Shaping the pharmacokinetic landscape for renally cleared antibiotics in obesity: Studies in adults, adolescents and children

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Population pharmacokinetics of vancomycin in obesity: finding the optimal dose for (morbidly) obese individuals

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British Journal Clinical Pharmacology 2020;86(2):303–17

ABSTRACT

Aims For vancomycin treatment in obese patients, there is no consensus on the optimal dose that will lead to the pharmacodynamic target (AUC 400 – 700 mg*h L^{-1}). This prospective study quantifies vancomycin pharmacokinetics in morbidly obese and non-obese individuals, in order to guide vancomycin dosing in the obese.

Methods Morbidly obese individuals (n = 20) undergoing bariatric surgery and non-obese healthy volunteers (n = 8) (total body weight (TBW) 60.0 – 234.6 kg) received a single vancomycin dose (obese: 12.5 mg kg^{-1}, maximum 2500 mg; non-obese: 1000 mg) with plasma concentrations measured over 48 hours (11 – 13 samples per individual). Modelling, internal validation, external validation using previously published data and simulations (n = 10.000 individuals, TBW 60 – 230 kg) were performed using NONMEM.

Results In a three-compartment model, peripheral volume of distribution and clearance increased with TBW (both p <0.001), which was confirmed in the external validation. A dose of 35 mg kg^{-1} per day (maximum 5500 mg/day) resulted in a >90% target attainment (AUC >400 mg*h L^{-1}) in individuals up to 200 kg, with corresponding trough concentrations of 5.7 – 14.6 mg L^{-1} (twice daily dosing). For continuous infusion, a loading dose of 1500 mg is required for steady state on day 1.

Conclusions In this prospective, rich sampling pharmacokinetic study, vancomycin clearance was well predicted using TBW. We recommend that in obese individuals without renal impairment, vancomycin should be dosed as 35 mg kg^{-1} per day (maximized at 5500 mg/day). When given over two daily doses, trough concentrations between 5.7 – 14.6 mg L^{-1} correspond to the target exposure in obese individuals.

INTRODUCTION

Over the past decades, the worldwide prevalence of obesity (defined as a body mass index (BMI) ≥30 kg m^{-2}) has dramatically increased [1]. Since 1975, the percentage of obese men and women increased from 3.2 and 6.4 % to 10.8 and 14.9 %, respectively. This corresponds with 641 million individuals being obese worldwide. If this trend continues, global obesity prevalence will reach 18 – 21% in 2025 [1]. Evidence suggests that these individuals are more prone to infections [2]. As a consequence, clinicians are increasingly facing (severely) obese patients requiring antibiotic treatment. It has been well established that due to pathophysiological changes that are associated with overweight, such as an increased cardiac output, increase in adipose tissue, changes in renal function and impacted metabolic enzyme activity, the pharmacokinetics (PK) of drugs can be significantly impacted, often requiring dose adaptations [3,4].

Vancomycin is a glycopeptide antibiotic, introduced in clinical practice over 60 years ago. Since then vancomycin has become a widely used agent predominantly for serious gram-positive infections and is considered first line treatment in methicillin-resistant *Staphylococcus aureus* (MRSA) infections [5]. For these indications the drug is administered intravenously using intermittent or continuous infusion regimens, preceded by a loading dose in the latter setting [6,7]. Around 80% is excreted unchanged renally, mostly by glomerular filtration but other (active) excretion pathways might also play an important role [6]. In *S. Aureus* infections, vancomycin efficacy closely correlates with a total 24-hour area-under-the-curve (AUC_{24h}) over the minimal inhibitory concentration (MIC). Target AUC_{24h} of vancomycin for efficacy for this indication have been well defined in the clinical setting, with thresholds of ≥345 – ≥451 mg*h L^{-1} found over the years, based on MICs up to 1 mg L^{-1} [8–12]. A comprehensive practice guideline published in 2009 advocated an efficacy target of AUC_{24h}/MIC ≥400 mg*h L^{-1} [13]. To reach this target with intermittent dose regimens, a target steady state trough concentration of 15-20 mg L^{-1} was advised [13]. There is however substantial evidence from other populations that lower trough concentration ranges might also be effective to reach the AUC_{24h} target [14,15]. To date, this has not been studied for the obese population. Regarding vancomycin toxicity, 700 mg*h L^{-1} was recently proposed as an AUC_{24h} upper limit for the first 48 hours of treatment [16]. Another study found an increasing risk of nephrotoxicity with steady state AUC_{24h} values over 1300 mg*h L^{-1} [17].

With respect to dosing guidelines, according to the FDA drug label, vancomycin should be given as a fixed dose of 2000 mg per day in adults with a normal renal function, without specific recommendations for obese patients [18]. Since the FDA-regimen has been shown to result in suboptimal exposure (AUC_{24h} around 100-250 mg*h L^{-1}) in normal weight adults, more recent guidelines recommend 15 – 20 mg kg^{-1} every 8-12 hours [13]. This rather broad dosing regimen is also recommended for obese patients, thereby resulting in a large variability of

dose regimens used for obese individuals in clinical practice [13] and is based on studies that are mostly performed with sparse data based on routine TDM peak and trough levels [19–24]. Most of these studies show that both volume of distribution and clearance increase in obese patients. Initially, total body weight (TBW) was shown to be the best predictor for vancomycin clearance [20,21]. However, these findings have been challenged by other studies in obese patients, including the most recent [19,22,24].

As a consequence, the exact dosing strategy for vancomycin in obese patients still remains to be established. This study aims to quantify the pharmacokinetics of vancomycin in morbidly obese and non-obese individuals. Using prospectively collected, rich data gathered over 48 hours after a single dose in individuals over a wide range in body weight, we aim to identify covariates that best predict changes in vancomycin clearance and volume of distribution in obesity. The model is externally validated using independent data and is ultimately applied to guide vancomycin dosing in the (morbidly) obese thereby optimizing target attainment.

METHODS

Subjects

Morbidly obese patients with an indication for bariatric surgery (BMI ≥40 kg m^{-2} or ≥35 kg m^{-2} with comorbidities), i.e. laparoscopic sleeve gastrectomy or gastric bypass, and non-obese healthy volunteers (BMI 18 – 25 kg m^{-2}) were considered for inclusion in this study. Participants were excluded when they were known to have an allergy to glycopeptides, were pregnant or breastfeeding, were renally impaired (defined as estimated glomerular filtration rate (eGFR) of <60 mL min^{-1} 1.73 m^{-2} (calculated using the Cockcroft-Gault (CG) formula with lean body weight (LBW) for obese [25] or CG with TBW for non-obese) or had used potentially nephrotoxic drugs (for example aminoglycosides, loop diuretics, or non-steroid anti-inflammatory drugs) in the week before surgery. All participants provided written informed consent prior to inclusion. This clinical trial was approved by the local human research and ethics committee (Medical Research Ethics Committees United, Nieuwegein, The Netherlands, NL52260.100.16) and registered in the Dutch Trial Registry (NL5885/NTR6058), and was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines.

Study design

Participants received a single intravenous infusion of vancomycin (obese patients: 12.5 mg kg^{-1}, maximum 2500 mg; non-obese 1000 mg as fixed dose, all infused in 10 mg min^{-1}). Obese patients received the infusion during or immediately after bariatric surgery. Blood samples were collected 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 12 hours after end of infusion. In the obese group, samples were also drawn during infusion, at 2 and 0.25 hours before end of infusion. Additional samples

were drawn around 24 hours and, if the individual was still admitted, 48 hours after start of infusion. Blood samples were collected in lithium-heparin tubes, centrifuged at 1900 g for 5 minutes, after which plasma was stored at -80 ^{o}C until analysis. For safety assessment, serum creatinine was measured before and 24 hours after administration of vancomycin. Estimated glomerular filtration rate (eGFR) was calculated using Modification of Diet in Renal Disease (MDRD) or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas, either the conventional Cockcroft-Gault (CG-TBW) formula or CG calculated with LBW instead of TBW for obese (CG-LBW). MDRD and CKD-EPI were corrected for body surface area (BSA) by multiplying the result (in mL min^{-1} 1.73 m^{-2}) by BSA/1.73. Lastly, 24-hour urine was collected on the study day to measure 24-hour creatinine clearance as marker for the glomerular filtration rate (GFR).

Sample assay

Vancomycin plasma concentrations were measured using a validated, commercially available immune-assay method (VANC3, Cobas® System, Roche Diagnostics GmbH, Mannheim, Germany) with a limit of detection (LOD) of 1.5 mg L^{-1}, lower limit of quantification (LLOQ) of 4 mg L^{-1} and upper limit of quantification (ULOQ) of 80 mg L^{-1}. Measured concentrations below LOD or LLOQ were reported in the dataset. Within-run and inter-day variability was 3.7% and 4.4%, respectively.

Pharmacokinetic analysis

Pharmacokinetic parameters were analysed using non-linear mixed-effects modelling (NONMEM 7.4, ICON Development Solutions, Hanover, USA) and Pearl-speaks-NONMEM 4.8.1 [26] using Pirana 2.9.7 (Certara USA, Inc, Princeton, USA) [27,28]. One-, two- and three-compartmental models were evaluated with the ADVAN 1, 3 or 11 routine, respectively, using the first order conditional estimation method with interaction (FOCE-I) and addition of the LAPLACIAN method. Interindividual variability and residual variability were assumed to be respectively log-normally and normally distributed. NONMEM output was visualized with R 3.5.1 (Xpose package 4.6.1) [29] and GraphPad Prism 6.0 (GraphPad Software, La Jolla, USA). Values below LOD were analysed using the M3 method as described elsewhere [30]. Model building was performed in three stages: (1) selection of the structural model, i.e. a one-, two- or three-compartmental model, (2) selection of the statistical error model (additive, proportional or a combined error model) and (3) a covariate analysis. Nested models were compared using the drop in objective function value (OFV, -2 log likelihood function), where a difference of 3.84 corresponds with a p-value <0.05 with one parameter difference. In addition, goodness of fit plots (GOF), such as observed versus population and individual predictions, or conditional weighted residuals versus time after dose or population predictions were used for diagnostic purposes. Lastly, parameter estimate precision, shrinkage, individual fits, and prediction-corrected visual predictive checks (pcVPC) [31] were evaluated to identify the best model.

Potential covariates were identified by assessing trends in plots of the individual *post-hoc* parameter or the unexplained variability against the specific covariate. Covariates that were present in the dataset included TBW, LBW (calculated using the Janmahasatian formula [32]), adjusted body weight (ABW, calculated with correction factor 0.4 as described elsewhere [33]), BMI, ideal body weight (IBW, using the Devine formula [34]), sex, age, GFR (based on collection of 24-hour urine) and serum creatinine-based estimations of GFR such as CG-TBW, CG-LBW, MDRD or CKD-EPI (the latter two both normalized for BSA 1.73 m^2 and de-indexed for BSA by multiplying the original value by BSA/1.73). Covariates were implemented in the model using linear and power functions, standardized for a typical individual of 70 kg or median value of the covariate [35]. Inclusion was considered when step-by-step inclusion resulted in a drop in OFV of at least -3.84 ($p < 0.05$) and backward deletion gave an OFV increase of at least 10.8 points ($p < 0.001$). Furthermore, the contribution of a covariate was judged based on the reduction in interindividual variability and diagnostics described earlier.

Internal validation

The final model was internally validated by pcVPC based on 1000 simulations, split for obese and non-obese individuals. Parameter precision and robustness of the structural and final model were analysed by the sampling importance resampling (SIR) procedure [36].

External validation

Data from a previously published prospective study in which six obese (111 – 226 kg) and four non-obese (66 – 89 kg) individuals with normal renal function received a single infusion of 1000 mg vancomycin in 40 minutes, [21] were used to externally validate our pharmacokinetic (covariate) model. In the external validation study, vancomycin concentrations were measured using a validated immuno-assay with a LLOQ of 0.5 mg L^{-1}. External validation was done using pcVPC based on 1000 simulations, split for obese and non-obese individuals. Bias and precision of the model was quantified by calculation of the median prediction error (MPE) and root mean squared error (RMSE) according to equations (1) and (2),

$$PE_i(\%) = \frac{C_{pred,i} - C_{obs,i}}{C_{obs,i}} \times 100\% \quad (1)$$

$$RMSE\ (mg\ L^{-1}) = \sqrt{\frac{\sum\left(C_{pred,i} - C_{obs,i}\right)^2}{N}} \quad (2)$$

where PE_i and RMSE are the prediction error for the ith observation and root mean squared error of all observations, where $C_{pred,i}$ and $C_{obs,i}$ represent the predicted and observed vancomycin concentration for the ith observation and N is total number of observations. MPE under 20% and RMSE under 5 mg L^{-1} were considered accurate.

Simulation based comparison of dosing strategies

To guide the optimal dosing strategy in the obese, simulations using the final model with interindividual variability were performed with different dose regimens in 10,000 obese individuals (BMI >35 kg m^{-2}) with a uniform weight distribution between 90 and 230 kg. AUC_{24h} was calculated by implementing an AUC compartment equal to the central compartment in the NONMEM $DES subroutine. Based on literature, we chose a target for the probability of target attainment (PTA) and probability of toxicity (PTOX) an AUC_{24h} of >400 mg*h L^{-1} and AUC_{24h} >700 mg*h L^{-1}, respectively, both assessed at day 3 (when in steady state). We aimed for a PTA of at least 90% in obese individuals (BMI >35 mg kg^{-2}) with the lowest possible PTOX, as recommended by the European Medicine Agency. Simulated dose regimens consisted of continuous infusion regimens of 20, 25, 30, 35, 40 and 45 mg kg-1 per day (with or without a dose cap for the 24-hour dose) and 2000, 3000, 4000, 5000 and 6000 mg per day as fixed doses. In combination with the selected dose, loading doses of 500, 1000, 1500, 2000 or 2500 mg were evaluated. The loading doses, given as single infusions at a rate of 10 mg min^{-1}, were followed by a continuous infusion starting two hours after start of the loading dose. Different loading dose strategies were evaluated by comparing the mean and 95% confidence intervals of the AUC_{24h}-ratio per weight group, which is calculated by dividing the AUC_{24h} at day 1 by the AUC_{24h} at day 3. Ideally, the 95% confidence intervals of these ratios should contain 1, meaning that steady state is reached at day 1 and the loading dose is adequate.

Correlation of trough concentrations with achievement of target AUC_{24h}

For the selected vancomycin dose, trough concentrations related to the optimal target attainment (AUC_{24h} within the target of 400 – 700 mg*h L^{-1}) were investigated by simulations using the same weight distribution (n = 10,000). Administration of the dose over two or three administrations per day or a continuous infusion were investigated. At day 3, trough concentrations that corresponded to the 2.5-95 percentiles of the AUC_{24h} within the target of 400 – 700 mg*h L^{-1} were identified. This target AUC_{24h} was chosen since the current consensus guideline describes that the recommended target trough concentrations correspond to AUC_{24h} >400 mg* h L^{-1} [13]. Correlation between trough concentrations and AUC_{24h} at day 3 was assessed by linear regression using R 3.5.1.

RESULTS

In total, 20 obese individuals with a median weight of 139.0 kg (range 110.6 – 234.6 kg) and 8 non-obese individuals with a median weight of 69.5 kg (range 60.0 – 84.7 kg) were included. Participant demographics are shown in Table 1. A total of 326 samples was collected (238 in obese and 88 in non-obese individuals), with a median of 12 samples (range 11 – 13) per participant. 24 samples (7%) were below LOD and handled according to the M3 method [30]. Samples were collected up to 24 hours in all cases. For two obese patients and all non-obese individuals, vancomycin concentrations were obtained until 48 hours after dosing. Measured vancomycin concentrations versus time are shown in Figure S1 in the supplementary file.

Table 1. Summary of baseline characteristics.

Parameter	Morbidly obese group (n = 20)	Non-obese group (n = 8)
Weight (kg)	139.0 (110.6 - 234.6)	69.5 (60.0 - 84.7)
Height (cm)	173.5 (159 - 189)	182.5 (166 - 190)
Body mass index (kg m^{-2})	45.5 (40.8 - 65.7)	21.2 (20.4 - 25.0)
Age	38.0 (23 - 54)	25.5 (20 - 55)
Serum creatinine (mmol L^{-1})[a]	72 (41 - 101)	70 (60 - 86)
Glomerular filtration rate measured using 24-h urine collection (mL/min^{-1})	141.4 (80.7 - 260.7)	117.9 (88.1 - 147.0)
De-indexed Modification of Diet in Renal Disease (MDRD, mL min^{-1})	138.3 (89.5 - 220.6)	115.4 (72.8 - 144.7)
De-indexed Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI, mL min^{-1})	148.1 (95.5 - 221.6)	125.3 (77.1 - 139.3)
Cockcroft-Gault (conventional, (mL min^{-1})	249.2 (166.0 - 431.8)	140.1 (87.9 - 157.3)
Cockcroft Gault with lean body weight for obese (CG-LBW, mL min^{-1})	122.0 (83.1 - 191.0)	140.1 (87.9 - 157.3)

Data shown as median (range)

[a] Serum creatinine as measured before administration of vancomycin.

Pharmacokinetic analysis

A 3-compartment model with first order elimination and a combined proportional and additive residual error model with interindividual variability for clearance, V1 and V2 best described the data. Parameters of the structural model are shown in Table 2.

Implementation of TBW with a linear relationship on V2 gave the largest reduction in OFV (-24.5 [p <0.001]) and interindividual variability (from 37.1% to 5.8%). In the model with TBW on V2, interindividual variability on V2 was omitted from the model since this did not impact

the OFV (+0.11). In the following step, the best results were obtained by inclusion of (1) TBW with a power function on clearance using an estimated exponent, (2) ABW and (3) LBW, both with linear functions. This resulted in OFV reductions of -17.4 (1), -18.9 (2) and -15.5 (3) ($p < 0.001$ for all), resulting in a reduction in interindividual variability from 29.3% to 21.2, 20.5 and 21.9%, respectively. No significant differences were visible in goodness-of-fit plots between TBW, LBW and ABW-models. Since TBW is more readily available in clinical practice and is therefore preferable in the light of model-informed dose recommendations, we chose to include TBW on clearance. Inclusion of MDRD, CKD-EPI, CG-TBW, CG-LBW or GFR (based on 24-hour creatinine clearance) did not significantly improve the model ($p > 0.001$). After inclusion of TBW on clearance, no remaining covariates could be identified for this parameter. Lastly, introduction of age as covariate on V1 and V2 resulted in a decrease of OFV with -19.4 points and improved GOF ($p < 0.001$).

Since interindividual variability for clearance appeared to be significantly higher in the obese group, we estimated separate IIV values for both groups, resulting in an OFV drop of -11.8 and a resulting interindividual variability on clearance of 5.3% and 24.7% for non-obese and obese subpopulations, respectively. While the interindividual variability on clearance in the non-obese showed a high uncertainty and significant shrinkage, we decided to fix this parameter to 5.3% in the final model, since removing it from the model resulted in a penalty of 4 points increase in OFV. The final PK parameters of the resulting model are shown in Table 2. Goodness-of-fit plots for the final model are shown in Figure S2 in the supplementary file.

Internal validation

The pcVPC, shown in Figure 1 shows that the median and 2.5th and 97.5th percentiles of the prediction intervals correspond with the observations. The lower panel in Figure 1 shows that the model performs well in predicting the portion of observations that are below LOD. Confidence intervals of the model parameters based on the SIR procedure are presented in Table 2.

External validation

pcVPC of the external validation using data of the study from Blouin and colleagues (6 obese and 4 non-obese individuals) are shown in Figure 2. The VPC shows a good predictive performance of our model in the obese population without significant bias and good precision, while the model seems to slightly underpredict observations in non-obese individuals, mostly in higher concentrations (>20 mg L^{-1}). This is shown by MPE and RMSE, where acceptance criteria (MPE <20 %, RMSE <5 mg L^{-1}) are met only in the obese population (MPE for non-obese subgroup: -20.1 %, obese subgroup: -0.171 %, corresponding RMSE values 7.24 mg L^{-1} for the non-obese and 3.27 mg L^{-1} for the obese population).

Table 2. Pharmacokinetic parameter estimates of the structural and final (covariate) model.

Parameter	Structural model (RSE %) [95% CI]	Final model (RSE %) [95% CI]
Fixed effects		
CL (L h^{-1})	7.32 (14.0) [6.13 – 8.33]	-
$CL = CL_{70kg} \times \left(\frac{TBW}{70}\right)^{\theta_1}$		
CL_{70kg} (L h^{-1})	-	5.72 (5.0) [5.34 – 6.10]
θ_1	-	0.535 (20) [0.36 – 0.67]
V1 (L)	15.8 (27) [11.2-20.4]	-
$V1 = V1_{36.5yr} \times (1+ \theta_2 \times [age-36.5])$		
$V1_{36.5yr}$ (L)	-	16.7 (18) [12.9 – 21.2]
θ_2	-	0.0136 (31) [0.00575 – 0.0211]
Q_{V1-V2} (L h^{-1})	16.2 (20) [13.0 – 21.4]	15.8 (23) [11.6 – 21.7]
V2 (L)	13.2 (26) [9.48 – 17.2]	-
$V2 = V2_{70kg;36.5yr} \times \left(\left[\frac{TBW}{70}\right] \times (1+ \theta_2 * [age-36.5])\right)$		
$V2_{70kg;36.5yr}$ (L)	-	6.98 (17) [5.78 – 8.67]
θ_2	-	0.0136 (31) [0.00575 – 0.0211]
Q_{V1-V3} (L h^{-1})	4.37 (25) [2.88 – 6.07]	5.21 (21) [3.83 – 6.63]
V3 (L)	19.7 (21) [14.9 – 26.3]	19.5 (13) [15.0 – 24.1]
Inter-individual variability		
CL[a,b] (%)	31.9 (22) [25.3 – 41.6]	-
$CL_{non-obese}$[a,b] (%)	-	5.28 FIX
CL_{obese}[a,b] (%)	-	24.7 (19) [18.4 – 32.3]
V1[a,b] (%)	56.8 (44) [40.1 – 83.9]	45.3 (24) [34.9 – 62.0]
V2[a,b] (%)	37.1 (37) [23.4 – 50.9]	-
Residual variability		
Proportional error[c,d]	0.0401 (21) [0.0253 – 0.0568]	0.0392 (21) [0.0246 – 0.0541]
Additive error (mg L^{-1})[d]	1.03 (5.0) [0.923 – 1.13]	1.07 (5.0) [0.960 – 1.16]
OFV	682.82	609.89

Parameter estimates are shown with standard error of estimate reported as %RSE with 95% CI based on sampling importance resampling (SIR) procedure

[a] Shrinkage of inter-individual variability in the final model are below 20 % for all estimates

[b] Calculated by $\sqrt{(e^{\omega^2} - 1)}$

[c] Proportional error is shown as σ

[d] Epsilon shrinkage for the final model is 8%

CI confidence interval obtained from sampling importance resampling (SIR) procedure, *CL* clearance, CL_{70kg} clearance from the central compartment for an individual weighing 70 kg, *OFV* objective function value, Q_{V1-V2} inter-compartmental clearance between V1 and V2, Q_{V1-V3} inter-compartmental clearance between V1 and V3, *RSE* relative standard error based on covariance step in NONMEM, *TBW* total body weight, *V1* volume of distribution of the central compartment, $V1_{36.5yr}$ volume of distribution of the central compartment for an individual aged 36.5 years, *V2* volume of distribution of the second peripheral compartment, $V2_{70kg;36.5yr}$ volume of distribution of the second peripheral compartment for an individual aged 36.5 years and weighing 70 kg, *V3* volume of distribution of the third peripheral compartment.

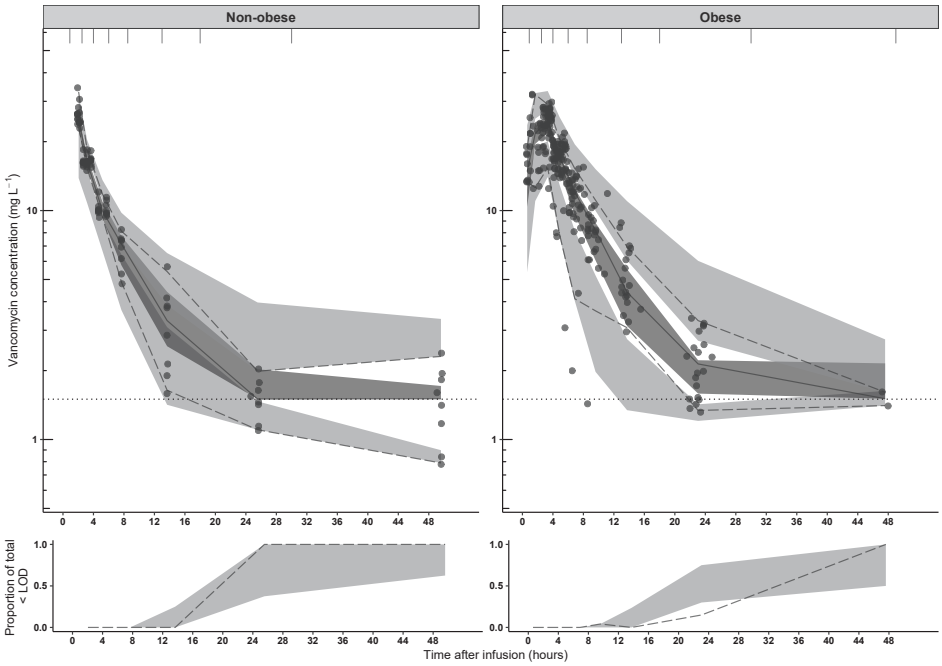

Figure 1. Prediction corrected visual predictive checks (pcVPC) of the final model split for non-obese (upper left panel) and obese (upper right panel) subgroups of the current study. The observed concentrations are shown as black circles, median, 2.5th and 97.5th percentiles of the observed data are shown as solid, lower and upper dashed lines. Grey shaded areas represent the 95% confidence intervals of the median (dark grey) and 2.5th and 97.5th percentiles (light grey) of simulated concentrations (n = 1000) based on the original dataset. The lower limit of detection (LOD) is depicted by the dotted grey line. Intervals of the bins are shown by the vertical ticks on the top of the plot. Lower panels show the observed proportion below the LOD (dashed line), where shaded areas represent the 95% confidence intervals based on simulated concentrations (n = 1000). *LOD* limit of detection.

Simulation based comparison of dosing strategies

Figure 3 shows the results of simulations in obese individuals ranging 90 – 230 kg upon weight-based dose regimens. In Figure 3, the left column shows the resulting mean AUC_{24h} with 95% percentiles, while in the right column PTA (AUC_{24h} >400) and PTOX (AUC_{24h} >700) at day 3 are presented. Figure S3 in the supplementary file shows the same plot for fixed dose regimens. Figure 3 shows that when the vancomycin dose is increased from 25 mg kg^{-1} per day to 45 mg kg^{-1} per day, both chances of achieving an AUC_{24h} >400 and >700 increase for all individuals. A high PTA could be achieved for all body weights using a dose regimen of 35 mg kg^{-1} per day, maximized at 5500 mg per day. For some weight categories where the PTA (AUC_{24h} >400) was below 90% (i.e. individuals under 110 kg and over 210 kg), PTA was still above 80%, and in all cases the probability of reaching an AUC_{24h} >350 mg*h L^{-1} was above 90% (data not shown). The highest PTOX (AUC >700) with this dose regimen is seen in individuals weighting around

150 – 160 kg. Notably, in this group still 94% of the individuals have an AUC_{24h} <900 mg*h L^{-1}. A fixed dose of 2000 mg per day, the recommended dose in the FDA drug label, results in unacceptably low PTA for both non-obese and obese individuals (Figure S3, supplementary file). All weight-based dosages evaluated in Figure 3 were maximized at 5500 mg per day, based on Monte Carlo simulations with fixed dosages (Figure S3 in the supplementary file) where a suboptimal PTA (AUC >400) is seen with dosages ≤5000 mg per day, and considerable PTOX (AUC >700) is seen with high body weights with 24-hour dosages ≥6000 mg. Figure 4 shows simulations with increasing loading doses in combination with a maintenance dose of 35 mg kg^{-1} per day illustrating that a loading dose of 1500 mg yields similar exposure at day 1 compared to day 3 without significant trends across body weights, with all mean AUC-ratio's close to 1 and all corresponding 95% confidence intervals containing 1. No clinically significant influence of age on simulated vancomycin concentrations was found for four typical individuals with age ranging 20–50 years and a TBW of 130 kg (Figure S4 in supplementary file).

Correlation of trough concentrations with achievement of target AUC_{24h}

A daily dose of 35 mg kg^{-1}, maximized at 5500 mg per day, was selected for simulation of trough concentrations at day 3 when given as intermittent or continuous infusion regimens. Figure 5 shows the AUC_{24h} versus trough concentrations for obese individuals at day 3. There is a strong relationship between AUC at day 3 and trough concentrations, with R^2 values of 0.92, 0.93 and 1.00 when the dose is given in two- or three-times dosages or as continuous infusion, respectively. Trough concentrations corresponding to 95% AUC_{24h} within target (400 – 700) are 5.70 – 14.6 (dose divided over two administrations), 7.8 – 17.8 (dose divided over three administrations) and 17.5 – 28.3 (continuous infusion) mg L^{-1}, as depicted by the red lines in Figure 5.

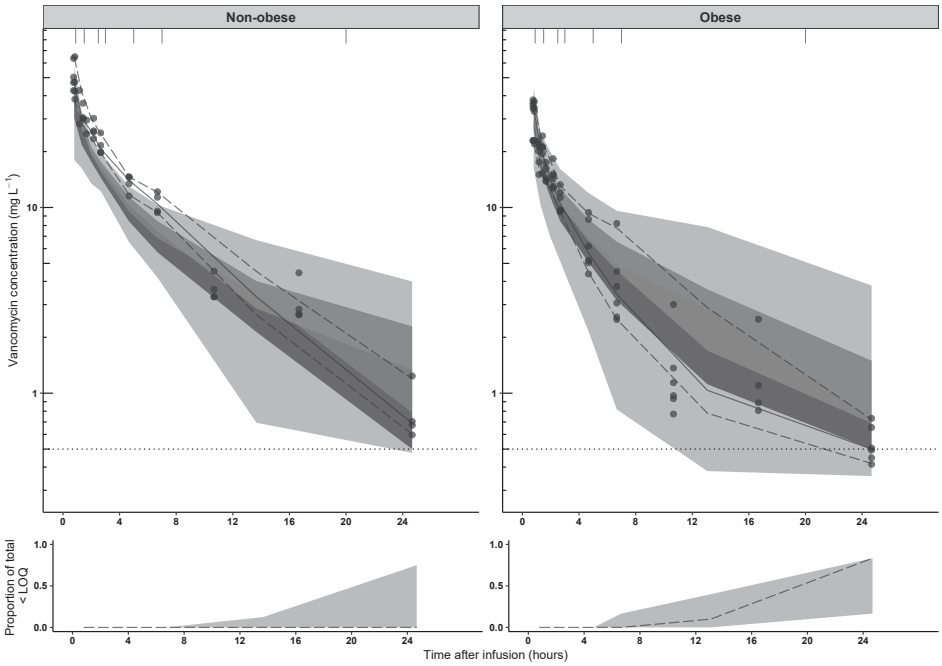

Figure 2. Prediction corrected visual predictive checks (pcVPC) of the final model split for non-obese (upper left panel) and obese (upper right panel) subgroups for the external dataset published by Blouin et al. [21]. The observed concentrations from the Blouin study are shown as black circles, median, 2.5th and 97.5th percentiles of the observed data are shown as solid, lower and upper dashed lines. Grey shaded areas represent the 95% confidence intervals of the median (dark grey) and 2.5th and 97.5th percentiles (light grey) of simulated concentrations (n = 1000) based on the original dataset. The lower limit of quantification (LOQ) is depicted by the dotted grey line. Intervals of the bins are shown by the vertical ticks on the top of the plot. Intervals of the bins are shown by the vertical ticks on the top of the plot. Lower panels show the observed proportion below the LOQ (dashed line), where shaded areas represent the 95% confidence intervals based on simulated concentrations (n = 1000). *LOQ* limit of quantification.

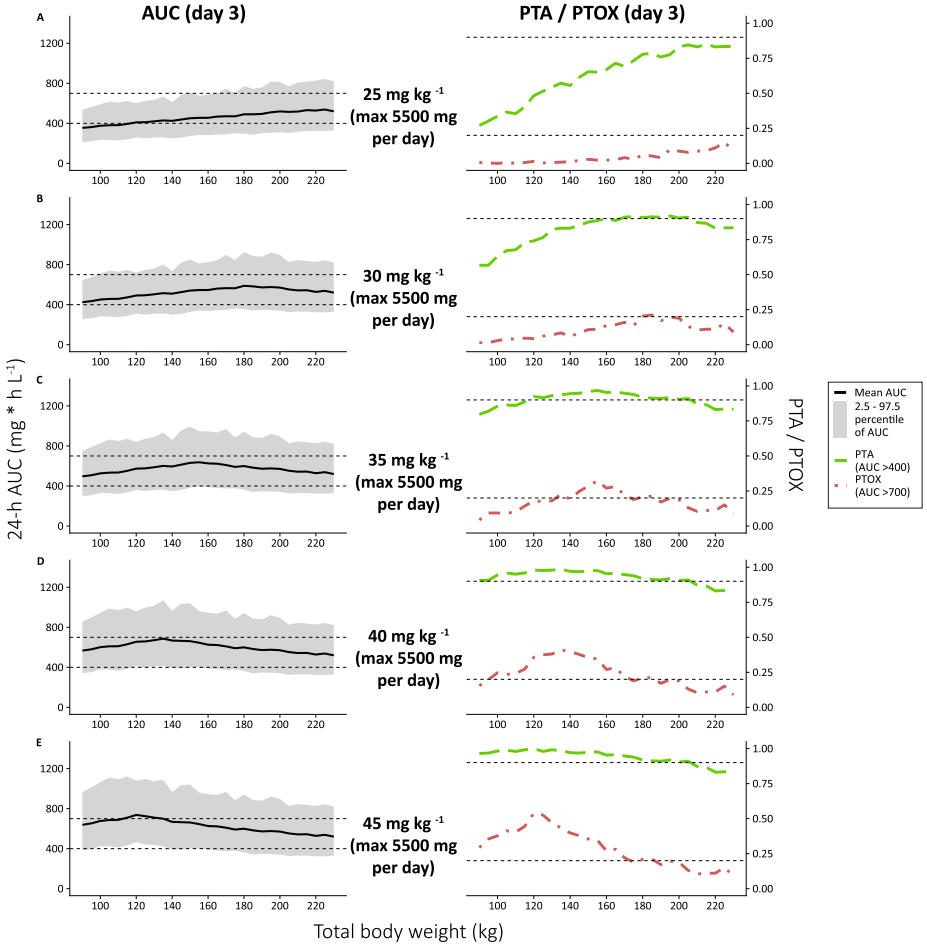

Figure 3. 24-hour area under the curve (AUC) values at day 3 (left column) and probability of target attainment (PTA, AUC_{24h} >400) or toxicity (PTOX, AUC_{24h} >700) (right column), shown versus weight (90 – 230 kg) for several dose regimens (n = 10.000 per dose regimen). Panels A – E show increasing dose regimens from 25 mg kg^{-1} per day to 45 mg kg^{-1} per day, all maximized at 5500 mg per day. In the left plots, the solid black line and grey area indicate mean observed AUC with 2.5 – 97.5 percentiles. Dashed grey line represents target AUC levels (400 and 700 mg*h L^{-1}). In the right plots, the dashed green line and dot-dashed red line indicate PTA and PTOX, respectively. Dashed grey lines represent the threshold for PTA (0.9) and, for reference, 20% PTOX (0.2). *AUC* 24-hour area under the curve at day 3, *PTA* Probability of Target Attainment (AUC >400) at day 3, *PTOX* Probability of Toxicity (AUC >700) at day 3.

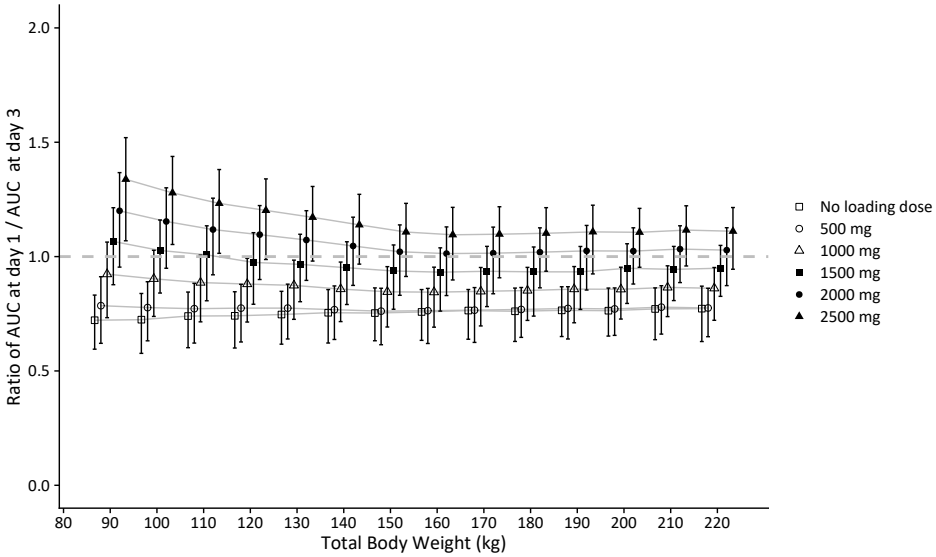

Figure 4. Mean ratio of AUC_{24h} at day 1/AUC_{24h} at day 3 with 95% confidence intervals, shown for different loading doses versus body weight (90–230 kg), based on Monte Carlo Simulations (n = 10.000 per loading dose). Each line represents one loading dose regimen. All individuals received 35 mg kg^{-1} continuous infusion started 2 hours after the loading dose (maximised at 5500 mg per day). Grey dashed line represents a ratio of 1. *AUC* 24-hour area under the curve.

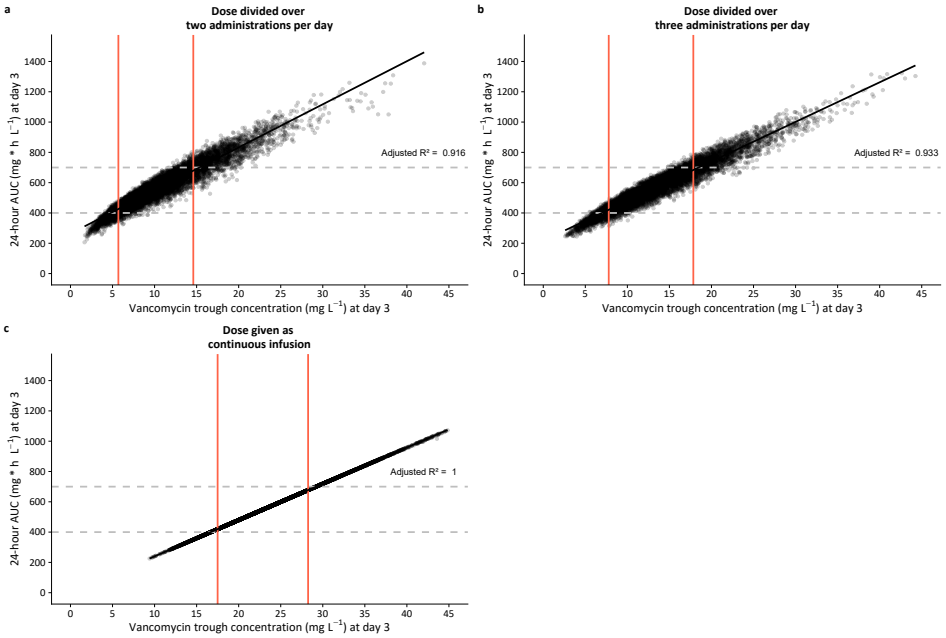

Figure 5. 24-hour area under the curve (AUC_{24h}) at day 3 versus individual trough concentrations at day 3 (measured 0.5 hour prior to the second dose) based on Monte Carlo Simulation in obese patients (n = 10,000, weight ranging 90 – 230 kg), using the final model. Vancomycin dose was 35 mg kg^{-1} per day, maximized at 5500 mg per day, (a) given over two infusions per day, (b) three infusions per day or (c) as a continuous infusion regimen. Each dot represents one simulated individual. Dashed horizontal lines show the target AUC window (400 - 700 mg*h L^{-1}). Trough concentrations corresponding to 95% of AUC_{24h} within this target are shown with red vertical lines. The black line represents the linear regression line, with corresponding adjusted R^2 value shown in the graph. *AUC* area under the curve.

DISCUSSION

Our study shows that vancomycin PK is significantly altered by obesity. We found that in obese individuals up to 235 kg without renal impairment, vancomycin clearance could be predicted by TBW (Table 2) using a power function with estimated exponent of 0.54, which was confirmed by the external validation. Monte Carlo simulations incorporating inter-individual variability showed that in obese individuals, the target exposure (at least 90% AUC_{24h} >400) could be attained when vancomycin is dosed as 35 mg kg^{-1} per day, maximized on 5500 mg per day. Using this regimen, PTOX (AUC_{24h} >700) was <20% for most individuals, despite a slight trend in increasing exposure with increasing body weight. In theory, a dose regimen based on TBW scaled to 0.54 (in accordance with the relationship found between CL and TBW) would result in an equal exposure across body weights, but is in our opinion less suitable for use in daily practice. For continuous infusion regimens of 35 mg kg^{-1} per day, a loading dose of 1500 mg is

sufficient for reaching steady at day 1 for all weight categories. A fixed dose regimen of 2000 mg per day as dictated by the FDA drug label, leads to unacceptable low PTA under 25% across the whole population, as was described earlier [13].

A strong aspect of our study is the prospective study design with intensive pharmacokinetic sampling in adults with a wide range of body weights across the included cohort from 60 to 235 kg, allowing for the characterisation of a three-compartment model. This is in contrast with other reports on vancomycin PK in obesity, that fully rely on TDM data, that consist mostly of peak and trough concentrations, making it difficult to estimate more than one compartment, thereby limiting the ability to adequately assess individual pharmacokinetic parameters [19,22]. Moreover, we used data from a previously performed study to externally validate our model [21]. Our model showed a high precision without bias in describing the data in the obese subgroup. Therefore, taken these results together with our internal validation, we can conclude that our PK-model shows an excellent performance in predicting vancomycin PK in the (morbidly) obese population up to 235 kg.

Our results on vancomycin clearance and volume of distribution in obese individuals puts forward what was known on vancomycin PK in obesity. Regarding clearance, predominantly retrospective studies also found a larger vancomycin clearance in obese compared to non-obese individuals [19,20,22,24]. One prospective rich sampling PK study in healthy obese individuals, similar to our study design but with only six obese individuals included, found a linear relationship of TBW with vancomycin clearance, in contrast to the power relationship as found in our study [21]. One retrospective study in 108 obese and 596 non-obese patients, found no difference in absolute vancomycin clearance between both groups [23]. This might be explained by the relatively low body weight in the obese group (mean TBW 94.3 kg). Other reports in which obese patients were included, show conflicting results on the best predictive covariate for vancomycin clearance, varying from CG with TBW [19], serum creatinine [24], or a combination of serum creatinine, age, TBW and gender [22]. These results might be explained by differences in studied body weights or employed sampling schedules (i.e. use of TDM data versus intensive sampling). Considering the fact that vancomycin is predominantly excreted renally, it is interesting that we found TBW to be a better predictor than any of the renal function estimates including GFR based on 24-hour urine clearance. This might be explained by the lack of individuals with renal impairment in our study. In addition, in our PK model vancomycin clearance of a typical individual of 70 kg is 5.72 L h^{-1}, corresponding to 95 mL min^{-1}, which is slightly below the average GFR in our relatively young population. This is in line with what has been reported in other studies and suggests that other processes besides glomerular filtration also play a role [6]. There is substantial evidence that obesity can influence both passive and active processes in the kidney's [37], which might explain why body weight is a better predictor for vancomycin clearance than renal function estimates in obese individuals without renal failure.

Results on vancomycin volume of distribution in obese seem to be more consistent across literature. Five studies reported on changes in volume of distribution, all describing an increase of volume of distribution with body weight in a linear fashion [19–21,23,24]. No study reported age as a covariate for volume of distribution. In our study we found age as covariate for volume of distribution, even though its impact was limited. As a consequence, increasing age does not impact the proposed dose regimen.

It is well known that vancomycin pharmacokinetics exhibits large inter-individual variability and has a small therapeutic window, and therefore the 2009 consensus guideline recommends that TDM is routinely applied when treating patients with vancomycin [13]. Our results further substantiate this recommendation for the obese populations, since our final PK model still shows considerable unexplained inter-individual variability for both clearance (25% in the obese subgroup) and volume of distribution (45% on V1). To obtain an adequate AUC_{24h} between 400 and 700 mg*h L^{-1}, guidelines recommend to target trough concentrations between 15 – 20 mg L^{-1} [13]. We show that in obese individuals, steady state trough concentrations of 5.7 – 14.6 mg L^{-1} (when dosed two times daily) are sufficient to assure adequate exposure. This discrepancy with the guideline recommendation has been reported for several other special populations as well [14,15]. Plots with individual *post-hoc* clearance and volume of distribution values visualized by colour (shown in Figure S5 in the supplementary file) point out that the variability in volume of distribution explains why we see this range in trough concentrations with similar AUC_{24} values. To circumvent this problem in translating trough concentrations to exposure, it might be preferable to measure the AUC directly using a limited sampling strategy (for example with peak-and-trough concentrations) along with the employment of Bayesian forecasting software. This recommendation has also been incorporated in the revision of the 2009 vancomycin TDM guideline, which is currently under development [38]. If resources or knowledge is unavailable, clinicians should be aware that in obese individuals, trough concentrations below 15 mg L^{-1} do not necessarily correspond to a subtherapeutic exposures and therefore do not always require dose adjustments.

Some limitations apply to our study. First, our participants received only a single vancomycin infusion. Therefore, extension of our PK model to simulate continuous infusions should be done with caution. Yet, the maintenance dose is merely dependent on vancomycin clearance which can be adequately estimated in the current study design. Second, in interpreting the simulations, we chose a target PTA of 90% for selection of the best dose regimen, as advocated by the EMA [39]. However, certain situations may call for a higher target PTA and therefore a higher dosage, for example in serious life-threatening infections [39,40]. In addition, the target for PTA (AUC_{24} >400 mg h L^{-1}), has only been established for *S. Aureus* infections. We still remain fairly ignorant as to the appropriate targets for other infections where vancomycin is indicated. Third, obese individuals underwent bariatric surgery during

the PK study, which could theoretically interfere with the results. However, the concerning operations are performed laparoscopically, with a short duration (<1 h), and minimal blood loss (<50 mL). Therefore, we consider this influence to be negligible. Last, the participants in our study were, besides being obese, otherwise healthy individuals with adequate renal function. Therefore, one should apply caution in extrapolating of our results to individuals with renal impairment or critical illness and always perform TDM in these populations.

In conclusion, our study shows that in order to obtain optimal exposure with minimal risk on toxicity, vancomycin should be dosed as 35 mg kg^{-1} per day in obese individuals without renal impairment. For continuous infusion regimens, a loading dose of 1500 mg is sufficient for the whole population to obtain steady state at day 1.

ACKNOWLEDGEMENTS AND DISCLOSURES

The authors like to thank all study participants. The authors also like to thank Ingeborg Lange, Marieke van Donselaar, Angela Colbers, Brigitte Bliemer and Sylvia Samson for aiding in the recruitment of participants and conduct of the trial.

Dr. Brüggemann declares that he has no conflicts of interest with regards to this work. Outside of this work, he has served as consultant to and has received unrestricted research grants from Astellas Pharma Inc., F2G, Gilead Sciences, Merck Sharpe and Dohme Corp., and Pfizer Inc. All payments were invoiced by the Radboud University Medical Centre. All other authors declare no conflicts of interest.

This study was funded by an institutional research from The Netherlands Organization for Health Research and Development (ZonMW) under grant number 836041004.

Contributors

C.S., M.J.W., E.P.A.D., J.W.M., R.J.M.B, and C.A.J.K. designed the study, C.S., R.E.W and E.P.A.D. performed the study, C.S., R.E.W., S.C.G., C.A.J.K. analysed the data and C.S., R.E.W., S.C.G., M.J.W., E.P.A.D., J.W.M., R.J.M.B. and C.A.J.K. wrote the manuscript.

Data sharing

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

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SUPPLEMENTARY FILE

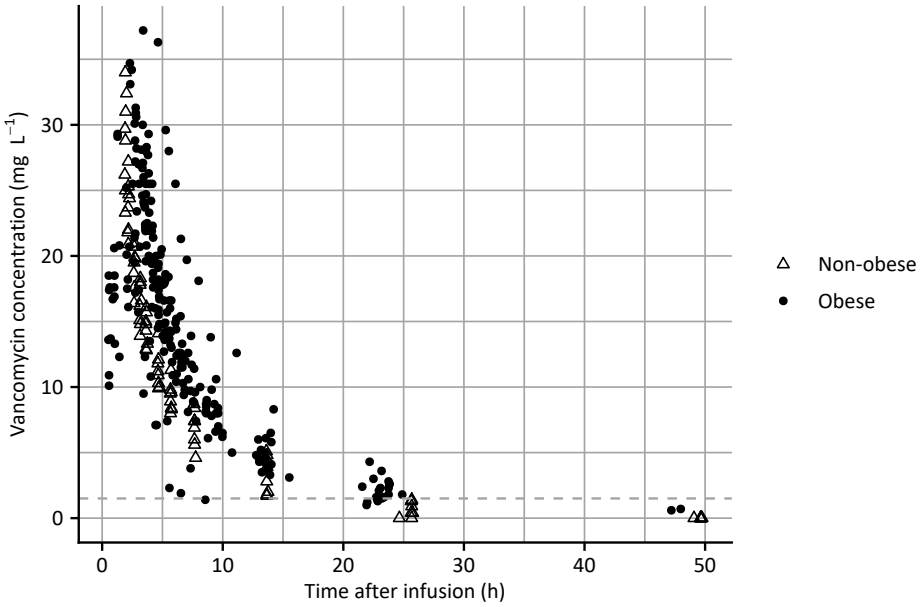

Figure S1. Measured vancomycin concentration versus time after infusion. Non-obese participants (n = 8 individuals, dose 1000 mg) are shown as triangles, obese participants as circles (n = 20 individuals, dose 12.5 mg kg^{-1}, maximum 2500 mg)). The limit of detection (LOD) of 1.5 mg L^{-1} is shown with the grey dashed line.

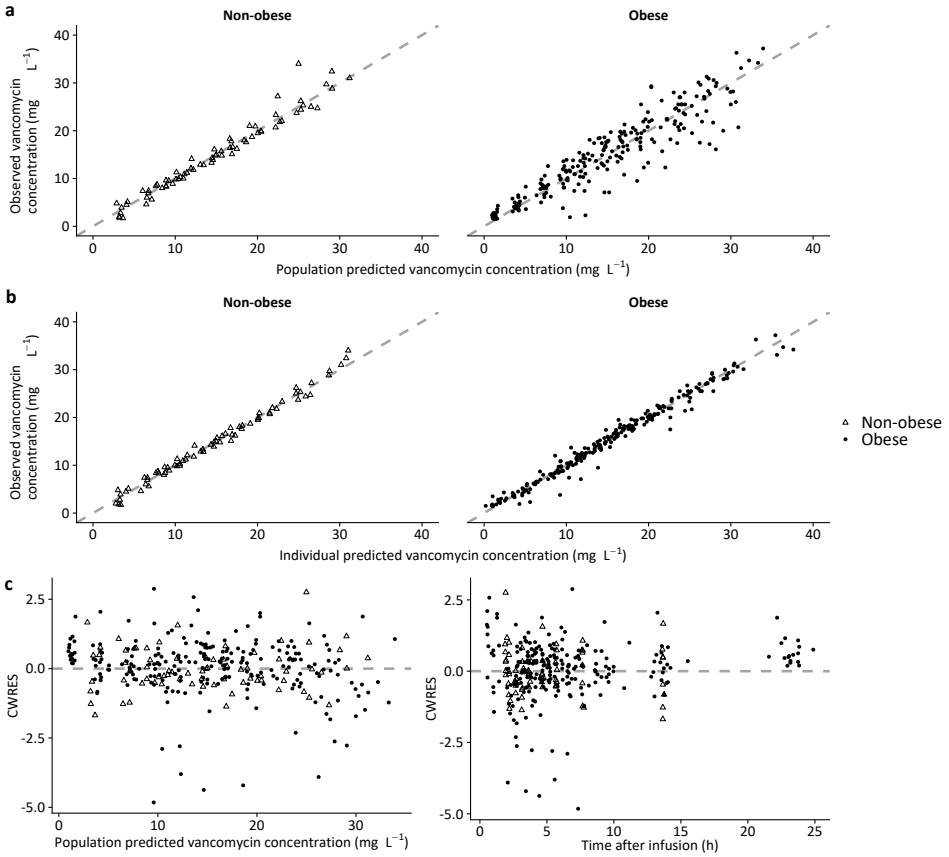

Figure S2. Goodness-of-fit plots of the final pharmacokinetic model for non-obese individuals (n = 8, white triangles) and morbidly obese individuals (n = 20, black dots). (a) Observed versus population predicted vancomycin concentration, (b) observed versus individual predicted vancomycin concentration and (c) conditional weighted residuals (CWRES) versus population predicted vancomycin concentration (left panel) and CWRES versus time after start of infusion (right panel). Grey dashed lines in plots (a) and (b) represent the line of identity (x = y), grey dashed lines in (c) represent a CWRES of 0. *CWRES* conditional weighted residuals.

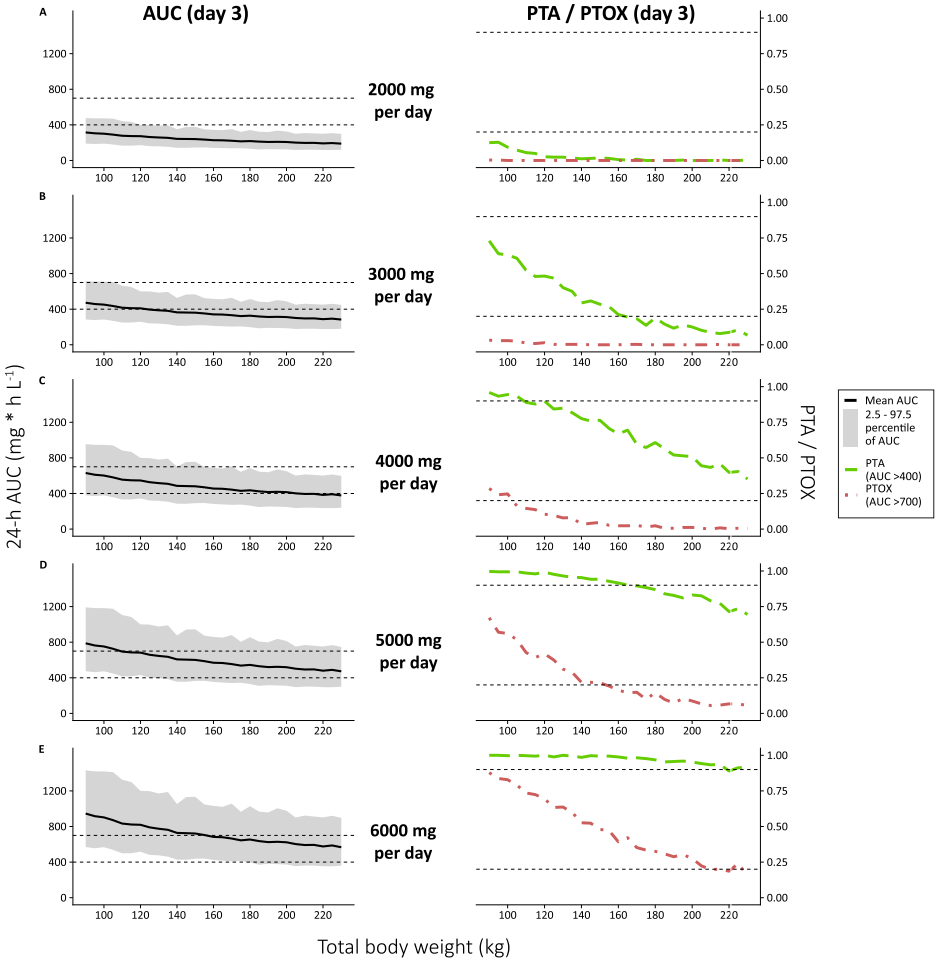

Figure S3. 24-hour area under the curve (AUC) values at day 3 (left column) and probability of target attainment (PTA, AUC_{24h} >400) or toxicity (PTOX, AUC_{24h} >700) (right column), shown versus weight (90 – 230 kg) for several fixed dose regimens (n = 10.000 per dose regimen). Panels A – E show increasing dose regimens from 2000 mg per day to 6000 mg per day. In the left plots, the solid black line and grey area indicate mean observed AUC with 2.5 – 97.5 percentiles. Dashed grey line represents target AUC levels (400 and 700 mg*h L-1). In the right plots, the dashed green line and dot-dashed red line indicate PTA and PTOX, respectively. Dashed grey lines represent the threshold for PTA (0.9) and, for reference, 20% PTOX (0.2). *AUC*, 24 hour area under the curve at day 3; *PTA*, Probability of Target Attainment (AUC >400) at day 3; *PTOX*, Probability of Toxicity (AUC >700) at day 3.

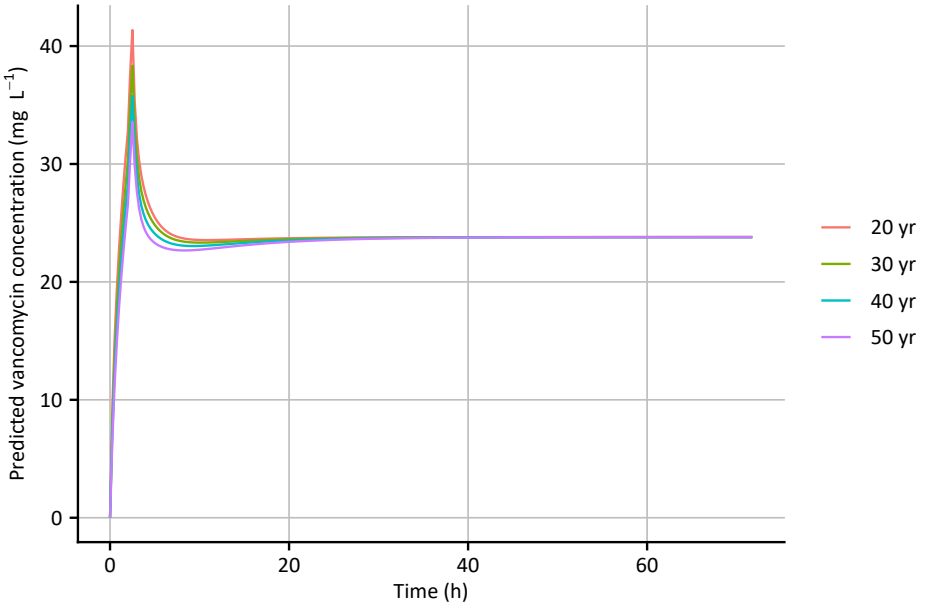

Figure S4. Predicted vancomycin concentrations when administered to 4 individuals weighing 130 kg with varying age after administration of a vancomycin dose of 1500 mg (infusion rate 10 mg min^{-1}) followed after 2 hours by a continuous infusion of 35 mg kg^{-1} per day (maximized at 5500 mg per day). Each line represents population predicted vancomycin concentrations over time for 1 individual.

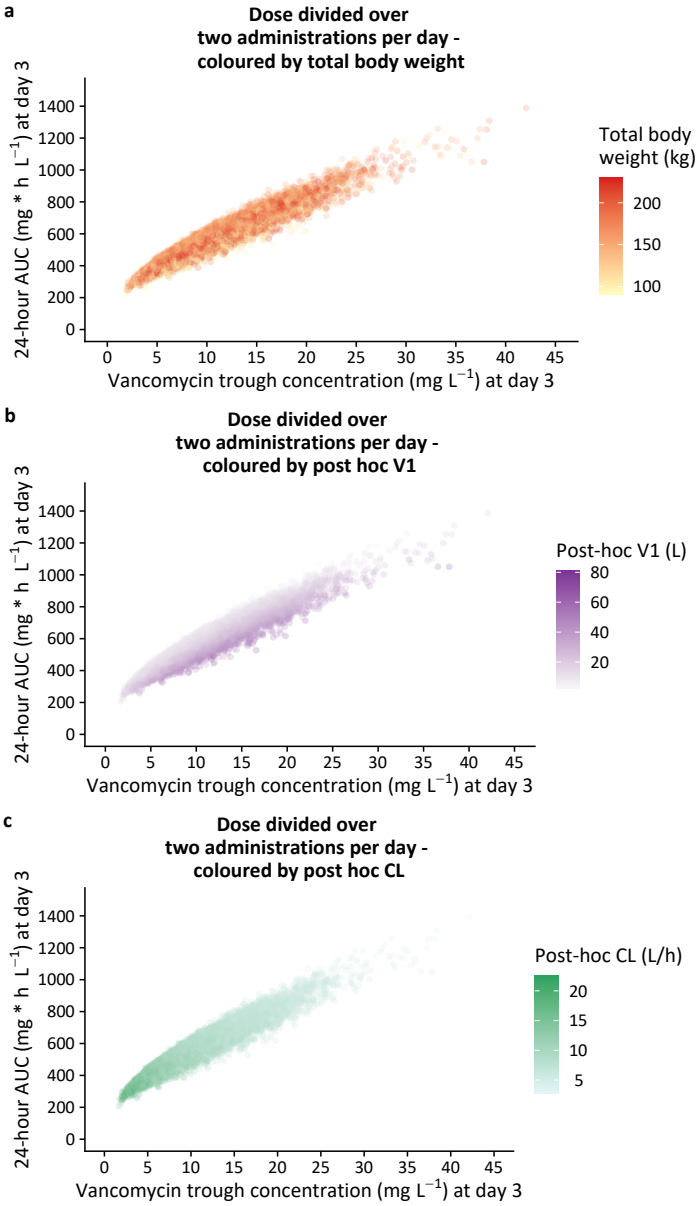

Figure S5. 24-hour area under the curve (AUC_{24h}) at day 3 versus individual trough concentrations at day 3 (measured 0.5 hour prior to the second dose) based on Monte Carlo Simulation in obese patients (n = 10.000, weight ranging 90 – 230 kg), using the final model. Vancomycin dose was 35 mg kg^{-1} per day, maximized at 5500 mg per day, given over two infusions per day. Each dot represents one simulated individual. Each dot is coloured according to the individual's (a) total body weight, (b) post-hoc volume of distribution of central compartment and (c) post-hoc clearance. *AUC* area under the curve, *CL* clearance, *V1* central volume of distribution.

NONMEM CONTROL STREAM FOR THE FINAL MODEL

```
$PROBLEM VANCO
$INPUT ID TIME AMT RATE DV LNDV=DROP MDV LLOQ
LOD DURING OK GFR WT LBW BMI IBW ABW AGE
BSA SEX RACE HIST PHASE SURG GRP CG MDRD CREAT
CKD CGTBW
$DATA nonmem_all.prn IGNORE=#
$SUBROUTINE ADVAN11 TRANS4
$PK
TVCL = THETA(1)*((WT/70)**THETA(10)); TVCL
TVV1 = THETA(2)*(1+THETA(11)*(AGE-36.5)); TVV1
TVQ2 = THETA(3); TVQ2
TVV2 = THETA(4)*((WT/70)**THETA(9))*(1+THETA(11)*(AGE-36.5)); TVV2
TVQ3 = THETA(5);TVQ3
TVV3 = THETA(6);TVV3
;
IF (GRP.EQ.0) THEN
CL = TVCL*EXP(ETA(1))
ELSE
CL = TVCL*EXP(ETA(7))
ENDIF
;
V1 = TVV1*EXP(ETA(2))
Q2 = TVQ2*EXP(ETA(3))
V2 = TVV2*EXP(ETA(4))
Q3 = TVQ3*EXP(ETA(5))
V3 = TVV3*EXP(ETA(6))
;
S1 = V1 ;
;
ET1_0=ETA(1)
ET1_1=ETA(7)
ET2=ETA(2)
ET3=ETA(3)
ET4=ETA(4)
ET5=ETA(5)
ET6=ETA(6)
```

```
;
$THETA
(0, 5.72) ; TVCL
(0, 16.7) ; TVV1
(0, 15.8) ; TVQ2
(0, 6.99) ; TVV2
(0, 5.21) ; TVQ3
(0, 19.5) ; TVV3
(0.0392) ; SD PROPORTIONAL ERR
(1.07) ; SD ADD ERROR
(1) FIX ; EXP V1 WT
(0, 0.535) ; EXP CL-WT
(-0.054, 0.0136,0.0606) ; SLOPE V1-V2-AGE
;
$OMEGA
0.00278 FIX ; CL ETA 1_0 (NON-OBESE)
0.187 ; V1 ETA 2
0 FIX ; Q2 ETA 3
0 FIX ; V2 ETA 4
0 FIX ; Q3 ETA 5
0 FIX ; V3 ETA 6
0.0593 ; CL ETA 1_1 (OBESE)
;
$ERROR
TYPE=1
IF(DV.LT.LOD) TYPE = 2
;
PROP=THETA(7)*F ; proportional part
ADD=THETA(8) ; additive part
SD=SQRT(PROP*PROP + ADD*ADD) ;
;
IPRED = F
DUM = (LOD - IPRED) / SD
CUMD = PHI(DUM)
IF (TYPE .EQ. 1.OR.NPDE_MODE.EQ.1) THEN
F_FLAG = 0
Y = IPRED + SD * ERR(1)
ENDIF
IF (TYPE .EQ. 2.AND.NPDE_MODE.EQ.0) THEN
```

```
F_FLAG = 1
Y = CUMD
MDVRES=1
ENDIF
IF(TYPE.EQ.2) DV_LOQ=LOD
;
IRES = DV - IPRED
IWRES = IRES/SD
;
$SIGMA
1 FIX ; ERR 1
;
$ESTIMATION METHOD=1 INTER MAXEVAL=9999 POSTHOC LAPLACIAN NOABORT
NUMERICAL SLOW ;
$COVARIANCE MATRIX=S PRINT=E SLOW;
;
$TABLE ID TIME IPRED CWRES NPDE AMT TVCL CL NPDE TVV1 V1 TVQ2 Q2 TVV2 V2
TVQ3 Q3 TVV3 V3 ET1_1 ET1_0 ET2 ET3 ET4 ET5 ET6 MDV GFR LLOQ WT LOD IWRES LBW
BMI IBW ABW AGE BSA SEX RACE HIST PHASE OK DURING SURG GRP CG MDRD CREAT
CKD CGTBW NOPRINT ONEHEADER
```