Pharmacokinetics Of Gamithromycin In Pigs

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Introduction

Gamithromycin (GAM), a 15-membered semi-synthetic macrolide antibiotic of the azalide subclass, has recently been developed for the treatment and prevention of bovine respiratory disease. Besides the anti-infectious properties, macrolides have frequently been reported to be able to influence various inflammatory processes.
The aim of this study was to determine the pharmacokinetic (PK) parameters of gamithromycin in pigs, whereafter the disposition of the antibiotic can be used in further research to investigate its immunomodulating properties in a porcine lipopolysaccharide (LPS) inflammation model.

Results

The semi-logarithmic plots of the plasma concentration-time curves after IV and SC administration are depicted in Fig. 3.

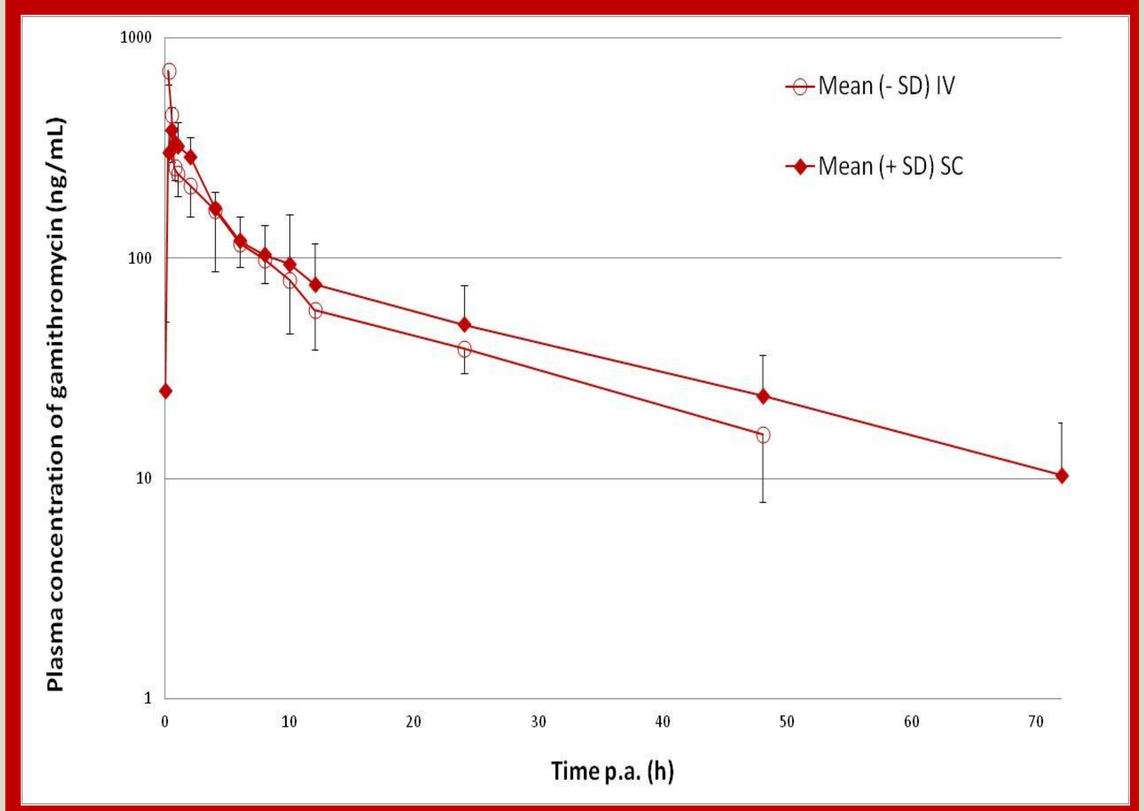

Figure 3. Mean (± SD) plasma concentration-time profiles of gamithromycin after IV (n=6) and SC (n=6) bolus administration of 6 mg/kg BW in pigs

Table 1. Pharmacokinetic parameters for gamithromycin in pigs after IV (n=6) and SC (n=6) bolus administration of 6 mg/kg BW (mean ± SD)

Parameter	Unit	IV	SC
AUC_{last}	µg.h/mL	3.24 ± 0.56	3.48 ±1.90
AUC_{inf}	µg.h/mL	3.67 ± 0.75	4.31 ± 1.14
λz	/h	0.043 ± 0.011	0.037 ± 0.009
$T_{1/2\lambda z}$	h	16.03[A]	18.76[A]
V_z	L/kg	40.47 ± 8.73	42.70 ± 16.16
V_{ss}	L/kg	31.03 ± 6.68	-
Cl	L/h.kg	1.69 ± 0.33	1.47 ± 0.40
T_{max}	h	-	0.63 ± 0.21
C_0	µg/mL	1.37 ± 1.09	-
C_{max}	µg/mL	-	0.41 ± 0.090
F	%	-	117.56 ± 39.36

[A]:harmonic mean

Materials and Methods

Experimental protocol

The experiment was conducted according to a single dose parallel design with each group containing six 9-week-old male pigs. The animals received a bolus of 6 mg/kg body weight GAM (Zactran®, Merial, see Fig. 1) intravenously (IV) in the ear vein (n=6) or subcutaneously (SC) in the flank region (n=6). Blood was collected from the jugular vein before administration (time 0), at 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 10, 12 h post-administration (p.a.) and once daily from day 2 to day 14 p.a. Plasma was stored at ≤ -15°C until analysis.

GAM analysis

Quantitation of GAM in porcine plasma was carried out using an in-house developed and validated liquid chromatography-tandem mass spectometry (LC-MS/MS) method. The sample preparation is shown in Fig 2.

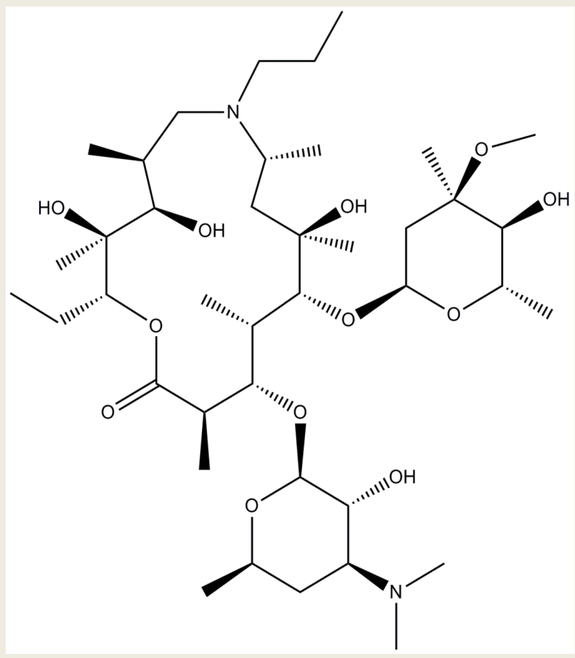

Figure 1. Chemical structure of GAM

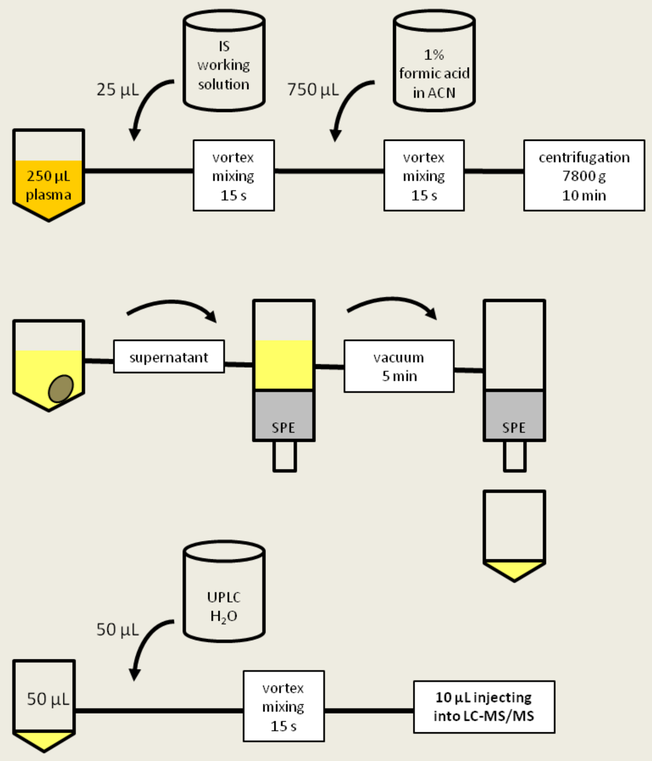

Figure 2. Diagram of GAM sample preparation steps before LC-MS/MS analysis

PK and Statistical analysis

The PK parameters were analysed using WinNonlin®, version 6.2.0 (Pharsight). A non-compartmental model was used to determine the area under the plasma concentration-time curve from 0 to the last quantifiable time point (AUC_{last}), the AUC extrapolated to infinity (AUC_{inf}), the elimination rate constant (λz), the terminal half-life ($t_{1/2\lambda z}$, expressed as the harmonic mean), volume of distribution (V_{ss}), plasma clearance (Cl), maximum plasma concentration (C_{max}) and time to C_{max} (T_{max}).
The absolute bioavailability (F) was calculated from the following equation:

$$F\ (\%) = (AUC_{inf\ SC} / AUC_{inf\ IV}) \times 100$$

The data were statistically analysed by means of single-factor analysis of variance (ANOVA), using PASW Statistics 20 (IBM SPSS Software). A value of $P<0.05$ was considered significant.

Discussion and Conclusion

In pigs a higher clearance of GAM is observed compared to cattle (1.69 vs 0.71 L/h.kg), resulting in a shorter half-life of elimination (16.03 and 44.9 h after IV administration in pigs and cattle, respectively). The volume of distribution is very high (31.03 and 24.9 L/kg in pigs and cattle, respectively), indicating a distinct tissue penetration and intracellular levels.
None of the pharmacokinetic parameters were significantly different between both administration routes.

We can conclude that there is a fast and complete absorption (F = 117%), a distinct tissue penetration and a faster elimination compared to cattle of GAM following SC administration in pigs.

In future research, these pharmacokinetics will be applied in a porcine LPS-inflammation model to investigate the immunomodulatory properties of GAM. The influence of GAM on the protein expression of pro-inflammatory cytokines, acute phase proteins and fever suppression will be investigated.

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