Assessment of dosage regimens of tigecycline in hospitalised patients

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Introduction

Tigecycline is the first available glycycycline derived from minocycline. It possesses broad-spectrum activity against aerobic and anaerobic bacteria including multidrug resistant gram positive and gram negative pathogens. No data regarding Therapeutic Drug Monitoring (TDM) application to tigecycline administration are available.

Objectives

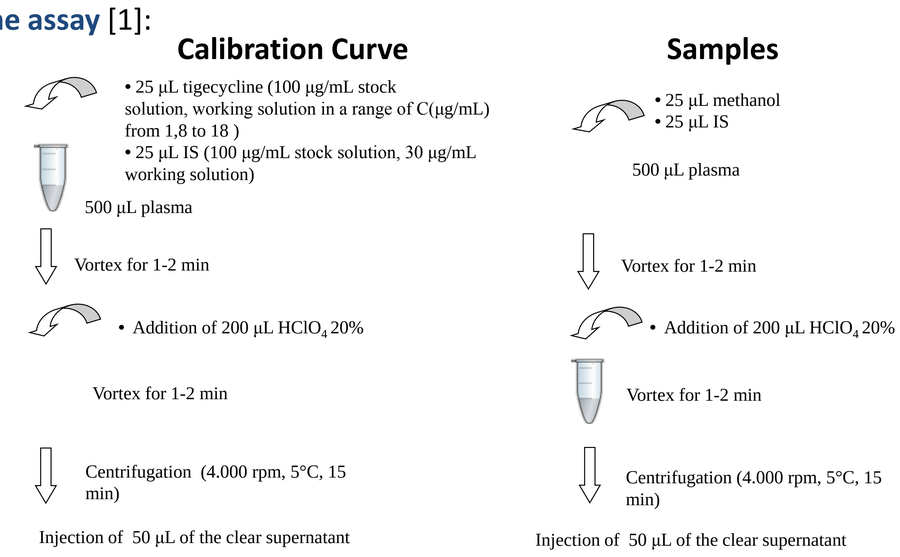
Study of various dose regimens for the antibiotic tigecycline in a group of 14 hospitalized patients and assessment of the potential applicability of TDM for this drug.

Methods

Blood samples from 14 hospitalised patients were collected, during treatment with tigecycline. The patients were treated for about 2 weeks and were administered either 50 mg bid (8 patients) or 50 mg tid (6 patients) with or without a loading dose of 100 mg.

The quantification of tigecycline in patients plasma was conducted with an HPLC method. Minocycline was used as internal standard in the sample preparation in order to minimize the impact of potential variances in experimental conditions. The mobile phase was consisted of 0.070M phoshate buffer with pH 7.1 and acetonitrile, appropriate for detections in the far UV, with volume ratio 76:24 (v/v). The detection length that was used is 350 nm, the flow rate was 1ml/min and the injection volume 50 µl.

Tigecycline assay [1]:



Modeling and Simulations

We used literature population priors for two-compartment pharmacokinetic parameters [2] (see table 1), and the following covariate model for clearance [2]:

$$CL = 19.6+[10.2 \times (BSA-1.73)]+[0.0638 \times (CrCL-100) \quad (1)$$

where BSA is the Body surface area and CrCL is the Creatinine Clearance.

Empirical Bayes Estimates (EBE) were derived for each of the patients' PK parameters with NONMEM and especially the Clearance of each patient and the corresponding AUC_{24}/MIC were calculated, since for Tigecycline AUC_{24}/MIC is considered a pharmacodynamic index predictive of in vivo efficacy.

Furthermore, Monte Carlo simulations were performed and the distributions of AUC_{24}/MIC ratio for the 2x50 mg and 3x50 mg dose regimens were computed to assess the applicability of the different dosing schemes. Monte Carlo simulations were performed using Eq. 1 and the distributions of BSA, CrCL and the omega of clearance (see table 1).

The breakpoint of AUC_{24}/MIC = 17.9 was used as predictor of the clinical outcome [3] in the population for both the MC simulations and the EBE derived parameters of the real patients.

Table 1. Parameter values taken from literature and used for the EBE estimates and the MC simulations.

Parameters	Mean	BSV %
CL (L/hr)	Eq. 1	40.4
V1 (L)	65.2	82.1
Q (L/hr)	85.1	110
V2 (L)	398	40.2
BSA (m^2)	1.83	12.6
CrCL (ml/min/1.73 m^2)	79.7	44.0

Results

Figure 1: 1000 patients for each dosing regimen were simulated using Eq.1 and the corresponding AUC_{24}/MIC values were calculated. The probability density plot of AUC_{24}/MIC is shown together with the breakpoint of 17.9 (dashed line) bellow which subtherapeutic exposure is expected [3]. For the 2x50 mg dose 19.8% of patients are bellow the breakpoint, while for 3x50 mg dose it is 3.2%.

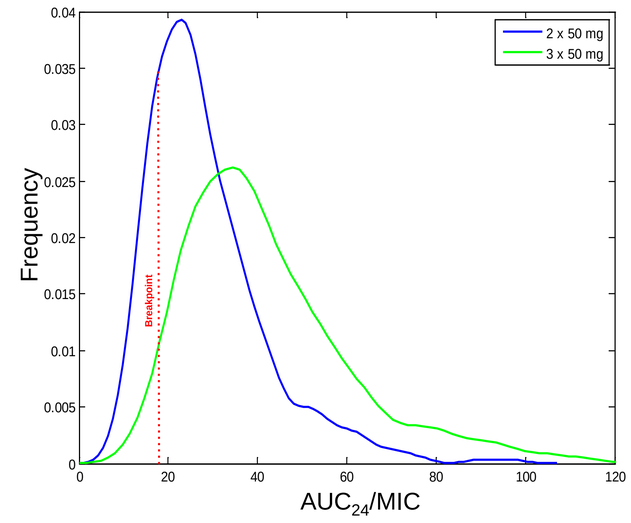


Figure 2: Percentage of patients with AUC_{24}/MIC bellow 17.9 for the two dosing regimens as calculated from the EBE estimates.

For the 2x50 mg dose 25% of patients were found to be bellow 17.9, while for 3x50 mg dose no patients were found. This is in close agreement with the respective values of 19.8% and 3.2% of the MC simulation.

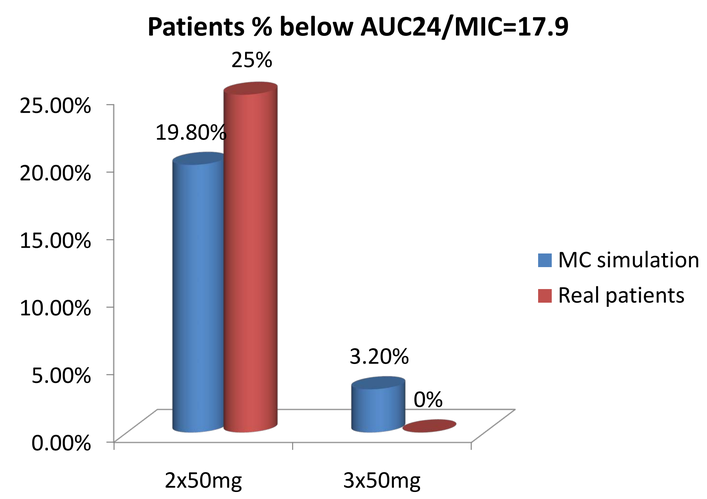


Figure 3: Significant number of patients (50%) was found not to respond to treatment for the 2x50 mg dose (based on CRP and WBC counts, clinical assessment and adverse events) while, none for the 3x50 mg dose (excluding those with adverse events). This finding agrees with the results of the AUC_{24}/MIC analysis (Figs. 1 & 2)

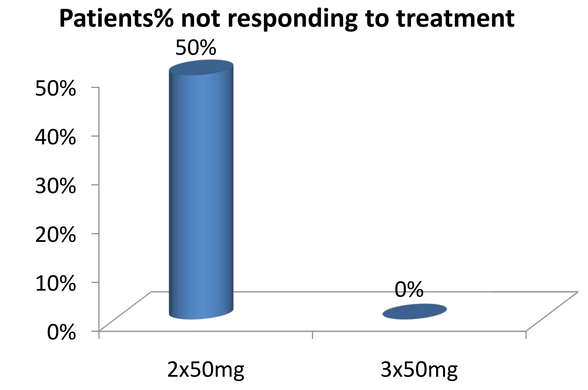
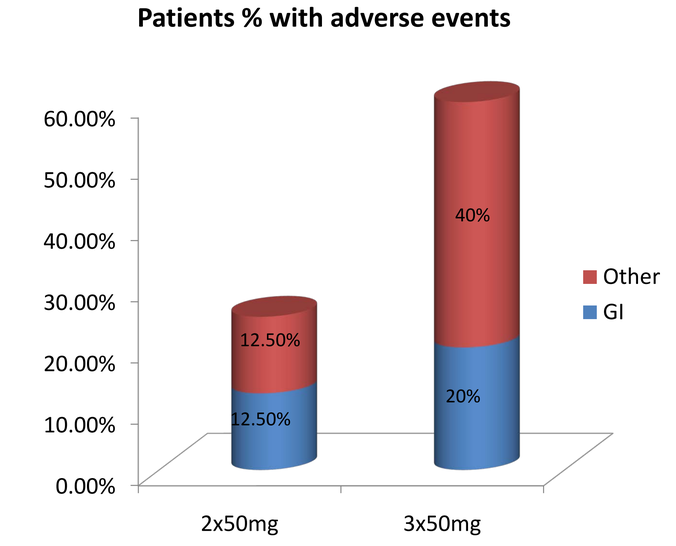


Figure 4: Adverse events (divided to GI and not GI related) were observed to be significantly more frequent for the 3x50 mg dose (60% in total) than for the 2x50 mg dose (25% in total).



Conclusions

- A significant number of patients (25%) were found to be potentially at subtherapeutic risk for the 2x50 mg dose while no patients were found subtherapeutic for the 3x50 mg dose.
- However, adverse events were observed to a significant number of patients (60%) for the 3x50 mg dose.
- Therefore TDM may be applicable to tigecycline treatment.

References

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2. Rubino CM, Forrest A, Bhavnani SM, Dukart G, Cooper A, Korth-Bradley J, Ambrose PG. Tigecycline population pharmacokinetics in patients with community- or hospital-acquired pneumonia. Antimicrob Agents Chemother. 2010, 54:5180-6
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