Pharmacokinetics and pulmonary distribution of chronic clarithromycin after simultaneous and consecutive administration of rifampicin in foals

S. Berlin[1], L. Spieckermann[2], S. Oswald[1], M. Keiser[1], J. Penski[1], D. Wegner[1], M. Venner[2], W. Siegmund[1]

[1]Department of Clinical Pharmacology, Center of Drug Absorption and Transport, University Medicine Greifswald, Germany
[2]Clinic for Horses, University of Veterinary Medicine Hannover, Germany

Introduction

Clarithromycin (CLA) and rifampicin (RIF) are first line treatment options for severe pneumonia in foals caused by *Rhodococcus equi* (Hillidge et al., Vet. Microbiol., 1987).

The delivery of CLA to its site of action, i.e. bronchial epithelial lining fluid (ELF) and bronchoalveolar cells (BAC), is influenced by CYP3A4 and drug transporters (e.g. ABCB1/P-gp) which are also expressed in the bronchoalveolar system (Fig. 1). Since RIF is a potent inducer of both, CYP3A4 and P-gp, chronic coadministration of both antibiotics causes an over 90 % loss in systemic CLA bioavailability together with a dramatic drop in drug levels at its site of action (Peters et al., DMD, 2011).

However, since RIF is also a potent inhibitor of drug uptake transporters (e.g. OATPs), inhibition of CLA uptake by simultaneously administered RIF may be an additional explanation for reduced bioavailability.

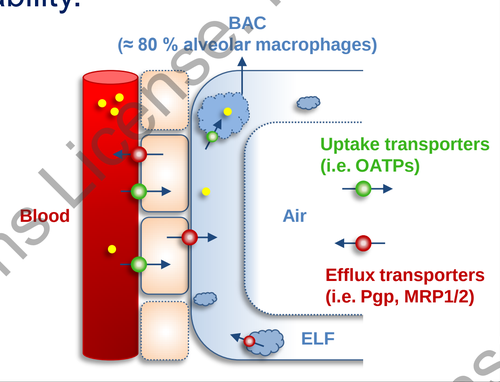


Figure 1: Schematic representation of the drug transport from the blood across the membrane of the endothelial and bronchial/alveolar epithelial cells into the ELF, and from the ELF into the BACs.

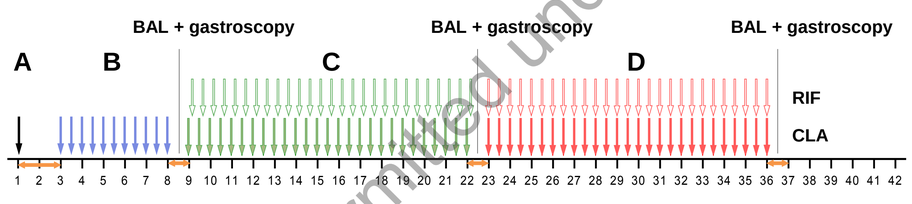
Objectives

To investigate if consecutive oral administration of CLA and RIF is superior to simultaneous administration.

Methods

Study protocol

- Design: controlled, randomized, cross-over study
- Subjects: 12 healthy foals (7 ♂ and 5 ♀, 6-10 weeks, 90-140 kg)
- Treatment periods:
  - **A:** 7.5 mg/kg CLA, i.v.
  - **B:** 2x7.5 mg/kg CLA p.o.
  - **C:** 2x7.5 mg/kg CLA + 2x10 mg/kg RIF p.o. (simultaneous)
  - **D:** 2x7.5 mg/kg CLA + 2x10 mg/kg RIF p.o. (consecutive)
- Sequences: Sequence 1 - ABCD / Sequence 2 - ABDC



- Sampling: plasma (i.v.: 0-48 h, p.o.: 0-24 h)
  bronchoalveolar lavage (BAL) and gastroscopy 12 h after the last application of CLA

Results

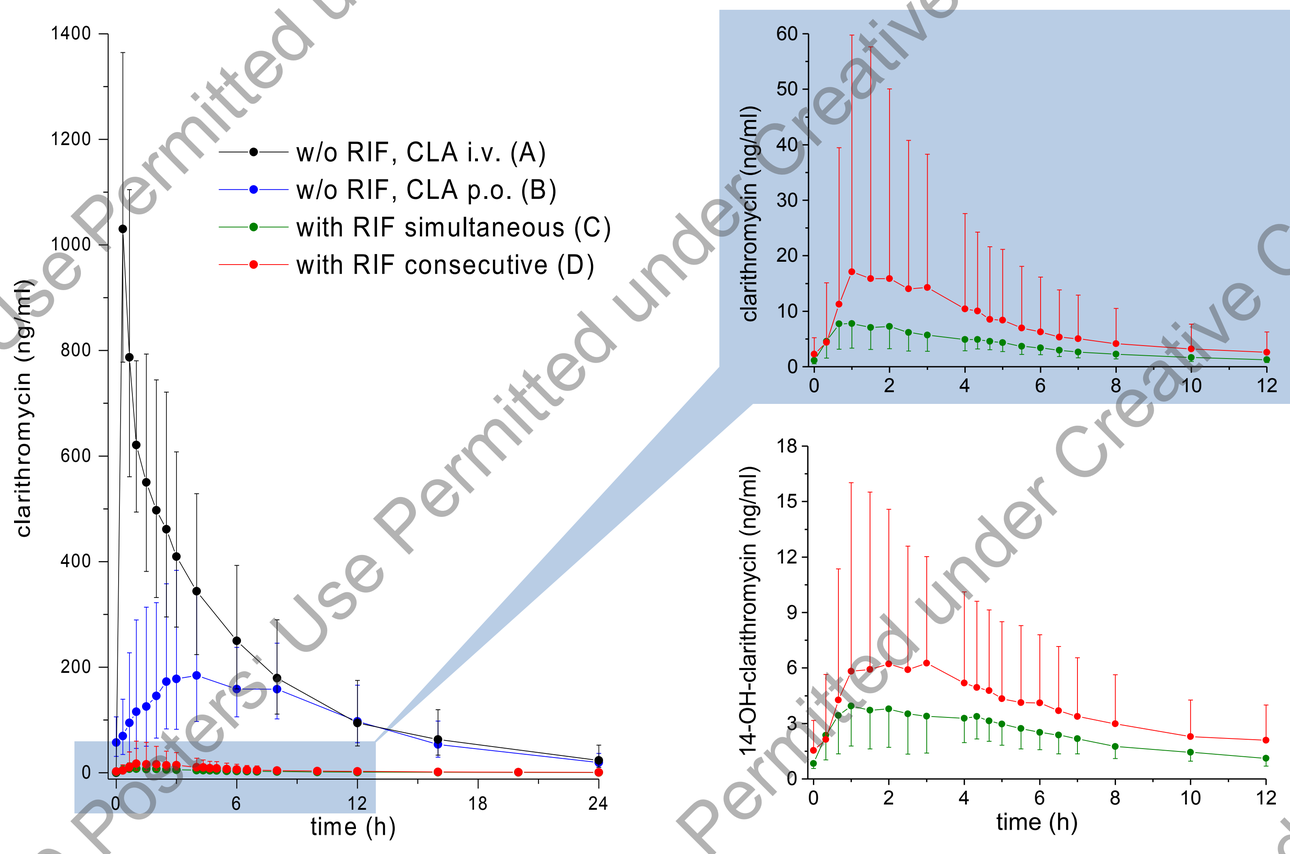


Figure 2/Table 1: LC-MS/MS-based quantification of [CLA] and [14-OH-CLA] in plasma, ELF and BACs. Plasma concentration-time curves of CLA and 14-OH-CLA without RIF after intravenous (-●-) and oral (-●-) administration of CLA and with simultaneous (-●-) or consecutive (-●-) co-medication of rifampicin, respectively (GM±SD are given). Pharmacokinetic parameters for all treatment regimes are given in the table.

	$AUC_{0-\infty}$ or $AUC_{0-12\,h}$	F_{abs}	C_{max}	C_{min}	t_{max}	$Plasma_{12\,h}$	$ELF_{12\,h}$	$BALC_{12\,h}$
	ng×h/ml	%		ng/ml	h		ng/ml	
CLA								
w/o RIF, CLA i.v. (A)	5160 ± 1840	-	1710 ± 1580	-	-	-	-	-
w/o RIF, CLA p.o. (B)	1980 ± 903†	40.5 ± 19.1	270 ± 116†	62.1 ± 31.8	4.21 ± 2.65	102 ± 61.5	2770 ± 2500	47000 ± 26700
with RIF simultaneous (C)	55.3 ± 32.7†‡	1.19 ± 0.71‡	13.5 ± 10.1†‡	0.92 ± 0.54‡	1.79 ± 1.87‡	1.40 ± 0.67‡	71.8 ± 49.6‡	748 ± 849‡
with RIF consecutive (D)	158 ± 181†‡*	3.24 ± 3.76‡*	40.8 ± 52.3†‡*	2.48 ± 2.13‡*	1.79 ± 0.81‡	3.33 ± 3.08‡*	180 ± 161‡*	1680 ± 1760‡*
14-OH-CLA								
w/o RIF, CLA i.v. (A)	97.4 ± 41.5	-	7.47 ± 3.07	-	2.45 ± 1.19	-	-	-
w/o RIF, CLA p.o. (B)	59.1 ± 31.4†	68.4 ± 49.3	7.20 ± 3.34	2.30 ± 1.47	4.37 ± 2.70†	3.55 ± 2.17	16.9 ± 7.68	301 ± 137
with RIF simultaneous (C)	34.3 ± 15.5†‡	43.3 ± 30.7	6.60 ± 3.34	0.72 ± 0.21‡	2.43 ± 2.20‡	39.6 ± 7.29†‡	9.27 ± 4.97‡	39.3 ± 21.5‡
with RIF consecutive (D)	61.0 ± 50.3†*	65.2 ± 43.4	10.5 ± 9.17	1.72 ± 1.09*	2.17 ± 0.78‡	34.2 ± 8.67†‡*	14.7 ± 7.94	79.9 ± 73.9‡*

† vs. A, ‡ vs. B, * vs. C ($P \leq 0.05$, Wilcoxon-Test)

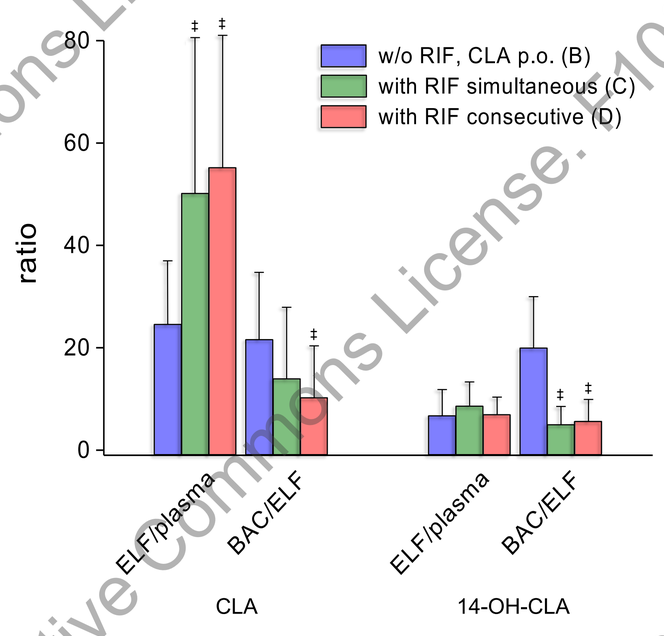


Figure 3: Ratios of CLA and 14-OH-CLA in ELF/plasma and BAC/ELF 12 h after the last administration of CLA for the different treatment regimes (MW±SD are given; ‡ vs. w/o RIF, CLA p.o. (B); $P \leq 0.05$, Wilcoxon-Test).

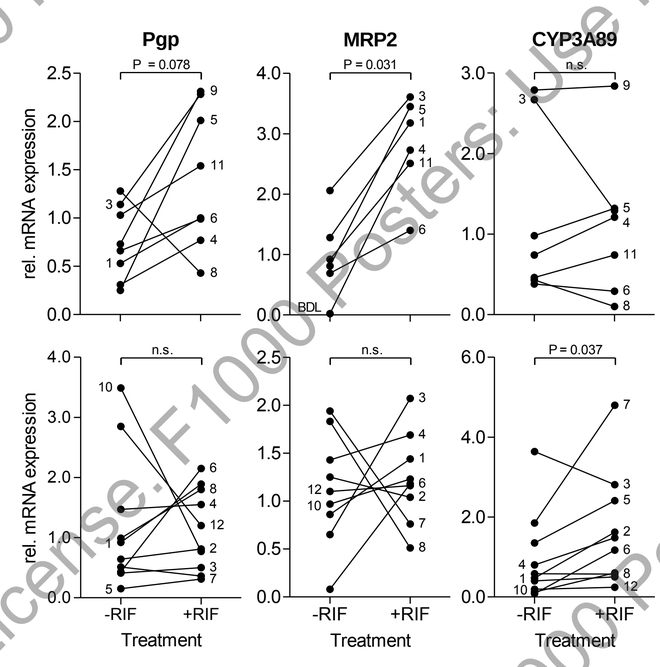


Figure 4: RNA was isolated from intestinal biopsies and BACs. After cDNA synthesis mRNA expression of P-gp, CYP3A89, and MRP2 in intestinal biopsies (top figures) and BACs (bottom figures) before (-RIF) and after (+RIF, mean value of C+D) RIF treatment, was measured by qPCR. Results were normalized to *18S* rRNA expression and depicted in relation to the mean expression of all samples.

Conclusion

- Consecutive administration of RIF significantly enhanced systemic CLA bioavailability compared to the simultaneous administration.
- However, compared to CLA treatment alone both treatment regimes with RIF lead to a dramatic loss in CLA bioavailability by about 97 % and 92 %, respectively. A similar effect was observed at the site of action, in the ELF and BACs.
- In summary, direct uptake inhibition of CLA by RIF is negligible in combined therapies, therefore consecutive administration of RIF is not a suitable approach to overcome the severe adverse drug interactions between CLA and RIF in foals.

contact: S. Berlin, e-mail: sarah.berlin@uni-greifswald.de
phone: +49 3834-865667

This work was supported by the German Federal Ministry of Education and Research (BMBF) initiative *„Unternehmen Region“ - InnoProfile-Transfer* (grant # :03IPT612A/E)

GEFÖRDERT VOM Bundesministerium für Bildung und Forschung
INNOPROFILE UNTERNEHMEN REGION Die BMBF-Innovationsinitiative Neue Länder