Standard dosing of amikacin and gentamicin in critically ill patients results in variable and subtherapeutic concentrations

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ABSTRACT

Low peak plasma concentrations (C_{max}) of amikacin and gentamicin are reported in intensive care unit (ICU) patients after administration of the first dose. The present study aimed to describe the proportion of ICU patients in whom an adequate C_{max} was achieved throughout the course of therapy. Septic ICU patients with an indication for intravenous amikacin or gentamicin were eligible for inclusion in this single-centre observational study. The first and subsequent doses and the corresponding C_{max} values were recorded. The target C_{max} was ≥60 mg/L for amikacin and ≥30 mg/L for gentamicin. Amikacin and gentamicin plasma concentrations were available in 66 and 24 patients, respectively (59 ± 17 years; 79 ± 19 kg; height 169 ± 12 cm; SAPS II score 46 ± 19). Pulmonary, abdominal and urinary tract infections were diagnosed in 64 patients. Culture-positive infection was confirmed in 65 patients (72%). A target first C_{max} was achieved in 17/90 patients (19%). For amikacin, the target C_{max} was achieved in 16/66 patients (24%) after the initial dose. In the 50 remaining patients, a change in dosing was performed in 14 patients, leading adequate peak plasma level in 2 patients. For gentamicin, the targeted C_{max} was achieved in only 1/24 patient (4%) after the initial dose and was never achieved after the third dose. In conclusion, standard dosing of amikacin or gentamicin led to adequate C_{max} in only 19% of patients. Subtherapeutic C_{max} were not significantly corrected after subsequent doses.

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1. Introduction

Early and appropriate treatment of infections is a priority in the management of intensive care unit (ICU) patients and could reduce mortality rates in patients with severe sepsis or septic shock [1,2]. Therefore, empirical broad-spectrum anti-infective therapy, often using multiple agents, is recommended for the initial treatment of severe sepsis [3]. Although some specific anti-infective combinations remain controversial, a survival improvement has been reported with the use of combination therapy in patients with septic shock [4,5]. Therefore, aminoglycosides are often given as part of empirical therapy for severe sepsis and septic shock, especially when Gram-negative bacteria are suspected [6].

One of the main conditions for aminoglycoside therapy to be efficient is to achieve therapeutic drug concentrations at the site of infection [7]. As tissue concentrations of anti-infective drugs cannot be routinely measured, plasma concentrations are classically used as a surrogate to confirm the appropriateness of dosing and anti-infective exposure. From a pharmacodynamic perspective, for aminoglycosides the ratio between the peak plasma concentration (C_{max}) and the minimum inhibitory concentration (MIC) of the

infecting pathogen (C_{max}/MIC) is considered as the best index of bacterial killing and the subsequent success of anti-infective treatment [8]. Maximum antibacterial activity is achieved when C_{max} is 8–10 times greater than the MIC [9–11]. Although the ratio of the area under the concentration–time curve from 0–24 h (AUC_{0-24}) to the MIC (AUC_{0-24}/MIC) for the first dose is also correlated with maximum aminoglycoside activity [12], for convenience peak concentrations are used for therapeutic concentration monitoring [13]. Despite a large possible distribution of MICs for different pathogens, recent French recommendations for the use of aminoglycosides targeted C_{max} of 30–40 mg/L and 60–80 mg/L for gentamicin and amikacin, respectively [14]. These recommendations are closest to the recommended peak concentrations in recent publications [15–17]. As aminoglycosides are nephrotoxic, residual plasma concentrations should be monitored to minimise the likelihood of nephrotoxicity and ototoxicity [13,14].

Although the pharmacokinetics of aminoglycosides in ICU patients has previously been described, studies on optimal dosing regimens for patients with sepsis have had several limitations [18,19]. Many factors can influence the pharmacokinetics of different anti-infective drugs [20]. Indeed, alterations in the volume of distribution, plasma albumin concentration, increased cardiac output, increased blood volume, and paradoxical renal and hepatic clearance increase can be observed in the early stage of severe sepsis and are frequently observed in ICU patients [20]. Some studies have previously shown a low aminoglycoside concentration in the early phase of therapy in ICU patients [17,21]. Taccone et al. [17] and de Montmollin et al. [15] recently reported 30% and 33% of patients with a first amikacin C_{max} of <60 mg/L after a first dose of 25 mg/kg, respectively. Gálvez et al. [16] compared three initial doses of amikacin (15, 25 and 30 mg/kg) and reported a target C_{max} of >60 mg/L in 0%, 39% and 76% of patients, respectively. Unfortunately, neither of these previous studies provided concentration data for the subsequent doses of aminoglycosides. Therefore, to address this deficiency in the literature, an observational study was performed to describe the proportion of ICU patients achieving target peak plasma aminoglycoside concentrations after the first dose as well as after subsequent aminoglycoside doses.

2. Materials and methods

This was a single-centre observational cohort study. As this was a non-interventional study to assess the daily practice of aminoglycoside monitoring in the ICU of Nîmes University Hospital (Nîmes, France), approval by the Comité de Protection des Personnes was not required according to French law. Therefore, the study was approved by the Institutional Review Board of Nîmes University Hospital and was declared to the Commission nationale de l'informatique et des liberté (CNIL). For this reason, the need for written informed consent from patients was waived. However, all patients and/or their next of kin were verbally informed of the data collection and could refuse to participate.

All ICU patients with infection in whom the physician in charge prescribed intravenous (i.v.) administration of aminoglycosides were eligible for inclusion. Patients were excluded if they were <18 years of age or had a known allergy to aminoglycosides. Finally, patients who were under guardianship or prisoners could not participate. Patients with a confirmed and/or suspected myasthenia and/or ICU-acquired neuromuscular disorder were also excluded. No patient was included more than once in the data collection.

The aminoglycoside was given in combination with broadspectrum antibiotics according to the suspected pathogens and to local clinical practice. In our ICU, a once-daily dosing regimen is used as follows: ≥15 mg/kg for amikacin and ≥3 mg/kg for gentamicin based on actual weight at admission. For obese patients, the weight used for dosing was left to the physician's discretion. All aminoglycosides were given as a 30-min i.v. infusion in glucose 5% solution. The timing of C_{max} sampling was 30 min after the end of initial infusion. When subsequent doses of aminoglycoside were recommended as part of the patient's treatment plan, trough plasma concentrations (taken at 16–24 h post-infusion) (C_{min}) and C_{max} were collected as part of unit practice.

The targeted concentrations for amikacin and gentamicin were as follows [14]: amikacin, peak ≥60 mg/L and trough <2.5 mg/L; and gentamicin, peak ≥30 mg/L and trough <0.5 mg/L.

The following data were collected:

- demographic characteristics: age, sex, and height and weight with calculated body mass index (BMI);
- medical history, initial reason for ICU admission and Simplified Acute Physiology Score II (SAPS II) [22] at ICU admission;
- clinical parameters: urine output was classically collected every 2 h; the Sequential Organ Failure Assessment (SOFA) [23] score and the Acute Kidney Injury Network (AKIN) [24] score were calculated daily from the initiation of aminoglycoside therapy;
- presence of renal replacement therapy (RRT);
- co-prescription of nephrotoxins (e.g. glycopeptides, diuretics);
- biological parameters: serum creatinine concentration, hepatic function (serum total bilirubin and transaminase) and platelets that were daily dosed in daily practice;
- type of infection and anti-infective therapy: type of infection, anti-infective agent(s) administered and microbiological cultures collected; and
- amikacin and gentamicin assays: amikacin and gentamicin concentrations were measured using automated immunoassays (Roche Diagnostics GmbH, Mannheim, Germany) on a COBAS® C System. Three levels of quality controls were performed daily (5, 14 and 27 mg/L for amikacin and 1.7, 4.5 and 6.8 mg/L for gentamicin). As mentioned in the supplier's data sheet, the limit of quantification is 0.8 mg/L for amikacin and 0.3 mg/L for gentamicin.

2.1. Statistical analysis

Data are expressed as the mean ± standard deviation (S.D.) for quantitative variables. Qualitative data are expressed as absolute values with percentage.

A univariate analysis and a multivariate regression model using stepwise selection were performed to determine predictive factors of not achieving target C_{max}. When groups were compared, Mann–Whitney U-test, Student's t-test and χ^2 test were performed as appropriate. Statistical significance was set at $P < 0.05$.

3. Results

3.1. Patients

From 2 June 2013 to 29 November 2013, 325 patients (197 male; age 61 ± 17 years; SAPS II score 40.4 ± 20.2; length of stay in the ICU 7.9 ± 12.6 days; mortality rate 30%) were admitted to the ICU. Among them, 130 patients (87 male) were administered aminoglycosides (Fig. 1). Tobramycin was given to 6 patients who did not participate and in another 34 patients a concentration from the first dose of aminoglycosides was not available; thus, 90 eligible patients were included in the study (Fig. 1). The characteristics of the patient cohort are shown in Fig. 1. At the time of initiation of antibiotics, SOFA and AKIN scores were 6.4 ± 4.1 and 0.5 ± 1.0, respectively. RRT was applied in 16 patients (18%) and concurrent nephrotoxic agents were given to 39 patients (43%).
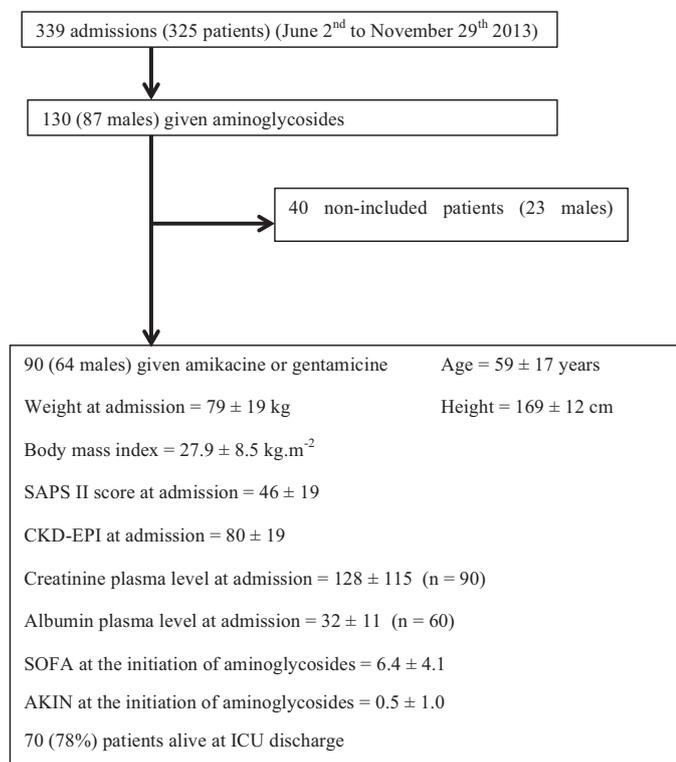
Fig. 1. Flow chart for study inclusion and characteristics of the patient cohort. There was no statistical difference between included and non-included patients. SAPS II, Simplified Acute Physiology Score II; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration (formula to estimate the glomerular filtration rate); SOFA, Sequential Organ Failure Assessment score; AKIN, Acute Kidney Injury Network score; ICU, intensive care unit.

3.2. Infections

As described in Table 1, pulmonary, abdominal and urinary tract infections were diagnosed in more than two-thirds of patients. Culture-positive infection was present in 65 patients (72%). Gram-positive bacteria, Gram-negative bacteria and both pathogens were present in 22 (24%), 26 (29%) and 6 (7%) patients, respectively. *Staphylococcus aureus* and *Escherichia coli* were the most commonly isolated pathogens. Polymicrobial infection was diagnosed in 11 patients (12%) and yeast was isolated in 11 patients (12%).

3.3. Aminoglycoside therapy

3.3.1. Efficacy of the first dose

Amikacin and gentamicin were given in 66 (73%) and 24 (27%) patients, respectively. Fig. 2 shows the individual C_{max} according to the given dose of amikacin or gentamicin. Seventeen patients (19%) had a C_{max} above the recommended target. Using a multivariate regression model with stepwise selection, only a low first dosing of aminoglycoside was associated with a low first C_{max} ($P < 0.01$).

3.3.2. Amikacin therapy (66 patients)

The mean ± S.D. first dose was 22.6 ± 6.9 mg/kg (median 21.9 mg/kg) of ICU admission body weight. Seven patients were given <15 mg/kg. The mean ± S.D. C_{max} was 50.9 ± 19.1 mg/L. Sixteen patients (24%) given amikacin had an actual C_{max} above the recommended peak value (Fig. 2A).

The peak and trough concentrations during the treatment course are shown in Fig. 3A. From Day 2 to Day 5, 6/27, 3/33, 1/19 and 4/10 patients, respectively, had an actual $C_{max} \geq 60$ mg/L. The median dose of amikacin did not change throughout therapy, although 75% of C_{max} concentrations were <60 mg/L (Fig. 3A).

Table 1
Types of infection and pathogens.

	n
Site of infection	
Pulmonary	39
Abdominal	12
Urinary tract	13
Septicaemia	9
Other	3
Unknown	13
Isolated pathogens in 65 patients (72%)	
Staphylococcus aureus	15
Other staphylococci	6
Enterococcus faecalis	5
Haemophilus influenzae	2
Escherichia coli	11
Klebsiella pneumoniae	8
Proteus mirabilis	3
Enterobacter aerogenes	4
Enterobacter cloacae	3
Serratia marcescens	3
Pseudomonas aeruginosa	4
Candida albicans	11
None	25

Dosing of amikacin was increased in 14 of 50 patients with a first $C_{max} < 60$ mg/L. These results led to an adequate C_{max} in two patients at Day 5. Fig. 3B shows the course of treatment with amikacin. The therapy was ended between Day 3 and Day 5. When a new injection was performed, the subsequent C_{max} was measured in 27/45, 33/44, 19/28 and 10/11 patients at Days 2, 3, 4 and 5, respectively (Fig. 3B).

Among 16 patients with $C_{max} \geq 60$ mg/L, there were 4 deaths (25%) versus 14 deaths (28%) among 50 patients with $C_{max} < 60$ mg/L ($P = 0.82$).

3.3.3. Gentamicin therapy (24 patients)

The mean ± S.D. first dose of gentamicin was 6.6 ± 2.3 mg/kg (median 5.9 mg/kg). No patient was given <3 mg/kg. The mean ± S.D. C_{max} was 15.7 ± 7.3 mg/L. Twenty-three patients (96%) given gentamicin had an actual C_{max} under the recommended peak value (Fig. 2B).

The peak and trough concentrations of gentamicin during the treatment course are shown in Fig. 4. Although the median given dose was two-fold higher than the recommended dose, a target C_{max} was reached in only one patient at Day 1 and Day 2 and was not achieved on any other days of therapy. From Day 2 to Day 5, 1/17, 0/15, 0/11 and 0/3 patients, respectively, had an actual $C_{max} \geq 30$ mg/L (Fig. 4A). Among 23 patients with a first $C_{max} < 30$ mg/L, there were one, two or three increases in dosing of gentamicin in 8, 4 and 1 patients, respectively.

These results never led to an adequate C_{max}. Fig. 4B shows the course of treatment with gentamicin. The therapy was ended between Day 2 and Day 5. When a new injection was performed, the subsequent C_{max} was measured in 17/20, 15/16, 11/15 and 3/7 patients at Days 2, 3, 4 and 5, respectively (Fig. 4B).

Among these 24 patients, there were two deaths with first C_{max} at 11.5 mg/L and 18 mg/L, respectively.

4. Discussion

The present study assessed the daily practice of amikacin and gentamicin administration relative to a French aminoglycoside dosing guideline [14]. A first C_{max} was performed in 90 of 130 patients administered aminoglycosides. An adequate first C_{max} was reported in only 17 (19%) of 90 patients (16/66 for amikacin and 1/24 for gentamicin). For subsequent doses, when C_{min} and C_{max}
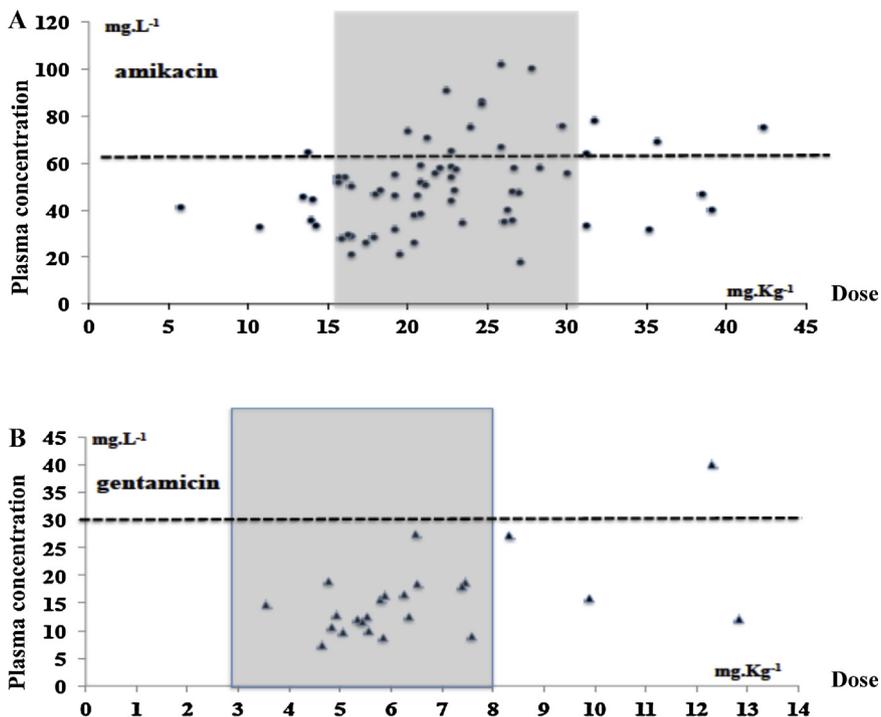
Fig. 2. Peak plasma concentration (mg/L) according to the given dose (mg/kg) for the first dose of (A) amikacin and (B) gentamicin. The dotted line shows the recommended peak plasma concentration (mg/L). The grey zone shows the recommended dose (mg/kg).
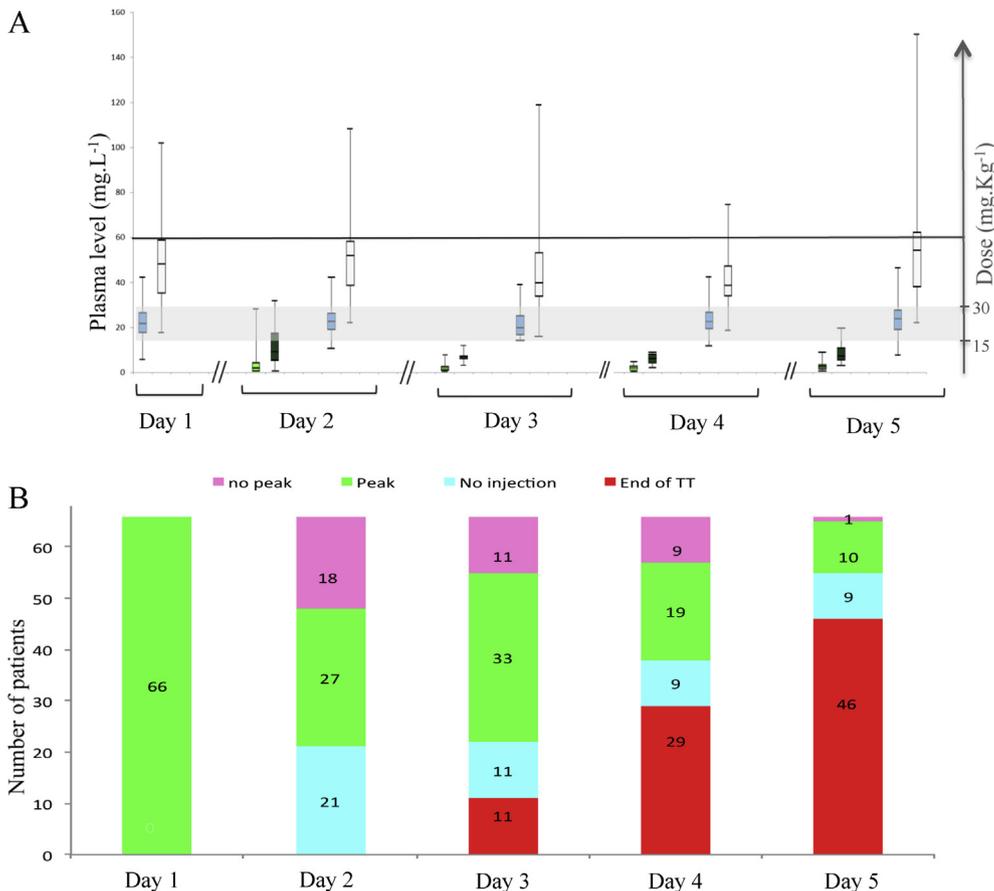

Fig. 3. (A) Course of dosing, and peak and trough plasma concentrations of amikacin according to the day of therapy. Dosing is shown in the blue box plot and peak plasma concentrations in the white box plot. Trough plasma concentrations are shown for patients in whom a new injection was performed (light green box plot) and for patients in whom a new injection was not performed (end of the therapy, trough level too high) (dark green box plot). The black line shows the targeted peak (60 mg/L). (B) Distribution of patients receiving amikacin and patients in whom a new peak was not measured [end of treatment (TT), high trough, no blood sample]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
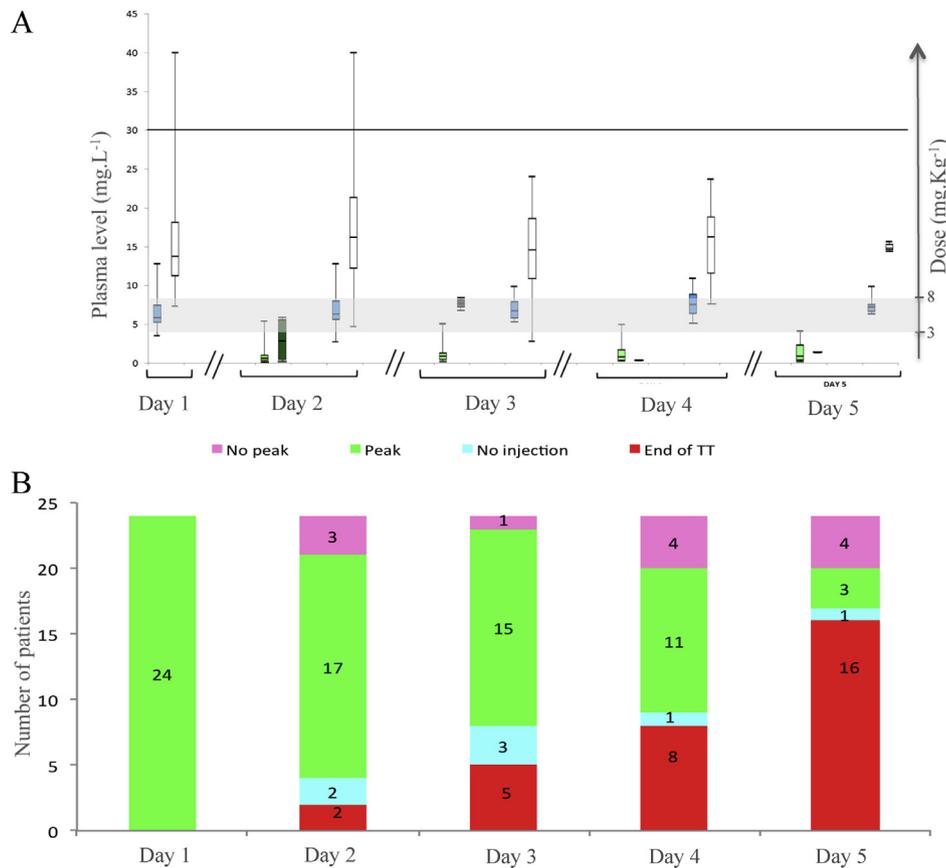
Fig. 4. (A) Course of dosing, and peak and trough plasma concentrations of gentamicin according to the day of therapy. Dosing is shown in blue box plot and peak plasma concentrations in the white box plot. Trough plasma concentrations are shown for patients in whom a new injection was performed (light green box plot) and for patients in whom a new injection was not performed (end of the therapy, trough concentration too high) (dark green box plot). The black line shows the targeted peak (30 mg/L). (B) Distribution of patients receiving gentamicin and patients in whom a new peak concentration was not measured [end of treatment (TT), high trough, no blood sample]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

were monitored, dose changes were not commonly performed, leading to adequate C_{max} being observed in only 25% of patients with amikacin therapy and in none of the patients receiving gentamicin therapy.

The present study was performed in a French ICU that could be considered as broadly representative of southern French ICUs [25]. The sources of infection and the most frequent pathogens are similar to previous studies [1,26,27]. In our unit, we give aminoglycosides as part of broad empirical anti-infective therapy in order to increase the probability of appropriate pathogen coverage [3]. In this context, gentamicin is usually given in community-acquired infection when a Gram-positive pathogen is suspected. Amikacin is usually given when a Gram-negative pathogen is suspected, especially in cases of nosocomial infection. Regarding aminoglycoside sampling, some bloods were not withdrawn in line with the protocol (34/40 non-included patients). In a recent study reported by de Montmollin et al., 36/67 episodes of amikacin administration had incorrect or no measurement of C_{max} [15].

In contrast to the two previous studies reported by Taccone et al. [17] and de Montmollin et al. [15], no regimen of high initial dose of aminoglycoside was recommended. Therefore, the present study tests the daily practice of aminoglycoside prescription on the basis of 15 mg/kg for amikacin and 3 mg/kg for gentamicin. The mean initial doses of amikacin and gentamicin were 22.6 ± 6.9 mg/kg [corresponding to a dosing ratio (given dose/recommended minimal dose) of 1.50 ± 0.46] and 6.6 ± 2.3 mg/kg (corresponding to a dosing ratio of 2.20 ± 0.76), respectively. These results show that physicians applied usual recommendations for high doses

of antibiotics in the ICU. Despite the use of such theoretical high doses, the initial infusion led to only 4% and 24% of patients having an adequate C_{max} with gentamicin and amikacin, respectively.

The proportion of patients with an adequate C_{max} with amikacin is far less than that reported by Taccone et al. [17] and de Montmollin et al. [15] who used higher initial doses of amikacin (25 mg/kg) leading to approximately two-thirds of patients having adequate C_{max}. In a randomised trial, Gálvez et al. [16] compared three initial doses of amikacin (15, 25 and 30 mg/kg). They reported that a targeted C_{max} of >60 mg/L was more easily reached in patients given 30 mg/kg (76% of patients). In critically ill haematological malignancy patients with infection requiring aminoglycoside therapy, Blackburn et al. [28] recently reported a median first dose of tobramycin and amikacin of 5.8 mg/kg and 13.8 mg/kg, respectively. As in the present study, the authors reported only 25% achievement of adequate first C_{max} even with lower target concentrations (tobramycin 20 mg/L and amikacin 40 mg/L).

To the best of our knowledge, few studies have focused on the concentrations of aminoglycosides throughout the course of therapy in ICU patients. In contrast to the two previous studies, we performed an audit of two agents, amikacin and gentamicin, to describe how target concentration achievement changed with time. First, even though the mean initial dose of gentamicin was nearly two-fold the minimum recommended dose (6.6 ± 2.3 mg/kg), an adequate C_{max} was reached in only 1 of 24 patients on Day 1. For amikacin, an initial mean dose of 22.6 ± 6.9 mg/kg led to an adequate first C_{max} in only 16/66 patients (24%). Second, the clinical practice of aminoglycoside therapy

appears to be very heterogeneous for the duration of treatment (2–5 days).

Moreover, C_{max} and C_{min} were not systematically measured on subsequent days. When the monitoring of C_{max} of amikacin and gentamicin was performed, it led to a change in dosing of amikacin and gentamicin in only 14/50 and 13/23 patients given amikacin and gentamicin, respectively. In these patients with dosing adjustment, the targeted C_{max} was only achieved in 2 patients given amikacin and none of the patients given gentamicin.

The lack of adherence to the French dosing guideline in this study highlights the difficulty in implementing dosing recommendations in clinical daily practice [14,29]. However, this evaluation should help improve local practice: first, by using higher doses of gentamicin or amikacin; second, by being rigorous for peak and trough concentration assessments; and third, by adjusting doses according to measured peak concentrations.

This is probably a hard objective to reach, as many barriers exist for implementing recommendations [30]. Indeed, some physicians could be reluctant to give high doses of aminoglycosides in patients at risk of renal insufficiency. Some of them did not probably know the recommendation to give the highest dose of aminoglycosides in patients with a suspected increased volume of distribution such as ICU patients [14,20]. Interestingly, Taccone et al. [17] and de Montmollin et al. [15] proposed to give 25 mg/kg of total body weight. Therefore, many efforts are required for optimising aminoglycoside administration. Moreover, as the targeted peak levels have been determined according the worst (highest) MIC, some doses were probably efficient with a favourable patient outcome making the physician reluctant to use higher doses on subsequent days.

The lack of achievement of C_{max} should bring into question current dosing recommendations and the potential to lead to clinical failure or the emergence of resistant pathogens [9]. Moreover, the present study highlights the importance of the first dose as subsequent doses were rarely adapted and, when adapted, the dosing rarely led to adequate peak plasma levels.

In addition to low initial dosing, the findings of the present study could be explained by the altered pharmacokinetics of aminoglycosides in ICU patients. In such patients, alterations in the volume of distribution and creatinine clearance could lead to decreased C_{max} and explain the low proportion of patients with adequate C_{max} in the present study [20]. However, of concern, the multivariate analysis did not isolate any factor associated with low C_{max}. This result was the same as that observed by Taccone et al. [17] but not by de Montmollin et al. [15] who found that a positive 24-h fluid balance was associated with lower C_{max}.

The present study has some limitations. First, only gentamicin and amikacin were surveyed and we cannot extrapolate the findings to other aminoglycosides. Second, some factors that could alter the pharmacokinetics of aminoglycosides were not analysed (albumin, creatinine clearance) [20]. Third, we assumed that adequate C_{max} were 60 mg/L and 30 mg/L, which are the targets recommended by current dosing guidelines that take into account the highest MIC of susceptible pathogens [14]. As the MIC of the pathogen was not determined in this study, we can suspect that some C_{max} values were adequate for clinical treatment ($8–10 \times MIC$). Moreover, aminoglycosides are always co-administered with another antibiotic to extend the spectrum of initial antibiotic therapy, and the additive/synergistic effects of the second antibiotic could reduce the impact of not achieving an adequate first C_{max}. However, our approach is pragmatic and representative of contemporary approaches to aminoglycoside dosing. Finally, we did not observe a difference in patient outcome with an increasing magnitude of the first C_{max}, in contrast to the findings reported by Moore et al. [8,9]. This could be explained by differences in recruited patients (Moore et al., bacteraemia, 100% culture-positive microbiology versus this study, severe

sepsis, 72% culture-positive microbiology) and the differences in the targeted C_{max} (two-fold lower in Moore's studies). The current study was also not powered for showing a difference in mortality rate, although such a study is certainly suggested.

In clinical practice, the present study confirms the data reported by Taccone et al. [17] and de Montmollin et al. [15] that contemporary recommended doses of aminoglycosides do not reliably achieve contemporary recommended target peak concentrations. These results support the use of higher doses of aminoglycosides in ICU patients (amikacin 30 mg/kg or gentamicin 8 mg/kg). Such dosing would be valuable particularly when risk factors of low peak plasma concentrations are present (i.e. positive fluid balance, increased creatinine clearance, high cardiac output, systemic inflammation response syndrome) [14]. Moreover, the present study shows that monitoring C_{max} should be better implemented and could lead to adapting the aminoglycoside dosing in order to avoid too low C_{max} that could be associated with inefficient therapy. Monitoring of peak and trough plasma concentrations should help the physician to achieve adequate therapy throughout the course of treatment. Further studies must be performed to assess such a strategy. All of these objectives required efforts from each physician (for knowing and applying recommendations) and from each institution and scientific societies (for divulging and helping the implementation of good clinical practices) [30].

5. Conclusion

The present study showed that standard dosing of amikacin or gentamicin led to adequate C_{max} in only 19% of patients. A first insufficient dose is associated with subsequent subtherapeutic doses. This emphasises the importance of the first dose to detect a subtherapeutic regimen and potentially adapt the following doses. This brings into question the appropriateness of current dosing recommendations and supports the initiation of aminoglycoside therapy with higher doses in ICU patients with severe sepsis.

Competing interests

None declared.

Ethical approval

As this was a non-interventional study to assess the daily practice of aminoglycoside monitoring in the ICU of Nîmes University Hospital (Nîmes, France), approval by the Comité de Protection des Personnes was not required according to French law. Therefore, the study was approved by the Institutional Review Board of Nîmes University Hospital [IRB 13/10-02] and was declared to the Commission nationale de l'informatique et liberté [CNIL # 1713434]. For this reason, the need for written informed consent from patients was waived. However, all patients and/or their next of kin were verbally informed of the data collection and could refuse to participate.

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