International Journal of Antimicrobial Agents 51 (2018) 562–570

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

# Higher versus standard amikacin single dose in emergency department patients with severe sepsis and septic shock: a randomised controlled trial

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ARTICLE INFO

*Article history:*
Received 28 February 2017
Accepted 18 November 2017
Editor: Professor Jeffrey Lipman

*Keywords:*
Aminoglycosides
Pharmacokinetics
Pharmacodynamics
Sepsis
Septic shock
Emergency department

ABSTRACT

Recent studies suggest that intensive care unit patients treated with amikacin frequently do not attain the desired pharmacokinetic/pharmacodynamic (PK/PD) target, i.e. peak amikacin concentration ($C_{peak}$) to minimum inhibitory concentration (MIC) ratio of ≥8, when a single dose of 15 mg/kg is used. No data are available for patients admitted to the emergency department (ED). The aim of this prospective randomised controlled study was to determine PK/PD target attainment in ED patients presenting with severe sepsis or septic shock treated with 15 mg/kg versus 25 mg/kg amikacin. Patients were randomly assigned to receive amikacin 25 mg/kg or 15 mg/kg. Amikacin $C_{peak}$ values were determined. The primary outcome was target attainment defined as $C_{peak}$/MIC ≥ 8 both using EUCAST susceptibility breakpoints and actually documented MICs as denominator. A total of 104 patients were included. The EUCAST-based target was attained in 76% vs. 40% of patients assigned to the 25 mg/kg vs. 15 mg/kg dose groups ($P < 0.0001$). Target attainment using actual MICs (median of 2 mg/L, documented in 48 isolated Gram-negative pathogens) was achieved in 95% vs. 94% of patients in the 25 mg/kg vs. 15 mg/kg dose groups ($P = 0.969$). Risk factors associated with PK/PD target failure were identified in the multivariable analysis. At least 25 mg/kg amikacin as a single dose should be used in ED patients with severe sepsis and septic shock to attain the EUCAST-based PK/PD target. However, when using local epidemiology as denominator, 15 mg/kg appears to be sufficient. [ClinicalTrials.gov ID: NCT02365272.


## 1. Introduction

Management of severe infection in the emergency department (ED) constitutes a serious challenge. Prompt initiation of antibiotics is one of the critical interventions contributing to improved patient survival [1,2]. Empirical combination therapy with aminoglycosides is commonly used to broaden the coverage of Gram-negative bacteria and showed survival improvement over monotherapy in patients with septic shock [3].

For aminoglycosides, the two relevant pharmacokinetic/pharmacodynamic (PK/PD) parameters predictive of bacterial killing and clinical response are ratio of the peak serum concentration ($C_{peak}$) to minimum inhibitory concentration (MIC) of the targeted pathogen ($C_{peak}$/MIC) of ≥8 and ratio of the area under the concentration–time curve (AUC) to MIC of the targeted pathogen (AUC/MIC) of ≥70, of which $C_{peak}$/MIC has been reported to be the most predictive [4–8]. In critically ill patients admitted to the intensive care unit (ICU), empirical antibiotic therapy should target less-susceptible pathogens such as Enterobacteriaceae and *Pseudomonas aeruginosa*, and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints for susceptibility (i.e. 8 mg/L in case of

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https://doi.org/10.1016/j.ijantimicag.2017.11.009
0924-8579/

Enterobacteriaceae and *P. aeruginosa*) are therefore often used as denominator [9]. Moreover, PK characteristics are significantly different from those in less severely ill patients [10,11]. Studies undertaken in the ICU demonstrated an increased volume of distribution ($V_d$) of aminoglycosides, for which higher than standard first doses are required [12–14]. Whether this is applicable in the early phase of sepsis, as encountered in the ED, remains to be proven.

Recently, three groups have prospectively evaluated the first dose of amikacin in patients with severe sepsis and septic shock, all admitted to the ICU [15–17]. These studies demonstrated that the PK/PD target is not attained in >90% of patients with a standard dose of 15 mg/kg [15,16]. Even when using a higher dose of 25 mg/kg, the target is not attained in ≥25% of patients [15–17].

No PK/PD data on amikacin are available for ED patients with severe sepsis and septic shock, despite its frequent use in this setting. It is not clear whether higher doses as used in the ICU should be extrapolated to patients admitted at the ED as fluid resuscitation has just been initiated in the ED setting. Besides, the epidemiology of infecting pathogens is expected to be different, as ED patients more frequently suffer from community-acquired infections, presumed to be caused by more-susceptible pathogens with lower MICs.

The primary objective of this study was to determine whether the PK/PD target is attained when applying a single dose of 15 mg/kg amikacin (standard dose) versus 25 mg/kg amikacin in patients with severe sepsis or septic shock admitted at the ED. Secondary endpoints were identification of factors associated with target attainment as well as documentation of clinical and microbiological outcomes.

## 2. Materials and methods

### 2.1. Study design and setting

This prospective randomised controlled study was conducted at the ED of a 1900-bed tertiary care teaching hospital (University Hospitals Leuven, Leuven, Belgium).

### 2.2. Selection of participants

Patients admitted to the ED between 08:00h and 17:00h on week days with a diagnosis of severe sepsis or septic shock according to standard criteria in whom amikacin was initiated were consecutively enrolled in the study [1]. The research team was alerted by the ED staff and received an email in real time when amikacin was prescribed. Exclusion criteria were (i) age <18 years, (ii) pregnancy, (iii) burns, (iv) amikacin treatment 2 weeks prior to inclusion, (v) known allergy to aminoglycosides and (vi) a 'Do Not Resuscitate' code. Post-hoc exclusions were (i) absent or incorrect $C_{peak}$ measurement and (ii) amikacin administration not according to the study protocol.

### 2.3. Ethics, consent and permissions

The study received institutional approval from the Clinical Trial Center of University Hospitals Leuven and was registered on ClinicalTrials.gov (NCT02365272). Written informed consent was obtained from each patient or relative. The CONSORT statement was used to construct this report.

### 2.4. Intervention

Envelope randomisation was used to randomly assign patients to a single amikacin dose of 25 mg/kg or 15 mg/kg, using total body weight (TBW) for dose calculation. None of the investigators, patients or healthcare providers were blinded to dose allocation. Weight was based on patient information or, if not available, was estimated by the physician or nurse. TBW was rounded up per 5 kg. The dose was limited to 1.2 g and 2 g in the 15 mg/kg and 25 mg/kg dose groups for patients with a TBW >80 kg. Amikacin (Amukin®; Bristol-Myers Squibb, Braine-l'Alleud, Belgium) was diluted in 50 mL of normal saline and was administered over a 30-min period using a syringe driver. The infusion line was immediately flushed with normal saline after amikacin administration. Amikacin was given in combination with other antibiotics prescribed at the discretion of the treating clinician.

### 2.5. Data collection

Data were collected using a standardised form. Demographic data, i.e. age, sex, residence before ED admission, TBW, body mass index (BMI), relevant co-morbidities, and Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores calculated on ED admission [18,19], were recorded.

At study inclusion, which was defined as the time of amikacin administration, patient temperature, heart rate, mean arterial pressure, lactate, mechanical ventilation or vasopressor need, and biochemical parameters including complete blood count, electrolytes (serum sodium and potassium), C-reactive protein (CRP), total protein, serum albumin, urea and serum creatinine (SCr) were documented. Estimated glomerular filtration rate (eGFR) was estimated using the CKD-EPI formula; augmented renal clearance (ARC) was defined as an eGFR > 90 mL/min/1.73 m$^2$ [20]. The presence of severe sepsis versus septic shock at inclusion, length of ICU stay and mortality after 72 h were recorded. Temperature, treatment with antipyretics (paracetamol and acetylsalicylic acid), CRP, SCr, eGFR, and acute kidney injury (AKI) according to the Acute Kidney Injury Network (AKIN) classification were recorded daily until 72 h after study inclusion [21]. The presence of AKI at hospital discharge was also registered.

Fluid therapy was recorded within two intervals: from 6 h before inclusion until inclusion; and from inclusion up to 24 h after inclusion. Fluid therapy included crystalloids, colloids and blood products. Diuresis and fluid balance were also registered within the same time frames.

Microbiological data, including type of infection (community versus hospital-acquired), infection focus and identified pathogens along with the individual MICs for amikacin determined with a drug susceptibility test (VITEK®2 AST-N205; bioMérieux, Schaerbeek, Belgium) were documented. Hospital-acquired infection was defined as onset of infection at the earliest (i) on Day 3 after hospital admission, (ii) on admission in patients discharged from acute-care hospitals in the preceding 72 h and (iii) on admission in patients with suspected surgical site infection occurring within 30 days after surgery if no implant is left or within 1 year if implant is in place [22]. Blood cultures were collected in duplicate just before inclusion and 6 h later with a fixed amount of 10 mL each and were immediately sent to the microbiology laboratory and loaded into a blood culture instrument (BacT/ALERT®; bioMérieux) at any time of day (24 h a day, 7 days a week).

### 2.6. Pharmacokinetic analysis

Blood samples for PK analysis were collected in lithium heparin tubes at 1 h ($C_{peak}$), 6 h ($C_{6h}$) and 24 h ($C_{min}$) after the start of amikacin infusion and were immediately analysed using a validated homogeneous turbidimetric immunoassay method [23]. The lower limit of quantification was 0.3 mg/L.

When amikacin $C_{peak}$, $C_{6h}$ and $C_{min}$ were available, single-dose PK parameters were calculated using non-compartmental analysis and included 24-h AUC ($AUC_{0–24}$), total amikacin clearance (CL) and elimination half-life ($t_{1/2}$) [24]. The volume of distribution of the central