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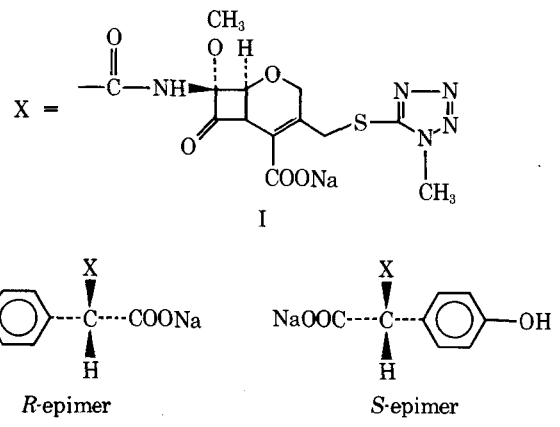
Plasma Protein Binding and Urinary Excretion of *R*- and *S*-Epimers of an Arylmalonylamino 1-Oxacephem I: In Humans

Keyphrases □ Stereoisomers, arylmalonylamino 1-oxacephem—new β-lactam antibacterial agent, renal clearance, plasma protein binding, humans □ Renal clearance—arylmalonylamino 1-oxacephem stereoisomers, effect of plasma protein binding, humans □ Protein binding, human plasma—arylmalonylamino 1-oxacephem stereoisomers, effect on renal clearance

To the Editor:

A new antibacterial agent, 7β-[2-carboxy-2-(4-hydroxyphenyl)acetamido]-7α-methoxy-3-[[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl]-1-oxa-1-dethia -3- cephem-4-carboxylic acid disodium salt (I), is an arylmalonylamino 1-oxacephem derivative that was discovered and is being developed in our laboratories (1, 2). It consists of the *R*- and *S*-epimers in about a 1:1 ratio. This drug is not metabolized and almost all of the dose, ~90% or more, is excreted into the urine in humans (3, 4), ~80% is excreted into the urine in rats, and 86–90% is excreted into the urine in dogs (5, 6) when assayed by agar diffusion using *Escherichia coli* 7437 (2). This study was carried out to elucidate the behavior of the *R*- and *S*-epimers of I in the human body.

Plasma and urine samples were collected from four healthy volunteers after intravenous injection of 1 g of I. Concentrations of *R*- and *S*-epimers in the samples were determined separately by high-performance liquid chromatography [Nucleosil $10C_{18}$, using pH 6.0 ammonium acetate buffer–methanol (11.5:1) for the plasma samples and pH 6.0 phosphate buffer containing 0.005 *M* tetra-*n*-butylammonium hydroxide–methanol (75:25) for the urine samples][1]. Plasma concentration–time curves for the *R*- and *S*-epimers indicated that the *R*-epimer was eliminated faster than the *S*-epimer (Fig. 1). The time course of the concentration ratio between the *R*- and *S*-epimers in urine also showed that the excretion of the *R*-epimer was faster than that of the *S*-epimer[1]. The renal clearances calculated from these data were 65.5 ± 3.4 and 43.5 ± 3.1 ml/min/1.48 m^2 for the *R*- and *S*-epimers, respectively.



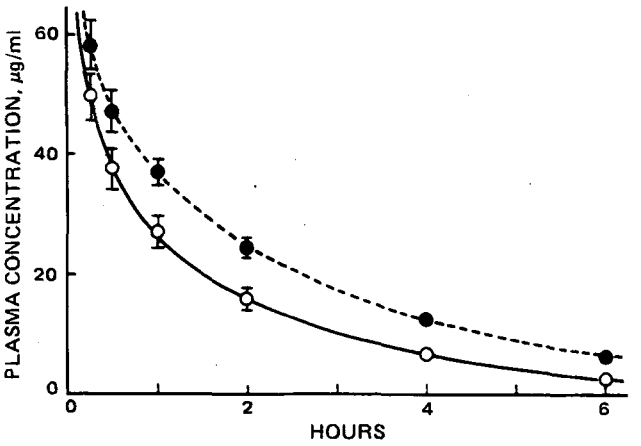


Figure 1—*Plasma concentration of* R- (○) *and* S- (●) *epimers after intravenous administration of I. Each data point gives the mean and standard deviation of four healthy volunteers.*

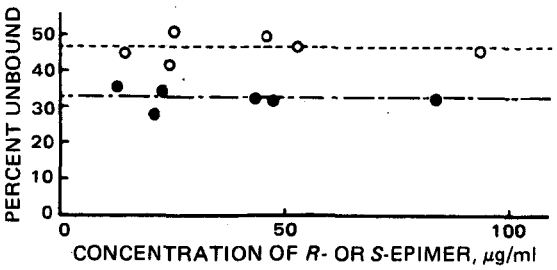


Figure 2—*Human plasma protein binding of* R- (○) *and* S- (●) *epimers of I. The epimer concentration includes both bound and unbound epimer.*

To investigate this difference, protein binding of these epimers was examined by ultrafiltration[2] of fresh human plasma containing I at 37°. The results indicated that the fraction of the unbound *R*-epimer was higher than that of the *S*-epimer (Fig. 2). The mean unbound ratio of the *R*-epimer was 47%, and that of the *S*-epimer was 33%.

The renal clearance of unbound *R*- and *S*-epimers calculated from these results was 140.2 ± 8.1 and 132.2 ± 7.0 ml/min/1.48 m^2, respectively. These two values were not significantly different.

These results suggest that the faster excretion of the *R*-epimer of I compared to the excretion of the *S*-epimer can be explained by the larger unbound fraction of the former in human plasma.

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Plasma Protein Binding and Urinary Excretion of *R*- and *S*-Epimers of an Arylmalonylamino 1-Oxacephem II: In Rats

Keyphrases □ Stereoisomers, arylmalonylamino 1-oxacephem—new β-lactam antibacterial agent, renal clearance, plasma protein binding, rats □ Renal clearance—new antibacterial agent, arylmalonylamino 1-oxacephem stereoisomers, effect of plasma protein binding, comparison of rat and human data □ Protein binding, rat plasma—new antibacterial agent, arylmalonylamino 1-oxacephem stereoisomers, effect on renal clearance, comparison with human data

To the Editor:

In Part I (1), we reported that the *R*-epimer of an arylmalonylamino 1-oxacephem derivative {7β-[2-carboxy -2- (4-hydroxyphenyl)acetamido] -7α- methoxy-3-[[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl] -1- oxa-1-dethia-3-cephem-4-carboxylic acid disodium salt (I)}, a new antibacterial agent, was excreted into the urine faster than the *S*-epimer in humans. It was concluded that the phenomenon was due to the difference between the binding of human plasma protein with *R*- and *S*-epimers.

To confirm that conclusion, studies were carried out using rats in which I was not metabolized and was excreted mainly into the urine, as in humans. The extent of protein binding of the *R*- and *S*-epimers in rat plasma was measured by the same method described previously (1). Unlike in humans, there was no difference in plasma protein binding between the *R*- and *S*-epimers in rats (Fig. 1). Thus, taking into consideration our conclusion in the previous study (1), the urinary excretion rates of the *R*- and *S*-epimers in rats should be the same.

To confirm this prediction, the plasma concentration and urinary excretion rate of the *R*- and *S*-epimers after intravenous injection of I (70 mg/kg) to three rats were measured by the method described previously (1). The plasma concentration–time curves for the *R*- and *S*-epimers were the same (Fig. 2), and the renal clearance values were 0.85 ± 0.04 and 0.83 ± 0.04 ml/min/100 g for the *R*- and *S*-epimers, respectively. As expected, there was no difference in the renal clearance in rats between these epimers.

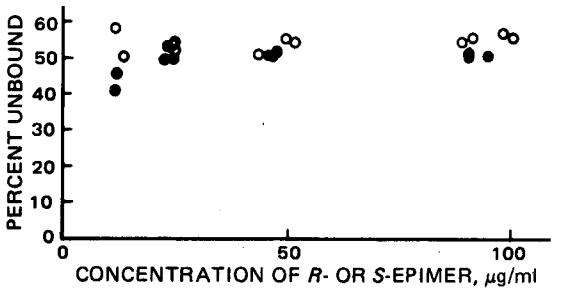

Figure 1—*Rat plasma protein binding of* R- (○) *and* S- (●) *epimers of I.*

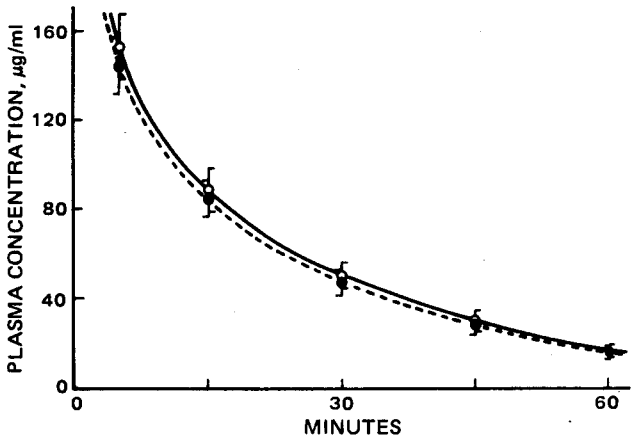

Figure 2—*Plasma concentration of* R- (—○) *and* S- (- -●) *epimers after intravenous administration of I. Each data point gives the mean and standard deviation of three rats.*

These stereospecific differences in plasma protein binding have been reported for other drugs (2–5) and vary between species.

In vitro studies[1] of the protein binding of I in dog plasma showed that the percentage of the unbound fraction of the *R*-epimer was larger than that of the *S*-epimer; these results were similar to those on human plasma protein binding. This finding suggested that urinary excretion of the *R*-epimer was faster than that of the *S*-epimer in dogs, as in humans, and this prediction was confirmed experimentally[1].

These findings support the previous conclusion that the difference in the urinary excretion rate between *R*- and *S*-epimers of I in humans is due to the difference in protein binding of human plasma between these epimers.

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