Algerian journal of pharmacy. Vol. 01 Num. 02 (11-2019) 2602-975X

الفدرالية الجزائرية للصيدلة
FÉDÉRATION ALGÉRIENNE DE PHARMACIE

Disponible en ligne sur
ASJP
Algerian Scientific Journal Platform
https://www.asjp.cerist.dz/en/PresentationRevue/436

ARTICLE ORIGINAL

Pharmacocinétique et pharmacodynamie de la Vancomycine chez des patients Algériens (sous-populations à haut risque) : Situation actuelle.

Vancomycin pharmacokinetic and pharmacodynamic in Algerian patients (High-risk subpopulations): Current situation.

Khaled Sobhi[1,2]*, Amira Hadri[2], Roza Kerrouche[2], Nadjet Aggoune[2,3], Ali Zerrouki[2,3], Djamel Sadouki[1,2] and Mohamed Mammar[1,2]

[1]Toxicology Laboratory, Central Hospital of the army, Algiers, Algeria; [2]Department of Pharmacy, Faculty of Medicine, University of Algiers Benyoucef Benkhedda, Algeria; [3]Microbiology service, Central Hospital of the army, Algiers, Algeria

Mots clés : vancomycine, suivi thérapeutique pharmacologique, pharmacocinétique-pharmacodynamique, l'efficacité clinico-bactérienne.

RÉSUMÉ

Contexte : Il y a un manque de données sur la pharmacocinétique de la vancomycine chez les patients algériens.

Objectifs : Le but de cette étude est d'appliquer un suivi thérapeutique de la vancomycine chez des patients algériens, d'étudier la relation entre les concentrations de vancomycine et les résultats cliniques et de s'intéresser à l'approche pharmacocinétique-pharmacodynamie (PK-PD) afin d'expliquer le succès thérapeutique.

Méthodes : Une étude prospective est menée à l'Hôpital Central de l'Armée de d'Alger. Elle comprend soixante-trois patients recevant une perfusion de vancomycine. Les concentrations sériques de vancomycine sont obtenues par une méthode validée de chromatographie liquide. Les concentrations minimales inhibitrices (CMI) sont effectuées dans le service de microbiologie. Nous utilisons l'approche PK-PD pour contrôler l'efficacité clinico-bactérienne.

Résultats : Seulement 22,2% des concentrations de vancomycine étaient dans la plage thérapeutique. Dans notre population, 61,9% des concentrations n'ont pas atteint les niveaux thérapeutiques exposant les patients au risque d'échec de l'antibiothérapie et à l'émergence d'une résistance bactérienne. 15,9% des patients ont été surdosés et exposés à un risque de néphrotoxicité.

Le taux de guérison clinique était de 70,8% pour les patients qui ont reçu la vancomycine comme traitement curatif. La concentration minimale inhibitrice (CMI) de la bactérie et l'association à d'autres antibiotiques ont été prises en compte lors de l'interprétation du rétablissement clinique malgré un sous-dosage.

Conclusion : L'approche actuelle de la thérapie antibiotique PK-PD qui prend en compte la cinétique des antibiotiques et les caractéristiques de la bactérie constitue un outil puissant pour évaluer l'efficacité clinico-bactérienne.

Key words: vancomycin, therapeutic drug monitoring, Pharmacokinetic-pharmacodynamic, clinico-bacterial efficacy.

ABSTRACT

Background: there is a lack of data on the pharmacokinetics of vancomycin in Algerian patients.

Objectives: The aim of this study is to apply a therapeutic monitoring of vancomycin in Algerian patients, study the relationship between vancomycin concentrations and clinical outcomes and focus on the pharmacokinetic-pharmacodynamic (PK-PD) approach in order to explain the therapeutic success.

Methods: A prospective study is conducted at the Central Hospital of Army of Algeria. It includes sixty-three patients receiving vancomycin infusion. vancomycin serum concentrations are obtained by a validated liquid chromatography method. Minimum Inhibitory Concentrations (MICs) are performed at the microbiology service. We use the pk/pd approach for monitoring the clinico-bacterial efficacy.

Results: Vancomycin concentrations were analyzed and only 22.2% of concentrations were within the therapeutic range. 61.9% of concentrations did not reach therapeutic levels in our population exposing patients to the risk of failure of antibiotic therapy and the emergence of bacterial resistance. 15.9% of patients were overdosed and exposed to a risk of nephrotoxicity. The rate of clinical recovery was 70.8% for patients who received vancomycin as a curative treatment. Minimum Inhibitory Concentration (MIC) of the bacteria and combination of antibiotics were taken into consideration when interpreting the clinical recovery despite under-dosing.

Conclusion:

The current approach of antibiotic therapy (PK-PD) that considers the kinetic of antibiotics and characteristics of the bacteria is a powerful tool for assessing clinico-bacterial efficacy.

* Auteur correspondant :
Adresse e-mail : sobhikhaled@yahoo.fr

INTRODUCTION

Vancomycin is a glycopeptide antibiotic active against gram-positive bacteria by interfering with cell wall synthesis **(1)**. It is commonly used to treat patients with serious or multi-resistant gram-positive bacterial infections **(2)**.

Vancomycin has a narrow therapeutic range with nephrotoxicity and ototoxicity complicating the therapy **(3,4)** and therapeutic drug monitoring (TDM) is required for maximizing efficacy while minimizing the onset of these toxicities **(3)**.

It is considered that a ratio of the area under the curve (AUC) to the minimum inhibitory concentration (MIC) ≥ 400 is the best pharmacokinetic-pharmacodynamic (PK-PD) parameter associated with a clinical and bacteriological response to vancomycin **(3,5)**. However, it is difficult and impractical in the clinical setting to measure serum vancomycin concentration multiple times to determine the AUC **(5,6)**.

It has been shown that there is a significant correlation between AUC and trough concentration of vancomycin (C_{min}) which can therefore be used as a marker of efficacy **(6)**, but also of toxicity since too high residual levels seem to be associated with an increased risk of nephrotoxicity **(5,7)**.

In addition, because of the time-dependent activity of vancomycin, C_{min} appears to be the most correlated parameter to therapeutic success **(8)** and maintaining its value well above the MIC of the suspected or identified bacterium over the entire dosing interval (i.e. T>MIC of 100%) appears to be an important element of therapeutic success **(9)**.

In practice, steady state levels for vancomycin should achieve four to eight times the MIC of the infecting germ **(9)**.

Peak serum concentration of vancomycin is no longer used as a clinical indicator because C_{min}/MIC and C_{min} are sufficient to predict the efficacy and the safety of vancomycin **(10)**.

Trough serum levels should always be maintained above 10 µg/mL to avoid the development of bacterial resistance **(5)**.

Some physiological factors or pathological situations may change the pharmacokinetic of vancomycin: age, weigh, renal impairment, in burn patients... **(11,12)**. These factors define particular populations that should be controlled by TDM.

There is a lack of data among Algerian patients; we need first to evaluate the current situation of TDM of vancomycin. The aim of this study was to apply a therapeutic monitoring of vancomycin in Algerian patients, study the relationship between vancomycin concentrations and clinical outcomes and focus on the PK-PD approach in order to explain the therapeutic success.

MATERIALS AND METHODS

Population

A prospective study was conducted over two periods: from November 2013 to April 2014 (population 1 including forty patients), then from February to May 2015 (population 2 including twenty-three patients) at the Central Hospital of Army of Algeria.

A total of sixty-three Algerian patients receiving intravenous

infusion of vancomycin were monitored. Fifty-seven patients received an intermittent infusion of vancomycin while six patients received a continuous infusion.

Forty-eight patients received vancomycin as a curative treatment (alone or in combination with other antibiotics) and fifteen patients as a prophylactic antibiotic treatment.
Our population included twenty children, nine patients with renal impairment, six patients in intensive care unit and seven burn patients.

Population characteristics and therapeutic regimen are reported in table 1 and table 2 respectively.

An information sheet containing the patient data (including age, sex, weight, therapeutic regimen, antibiotic drug association, kidney function and microbiological tests) was set.

Table 1: Population characteristics

Total of patients	63
Sex: male/female	45/18
Age (years) : [Min-Max]	[0.5 - 79]
Mean ± SD	36.56 ± 25.70
Body weight (Kg) : [Min-Max]	[7 - 98]
Mean ± SD	55.40 ± 25.83
Creatinine clearance (mL/min): [Min-Max]	[8.82 - 307.37]
Mean ± SD	134.25 ± 70.27
Children	20
Patients with renal impairment (with Cl_{creat}<60ml/min)	09
Patients in intensive care unit	06
Burn patients	07

Therapeutic regimen	**Population**
Vancomycin infusion:	
Continuous infusion	06
Intermittent infusion	57
Vancomycin dosage:	
Children (mg/kg/day): [Min-Max]	[6.83 - 125]
Mean ± SD	47.06 ± 31.23
Adults (mg/kg/day): [Min-Max]	[2.85 - 41.67]
Mean ± SD	24.31 ± 8.28
(mg/day): [Min-Max]	[142.85 - 2550]
Mean ± SD	1725.42 ± 494.24
Use of vancomycin as :	
Preventive treatment	15
Curative treatment	48
Combination to other antibiotics	48

Table 2: Therapeutic regimen.

Blood sampling

Blood samples were collected in a 5 cc dry tubes. Trough concentrations were obtained 30 minutes prior to the next dose at steady-state conditions for intermittent infusion. For continuous infusion, samples were collected at any time once steady state achieved.

Analytical method

A Liquid Chromatography method with UV detection for determination of vancomycin has been developed and validated in the Toxicology Laboratory of the Central Hospital of the Army. Ceftazidime was used as internal standard. After pre-treatment and injection into the chromatographic system, peaks were eluted from a C-8 column (Thermo 150 x 4.6mm x 5µm) using a mobile phase consisting of acetonitrile: phosphate buffer 5 mM pH 2.8 with elution gradient at a rate of 1.5 ml/min. The detection wavelength was 210 nm

RESULTS AND DISCUSSION

Serum concentration of vancomycin

The results showed variations in vancomycin serum concentration. Indeed, if we refer to the therapeutic range recommended for trough levels (10-20 µg/mL) **(3)** and for continuous infusion concentration (20-40 µg/mL) **(13)**, only 22.2% of concentrations were within the therapeutic range.
61.9% of concentrations did not reach therapeutic levels in our population exposing patients to the risk of failure of antibiotic therapy and the emergence of bacterial resistance.
15.9% of patients were overdosed and exposed to a risk of nephrotoxicity.
These results are reported in table 3.

Table 3: Vancomycin serum levels

Serum levels	**Population (n=63)**
Trough serum concentration:	
10-20µg/mL	13
<10µg/mL	34
>20 µg/Ml	10
Continuous infusion concentration:	
≥20µg/mL	01
10-20µg/ml	02
<10 µg/mL	03

A part of under-dosing can be explained by a low daily dose. 27% of patients received less than the recommended dose and no patient in our population received a loading dose. But even with an appropriate vancomycin daily dose, serum concentrations still sub-optimal in our population.

Recently, The European Medicines Agency (EMA) recommended a starting dose of vancomycin based on the age and weight of the patient and that any subsequent dose adjustment should be based on serum concentrations to achieve the target therapeutic concentrations, since available data showed that the previously recommended daily dose often resulted in sub-optimal vancomycin serum concentrations **(14)**.

Subpopulations

Paediatric population (n=20)

Only 25% of children reached the therapeutic range in our study against 60% of under-dosing.

Children have an increased volume of distribution for vancomycin (**15)** and elimination twice faster than adults **(13)**.

Burn patients

Six from the seven burn patients were under-dosed with continuous or intermittent infusion. This can be explained by the fact that they have an increased clearance for vancomycin and therefore require higher daily doses **(13)**. Three of them received a lower dose while one paediatric patient received a very high dose of 125mg/Kg/day and despite still under-dosed. The latter can be explained by a very increased clearance, specific characteristic of paediatric patients too.

Patients in intensive care unit (ICU)

Pharmacokinetic changes are found in ICU patients: the volume of distribution is increased and the elimination half-life is variable leading to a decrease in serum concentrations at usual doses with a risk of under-dosing **(9)**. Six from seven patients admitted in intensive care unit were under-dosed in our study.

Patients with renal impairment

Since vancomycin is essentially eliminated by kidney, clearance decreases and the half-life increases with renal failure **(11)**. There is therefore a risk of accumulation by elimination delay **(12)** and maintenance doses of vancomycin should be guided by serum levels (**16)**.

Usually, a dose reduction is recommended. Six from nine patients with renal impairment in our population were overdosed. We noticed that four patients did not receive any dose adjustment and two others received an inappropriate one.

Clinical evolution and PK-PD approach

The rate of clinical recovery was 70.8% for the forty-eight patients who received vancomycin as a curative treatment. The interpretation of the recovery must take into account several factors such as combination of antibiotics, MIC of the bacteria...

Vancomycin was given in combination with other antibiotics in 76.2% of cases especially to imipenem and aminoglycosides without any alteration of renal function in population 1.

The clinical evolution was monitored for only population 1. There was 60.9% of clinical recovery in under-dosed patients. The combination with other antibiotics can explain the clinical recovery for some patients.

It is the example of patient 21 in whom the infecting germ was *Staphylococcus aureus* sensitive to vancomycin and imipenem, both used in combination to treat the infection. Similarly, the isolated germ from patient 7 was *Streptococcus pneumonia* sensitive to vancomycin and the associated cefotaxime.

In the other hand, the therapeutic success in under-dosed patients 24, 30 and 40 who were infected by MRSA is exclusively due to vancomycin despite the under-dosing. Vancomycin was used as monotherapy for the first two patients. For patient 40, the isolated MRSA was resistant to cefazolin used in combination to vancomycin.

In this case, only the confrontation of vancomycin serum concentration with MIC values could explain therapeutic success despite under-dosing.

Patient 40 illustrates this PK-PD approach. The latter had an MRSA infection with a MIC of 1.5 µg/mL and a C_{min} of 9.96 µg/mL. The residual inhibitory quotient (IQ_{res}) which represents the ratio C_{min}/MIC obtained was 6.64 in favour of therapeutic efficacy of vancomycin clinically confirmed by a favourable evolution after fourteen days of treatment. C_{min}/MIC recommended needs to be between four to eight **(9)**.

Also, the isolated MRSA from patient 22 had a MIC of 0.5 µg/mL. A favourable evolution was noted after eight days of antibiotic therapy despite the under-dosing (C_{min} of 6.57 µg/mL). The confrontation of C_{min} with MIC value resulted in an IQ_{res} of 13.14 well above the recommended values to obtain clinico-bacterial efficacy. But we have to be careful in interpretation since another antibiotic active against the bacterium (fusidic acid) was associated.

We noticed a case of therapeutic failure despite the therapeutic level of vancomycin. Patient 20 with a pneumococcal endocarditis, the two parameters C_{min} and IQ_{res} of 16.53 µg/mL and 5.51 respectively were in favour of therapeutic success. The isolated pneumococcal strain had a MIC of 3 µg/mL higher than those usually found (MIC<1µg /mL) suggesting vancomycin resistance of the germ and illustrating limits of the mentioned parameters when bacterial strain is resistant to the antibiotic used.

The confrontation between vancomycin serum level, MIC of the bacterium and clinical outcome for some patients are reported in table 4.

Table 4: Confrontation between vancomycin serum level, MIC of the bacterium and clinical outcome for some patients.

Patient	C_{min} (µg/mL)	Isolated germ	MIC* (µg/mL)	IQ_{res}	Associated antibiotic	Clinical and bacteriological evolution
P07	<5	*Streptococcus pneumoniae*	0.25		Cefotaxime	Therapeutic success
P08	16.08	*MRSA*	≤ 2	≥8.04	Imipénème Amikacine	Therapeutic success
P20	16.53	*Streptococcus pneumoniae*	3	5.51	No association	Therapeutic failure and change of the antibiotic
P21	<5	*Staphylococcus aureus*	0,75		Imipenem Amikacin	Therapeutic success
P22	6.57	*MRSA*	0.5	13.14	Ceftriaxone Fusidicacid	Therapeutic success
P24	<5	*MRSA*	≤2		No association	Therapeutic success
P40	9.96	*MRSA*	1.5	6.64	Cefazolin	Therapeutic success

* The MIC was obtained by E-test while the MIC approximation (≤ 2µg/mL) was obtained by referring to the diameter of inhibition of bacterial growth by vancomycin when performing the antibiogram.

CONCLUSION

This study allowed us to analyze the current situation in Algerian patients. TDM of antibiotics is little-known by our clinicians and the low monitoring request led us to carry out this study in order to raise awareness about the importance of this practice.

A larger homogeneous sample will allow to assess the impact of the factors studied on the kinetic of vancomycin and the clinical results of the treatment.

The current approach of antibiotic therapy (PK-PD) that considers the kinetic of antibiotics and the characteristics of the bacteria is a powerful tool for assessing clinico-bacterial efficacy.

Transparency declarations: None to declare.

REFERENCES

1. Khotaei G. T., Jam S., Seyed Alinaghi SA., Motamed F., Nejat F., Taghi M., Ashtiani H. and Izadyar M. (2010). Monitoring of Serum Vancomycin Concentrations in Paediatric Patients with Normal Renal Function. Acta Medica Iranica ; 48(2): 91-94.

2. Yoshida M., Yasuda N., Nishikata M., Okamoto K., Uchida T. and Matsuyama K. (2005). New recommendations for vancomycin dosage for patients with MRSA pneumonia with various degrees of renal function impairment. Japanese Society of Chemotherapy and The Japanese Association for Infectious Diseases. J Infect Chemother 11:182–188.

3. Matsumoto K., Takesue Y., Ohmagari N., Mochizuki T., Mikamo H., Seki M., Takakura S., Tokimatsu I., Takahashi Y., Kasahara K., Okada K., Igarashi M., Kobayashi M., Hamada Y., Kimura M., Nishi Y., Tanigawara Y., Kimura T. (2013). Practice guidelines for therapeutic drug monitoring of vancomycin: a consensus review of the Japanese Society of chemotherapy and the Japanese Society of Therapeutic Drug Monitoring. Journal of Infection and Chemotherapy. Vol 19: 365-380.

4. Robles-Piedras A. L., Gonzalez-Lopez E. H. (2009). Therapeutic Drug Monitoring of Vancomycin. Proceedings of the Western Pharmacology Society. Vol 52. P 21-23.

5. Rybak M., Lomaestro B., Rotschafer J.C., Moellering R.J., Craig W., Billeter M., Dalovisio J.R., Levine D.P. (2009). Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. American Journal of Health-System Pharmacy. Vol 66. No 1. P 82-98.

6. Thalakada R., Legal M., Lau T.Y., Luey T., Batterink J., Ensom M.H. (2012). Development and Validation of a Novel Vancomycin Dosing Nomogram for Achieving High-Target

Trough Levels at 2 Canadian Teaching Hospitals. The Canadian Journal of Hospital Pharmacy. Vol 65. No 3. P 180-187.

7. Coelho A. (2011). Impact de recommandations écrites sur le monitoring thérapeutique (TDM) de la gentamicine et de la vancomycine en néonatologie. Maîtrise Universitaire en Pharmacie .Faculté des sciences de l'Université de Genève. P9.

8. Taieb F., Le Monnier A., Bille E., Lanternier F., Mechai F., Ribadeau-Dumas F., Maenulein E., Forge C., Corriol O., Nassif X., Lortholary O., Zahar J.-R. (2009). Optimisation de la prescription de la vancomycine: étude prospective observationnelle dans un centre hospitalo-universitaire parisien. Médecine et maladies infectieuses. Vol 40. P 273-278.

9. Garraffo R., Lavrut T. (2005). Signification clinique des corrélations pharmacocinétique / pharmacodynamie des antibiotiques chez les patients de réanimation. Réanimation. Vol 14. P 264-275.

10. Suzuki Y., Kawasaki K., Sato Y., Tokimatsu I., Itoh H., Hiramatsu K., Takeyama M., Kadota J. (2012). Is Peak Concentration Needed in Therapeutic Drug Monitoring of Vancomycin? A Pharmacokinetic-Pharmacodynamic Analysis in Patients with Methicillin-Resistant *Staphylococcus aureus* Pneumonia. Chemotherapy. Vol 58. No 4. P 308-312.

11. Berny C., Boucher P., Feuillu A., Greffe J., Mialon A., Manchon M., Meley R. (2000). Cahier de formation Biologie médicale, Dosage des médicaments tome II, Paris : BIOFARMA, N°18. Vancomycine. P125-134.

12. Lacarelle B, Baltasat A, Bouquet S, Venisse N (2003). Suivi thérapeutique pharmacologique de la vancomycine. Biologie clinique [90-45-0065].

13. Marquet P. (2004). Le suivi thérapeutique pharmacologique pour l'adaptation de posologie des médicaments. Paris: Elsevier. P 34-37, 75-83.

14. European Medicines Agency (2017). EMA recommends changes to prescribing information for vancomycin antibiotics. EMA/306160/2017.

15. Therrien R., Perreault M., Lebel D. (2010). Évaluation de la pharmacocinétique de la vancomycine chez des enfants atteints de cancer. Pharmactuel.Vol 43. No 3. P 162-170.

16. Vinks A.A. Gyssens IC. and al. (2014). Fundamentals of Antimicrobial Pharmacokinetics. Glycopeptides ; Chapter 12.Springer. P 284.