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ORIGINAL ARTICLE

Therapeutic pharmacological monitoring of amikacin in a hospital setting: optimization of efficacy and prevention of toxicity

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ABSTRACT

Amikacin is an aminoglycoside antibiotic used for severe Gram-negative infections, characterized by a narrow therapeutic index and significant pharmacokinetic variability. Its use requires therapeutic drug monitoring (TDM) to optimize efficacy and prevent toxicity. The aim of this study was to perform therapeutic drug monitoring of amikacin after treatment initiation in order to optimize efficacy while preventing toxicity through individualized dosing based on plasma concentrations and clinical and renal parameters. This was a multicenter retrospective study including 50 hospitalized patients treated with amikacin. The mean age was 40 ± 22 years, mean weight 66 ± 19 kg, and mean estimated glomerular filtration rate (eGFR) was 115 mL/min/1.73 m². Plasma concentrations were measured using the EMIT method, with defined therapeutic targets: peak concentration (Cmax) 60–80 mg/L and trough concentration (Cmin) < 2.5 mg/L. Correlations between clinical and pharmacokinetic parameters were analyzed. The mean Cmin was 3.5 mg/L at first measurement, with approximately 60% exceeding the safety threshold. The mean Cmax was 50 mg/L, and only 22% of patients reached the therapeutic target. Only 12% of patients achieved both efficacy and safety targets simultaneously. Significant correlations were found between dose and weight (p = 0.01), Cmin and age (p = 0.03), and Cmax and administered dose (p = 0.007). These findings confirm a high pharmacokinetic variability of amikacin and the difficulty in simultaneously achieving therapeutic targets. The low proportion of patients reaching both targets highlights the limitations of standard dosing regimens and emphasizes the importance of individualized therapy guided by plasma concentration monitoring. Therapeutic drug monitoring of amikacin is essential to optimize exposure by balancing efficacy (Cmax 60–80 mg/L) and safety (Cmin < 2.5 mg/L), and remains crucial in hospital clinical practice.

Keywords: *Amikacin; therapeutic drug monitoring; trough concentration; peak concentration; efficacy; toxicity; dose individualization.*

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INTRODUCTION

Nosocomial infections are a major public health problem and represent a major challenge in the management of hospitalized patients. Their occurrence is associated with an increase in morbidity, mortality and a significant additional cost for health systems. The therapeutic failure of anti-infective treatments can be linked to several factors, including insufficiently adapted antibiotic therapy, limited distribution of the drug to certain difficult-to-access infectious sites (prostate, meninges, bone tissue or valve vegetations), inadequate consideration of pharmacodynamic parameters, local inactivation of the

antibiotic or lack of drainage of an infectious site.(Girou & Brun Buisson, 1999)(Schentag & Nightingale, 1999)

Aminoglycosides remain important in the treatment of severe infections due to their rapid bactericidal activity against many Gram-negative bacteria, especially enterobacteriaceae, as well as some Gram-positive bacteria. However, their use must be strictly controlled because of their narrow therapeutic range and the risk of renal and auditory toxicity. Thus, their prescription is based on limited indications, updated dosing regimens and appropriate therapeutic monitoring in order to optimize their effectiveness while minimizing adverse effects.(Agence Française de Sécurité Sanitaire des Produits de Santé, SPILF, GPIP, 2011)

Amikacin exerts concentration-dependent bactericidal activity and is characterized by a prolonged post-antibiotic effect, persisting even after plasma concentrations have become below the minimum inhibitory concentration (MIC), for a duration of up to 2 to 8 hours for Gram-negative bacilli. Its antimicrobial activity is based in particular on electrostatic interactions between the amino groups of the molecule and the acidic constituents of bacterial ribosomes, thus promoting its binding and efficiency. In addition, amikacin has better stability with respect to the bacterial enzymes responsible for the inactivation of aminoglycosides.(Gachet, 2022)(Agence Française de Sécurité Sanitaire des Produits de Santé, SPILF, GPIP, 2011)

Amikacin is administered parenterally, intravenously, or intramuscularly, as well as by inhalation in liposomal form. In practice, it is administered as a short infusion lasting 30 to 60 minutes, with a peak plasma concentration reached about 30 minutes after the end of the infusion. Its plasma protein binding is low, less than 10%. It is not metabolized, crosses the placental barrier, and is excreted in human milk.(Lovering & Reeves, 2010)(Evans, Schentag, & Jusko, 1992)(William & Ette, 2007)

Despite rigorous therapeutic monitoring, nephrotoxicity remains a common adverse reaction of aminoglycosides, while ototoxicity is closely correlated with cumulative exposure and duration of treatment. These toxicities, which are potentially irreversible, justify the implementation of regular pharmacological therapeutic monitoring in order to reconcile clinical efficacy and safety of use. (Aiju Endo, 2022)

A treatment duration limited to five days appears to be an optimal compromise between bactericidal efficacy and the reduction of the risk of renal or auditory toxicity. In this context, single daily dose administration is the most appropriate regimen to achieve target plasma concentrations. Recommended dosages of amikacin are usually between 15 and 30 mg/kg/day. (Zaske, 1992)

Amikacin has a narrow therapeutic index: its effectiveness depends on obtaining a high maximum concentration (Cmax), whereas toxicity, particularly renal and auditory, is associated with excessive residual concentrations (Cmin), reflecting intracellular accumulation. Its pharmacokinetics are marked by significant inter-individual variability, with an elimination half-life ranging from 0.5 to more than 70 hours and an apparent volume of distribution ranging from 0.15 to 0.8 L/kg. Significant intra-individual variability is also observed, which justifies regular therapeutic pharmacological monitoring (PTS) throughout treatment. (Site du Collège National de Pharmacologie Médicale, 2025)

The main pharmacokinetic parameters monitored are the peak concentration (Cmax), measured 30 minutes after the end of the infusion, and the trough concentration (Cmin), determined immediately before the administration of the next dose. The interpretation of the results should take into account the severity of the infection, the individual characteristics of the patient and the modalities of administration. A high Cmin usually requires a prolongation of the interval between administrations, while an insufficient Cmax, after analytical verification, may lead to a cautious increase in dosage. In addition, the Cmax target must be adapted to the minimum inhibitory concentration of the isolated germ, the objective being to obtain an inhibitory quotient (IQ = Cmax/MIC) greater than 8 . (Lacarelle, Baltasat, Bouquet, & Venisse, 2006) (Site du Collège National de Pharmacologie Médicale, 2025)

The objective of this study was to evaluate, through pharmacological therapeutic monitoring, the adequacy of amikacin plasma concentrations to the recommended therapeutic targets, in order to analyze its efficacy and tolerability in hospitalized patients.

MATERIAL AND METHODS

This is a multicenter, retrospective, cross-sectional and evaluative study with a descriptive aim, carried out in several Algerian university hospitals. The study included patients hospitalized in different specialized departments, including intensive care, nephrology, the burn department as well as other medical and surgical units, who received treatment with amikacin as monotherapy or in combination with other antibiotics. All patients included benefited from therapeutic pharmacological follow-up (STP) carried out as part of the usual clinical practice of the participating hospitals.

Standardized data collection sheets, developed by the pharmacology department of the EHU of Oran in collaboration with clinicians, were used for each patient meeting the inclusion criteria. These sheets

included key relevant demographic, clinical, biological, microbiological and therapeutic data, including patient characteristics, renal function parameters, associated anti-infective therapies and amikacin administration modalities.
Blood samples for therapeutic pharmacological monitoring were taken according to the usual recommendations. Peak plasma concentrations (Cmax) were measured 30 minutes after completion of the intravenous infusion, while trough concentrations (Cmin) were collected approximately 30 minutes prior to the administration of the next dose. These concentrations were used for the assessment of therapeutic efficacy and toxicity risk, respectively.
The plasma assay of amikacin was performed in the pharmacology-toxicology departments of the various participating university hospitals by EMIT (Enzyme Multiplied Immunoassay Technique) enzyme-linked immunoassay method on an automated analyzer.
The target plasma concentrations selected in this study corresponded to trough concentrations (Cmin) below 2.5 mg/L and maximum concentrations (Cmax) between 60 and 80 mg/L, in accordance with generally accepted recommendations for the use of aminoglycosides. The search for drug interactions involving amikacin was performed using specialized databases and tools, including the DrugBank monograph and other validated pharmacological references. The identified interactions were classified according to their level of severity into major, moderate or minor interactions, and then expressed as a percentage of observed cases.
Descriptive statistical analysis was performed by expressing qualitative variables as numbers and frequencies, while quantitative variables were presented as means ± standard deviation.

RESULTS

Demographic, Biological and Clinical Data

The study population included 50 patients (30 males and 20 females), with a mean age of 40 ± 22 years and an average weight of 66 ± 19 kg. Renal function was generally maintained with an average glomerular filtration rate (GFR) of between 102 and 127 ml/min. Patients were hospitalized in different departments of the participating university hospitals, including intensive care, urology, nephrology, burns department, infectious diseases, orthopedics, and other specialized units (Table 1).
Amikacin was administered as monotherapy or in combination for a variety of infections, mainly urinary, cutaneous, bronchopulmonary, as well as cases of sepsis, peritonitis and endocarditis. Antibiotic therapy was documented in 26% of cases. The most frequently isolated germs were *Pseudomonas spp.*, *Escherichia coli*, *Klebsiella spp.* and *Streptococcus spp.* (Table 1, Figure 1).

Drug interactions and associated treatments

The therapeutic combinations mainly involved beta-lactams, glycopeptides and fluoroquinolones, with a predominance of cefotaxime (Figure 1).
Clinically significant interactions involving amikacin were observed in more than 10% of patients. Vancomycin was the most common combination (61%), followed by furosemide (16%), vancomycin–furosemide (12%) and aciclovir (11%) (Figure 2). In terms of severity, 28% of the interactions required precautions for use, while 72% were to be monitored as part of therapeutic management.

Dosage and duration of treatment

Doses administered ranged from 150 to 2000 mg depending on the severity of the infection and the clinical setting. In terms of weight dosage, 30% of patients received less than 10 mg/kg, 35% between 10 and 15 mg/kg, 14% between 15 and 20 mg/kg, 6% between 20 and 25 mg/kg, and 10% between 25 and 30 mg/kg. This variability reflects the individual adaptation of prescriptions. The median duration of treatment was 5 days (Figure 3).

Plasma Concentration Assays

Out of 100 samples taken, 70 were compliant and usable for pharmacological analysis. The assays mainly concerned the trough (Cmin) and peak (Cmax) concentrations. Additional Cmin controls were performed when values approached or exceeded the toxicity threshold of 2.5 mg/L. Thus, 10 patients benefited from a second dose and 4 patients from a third dose in a context of enhanced surveillance.

Therapeutic pharmacological follow-up

Trough concentrations (Cmin)

Three Cmin series were performed. The first (Cmin1), systematic, had an average of 3.5 mg/L. The second (Cmin2), performed on 10 patients after therapeutic adaptation, showed an average of 2.6 mg/L. The third (Cmin3), performed in 4 patients requiring enhanced follow-up, had an average of 4.3 mg/L (Figure 4).
Approximately 60% of Cmin1 was below the safe threshold of 2.5 mg/L. This rate was 66.7% for Cmin2 and 33.3% for Cmin3 (Figure 5).

Peak Concentrations (Cmax)

Initial Cmax averaged 50 mg/L. A second measurement made after therapeutic adjustment found a mean value of 36 mg/L (Figure 6).

Based on the treatment objectives, 22% of concentrations were within the target range of 60 to 80 mg/L (Figure 7).

Pharmacokinetic correlations

A significant correlation was observed between daily intake and body weight ($p = 0.01$). Cmin were significantly associated with the age of the patients ($p = 0.03$). Cmax was correlated with the administered dose ($p = 0.007$) as well as the dosage in mg/kg ($p = 0.01$).

Table 1: Demographic and Biological Data

Variable	Patient weight (kg)	Age of patients (Years)	Sex ratio	DFG (mL/min)
N (%) or Avg±SD	66± 19	40±22	1.5	115.78 ± 13

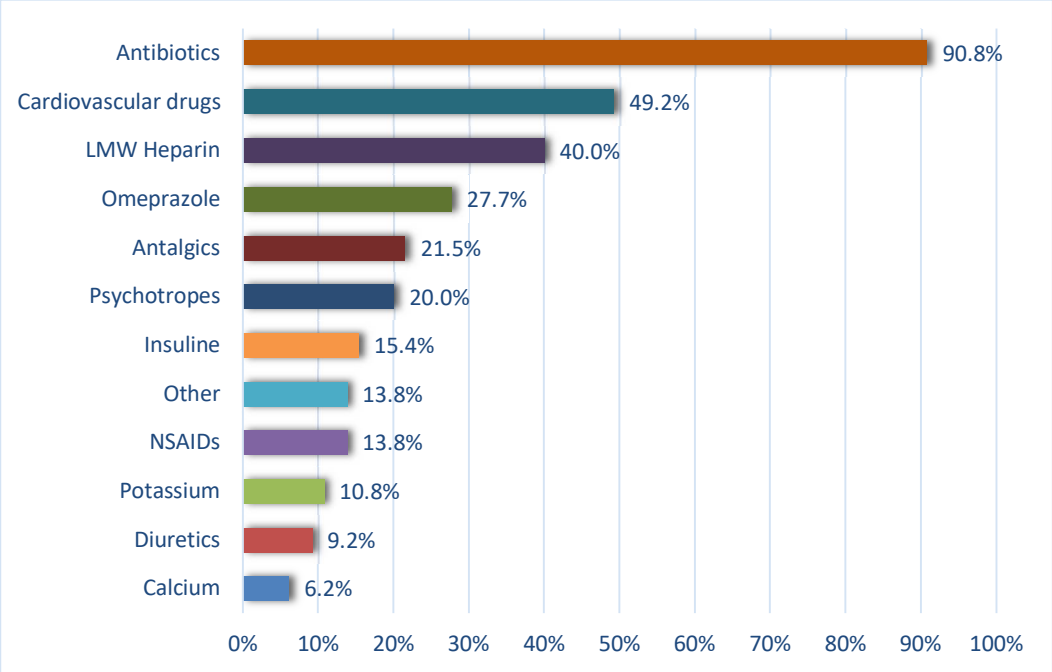

Figure 1 Percentages of amikacin combinations in the population

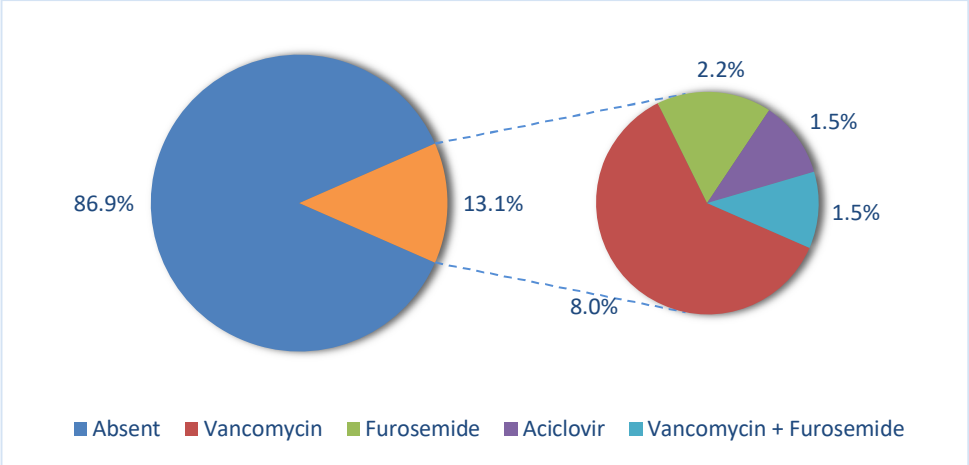

Figure 2 Percentage of drug interactions with amikacin compared to interactions experienced (13.1% in the population)

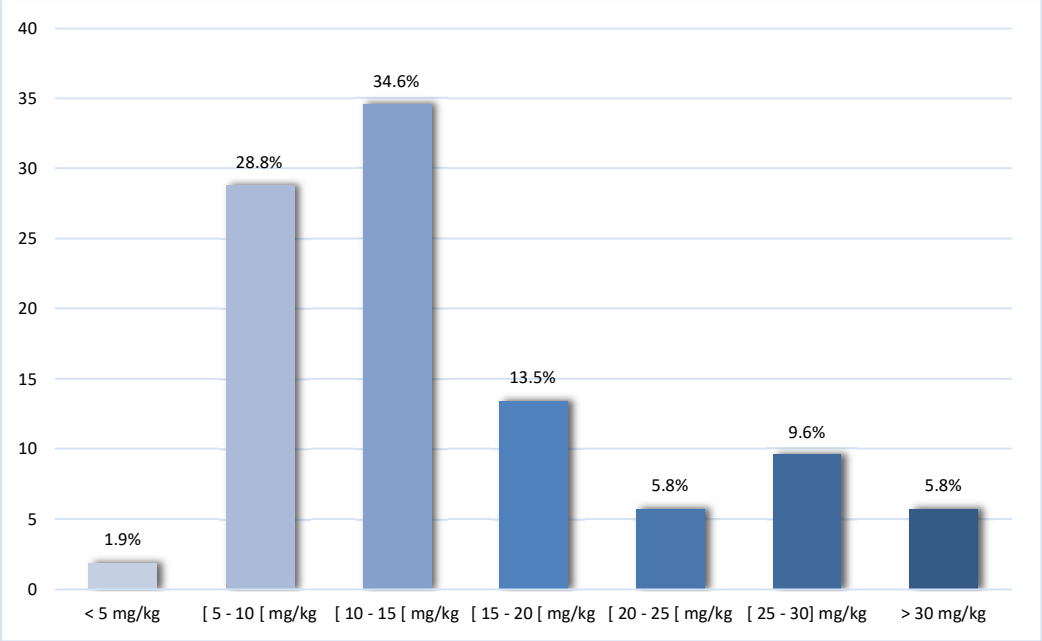

Figure 3 Amikacin dosage by body weight in mg/kg increments

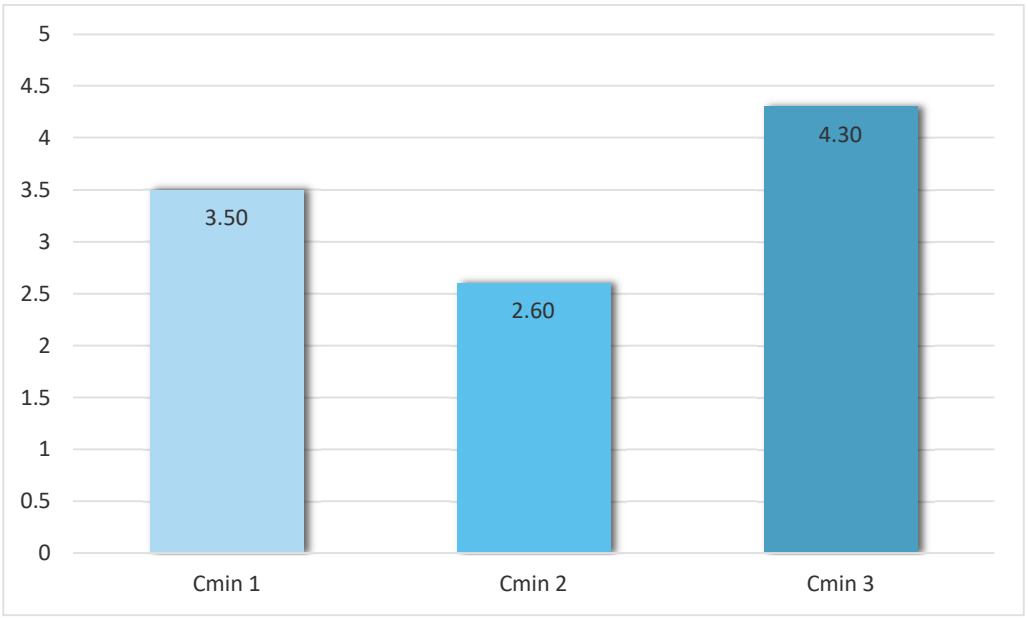

Figure 4: Average trough concentrations (Cmin) of amikacin per measurement point in mg/L

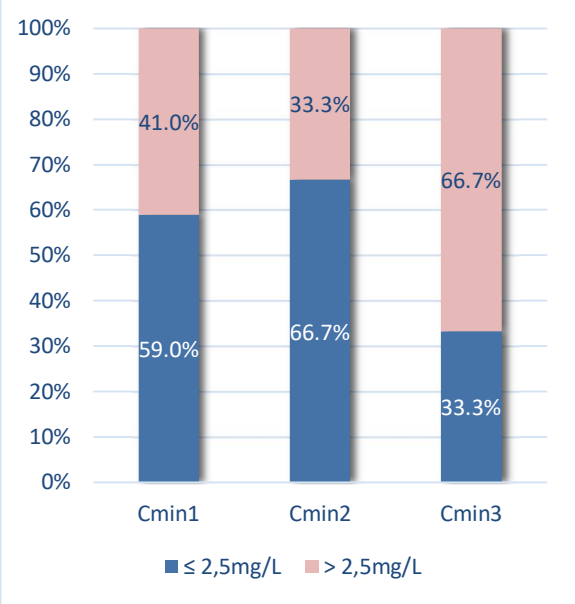

Figure 5: Percentage of trough concentrations of amikacin (Cmin) compared to the threshold value of 2.5mg/L

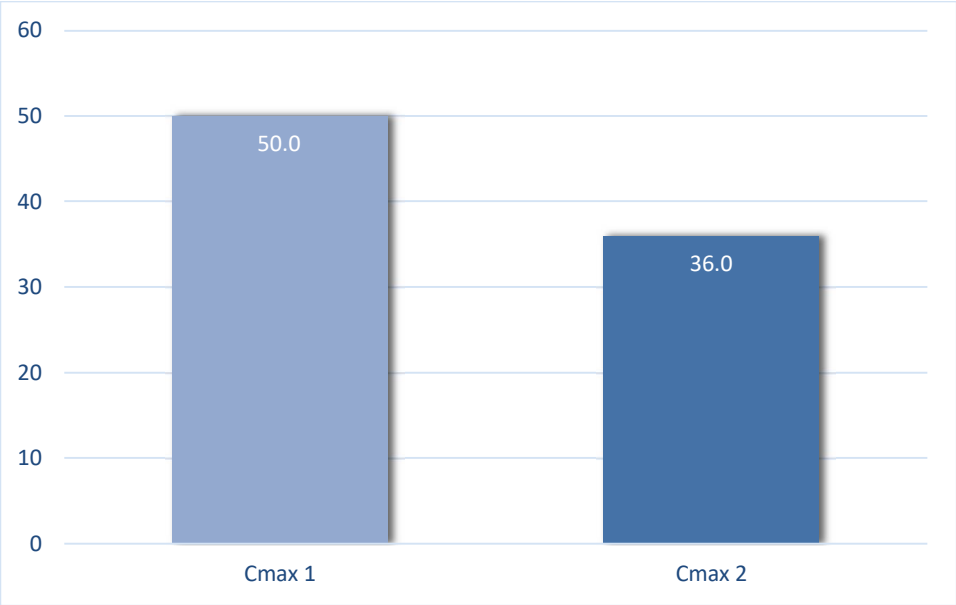

Figure 6: Average of first and second peak concentrations (Cmax) in mg/L

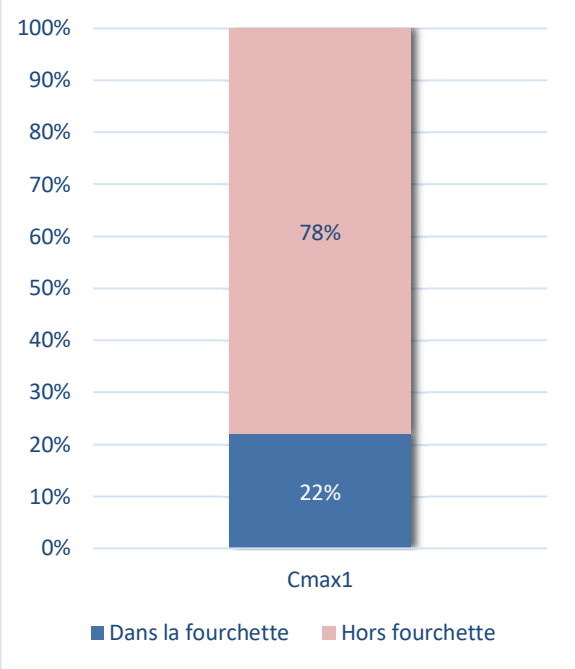

Figure 7 Percent of peak concentrations (Cmax) within range [60 - 80] mg/L

DISCUSSION

Despite its recognized clinical efficacy, amikacin remains associated with a significant risk of nephrotoxicity and ototoxicity. Its pharmacokinetics are characterized by significant inter-individual variability, while the relationships between plasma concentrations, antibacterial efficacy and toxicity are now well established. In addition, the management of Gram-negative infections is becoming increasingly complex due to the emergence of strains with decreased susceptibility to available antibiotics. This problem is accentuated by the pathophysiological changes observed in certain patient populations, likely to unpredictably alter the pharmacokinetic parameters of anti-infectives.(Venisse & Boulamery, 2011)(Padoin & C, 2017)

Population and clinical context: The characteristics of our population (50 patients) are generally comparable to those reported in the literature, in particular by Boidin et al. The main indications were dominated by urinary tract infections, skin infections and sepsis .(Boidin, Bourguignon, Cohen, & & al, 2019; Romano, et al., 1998)

Dosage and exposure: The doses administered (150–2000 mg, or 10 to 30 mg/kg in the majority of cases) remain generally below international recommendations, which may explain suboptimal exposure in some cases. These results are consistent with the observations of Boidin et al., and confirm that higher doses may be required in severe infections.(Boidin, Bourguignon, Cohen, & & al, 2019)(Jean-Bart, Debeurmea, Ducher, & Bourguinion, 2013)

Concentration monitoring and variability: The observed Cmin and Cmax illustrate a high pharmacokinetic variability. The decrease in adjusted Cmin (Cmin2) mainly reflects an adjustment of intervals or doses, reflecting a reduction in the risk of toxicity. Conversely, the increase observed in some patients during Cmin3 is likely related to fluctuating renal function and progressive accumulation. These results are consistent with those of Goutelle who worked on finding the optimal dose of amikacin using a dose of 25mg/kg and found that 54% of the trough concentrations were above the standard of 2.5mg/l. (Goutelle, et al., 2022)

These results are similar to those of Logre *et al* who obtained a percentage of 60% of the trough concentrations above 2.5 mg/l. Roger et al found comparable results, the trough concentration ≥ 2.5 mg/L in 49%; 60% and 60% of patients for Cmin1, Cmin2, Cmin3 respectively. (Logre, et al., 2020; Roger, et al., 2016)

Regarding Cmax, only a minority of patients reached the target range (60–80 mg/L), reflecting insufficient exposure in a large part of the population. The decrease observed after dose adjustment reflects a conservative strategy aimed at limiting toxicity, but which may compromise efficacy. The results are close to those of Logre *et al* who found a percentage of 45.9% of patients whose dose used is 25mg/kg who reached a peak concentration above 64mg/l (Logre, et al., 2020)

Compared to the data from Bressolle et al. (54.1 ± 17.3 mg/L) and Maller et al. (55 mg/L), our results are generally consistent but confirm a significant heterogeneity of exposures. (Bressolle, Gouby, Martinez, Joubert, & & al, 1996)(Maller, Isaksson, Nilsson, & Soren, 1988)

Limitations of standardized regimens: Only 12% of patients achieved both Cmin and Cmax goals simultaneously. This low proportion underlines the limitations of standard dosing regimens in a heterogeneous population and confirms the need for individualization of doses based on pharmacological therapeutic monitoring.

PHARMACOKINETIC CORRELATIONS AND DETERMINANTS

The lack of a robust correlation between weight and exposure confirms that weight alone is insufficient to predict concentrations. Age appears to be a factor influencing Cmin, while Cmax remains dose-dependent. These results are in line with the observations of Bourguignon et al. and Ducher et al. stressing the importance of renal function and physiological variations.(Bourguignon, et al., 2009) (Ducher, Maire, Cerutti, Bourhis, & & al, 2001)

Drug interactions and clinical implications: Combinations with vancomycin, furosemide, and some antivirals pose an increased risk of nephrotoxicity, requiring close monitoring. This combination with antibiotics is comparable to that described by J-Blanco et al. (Pe´rez-Blanco,, Ferna´ndez, Calvo, Lanao, & Martı´n-Sua´rez, 2020)

LIMITATIONS AND THERAPEUTIC OPTIMIZATION

A limited proportion of patients (n=6) simultaneously met efficacy and safety objectives, highlighting significant inter-individual variability in amikacin exposure. This observation highlights the limitations of standardized dosing regimens in a heterogeneous population and reinforces the need for therapeutic individualization based on the monitoring of plasma concentrations. It also suggests that the therapeutic thresholds currently used may require re-evaluation in certain clinical settings.

CONCLUSION

This study confirms the central role of amikacin in the treatment of severe Gram-negative infections. However, its optimal use is based on rigorous dosage adjustment, guided by pharmacological therapeutic monitoring, in order to balance efficacy and safety. The pharmacokinetic variability observed in clinical practice requires systematic individualization of doses to improve therapeutic exposure and reduce the risk of toxicity.

In addition, amikacin–vancomycin poses an increased risk of nephrotoxicity and ototoxicity due to pharmacodynamic interaction, which warrants close monitoring and appropriate therapeutic adjustment.

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