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Impact of 30 mg/kg amikacin and 8 mg/kg gentamicin on serum concentrations in critically ill patients with severe sepsis

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Objectives: Low first-dose peak serum concentrations of amikacin and gentamicin are commonly reported in ICU patients. The present study aimed to assess whether 30 mg/kg amikacin or 8 mg/kg gentamicin achieved target concentrations in ICU patients with severe sepsis.

Patients and methods: Sixty-three ICU patients (Simplified Acute Physiology Score II = 43 ± 16) with severe sepsis and an indication for intravenous amikacin (n = 47) or gentamicin (n = 16) were included. The first (30 mg/kg amikacin; 8 mg/kg gentamicin) and subsequent doses and corresponding peak concentrations (30 min after the completion of an infusion) were recorded. French guideline target concentrations were ≥60 and ≥30 mg/L for amikacin and gentamicin, respectively. A target pharmacokinetic/pharmacodynamic ratio of 10×MIC was also measured.

Results: Pulmonary, abdominal and urinary tract infections were diagnosed in 56 patients. Infection was confirmed in 37 patients (59%). The targeted first-dose peak concentration was achieved in 37/63 patients (59%) [amikacin 36/47 (77%) and gentamicin 1/16 (6%)], and 59/63 patients (94%) achieved the pharmacokinetic/pharmacodynamic ratio using the MIC data that were available from 21 patients. However, the second dose of aminoglycoside was withheld because of high trough concentrations in nearly half of patients who did not have renal dysfunction.

Conclusions: In this study, 30 mg/kg amikacin and 8 mg/kg gentamicin led to target peak serum concentrations in 59% of patients.

Introduction

In patients with severe sepsis, aminoglycosides are often given as part of empirical broad-spectrum anti-infective therapy.[1–5] Serum concentrations are used as a surrogate of tissue concentration to assess the appropriateness of dosing and anti-infective exposure. Maximal antibacterial activity is considered to occur when the ratio of the peak concentration to MIC for the infective pathogen (peak/MIC) is 8–10× greater than the MIC.[6,7] Recent recommendations suggest target peak concentrations of 30–40 mg/L for gentamicin and 60–80 mg/L for amikacin (EUCAST).[8–10] Standard doses of aminoglycosides are associated with low peak concentrations,[11,12] in contrast to those of higher doses of amikacin.[9,10] The alterations of pharmacokinetic characteristics can explain the difficulty in reaching adequate peak conentrations in ICU patients.[10,13]

In order to improve the achievement of target peak concentrations, either 30 mg/kg amikacin or 8 mg/kg gentamicin was prescribed in ICU patients with severe sepsis.[8] The aim of the present study was to report the rate of achievement of target peak concentrations using these doses.

Patients and methods

The Institutional Review Board approved this observational study. According to French law, patient written informed consent was waived.

However, patients or their surrogates were verbally informed and could refuse to participate.

From 27 October 2014 to 28 February 2015, ICU patients with severe sepsis treated with aminoglycosides were recruited. We excluded patients who were <18 years of age, who required renal replacement therapy (RRT), who had an allergy to aminoglycosides, who were confirmed and/or suspected to have myasthenia and/or ICU-acquired neuromuscular disorder, who were under guardianship or who were prisoners. No patient was included more than once in the data collection.

In combination with broad-spectrum antibiotics, according to the suspected pathogens and local clinical practice, 30 mg/kg amikacin or 8 mg/kg gentamicin was given (30 min intravenous infusion; the dosage ampoule was systematically emptied with a 5 mL flush). The weight metric used in this study was called an adapted body weight (ABW), which was determined as follows:

$$\text{For BMI } < 30 \text{ kg/m}^2,\ \text{ABW} = \text{total body weight (TBW)}$$

$$\text{For BMI} \geq 30 \text{ kg/m}^2,\ \text{ABW} = \text{ideal body weight (IBW)} + 0.43(\text{TBW} - \text{IBW})$$

IBW was calculated according to the Lorenz formula:

$$\text{IBW} = \text{height (cm)} - 100 - \{[\text{height(cm)} - 150]/X,$$
$$X = 4 \text{ for males and } X = 2.5 \text{ for females}$$

The peak serum concentration sampling occurred 30 min after the end of the infusion. Subsequent trough and peak concentrations were withdrawn as part of unit practice.

The targeted concentrations for amikacin and gentamicin were: amikacin, peak ≥60 mg/L and trough <2.5 mg/L; and gentamicin, peak ≥30 mg/L and trough <0.5 mg/L.[8]

Patient characteristics, medical history and Simplified Acute Physiology Score II (SAPS II) were collected at admission.[14] During each patient's ICU stay, the SOFA[15] score and the Acute Kidney Injury Network (AKIN)[16] score were recorded daily. The need for RRT and co-prescription of nephrotoxins (e.g. glycopeptides, diuretics) was recorded.

Type of infection and antibiotics given were recorded, and microbiological cultures were collected. Genus and species were determined using the MALDI-TOF technology Vitek MS (bioMérieux, Marcy-l'Étoile, France). Vitek2 (bioMérieux) was used to determine antibiotic susceptibilities. The MICs of aminoglycosides were determined using the Etest method (bioMérieux). Isolates were classified as susceptible (S), intermediate (I) or resistant (R) to the antibiotics according to the EUCAST breakpoints. When the MIC was not available, the susceptibility breakpoint MICs of amikacin and gentamicin were used to determine the local extrapolated target peak, defined as 10×highest MIC.[7]

The volume of distribution (*V*) was defined as first dose (mg/kg)/first serum peak (mg/L).

Amikacin and gentamicin concentrations were measured using automated immunoassays (Roche Diagnostics GmbH Mannheim) using a cobas c system.[12] The limits of quantification were 0.8 mg/L and 0.3 mg/L for amikacin and gentamicin, respectively.

Statistical analysis

We recently reported an achievement of target peak serum concentration in 19% of patients.[12] The present study was aimed at demonstrating that 30 mg/kg amikacin and 8 mg/kg gentamicin would lead to the achievement of a target level in 70% of patients as previously reported.[9,10] In order to determine whether the new regimens would increase the rate to 70% with α and β risks of 0.05 and 0.1, respectively, 14 patients would need to be included per aminoglycoside.

Data are expressed as mean ± SD or median (IQR) for quantitative variables according to the normality of their distribution. Qualitative data are expressed as absolute values with percentages. For comparisons, the χ^2 test, Student's *t*-test and Mann–Whitney *U*-test were performed. $P < 0.05$ was considered significant.

Results

Patients, infections and pathogens

Aminoglycosides were administered to 166 of 404 admitted patients. For 103 of the patients who received aminoglycosides,

Table 1. Included patients, types of infection and pathogens

Patients (male/female), *n* (*n*/*n*)	63 (39/24)
Patients given amikacin/gentamicin, *n*/*n*	47/16
Age (years), mean ± SD	68 ± 16
Height (cm), mean ± SD	168 ± 8
Total body weight at admission (kg), mean ± SD	75 ± 22
BMI at admission (kg/m^2), mean ± SD	26.5 ± 7.6
Patients with BMI ≥30 kg/m^2, *n* (%)	19 (30)
IBW (kg), mean ± SD	63 ± 6
ABW (kg), mean ± SD	68 ± 11
SAPS II at admission, mean ± SD (median)	43 ± 16 (39)
Creatinine plasma concentration at admission (μmol/L), mean ± SD	100 ± 52
Albumin plasma concentration at admission (g/L) (*n* = 48), mean ± SD	32 ± 6
SOFA at the initiation of aminoglycoside therapy, median (IQR)	7 (4–10)
AKIN at the initiation of aminoglycoside therapy, median (IQR)	0 (0–1)
Death in ICU, *n* (%)	16 (25)
Death in hospital (prior to discharge), *n* (%)	17 (27)
Type of infection, *n*	
pulmonary	40
abdominal	7
urinary tract	9
septicaemia	5
others	2
Isolated pathogen, *n*	
Staphylococcus aureus	6
Staphylococcus spp.	2
Enterococcus spp.	3
Haemophilus influenzae	2
Escherichia coli	14
Klebsiella pneumoniae	3
Proteus mirabilis	2
Enterobacter spp.	6
Serratia marcescens	1
Pseudomonas aeruginosa	2
Candida spp.	8
others	7
Patients with no isolated pathogen, *n* (%)	26 (41)
Patients with only 1 isolated pathogen, *n* (%)	15 (24)
Patients with >1 isolated pathogen, *n* (%)	22 (35)
Patients with MIC, *n* (%)	21 (33)
MIC of amikacin (mg/L), median (range)	≤2 (≤2 to ≤4)
MIC of gentamicin (mg/L), median (range)	≤1 (≤0.5 to ≤1)

first peak concentrations were not available, leading to the inclusion of 63 patients in the study (Table 1). Types of infection and pathogens are shown in Table 1. The highest MICs of amikacin and gentamicin were ≤4 and ≤1 mg/L, respectively.

Efficiency of the first dose

Thirty-seven patients (59%) had a first peak concentration above the recommended target (Figure 1a and b).

Amikacin therapy (47 patients)

Of the 47 patients who received amikacin, 36 patients (77%) had a peak concentration >60 mg/L (Figure 1a). The mean first dose was 29.6 ± 3.3 mg/kg ABW. The mean peak serum concentration was 75.8 ± 24.5 mg/L, corresponding to a *V* of 0.43 ± 0.17 L/kg. A dose ≥30 mg/kg would lead to 90% of the studied population achieving the targeted peak. The first peak was greater than 10×MIC (4 mg/L) in 15/16 patients with measured MIC. When this MIC was extrapolated to all patients, 43/47 (91%) first peaks were >10×MIC. A trough concentration ≥2.5 mg/L was reported in 23/47 (49%), 12/20 (60%) and 9/15 (60%) patients on days 2, 3 and 4, respectively, leading to withholding of the subsequent dose. Serum creatinine concentrations remained stable throughout amikacin therapy. Four patients required RRT, which was considered to be related to severe sepsis.

Gentamicin therapy (16 patients)

Of the 16 patients who received gentamicin, only one patient (6%) had a peak concentration >30 mg/L (Figure 1b). The mean first dose of gentamicin was 7.8 ± 1.3 mg/kg ABW. The mean first peak serum concentration was 20.4 ± 4.6 mg/L. The calculated *V* was 0.39 ± 0.07 L/kg. A dose ≥9 mg/kg would lead to 90% of the studied population achieving the targeted peak. The first peak was greater than 10×MIC (1 mg/L) in 5/5 patients with measured MIC. When this MIC was extrapolated to all patients, all first peak concentrations were greater than 10×MIC. A trough concentration ≥0.5 mg/L was reported in 9/16 (56%), 6/7 (86%) and 3/6 (50%) patients on days 2, 3 and 4, respectively, leading to

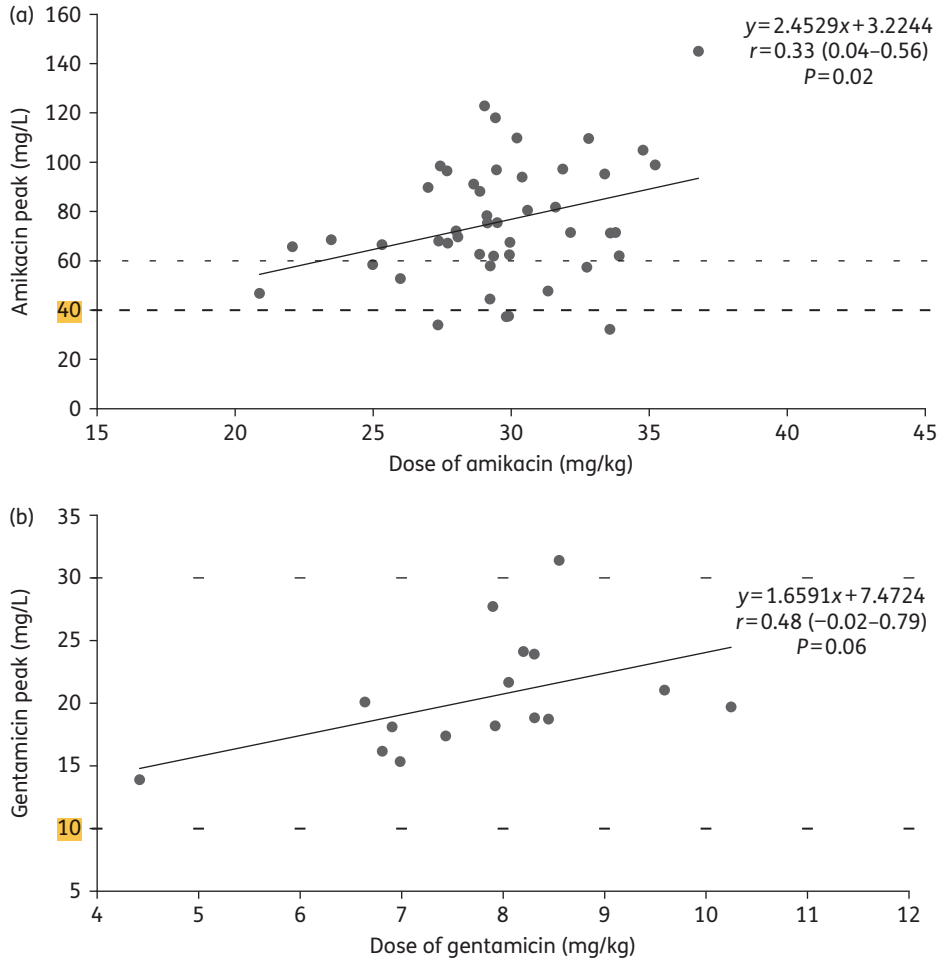

Figure 1. Observed and target peak serum concentrations of amikacin (a) or gentamicin (b). (a) Amikacin peak concentrations after the first dose with target concentrations according to EUCAST (60 mg/L) and local extrapolated target peak according to MIC data (40 mg/L). (b) Gentamicin peak concentrations after the first dose with target concentrations according to EUCAST (30 mg/L) and local extrapolated target peak according to MIC data (10 mg/L). Peak concentrations, filled circles; EUCAST target, upper broken line; local extrapolated target, lower broken line; correlation line, continuous line.

withholding of the subsequent dose. Serum creatinine concentrations remained stable throughout gentamicin therapy.

Discussion

In the present study, a first dose of 30 mg/kg amikacin or 8 mg/kg gentamicin led to achievement of targeted peak concentrations in 59% of patients (77% of patients given amikacin and 6% given gentamicin). This dosing was associated with high trough concentrations, which led to withholding of the subsequent dose in nearly half of patients on day 2 of treatment. No acute kidney injury related solely to aminoglycoside use was observed.

The doses of 30 mg/kg amikacin and 8 mg/kg gentamicin are recommended in patients with suspected increased *V* as seen in ICU patients.[8] The present study included patients similar to those included in previous studies of severe sepsis.[9–11,17–19] The magnitude of the first serum peak concentration of amikacin or gentamicin was similar to that reported in studies calculating the dosing from actual body weight.[9,10,19] The use of such dosing led to an increase in the rate of achievement of target peak concentrations from 24% to 77% after the first dose.[12]

In contrast to these previous studies, this study also recorded the peak and trough concentrations over the entire course of aminoglycoside treatment. With these high doses, nearly half of patients were not given a subsequent dose, because their trough concentration was above guideline recommendations, potentially exposing these patients to a greater risk of nephrotoxicity.[6] However, no impairment in renal function related to the use of aminoglycosides was observed. This finding could question the monitoring of trough concentrations when high doses of aminoglycosides are used, although clinicians were careful to withhold doses if high trough concentrations were observed, which may have reduced the development of nephrotoxicity. When taking into account data of the measured MICs, we found that nearly all patients reached the targeted peak aminoglycoside concentration after the first dose. In this context, knowledge of the local susceptibility patterns could allow more-accurate monitoring and lower dosing. This hypothesis is yet to be tested. Some limitations of this study should be declared. First, many patients had no monitoring of the first peak. This fact should lead us to reinforce the importance of adhering to the guidelines for aminoglycoside monitoring in our unit. Second, aminoglycosides are frequently co-administered with another antibiotic to extend the spectrum of initial antibiotic therapy, and the additive/synergistic effects of the second antibiotic are not measurable *in vivo*.[20] This factor could reduce the clinical consequences of not achieving the targeted first peak concentration. Third, the present study was not designed to measure the impact of these doses on patient outcome or on renal function.

Conclusions

Doses of 30 mg/kg amikacin or 8 mg/kg gentamicin led to targeted peak concentrations in 59% of patients, but they led to high trough concentrations in more than 50% of patients.

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Transparency declarations

None to declare.

Author contributions

C. R. participated in the design of the study, collecting patient data, analysing the data and writing the paper. B. N. participated in collecting patient data, analysing the data and writing the paper. B. L. participated in the design of the study, performing the statistical analysis, analysing the data and writing the paper. A. F. participated in the design of the study, analysing the data and writing the paper. H. K. participated in collecting patient data. A. E. participated in the design of the study and analysing the data. J.-P. L. participated in the design of the study, performing bacteriological analysis and analysing the bacteriological data. B. A. participated in the design of the study, analysing the data and writing the paper. J.-Y. L. participated in the design of the study, collecting patient data, analysing the data and writing the paper. J. A. R. participated in the design of the study, analysing the data and writing and revising the paper. L. M. participated in the design of the study, collecting patient data, analysing the data and writing the paper. All authors read and approved the final manuscript.

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