

# Pharmacokinetics of TR-701 (DA-7218), a New Oxazolidinone in Mice, Rats, and Dogs

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## Abstract

**Background:** TR-701 (DA-7218) is a new oxazolidinone antibiotic with excellent *in vitro* and *in vivo* efficacy against Gram-positive bacteria including resistant strains. We investigated the pharmacokinetics of TR-701 in mice, rats, and dogs.

**Methods:** The phosphate monoester prodrug TR-701 and the parent TR-700 (DA-7157), were administered intravenously or orally to mice, rats and dogs at the dose of 10 mg/kg. Blood was immediately centrifuged, and heparinized plasma was acidified to stabilize the prodrug TR-701 and then stored at -70°C until LC/MS/MS analysis. *In vitro* blood and plasma stability of TR-701 was also studied.

**Results:** TR-701, the phosphate prodrug of the active oxazolidinone antibiotic TR-700 (DA-7157), increased the exposure of TR-700 after oral administration. This was due to increased water solubility and rapid hydrolysis of the prodrug during the absorption process and in blood. TR-700 was observed in the first blood sampling after both intravenous and oral administration of TR-701 in all species studied. Elimination half lives of TR-700 were about 3.5 h (mice), 1.5-1.9 h (rat) and 0.6-0.9 h (dog).

**Conclusions:** TR-701 was rapidly converted to an active antibacterial agent TR-700 after intravenous and oral administration in all the species studied.

## Introduction

TR-701 (DA-7218), the phosphate monoester prodrug of TR-700 (DA-7157) is a new oxazolidinone antibiotic with excellent *in vitro* and *in vivo* efficacy against Gram-positive bacteria including resistant strains. We investigated the pharmacokinetics of TR-701 in mice, rats, and dogs.

## Methods

### Drug administration and blood sampling

- TR-701 was dissolved in distilled water.
- TR-700 was dissolved in DMA:PEG400:DW mixed solution for IV and suspended in 1% HPMC for oral administration.
- Blood was obtained by retro-orbital bleeding (mice) or cannulation in carotid artery (rat) or cannulation of cephalic vein (dog).

### *In vitro* stability in heparinized plasma

Fresh heparinized plasma was divided into 200  $\mu$ L aliquots to which TR-701 (DA-7218) was added in triplicate at a concentration of 2  $\mu$ g/mL. Plasma samples were incubated at 37°C for 0, 5, 10, 15, 20, 30 min, and 1, 2, 4 hr. At these specified time intervals, a 200  $\mu$ L aliquot of 1M HCl was added to prevent further conversion, and kept on ice.

### Analytical condition

- Plasma was acidified with 1M HCl to stabilize TR-701 and then liquid-liquid extracted with ethylacetate.
- TR-701 and TR-700 was analyzed with LC/MS/MS (API 3000).
- Analytical condition

Mobile phase	20mM Ammonium formate (pH2.2) : Acetonitrile = 65: 35, pH was adjusted with formic acid
Column	Atlantis™ dC <sub>18</sub> (2.1*100mm, 3 $\mu$ m) at 30°C
Flow rate	0.2ml/min
Retention time	DA-7218 = 2.1 min, IS (linezolid) = 2.8 min, DA-7157 = 3.8 min

## Results

- TR-701 was rapidly converted to TR-700 (its active metabolite) in all species studied (Figure 1). Only pharmacokinetic parameters of TR-700 was shown in Table 1. After intravenous administration of TR-701, TR-700, the active metabolite, was detected from the first blood sampling time (1 min), and its systemic conversion ratio (AUC<sub>TR-700</sub> after i.v. of TR-701 divided by AUC<sub>TR-700</sub> after i.v. of TR-700) was about 69% and 75% in mice and rat, respectively (Table 1).
- Terminal half life of TR-700 was independent of administered drug (active or prodrug) in mice and rats supporting that formation rate of TR-700 is fast and does not affect the elimination phase. Terminal half life of TR-700 was 3.42, 1.61, and 0.58 hr in mice, rats, and dogs, respectively (Table 1).
- After oral administration of TR-701, the relative bioavailability of TR-700 (AUC<sub>TR-700</sub> after oral of TR-701 divided by AUC<sub>TR-700</sub> after oral of TR-700) was 133% and 192% in mice and rat, respectively (Table 1). This could be due to increased absorption of TR-700 caused by high water solubility of TR-701, the phosphate monoester prodrug of TR-700.
- The conversion of TR-701 to TR-700 in mice, dog, and human plasma was expressed by plotting the decreasing of TR-701 against the increase in TR-700 in plasma versus time (Figure 1). *In vitro* disappearance half-life of TR-701 in plasma was independent of species studied, the value was 28.8, 28.3, and 36.1 min in mice, dog, and human plasma, respectively.

Table 1. Pharmacokinetic parameters of DA-7157 after single intravenous and oral administration of TR-700 (DA-7157) or TR-701 (DA-7218) to male ICR mice, SD rats and beagle dogs.

	Drug	Route	Dose (mg/kg)	PK parameters of DA-7157				
				T <sub>1/2</sub> (hr)	AUC ( $\mu$ g hr/mL)	T <sub>max</sub> (hr)	C <sub>max</sub> ( $\mu$ g/mL)	AUC <sub>oral</sub> / AUC <sub>iv</sub> Ratio (%)
Mice	TR-700 (DA-7157)	IV	10	3.49	103.4	0.0167	21.6	
		Oral	10	3.12	50.2	2	4.62	48.5
	TR-701 (DA-7218)	IV	7.46*	3.42	53.6	0.0167	8.81	
		Oral	7.46*	3.82	49.8	0.5	8.37	92.9
Rats	TR-700 (DA-7157)	IV	10	2.15	53.1	0.0167	246	
		Oral	10	3.59	15.8	5	1.87	29.8
	TR-701 (DA-7218)	IV	14.9*	1.61	59.3	0.06	42.4	
		Oral	14.9*	3.65	45.2	0.5	14.6	76.1
Dogs	TR-701 (DA-7218)	IV	7.46*	0.58	4.4	0.083	5.37	
		Oral	7.46*	0.64	2.78	1.67	1.38	63.2

\* Dose(mg/kg) of TR-701 (DA-7218) was shown as the dose of TR-700 (DA-7157).

Figure 1. Plasma concentration-time profiles of TR-701 (DA-7218, orange circle) and TR-700 (DA-7157, closed circle) after single intravenous administration of TR-701 in mice, rat, and dog. After oral administration of TR-701, only TR-700 was detected in plasma (shown as open circle).

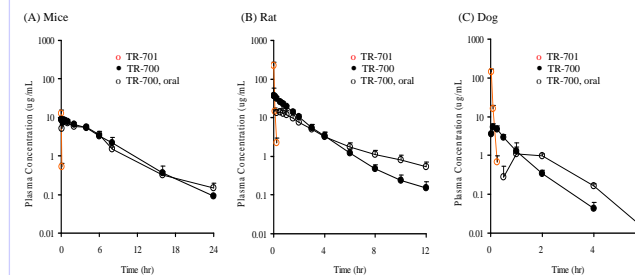
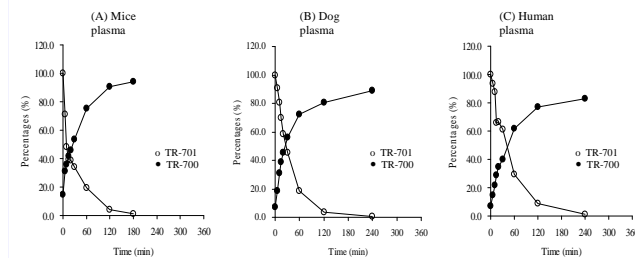


Figure 2. *In vitro* disappearance of TR-701 (DA-7218) and formation of TR-700 (DA-7157) after 37°C incubation of DA-7218 in fresh heparinized mice, dog, and human plasma at the concentration of 2000 ng/mL (N = 3, each).



## Conclusions

- TR-701 (DA-7218) was rapidly converted to the parent drug TR-700 (DA-7157) *in vivo* and *in vitro* in all the species studied.
- Administration of TR-701 (DA-7218) resulted in high oral availability, suitable T<sub>1/2</sub> and AUC for TR-700 (DA-7157) in all three animal species.