https://doi.org/10.36290/far.2022.014

Comparison of Mw\Pharm 3.30 (DOS) and Mw\Pharm ++ (Windows) Versions of Pharmacokinetic Software for PK/PD Modelling of Vancomycin in Continuous Administration

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Objective: For a long time, the Mw\Pharm software suite (MEDI\WARE, Prague, Czech Republic/Groningen, Netherlands) has been used for PK/PD modelling in therapeutic drug monitoring (TDM). The aim of this study was to find the best model in the newer Windows version of Mw\Pharm++ 1.3.5.558 (WIN) for continuous administration of vancomycin.

Patients: Twenty adult patients with a mean age of 66 ± 12 years, body weight 85 ± 16 kg, and median dose 1,625 g/24 h were repeatedly examined for vancomycin.

Methods: Concentrations predicted by *"#vancomycin_adult_k_C2"*, *"#vancomycin_adult_C2"*, *"vancomycin_adult_C2"*, *"vancomycin_C1"* WIN models and *"vancomycin (cont.inf.) %ahz"* (DOS1) and *"vancomycin adult"* DOS models were compared with the measured values and with the DOS1 model.

Statistics: Percentage prediction error (%PE) calculated as (predicted-measured)/measured or (predicted-DOS1)/DOS1, RMSE, Bland-Altman bias, Pearson's coefficient of rank correlation (R), Student's t-test. Statistical analysis was performed using the GraphPad Prism version 5.00 for Windows.

Results: %PE values varied between –3.2 ± 33.0% and –7.4 ± 36.7%, with the exception of *"vancomycin_C1"*, the only one-compartment model, where it was –20.8 ± 39.4%. The best outcomes were achieved with *"vancomycin adult"*. The *"#vancomycin_adult_k_C2"* model produced the lowest %PE, RMSE, and Bland-Altman bias among the WIN models, but its correlation (Pearson's R) was less tight. RMSE was the same in *"vancomycin_adult_C2"* while %PE and Bland-Altman bias were similar, with slightly better correlation when compared to *"#vancomycin_adult_k_C2"*. The %PE value between the two DOS models was 4.1 ± 13.9% (NS); *"vancomycin adult"* produced slightly better outcomes than DOS1.

Conclusion: *"vancomycin_adult_C2"* and *"#vancomycin_adult_k_C2"* produced the best outcomes between WIN models. Both DOS models produced lower bias and their prediction was comparable.

Key words: PK/PD modelling, vancomycin, Mw\Pharm, therapeutic drug monitoring, continuous administration.

Porovnání Mw\Pharm 3.30 (DOS) a Mw\Pharm ++ (Windows) verze farmakokinetického softwaru pro PK/PD modelování hladin vankomycinu aplikovaného v kontinuální infuzi

Účel studie: Mw\Pharm software (MEDI\WARE, Prague, Czech Republic / Groningen, Netherlands) je dlouhodobě používán pro PK/PD modelování pro terapeutické monitorování hladin léčiv (TDM). Cílem práce bylo najít nejvhodnější model pro kontinuální aplikaci vankomycinu v novější Windows verzi Mw\Pharm++ 1.3.5.558 (WIN).

Pacienti: 20 dospělých pacientů (průměrný věk 66 ± 12 let, hmotnost 85 ± 16 kg), bylo opakovaně vyšetřeno na hladinu vankomycinu. Medián dávky byl 1 625 g/24 h. Koncentrace vankomycinu predikované pomocí WIN modelů *„#vancomycin_adult_k_C2"*, *„#vancomycin_adult_C2"*, *„vancomycin_adult_C2"*, *„vancomycin_C1"* a DOS modelů *„vancomycin (cont.inf.) %ahz"* (DOS1) a *„vancomycin adult"* byly porovnány s naměřenou hodnotou a DOS1 modelem.

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Cit. zkr: Klin Farmakol Farm 2022;36(3):85-92
Článek přijat redakcí: 13. 5. 2022
Článek přijat k publikaci: 15. 7. 2022

Statistika: Průměrná procentuální chyba predikce (% PE) vypočtená jako (predikovaná – změřená)/změřená, příp. (predikovaná-DOS1)/DOS1, RMSE, Bland-Altmanova bias, Pearsonův korelační koeficient (R), Studentův t-test. Statistická analýza byla provedena pomocí GraphPad Prism version 5.00 pro Windows.

Výsledky: % PE se pohybovala mezi –3,2 ± 33,0 % a –7,4 ± 36,7 %, s výjimkou jednokompartmentového modelu *„vancomycin_C1"*, kde byla –20,8 ± 39,4 %. Nejlepší výsledky byly dosaženy modelem *„vancomycin adult"*. Model *„#vancomycin_adult_k_C2"* produkoval nejnižší % PE, RMSE and Bland-Altman bias mezi WIN modely, ale korelace byla slabší. Korelace byla mírně lepší u modelu *„vancomycin_adult_C2"* RMSE byl stejný, % PE a Bland-Altmanova bias byly obdobné jako u modelu *„#vancomycin_adult_k_C2"*. % PE mezi oběma DOS modely byla 4,1 ± 13,9 % (NS); *„vancomycin adult"* měl mírně lepší výsledky než DOS1.

Závěr: Z WIN modelů byly nejlepší výsledky dosaženy modely *„vancomycin_adult_C2"* a *„#vancomycin_adult_k_C2"*. Oba DOS modely produkovaly nízkou bias a jejich predikce byly srovnatelné.

Klíčová slova: PK/PD modelování, vankomycin, Mw\Pharm, terapeutické monitorování léků, kontinuální infuze.

Introduction

Vancomycin is a glycopeptide antibiotic used for the treatment of severe infection, with its use being limited by its nephrotoxicity and ototoxicity. Vancomycin nephrotoxicity can be avoided by therapeutic drug monitoring (TDM) (1–4). Vancomycin pharmacodynamics is time-dependent, which means that the clinical outcome is not dependent on the maximum concentration (C_{max}), but on the time above the minimum inhibitory concentration (MIC). The clinical effect can be better described by the area-under-the-concentration-curve (AUC) where 400–600 mg/L are required (3). As high C_{max} is not necessary, continuous administration could be more suitable than intermittent dosage. This method of administration allows to aim for a higher therapeutic range of 15–20 mg/L, compared to 10–20 mg/L when intermittent dosage is used. The target range can be increased to 20–25 mg/L in severe infection, especially at the beginning of treatment, with lower incidence of nephrotoxicity (5). The desired AUC can be obtained by multiplying the concentration with a factor of 24 (3). Even though the plateau concentration at steady state is in fact a straight line, in 1997 there were only two computer programs that were able to handle continuous vancomycin administration (6).

In our area, the treating doctor, with input from an antibiotic centre, chooses the vancomycin initial dose. Vancomycin plasma concentration measurement is recommended on the second or third day of treatment. Vancomycin dosage is then optimised using Bayesian modelling, with the aid of the Mw\Pharm 3 : 30 software (DOS) (7). A Windows version, with a broader spectrum of models, has been available since 2014 as a response to declining support of the DOS operating system on the later versions of Windows. After its release, the company had decided to discontinue the development of the DOS version. As the estimates produced by the available WIN models are not based on our population, and they differ from DOS, an assessment of WIN models prediction quality for extrapolation was necessary. Several models are available for vancomycin prediction in both DOS and WIN versions.

The aim of the study was to find the best model for vancomycin in both WIN and DOS versions of the Mw\Pharm software.

Methods

Patients

Request forms for routine TDM of vancomycin were used as data sources. Twenty adult patients repeatedly examined for vancomycin concentrations during 2016–2019 were included in the study. The exclusion criteria were fewer than two examinations and intermittent dialysis. The cohort characteristic is given in Table 1. The initial dose was estimated by the treating doctor. The median dose was 1,625 mg/24 hr (min 250 mg, max 5,000 mg), and the dose/kg was 19.6 mg/kg (min 0.25 mg/kg, max 58.8 mg/kg). A loading dose of 500–1,000 mg was given to seven patients – to six of them at the commencement of therapy and one patient (No. 20) received a bolus of 1,000 mg on day four (Add Fig. 1, Add Fig. 2). Six samples from four patients were taken by temporary interruption of administration due to high levels.

Tab. 1. *Patient characteristics*

	mean ± SD
Age (yrs)	66 ± 12
Gender (male/female)	13/7
Weight (kg)	85 ± 16
Height (cm)	170.0 ± 10.8
Serum creatinine (μmol/L)	112 ± 70
Site of infection	
lung	14
blood	19

The Ethics Committee of University Hospital Ostrava approved the study and all protocols on Feb 21st 2019. Reference number 163/2019.

Vancomycin analysis

Vancomycin serum concentration was analysed by LC-MS/MS (8). Commercial quality controls (Roche Diagnostics, Germany) at three levels (low, middle, and high) were measured every day, together with the batch of patients' samples, and their concentrations were in the declared range.

Pharmacokinetics analysis

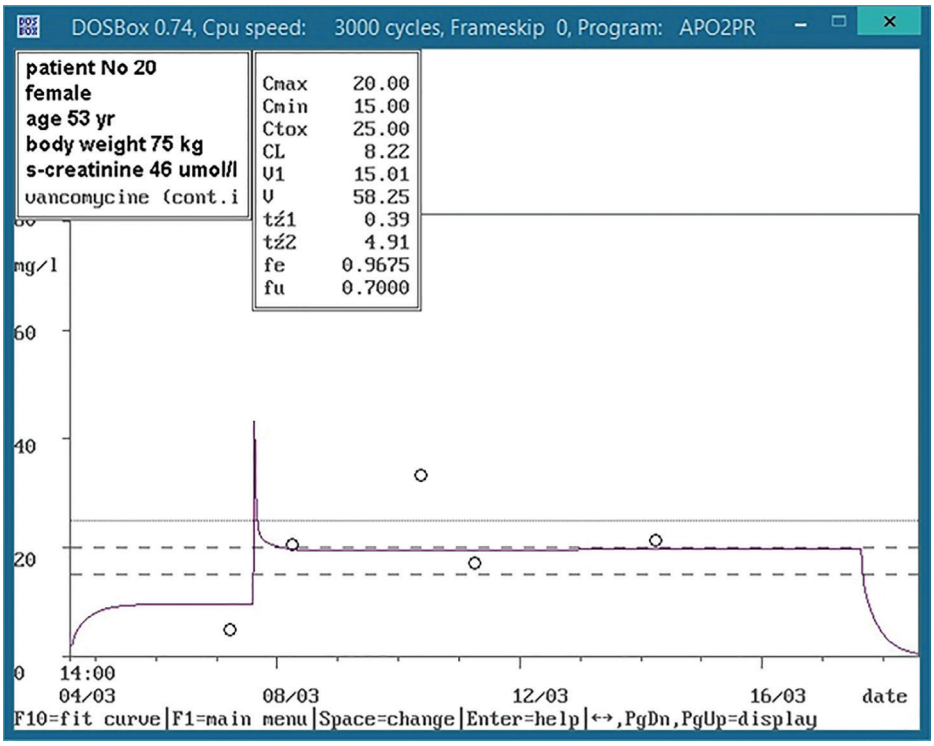
Pharmacokinetics analysis was performed by using two versions of the Mw\Pharm software (MEDI\WARE, Prague, Czech Republic/Groningen, Netherlands): Mw\Pharm 3 : 30 (1997) (DOS) and Mw\Pharm++ 1.3.5.558 (2016) (Windows).

The clearance (CL) of vancomycin was calculated by Formula 1.

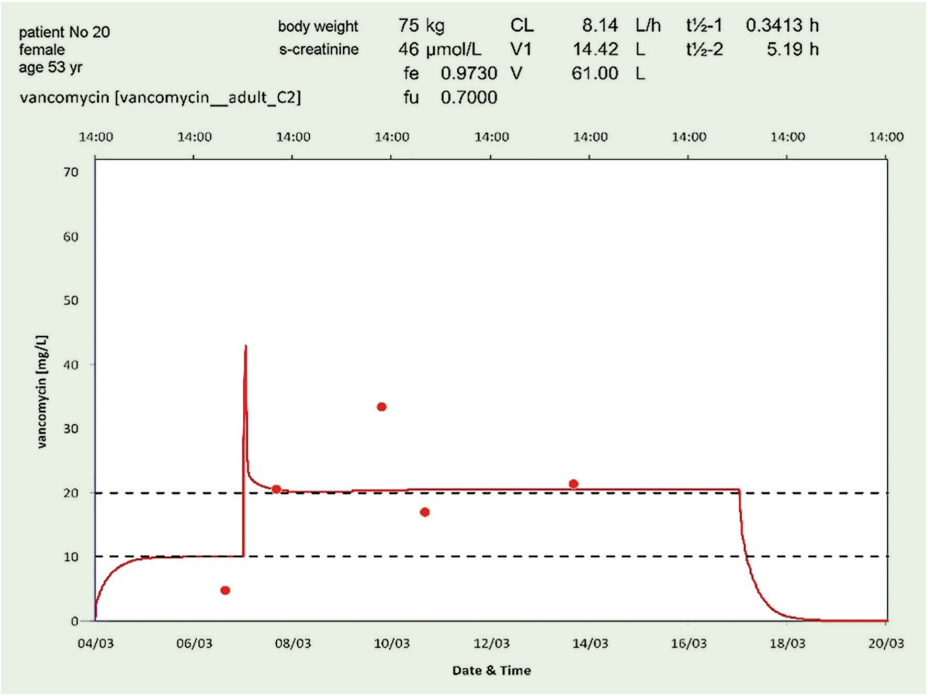
$$CL = CLm * \frac{BSA}{1.85} + fr * CLcr$$

CL – represents total clearance, CLm – non-renal clearance, BSA – body surface area, fr – renal fraction, CLcr – creatinine clearance

Add Fig. 1. *Graphical output of DOS1 model*



Add Fig. 2. *Graphical output of WIN3 model*



The formula is based on the assumptions that CL is related to the CLcr and CLm is linearly related to BSA. CLcr is calculated by Jelliffe II equation (9). BSA is calculated according to Du Bois and Du Bois (10). The *"#vancomycin_adult_k_C2"* model (WIN1) uses renal (kelr) and metabolic (kelm) elimination rate constants instead of fr or Clm, respectively. The parameters were converted by Formula 2 and Formula 3, respectively,

$$fr = kelr * V1 * LBMc * \frac{1000}{60} * \frac{1.73}{BSA} \quad (2)$$

$$Clm = kelm * V1 * LBMc * \frac{1.85}{BSA} \quad (3)$$

V1 represents the volume of distribution and LBMc is lean body mass corrected for fat distribution calculated according to Chennavasin (11). The population-based parameters of all the models are given in Table 2. The Marquardt algorithm was used for extrapolation.

Examples for graphical output of DOS1 and WIN3 models are shown in Add Fig. 1 and Add Fig. 2, respectively.

Model evaluation

Concentrations predicted by the *"vancomycin (cont.inf.) %ahz"* (DOS1) and *"vancomycin adult"* (DOS2) DOS models and by the *"#vancomycin_adult_k_C2"* (WIN1), *"#vancomycin_adult_C2"* (WIN2), *"vancomycin_adult_C2"* (WIN3), and *"vancomycin_C1"* (WIN4) Windows models were compared with the measured concentration and the concentration predicted by the DOS1 model. All models were two-compartmental, with the exception of WIN4 which is one-compartmental. Predictions by all models were evaluated retrospectively. Percentage prediction error (%PE), RMSE, and Bland-Altman plot were used for prediction precision evaluation. %PE was calculated as the difference between the predicted and the measured value (Formula 4), or as the difference between models (Formula 5). RMSE was calculated according to Formula 6.

$$\%PE = \frac{predicted - measured}{measured} \quad (4)$$

$$\%PE = \frac{predicted\ (WIN) - predicted\ (DOS1)}{predicted\ (DOS1)} \quad (5)$$

$$RMSE = \sqrt{\frac{1}{N} \times \Sigma(\%PE)^2} \quad (6)$$

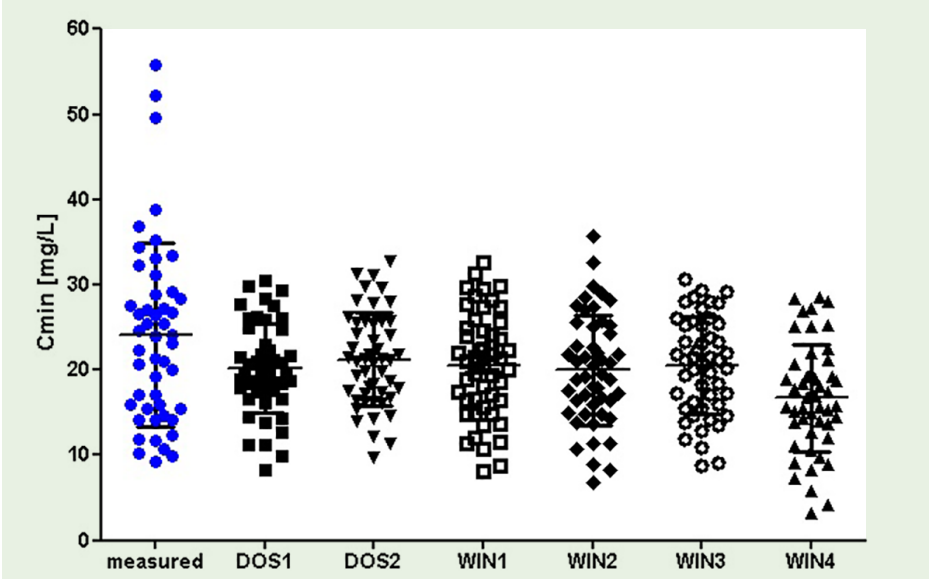
All values are presented as mean ± standard deviation (SD). Due to normal distribution of values, statistical analysis was performed by using paired Student's t-test. The Prism 5.0 software by GraphPad Software was used for statistical analysis (Pearson's R, Student's t-test, Bland-Altman plot).

Results

Best model selection

Vancomycin concentrations predicted by all models are shown in Fig. 1. Mean concentrations predicted by the models were significantly lower than the measured concentrations (Table 3). Mean values of %PE varied from –3.2 in DOS2 to –20.8% in WIN4.

Fig. 1. *Vancomycin concentration measured and predicted by models*



Tab. 2. *Pharmacokinetic parameters of vancomycin. k_{12}, k_{21} – rate constants, k_{elm} – elimination rate constant non-renal, k_{elr} – elimination rate constant renal, V1 – volume of distribution related to lean body mass, fr – renal fraction. Individualized data presented as mean ± standard deviation. ‡ P < 0.0001, ‖ P < 0.01, § P < 0.05 compared to population data; † P < 0.0001, * P < 0.05 compared to DOS1*

	V1	k_{12}	k_{21}	k_{elr}	fr	Cl_m	k_{elm}
population							
DOS1	0.17	0.92	0.46	0.0037			
DOS2	0.21	1.12	0.48		0.75	0.21	
WIN1	0.21	1.12	0.48	0.00327			0.0143
WIN2	0.21				0.75	0.21	
WIN3	0.21	1.12	0.48		0.75	0.21	
WIN4	0.39				0.79		
fitted							
DOS1	0.20 ± 0.03‡	0.99 ± 0.08‡	0.39 ± 0.14‖	0.004 ± 0.0007			
DOS2	0.31 ± 0.40	1.18 ± 0.17§,†	0.40 ± 0.11‡		0.84 ± 0.31		
WIN1	0.24 ± 0.03‡,†	1.27 ± 0.22‡,†	0.43 ± 0.06*,†	0.004 ± 0.001‖			
WIN2	0.22 ± 0.02‡,†				0.69 ± 0.47		
WIN3	0.23 ± 0.03‡,†	1.25 ± 0.18‡,†	0.44 ± 0.06‖,†		0.85 ± 0.33*		
WIN4	0.46 ± 0.20‡,*				0.72 ± 0.40		

Tab. 3. *Vancomycin serum levels (VCM), % prediction error (%PE), RMSE, Bland-Altman bias – comparison to measured values. Data presented as mean ± SD. ‡P < 0.0001, **P < 0.005, *P < 0.05 compared to measured; †P < 0.0001 compared to DOS1*

	VCM concentration [mg/L]	%PE [%]	RMSE [%]	Bland-Altman bias ± SD (95% limits of agreement)
measured	24.1 ± 10.8			
DOS1	20.2 ± 5.3**	–5.7 ± 34.5	35	3.96 ± 9.15 (–14.0–21.9)
DOS2	21.2 ± 5.5*	–3.2 ± 33.0	33	3.29 ± 8.74 (–13,8–20.4)
WIN1	20.6 ± 6.2*	–4.4 ± 36.4	36	3.55 ± 9.17 (–15.0–22.1)
WIN2	20.0 ± 6.4**	–7.4 ± 36.7	37	4.09 ± 9.10 (–13.7–21.9)
WIN3	20.5 ± 5.7*	–4.5 ± 36.2	36	3.64 ± 9.22 (–14.4–21.7)
WIN4	16.7 ± 6.3‡†	–20.8 ± 39.4†	44	7.41 ± 11.44 (–15.0–29.8)

Tab. 4. *Vancomycin serum levels (VCM), % prediction error (%PE), RMSE, Bland-Altman bias – comparison to DOS1 model. Data presented as mean ± SD*

	%PE [%]	RMSE [%]	Bland-Altman bias ± SD (95% limits of agreement)
DOS2	4.1 ± 13.9	14	–0.66 ± 2.48 (–5.5–4.2)
WIN	–16.8 ± 24.9	30	3.44 ± 5.06 (–6.5–13.4)
WIN1	1.7 ± 15.2	15	–0.42 ± 2.75 (–5.8–5.0)
WIN2	–1.4 ± 15.8	16	0.13 ± 3.03 (–5.8–6.1)
WIN3	1.7 ± 12.7	13	–0.33 ± 2.31 (–4.8–4.2)

The best outcomes in terms of %PE, RMSE, Bland-Altman bias as well as Pearson's R were obtained with the DOS2 model. WIN1 produced the lowest %PE and Bland-Altman bias (Table 3, Fig. 2) among the WIN models, but the correlation (Pearson's R) between the predicted and measured vancomycin values was less tight (Fig. 3). RMSE was the same while %PE and Bland-Altman bias were almost the same in the WIN3 model, with a slightly better correlation than the WIN1 model.

Comparison of pharmacokinetics parameters

The DOS2 and WIN1–3 models use the same population-based pharmacokinetics parameters (Table 2). The DOS1 model uses lower V1 and both rate constants, whereas the one-compartment WIN4 model uses higher V1 and renal fraction.

When compared to population-based data, all two-compartment models used higher V1, rate constant k_{12}, and fr, with the exception of fr in WIN2, while k_{21} was slightly lower. WIN4 used higher V1 and lower fr. WIN1–3 models used slightly higher V1 than DOS1, 0.22–0.24 vs. 0.20 L/kg LBMc, P < 0.0001. k_{12} was higher in WIN1 and WIN3 –1.27 and 1.25, respectively vs. 0.99, P < 0.0001. DOS2 used higher V1 and k_{12}, whereas its k_{21} was similar to DOS1 (Table 2).

Comparison to DOS1 model

All three two-compartment WIN models (WIN1-WIN3) produced similar %PE and RMSE when compared with the DOS1 model (Table 4). %PE and Bland-Altman bias were the lowest in the WIN2 model, whereas RMSE was the lowest and Pearson's R was the highest in the WIN3 model. %PE, Bland-Altman bias, and Pearson's R were higher, but RMSE was similar in the DOS2 model, compared to the WIN models. The one-compartment WIN4 model differed most from the DOS2 model. Bland-Altman plots for all model comparisons are shown in Fig. 4.

The Pearson's R between vancomycin concentrations predicted by the WIN and DOS models varied from 0.631 to 0.941, P < 0.0001 (Fig. 5).

The Pearson's R between %PE produced by DOS1 and those produced by other models varied from 0.830 to 0.930 (Fig. 6), P < 0.0001.

Fig. 2. *Bland-Altman analysis of measured and predicted vancomycin concentrations by (A) WIN1, (B) WIN2, (C) WIN3, (D) WIN4, (E) DOS1. (F) DOS2*

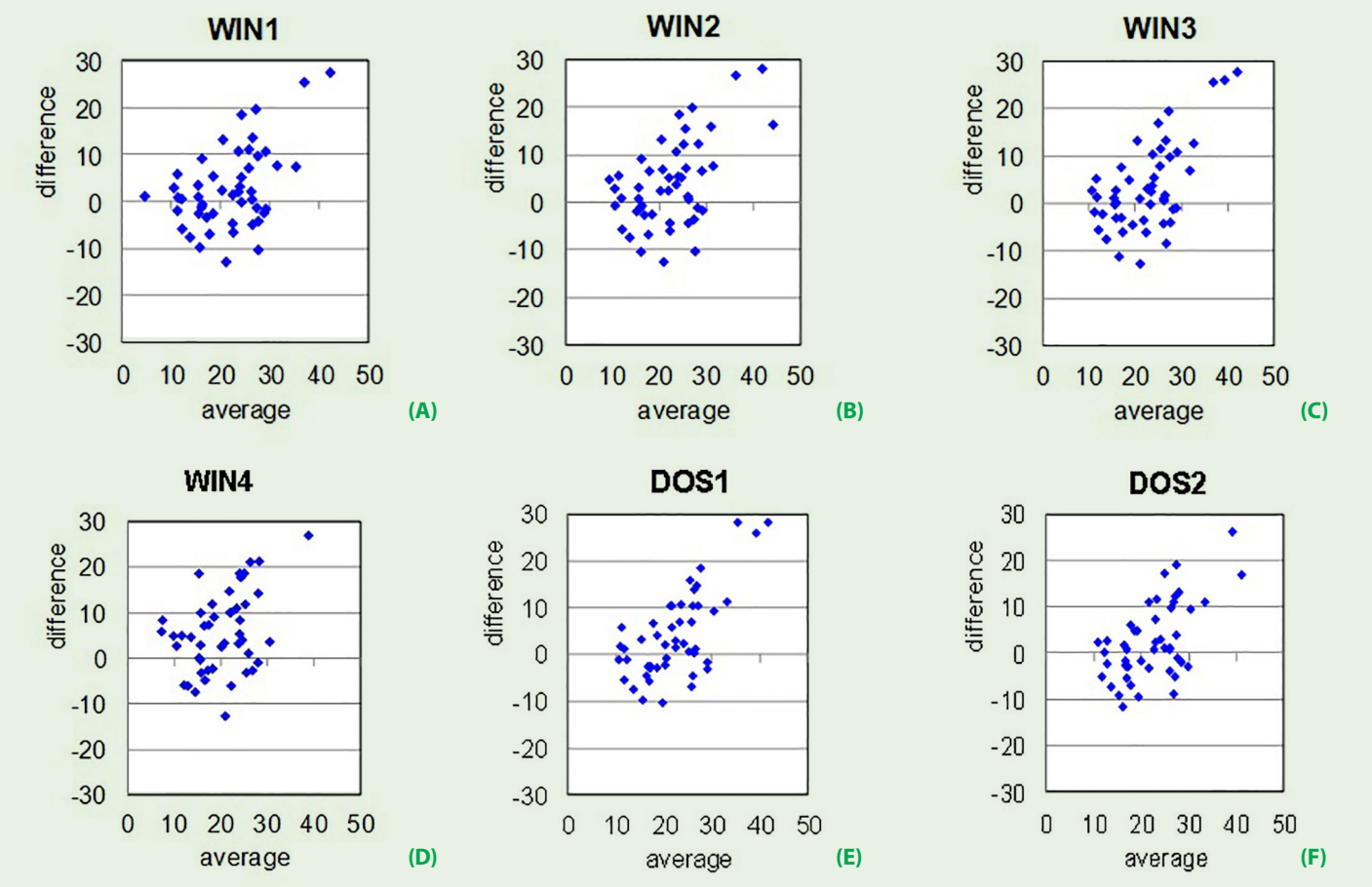


Fig. 3. *Comparison of vancomycin concentrations predicted by DOS1 and predicted by (A) WIN1 model, (B) WIN2 model, (C) WIN3 model, (D) WIN4 model, (E) DOS1 model. The full line represents linear regression, while the dashed line is the line of identity (y = x). R = Pearson's R*

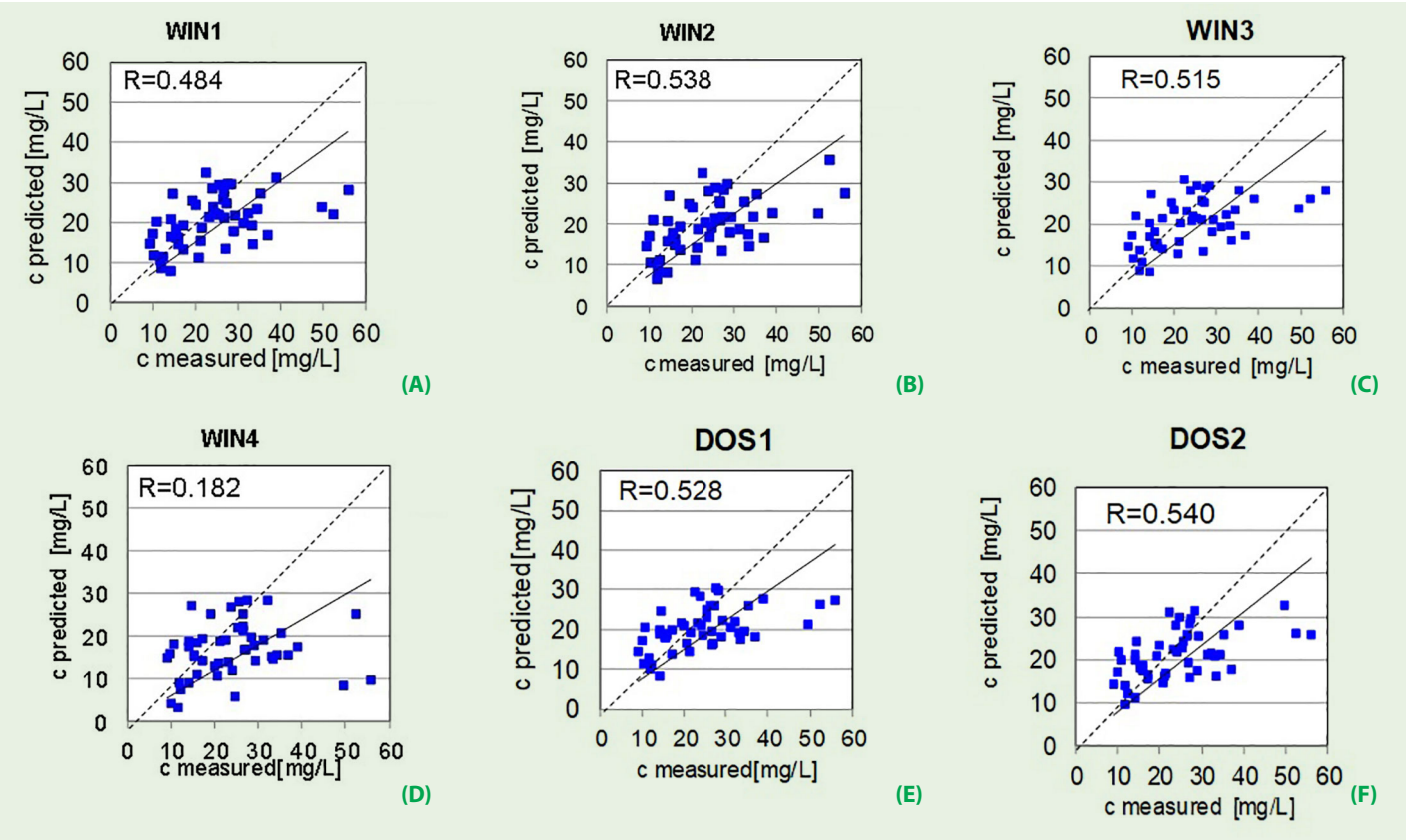


Fig. 4. *Bland-Altman analysis of predicted vancomycin concentrations by (A) WIN1 and DOS1, (B) WIN2 and DOS1, (C) WIN3 and DOS1, (D) WIN and DOS1, (E) DOS1 and DOS2*

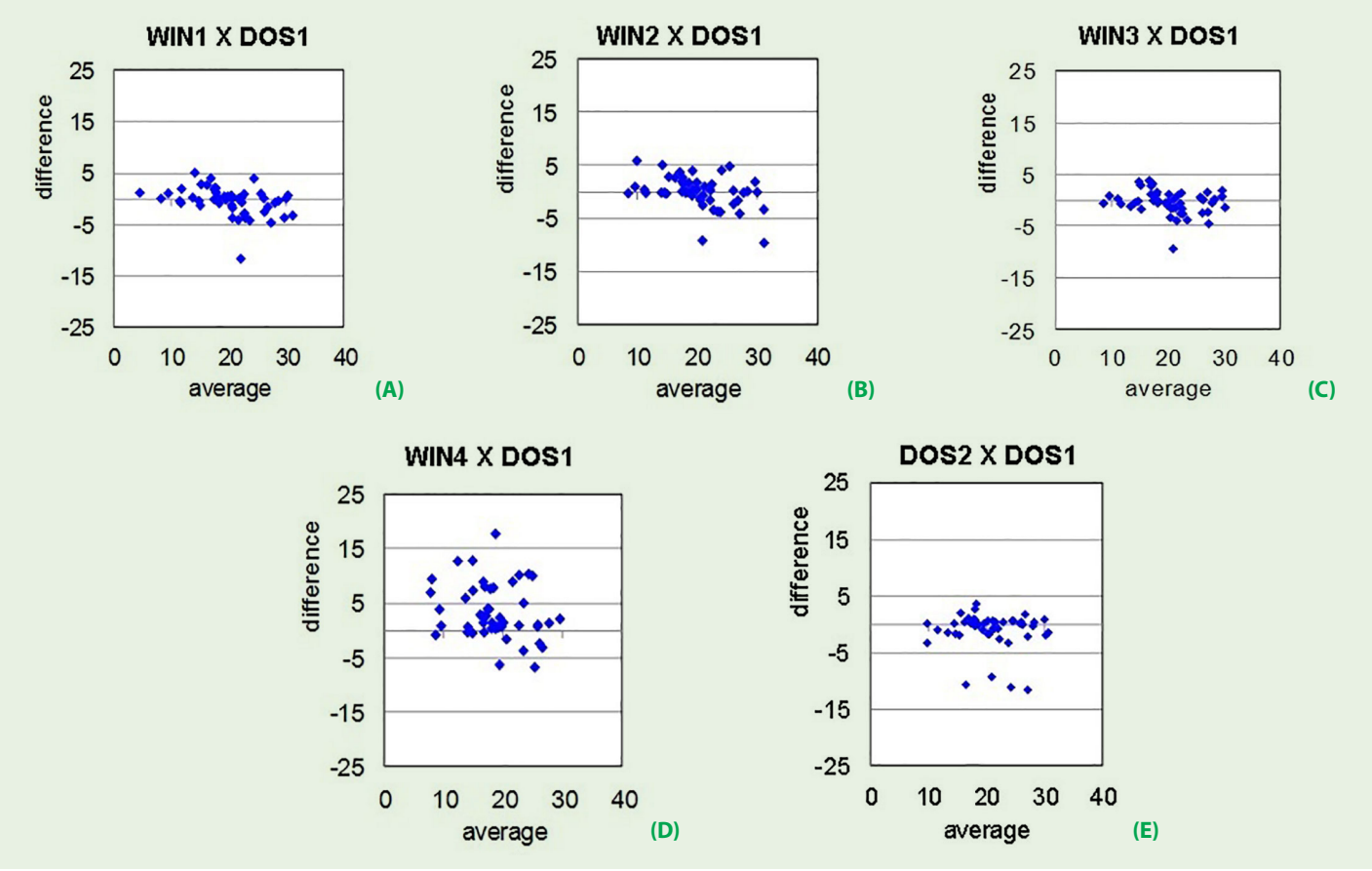
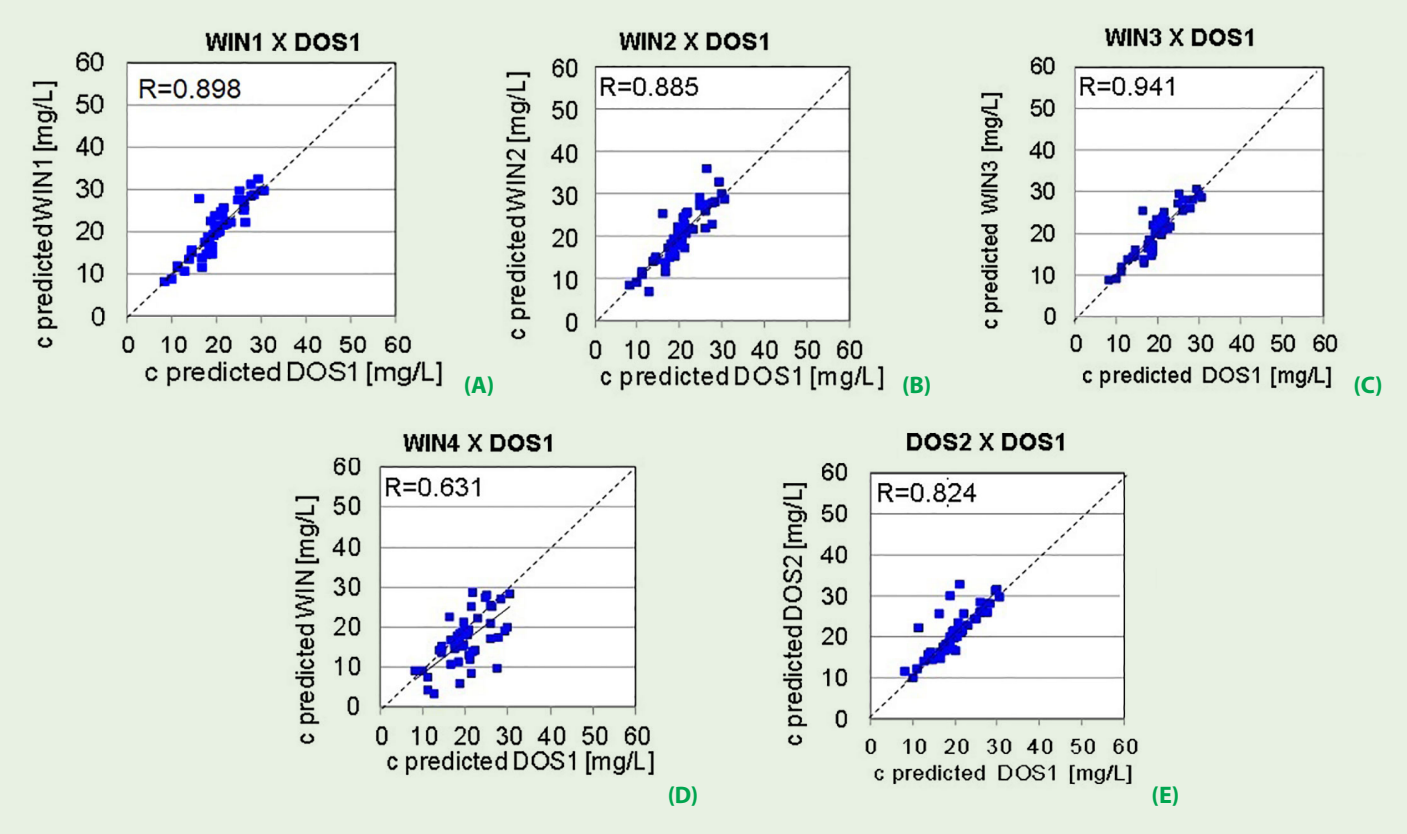


Fig. 5. *Comparison of vancomycin concentrations (A) WIN1 model, (B) WIN2 model, (C) WIN3 model, (D) WIN4 model, (E) DOS1 model. The full line represents linear regression, while the dashed line is the line of identity (y = x). R = Pearson's R, P < 0.0001*



Linear regressions were near ideal, with the exception of the one-compartment WIN4 model.

Discussion

Continuous administration

The advantage of continuous administration of vancomycin is a lower risk of nephrotoxicity, despite aiming for a higher therapeutic range. As described by Flannery et al.'s (5) meta-analysis of critically ill patients, the odds of acute kidney injury declined by 50% compared to intermittent administration. However, continuous administration of vancomycin is rarely used in our area, and if so, only in intensive care units (ICU), as it is preferable to use a central line due to possible endothelial cell toxicity (5). The disadvantages are: one intravenous access is permanently occupied, the patient's movement is restricted, and, from the clinical point of view, in the case of underdosing the plasma levels remain insufficient for the entire duration of the dosing interval.

Model selection

The Mw\Pharm DOS version offers two models for continuous vancomycin administration, while the Windows version offers several models for the prediction of vancomycin kinetics. With paediatric models excluded, four WIN models remained available for the prediction of continuous vancomycin administration in adults. According to the MW\Pharm manual (12) and manufacturer personal information (13), the source of population-based data for the DOS2 and WIN models was a study performed by Rodvold et al. (14). Patients in the reference group, compared to our patient group, were younger (55 ± 16 yrs vs. 66 ± 12 yrs), their body weight was slightly higher (88 ± 21 kg vs. 85 ± 16 kg), and had lower renal function (serum creatinine 1.4 ± 0.8 mg/dL, i.e. 123.8 µmol/L ± 70.7 µmol/L vs. 112 ± 70 µmol/L).

Because of the high correlation between fluorescence polarization immunoassay (FPIA) and LC-MS/MS analytical techniques, where linear regression models are near ideal (8), the choice of analytical method for model estimation (i.e. FPIA) is not expected to have been responsible for any significant differences in model outcomes.

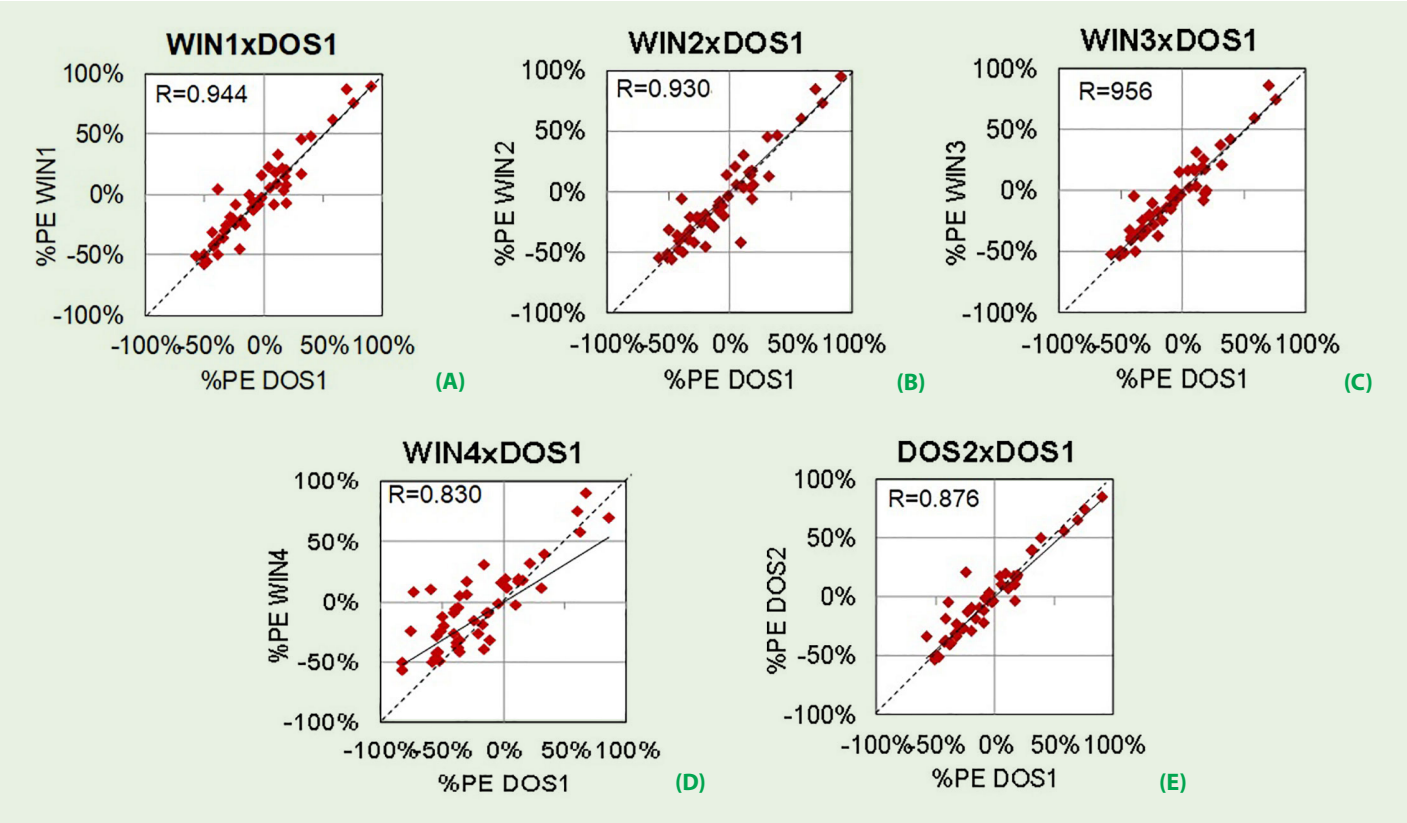
As models are usually based on a different reference population than the population that is being examined, their potential differences must be considered to avoid inaccurate prediction and insufficient therapy.

Four WIN models and two DOS models for prediction of vancomycin concentration during continuous administration were compared with the values measured. The results presented show that vancomycin concentrations predicted by all models were statistically different from the values measured. %PE in two-compartment models (DOS1, DOS2, WIN1-WIN3) varied from –7.4 to –3.2%, which could be considered as clinically insignificant. The %PE values produced by DOS1 and by other models were in high correlation with linear regression line (near ideal). This means that the large bias produced by unexpected outlier values was caused either by sampling error or unstable condition of a critically ill patient, something not possible to be predicted by any model, as seen in Add Fig. 1 and Add Fig. 2.

Even though only an error of 8% for the one-compartment model has been described in the literature (15), the WIN4 one-compartment model produced a %PE of –21%, which makes it unsuitable for TDM of vancomycin under continuous administration.

As a different (higher) therapeutic range is used for continuous administration, it might

Fig. 6. *Comparison of %PE produced by (A) WIN1 and DOS1 model, (B) WIN2 and DOS1 model, (C) WIN3 and DOS1 model, (D) WIN4 and DOS1, (E) DOS1 and DOS2. The full line represents linear regression, while the dashed line is the line of identity (y = x). R = Pearson's R, P < 0.0001*



be useful to use one model for intermittent and another for continuous administration, with respective therapeutic ranges saved into each model, preferably WIN3 / DOS2 and WIN1/DOS1, respectively (16).

We did not identify any papers in the literature (PubMed) testing the predictive performance of the Mw\Pharm models. Fuchs et al. (6) compared 12 programs for TDM in 2013. All programs were scored against pharmacokinetic relevance, user-friendliness, computing aspects, interfacing, and storage. Mw\Pharm and TCIWorks scored the highest. Altogether, five programs were able to handle data for continuous administration, irregular regimens, and changes in the drug kinetics due to changes in renal function or interruption of drug treatment (Mw\Pharm, TCIWorks, MM-USC*PACK©, Kinetidex®, and T.D.M.S. 2000TM).

Avent et al. (17) compared seven Bayesian dosing programs for antimicrobial therapy, including Mw\Pharm, that were available in 2019. All of those programs allow an a-priori regimen, the first dose handled, and a non-steady-state situation. The programs were not assessed for continuous administration. All programs allow the flexibility to choose appropriate target parameters to tailor the recommendations to a given patient. However, they require skilled personnel with an understanding of pharmacokinetics and pharmacodynamics to use and interpret the information.

Conclusion

The Windows models *"#vancomycin_adult_k_C2"*, *"#vancomycin_adult_C2"*, *"vancomycin_adult_C2"*, *"vancomycin_C1"* and DOS models *"vancomycin (cont.inf.) %ahz"* and *"vancomycin adult"* in the Mw\Pharm software versions ++1.3.5.558 (Windows) and 3 : 30 (DOS) were compared. Both DOS models produced comparable results. The best results among the WIN models were achieved by using the *"vancomycin_adult_C2"* (WIN3) and *"#vancomycin_adult_k_C2"* (WIN1) models. As the predictions made by the DOS models produced lower bias, we recommend the addition of the DOS vancomycin models into the WIN software version.

Limitations

The models are used to assess extrapolations and the conclusions are also limited to the accuracy of these particular extrapolations, not to the accuracy of the models in general. For optimal pharmacokinetic modelling in the Mw\Pharm, all users need to assess the extrapolations for their patients.

Acknowledgement

Supported by the grant of University of Ostrava SGS08/LF2019–2020.

REFERENCES

1. He N, Su S, Yan Y et al. The benefit of individualized vancomycin dosing via pharmacokinetic tools: a systematic review and meta-analysis. Ann Pharmacother. 2020;54:331-343.
2. Rybak MJ. The pharmacokinetic and pharmacodynamic properties of vancomycin. Clin Inf Dis. 2006;42:S35-S39.
3. Rybak MJ, Le J, Lodise T et al. Executive summary: therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: A revised consensus guideline and review of the American Society of Health-system Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. Pharmacotherapy 2020;40:363-367.
4. Abdul-Aziz MH, Alffenaar JVC, Bassetti M et al. Antimicrobial therapeutic drug monitoring in critically ill adult patiens: a position paper. Intensive Care Med. 2020;46:1127-1153.
5. Flannery AH, Bissell BD et al. Continuous versus intermittent infusion of vancomycin and the risk of acute kidney injury in critically ill adults: a systematic review and meta-analysis. Crit Care Med. 2020;48:912-918.
6. Fuchs A, Csajka C, Thoma Y et al. Benchmarking therapeutic drug monitoring software: a review of available computer tools, Clin Pharmacokinet. 2013;52:9-22.
7. Mw\Pharm 3:30 a MediWare Product in cooperation with: University Center for Pharmacy, Dept of Pharmackokinetics and Drug Delivery, University of Groningen, The Netherlands. Supervision DKF Meier, JH Proost. Copyright 1987-1999 MediWare.
8. Brozmanova H, Kacirova I, Urinovska R et al. New liquid chromatography-tandem mass spectrometry methods for routine TDM of vancomycin in patients with both normal and impaired renal functions and comparison with results of polarization fluoroimmunoassay in light of varying creatinine concentrations. Clin Chim Acta 2017;469:136-143.
9. Jelliffe RW, Jelliffe SM. A computer program for estimation of creatinine clearance from unstable serum creatinine levels, age, sex, and weight. Math. Biosc.1972;14:17-24.
10. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. Arch Intern Med. 1916;17:863-871.
11. Chennavasin P, Brater DC. Aminoglycoside dosage adjustment in renal failure: a hand-held calculator program. Eur J Clin Pharmacol. 1982;22:91-94.
12. MW\Pharm Manual version 3.15, 1995.
13. https://tdm-monografie.org/monografie/vancomycine [in Dutch], assessed Jan 3rd, 2022.
14. Rodvold KA, Pryka RD, Garrison M, et al. Evaluation of a two-compartment Bayesian forecasting program for predicting vancomycin concentrations Ther Drug Monit. 1989;11:269-275.
15. Shingde RV, Graham GG, Reuter SE et al. Comparison of the area under the curve for vancomycin estimated using compartmental and noncompartmental methods in adult patients with normal renal fiction. Ther. Drug. Monit. 2019;41:726-731.
16. Schön K, Koristkova B, Kacirova I et al. Comparison of Mw\Pharm 3.30 and Mw\Pharm ++ a Windows version of pharmacokinetic software for PK/PD monitoring of vancomycin. Part 1 – a posteriori modelling. Comput Methods Programs Biomed 2021. Comput Methods Programs Biomed 2022;214, https://doi.org/10.1016/j.cmpb.2021.106552.
17. Avent ML, Rogers BA. Optimising antimicrobial therapy through the use of Bayesian dosing programs. Int J Clin Pharm 2019;41:1121-1130.