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Appraisal of potential effect of subcutaneous administration on antibiotics pharmacokinetics-pharmacodynamics

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► To cite this version:

Alexia Chauzy, Nicolas Grégoire, Sandrine Marchand, Olivier Mimoz, Marc Paccalin, et al.. Appraisal of potential effect of subcutaneous administration on antibiotics pharmacokinetics-pharmacodynamics. the 25th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Apr 2015, Copenhagen, Denmark. <hal-02512083>

HAL Id: hal-02512083

<https://hal.science/hal-02512083v1>

Submitted on 19 Mar 2020

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Introduction

- Subcutaneous (SC) infusion of antibiotics may constitute an interesting alternative to oral or intravenous (IV) administration in elderly patients [1]. However only ceftriaxone and amikacin are officially approved for SC administration in France [1].
- The aim of this study was to identify which of the infusion or absorption rate, is the rate limiting step using previously published ertapenem data, and to predict the pharmacokinetic-pharmacodynamic (PK-PD) consequences for concentration dependent and time dependent antibiotics.

Methods

Study Design

- Data obtained in intensive care patients treated by ertapenem IV and SC [2].
- Six male patients aged 56±19 were included in the analysis. They received 1g of ertapenem once daily through a 30-min IV-infusion for 4-7 days. Then treatment was shifted to the SC route.
- Ertapenem plasma concentrations were assayed by LC-MS/MS after IV and SC infusions.

PK and PK-PD analysis

- A population PK analysis was performed with NONMEM (v7.2.) using a two-compartment model with multiple zero-order infusions after IV administrations and by adding a depot compartment after SC administration to take into account the transfer of drug from the SC tissue to the plasma with a first-order absorption rate constant K_a (Figure 1).
- PK-PD simulations were performed from unbound concentrations with $f_u = 10\%$, after changing the infusion (15-60 min) or SC absorption rates with Berkeley Madonna (v8.3.18.) software.

Results

- SC infusion shifted the plasma concentration-time profiles to the right with major reduction of peak concentration (C_{max}) and delayed time to peak (t_{max}) (Fig. 2)
- According to the PK model, changing SC infusion duration in a 15-60 min range has no effect on plasma concentrations versus time profiles, suggesting that SC absorption rate is the rate limiting step.
- The reduction of C_{max}/MIC after SC administrations could dramatically reduce the antimicrobial efficacy of concentration dependent antibiotics such as amikacin (Figures 3.a and 4.a). By contrast the dosing interval during which drug concentrations exceeds the MIC ($t > MIC$) would not be significantly affected by the route of administration (Figures 3.b and 4.b), suggesting that time dependent antibiotics such as ertapenem or ceftriaxone, should be good candidates for SC infusion.

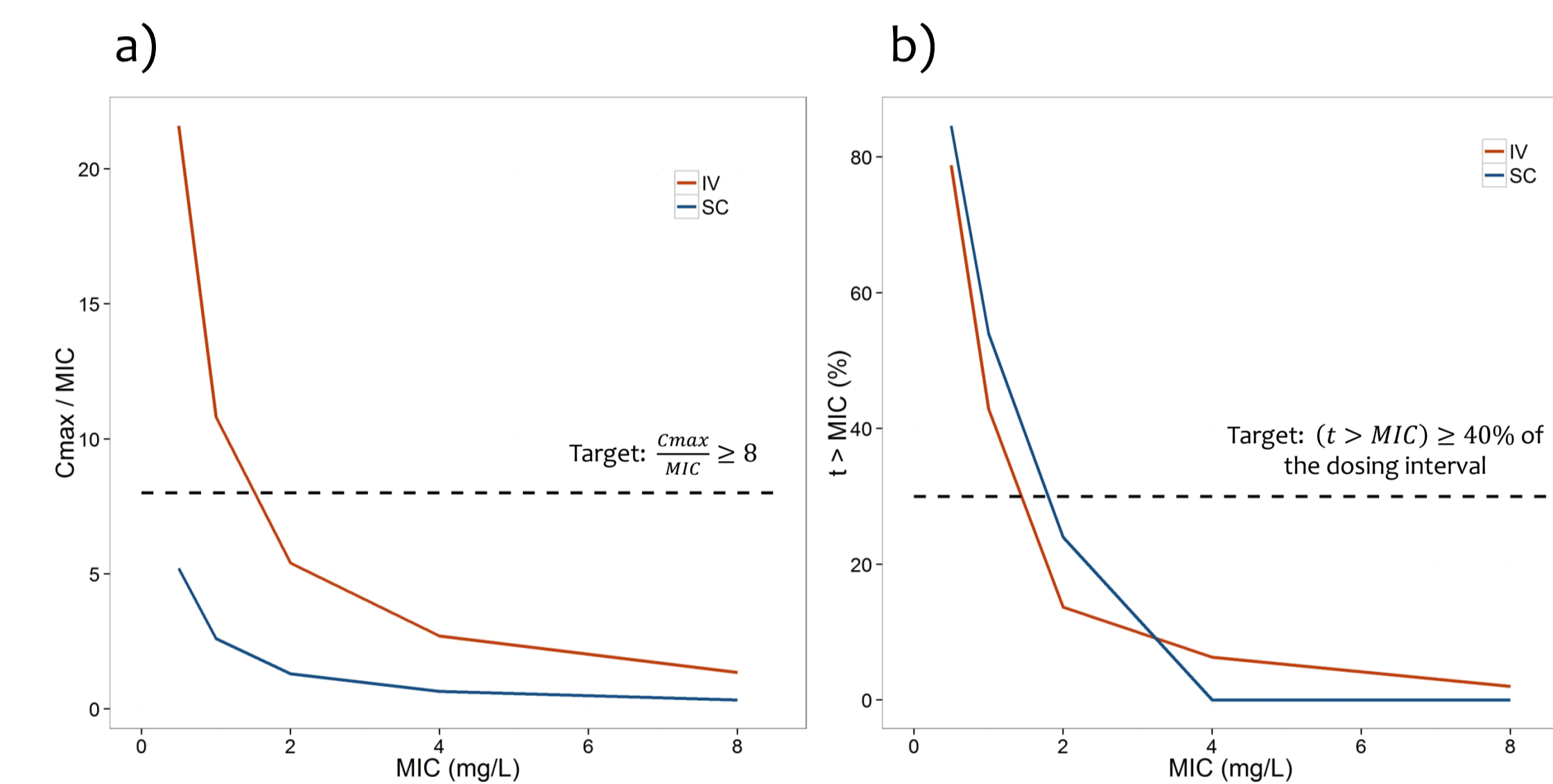
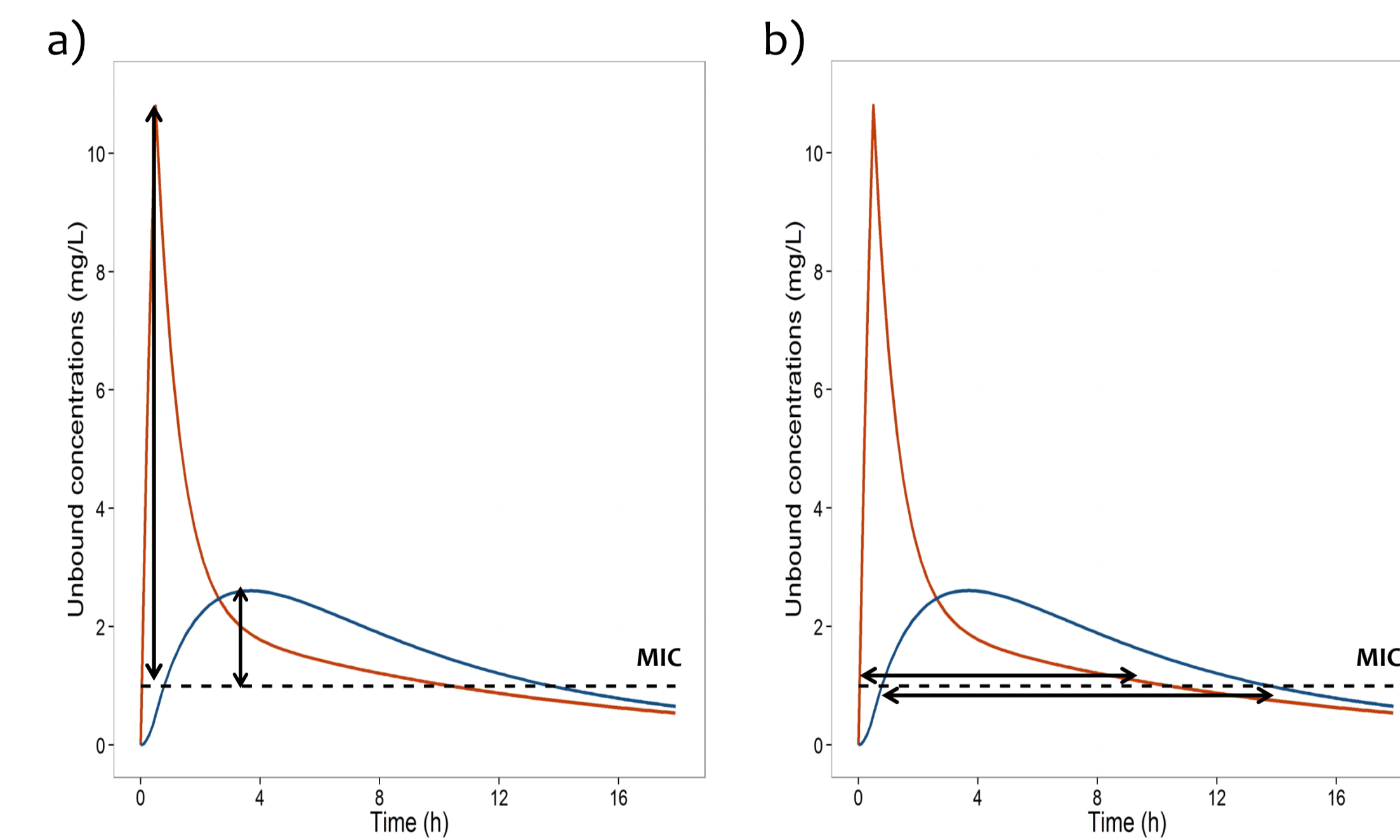


Figure 3. Simulated unbound concentrations vs time after IV (red lines) and SC infusions (blue lines) illustrating that C_{max}/MIC (a) but not $t > MIC$ (b), is likely to be considerably reduced after SC infusion.

Figure 4. C_{max}/MIC (a) and $t > MIC$ (b) as a function of MIC for IV and SC infusions.

Conclusions

- SC administration may represent an interesting alternative to IV infusion or oral administration for patients with reduced vascular access, that should be preferentially indicated for time dependent antibiotics.

References

- Forestier E et al., Clin Microbiol Infect, Clin Microbiol Infect. 2014 Nov 23. [Epub ahead of print]
- Frasca D et al., Antimicrob Agents Chemother. 2009

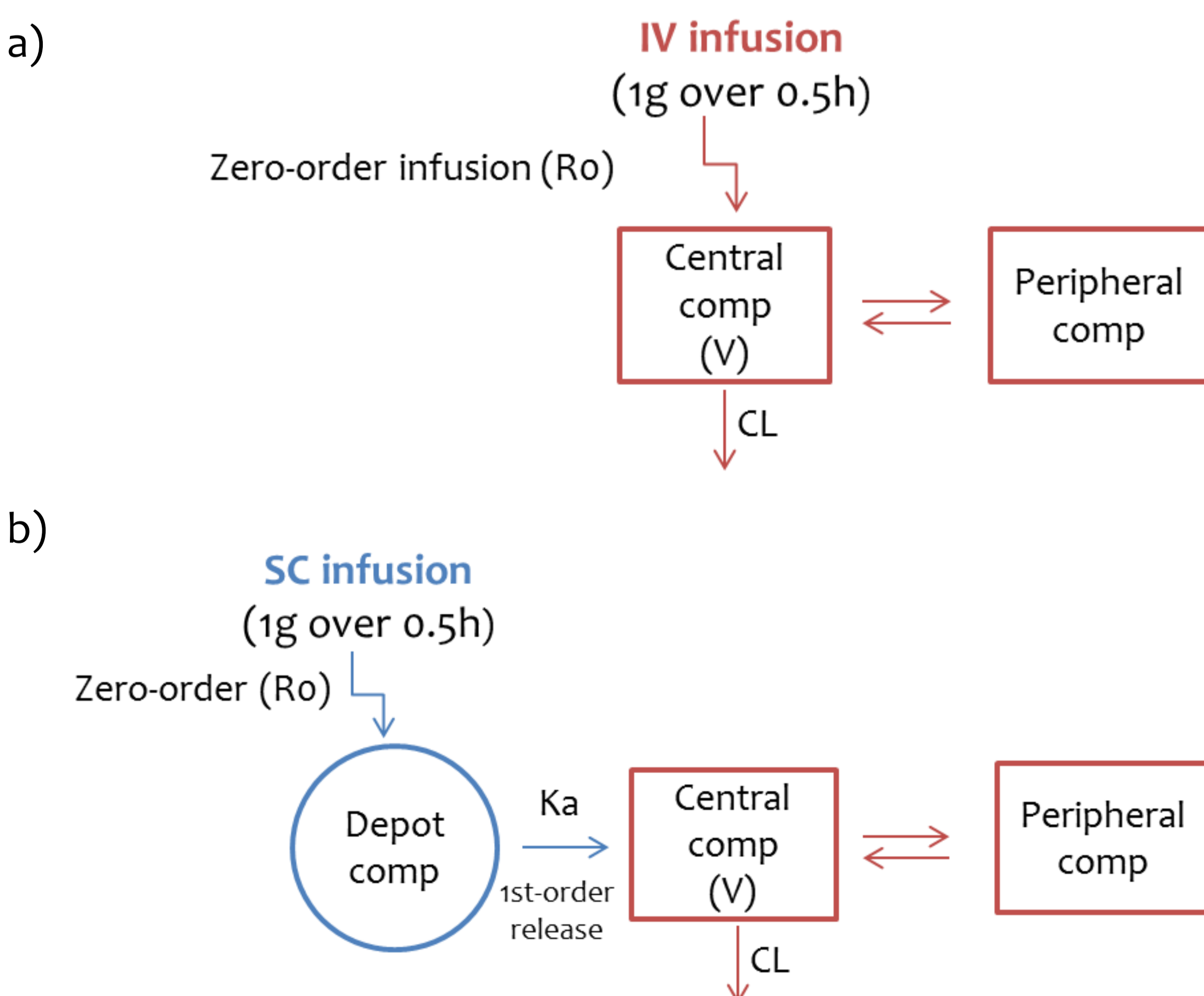


Figure 1. Structural PK model : a) After IV infusion. b) After SC infusion.

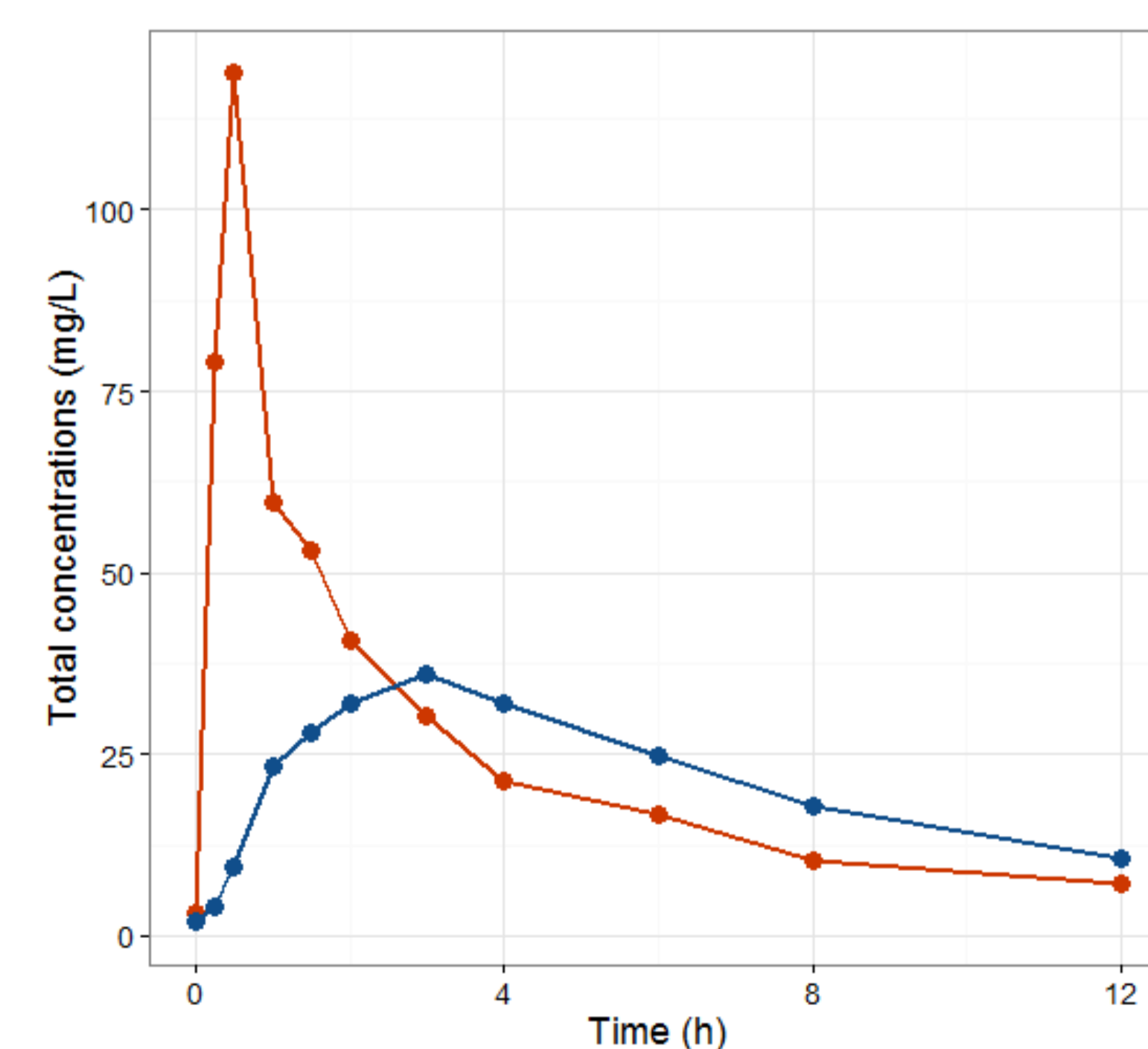


Figure 2. Mean measured total ertapenem concentrations in plasma after multiple daily IV infusions (red symbols and line) followed by a SC infusion (blue symbols and line).