

Protein binding of rifampicin is not saturated when using high-dose rifampicin

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Aims

- Protein binding of rifampicin
- Prediction of unbound rifampicin exposures

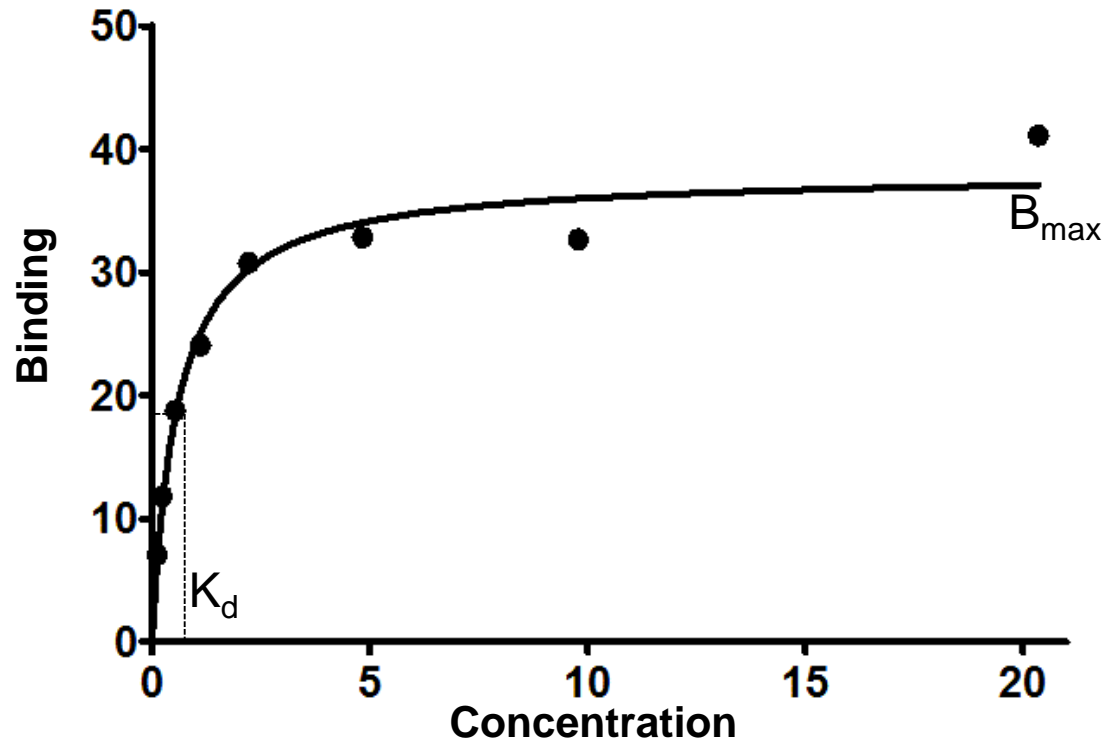
Introduction – rifampicin

- Rifampicin cornerstone TB treatment
- 10 mg/kg dose selected in 1966
- 35 mg/kg
 - nonlinear increase in exposure
 - increased efficacy



Introduction – protein binding

- Protein-unbound drug → PD effect

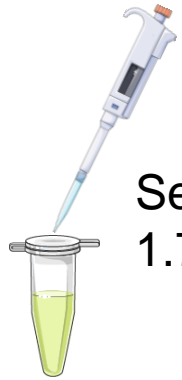


Hypothesis

- Saturation of plasma proteins \rightarrow free fraction $\uparrow \rightarrow$ total concentration misrepresentative for unbound (active) concentration

Method

In vitro:



Serum spiked with
1.7 – 64 mg/L rifampicin

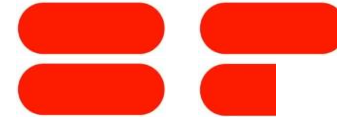
In vivo:



10 mg/kg (n=10)



35 mg/kg (n=10)

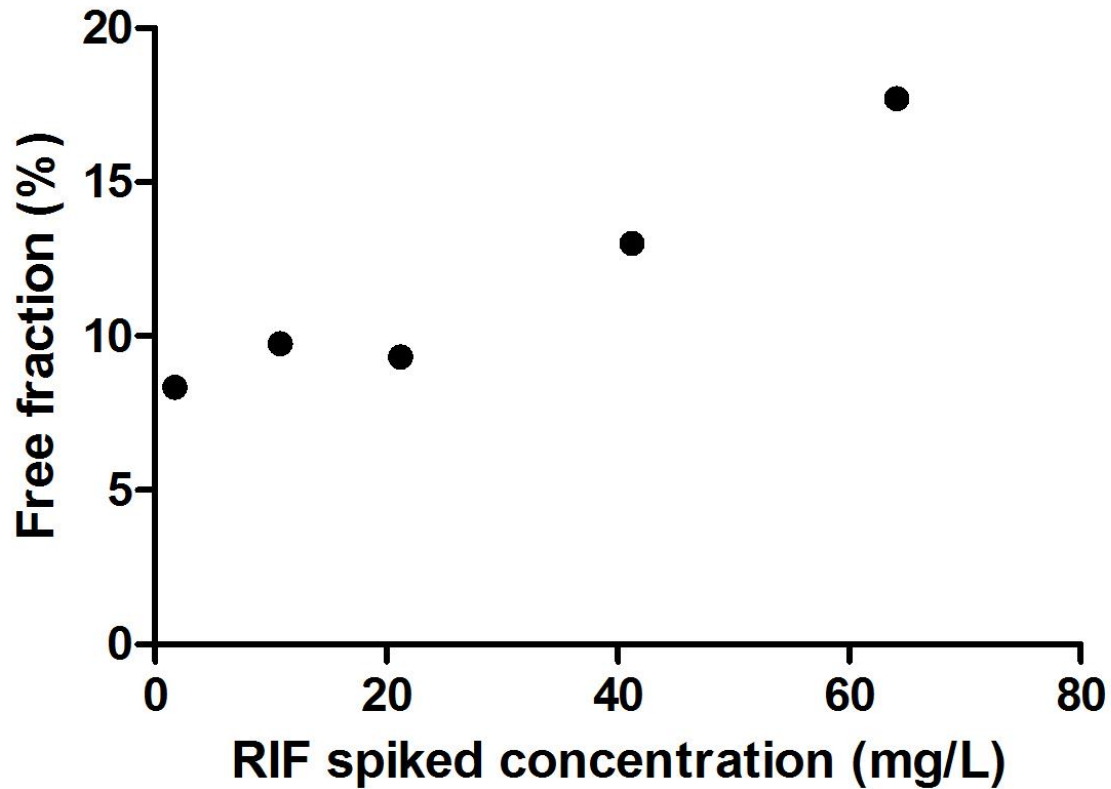


Ultrafiltration



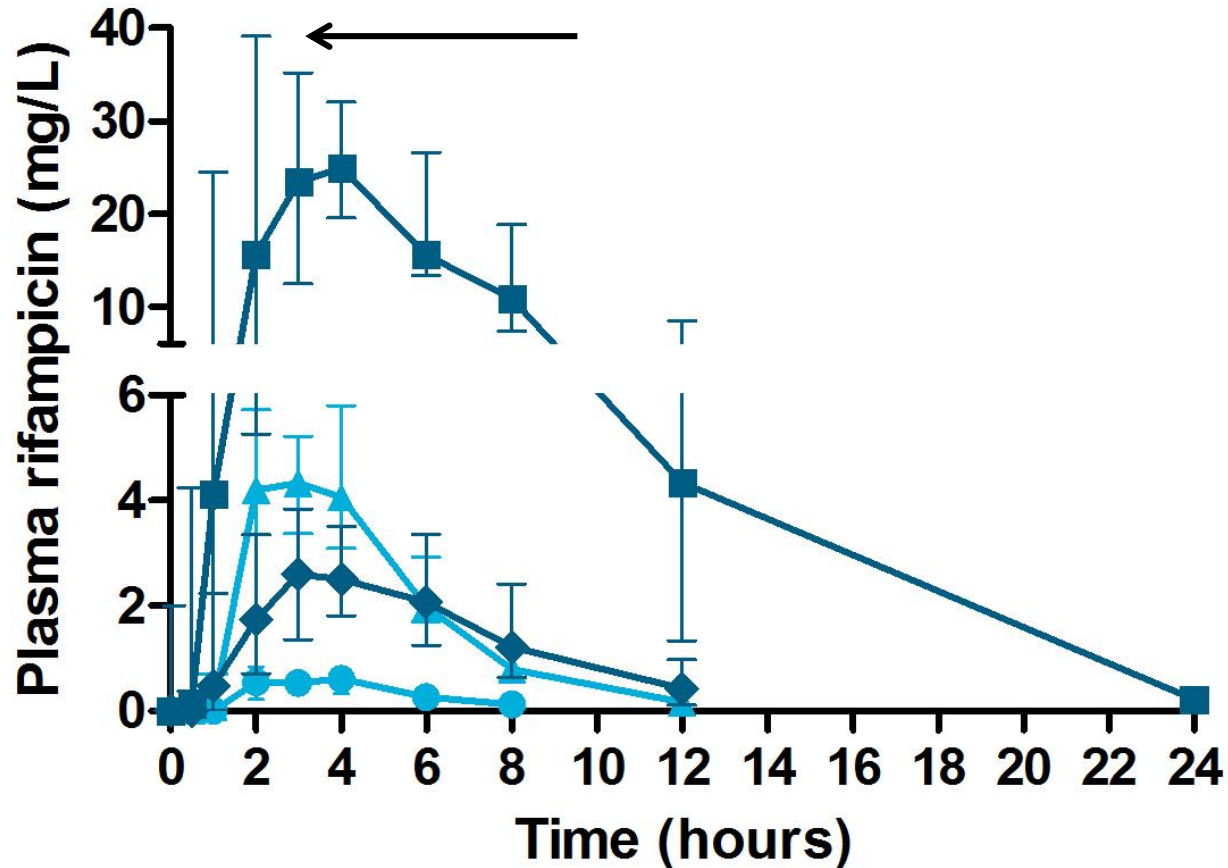
Free rifampicin analysis
using a validated
UPLC assay

In vitro result





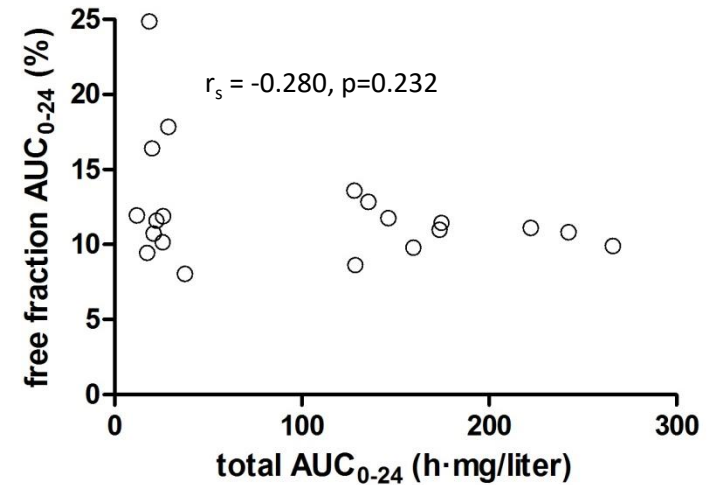
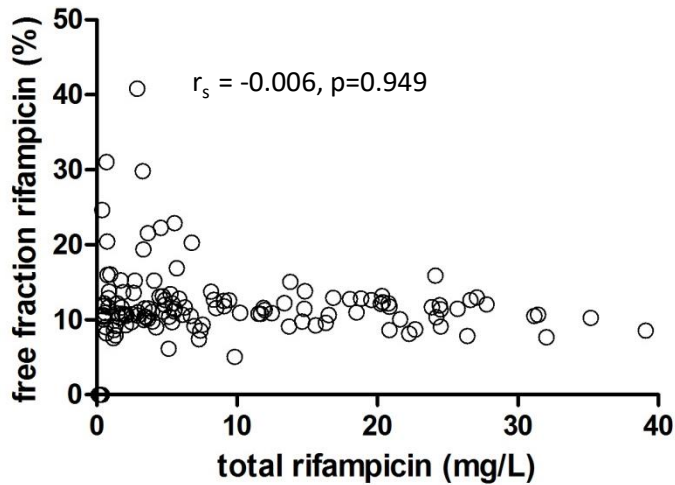
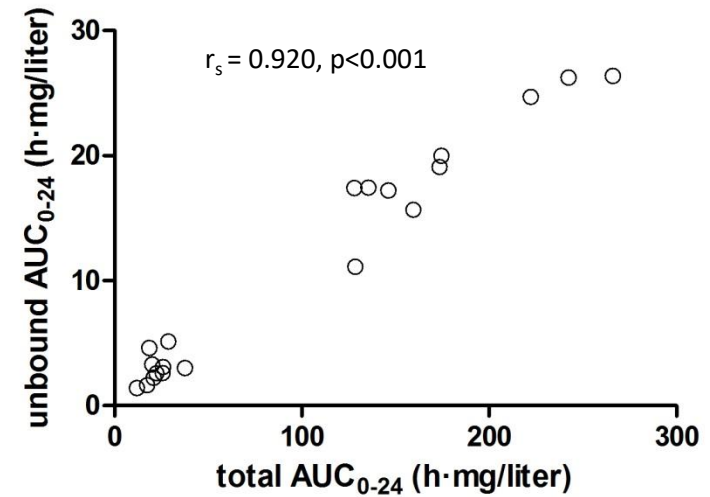
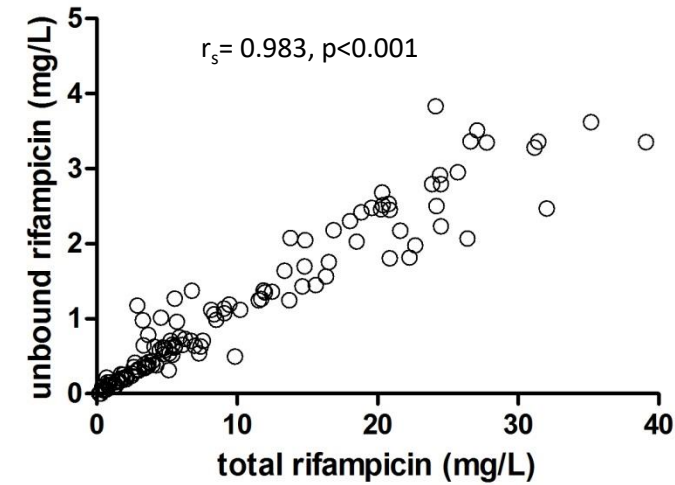
In vivo results – PK curve



In vivo results – PK differences

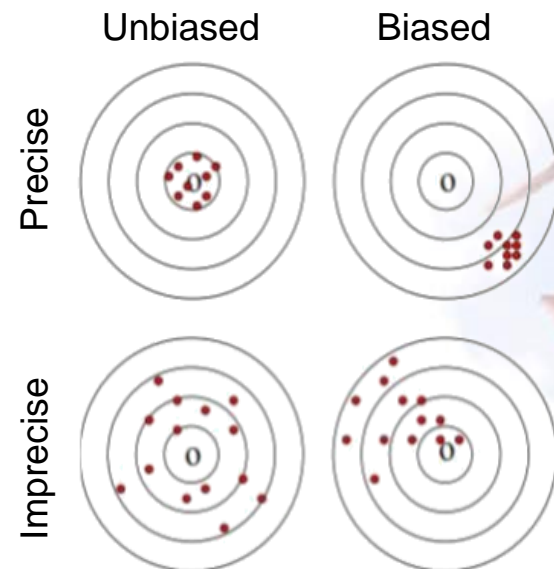
- Total and unbound AUC_{0-24} and C_{max}
 - Large and more than proportional increase (8-fold and 5-fold)
- Free fraction
 - Control group: 13.3%
 - High-dose group: 11.1%
 - $p=0.214$

In vivo results – correlations



Predictive value total AUC_{0-24}

- Predictive performance
 - Median unbound AUC_{0-24} / total AUC_{0-24}
 - Jackknife resampling method
 - MPPE and MAPE



In vivo results – predictive value total AUC_{0-24}

- Predictive performance
 - MPPE (bias): -0.05%
 - MAPE (precision): 13.2%



Discussion

- No patients with total concentration ≥ 40 mg/L
 - 50 mg/kg dose \rightarrow plasma saturation?
- Albumin levels
- Inter-individual variability

Take home message

- No plasma protein saturation *in vivo*
- No increased free fraction

**Unbound exposures well predicted
from total exposures**

Acknowledgements

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