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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.

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

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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 broad-spectrum 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%).