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First-dose pharmacokinetics of aminoglycosides in critically ill haematological malignancy patients

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ABSTRACT

The primary objective of this study was to determine the volume of distribution (V_d) (L/kg) of intravenous aminoglycosides (AGs) in critically ill haematological malignancy patients. Secondary objectives were to determine the body weight (actual, ideal, adjusted or lean) that yields the most precise estimate of V_d when normalised in L/kg as well as the frequency that current first-dose strategies result in post-distributional peak concentrations (C_{peak}) within the target range (tobramycin 16–24 mg/L; amikacin 32–48 mg/L). In total, 58 AG doses were included (tobramycin, $n = 34$; amikacin, $n = 24$). Median V_d was 0.38 L/kg normalised per the most precise dose weight, which was actual body weight (ABW). The median dose was 445 mg (5.8 mg/kg ABW) for tobramycin and 1200 mg (13.8 mg/kg ABW) for amikacin. Target C_{peak} (tobramycin 20 mg/L; amikacin 40 mg/L) was achieved in only 25% of all AG episodes, with 4% exceeding the target and 71% falling below the target. Twenty-four organisms were isolated in the study sample; target C_{peak} achievement (tobramycin 20 mg/L; amikacin 40 mg/L) would yield a peak:minimum inhibitory concentration of 10 in 75% and 52% of organisms, respectively. In conclusion, an increased V_d of AGs was identified in this critically ill haematological malignancy patient sample, and current dosing yielded a suboptimal C_{peak} in the majority of patients.

1. Introduction

Gram-negative infections pose a significant danger to patients. Aminoglycosides (AGs) are commonly utilised in combination with β-lactams to treat Gram-negative infections in critically ill patients. They remain key agents in the treatment of infections caused by multi-drug-resistant organisms [1]. AGs exhibit concentration-dependent activity with optimal efficacy achieved when the peak serum concentration to minimum inhibitory concentration (MIC) ratio is ≥10 [2]. Extended-interval AG dosing (EIAD) was developed to help achieve this pharmacokinetic/pharmacodynamic (PK/PD) target and to minimise trough-dependent toxicity [3].

Concerns exist that current doses used in EIAD regimens may not reliably result in achievement of the target peak serum concentration/MIC ratio in critically ill patients, due in part to an increased volume of distribution (V_d) [4]. Literature evaluating the V_d of AGs in critically ill patients is limited by a minimal number of trials, small sample sizes, varying populations and methodological differences [5–7]. Regardless, these studies have demonstrated an overall increase in AG V_d in the critically ill. The aetiology for the increased V_d has been proposed to include aggressive fluid resuscitation, capillary leak and altered protein binding [8,9].

Cancer patients also exhibit an increased V_d compared with the general population although the aetiology is unknown [10]. The impact of an increased V_d on antimicrobial dosing is of great concern in cancer patients owing to the diminished innate immune response, particularly in those with haematological malignancy. In a previous study, severe sepsis patients with malignancy had a 52% higher mortality rate compared with those without malignancy [11]. As such, the purpose of this study was to evaluate the first-dose kinetics of intravenous (i.v.) AGs in a critically ill haematological malignancy population.

The primary objective was to determine the V_d (L/kg) of i.v. AGs in critically ill haematological malignancy patients. Secondary objectives were to determine the body weight [actual (ABW), ideal (IBW), adjusted (AdjBW) or lean (LBW)] that yields the most precise estimate of V_d when normalised on a L/kg basis as well as the frequency that current first doses result in post-distributional peak concentrations (C_{peak}) within the target range.

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2. Methods

2.1. Study design and sample

This was a single-centre, retrospective cohort study performed at The University of Texas MD Anderson Cancer Center (MDACC) in Houston, TX. MDACC is a National Cancer Institute-recognised comprehensive cancer centre with a 26-bed medical intensive care unit (MICU) managed by full-time intensivists and multidisciplinary personnel. The study was approved by the Investigational Review Board of MDACC. A waiver of informed consent was granted.

Patients were included if they were aged ≥19 years, diagnosed with haematological malignancy, admitted to the MICU between 1 August 2009 and 31 August 2011, received a dose of i.v. AG in the emergency centre (while awaiting MICU transfer) or in the MICU, and had two serum levels obtained within 24 h of the first AG dose. The first AG serum level must have been obtained between 3 and 9 h after the dose, and the second level ≥3 h after the first level. This was done to ensure post-distributional levels and at least one typical half-life of 3 h between the two levels [12,13]. Patients were excluded if they received more than one dose of the current AG within 48 h prior to the dose being evaluated, were receiving renal replacement therapy or plasmapheresis, or were pregnant.

2.2. Current aminoglycoside practice and pharmacokinetic analysis

Within the MICU of MDACC, AGs are typically dosed via an EIAD strategy. This consists of 7 mg/kg tobramycin or gentamicin and 15–20 mg/kg amikacin using IBW (or AdjBW if >120% IBW), with each dose infused over 1 h. According to MDACC clinical pharmacy practice, AG serum levels are obtained in most patients 4 h and 10 h following completion of the infusion for pharmacokinetic analysis. Tobramycin and amikacin are the predominant AGs prescribed for the treatment of Gram-negative infections.

The elimination rate constant (k_e), half-life ($t_{1/2}$), C_{max}, V_d, C_{peak} and C_{trough} were calculated using a one-compartment, i.v. infusion model based on the Sawchuk–Zaske method (equations shown in Table 1) [14,15]. C_{max} corresponds to the concentration at the end of a 1-h infusion and was used to calculate V_d in Eq. 6. C_{peak} was the concentration determined utilising Eq. 4 and a t = 1.7 h, corresponding to the time after the end of infusion when the distribution phase is expected to be complete following large-dose AG administration [12]. C_{trough} was the concentration calculated at 24 h (Fig. 1).

The target C_{peak} for tobramycin and amikacin were 20 mg/L and 40 mg/L, respectively [3]. Given variability in peak concentrations with EIAD reported previously [3], a 20% variability was incorporated, resulting in a target C_{peak} range of 16–24 mg/L for tobramycin and 32–48 mg/L for amikacin. These concentrations were established to target a peak:MIC of 10 for organisms with a MIC of 2 mg/L for tobramycin and 4 mg/L for amikacin.

Table 1
Pharmacokinetic equations (one-compartment model).

Eq. 1	$k_e = (\ln C_1 - \ln C_2)/(t_{interval})$
	k_e = elimination rate constant (h^{-1})
	C_1 = first level obtained (mg/L)
	C_2 = second level obtained (mg/L)
	$t_{interval}$ = time between levels (h)
Eq. 2	$t_{1/2} = 0.693/k_e$
Eq. 3	$C_{max} = C_0/e^{-k_e \times t}$
	$C_0 = C_1$
	t = time from the end of infusion to C_0
Eq. 4	$C_{peak} = C_{max} \times e^{-k_e \times t}$
	t = time from C_{max} to C_{peak} (1.7 h)
Eq. 5	$C_{trough} = C_{peak} \times e^{-ke \times t}$
	t = time from C_{peak} to 24 h (21.3 h)
Eq. 6	$V_d = (D/t') \times (1/k_e) \times (1 - e^{-k_e \times t'})/(C_{max} - C_0 e^{-k_e \times t'})$
	D = dose in mg
	t' = length of infusion (i.e. 1 h)
Eq. 7	$D/X = (V_d/X) \times t' \times k_e \times (C_{max} - C_0 e^{-k_e \times t'}) \times [1/(1 - e^{-k_e \times t'})]$
	X = patient weight in kg
	D/X = dose in mg/kg
	V_d/X = volume of distribution in L/kg

2.3. Weight analysis

In addition to ABW, three other definitions of weight (kg) were utilised according to the following equations:

$$\text{AdjBW} = \text{IBW} + 0.4(\text{ABW} - \text{IBW}), \quad \text{if ABW is} > 20\% \text{ IBW} \tag{1}$$

$$\begin{aligned} \text{IBW male} &= 50 + (2.3 \times \text{in.} > 60) \\ \text{IBW female} &= 45.5 + (2.3 \times \text{in.} > 60) \end{aligned} \tag{2}$$

$$\begin{aligned} \text{LBW male} &= \frac{9270 \times \text{ABW}}{6680 + 216 \times \text{BMI}} \\ \text{LBW female} &= \frac{9270 \times \text{ABW}}{8780 + 244 \times \text{BMI}} \end{aligned} \tag{3}$$

where BMI is the body mass index.

The V_d (L/kg) for each patient was normalised to L/kg by dividing the calculated V_d (L) by each specific definition of weight (kg).

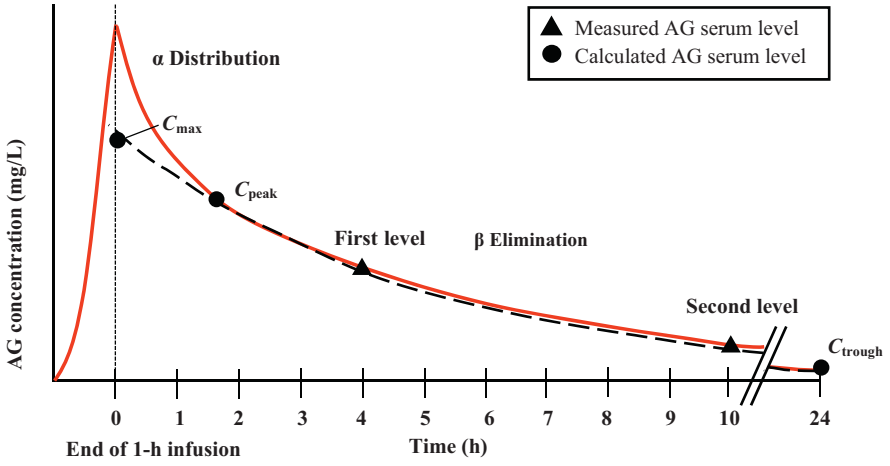

Fig. 1. Pharmacokinetic analysis of aminoglycoside (AG) dosing.