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Pharmacokinetics of a loading dose of amikacin in septic patients undergoing continuous renal replacement therapy

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ABSTRACT

Data on the optimal amikacin regimen during continuous renal replacement therapy (CRRT) are scarce and the proposed loading dose of 10 mg/kg may result in inadequate drug levels. The aim of this study was to describe the pharmacokinetics of a 25 mg/kg first dose of amikacin in septic shock patients treated with CRRT. Serum samples were collected before ($t = 0$ h) and at 1 (peak), 1.5, 4.5, 8 and 24 h after a 30-min amikacin infusion in 13 consecutive patients treated with a combination of amikacin and β -lactam. Blood amikacin levels were measured using a validated fluorescence polarisation immunoassay method. In 9 patients (69%) the peak concentration was >64 mg/L, which corresponds to eight times the minimal inhibitory concentration breakpoints defined by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for Enterobacteriaceae and *Pseudomonas aeruginosa* (susceptible <8 mg/L, resistant >16 mg/L). The median (range) total volume of distribution was 0.50 L/Kg (0.22–4.05 L/Kg), the elimination half-life was 6.5 h (4.5–279.6 h) and total drug clearance (CL) was 1.26 mL/min/kg (0.1–3.30 mL/min/kg). Only three patients had drug concentrations at 24 h (C_{\min}) of <5 mg/L and the median predicted time needed to reach this value was 34 h (14–76 h). There was no correlation between CRRT parameters and C_{\min} , CL or the time to $C_{\min} < 5$ mg/L. In septic shock patients treated with CRRT, a first dose of ≥ 25 mg/kg amikacin is therefore required to reach therapeutic peak concentrations. However, as drug clearance is reduced, amikacin concentrations remained above the threshold of renal toxicity at 24 h. The therapeutic benefit of high-dose aminoglycoside therapy should be balanced with its potential renal effects in septic patients receiving CRRT.

1. Introduction

Early and appropriate antibiotic treatment in terms of spectrum of activity or dose and frequency of administration is associated with better outcomes in septic patients [1]. However, because of various alterations in the pharmacokinetics of antibiotics during sepsis [2,3], standard antimicrobial regimens can result in subtherapeutic serum drug concentrations in septic patients. The problem of optimal antibiotic doses becomes even more complex when there is concomitant renal failure because drug clearance is reduced and accumulation of antimicrobials in the blood and tissues may potentially contribute to increased adverse side effects [4].

Continuous renal replacement therapy (CRRT) is increasingly used in the routine clinical management of septic patients as, in contrast to standard haemodialysis, it provides similar removal of solutes without adversely affecting cardiovascular stability [5,6]. However, there are relatively few publications regarding antibiotic dosing during CRRT in critically ill patients, and dosing of antibiotics based on predicted clearances yields only rough estimates [7].

Amikacin is a valuable therapeutic option for life-threatening aerobic Gram-negative organisms, especially *Pseudomonas aeruginosa* [8,9]. Optimum antibacterial activity is achieved when the peak serum concentration is at least eight to ten times the minimal inhibitory concentration of the causative Gram-negative pathogen [10,11]. The current regimen proposed for amikacin during CRRT is a loading dose of 10 mg/kg [7]. Although we have recently shown that a 25 mg/kg loading dose of amikacin is necessary in patients with severe sepsis or septic shock in order to achieve therapeutic peak concentrations [3], aminoglycosides are potentially

nephrotoxic and clinical studies have suggested that renal impairment is more prevalent when there is pre-existing kidney dysfunction [12]. We therefore wondered whether optimising peak amikacin concentrations during CRRT with a higher dose regimen would be associated with prolonged high drug concentrations, which can potentially worsen renal function.

The aim of this study was to evaluate the pharmacokinetics of a 25 mg/kg loading dose of amikacin in patients with septic shock treated with CRRT.

2. Methods and patients

This is an analysis of a subgroup of patients with severe sepsis/septic shock treated with CRRT who were included in an open, prospective, multicentre, non-comparative study performed in four Departments of Intensive Care in Belgium [3]. The study protocol was approved by the Ethics Committees of the different hospitals. Written informed consent was obtained from the patient or his/her legal guardian. Inclusion and exclusion criteria as well as data collection have been described elsewhere [3].

All patients received a first loading dose of 25 mg/kg amikacin intravenously based on recent weight determination or, if not available, on best weight estimation. The drug was administered over 30 min using an infusion pump. All patients also concomitantly received a broad-spectrum β -lactam. Blood samples for drug assays were drawn immediately before administration (0 h) and then 1 (peak), 1.5, 4.5, 8 and 24 h later. Blood was collected in a 5-mL plain tube (without anticoagulation) and when a clot had completely formed (15–30 min) the sample was centrifuged at 4

°C and the serum was transferred into another tube to be stored at –80 °C until analysis. Serum amikacin concentrations were determined using a validated fluorescence polarisation immunoassay method (Abbott Laboratories, Abbott Park, IL).

Serum amikacin concentrations were analysed using WinNonlin® Pharsight Professional Software version 5.0.1 (Pharsight Corp., Mountain View, CA). The selected model was based on a two-compartment model with first-order elimination. The following pharmacokinetic (PK) variables were calculated for each patient: volume of distribution in the central (V_{d1}) and peripheral (V_{d2}) compartments; total volume of distribution (V_{ss}); total drug clearance (CL); elimination half-life ($t_{1/2}$); maximum drug concentration calculated by extrapolation of the distribution phase; and drug concentration 24 h after the start of infusion (C_{min}). Amikacin levels measured at 1 h (peak) were considered as the target concentration. The optimal peak was considered as >64 mg/L, whereas the potential toxicity threshold was determined by a $C_{min} \geq 5$ mg/L [3,13]. Using the same PK software, the PK parameters of the patients were used to generate a simulation of peak and C_{min} for a 10 mg/kg and 15 mg/kg loading dose of amikacin.

The decision to initiate CRRT was made according to local clinical practice. CRRT was performed through a double-lumen catheter inserted into the subclavian, femoral or internal jugular vein. Continuous venovenous haemodiafiltration (CVVHDF) was performed using a Prisma™ or PrismaFlex™ machine (Hospal, Meyzieu, France), with a polyacrylonitrile cylinder (AN69; Hospal) or polysulfone haemofilters (Gambro Lundia AB, Lund, Sweden). An initial bolus dose of 1000–

2500 U heparin followed by a continuous heparin infusion was delivered before the haemofilter for anticoagulation of the circuit. Characteristics of the CRRT, including blood flow, ultrafiltration and dialysate flow rates, were recorded for each patient and remained unchanged throughout the study. Data are expressed as counts (percentage) or median (range) as appropriate.

3. Results

Thirteen patients were included in the study (Table 1). Eight patients were medical admissions, and nine patients had nosocomial infections. Median Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores at inclusion were 28 and 12, respectively. All patients had septic shock and were treated with mechanical ventilation. Urine output was <500 mL/day in 12 of the 13 patients. Intensive care Unit (ICU) mortality was 62% (8/13). Most of the infections were pulmonary ($n = 6$) or abdominal ($n = 4$), and concomitant bacteraemia was found in 8 patients (62%). Ten patients (77%) had infections due to Gram-negative bacteria (*P. aeruginosa* and *Escherichia coli* each in three patients, and *Klebsiella pneumonia*, *Hafnia alvei*, *Citrobacter freundii* and *Serratia marcescens* each in one patient).

The median dose of amikacin was 1625 mg (1000–2500 mg). For CVVHDF, median blood flow was 150 mL/min (130–200 mL/min), median dialysate flow rate was 29 mL/kg/h (20–40 mL/kg/h) and the ultrafiltration rate was 33 mL/kg/h (25–50 mL/kg/h), with fluid removal in eight patients (Table 2). The duration of CVVHDF on the first day of amikacin therapy ranged from 16 h to 24 h. The PK profile of amikacin is shown in Fig. 1. Median serum concentrations of amikacin were 0.2, 68.2, 60.4,

38.5, 23.8 and 11.5 mg/L before injection (0 h) and 1, 1.5, 4.5, 8 and 24 h after the onset of the infusion, respectively. In 9 patients (69%) the peak concentration was >64 mg/L. Only three patients had a $C_{\min} < 5$ mg/L. PK variables for amikacin were as follows: $V_{d1} = 0.29$ L/kg (0.21–0.62 L/kg); $V_{d2} = 0.23$ L/kg (0.01–3.44 L/kg); $V_{ss} = 0.50$ L/kg (0.22–4.05 L/kg); $t_{1/2} = 6.5$ h (4.5–279.6 h); and $CL = 1.26$ mL/min/kg (0.1–3.30 mL/min/kg) (Table 1). The median predicted time required to reach a $C_{\min} < 5$ mg/L was 34 h (14–76 h). Using simulated amikacin doses of 10 mg/kg and 15 mg/kg, it was observed that none of the patients would have reached a peak concentration >64 mg/L [median peak 27.3 mg/L (14.5–39.0 mg/L) and 40.9 mg/L (21.7–51.2 mg/L), respectively]. There would have been 8/13 (62%) and 6/13 (46%) patients, respectively, with a $C_{\min} < 5$ mg/L. There was no correlation between CRRT parameters and C_{\min} , CL or time to $C_{\min} < 5$ mg/L.

4. Discussion

In this study it was shown that a loading dose of ≥ 25 mg/kg amikacin is necessary to achieve optimal peak concentrations in patients with septic shock undergoing CRRT. However, as amikacin clearance is reduced, C_{\min} was significantly higher than recommended thresholds at 24 h and a longer dosage interval would be required to avoid accumulation of the aminoglycoside and to limit potential toxicity.

Two PK variables are essential determinants of the aminoglycoside regimen: the V_d , used to predict the drug dose; and the elimination rate, which is important to determine the required dosing interval. Insufficient peak levels in septic ICU patients are largely explained by a larger V_d in this population compared with the V_d found in healthy volunteers or in patients with less severe infections [3,14,15]. Thus, a larger

amikacin dose of 25 mg/kg provided adequate peak levels in a large ICU population with severe sepsis and septic shock [3]. The goal of this dosing regimen was to keep peak concentrations above the limit of susceptibility for the most troublesome pathogens, such as Enterobacteriaceae and *P. aeruginosa*, which are frequently isolated in ICU infections and are associated with high mortality rates [16,17]. Because the peak concentration of a drug is independent of its clearance, it was observed that this dose regimen might provide optimum amikacin peak concentrations even when renal function is impaired, such as when CRRT is required. Use of the recommended 10 mg/kg dose or even a standard dose of 15 mg/kg would have resulted in subtherapeutic peak concentrations in all patients and could potentially have contributed to therapeutic failure [18].

Clearance of amikacin in subjects with normal renal function is 100–120 mL/min and the $t_{1/2}$ is ca. 2 h [19]. Amikacin elimination is reduced when renal function is impaired, and in patients with creatinine clearance (CL_{Cr}) <10 mL/min the $t_{1/2}$ can be prolonged up to 30 h. Amikacin has a molecular weight significantly less (<2000 Da) than the CRRT haemofilter cut-off (30 000–50 000 Da) and has high hydrophilicity and poor plasma protein binding. CRRT would therefore be able to remove the aminoglycoside at a rate equivalent to a CL_{Cr} of 10–40 mL/min [20]. Drug removal is expected to be greater in CVVHDF than continuous venovenous haemofiltration (CVVH), but total CL may also depend on the CRRT device characteristics (surface area, haemofilter) and operating conditions (pre-dilution, post-dilution, ultrafiltration and/or dialysate flow rates) [5].

Effective removal of amikacin by standard haemodialysis is well documented. Extracorporeal clearance has been estimated at between 58 mL/min and 126 mL/min, and $t_{1/2}$ was 3–7 h during treatment [21]. In eight critically ill patients, amikacin clearance increased from 7.3 ± 4.8 mL/min to 37.5 ± 8.1 mL/min during dialysis [22]. In six ICU patients treated with slow haemodialysis, total CL was calculated at 35 mL/min with an elimination $t_{1/2}$ of 10.5 h [23]. In contrast, peritoneal dialysis has been reported to be less effective at removing amikacin [24]. Data on elimination of amikacin during CRRT are scarce. In one patient with acute renal failure and CVVH, $t_{1/2}$ was 29.7 h and total CL was ca. 22 mL/min [25]. In two oliguric patients receiving CVVH, amikacin given twice daily had a $t_{1/2}$ of 16 h and total CL of ca. 35 mL/min [26]. In the present cohort, $t_{1/2}$ was 6.5 h and median CL was 43.6 mL/min (19.5–86.4 mL/min). The higher drug CL can be explained by the routine use of higher ultrafiltration and blood flow rates than in previous reports, which may achieve higher drug clearance. However, there was also considerable CL variability in the cohort that, together with the lack of correlation between drug CL and CRRT parameters, suggests that additional drug removal, such as through residual renal clearance or potential haemofilter absorption [27], plays an important role in determining total aminoglycoside CL in patients undergoing CRRT.

In this study the median 24-h concentration was 11.5 mg/L and only three patients had $C_{\min} < 5$ mg/L, considered as the limit of potential toxicity. It was calculated that a median of 34 h was required before C_{\min} would fall below this threshold and a new dose of amikacin could be administered. The implications of this finding relate to the potential nephrotoxic effects of persistently high serum concentrations and the extended delay between drug injections. Data on the occurrence of nephrotoxicity

when higher doses of amikacin are used in critically ill patients are scarce. In one study, a group of patients in which amikacin concentrations were monitored in order to target a peak >60 mg/L had a mean C_{\min} of 9 mg/L [13]; however, the degree of renal toxicity was similar to that in patients treated with a conventional regimen. Nevertheless, no patient in that study was treated with CRRT. Although a maximum therapeutic response with an optimum peak may result in shorter courses of amikacin therapy and minimise the risk of accumulation, for patients on CRRT with reduced drug clearance modification of the dosing interval up to 40–50 h is necessary to allow a drug-free period and to reduce the risk of accumulation and toxicity [28]. This extended period between injections may reduce the antimicrobial effect related to the high peak concentration. Nevertheless, we recently showed that CRRT could be used in combination with high-dose amikacin in patients with septic shock and renal dysfunction allowing daily drug administration because of removal by the extracorporeal device [29]. Thus, CRRT parameters could be adapted to improve drug elimination when high-dose amikacin regimens are required in septic patients.

This study has some limitations. First, the PK profile of amikacin was evaluated only during the first 24 h of administration and thus we cannot make any statement about subsequent doses. Second, data regarding the impact of amikacin on renal function are not available and the potential side effects of aminoglycosides should be taken into consideration when administered. Nevertheless, the evidence that $C_{\min} < 5$ mg/L is critical for avoiding kidney dysfunction in critically ill patients is controversial and, for short-time therapy, attaining satisfactory peak levels may have beneficial effects on infection cure that may overcome the risk for renal toxicity [29]. Third, we could

not use the sieving coefficient for amikacin to calculate the predicted drug clearance because this coefficient has been validated for ultrafiltration rates <1 L/h and may be significantly different at higher rates, such those used in the current cohort [30]. Forth, we did not record whether re-injection fluid was given before or after the haemofilter or any possible discrepancy between prescribed and real CRRT flow rates, all of which have important implications on drug removal during CRRT. Finally, concomitant administration of some penicillins can inactivate aminoglycosides, especially in the case of reduced drug clearance, and have an important impact on drug level monitoring. However, amikacin is less affected by this phenomenon and frozen samples, as those used in this study, may further minimise any drug inactivation [31].

5. Conclusions

A loading dose of ≥ 25 mg/kg amikacin in patients with acute oliguric renal failure and septic shock undergoing CRRT is required to obtain a therapeutic effect on less susceptible pathogens. Total CL is lower in these patients than in those without renal failure, so that accumulation of the drug is expected over time. To maintain an adequate peak concentration with daily administration of the drug, high-flow CRRT should be used, especially in patients receiving prolonged aminoglycoside therapy.

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Competing interests

None declared.

Ethical approval

Ethical approval for this study was given by local Ethics Committees of the different hospitals. Written informed consent was obtained from the patient or his/her legal guardian.

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Fig. 1. Individual pharmacokinetic profiles of amikacin. Dashed line indicates a concentration of 64 mg/L.

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Table 1

Characteristics and pharmacokinetic data of the study patients

Pt. No.	Age (years)	BMI	Sex	APACHE II	SOF A	Site of infection	AMK dose (mg)	V_d (L/kg)	Peak AMK concentration (mg/L)	C_{min} (mg/L)	CL (mL/min/kg)	$t_{1/2}$ (h)	Time to C_{min} < 5 mg (h)
1	70	29.2	M	28	13	Acute cholecystitis	2500	0.41	70.0	11.5	2.84	5.5	34
2	57	24.2	M	24	5	Primary bacteraemia	1750	0.32	92.8	4.1	2.77	4.4	23
3	77	27.8	M	37	15	HAP	2250	2.65	71.7	9.6	0.14	141.2	32
4	56	17.2	M	33	14	VAP	1125	0.55	52.7	12.3	1.38	6.5	39
5	44	21.2	M	27	19	HAP	1625	0.27	94.6	18.4	1.26	4.5	44
6	59	20.5	M	12	9	Secondary peritonitis	1750	0.43	75.8	24.7	1.02	12.1	60

7	61	14.	F	20	10	HAP	100	0.83	40.3	17.2	0.84	12.1	59
		8					0						
8	59	20.	M	25	18	Primary	162	0.50	70.5	29.9	0.64	19.2	76
		1				bacteraemia	5						
9	44	18.	F	33	11	CAP	125	0.39	66.3	8.1	1.66	6.2	29
		4					0						
10	89	22.	M	28	11	Aspiration	170	4.06	39.4	8.0	0.10	279.	30
		5				pneumonia	0					6	
11	69	23.	F	43	14	Pyelonephriti	150	2.61	46.3	4.1	2.22	6.7	22
		4				s	0						
12	58	24.	F	37	5	Necrotizing	150	0.85	74.0	3.1	3.31	5.6	15
		7				fasciitis	0						
13	77	24.	M	30	12	Secondary	200	0.22	38.3	9.1	2.97	4.5	34
		2				peritonitis	0						
Media	59	22.		28	12		162	0.5	70.0	9.6	1.26	6.5	34
n		5					5						

Pt., patient; BMI, body mass index; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; AMK, amikacin; V_d , volume of distribution; C_{min} , drug concentration at 24 h; CL, total drug clearance; $t_{1/2}$, elimination half-life; HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia; CAP, community-acquired pneumonia.

Table 2

Individual characteristics of continuous venovenous haemodiafiltration (CVVHDF) parameters

Pt. No.	Duration (h)	Membrane	Blood flow (mL/min)	Dialysate flow rate (mL/kg h)	Ultrafiltration rate (mL/kg h)	Fluid removal (mL/h)
1	16	AN69	150	20	25	0
2	17	AN69	150	29	36	0
3	21	AN69	130	28	33	20
4	24	F40S	200	33	44	97
5	24	Polysulfone	200	31	35	98
6	24	Polysulfone	200	29	29	17
7	21	Polysulfone	200	39	39	0
8	24	Polysulfone	200	38	46	21
9	22	Polysulfone	150	40	50	110
10	22	Polysulfone	150	23	31	17
11	24	Polysulfone	150	33	33	38
12	16	Polysulfone	150	25	33	0
13	24	Polysulfone	150	29	29	0

Pt., patient.

