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Impact of the PK/PD Approach in Therapeutic Drug Monitoring of Gentamicin

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Abstract: Gentamicin, a commonly used hospital aminoglycoside, exhibits a narrow therapeutic index, necessitating careful administration to prevent serious adverse effects. Our study aimed to assess the impact of Therapeutic drug Monitoring (TDM) by integrating Minimum Inhibitory Concentration (MIC) to customize dosage based on bacterial sensitivity. This was prospective study, conducted on a sample of 35 adult patients hospitalized in three university hospital centers in Eastern Algeria. Included patients underwent Therapeutic Drug Monitoring (TDM) of gentamicin based on the determination of Maximum concentration (Cmax), considering the determination of the MIC and achieving a Cmax/CMI ratio ≥ 8 to 10. Pharmaceutical interventions were suggested to clinicians to improve patient care. The mean age of our patients was 51.66 ± 16.72 years. All patients had Cmax values below the therapeutic range. Pathogenic microorganisms were identified in 64% of cases, and only two patients achieved the Cmax/CMI target of 8 to 10 prior to our interventions. In 41% of cases, clinicians heeded our guidance on regular therapeutic monitoring and dose adjustments. The therapeutic target was achieved in 66.6% of cases, with a Cmax/CMI target attainment rate of 44.4%.The use of individualized initial doses of gentamicin, combined with Therapeutic Drug Monitoring based on PK/PD parameters, enhances the chances of therapeutic success and restricts the emergence of bacterial resistance.

Keywords: Gentamicin, Cmax, Cmax/ MIC, PK/PD.

Introduction

Gentamicin, an aminoglycoside commonly prescribed in the hospital for the treatment of severe gram-negative bacterial infections, maintains its role in the management of nosocomial infections due to the possibility of daily single-dose administration. Furthermore, the benefits of combination therapy with a beta-lactam antibiotic are being assessed when dealing with certain gram-negative bacilli (such as Pseudomonas aeruginosa, Enterobacter,

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Citrobacter, etc.), as well as in the context of treating endocarditis caused by streptococci, enterococci, or methicillin-sensitive Staphylococcus (Padoin et al., 2004).
This is a highly potent and rapidly bactericidal antibiotic, with concentration-dependent killing closely proportional to the maximum serum antibiotic concentration (C_{max}) (Boudia et al., 2023; Mohamed et al., 2012). The therapeutic target ranges from 15 to 25 µg/ml for a daily single dose. In the case of fractionated dosing, the suggested peaks depend on the site of infection. For instance, in Gram-positive infections such as endocarditis, where synergy is sought, gentamicin C_{max} levels should be between 3 and 5 µg/m (Gauzit et al., 2011; Widmer et al., 2008)

However, this medication possesses a narrow therapeutic index and significant inter-individual pharmacokinetic variability (changes in drug blood concentrations based on the patient) as well as intra-individual variability (changes in drug blood concentrations based on variations in physiopathological status) (Bourguignon et al., 2015; Bruno Lacarelle et al., 2007).

As a result, the initially calculated dosage aimed at achieving the desired target at the beginning of treatment may become inadequate after a few days. This can lead to treatment inefficacy and the development of bacterial resistance, as well as potential toxicity, especially nephrotoxicity and ototoxicity, particularly in prolonged treatment (Bourguignon et al., 2010). This renal and auditory toxicity is directly associated with elevated residual concentrations (C_0) (Blunston et al., 2015; Boudia et al., 2023; Hayward et al., 2018).

Therefore, it is advisable to perform frequent monitoring of drug blood concentrations throughout the treatment, to ensure the attainment of pharmacokinetic and pharmacodynamic (PK/PD) targets. This primarily depends on the maximum concentration (C_{max}), which should be eight to ten times higher than the minimum inhibitory concentration (MIC) (C_{max}/MIC $\geq$ 8-10). Furthermore, it is crucial to maintain residual concentrations (C_0) below 1 to 2 µg/l to prevent associated renal and auditory toxicity (Bland et al., 2018; Blunston et al., 2015). Our study aimed to assess the impact of therapeutic drug monitoring of gentamicin (TDM) by incorporating MIC to personalize dosing based on bacterial sensitivity.

Patients and Method

This is a descriptive, prospective study conducted in three university hospital centers in the eastern region of Algeria. The study was carried out on a group of 35 adult patients, hospitalized in various departments of these institutions, who had received gentamicin for a period of at least 5 days. Patient data were extracted from specially designed records, encompassing demographic, clinical information, microbiological data, details on gentamicin dosage, administration methods, as well as the monitoring parameters required for result analysis and interpretation. Informed and voluntary consent was obtained from the patients.

Gentamicin blood samples were collected after reaching a steady-state condition, 48 hours after the first administration. The residual concentration (C_0) was measured at the end of a gentamicin administration interval, approximately 30 minutes before the next dose. Meanwhile, C_{max} was measured 30 to 45 minutes after the completion of the intravenous gentamicin infusion. Gentamicin assay was performed using an enzyme immunoassay (EMIT) method on a Siemens VIVA-E automatic analyzer.

When a severe infection was suspected, specific bacteriological samples were collected based on the type and presumed site of the infection. The objective of these samples was to identify the pathogenic microorganism responsible for the infection, determine its antibiotic sensitivity, and establish the minimum inhibitory concentration (MIC). The liquid dilution method was used to determine MIC values.

Data collection and analysis were carried out using IBM SPSS Statistics version 25. Descriptive analysis results were expressed as frequencies for qualitative variables and as means (± Standard Deviation) for quantitative variables. Bivariate analysis (comparison of qualitative variables) was performed using the Chi-square test. A p-value < 0.05 was considered significant.

Results and Discussion

The 35 patients included in our study were receiving gentamicin in various hospital departments, whether they were medical or surgical in nature. This highlights the relevance of this medication in the management of infections and medical conditions that require its use. The bacteriological profile was documented in 64% of the

patients. The empirical use of gentamicin is based on a thorough examination of the patient's medical history, risk factors, and the potential for bacterial resistance to the antibiotic. During our study, we considered the renal function of our patients by measuring creatinine clearance levels, which were normal in 69.4% of cases. Demographic, clinical, and bacteriological data of the patients are summarized in Table 1.

Table 1. Demographic, clinical, and bacteriological characteristics of the study patients.

Variables		Frequency
Mean Age (years)		51,66 ± 16.72 (18 à 79 years)
Gender		F: 60 %.M: 40 % Sex Ratio: 0.667
Creatinine Clearance (ml/min)		105,42 ± 37,57
Co-morbidity	Arterial Hypertension	33.3 %
	Diabetes	31.0 %
	Dyslipidemia	11.9 %
	Other	23.8 %
Type of infection	Sepsis	45.5 %
	Endocarditis	13.6 %
	Surgical Wound Infection	13.6 %
bacteriological Profile	Empirical	36 %
	Documented	64 %
Isolated Pathogens	Staphylococcus aureus	MIC = 0.5 (30 %) MIC =1.00 (10 %)
	Pseudomonas aeruginosa	MIC = 2 (20 %)
	Klebsiella	MIC = 2 (20 %)
	Escherichia coli	MIC = 1 (10 %)
	Enterobacter	MIC = 1 (10 %)

None of our patients treated with gentamicin received an initial loading dose. Several studies suggest the use of a loading dose based on the patient's ideal body weight to rapidly achieve therapeutic concentrations in the bloodstream and ensure adequate efficacy (Avent et al., 2011; Sous comité de suveillance de l'utilisation des Antibiotiques, 2016; The Gentamicin Improvement Project Group, 2018). In the context of our study, the average daily dose of gentamicin administered was 1.92 ± 0.75 mg/kg via single daily intravenous infusion in 57% of cases, and was fractionated into two administrations per day in 5.7% of cases.

These doses are lower than those reported in other studies, such as the study conducted by Claire Roger and her colleagues in France in 2015, which included 24 patients treated with gentamicin. The average initial dose of gentamicin was 6.6 ± 2.3 mg/kg with a median of 5.9 mg/kg. None of the patients received a dose lower than 3 mg/kg (Roger et al., 2015). It has been demonstrated that a daily single dose of gentamicine achieves PK/PD targets for numerous bacterial strains and enhances tissue penetration due to higher plasma/tissue concentration gradients (Hansen et al., 2001; Kovačević et al., 2016). However, for the treatment of endocarditis, fractionated dosing is preferred, with the daily dosage typically divided into 2 to 3 injections per day, every 8 or 12 hours (Gauzit et al., 2011).

The residual concentrations C_0 were measured for the 35 patients in our study, and it was found that 82.9% of the patients had C0 levels below 1 µg/ml, and these levels were correlated with the daily doses administered (p-value = 0.040). Our results are consistent with those of Kovacevic T. et al, conducted in 2016. The C0 concentrations of 25 out of 31 patients (80.6%) were within the therapeutic range (Kovačević et al., 2016). Among the 31 patients treated with gentamicin, the determination of C_{max} revealed under-dosing, with levels below 15 µg/ml, averaging 5.28 ± 2.74 µg/ml.

In the 4 cases where gentamicin was used to achieve synergy in the treatment of infective endocarditis, 3 cases, or 75%, had a C_{max} within the therapeutic range (3 - 5 µg/ml), while only one case had a Cmax exceeding 5 µg/ml, indicating an overdose. In the study by Kovacevic T. et al., conducted in 2016, 80.6% of C_{max} values were within the therapeutic range established at 8-10 mg/ml (Kovačević et al., 2016). This disparity can be attributed to the administration of significantly lower doses in our patient population (p-value = 0.001).

In our study, only two cases achieved the target C_{max}/CMI ratio of 8 to 10 prior to our interventions. In contrast, the study conducted by Coste A. on 49 patients treated with gentamicin at the university hospital of Nantes in France in 2019, demonstrated that all patients had a C_{max}/CMI ratio greater than or equal to 8 (Coste et al., 2020) Following the results of gentamicin assays and after analyzing the physiopathological characteristics of each patient, their biological and bacteriological parameters, pharmaceutical issues in gentamicin prescription were identified. In 32% of cases, dosages were sub-therapeutic, requiring dosage adjustments and regular therapeutic monitoring.

In 41% of cases, clinicians followed our recommendations. Dosage adjustments were made for 8 patients, and the therapeutic target was achieved in 66.6% of cases, with an increase in daily doses administered (average of 195 ± 72.31 mg). These dosages were closely correlated with patient weight and clearance (p-value of 0.05 and 0.014, respectively). After each dose adjustment, new blood samples were taken 48 hours later. C_{max} levels entered the therapeutic range in 62.5% of cases, with an increase in the average to 9.55 ± 8.74 mg (Figure1).

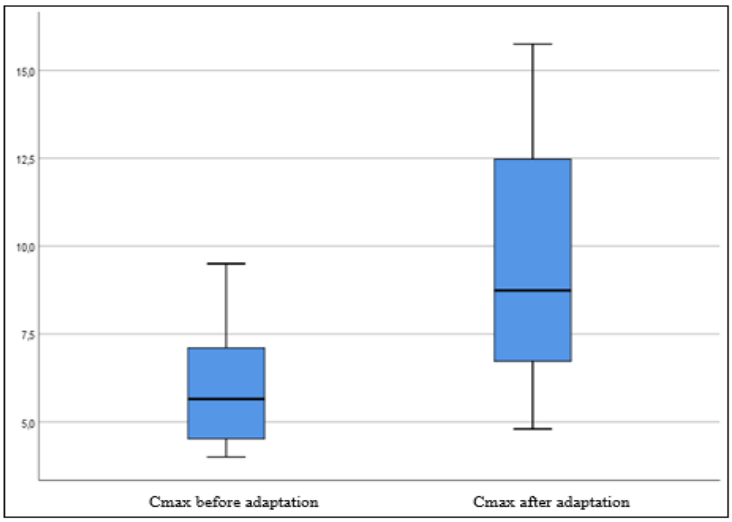

Figure 1. Schéma de la différence de médianes des Cmax avant et aprés adaptation posologique

The specific objective of a C_{max}/CMI ratio between 8 and 10 was achieved in 44.4% of cases, showing a significant correlation with the patients' creatinine clearance (p-value = 0.047).

Conclusion

The use of individualized initial doses of gentamicin, combined with therapeutic drug monitoring based on pharmacokinetic/pharmacodynamic (PK/PD) parameters, enhances the chances of therapeutic success and limits the emergence of bacterial resistance. Our study revealed a significant rate of underdosing due to sub-therapeutic initial doses and inadequate administration methods. All these factors expose patients to therapeutic failure or an increased duration of hospitalization.

The implementation of therapeutic drug monitoring based on the PK/PD approach represents a significant advancement and provides the rational basis for improving the selection of appropriate gentamicin doses and their administration methods based on the bacteria involved and the patient's pharmacokinetic characteristics, with a promising prospect of enhancing the management of severe patients."

Recommendations

For optimal use of gentamicin, it is imperative to select an individualized dose based on body weight and renal function. Furthermore, it is essential to regularly monitor gentamicin blood concentrations. The use of PK/PD principles should guide the selection of doses and administration methods based on the bacteria involved and patient characteristics, especially for serious infections. It is also crucial to optimize the route and timing of administration, taking into account the patient's condition and the site of infection. Finally, close collaboration with pharmacists is necessary to ensure compliance with dosing guidelines, appropriate monitoring, and personalized dose adjustments.

Scientific Ethics Declaration

The authors declare that the scientific ethical and legal responsibility of this article published in EPHELS journal belongs to the authors.

Acknowledgements or Notes

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