDM in 2 h in plasma after its administration to rabbits appeared to be bimodal as described by Imamura et al (1988), rabbits with less than 25% acetylation were classified as slow acetylators and those with greater than 25%, fast acetylators.

Fig. 1 shows the time course of the plasma concentration of SDM after intravenous bolus administration of SDM alone or in combination with ketoprofen to fast and slow acetylator rabbits. In fast acetylators, the co-administration of ketoprofen decreased the plasma concentration of SDM (Fig. 1), with the markedly increased N^4-AcSDM concentration in plasma as shown in Fig. 2. Furthermore, ketoprofen significantly increased the CL_{tot} and Vd_{ss} of SDM in fast acetylators (Table 1). These results were in good agreement with those of Imamura et al (1987). Therefore, it is concluded that in fast acetylator rabbits, the co-administration of ketoprofen causes a change in the pharmacokinetic behaviour of SDM through the effect of N^4-AcSDM which strongly displaces SDM from its binding sites.

The co-administration of ketoprofen had little effect on the plasma concentration of SDM in slow acetylator rabbits (Fig. 1), thereby causing no significant change in the CL_{tot} and Vd_{ss} of

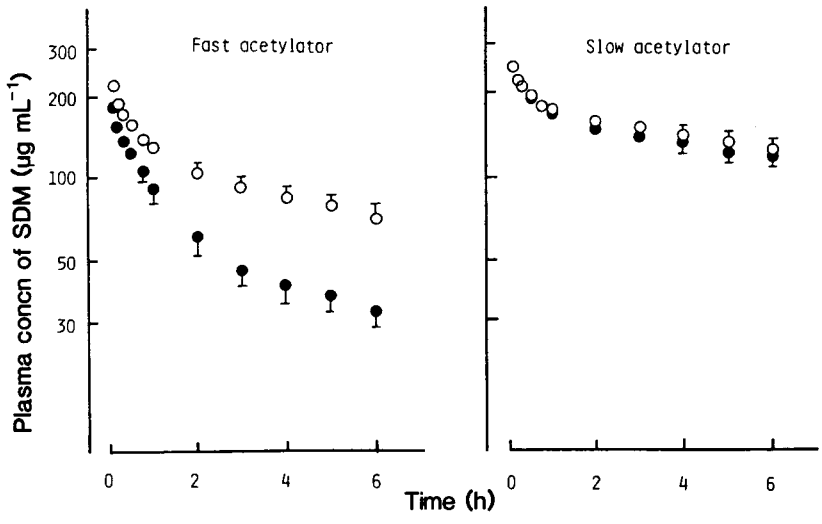

FIG. 1. Time course of plasma concentration of SDM after intravenous bolus administration of SDM alone (○) or in combination with ketoprofen (●) to fast and slow acetylator rabbits. Each point represents the mean ± s.e. (n = 4).

SDM (Table 1). In slow acetylators an interaction was not observed with respect to changes in SDM disposition. The reason for this is that when SDM is intravenously administered in combination with ketoprofen, the increase in the plasma concentration of N^4-AcSDM in slow acetylators is much smaller than that in fast acetylators (Fig. 2); ketoprofen itself had no effect on the serum protein binding of SDM (Imamura et al 1987).

Table 1. Effect of KPF on pharmacokinetic parameters of SDM in fast and slow acetylator rabbits.

	Fast acetylator		Slow acetylator	
Parameter	SDM alone	with KPF	SDM alone	with KPF
CL_{tot} (mL h^{-1} kg^{-1})	32·0 ± 3·7	77·1 ± 9·7*	16·1 ± 1·3	17·5 ± 0·8
Vd_{ss} (mL kg^{-1})	397 ± 20	646 ± 60*	282 ± 15	294 ± 13

Each value represents the mean ± s.e. (n = 4).
* Significantly different from SDM alone in fast acetylator, $P < 0.05$.

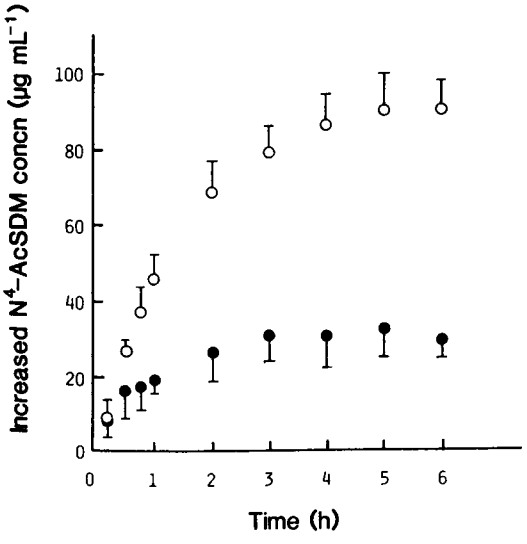

FIG. 2. Increased N^4-AcSDM concentration in plasma after intravenous bolus administration of SDM in combination with KPF to fast (○) and slow (●) acetylator rabbits. The increased N^4-AcSDM concentration in plasma was determined by subtracting the plasma concentration of N^4-AcSDM after the administration of SDM alone from that after the administration of SDM in combination with ketoprofen. Each point represents the mean ± s.e. (n = 4).

In conclusion, we provide evidence that the differential effects of ketoprofen on the pharmacokinetic behaviour of SDM are observed in fast and slow acetylator rabbits, and the acetylation capacity for SDM plays a role in the SDM-KPF interaction.

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