THERAPEUTIC MONITORING OF VANCOMYCIN IN CLINICAL PRACTICE

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Introduction and objective: Routine therapeutic drug monitoring (TDM) of vancomycin is recommended in clinical practice for dose and drug exposure optimisation. Recent guidelines on vancomycin TDM recommend monitoring of through concentrations only with somewhat higher target ranges. The aim of the study was to evaluate the practice of vancomycin TDM in the University Hospital Olomouc and to assess the potential effect of new recommendations on dosing strategies.
Methods: A retrospective analysis of vancomycin plasma levels determined during a two-year period was performed. Values with uncertain sample timing and patients on haemodialysis were excluded. The values were assessed according to both the older and the new guidelines. Consecutively, pharmacokinetic modelling was performed for every patient to estimate individual pharmacokinetic-pharmacodynamic indices.
Results: A total of 468 vancomycin concentrations were included which represented 260 individual monitoring events performed in 131 patients. Vancomycin was most commonly prescribed for suspected or proven sepsis (49.6 % of all patients). Pathogens with MIC > 1 mg/L were responsible for 18.5 % of all infections. Clinical pharmacologist trained in TDM was consulted in 18.1 % of all events. According to the new guidelines, patients were underdosed in 38.5 % of the events, and overdosed in 39.2 %. Pharmacokinetic simulations showed suboptimal dosing in 28.1 % of the events, and too high dosing in 36.9 % of the events.
Conclusion: Dosage adjustments based only upon pre-dose concentrations may be inappropriate, especially if the value is interpreted by a person with lack of experience in the field of TDM.

Key words: pharmacokinetics, pharmacodynamics, vancomycin, dosing, trough.

Introduction

Vancomycin is a glycopeptide bactericidal antibiotic with high efficiency against Gram-positive aerobic cocci (*Staphylococci*, *Streptococci*, or *Enterococci*) and rods (for example *Corynebacteria* or *Clostridia*) and some Gram-positive anaerobic microorganisms. It is the most commonly used antibiotic in the treatment of infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), which include sepsis, infective endocarditis, nosocomial pneumonia, skin and soft tissue infections, or osteomyelitis. Although it has been replaced by less toxic agents in many indications during recent years, vancomycin remains the drug of choice when these antibiotics may not be used due to allergies or pathogen resistance, and thus is highly valuable in empiric therapy of Gram-positive infections, in nosocomial urinary tract infections, and in some other indications (1).

Vancomycin has very limited absorption when administered orally, it needs to be administered intravenously for systemic therapy. To reduce the risk of *red man syndrome*, the duration of the infusion should be at least 1 to 2 hours, especially with higher doses. Oral vancomycin is recommended for treatment of enteric *Clostridium difficile* infection or staphylococcal enterocolitis (1).

From the pharmacokinetic-pharmacodynamic (PK/PD) perspective, the efficacy of vancomycin is time, or more precisely exposure, dependent. The ratio of the area under the concentration versus time curve (AUC) to the minimum inhibitory concentration (MIC) of the causative pathogen is the PK/PD parameter that best correlates with its efficacy. A value of $AUC/MIC_{0-24} \geq 400$ was proposed as the target since it was associated with better clinical and microbiological outcome (2).

Therapeutic drug monitoring (TDM) may help to optimise dosing of drugs and thus improve their efficacy, minimise the risk of toxicity, and reduce healthcare costs. Additionally, therapeutic monitoring of antibiotics may potentially reduce the emergence of bacterial resistance (3). Routine TDM of vancomycin has been shown to be cost-effective (4) and is thus

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recommended (5). Dosing adjustment according to the proposed target PK/PD index is complicated in clinical practice, since calculation of the AUC_{0-24}/MIC index is not trivial.

It has been therefore suggested to adjust vancomycin dosing based on the concentrations measured just prior to the next dose (trough concentration, C_{min}) and after administration of the infusion (peak concentration, C_{max}) since these values can serve as an acceptable surrogate of AUC_{0-24} (2).

In 2009, a joint initiative of the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists published consensus guidelines on the TDM of vancomycin in adults (the new guidelines). The aim of these recommendations was to standardise the use of vancomycin and its monitoring with respect to increasing resistance of pathogens, particularly of *Staphylococcus aureus* strains. In the new guidelines, the experts stated number of proposals related to the timing of sampling, frequency of monitoring, dosing regimens, identification of patients in whom monitoring is not necessary, and finally the issue of the therapeutic range (6).

The fundamental innovation that was suggested by the guideline committee and which later raised certain objections (7–9) was the recommendation of measuring only C_{min}, which according to the authors is the most accurate and practical method of monitoring efficacy. According to the guidelines, measurement of C_{max} should be abandoned as data confirming a correlation between C_{max} and efficiency or toxicity are lacking (6). Target C_{min} values proposed by the authors were 15–20 mg/L in case of invasive infections and/or when less susceptible pathogens with MIC > 1 mg/L are involved, otherwise it is recommended as 10–15 mg/L.

The aim of our study was to describe the actual practice of vancomycin therapeutic monitoring in the University Hospital Olomouc (FNOL) and to assess the potential impact of the new guidelines on the dosing strategies.

Materials and methods

A retrospective analysis of all vancomycin plasma levels determined during a 2-year period (January 2013 – December 2014) in patients treated with intravenous vancomycin in University Hospital Olomouc was performed. Values with uncertain sample timing with respect to the time of administration were excluded and so were haemodialysed patients treated either with intermittent or continuous methods and patients in whom demographic and clinical data were not available.

A chemiluminescent immunoassay method based on magnetic microparticles (Architect i1000 Analyzer, Abbott) was utilised to determine vancomycin concentration. Vancomycin concentrations are routinely measured on daily basis in the Department of Clinical Biochemistry, University Hospital Olomouc. The results are given as a simple value without interpretation with respect to therapeutic range or recommendation regarding dosing. For interpretation, the Department of Pharmacology can be consulted.

Basic demographic, biochemical, and clinical data essential for vancomycin concentration interpretation or pharmacokinetic modelling were obtained from the hospital electronic health records. These data included patients' age, height, weight, serum creatinine level, clinical diagnosis for which vancomycin was prescribed, presumed causative pathogen and its minimum inhibitory concentration for vancomycin determined by standard microdilution technique (if more agents were involved, the pathogen with the highest MIC value for vancomycin was included), vancomycin dosing, length of treatment and whether a clinical pharmacologist who has access to and an expertise with a pharmacokinetic modelling software (MW\Pharm 3.30, Mediware) was consulted. All data were subsequently processed anonymously.

If both trough and peak concentrations were determined, this was counted as one event. Each value was compared with the older guidelines (with target ranges of 10–15 mg/L for C_{min}, and 20–40 mg/L for C_{max}) and the new guidelines with regard to the type of infection and the MIC of the pathogen involved. Consecutively, pharmacokinetic modelling using MW\Pharm 3.3 software was performed for every patient to assess individual PK/PD indices. The dosage regimen was then classified either as subtherapeutic, optimal, or supratherapeutic.

At our pharmacology department, TDM of vancomycin is routinely performed using pharmacokinetic software to model the individual concentration versus time curves. Dosing recommendations are given with regard to the clinical diagnosis, susceptibility of the causative pathogen and concomitant antibiotic therapy in order to achieve adequate antibiotic exposure.

In our study, we aimed to test the following hypothesis: dosage adjustments that are based solely on the measured concentrations, and in particular with regard to the "aggressive" target levels specified in the new recommendations, may be inappropriate, especially when the concentrations are interpreted by a clinician who lacks expertise in TDM.

The study was approved by the hospital Ethics Committee FNOL No. 183/14 and was conducted in accordance with the ethical principles of the Declaration of Helsinki. All data were obtained from the hospital information system. Blood sampling for vancomycin concentration measurements was conducted on the request of the attending physician as part of standard care for patients. Written informed consent with participation in the study was not required because of the non-intervention retrospective nature of the study.

Results

A total of 621 vancomycin concentrations were determined in University Hospital Olomouc during the study period, of which 468 values were included into the analysis according to the inclusion and exclusion criteria. These values represented 206 monitoring events in 131 patients. In 4 patients, there were two courses of vancomycin therapy with concentration measurements in the study period; each course of therapy was evaluated separately. Our cohort of patients included 42.7 % women and 57.3 % men, the average patient age was 63.0 ± 18.0 years.

Sepsis or bacteraemia was the most common indication for vancomycin, identified in 49.6 % of patients. The second most common indication was septic arthritis and/or osteomyelitis, followed by wound infections. Other clinical diagnoses appeared with frequencies of not more than 10 % (Figure 1).

The etiological agent and its MIC for vancomycin were identified in more than 96 % of patients (Table 1). Less susceptible agents (with MIC > 1 mg/L) were found in 18.5 % of cases. MRSA isolates were responsible for 6.7 % of all infections; a less susceptible MRSA strain with MIC > 1 mg/L was identified only in one patient.

In almost two thirds of patients, the initial vancomycin dosing was 1 g every 12 hours. Dosing regimens of 1 g every 8 hours and 500 mg every 8 hours were also frequent, each occurred in more than 10 % of patients (Figure 2). Vancomycin was administered exclusively as intermittent infusion. Administration by continuous infusion was not used in any patients.

Vancomycin administration was initiated with a loading dose(s) only in 5 patients. In three patients, this was represented by shortening of the dosing interval between individual doses on the first day while keeping the single dose unchanged (1 g or 500 mg given every 12 hours on the first day, followed by 1 g or 500 mg, respectively, once daily). In two other patients a true loading dose was given; the regimen was 1 g every 12 hours on the first day of vancomycin therapy followed by 500 mg every 12 hours in both patients.

Vancomycin was first monitored most frequently during the second (in 30.4 % of patients), third (in 28.1 %) and fourth (in 22.2 %) day of therapy. On average, the first monitoring was done after 3.52 ± 1.87 days of treatment (mean ± standard deviation). Occasionally, vancomycin was monitored for the first time on 11th (in 2 patients) or 12th (in 1 patient) day of therapy.

Vancomycin was monitored only once during the treatment in more than half of all patients (52.6 %), whereas two and three monitoring events were found in 22.2 % and 14.8 % of patients, respectively. More than five events of monitoring were observed only in 3 patients.

According to the older recommendations, dosing regimen would be considered optimal in 22.7 % of events, whereas in 28.5 % of cases it would be consider subtherapeutic and in almost half of all cases (48.8 %) as supratherapeutic. According to the new guidelines, dosing regimen would classify as optimal only in 21.9 % of monitoring events, in the remaining cases, the dosage would be considered subtherapeutic almost as often as supratherapeutic (38.5 %, and 39.2 %, respectively).

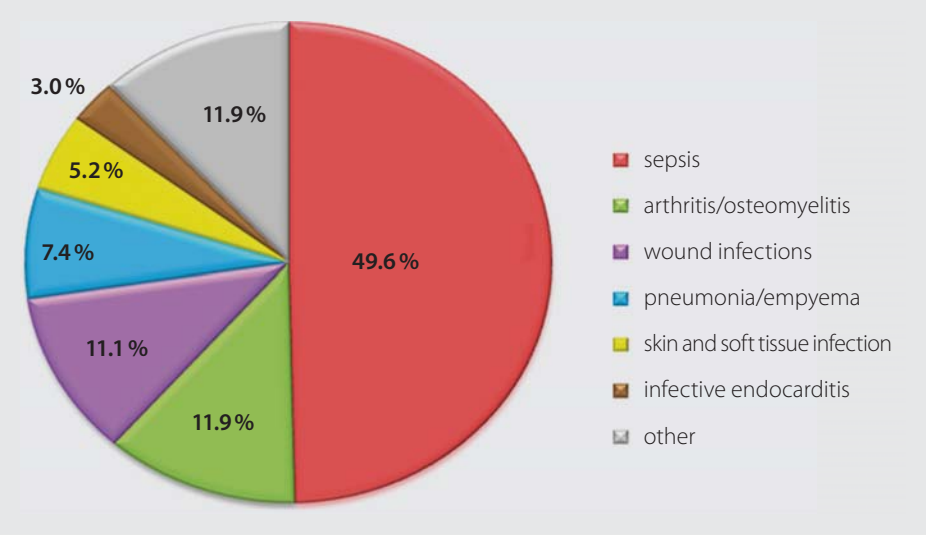
If the concentrations were interpreted by a clinical pharmacologist or another specialist with expertise in TDM and involved the pharmacokinetic analysis with Bayesian prediction approach, the dosage regimen would be consider optimal, subtherapeutic and supratherapeutic in 35 %, 28.1 % and 36.9 % of all cases, respectively (Figure 3).

Tab. 1. *Causative agents identified in patients treated with vancomycin in whom therapeutic monitoring was performed. In case of more agents involved, pathogen with the highest MIC value for vancomycin was included*

Agent	MIC	Number of pathogens (%)
***Staphylococcus species** **	0.5	9.6 %
	1	37.0 %
	2	14.8 %
	4	0.7 %
	N	0.7 %
Enterococcus species	0.25	0.7 %
	0.5	8.1 %
	1	15.6 %
	2	1.5 %
	4	0.7 %
	N	0.7 %
MRSA	0.25	1.5 %
	0.5	2.2 %
	1	2.2 %
	2	0.7 %
Streptococcus species	N	0.7 %
Corynebacteria	N	1.5 %
N	N	0.7 %

MIC, minimal inhibitory concentration (mg/L); *, MRSA strains not included; MRSA, methicillin-resistant *Staphylococcus aureus*; N, unknown/unidentified

Fig. 1. *Clinical diagnoses and their frequencies in patients treated with vancomycin*



A clinical pharmacologist was consulted by the attending physician in 18.1 % of vancomycin monitoring events (in 17 % of patients); a dosage adjustment was recommended in 59.6 % of these consultations.

Discussion

Vancomycin TDM was originally introduced as a method to reduce vancomycin toxicity. Improved clinical outcome and reduction of bacterial resistance were later recognised as other potential advantages of vancomycin TDM and nowadays are considered at least as important as the safety issues (10). The results of a meta-analysis from 2013 showed that vancomycin therapy had significantly higher clinical efficacy and was associated with lower risk of nephrotoxicity in patients in whom TDM was performed in comparison to non-TDM groups. The duration of therapy and length of hospital stay were similar in both groups with a trend toward a shorter duration in the TDM groups; as the authors suggested this might be explained by the fact that a significant proportion of patients in both groups did not achieve the desired therapeutic concentrations. As concluded by the authors, TDM should be routinely performed during systemic vancomycin therapy (4).

Cardile et al. compared clinical outcome of a historic cohort of patients who had been

Fig. 2. *Vancomycin dosing regimens and their frequencies at the first monitoring (initial dosing)*

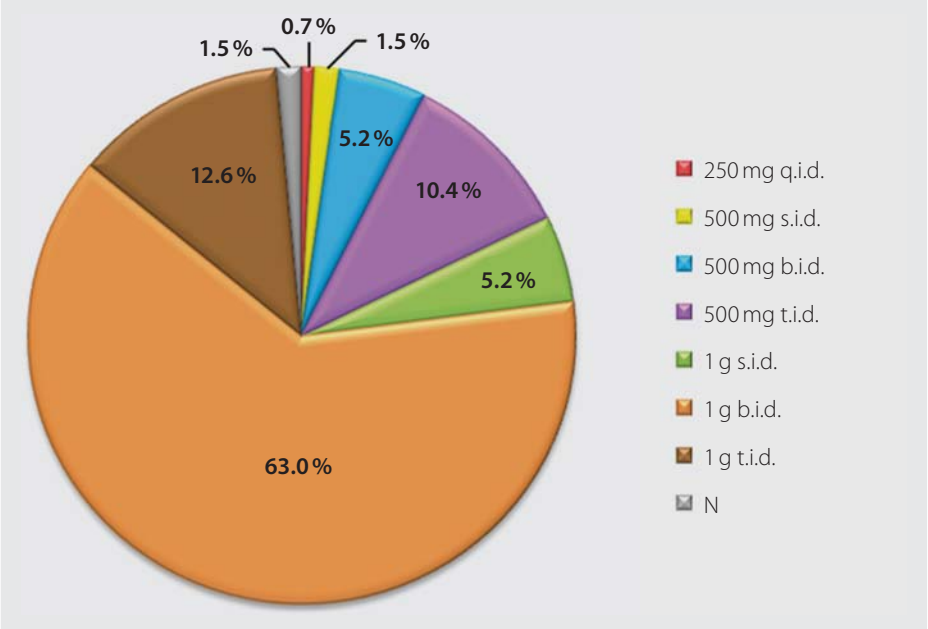
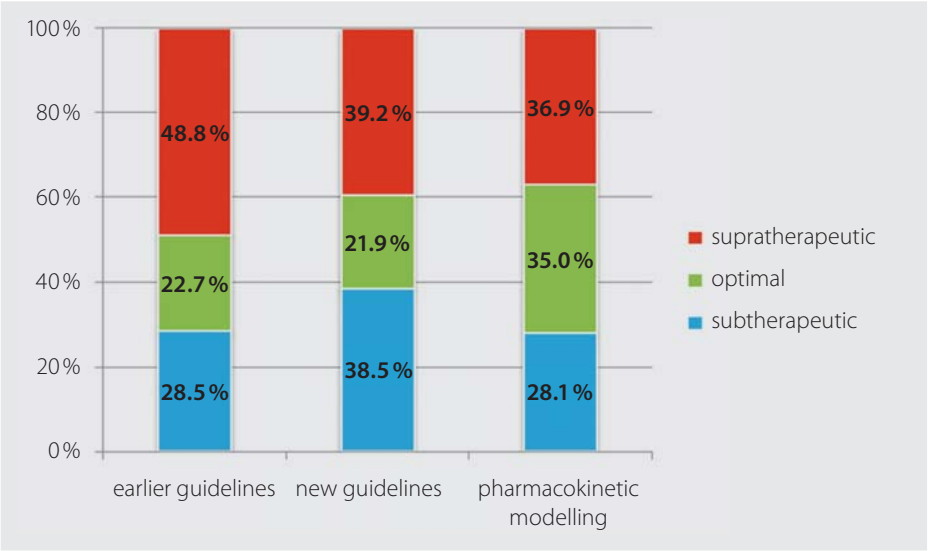


Fig. 3. *Appropriateness of vancomycin dosing evaluated according to the earlier (target trough concentrations of 10–15 mg/L and peak concentrations of 20–40 mg/L) and the new guidelines (target trough concentration of 15–20 mg/L in severe invasive infections and/or when less susceptible microorganisms involved; otherwise target trough concentrations of 10–15 mg/L) and when assessed by pharmacokinetic modelling expressed as fraction of patients with subtherapeutic, optimal, and supratherapeutic dosing*



treated with physician-guided vancomycin therapy (in whom dosing was adjusted according to the concentrations at physician's discretion) to a cohort of patients treated with pharmacist-guided vancomycin therapy that incorporated TDM. The TDM programme was initiated in their hospital to reduce the time necessary to reach target therapeutic concentrations. The TDM group achieved target concentrations significantly more often and earlier than the control group, there were significantly fewer vancomycin trough levels drawn per patient in the TDM group, patients in TDM group had shorter hospital stays, reached clinical stability faster and also had shorter courses of vancomycin treatment than the control group. Nephrotoxicity, as well as all cause in-hospital mortality, occurred at comparable rates in both groups. This study shows that vancomycin TDM can significantly reduce time to reach target concentrations and this improves clinical outcome of patients (11).

Our study demonstrates that in the University Hospital Olomouc, simple level measurements are more common than true therapeutic monitoring. Only one in six measurements are interpreted by a clinical pharmacologist even though our data shows that a dose adjustment would be recommended in approximately two thirds of patients. The Department of Pharmacology in the hospital is not directly linked to the Department of Clinical Biochemistry, so the ordering physician must request a separate request form for a pharmacology consultation. This, coupled with a low awareness of the service, explains the relatively low number or consultations requested.

Expert consensus is that the best PK/PD predictor of vancomycin efficacy is the AUC_{0-24}/MIC ratio with target values ≥ 400 mg•h/L (6). AUC calculations are not trivial and require concentration measurements in short time intervals using the trapezoid rule to calculate the area under concentration curve. This method places a burden both on the patient and the hospital and is seldom used today. The alternative method that allows for an estimation of AUC with high precision requires availability of population modelling software (8).

The above mentioned expert group states in the new guidelines that vancomycin dosing should be guided by C_{min} as it can replace AUC while being easier to measure (6). It is however important to remember that C_{min} is only one point at the end of the dosing interval and it cannot fully reflect the course of the concentration time curve (8).

Neely et al. used PK/PD modelling to show that AUC prediction based on C_{min} alone underestimates true AUC by 25 % on average. Due to interindividual variability of pharmacokinetics this value can be much higher in some patients. The authors also state that between 50 and 60 % of adult patients with normal renal function can reach the desired AUC_{0-24}/MIC of ≥ 400 mg•h/L (for a pathogen with MIC = 1 mg/L) even with C_{min} below 15 mg/L (i.e. lower than those recommended for severe infections). When these patients are dosed based on C_{min} alone they can be exposed to unnecessarily high concentrations with higher risk of toxicity. The authors believe that vancomycin toxicity depends on exposure the same way the efficacy does; the risk of toxicity rises significantly with AUC_{0-24} > 700 mg•h/L (9).

Results of a study by Czech authors describing PK of vancomycin in septic patients with acute kidney injury and continuous re-

nal replacement therapy also show that C_{min} is a very unreliable predictor of AUC or AUC_{0-24}/MIC. The target C_{min} was reached only by 27 % of patients at the end of the first day while 80 % had AUC_{0-24}/MIC values ≥ 400 mg•h/L.This result was partially caused by susceptibility pattern of etiological agents – in two thirds of patients the MIC values were ≤ 0.5 mg/L (12).

The aim of our study was to test the hypothesis that assessment of adequate dosing based on C_{min} and C_{max} alone (older recommendations) or C_{min} only (given the targets of the newer guidelines) without predictive analysis can be misleading. Our results confirm this (Figure 3). The older recommendations tend to overestimate the levels and dosing which can lead to non-indicated dose reductions and risk of treatment failure. Newer guidelines have the opposite effect with risk of classifying optimal (or even supratherapeutic) levels as suboptimal leading to unnecessarily high doses with risk of toxicity.

The presented study has several limitations. Our analysis only included those patients who had a vancomycin level measured during their therapy, not all treated patients. Also, the adequacy of dosing was not assessed using AUC_{0-24}/MIC. This assessment is not routine at our department and our goal was to assess the effect of newer recommendations. The expert consensus on whether to use AUC_{0-24}/MIC is still not final, even though the most recent meta-analysis published this year supports this conclusion (13).

Conclusion

Therapeutic drug monitoring is a specific branch of clinical biochemistry and clinical pharmacology that helps to optimise drug dosing. Beside drug concentration measurement, TDM involves interpretation of the drug level with respect to the sample timing, clinical indication, and other factors. During vancomycin therapy, TDM should be routinely performed. The new guidelines for vancomycin TDM from 2009 recommend determination of C_{max} to be omitted and vancomycin dosing to be adjusted based on trough concentrations only.

Our study shows that dosing adjustment based solely on C_{min} may lead to unnecessarily aggressive dosing with associated increase in the risk of toxicity on one hand and to therapeutic failure on the other, especially if the concentration is not interpreted by a person with enough clinical experience in TDM. To optimise vancomycin prescribing, routine TDM programme that involves a clinical pharmacologist's consultation should be implemented.

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