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ORIGINAL RESEARCH ARTICLE

Vancomycin Clearance in Obese Adults is not Predictive of Clearance in Obese Adolescents

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Abstract

Background and Objective Contradictory pharmacokinetic (PK) results have been observed between obese adults and obese adolescents, with absolute clearance (CL) reported to be either unaltered, lower, or higher in obese adolescents compared to obese adults. This study investigates the PK of vancomycin in adolescents and adults who are overweight or obese.

Methods Data from 125 overweight and obese adolescents (aged 10–18 years, weight 28.3–188 kg) and 81 overweight and obese adults (aged 29–88 years, weight 66.7–143 kg) were analysed using population PK modelling. In addition to age, sex, renal function estimates, and regular weight descriptors, we evaluated standard weight ($WT_{standard}$, defined as weight for length, age, and sex in adolescents and weight for length in adults) and excess weight (WT_{excess}, defined as total body weight (TBW) minus $WT_{standard}$) as covariates in order to distinguish between weight resulting from length versus weight resulting from obesity.

Results Analyzing adolescents and adults together, vancomycin CL was found to increase with TBW and decrease with increasing age ($p < 0.001$). A covariate analysis investigating adolescents and adults separately found that vancomycin CL increased with $WT_{standard}$ in adolescents and adults, albeit with different functions, with adolescents having a higher CL per $WT_{standard}$ than adults. Moreover, in this separate model, adolescent males had 21% higher CL than adolescent females of the same $WT_{standard}$, while in adults, CL decreased with increasing age ($p < 0.001$).

Conclusion There are apparent differences in vancomycin CL in overweight and obese adults versus overweight and obese adolescents, implying that dosing of vancomycin cannot be directly extrapolated between these populations.

1 Introduction

Overweight and obesity in adults are defined as a body mass index (BMI) ≥ 25 kg/m^2 and ≥ 30 kg/m^2, respectively, and in adolescents as a BMI corrected for age and sex ≥ 85th percentile and ≥ 95th percentile, respectively [1]. Obesity is associated with many physiological changes beyond increased adipose and lean tissue, such as increased cardiac output and blood flow, decreased tissue perfusion, and a permanent state of low-grade inflammation, all of which may influence the pharmacokinetics (PK) and, therefore, the required dosing regimen of drugs [2]. However, for many drugs there is limited information on how these changes translate into PK differences and dosage requirements in obese adults, and this information is even more scarce in obese adolescents, a population in which growth and maturation may still play a role [3, 4]. As the prevalence of overweight and obesity is increasing rapidly, clinicians are confronted with a growing number of dosing challenges [5, 6].

Extrapolation approaches to derive PK and dosing information for obese adolescents in the absence of actual data are sought. It has been suggested that maturation in adolescents is complete, leaving only size-related differences compared to adults, suggesting that PK values and dosing information from obese adults could be predictive for obese adolescents [7–10]. One study on busulfan, a

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Key Points

Vancomycin clearance (CL) in overweight and obese adolescents is on average higher than in overweight and obese adults, and vancomycin doses therefore cannot be directly scaled between these populations.

In obese adolescents, males have higher vancomycin CL than females, while in obese adults, CL decreases with increasing age.

Vancomycin CL is higher in our population of overweight and obese individuals compared to reported values in the non-obese, but within our population of overweight and obese individuals, vancomycin CL is stronger correlated with standard bodyweight compared to excess bodyweight.

hepatically cleared drug, found that clearance (CL) is influenced only by body weight, indicating CL in obese adults can be scaled to obese adolescents [11, 12]. However, contradictory PK results have been observed between obese adults and obese adolescents for other hepatically cleared drugs, with the absolute CL of propofol [13] being lower in obese adolescents and the absolute CL of midazolam being higher [14]. These studies found that in addition to body weight, covariates like age or growth- and obesity-related metrics are essential to describe inter-individual variability in PK parameters, indicating that PK values and dosing information in obese adults are likely not generalizable for obese adolescents for hepatically cleared drugs.

For renally cleared drugs, one study on metformin found comparable PK values between obese adolescents and obese adults, indicating that adult dosages of this drug could be used in obese adolescents [15]. However, for other renally cleared drugs such as vancomycin, a glycopeptide antibiotic commonly used in severe gram-positive infections, no study simultaneously analyzing drug PK in obese adolescents and obese adults has been performed. Therefore, in our study we investigate the PK of vancomycin in adolescents and adults who are overweight or obese using population PK modelling.

2 Methods

2.1 Data and Patients

Data on overweight and obese adolescents were taken from a previously published, retrospective PK dataset, including data on pediatric patients from 21 hospitals in Utah, USA, receiving vancomycin [16]. Selected subjects from this dataset were aged between 10 and 18 years and had a BMI corrected for age and sex that was higher than the 85th percentile of the Centers for Disease Control and Prevention (CDC) growth charts. Subjects with a reduced renal function, defined as estimated glomerular filtration rate (eGFR estimated using the equation of bedside Schwartz [17]) < 60 mL/min/1.73 m^2, were excluded. According to routine practice, subjects received a 15–20 mg/kg vancomycin dose two to four times a day per 60-minute infusion. Blood samples taken for therapeutic drug monitoring (TDM) were drawn within 30 min before dosing and/or 30 min after the end of infusion or opportunistically at random time points. The requirement of informed consent was waived by the Intermountain Healthcare and University of Utah Institutional Review Boards [16].

Data of overweight and obese adolescents were combined with the data of overweight and obese adults extracted from the St. Antonius Hospital's electronic health records in Nieuwegein, the Netherlands. Data were used from subjects with a BMI higher than 25 kg/m^2, were admitted to the general ward, received one or more vancomycin doses, had at least one vancomycin plasma concentration measurement, and had at least one body weight measurement between start and end of vancomycin treatment. Similar to adolescents, adults were omitted if they had a reduced renal function (eGFR estimated using the equation of chronic kidney disease epidemiology collaboration [CKD-EPI] < 60 mL/min/1.73 m^2 [18]). Vancomycin dosing was based on protocols for routine clinical practice and included a loading dose of 1000 mg or 1500 mg. Intermittent vancomycin infusions consisted of doses of 500–1500 mg twice or three times daily. Continuous infusion of vancomycin varied between 1000 mg/day and 3500 mg/day. The Institutional Review Board (IRB) approved the study and waived the informed consent requirement.

2.2 Population Pharmacokinetic Analysis

To analyze the data, a nonlinear mixed effect modelling analysis was performed using NONMEM 7.4. (Icon Development Solutions, Hanover, MD, USA) with Perl-speaks-NONMEM (4.9.0) and the Pirana interface (2.9.9) (Certara USA, Inc, Princeton, USA) [19, 20]. R 4.0.3 (Xpose4 package 4.7.1) and Rstudio (2022.02.3) were used for data management and visualization. Using first-order conditional estimation, the population PK model was developed under the ADVAN3 TRANS4 subroutine.

2.2.1 Structural and Stochastic Model Development

The 1-, 2-, and 3-compartment models with linear elimination were tested as structural models. Inter-individual variability was assumed to be log-normally distributed and tested on each model parameter. Additive, proportional, and combined error models were investigated for the unexplained residual variability. Nested models were compared and selected according to the objective function value (OFV, i.e., 2log likelihood function). A decrease in OFV (ΔOFV) of more than 3.84, corresponding to $p < 0.05$ for one degree of freedom, was considered statistically significant.

2.2.2 Covariate Model Development

Covariates that were considered in the analysis included age, sex, length, BMI, total body weight (TBW), lean body weight (LBW, calculated according to the equation of Janmahasatian et al. [21], Peters et al. [22] and Foster et al. [23]), adjusted body weight (ABW), ideal body weight (IBW), serum creatinine concentration, and eGFR calculated by the equations of bedside Schwartz [17] (for adolescents only), chronic kidney disease epidemiology (CKD-EPI), Cockcroft–Gault (CG), and modification of diet in renal disease (MDRD). The values of eGFR estimates for adolescents were capped at 200 mL/min/1.73 m^2 during covariate analysis. The equations for calculating body weight descriptors and eGFR can be found in Supplemental materials Table S1. Additionally, standard weight and excess weight were defined to distinguish between weight resulting from the length and weight resulting from obesity [12]. For adolescents, standard weight ($WT_{standard\_adol}$) was calculated using the 50th percentile in BMI ($BMI_{50th\ percentile}$) for the subject's age and sex according to the CDC growth charts [1] and the length of the subject in meters (Eq. 1). For adults, standard weight ($WT_{standard\_adu}$) was calculated based on a BMI of 22 kg/m^2 and the subject's length in meters (Eq. 2). Absolute and relative excess weight (WT_{excess}) were defined as the difference between the standard weight and TBW.

$$WT_{standard\_adol} = BMI_{50th\ percentile} \times length^2 \quad (1)$$

$$WT_{standard\_adu} = 22 \times length^2 \quad (2)$$

Continuous covariates were tested using Eqs. 3 and 4 for linear and exponential relations, respectively, and binary covariates were tested using Eq. 5:

$$P = TV_p \times \left(1 + \theta_x \times \left(COV - COV_{median}\right)\right) \quad (3)$$

$$P = TV_p \times \left(\frac{COV}{COV_{median}}\right)^{\theta_y} \quad (4)$$

$$P = TV_p \times \theta_z^{COV}, \quad (5)$$

where P is the parameter value, which is based on TV_P, which is the typical value or population estimate of the parameter, COV, which is the value of the covariate, COV_{median}, which is the median value of the covariate, θ_X, which is the slope parameter for linear covariate relationships, θ_Y, which is the exponent for power functions, and θ_Z, which is the proportional change of the parameter. In Eq. 5, values of zero and one are used for COV to indicate the absence or presence of a binary covariate, respectively. Covariates of standard weight and excess weight were also tested using a so-called excess weight covariate model adapted from Van Rongen et al. [15] as defined in Eq. 6:

$$P = TV_p \times \left(\frac{WT_{standard}}{WT_{stamdard\_median}}\right)^{\theta_u} + \left(\theta_w \times WT_{excess}\right), \quad (6)$$

where θ_U is the scaling exponent for $WT_{standard}$, which was either fixed to 0.75 or estimated, and θ_W is the linear influence of WT_{excess} on the parameter value.

For covariate model selection, ΔOFV of more than 10.83 ($p < 0.001$) was considered statistically significant. Shark plots [24] were used to ascertain a sufficient number of individuals drove statistical significance. Additional assessments included visual inspection of basic goodness-of-fit plots, plots of conditional weighted residuals (CWRES) or individual post hoc parameter estimates versus individual covariate values, and plots displaying obtained covariate relationships. All plots were constructed with different stratifications that included sex, age- and weight-related covariates. Lastly, the plausibility and precision of parameter estimates were considered, where for the latter, values of the relative standard error of the estimates (RSE) of < 50% were considered acceptable.

The covariate analysis was conducted using data from adolescents and adults simultaneously. When visual inspection of the graphical output suggested different covariate relationships may be needed for the adolescents and adults, separate covariate analyses for adolescents and adults were also performed. This resulted in a final simultaneous model and a final separate model.

2.2.3 Validation of the Final Models

The final models were internally validated by a bootstrap resampling analysis using PsN [19], with 1000 replicates

stratified on the two populations (adolescents and adults). A normalized prediction distribution error (NPDE) analysis based on 1000 simulated datasets using the NPDE package in R [25] was performed to assess the predictive performance of the final model. Also, for the NPDE, stratification based on population (adolescents and adults) was used.

3 Results

3.1 Data and Patients

The PK analysis was based on 364 concentrations from 125 overweight and obese adolescents (aged 10–18 years, TBW 28.3–188 kg, BMI 20.2–60.0 kg/m^2) [16], and 393 concentrations from 81 overweight and obese adults (age 29–88 years, TBW 66.7–143 kg, BMI 25.1–40.8 kg/m^2). A summary of baseline demographic and clinical data characteristics is shown in Table 1.

3.2 Population Pharmacokinetic Analysis

3.2.1 Structural and Stochastic Model Development

Regarding the structural and statistical structure of the base model, a two-compartment model with a proportional error model with inter-individual variability on CL and peripheral volume of distribution (Vp) best described all data from adults and adolescents. For this base model without covariates, boxplots depicted in Fig.1 show that absolute vancomycin CL in obese adolescents is, on average, higher than in obese adults ($p < 0.01$). This is even

Table 1 Demographic and clinical data characteristics from the overweight and obese adult and overweight and obese adolescent patients included in this analysis

Parameters	Adolescents	Adults	Total
Number of individuals (*n*)	125	81	206
Male/female (% male of total)	67/58 (53.6)	51/30 (63.0)	118/88 (57.3)
Age (years)	13 (10–18)	68 (29–88)	40 (10–88)
Overweight/obese (% obese of total)	56/69 (55.2)	49/32 (39.5)	105/101 (49.0)
Body size descriptors			
Height (m)	1.59 (1.13–1.96)	1.74 (1.50–1.95)	1.67 (1.13–1.96)
BMI (kg/m^2)	26.4 (20.2–60.0)	28.7 (25.1–40.8)	27.9 (20.2–60.0)
Total body weight (kg)	70.4 (28.3–188)	90.3 (66.7–143)	83.8 (28.3–188)
Lean body weight (kg)	44.7 (19.5–90.0)	61.3 (40.5–85.4)	52.8 (19.5–90.0)
Adjusted body weight (kg)	60.4 (18.3–119)	78.0 (57.1–106)	70.3 (18.3–119)
Ideal body weight (kg)	52.4 (11.6–89.5)	67.8 (43.3–88.6)	59.6 (11.6–89.5)
$WT_{standard\_adol/adu}$ (kg)	47.3 (21.3–81.6)	66.6 (49.5–83.7)	59.2 (21.3–83.7)
WT_{excess} (kg)	18.6 (5.20–124)	21.4 (8.26–65.8)	20.2 (5.20–124)
Percentage of WT_{excess} (%)	41.4 (18.2–200)	30.6 (14.1–85.5)	34.5 (14.1–200)
Estimated renal function			
Serum creatinine (µmol/L)	49.5 (18.6–95.5)	62.0 (24.0–107)	56.0 (18.6–107)
Bedside Schwartz (mL/min/1.73 m^2)	112 (60.5–264)	–	–
CKD-EPI (mL/min/1.73 m^2)	145 (83.3–231)	91.5(60.1–157)	120 (60.1–231)
Cockcroft–Gault (mL/min)	192 (66.4–463)	115 (61.6–378)	152 (61.6–463)
MDRD (mL/min/1.73 m^2)	168 (77.1–606)	108 (57.6–285)	126 (57.6–606)
Dose information			
Vancomycin dose (mg)	1000 (300–2500)	1250 (500–4000)	1000 (300–4000)
Vancomycin dose (mg/kg)	14.7 (2.66–26.8)	15.1 (3.50–46.1)	14.8 (2.66–46.1)
No. of samples (*n*)	364	393	757
No. of samples per individual (*n*)	2 (1–27)	4 (1–19)	2 (1–27)
Time after dose (h)	6.10 (1.32–34.6)	10.8 (1.03–44.6)	9.37 (1.03–44.6)

Data are shown as median (range) unless specified otherwise

BMI body mass index, *CKD-EPI* renal function estimate calculated by chronic kidney disease epidemiology collaboration, *MDRD* renal function estimate calculated by modification of diet in renal disease, $WT_{standard\_adol}$ standard body weight defined in adolescents as body weight for length and age and sex according to Eq. 4 and $WT_{standard\_adu}$ in adults as body weight for length according to Eq. 5, WT_{excess} excess weight defined as standard body weight minus total body weight

Equations for body size descriptors and renal function estimates can be found in Supplemental Table S1

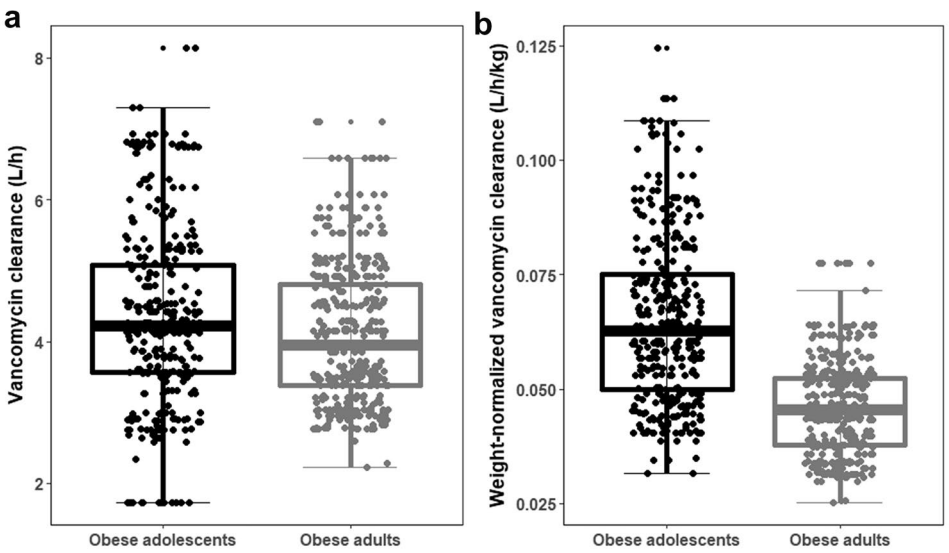

Fig. 1 Individual post hoc parameter estimates were obtained from the base model for **a** absolute vancomycin clearance and **b** weight-normalized vancomycin clearance of overweight and obese adolescents (black) and overweight and obese adults (gray). Boxplots are depicted based on both median and interquartile ranges of clearance. Dots represent each individual's post hoc estimate of clearance

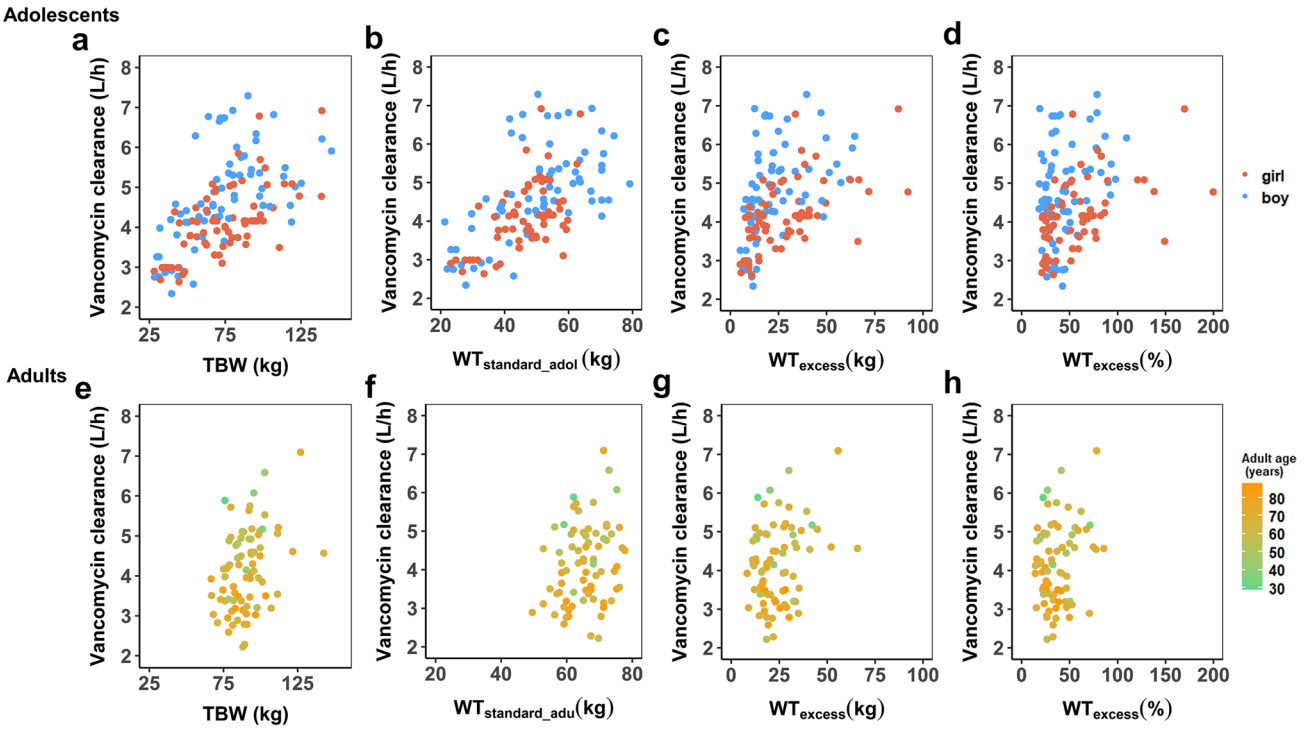

Fig. 2 Individual post hoc parameter estimates obtained from the base model for absolute vancomycin clearance in **a-d** overweight and obese adolescents **e**–**h** and overweight and obese adults versus **a**, **e** total body weight (TBW), **b**, **f** standard weight ($WT_{standard}$), **c**, **g** excess body weight (WT_{excess}) and **d**, **h** relative excess body weight ($\%WT_{excess}$)

more clear when CL is normalized by total body weight (TBW) ($p < 0.001$). Additional plots from the base model in Fig. 2 suggest that the covariate relationships may not be the same for overweight and obese adolescents and overweight and obese adults with trends of $WT_{standard}$ and sex for adolescents and age for adults.

3.2.2 Covariates in the Simultaneous Model for Adolescents and Adults

Although all GFR estimates and serum creatinine were statistically significantly correlated with CL, the magnitude of statistical significance of the covariate effects differed greatly, with ΔOFV ranging from − 8.01 to − 92.1. This can be explained by the fact that the GFR estimates are composite measures, calculated by combining measured serum creatinine with other covariates, such as age, sex, body weight, race and/or height (see Supplementary material Table S1). This could suggest that the impact of the GFR estimates is driven by the covariates used in their calculations, rather than by an actual impact of renal function. This was further supported by the finding that only two individuals (0.97%) contributed to reaching statistical significance for the relation between serum creatinine and CL and by the plot of CWRES versus serum creatinine of the base model showing no trend (Supplementary material Fig. S1). Additionally, of the GFR estimates, only the inclusion of CG that uses TBW in its calculation, resulted in a higher ΔOFV than the drop obtained with TBW on its own (ΔOFV − 92.1 and − 57.6, respectively). Therefore, the covariate analysis was continued based on the covariates unrelated to renal function.

Total body weight, in a power function on CL, was the most significant covariate and included first. Age was subsequently found to have a negative linear correlation with CL. Moreover, the central volume of distribution (Vc) increased statistically significantly with TBW in an exponential relation. Although sex did not have a statistically significant impact on vancomycin PK, there was a trend for sex in the adolescent (Supplementary material Fig S2).

The obtained covariate relationships for CL in the simultaneous model for adolescents and adults are visualized in Fig. 3a. This figure shows that CL decreases with age in subjects with the same TBW, suggesting that even if obese adolescents have the same weight as obese adults, dose information for obese adults is not directly applicable to obese adolescents. The parameter values and bootstrap estimates for this final simultaneous model are summarized in Table 2.

3.2.3 Covariates in the Separate Models for Adolescents and Adults

Results regarding covariates related to renal function were similar to those found in the simultaneous model. Following the same reasoning, these covariates were excluded from the covariate analysis.

In overweight and obese adolescents, $WT_{standard\_adol}$ in a power function was identified as the most predictive covariate based on the defined statistical criteria and visual assessments. The model incorporating $WT_{standard\_adol}$ and $WT_{excess,}$ shown in Eq. 6, resulted in a comparable OFV and diagnostic plots as the model with only $WT_{standard\_adol}$ as a covariate on CL, indicating that CL in adolescents is correlated with standard weight rather than excess weight. Sex was another covariate on CL in adolescents, with CL in males being 21% higher than in females of the same $WT_{standard\_adol}$. The Vc was found to increase with $WT_{standard\_adol}$ in a power function. After including all the covariates in adolescents, the exponents in power functions of $WT_{standard\_adol}$ on CL and Vc were 1.09 and 1.10, respectively. Since fixing these exponents to one increased the OFV by only 0.818 points, they were fixed to one to simplify the model to a linear function.

In overweight and obese adults, a negative linear relationship between age and CL was found ($p < 0.001$). Besides, TBW and $WT_{standard\_adu}$ were found to be correlated with CL (ΔOFV= − 13.0 and − 11.3, respectively). Given the slight difference in OFV between these covariates, the

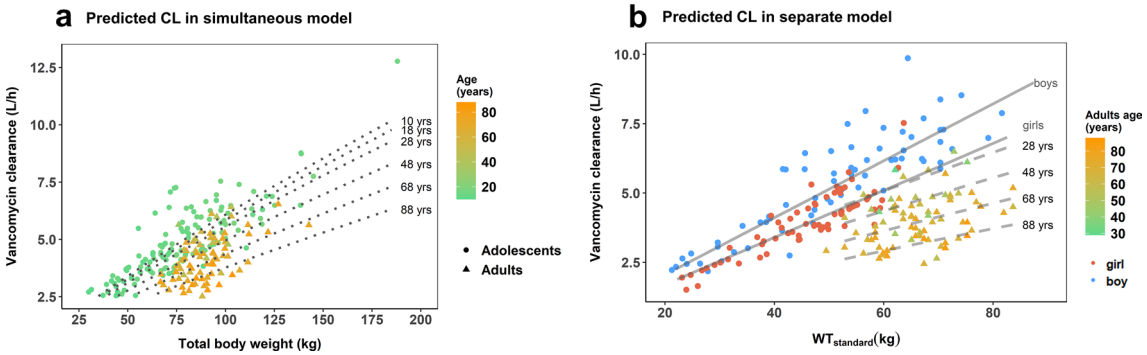

Fig. 3 **a** Vancomycin clearance in the final simultaneous model, and **b** vancomycin clearance in the final separate models. Dotted lines represent the decreasing CL for adolescents and adults of 10, 18, 28, 48, 68 and 88 years; solid lines represent the obtained covariate relationship for adolescent males and females, while dashed lines represent the decreasing CL for adults of 28, 48, 68 and 88 years. Symbols represent individual clearance values

Table 2 Population pharmacokinetic parameters and bootstrap medians of vancomycin in overweight and obese adolescents and adults for the final simultaneous model and the final separate model

Parameters	The final model (RSE%)	Bootstrap median for the final model [95% CI]
Simultaneous model		
Structural parameters		
$CL_{adolescents\ and\ adults}$ (L/h) = TVCL1 × (TBW/60)$^{\theta 1}$ × [1 + θ2 × (AGE – 40)]		
TVCL1	3.39 (3)	3.36 (2.80–3.60)
θ1	0.836 (8)	0.849 (0.638–1.029)
θ2	− 0.00570 (13)	− 0.00559 (− 0.00744 to − 0.00410)
$Vc_{adolescents\ and\ adults}$ (L) = TVVc1 × (TBW/60)$^{\theta 3}$		
TVVc1	20.0 (4)	19.9 (16.4–22.9)
θ3	0.775 (16)	0.768 (0.381–0.994)
Q(L/h)	2.27 (4)	2.27 (1.62–2.92)
Vp (L)	56.4 (10)	57.3 (33.5–105.4)
Inter-individual variability		
CL (%)	20.6 (9)	20.4 (15.8–23.9)
Vp (%)	94.8 (14)	94.2 (61.8–120)
Residual variability		
Proportional error	0.0383 (3)	0.0371 (0.0218–0.0514)
Separate model		
Structural parameters		
$CL_{adolescents}$ (L/h) = TVCL2 × ($WT_{standard\_adol}$/47) × $\theta 4^{sex}$ CL_{adults} (L/h) = TVCL2 × [1 + θ5 × (AGE – 68)] × ($WT_{standard_adu}$/67)$^{\theta 6}$		
TVCL2	3.99 (3)	3.98 (3.74–4.22)
θ4	1.21 (4)	1.20 (1.11–1.31)
θ5	− 0.00990 (32)	− 0.0100 (− 0.0143 to − 0.00520)
θ6	0.842 (39)	0.830 (0.430–1.23)
$Vc_{adolescents}$ (L) = TVVc2 × ($WT_{standard\_adol}$/47) Vc_{adults} (L) = TVVc2		
TVVc2	22.7 (4)	22.7 (19.9–25.2)
Q(L/h)	2.43 (6)	2.43 (1.96–3.12)
Vp (L)	52.8(12)	53.0 (38.0–73.4)
Inter-individual variability		
CL (%)	19.9 (8)	19.5 (15.2–23.5)
Vp (%)	92.7 (12)	92.2 (65.0–115)
Residual variability		
Proportional error	0.0381 (3)	0.0370 (0.0260–0.0510)

CL clearance, *Q* inter-compartmental clearance, *RSE* relative standard error based on the covariance step in NONMEM, *TVCL1 and TVCL2* represent the value of typical clearance in simultaneous model and separate model respectively, *TVVc1 and TVVc2* represent the value of typical central volume in simultaneous model and separate model respectively, *Vc* the volume of distribution of central compartment, *Vp* the volume of distribution of peripheral compartment, $WT_{standard\_adol}$ standard body weight defined in adolescents as body weight for length and age and sex and $WT_{standard\_adu}$ in adults as body weight for length

$WT_{standard\_adu}$ was selected to enable a comparison of the covariate relationship on CL between both populations. Similar to adolescents, incorporating WT_{excess} in addition to $WT_{standard\_adu}$ did not lead to a significant OFV drop, indicating CL is mainly correlated with standard weight rather than excess weight in adults. No covariates were found for Vc in adults.

Figure 3b illustrates the influence of covariates on vancomycin CL in the separate populations of overweight and obese adolescents and adults. The obtained parameter values and bootstrap estimates for the final separate model are presented in Table 2.

3.2.4 Validation of the Final Models

For both the final simultaneous model and the final separate models, the RSE values of the obtained parameters are all below 40%, indicating that the models are well supported by the data. The bootstrap analyses confirm the robustness of parameter estimates, as the bootstrap medians deviate less than 10% from the original estimate and as the obtained estimates are all within the 95% confidence interval (CI) of the bootstrapped values. The goodness-of-fit plots stratified by age groups did not show model misspecifications across any subpopulations (Supplementary material Fig. S3). The NPDE analyses indicate that the models can accurately predict typical trends as well as the variability in the populations. Statistical tests and visual inspection of the results show that the final models have a good predictive performance for subpopulations of different ages (Supplementary material Fig. S4).

4 Discussion

This study investigates the PK of vancomycin in adolescents and adults who are overweight or obese. Our model indicates that the PK of vancomycin in overweight and obese adolescents differs from that in overweight and obese adults, with CL being generally higher in adolescents compared to adults.

Vancomycin is primarily eliminated via glomerular filtration. It has been suggested that GFR in normal-weight children is lower than in adults and increases from birth until it reaches adult levels [26]. However, our results in overweight and obese adolescents and adults show an opposite trend, with both absolute and relative CL being, on average, higher in adolescents compared to adults. It should be noted that the data from the adults in this study originate from a different country (Netherlands) than the data from the adolescents (USA), which could introduce confounding factors that drive the differences that we found. However, supporting evidence and explanations for these findings do exist in literature. A potential explanation is that the renal function in obese adolescents is generally better than in obese adults although all included subjects had a normal renal function (e.g., median CKD-EPI for adolescents and adults are 145.23 and 91.54 mL/min/1.73 m^2, respectively). In literature, GFR is reported to be increased in obese patients due to the number or efficiency of functional nephrons being enhanced and/or renal blood flow being increased as a consequence of the increased cardiac output [27–30]. Along with the increased GFR, CL of some renally cleared drugs such as gentamicin and tobramycin is increased in obese individuals [16, 31–33]. However, for other renally cleared drugs such as cefazolin and ciprofloxacin [34–36], CL remains unchanged with obesity. Alternatively, long-term obesity is also highly associated with decreased renal function as the result of (chronic) kidney disease, compensating for an initial increase in GFR, eventually leading to an unaltered or even decreased CL of drugs. Therefore, we anticipate that adolescents, who have generally been overweight or obese for a shorter duration than adults, may have an obesity-induced higher GFR that is not yet impaired in comparison to overweight or obese adults. In a study on midazolam, a hepatically cleared drug, Van Rongen et al. reported that the duration of obesity might influence (patho)physiological changes related to obesity [14]. They found that CL of midazolam in obese adolescents increases mainly with obesity-related weight changes. However, in adults, this increase in CL was no longer apparent, possibly due to prolonged and/or more extensive obesity-induced suppression of CYP3A activity. As the duration of obesity has a possible influence on drug PK, the PK parameter values in overweight and obese adults may differ from those in overweight and obese adolescents and cannot be extrapolated between the populations. The value of vancomycin CL in overweight and obese adolescents in our study (e.g. 6.03 L/h with TBW of 100 kg and age of 12 years) is higher than the value reported in the literature in normal-weight adolescents of the same age (e.g., 3.38 L/h with TBW of 40 kg and age of 12 years [16]), and also higher than the value reported in normal-weight adults (e.g., 2.55 L/h with TBW of 65 kg and age of 60 years [37]). The increased CL in obese adolescents compared to normal-weight adolescents or adults might be explained by the increased GFR in obesity [38]. This difference in CL indicates that, similar to overweight and obese adults, the PK data and dosing information from non-obese adolescents or adults cannot be extrapolated to overweight or obese adolescents.

The obtained simultaneous and separate models have comparable OFV values (2916 vs 2914), and both show that the PK values in obese adolescents differ from those in obese adults. Both models found that CL is influenced by sex in adolescents. Although this is not statistically significant in the simultaneous model, Supplementary material Figure S5 shows that population-predicted concentrations obtained from the simultaneous model tend to be higher for male adolescents and lower for female adolescents than the concentrations from the separate model. From this figure it can be concluded that the two models have different predictive performances for vancomycin PK in obese adolescents, with the separate model being able to predict PK for both sexes in adolescents, whereas the simultaneous model shows bias. However, for adults, no difference between sexes is visible in Figure S5 in either of the two models, indicating that these two models have comparable abilities to predict the PK in obese adults. Interestingly, in the separate models for adolescents and adults, in addition

to $WT_{standard}$, which already includes a correction for sex (and age and length), sex was found to be an additional covariate on vancomycin CL in overweight and obese adolescents, with males having larger CL than females. This suggests that in these adolescents, besides sex-related differences in body weight, other factors that vary between sexes also impact CL. During puberty, whole kidney GFR and single nephron GFR have been reported to be higher in male rats, possibly due to higher renal plasma flow and lower vascular resistance caused by the anabolic effects of testosterone on proximal tubular cells in males [39, 40]. However, after puberty until the age of 50 years, overall sex differences in GFR are no longer evident [41, 42]. GFR changes can also account for age as an independent covariate on CL in adults, as it has been recognized that the GFR declines steadily with ageing, beginning around 30–40 years, due to reductions in the glomerular capillary plasma flow rate, and the glomerular capillary ultrafiltration coefficient [43]. In addition, other age-associated changes, such as the decreased renal blood flow in concert with the structural change in diminished kidney mass, can also decrease kidney function and thereby influence the renal CL of drugs [44]. Interestingly, the CL values of the adolescents in this study seem to be more in line with what can be expected based on extrapolations from the adult population, taking into account the relationships with both standard weight and age, although the underlying mechanisms driving the relationship of age at both ends of the age-range may be different.

Despite all individuals having normal renal function values, GFR estimates were significantly correlated with CL. However, these were not implemented in the final models, as we suspected that this finding was driven by the covariates included in the calculations of eGFR rather than by actual renal function. Moreover, the equation of CG has been reported to have a low accuracy and high bias in estimating GFR in patients with obesity [45, 46] and other equations used to derive eGFR have not been validated for the obese population [46]. As this study aimed to compare the PK between two populations, we continued by testing the single covariate instead of implementing eGFR as a composite covariate that may mask covariates that are driving the correlation. When testing GFR estimates again in the final simultaneous and final separate models, this did lead to statistically significant improvements in the model fits, but this was again driven by very few individuals. It was noted that this also leads to very different functions being estimated for the covariates that were already included in the models, further driving our suspicion that in obese patients with good renal function, the predictive value of GFR estimates to reflect kidney function is limited. Finally, the fact that serum creatinine concentration was only a significant covariate due to two individuals, confirmed the idea that the covariates in the GFR functions instead of the creatinine values itself drive the significance of the GFR functions. Future studies conducted in obese adolescents and adults with different renal functions are needed to extrapolate these models and quantify the impact of renal function on vancomycin CL.

When body weight impacts drug PK in obese individuals, it is essential to distinguish between weight resulting from the length and weight resulting from obesity [47]. Our study shows that in a population of overweight and obese individuals, vancomycin CL increases with TBW in adolescents and adults and that this increase is best correlated to standard weight rather than excess weight. Besides, this study also shows that the increase in vancomycin Vc with TBW in both populations is also mainly driven by standard weight, not excess weight, in overweight and obese adolescents. Finally, it should be noted that LBW, another covariate that can be used to describe the altered body composition and to predict the PK differences between sexes in obese individuals, was not superior to $WT_{standard\_adol/adu}$ or the combination of $WT_{standard\_adol}$ and sex ($\Delta OFV = -57.288$ [$p < 0.001$], -66.634 [$p < 0.001$] -78.416 [$p < 0.001$] respectively) in this study.

5 Conclusion

Vancomycin CL in overweight and obese adolescents is generally higher than in overweight and obese adults, with male adolescents having larger CL than female adolescents. Therefore, vancomycin CL in overweight and obese adults is not predictive of vancomycin CL, and as a result, vancomycin dose cannot be directly scaled from overweight and obese adults to overweight and obese adolescents.

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Declarations

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Conflict of interest No authors have a conflict of interest to declare.

Availability of data and material Data are available from the corresponding author upon request.

Ethics approval A waiver was obtained from the local Medical Ethical Review Committees as data collection was not within the scope of the Dutch Human Research Act and the US National Research Act.

Consent to participate Not applicable.

Consent for publication Not applicable.

Code availability The final model code will be made available in the DDMoRe model repository (http://repository.ddmore.eu/).

Author contributions Conception and design of the research: TZ, CAJK and EHJK; data collection: CS and CMTS; data analysis: TZ; interpretation of findings: TZ, CS, CMTS, CAJK, and EHJK; drafting the manuscript: TZ; critical revision of manuscript: CS, CMTS, CAJK, and EHJK. All authors provided the final manuscript approval.

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