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Therapeutic drug monitoring of vancomycin and meropenem: Illustration of the impact of inaccurate information in dose administration time

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ABSTRACT

Objectives: To illustrate the impact of errors in documented dose administration time on therapeutic drug monitoring (TDM)-based target attainment evaluation for vancomycin and meropenem, and to explore the influence of drug and patient characteristics, and TDM sampling strategies.
Methods: Bedside observations of errors in documented dose administration times were collected. Population pharmacokinetic simulations were performed for vancomycin and meropenem, evaluating different one- and two-sampling strategies for populations with estimated creatinine clearance (CLcr) of 30, 80 or 130 mL/min. The impact of errors was evaluated as the proportion of individuals incorrectly considered to have reached the target.
Results: Of 143 observed dose administrations, 97% of doses were given within ±30 min of the documented time. For vancomycin, a +30 min error was predicted to result in a 0.1–3.9 percentage point increase of cases incorrectly evaluated as reaching area under the concentration-time curve during a 24-hour period (AUC_{24})/minimum inhibitory concentration (MIC) >400, with the largest increase for patients with augmented renal clearance and peak and trough sampling. For meropenem, a +30 min error resulted in a 1.3–6.4 and 0–20 percentage point increase of cases incorrectly evaluated as reaching 100% $T_{>MIC}$, and 50% $T_{>MIC}$, respectively. Overall, mid-dose and trough sampling was most favourable for both antibiotics.
Conclusions: For vancomycin, simulations indicate that TDM-based target attainment evaluation is robust with respect to the observed errors in dose administration time of ±30 min; however, the errors had a potentially clinically important impact in patients with augmented renal clearance. For meropenem, extra measures to promote correct documentation are warranted when using TDM, as the impact of errors was evident even in patients with normal renal function.

1. Introduction

Therapeutic drug monitoring (TDM) is an important tool in the individualisation of antibiotic treatment [1]. Dose decisions in TDM are based on plasma drug concentrations, interpreted in relation to the documented times of dose administration and sampling. Inaccurate documentation is a potential source of error that may lead to erroneous dose decisions [2]. Hence, documentation errors need to be considered when assessing the quality of current TDM practices and when implementing new TDM routines.

Conventionally, the measured plasma concentrations are interpreted in relation to a concentration target range [1]. Model-based dose individualisation utilises plasma concentrations, patient information and prior knowledge on drug pharmacokinetics (PK) in a population PK model. Although timing of sampling is more flexible using a model-based approach, accurate information is important for all TDM methods.

Abbreviations: TDM, Therapeutic drug monitoring; PK, Pharmacokinetic; PK/PD, Pharmacokinetic/pharmacodynamic; AUC_{24}, Area under the concentration-time curve during a 24-hour period; ICU, Intensive care unit; MIC, Minimum inhibitory concentration; $T_{>MIC}$, Time the drug concentration exceeds the MIC; CLcr, Creatinine clearance; EMR, Electronic medical record; ARC, Augmented renal clearance; LLOQ, Lower limit of quantification.

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Deviations from planned sampling times [3,4] and inaccurate documentation of dose administration times [2] occur in clinical practice, and the question is when these errors lead to clinically relevant consequences. Potential consequences have been explored in previous studies [2,5,6]. For example, Alihodzic et al. [5] concluded in a simulation study that uncertainties of just 5 min in documented times can cause significant bias and imprecision in the individual PK parameters. However, this might not necessarily result in erroneous dose decisions.

It is important to define the magnitude of errors in documentation time that has potential clinical implications in the assessment of target attainment. However, this task is complex because the clinical relevance of documentation errors in TDM also depends on patient factors such as renal function, the selected dosing regimen and sampling strategy, and the pharmacokinetic/pharmacodynamic (PK/PD) target that defines the drug-bug combination. Based on current TDM practice for antibiotics, vancomycin and meropenem are relevant drugs to study. TDM-based dose individualisation has been recommended for vancomycin for many years and that for β-lactams, such as meropenem, is becoming more widely available.

Vancomycin has a half-life of 6–12 h [7] and is monitored to increase efficacy and avoid toxicity, applying the ratio of the area under the concentration-time curve during a 24-hour period (AUC_{24})/minimum inhibitory concentration (MIC) of 400–600 as a PK/PD target [8]. For meropenem, with a half-life of 1 h [9], TDM is mainly used to ensure efficacy in intensive care unit (ICU) patients, who are at high risk of suboptimal drug exposure due to altered PK [1]. Different targets for clinical efficacy between 50% and 100% of time the drug concentration exceeds the MIC ($T_{>MIC}$) have been suggested [10].

The aim of this study was to illustrate the impact of errors in documented dose administration time on TDM-based target attainment evaluation for vancomycin and meropenem. Specific objectives were to (i) assess the direction and magnitude of errors in documented administration times at a tertiary hospital, and (ii) illustrate using simulations how such errors influence the model-based target attainment evaluation at various levels of renal function, when applying different TDM sampling strategies.

2. Methods

The magnitude and direction of errors in the documented time for dose administrations were described through bedside observations. The range of the observed errors was used as a basis for population PK simulations (Figure 1). In the simulations, datasets were generated for three hypothetical patient populations receiving vancomycin and meropenem, with three different levels of estimated creatinine clearance (CLcr). Correct dose administration time and varying degrees of error in dose administration time were implemented. The simulated concentration data were used for individual PK/PD target attainment evaluation at established clinical cut points, where subsequent changes in dosing would be made.

2.1. Observation of dose administrations

Observations of time of any intravenous antimicrobial dose administrations were conducted at a general ICU (February-March 2020) and an orthopaedic ward (February 2021) at Uppsala University Hospital. At this hospital, nurses manually enter administration start times in the electronic medical records (EMR) in conjunction to the administration.

The observations were performed in line with the principles of the Declaration of Helsinki and its revisions and were approved by the Swedish Ethical Review Authority (Dnr: 2019-04974 and 2020-06080). Permission to access information about antimicrobial administrations in the EMR was obtained by the observers through oral informed consent from patients, or consultation of next of kin. Patient demographics were not recorded.

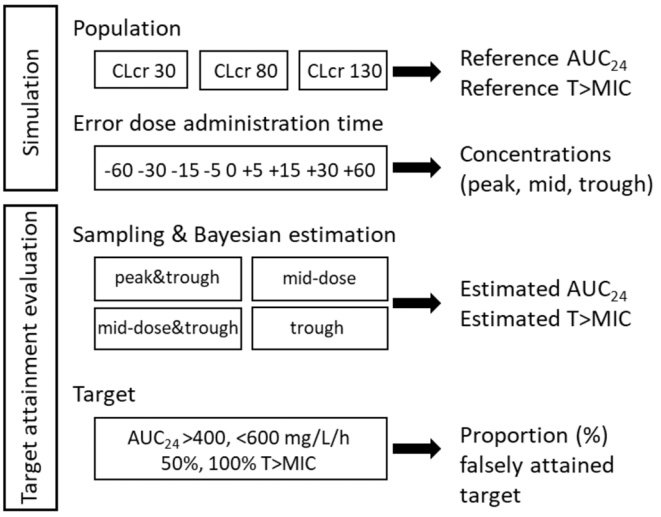

Figure 1. Workflow of the simulation process and target attainment evaluation. Simulation: The simulation was performed for all selected populations and all defined errors in dose administration time, for both vancomycin and meropenem. Individual PK parameters were simulated, from which *reference* AUC_{24} for vancomycin and $T_{>MIC}$ for meropenem were derived. Concentrations of vancomycin and meropenem at different errors in dose administration time were simulated. Target attainment evaluation: Using the simulated concentrations, individual PK parameters were estimated, from which *estimated* AUC_{24} for vancomycin and $T_{>MIC}$ for meropenem were derived. Target attainment was evaluated for *reference* and *estimated* AUC_{24} and $T_{>MIC}$ and compared to obtain the outcome proportion (%) falsely attained target.
AUC_{24}, area under the concentration-time curve during a 24-hour period; $T_{>MIC}$, the time that the drug concentration remains above the MIC during a dosing interval

Patients admitted to the wards and receiving antibiotics were identified through review of the EMR. Administration start times were observed and compared to the documented times in the EMR. Errors were defined as the difference between the observed and the documented times, in minutes, and are referred to as errors in dose administration time.

The observers were one PhD student (general ICU) and one Master's student (orthopaedic ward) who had no prior connection to the study wards. The staff being observed were informed about the overarching purpose of the study, i.e., to review how antibiotics are administered, but were not advised about the exact study hypothesis or the focus on documented time of administration and TDM.

2.2. Simulations

2.2.1. Population PK models for the study drugs

The selected population PK model for vancomycin [11] was based on retrospective routine TDM data from 398 hospitalised adult patients (1557 samples). The meropenem model [12] was based on clinical trial data from 79 adult patients (341 samples) who had intra-abdominal infections, or community acquired- or ventilator-associated pneumonia. Both these population PK models were two-compartment models: CLcr and body weight were included as covariates for vancomycin, whereas CLcr, body weight and age were included as covariates for meropenem.

2.2.2. Dosing regimen

Dosing regimens were selected in line with institutional clinical treatment guidelines for initial dosing [13].

Table 1
Patient characteristics used in the simulations.

Covariate	Value
CLcr [mL/min]	30, 80, 130
Age [years]	50
Body weight [kg]	70

CLcr, creatinine clearance

- vancomycin 1000 mg q24h (CLcr 30 mL/min), q12h (CLcr 80 mL/min) and q8h (CLcr 130 mL/min) following a weight-based loading dose of 2000 mg, with an infusion duration of 1 h.
- meropenem 1000 mg q8h for all levels of CLcr, with an extra dose after 4 h and an infusion duration of 30 min.

2.2.3. Blood sampling

TDM sampling was assumed to occur during the dosing interval starting 24 h after the start of treatment and as planned in relation to the documented time. To cover TDM sampling strategies currently in clinical use, and to explore potential future strategies, different sampling timepoints were included: the post-distributional peak (1 h after the end of vancomycin infusion [8] and 30 min after end of meropenem infusion [14]), mid-dose (middle of the dosing interval), and trough (5 min before next dose).

2.2.4. Errors in dose administration time

In the simulations, errors in dose administration time of -60, -30, -15, -5, 0, +5, +15, +30, and +60 min, were implemented to the dose prior to TDM sampling to cover the full range of observed errors. For example, a dose documented as being administered at 10:00 hours that was actually administered at 09:00 hours would be defined as -60 min in the simulation.

As a comparative sensitivity analysis, errors in sampling time were also investigated assuming a -30 min sampling time error, i.e., a scenario in which actual sampling was 30 min before documented sampling time.

2.2.5. Applied patient characteristics and simulated data

To illustrate the effect of errors in dose administration time in relation to renal function, three populations with different levels of CLcr were explored in the simulations: reduced (30 mL/min), normal (80 mL/min) and augmented renal clearance (ARC) (130 mL/min). Applied patient characteristics are summarised in Table 1.

The population PK models were used to simulate individual PK parameters and antibiotic concentrations for the three populations, each of which consisted of 1000 hypothetical individuals. Each individual in the simulations had antibiotic administered with varying degrees of error in dose administration time (or sampling time for the comparative sensitivity analysis). The residual error for concentrations was kept constant within an individual.

The simulated individual PK parameters were used to generate vancomycin AUC_{24} and meropenem $T_{>MIC}$, later referred to as *reference* values.

2.3. PK/PD target attainment evaluation based on simulations

2.3.1. PK/PD target definitions

For vancomycin, clinical cut points where a dose change would be necessary were derived from the recommended target AUC_{24}/MIC 400-600, assuming an MIC of 1 mg/L [8]. For meropenem, two target levels of 50% and 100% of $T_{>MIC}$ [10] were implemented, with MIC set to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoint for susceptibility in *Pseudomonas aeruginosa*, 2 mg/L [15]. The simulations were based on total drug concentrations for both antibiotics, as the target applies to total drug concentrations for vancomycin and protein binding is negligible for meropenem [16].

2.3.2. Bayesian estimation of PK/PD targets

Based on the simulated concentrations and the population PK models [11,12], individual PK parameters were obtained by Bayesian estimation, from which vancomycin AUC_{24} and meropenem $T_{>MIC}$ were derived, later referred to as *estimated* values. The estimations were based on sampling at one timepoint (mid-dose or trough) or two timepoints (peak and trough, or mid-dose and trough).

2.3.3. PK/PD target attainment evaluation

The outcome, proportion (%) falsely attained PK/PD target, represents the proportion of patients where a necessary dose change would not be performed although needed. It was defined as vancomycin AUC_{24} incorrectly evaluated as >400 or <600 mg/L/h and meropenem $T_{>MIC}$ incorrectly perceived as >50% or 100%. The outcome was obtained by comparing target attainment for *estimated* and *reference* AUC_{24} or $T_{>MIC}$.

The impact of different errors in dose administration time was described by the difference in outcome, in percentage points, from the 0-min error scenario.

2.4. Software

Simulation and maximum *a posteriori* Bayesian estimation [17] were performed using NONMEM (version 7.4, Icon Development Solutions, Hanover, MD, USA) [18] and Pearl-Speaks-NONMEM [19]. The first-order conditional estimation method with interaction was used for parameter estimation. R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) was used to generate datasets and for data management.

The lower limit of quantification (LLOQ) was set to 0.2 mg/L for meropenem and 1 mg/L for vancomycin. Simulated concentrations below LLOQ were replaced with LLOQ/2 [20]. AUC_{24} and $T_{>MIC}$ were calculated by integration of the concentration over time from 24–48h and 24–32h, respectively.

3. Results

3.1. Observation of dose administrations

A total of 143 dose administrations from 43 patients were observed (Figure 2). Administrations of β-lactams represented 69% of the observations and vancomycin represented 18%. Of the observations, 67% were performed during the day (07:00–14:59 hours), 29% during the evening (15:00–21:59 hours) and 4% during the night (22:00–06:59 hours). The median error of the observed dose administration times was 2 min (range -20–55 min), with 90% of administrations given within ±15 min of documented time and 97% within ±30 min.

3.2. Simulated data

The simulated concentrations without errors in dose administration time (Supplementary Figure S1) were in overall agreement with the published model development data [11,12].

Reference vancomycin AUC_{24} was within the targeted range for 51–56% of individuals, regardless of renal function (Supplementary Figure S2). For meropenem, for which flat dosing was applied, the dosing resulted in 83% of individuals reaching 100% $T_{>MIC}$ at CLcr 30 mL/min, whereas only 10% achieved 100% $T_{>MIC}$ at CLcr 130 mL/min (Supplementary Figure S2).

The proportion of samples below LLOQ was small (maximum 3.5% at each sampling timepoint), except for the trough concentrations of meropenem for individuals with normal renal clearance or

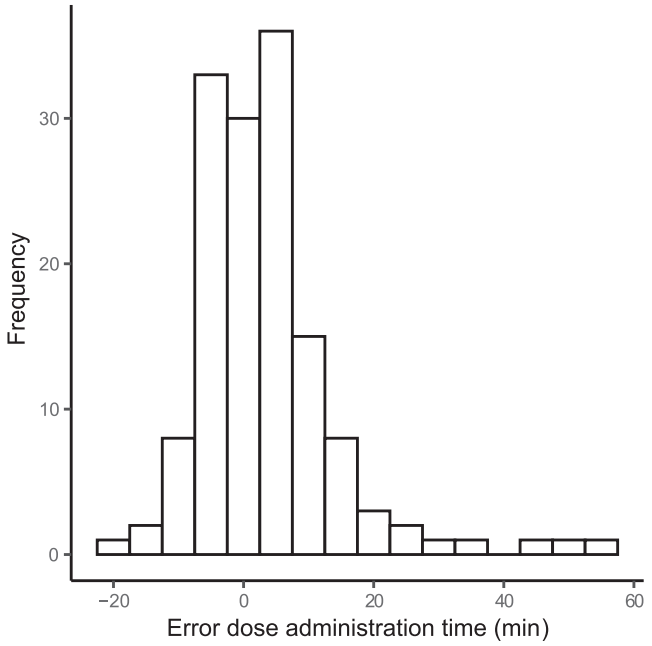

Figure 2. The distribution of 143 observed errors in documented dose administration time of intravenous antimicrobial administrations at an ICU ward (n=63) and an orthopaedic ward (n=80).
Error (min) = observed administration time – documented time.

ARC (15.4% and 31.3% at CLcr 80 mL/min and 130 mL/min, respectively). Simulated trough concentrations at different levels of error in dose administration time are summarised in Table 2.

3.3. Vancomycin PK/PD target attainment

The proportions of simulated patients being incorrectly assessed as attaining an AUC_{24} >400 or <600 mg/L/h in each simulated scenario are presented in Figure 3 and Supplementary Table S1. For example, when applying trough-based sampling in individuals with normal renal function, a +30 min error in dose administration time would result in 8.3% of cases incorrectly evaluated as AUC_{24} >400 mg/L/h (risking underdosing), compared with 7% in a scenario with correct timing. This corresponds to a 1.3 percentage point increase in cases incorrectly evaluated as above target due to errors in dose administration time (Table 3). Considering both under- and overdosing in this scenario, 15.4% of patients could potentially be given the wrong dose at errors ±30 min, compared with 13.6% at correct timing. The differences between estimated and reference AUC_{24} are illustrated in Figure 4.

The impact of errors in dose administration time ±30 min (Table 3) was generally small but increased with CLcr. The greatest impact was shown in cases of ARC, where +30 and +60 min errors resulted in a 3.9 and 7.9 percentage point increase of cases being incorrectly assessed as reaching AUC_{24} >400 mg/L/h, respectively, if applying peak and trough sampling.

Overall, results favoured mid-dose and trough sampling, with a 2.7 percentage point increase of cases incorrectly interpreted as above AUC_{24} 400 mg/L/h at +30 min errors and CLcr 130 mL/min. The estimated AUC_{24} using mid-dose and trough sampling at different errors in dose administration time is summarised in Table 2.

As expected, applying a two-sampling strategy in the estimation of vancomycin AUC_{24} resulted in the lowest proportion falsely attained target (Figure 3) and most precise AUC_{24} estimates (Figure 4, Supplementary Table S2). This trend was consis-

Table 2
The median (2.5th/97.5th percentiles) simulated trough concentrations (upper panel) and *estimated* vancomycin AUC_{24} and meropenem $T_{>MIC}$ (lower panel) at different magnitudes of error in dose administration time, for three populations dosed according to CLcr 30, 80 or 130 mL/min.

	Vancomycin			Meropenem		
CLcr [mL/min]	±0 min	-30 min +30 min	-60 min +60 min	±0 min	-30 min +30 min	-60 min +60 min
	Simulated trough [mg/L]			Simulated trough[1] [mg/L]		
30	14.5 (3.7/29.4)	14.4 (3.7/29.3) 14.6 (3.8/29.5)	14.3 (3.6/29.2) 14.7 (3.9/29.6)	5.4 (0.5/23.7)	4.9 (0.3/22.6) 6.0 (0.7/24.5)	4.4 (0.1/21.5) 6.7 (0.9/25.8)
80	11.4 (3.9/23.8)	11.2 (3.7/23.6) 11.7 (4.1/24.1)	11.0 (3.5/23.3) 12.0 (4.4/24.3)	1.2 (0.1/7.8)	1.0 (0.1/7.2) 1.4 (0.1/8.6)	0.9 (0.1/6.7) 1.7 (0.1/9.3)
130	11.0 (3.2/24.6)	10.6 (2.9/24.1) 11.5 (3.7/24.9)	10.2 (2.6/23.7) 12.0 (4.2/25.2)	0.6 (0.1/4.2)	0.5 (0.1/3.8) 0.7 (0.1/4.7)	0.4 (0.1/3.4) 0.8 (0.1/5.2)
	Estimated[2] AUC_{24} [mg/L/h]			Estimated[2] $T_{>MIC}$ [%]		
30	506 (275/782)	502 (270/779) 509 (280/785)	499 (265/777) 513 (285/787)	100 (71/100)	100 (65/100) 100 (78/100)	100 (59/100) 100 (85/100)
80	448 (292/700)	440 (284/694) 457 (301/705)	432 (277/689) 467 (310/713)	80 (41/100)	73 (39/100) 87 (46/100)	67 (37/100) 95 (51/100)
130	440 (285/701)	427 (273/689) 454 (297/717)	415 (264/677) 470 (315/727)	59 (34/100)	53 (34/100) 65 (36/100)	49 (34/100) 72 (40/100)

[1] Meropenem trough concentrations below the limit of quantification were reported as 0.1.
[2] Estimated vancomycin AUC_{24} and meropenem $T_{>MIC}$ were derived from individual PK parameters obtained by Bayesian estimation using the simulated concentrations at mid-dose and trough, and the population PK models.
AUC_{24}, area under the concentration-time curve during a 24-hour period; $T_{>MIC}$, the time that the drug concentration remains above the MIC during a dosing interval; CLcr, creatinine clearance

Table 3
Impact of errors in dose administration time ±30 min: maximum increase in proportion (%) falsely attained target from the 0-min error scenario, for vancomycin AUC_{24} (upper panel) and meropenem $T_{>MIC}$ (lower panel) and three populations dosed according to CLcr 30, 80 or 130 mL/min. Values for +30 min errors are reported for efficacy targets, and -30 min for vancomycin toxicity target AUC_{24} <600 mg/L/h.

CLcr [mL/min]	Impact of error [percentage points]							
	Vancomycin							
	AUC_{24} >400 mg/L/h				AUC_{24} <600 mg/L/h			
	M	M&T	P&T	T	M	M&T	P&T	T
30	0.9	0.1	0.1	0.2	0.2	0.4	0.7	0.3
80	2.8	1.8	1.7	1.3	0.4	0.5	0.7	0.5
130	3.4	2.7	3.9	1.4	0.8	0.7	1.0	0.4
	Meropenem							
	50% $T_{>MIC}$				100% $T_{>MIC}$			
	M	M&T	P&T	T	M	M&T	P&T	T
30	0.2	0.2	0.0	0.0	4.4	2.9	2.3	1.3
80	3.0	3.2	2.5	0.0	4.7	4.0	6.4	3.6
130	5.8	6.0	19.9	0.0	2.7	1.8	3.0	1.6

AUC_{24}, area under the concentration-time curve during a 24-hour period; $T_{>MIC}$, the time that the drug concentration remains above the MIC during a dosing interval; CLcr, creatinine clearance; P, peak sampling; M, mid-dose sampling; T, trough sampling

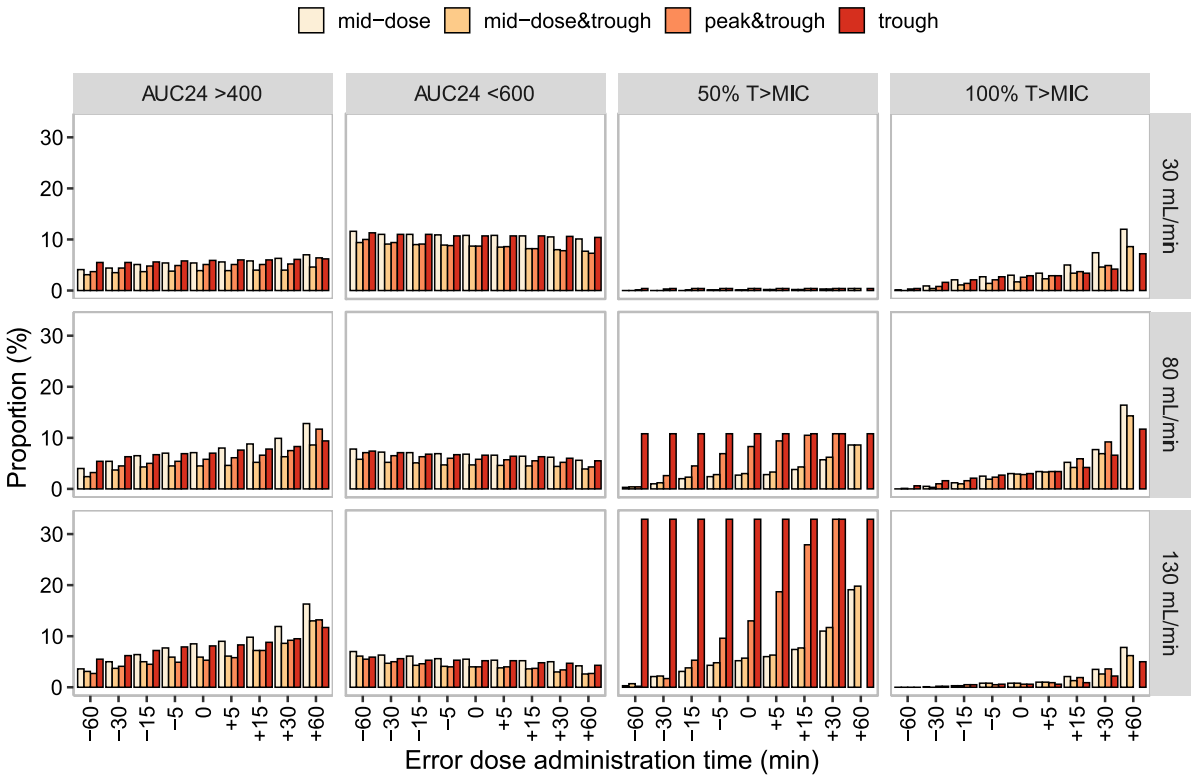

Figure 3. Proportion (%) of individuals falsely attaining target, using a model-based TDM approach, stratified for renal function. The two left panels illustrate results for vancomycin and the two right panels show results for meropenem. Bars represent the proportion of simulated individuals falsely within target using different TDM sampling strategies at different magnitudes of error in dose administration time. The difference in proportion from the 0-min scenario illustrates the impact of errors. Note that $T_{>MIC}$ for meropenem is not determined for peak and trough sampling at time deviation +60 min as sampling would happen at the time of dose administration.
AUC_{24}, area under the concentration-time curve during a 24-hour period; $T_{>MIC}$, the time that the drug concentration remains above the MIC during a dosing interval; TDM, therapeutic drug monitoring; CLcr, creatinine clearance

tent across the evaluated magnitude of errors, even though the mid-dose and peak samples was shown to be more sensitive to errors in dose administration time than the trough sample.

3.4. Meropenem PK/PD target attainment

As shown in Figures 3 and 4 and Supplementary Table S3, the impact of errors in dose administration time was greater for meropenem than for vancomycin.

The greatest impact of errors at target level 100% $T_{>MIC}$ was shown for peak and trough sampling, where +30 min errors resulted in an increase in false target attainment evaluations of 6.4 percentage points at CLcr 80 mL/min (Table 3). For target level 50% $T_{>MIC}$ and CLcr 130 mL/min, peak and trough sampling resulted in a marked impact of errors, where +30 min errors resulted in a 20 percentage point increase of false target attainment evaluations.

Simulated individuals with ARC were well below 100% $T_{>MIC}$ and the target attainment evaluation was thus not as affected at this dose level. Similarly, at target level 50% $T_{>MIC}$, patients with CLcr 30 mL/min were well above the target, with target attainment unaffected by dose administration time errors.

For trough sampling only, the proportion falsely attained target was mainly unaffected by errors in dose administration time. However, this result is likely because trough samples below LLOQ (imputed with LLOQ/2) contributed to an over-estimation of $T_{>MIC}$ and led to 11% and 33% of simulated individuals with CLcr 80 and 130 mL/min, respectively, being incorrectly evaluated as above the 50% target across the range of errors.

Overall, and considering both target levels, the findings indicated that mid-dose and trough sampling was preferable, with a 6-percentage point increase of cases incorrectly interpreted above 50% $T_{>MIC}$ at +30 min errors and CLcr 130 mL/min (Table 2 and 3). However, the benefit over mid-dose sampling only was modest.

3.5. Comparative analysis

Errors in sampling time -30 min resulted in similar proportions of simulated patients (80 mL/min) being incorrectly assessed as attaining target compared to errors in dose administration time +30 min (Supplementary Figure S3).

4. Discussion

In this study, bedside observations of errors in documented dose administration time are presented. Simulations illustrate the impact of such errors on the evaluation of model-based target attainment for vancomycin and meropenem when applying TDM. The consequences of errors were explored for a range of magnitudes in both directions, for simulated patient populations with three different levels of CLcr, applying four different TDM sampling strategies.

The observed errors in dose administration time (median 2 min, range -20–55 min) were smaller than those observed in a comprehensive study by Roydhouse et al. [2] (median 16 min, range 2–293 min). Differences between clinical settings are expected due to variations in routines, staffing and technical solutions in the EMR. This underlines the need for local quality assessments of EMR documentation. In the observed setting, manual entry of dose times is routine. Automatic entry from infusion pumps or the use of barcodes might reduce the risk of documentation errors.

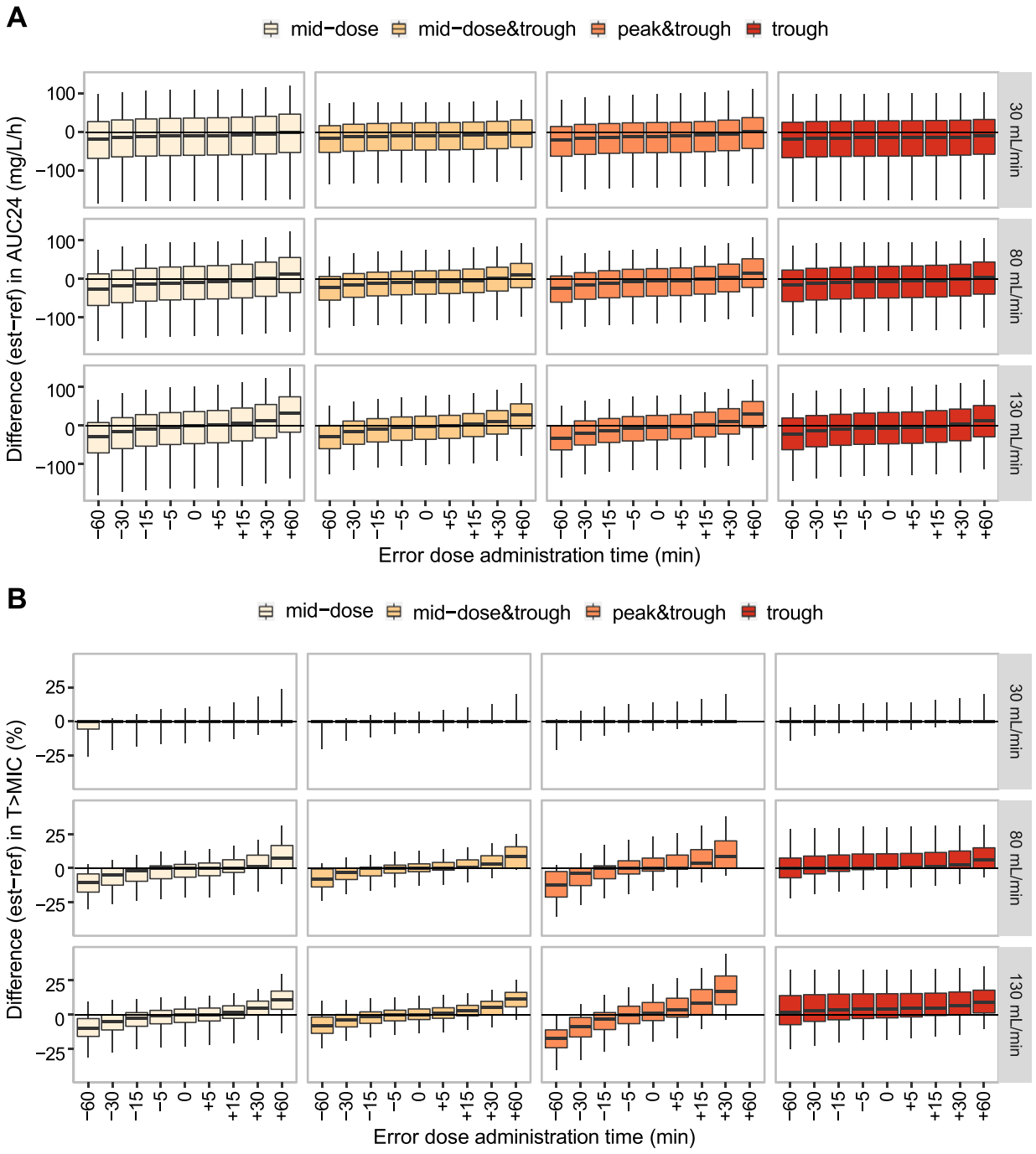

Figure 4. Differences between estimated and reference vancomycin AUC_{24} (panel A) and meropenem $T_{>MIC}$ (panel B), when applying model-based TDM using different sampling strategies, at different magnitudes of error in dose administration time, stratified for renal function. Note that $T_{>MIC}$ for meropenem is not determined for peak and trough sampling at time deviation +60 min as sampling would happen at the time of dose administration.
Black line marks the median, the box marks the interquartile range, the whiskers mark the 2.5 and 97.5 percentiles of the data.
AUC_{24}, area under the concentration-time curve during a 24-hour period; $T_{>MIC}$, the fraction (%) of time that the drug concentration remains above the MIC during a dosing interval; TDM, therapeutic drug monitoring; CLcr, creatinine clearance

For vancomycin, the impact of errors in dose administration time ±30 min on model-based AUC_{24} target attainment evaluation was small, with a <5-percentage point increase of cases incorrectly evaluated as attaining target, but increasing with CLcr. The results align with a previous simulation study for caspofungin [5], with similar half-life, which showed marginal effects of documentation errors (standard deviation ±30 min) on AUC estimation. However, the current study results contradict those of Roydhouse et al. [2], who explored a vancomycin TDM approach with interpretation of trough concentrations, and illustrated that an inappropriate dose would be selected in more than 50% of cases even at very small dose time discrepancies (2 min). However, the analysis by Roydhouse et al. includes several factors that contribute to the residual error of measured concentrations (e.g., assay-, dosing- and sampling-based error), and the primary cause is difficult to distinguish. In the current simulations, the impact of errors in

dose administration time were examined specifically, and the estimated AUC_{24}, as well as the trough concentrations, are shown to be marginally affected.

Although the evaluation of vancomycin target attainment is only marginally affected by errors in dose administration time according to the current study simulations, other factors are important to consider when choosing a vancomycin TDM routine. Previous studies [21–23] showed that the number of samples, as well as selecting informative sampling timepoints, are important considerations to improve vancomycin AUC_{24} estimates. Herein, this is extended to evaluate the impact of errors in dose administration times. Uster et al. [21] suggested a first sampling timepoint for vancomycin of 2–6.5 h post-dose, and that a second sample could further improve the predictive performance of TDM. In the current study, mid-dose sampling (4–12 h post-dose) was evaluated alone and in combination with a trough sample. The current study results confirm that the precision of AUC_{24} estimates increases with a two-sampling strategy, with mid-dose and trough sampling being the most favourable option overall because there is less impact from time errors compared with peak and trough sampling.

As meropenem has a short half-life, PK parameters for this antimicrobial are expected to be more affected by time deviations than those for vancomycin [5]. The current study simulations illustrate that dose time errors have a greater impact on the model-based target attainment evaluation for meropenem than for vancomycin in patients with normal renal function, and an even more pronounced impact in patients with ARC (Table 3). The simulated trough concentrations, which could be interpreted directly in relation to a target concentration, similarly show a trend towards a greater effect on the median differences for meropenem compared with vancomycin, but the effects should be interpreted in relation to assay error [24]. Extra attention to correct documentation is needed for TDM in critically ill patients with septic shock, in whom ARC is most commonly observed [25], and in whom the consequences of suboptimal dosing may have severe implications for clinical outcomes.

In the current study estimations of meropenem $T_{>MIC}$, strategies including a mid-dose sample gave the best precision and resulted in the most accurate target evaluations. The peak and trough sampling strategy was highly affected by errors in dose administration time. Thus, extra measures to ensure accurate documentation are recommended when using this sampling strategy. The relatively high risk of meropenem trough concentrations below LLOQ when applying recommended initial dosing renders a trough-sampling-only approach less optimal. When targeting $T_{>MIC}$ 100%, a single trough sample below LLOQ would give a direct and correct evaluation of target attainment, but would be uninformative for subsequent dose predictions. Sampling strategies for β-lactams in the literature include trough or peak and trough sampling [10,14], thus the current simulations indicate a need to evaluate strategies including mid-dose sampling for meropenem in a broader context.

Conventionally, trough sampling is used for TDM of vancomycin and meropenem [1]. In the current study simulations, trough sampling was evaluated, as well as other sampling strategies that might become more common in the future, if transferring to a model-based TDM approach.

In the current study simulations, the outcome was based on target attainment at globally accepted cut-point levels, where dose changes are warranted if outside the target. Subsequent dose decisions were not evaluated because dosing recommendations (e.g., dose increments, dose intervals) vary between institutions. The current approach makes the results more applicable to different institutions.

Just as there are differences in half-life between antibiotics, there are differences between individuals with different renal function. Therefore, this aspect was illustrated in the current study simulations. Variations in other included covariates (age, body weight) were not explored in this analysis.

Limitations in the current study observations include a risk of an observer effect [26], despite the measures taken to reduce this. The fact that oral consent was needed from the patients to access the EMR made the observations more intrusive. In addition, the observation time was short, reducing habituation [26], and administrations were mainly captured during the day. However, the observations showed that errors did not exceed 60 min in any direction, which was considered a representative basis for the simulations. The observations mirror errors in dose administration time that occur in routine practice, but do not reflect special cases, such as large delays due to surgery or imaging, or completely missed doses.

Further, the simulations were limited to errors in dose administration time, assuming correct sampling. A comparative analysis showed that results are not expected to differ much from a simulation of deviations in sampling, as it is the time interval between dose and sample that mainly influences the estimated PK parameters. However, additional errors on sampling need to be considered when applying the results in practice.

Population-based simulation enables the impact of different scenarios and factors to be explored in a controlled setting. As with all simulation studies, the interpretation of the results is limited by the assumptions with regard to the selected PK model, patient characteristics, dosing and sampling strategies, and PK/PD targets.

In conclusion, simulations for vancomycin indicate that the TDM-based target attainment evaluation is robust with respect to the observed errors in dose administration time of ±30 min regardless of evaluated sampling strategy. However, impact of potential clinical importance was noted in patients with ARC. For meropenem, the impact of errors was evident at normal renal function and was pronounced in ARC, with peak and trough sampling most affected. This indicates that extra measures to promote correct documentation are needed when using TDM for meropenem, particularly in intensive care.

At our institution, nearly all doses were observed as administered within ±30 min of documented time. Clinical routines differ between institutions; therefore, local evaluation of documentation errors is an important step in quality assurance of TDM practices. The simulations in this study can be used as a guide to potential consequences of locally observed errors.

Declarations

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Sequence Information: Not applicable

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All authors reviewed and edited the manuscript. All authors read and approved the final version to be published.

Access to data: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2023.107032.

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