**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*