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Higher than recommended amikacin loading doses achieve pharmacokinetic targets without associated toxicity

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ABSTRACT

Antibiotic therapy improves the outcome of severe sepsis and septic shock, however pharmacokinetic properties are altered in this scenario. Amikacin (AMK) is an option to treat community or nosocomial infections, although standard doses might be insufficient in critically ill patients. The aim of this study was to evaluate two AMK dosage regimens in comparison with standard therapy with regard to efficacy in achieving adequate plasma levels as well as safety. In total, 99 patients with severe sepsis or septic shock were randomised to different AMK dose protocols: Group 1, 25 mg/kg/day; Group 2, 30 mg/kg/day; and Group 3, historical standard dose (15 mg/kg/day). Peak plasma concentrations at 1 h (C_{max}) were determined. Pharmacokinetics was determined and renal function was monitored to evaluate toxicity. Groups were compared using bilateral *T*-test. Demographic characteristics of the three groups were comparable. AMK C_{max} values were 57.4 ± 9.8, 72.1 ± 18.4 and 35.2 ± 9.4 μg/mL, respectively ($P < 0.001$ between Groups 1 and 2 versus Group 3, and $P < 0.01$ between Group 1 versus Group 2). A $C_{max} > 60$ μg/mL was reached by 39%, 76% and 0% of patients in Groups 1, 2 and 3, respectively ($P < 0.001$) and creatinine clearance at Day 28 was 95.6 ± 47.4, 89.7 ± 26.6 and 56.4 ± 18.4 mL/min, respectively. In conclusion, a 30 mg/kg daily dose of AMK presents significantly higher C_{max} compared with the other groups, with 76% of patients reaching recommended peak plasma levels with no association with higher nephrotoxicity. Standard doses are insufficient in critically ill patients to reach the recommended C_{max}.

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1. Introduction

Optimum use of antibiotics in critically ill patients is based on their in vitro activity and pharmacokinetic properties. Nevertheless, antibiotic–bacteria interactions, membrane penetration, target binding, fast antibacterial action and minimum inhibitory concentration (MIC), amongst others, have a significant influence on the choice of route of administration. These circumstances have been considered to create treatment guidelines to improve clinical efficacy and tolerability [1]. Antibiotic pharmacokinetic properties are altered in critically ill patients. There is a higher volume of distribution (V_d), greater clearance of drugs in relation to renal and/or liver dysfunction, and lower plasma concentrations of free drug exacerbated by hypoalbuminemia secondary to systemic inflammatory processes [2–9]. However, generally these changes are not considered when deciding antibiotic doses for these patients.

Aminoglycosides are used with limitations in critically ill patients owing to their potential renal and vestibular toxicity [10–13]. Amongst them, amikacin (AMK) has an excellent drug profile, with antibacterial activity depending on the peak plasma concentration (C_{max}), broad antibacterial spectrum, long post-antibiotic effect and a high capacity to prevent emergence of resistant bacteria [2,14]. Since bactericidal activity is concentration-dependent, there has been an attempt to define the optimum plasma concentration in critically ill patients to achieve the best antibacterial effect with the lowest risk of toxicity. Administered AMK doses must be targeted to reach a C_{max} of 60 μg/mL in 90% of patients. Beaucaire et al. [15] showed a worse outcome in critically ill patients when the C_{max} remained <40 μg/mL [2,16–20].

The aim of this study was to evaluate the efficacy of two different AMK dosage regimens in achieving the suggested goal of C_{max} of 60 μg/mL compared with the standard dose. Safety of the dose regimens was also assessed by evaluating the impact on renal function until Day 28.

2. Patients and methods

This study was approved by the Ethics Committee of the Hospital Clínico Universidad de Chile (Santiago de Chile, Chile). Patients were eligible for the study if they had a diagnosis of severe sepsis

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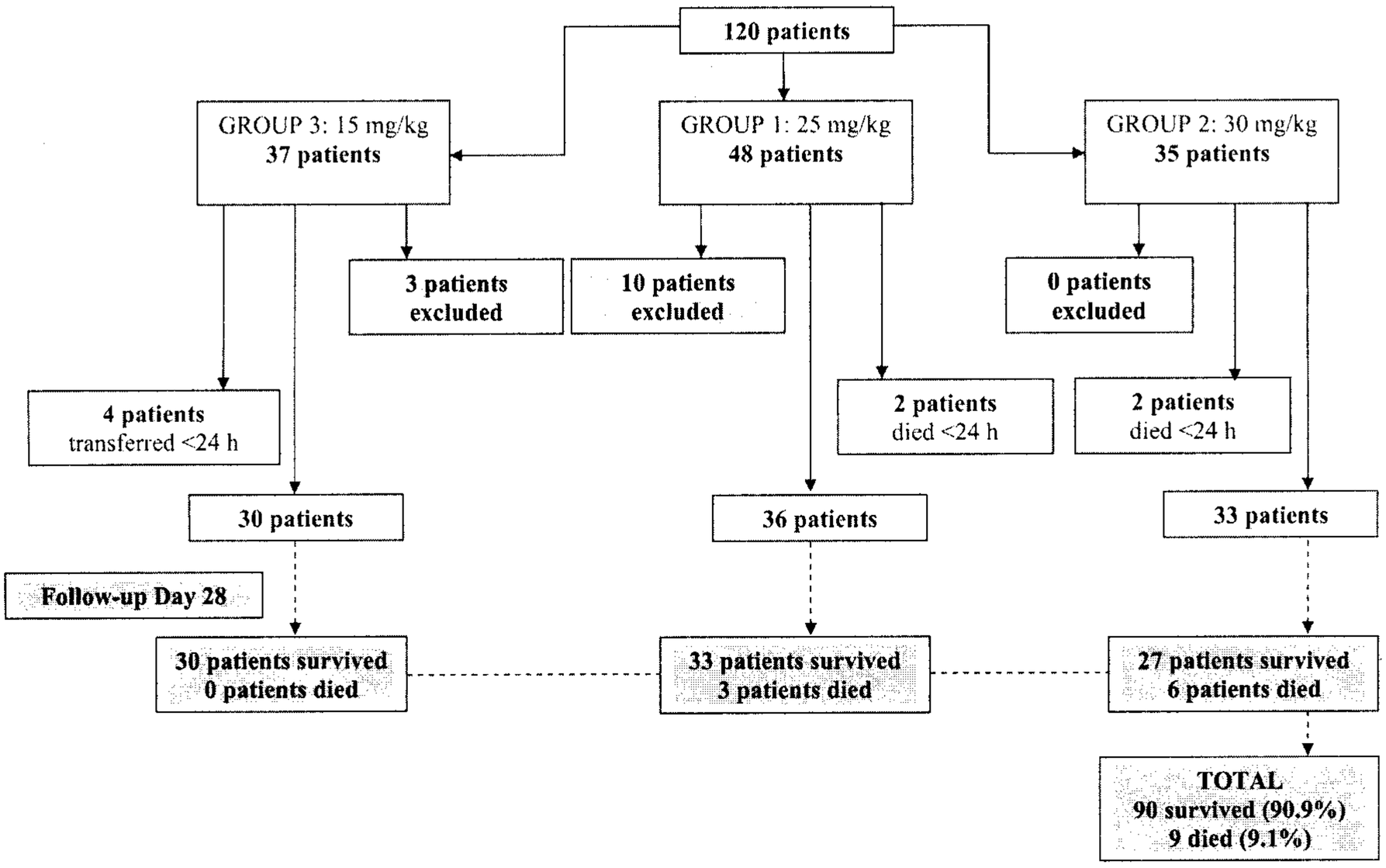

Fig. 1. Flow diagram showing eligibility and distribution of patients in the study.

or septic shock according to the American–European 2001 Consensus Conference criteria [21], probable or confirmed Gram-negative infection and no exclusion criteria [AMK treatment within the 15 previous days, inadequate loading dose, allergy to AMK, pregnancy, Acute Physiology and Chronic Health Evaluation (APACHE) II score >35, life expectancy <48 h or baseline disease with life expectancy <28 days, severe neutropenia not related to sepsis, meningitis, no blood sample available for C_{max} measurement or technical failure on blood sampling]. Between March 2006 and December 2008, 120 patients were admitted to the Intensive Care Unit of Hospital Clínico Universidad de Chile, of which 99 were eligible for inclusion in the study (Fig. 1).

Patients were randomised to two treatment groups according to AMK dose in two phases. In the first phase, a loading dose of 25 mg/kg/day (Group 1), according to the study by Taccone et al. [22] and EUCAST data [23], was compared with the historical recommended dose of 15 mg/kg/day with renal function adjustment [according to creatinine clearance (CL_{Cr}) determined by the Cockcroft–Gault formula] (Group 3). After 12 months, an interim analysis of the collected data revealed that even patients receiving 25 mg/kg/day did not reach C_{max} of 60 μg/mL. Therefore, it was decided to perform a second study phase increasing the loading dose to 30 mg/kg/day (Group 2) and compared this new group with the historical dose (Group 3). Treatment with AMK was decided by clinical staff in charge, and dose randomisation was made with sealed envelopes by the research team. In all groups, a once-daily dose was used and doses in treatment Groups 1 and 2 were not adjusted by renal function. If weight was not available, ideal body weight was calculated using the Robinson's formula [24]. The drug used was AMK (Laboratorio Biosano SA, Santiago, Chile) diluted in 20 mL of NaCl 0.9% for intravenous administration. The total dose was diluted in 100 mL of NaCl 0.9% solution (Laboratorio Sanderson SA, Santiago, Chile) and was administered over 30 min using a Continuous Infusion System Pump (Lifecare® 5000 version 1.6; Hospira Inc., Lake Forest, IL). Thirty minutes after finishing administration, arterial blood was sampled to measure plasma concentrations. In each group, C_{max} was measured and V_d was calculated. Patients who were admitted with renal failure (defined as plasma creatinine >2 mg/dL) were analysed in subgroups.

AMK peak serum concentrations at 1 h (C_{max}) were measured by fluorescence polarisation immunoassay technique. Renal function tests were calculated; 24-h CL_{Cr} was measured on Days 14 and 28. The protocol duration was adjusted to five doses, with the exception of Group 3 for which patients received treatment for, on average, 10 days. Continuous variables were compared using bilateral *T*-test. A *P*-value of <0.05 was considered significant. Data were analysed using SPSS 12.0 software (SPSS Inc., Chicago, IL).

3. Results

Patients were enrolled over a 34-month period between March 2006 and December 2008 (Fig. 1). There were no significant differences in gender, APACHE II score (23 ± 5, 23 ± 9 and 25 ± 5 in Groups 1, 2 and 3, respectively) or Sequential Organ Failure Assessment (SOFA) score (Day 1, 10 ± 3, 10 ± 4 and 11 ± 3, respectively) between groups. Demographic data are shown in Table 1. Average AMK doses for Groups 1, 2 and 3 were 1926 ± 294, 2209 ± 454 and 909 ± 290 mg, respectively (Table 2).

C_{max} values were 57.4 ± 9.8, 72.1 ± 18.4 and 35.2 ± 9.4 μg/mL in Groups 1, 2 and 3, respectively ($P < 0.001$ between Groups 1 and 2 versus Group 3, and $P < 0.01$ between Group 1 versus Group 2) (Table 2). No patient achieved a C_{max} of 60 μg/mL in Group 3, but 39% of patients achieved it in Group 1 and 76% in Group 2 ($P < 0.001$) (Fig. 2). Values of V_d did not show wide variations amongst the different groups, with values of 0.44 ± 0.08, 0.45 ± 0.18 and 0.39 ± 0.21 L/kg, respectively, and were comparable with healthy volunteers (0.27 ± 0.06 L/kg) [25] (Table 2; Fig. 3).

Renal function was assessed by following plasma creatinine levels from Days 1 to 5 and again at Day 28, looking for the appearance of renal failure. Patients who were admitted to the study with renal failure were analysed separately (Table 3). Baseline plasma creatinine levels in the different groups were 1.87 ± 1.14,

Table 1
Epidemiological data for patients in the study according to dosage group.

Characteristic	Group 1 (25 mg/kg/day)	Group 2 (30 mg/kg/day)	Group 3 (15 mg/kg/day)
Total no. of patients/no. female	36/14	33/18	30/18
Age (years) (mean ± S.D.)	60.7 ± 13.4	54.5 ± 17.1	61.4 ± 11
Weight (kg) (mean ± S.D.)	77.3 ± 12.1	74.1 ± 17.7	72.4 ± 13.7
Severity scores (mean ± S.D.)			
APACHE II	23 ± 5	23 ± 9	25 ± 5
SOFA Day 1	10 ± 3	10 ± 4	11 ± 3
SOFA Day 2	9 ± 3	7 ± 3	10 ± 3
SOFA Day 3	8 ± 3	6 ± 3	7 ± 2
Focus [*n* (%)]			
Respiratory	11 (31)	10 (30)	7 (23)
Abdominal	21 (58)	9 (27)	18 (60)
Blood	1 (3)	2 (6)	2 (7)
Urinary	3 (8)	12 (36)	3 (10)
Infectious agent [*n* (%)]			
Pseudomonas aeruginosa	21 (58)	15 (45)	15 (50)
Acinetobacter baumannii	4 (11)	5 (15)	8 (27)
Klebsiella pneumoniae	4 (11)	4 (12)	1 (3)
Escherichia coli	5 (14)	7 (21)	1 (3)
Others Gram-negative bacteria	2 (6)	2 (6)	5 (17)

S.D., standard deviation; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.

Table 2
Pharmacokinetic parameters of the different treatment groups[a].

Pharmacokinetic parameter	Group 1 (25 mg/kg/day)	Group 2 (30 mg/kg/day)	Group 3 (15 mg/kg/day)
Daily dose (mg)	1926 ± 294	2209 ± 454	909 ± 290
C_{max} (μg/mL)*	57.4 ± 9.8	72.1 ± 18.4	35.2 ± 9.4
C_{max}/MIC (median ± S.D.)	3.8 ± 13.5	12.5 ± 9.5	3.13 ± 9.04
C_{min} (μg/mL)	N/D	1.14 ± 1.56	N/D
V_d (L/kg)	0.44 ± 0.08	0.45 ± 0.18	0.39 ± 0.21

C_{max}, peak plasma concentration at 1 h post dose; MIC, minimum inhibitory concentration; S.D., standard deviation; C_{min}, trough plasma concentration; V_d, volume of distribution; N/D, no data.

[a] Data are mean + S.D. unless stated otherwise.

* $P < 0.001$ between Groups 1 and 2 versus Group 3; $P < 0.01$ between Group 1 versus Group 2.

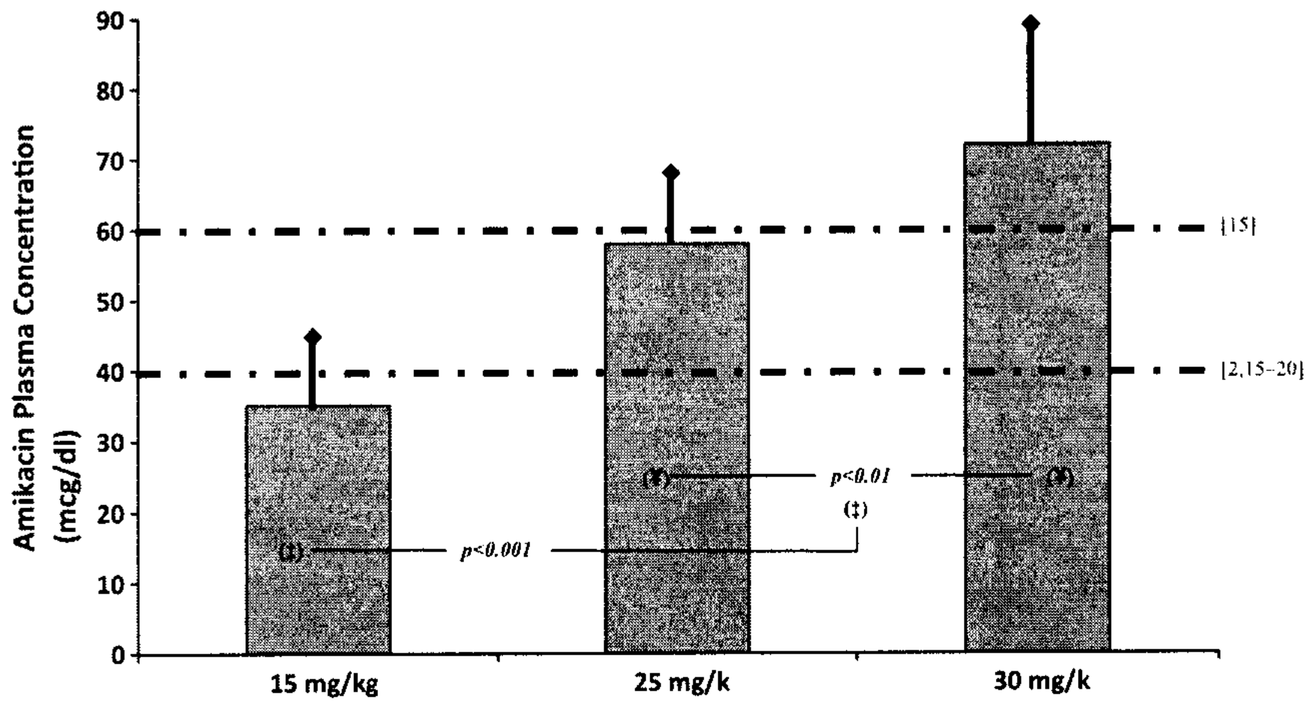

Fig. 2. Distribution of amikacin peak plasma concentration at 1 h post dose (C_{max}) in the different treatment groups. Upper dotted line shows the threshold for best bactericidal activity with lower toxicity [15]. Lower dotted line shows the limit below which clinical outcome is worse [2,15–20]. ‡$P < 0.001$ between Groups 1 (25 mg/kg) and 2 (30 mg/kg) versus Group 3 (15 mg/kg); and ¥$P < 0.01$ between Group 1 versus Group 2.

Table 3
Pharmacokinetic parameters and renal function followed up until Day 28 for patients admitted to the study with renal failure (plasma creatinine >2 mg/dL)[a].

Pharmacokinetic parameter	Group 1 (25 mg/kg/day)	Group 2 (30 mg/kg/day)	Group 3 (15 mg/kg/day)
Patients [*n* (%) of corresponding group]	12 (33.3)	9(27.3)	11 (36.7)
Amikacin (mg)	1825 ± 379	2439 ± 494	618 ± 162
C_{max} (μg/mL)	57.4 ± 13.5	91.4 ± 6.2	33.8 ± 8.9
C_{min} (μg/mL)	N/D	1.37 ± 1.95	N/D
CL_{Cr} baseline (mL/min)	23.7 ± 8.8	29.9 ± 10.6	27.1 ± 11.2
CL_{Cr} Day 28 (mL/min)	68.5 ± 22.4	75.2 ± 16	49 ± 11.9
V_d (L/kg)	0.45 ± 0.08	0.33 ± 0.03	0.31 ± 0.16

C_{max}, peak plasma concentration at 1 h post dose; C_{min}, trough plasma concentration; CL_{Cr}, creatinine clearance; V_d, volume of distribution; N/D, no data.

[a] Data are mean ± standard deviation unless stated otherwise.

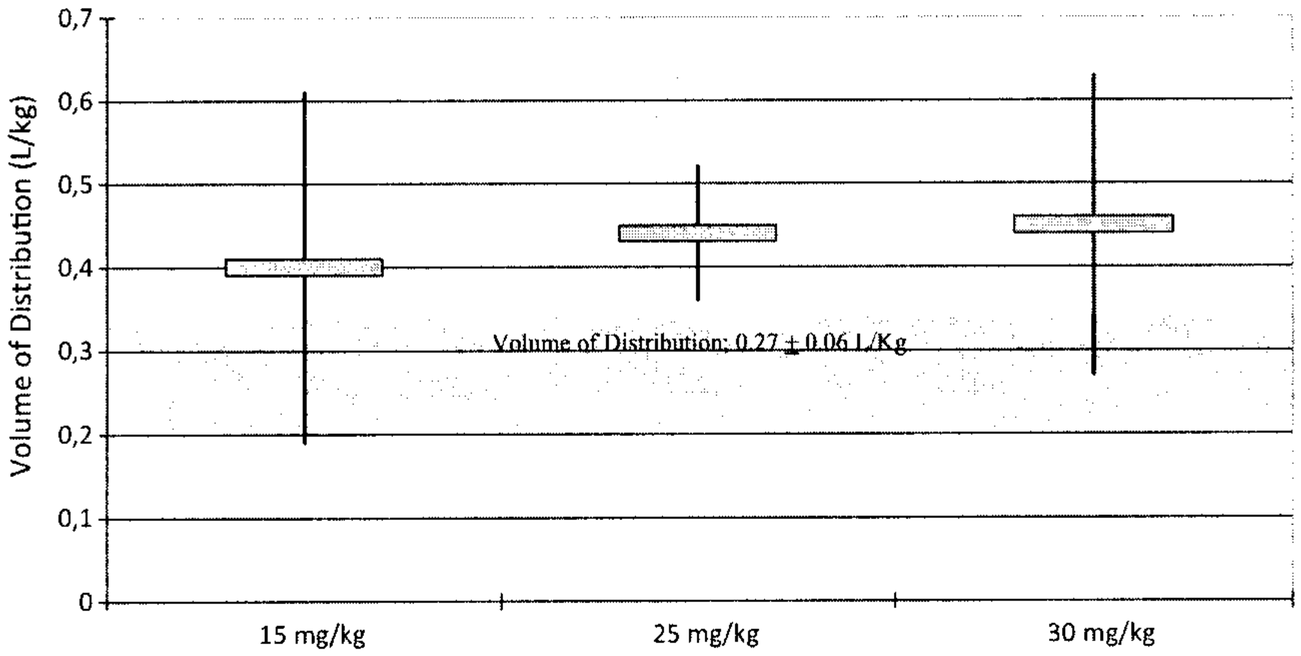

Fig. 3. Volume of distribution (V_d) of the different treatment groups in relation to the normal value according to Goodman and Gillman [25]. Data are presented as mean ± standard deviation.

Table 4
Renal function in the three study groups: follow-up of plasma creatinine and 24-h creatinine clearance (CL_{Cr})[a].

Parameter	Group 1 (25 mg/kg/day)	Group 2 (30 mg/kg/day)	Group 3 (15 mg/kg/day)
Creatinine (mg/dL)			
Day 1 (admission)	1.87 ± 1.14	1.76 ± 0.89	1.89 ± 1.19
Day 5	1.7 ± 0.97	1.58 ± 1.10	1.55 ± 0.72
Day 14	1.3 ± 0.82	1.31 ± 0.89	1.2 ± 0.52
24-h CL_{Cr} (mL/min)			
Day 14	85.9 ± 51.8	68.7 ± 30.2	69 ± 35.7
Day 28	95.6 ± 47.4	89.7 ± 26.6	56.4 ± 18.4

[a] Data are mean + standard deviation.

1.76 ± 0.89 and 1.89 ± 1.19 mg/dL, respectively, and differences did not reach statistical significance (Table 4). There was no evidence of renal function impairment at Day 28, with 24-h CL_{Cr} of 95.6 ± 47.4, 89.7 ± 26.6 and 56.4 ± 18.4 mL/min, respectively. Only nine patients died during the follow-up until Day 28, with a whole-group mortality of 9.1% (Fig. 1).

4. Discussion

The rationale for the use of a single dose of aminoglycosides in critically ill patients has been widely demonstrated [2,16,26,27]. Nowadays, studies of pharmacokinetic and pharmacodynamic parameters of AMK in critically ill patients aim to obtain the most benefits whilst reducing the risk of toxicity. Both in vitro and in vivo models in animals and humans have shown that when the C_{max}/MIC ratio of aminoglycosides is >8, antibacterial action is better and faster [2,28–32], being yet proposed as a healing [33] and low mortality predictor [34,35]. Clinical experience is quite large and has been collected in several meta-analyses [36–43]. However, the optimum C_{max} in critically ill patients is unknown. It is known that at standard doses C_{max} in these patients is lower than in other populations and that a C_{max} <40 μg/mL is associated with worse outcome [2,15–19,44,45]. In this study, dose adjustment was based on Beaucaire et al. [15] and achieved an increase in C_{max} (Fig. 2) and C_{max}/MIC ratio in Groups 1 and 2 (Table 2) without increasing renal toxicity (Table 4). However, despite the increase in AMK doses, only 39% of patients in Group 1 reached the C_{max} goal of 60 μg/mL, which is comparable with the data of Taccone et al. [22,46] and reflects the alteration of pharmacokinetics in critically ill patients. Group 2 did largely better, with 76% of patients reaching the C_{max} goal and a mean peak serum concentration of 72.1 ± 18.4 μg/mL. In addition, critically ill patients in the different groups gained volume during the first hours of resuscitation. They increased their V_d in 63%, 67% and 44%, respectively, and in 67%, 22% and 14%, respectively, in the subgroup admitted with renal failure in comparison with AMK V_d in healthy volunteers (0.27 ± 0.06 L/kg) [25]. Both the increase in V_d and the impairment in pharmacokinetics explain why only a certain percentage of patients achieved optimal C_{max}. Whether higher loading doses might improve this percentage and its potential clinical benefit versus the increase in risk of toxicity requires further studies.

Renal dysfunction in critically ill patients is variable and multifactorial. Therefore, it is not clear how much it should influence the decision for AMK dosing. Moreover, there is no clear definition of AMK nephrotoxicity in the literature, and authors consider aminoglycosides as a single risk factor (univariate analysis) when renal damage in this context is always multifactorial [32]. The International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer studied a single dose of AMK in critically ill patients. They found an incidence of nephrotoxicity of 3%, which developed only in the presence of other nephrotoxic drugs [2,16]. In the present study, one of our main concerns was patients with renal failure. Since AMK loading doses were not adjusted by renal function, there was in theory a risk of attaining higher C_{max} and potential toxicity. However, we found an increase of C_{max} independent of renal function, and trough plasma concentration (C_{min}) values that stayed below the level of toxicity (5 μg/mL) in the whole group as well as in patients with renal dysfunction when analysed separately. Thus, there was no further impact on renal function, and both renal function parameters (plasma creatinine levels and 24-h CL_{Cr} at Day 28) improved or returned to normal or baseline levels at Day 28. This suggests that in critical care patients with septic shock there is no indication for loading dose adjustment guided by renal function. Patients with renal dysfunction behaved similarly to those with normal function, and using lower doses for them would lead to a lower C_{max}. An independent decision is feasible, even in the presence of renal dysfunction, but must be associated with close monitoring of plasma levels [47]. The same conduct should be applied to patients

requiring renal replacement therapy, in whom the literature has shown a dramatic reduction of plasma antibiotic concentrations a few hours after administration, leaving patients without real antibiotic coverage for a significant percentage of the time [48]. Global management of critically ill patients oriented by haemodynamic and perfusion goals, like in the present study, and the increment in V_d might have played a protective role against AMK toxicity. Optimised antibiotic regimens guided by pharmacokinetic parameters when available also have a role both in antibacterial efficiency and in reduction of toxicity. The phrase 'high dose is high risk of toxicity' may be partly corrected by lowering the total length of therapy. In the current series, dose adjustment in patients with renal failure prior to injury was based only on close monitoring of pharmacokinetic parameters (C_{max}) and renal function tests [49]. Shortened duration of therapy was associated with recovery of renal function parameters at Day 28 (Table 4). In contrast, low doses or administration intervals too far apart, with a longer duration of therapy showed an increased risk of toxicity (Group 3, standard doses), consistent with the studies of Beaucaire et al. [15] and Marik et al. [44].

This study has certain limitations. The AMK loading doses used in the protocol were calculated using ideal body weight in those patients whose real body weight was unavailable. Although this was not the case in all critically ill patients, it might have changed in some percentage the dose of AMK administer and should be optimised in future research. However, we do not estimate that this variation had a significant impact on the global doses and results of the study.

In conclusion, standard doses of AMK are insufficient to reach the C_{max} suggested and recommended for critically ill patients. A treatment schedule of 30 mg/kg AMK reached significantly higher C_{max} and C_{max}/MIC ratio, with a greater proportion of patients (76%) achieving the recommended peak plasma concentration of >60 μg/mL without increasing renal toxicity, even in patients admitted with renal failure. The potential effect on bacterial strain susceptibilities remains to be defined and needs more study.

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Ethical approval: This study was approved by the Ethics Committee of the Hospital Clínico Universidad de Chile (Santiago de Chile, Chile) [signed for the President Guillermo Piwonka M.D. (Memo N° 91)].

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