Aminoglycosides ICU patients PopPK models

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Aminoglycosides are a class of antibiotics used as treatment for Gram-negative infections in patients hospitalized in intensive care units (ICUs). Life-threatening infections, often caused by Gram-negative bacteria [1,2], may lead to pathophysiological conditions, such as sepsis, influencing the pharmacokinetics (PK) of many drugs including antibiotics [3]. Antibiotic dosing regimens have been developed with the help of population pharmacokinetic (PopPK) modeling and simulation [11]. Multiple studies have established PopPK models to characterize PK parameters and to gain a better understanding of the variability of aminoglycoside clinical response based on ICU patients' characteristics. These studies have used nonlinear mixed effects modeling to target and quantify the contribution of specific demographic and pathophysiological characteristics that may influence the aminoglycoside PK profile.

Keywords: aminoglycosides ; population pharmacokinetic modeling ; intensive care unit ; critically ill

1. Introduction

As aminoglycosides follow concentration-dependent pharmacodynamics, the achievement of a peak concentration (C_{max}) over minimum inhibitory concentration (MIC) ratio greater than 10 is warranted for a clinical response [1]. Although the C_{max}/MIC target is primarily used in clinical situations due to its simplicity, multiple studies have shown that an area under the curve (AUC) to MIC ratio greater than 80–100 is the better pharmacokinetic/pharmacodynamic (PK/PD) indicator for efficacy [1][2][3]. Considering the narrow therapeutic index of aminoglycosides with potential nephrotoxicity and ototoxicity, therapeutic drug monitoring (TDM) has been used to achieve these targets while minimizing toxicity by individualizing treatments [4]. This practice is especially crucial in ICU patients that suffer from septic shock where the survival rate is increased with the timely administration of an appropriate antibiotic [5].

PopPK models can also be used to develop dosing recommendations by simulating several dosing regimens based on different PK/PD targets. However, it is also important to assess the validity of these models and the efficacy of the dosing recommendations in actual clinical settings in large populations. Generally, clinical pharmacokinetic studies must present several key items to better ensure transparency in the reporting of the results [6].

2. Population PK Modeling of Aminoglycosides in the Intensive Care Unit

To treat severe infections, the administration of aminoglycosides in special populations has led to an increase in interest in aminoglycoside pharmacokinetics. Noticeably, a considerable number of PopPK models have been developed for ICU patients in the last decade [7][8][9][10][11][12][13][14][15][16][17][18]. In fact, Marsot et al. suggested in their review that single-compartment models could lead to an inaccurate estimation of aminoglycoside Vd [19]. Although median CL and Vd values were comparable across aminoglycosides, as shown in **Figure 1**, the parameter values tended to vary from one study to another for each drug. As described previously, ICU patients are prone to present additional comorbidities, such as cardiovascular dysfunction, sepsis, burns, or use of vasopressors, and/or develop complications, such as acute kidney injury (AKI) or, conversely, augmented renal clearance (ARC). These complications usually lead to divergence in PK values as compared to healthy patients [20]. As per **Figure 1**a, based on a similar dosing regimen, median CL values for all three drugs in this present study were generally lower as compared to values in healthy volunteers: 6.48 L/h, 4.03 L/h, and 7.02 L/h for amikacin, gentamicin, and tobramycin, respectively [21][22][23][24].

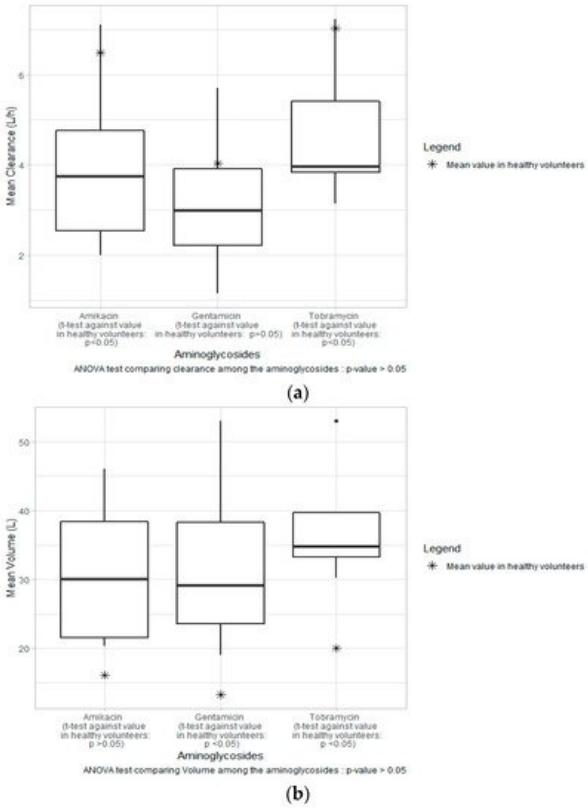

Figure 1. (**a**) Range of mean clearance across studies stratified by aminoglycosides (amikacin, gentamicin, and tobramycin) with mean clearance value in healthy volunteers (dotted line). (**b**) Range of mean volume of distribution across studies stratified by aminoglycosides (amikacin, gentamicin, and tobramycin) with mean volume of distribution value in healthy volunteers (dotted line).

2.1. Major Covariates

In addition of the changes due to critical illness, ICU patients may present other physiological characteristics potentially impacting aminoglycoside pharmacokinetics. To better understand the inter- and intra-variability of aminoglycosides pharmacokinetics, the following covariates were the most retained in PopPK models: bodyweight (n = 7) and renal clearance (n = 8).

2.1.1. Renal Function

To illustrate the impact of CL_{CR} on aminoglycoside CL, we plotted aminoglycoside CL against this covariate according to the values and model equations reported by the studies that included CL_{CR} (**Figure 2**). This plot shows how differences in CL_{CR} caused important variations in aminoglycosides CL within the same study group. Considering that the CL_{CG} includes the age, total bodyweight, and sex of an individual, these variables are, therefore, also considered in the estimation of aminoglycoside CL or Vd.

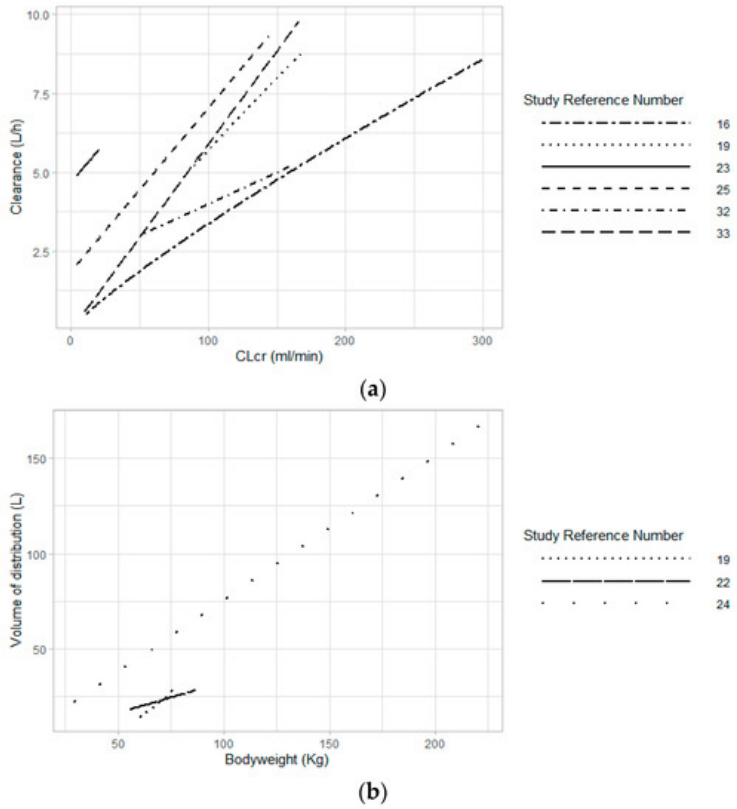

Figure 2. (**a**) Aminoglycoside clearance values against range of creatinine clearance in the respective studies. (**b**) Aminoglycoside volume of distribution values against range of bodyweight in the respective studies. Note: Two studies used IBW [10][14] and one used TBW [25] in their model.

Although CL_{CG} seems to be frequently used in guidelines [26], it might not represent the most accurate way of estimating aminoglycoside clearance [27]. In fact, CL_{CG} is known to overestimate the CL_{CR} in underweight individuals [28]. As for obese individuals, the usage of CL_{CG} with IBW tends to underestimate the CL_{CR}, while the usage of TBW overestimates the CL_{CR} [28]. Many studies have suggested that CL_{CG} should not be used in intensive care settings [29][30][31][32]. Moreover, since CL_{CR} considers glomerular filtration, as well as tubular secretion [33], measurements of GFR have been suggested to be a more precise estimate of aminoglycoside clearance [34]. In fact, the aminoglycoside elimination pathway mainly involves glomerular filtration, while tubular secretion and reabsorption are minimal, even when GFR levels are low. Zarowitz et al. compared gentamicin and tobramycin clearances to inulin (GFR) and CL_{CG}, and their results showed a better linear regression between inulin and GFR (R^2 = 0.93) compared to the linear regression between inulin and CL_{CG} (R^2 = 0.76) [34]. Moreover, Lim et al. also compared different estimators of GFR with the traditional CL_{CG}, and they determined that the best predictor of aminoglycoside clearance would be the estimation of glomerular filtration rate by CKD-EPI adjusted for BSA [26]. Considering the high prevalence of CL_{CG} among the studies included in this review and its frequent usage in dosing guidelines, the better estimator between CL_{CG} and GFR, in terms of accuracy and efficacy in clinical settings, is still debatable.

Despite age not being a significant covariate in the estimation of aminoglycoside PK parameters in ICU patients, except when considered in the CG equation, advanced age is often associated with several physiological changes such as loss of kidney function and modifications in body composition influencing drug absorption and distribution of drugs [35]. In fact, it has been suggested that gentamicin renal clearance seemed to decline more significantly after reaching 60 to 70 years of age [36]. However, it was also mentioned that this decrease in gentamicin clearance might also be caused by other underlying diseases. The authors pointed out that the gentamicin Vd slightly varied across different ranges of age (39, 61, and 80 years old). Although age has been considered as an independent factor of nephrotoxicity and ototoxicity, several clinical studies mentioned that gentamicin clearance was influenced mainly by renal function and that the impact of age, by itself, is not significant [36][37][38].

2.1.2. Bodyweight and Body Size

Since aminoglycosides are administered following a weight-based dose, the selection of the right weight parameter is essential to avoid overestimating or underestimating the dose needed. For example, in overweight patients, it is recommended to use an adjusted bodyweight that will consider a fraction of the excess bodyweight (total bodyweight–ideal bodyweight) [28]. Obesity is associated with major physiological changes such as an increased Vd for antibiotics, e.g., aminoglycosides [39]. Therefore, administration of higher doses to reach targeted serum concentrations is needed. In

several studies presented in this review, patient weight was determined significant in the estimation of amikacin and gentamicin clearances (n = 3) [8][12][15] and volume of distribution (n = 3) [10][12][25]. To illustrate the impact of bodyweight in general on aminoglycoside Vd, the latter was plotted against this covariate according to the values and model equations reported by the studies that included a BW variable (**Figure 3**). Variations within BW from a same study seem to imply changes in aminoglycoside Vd. As mentioned earlier, bodyweight also has an influence on the estimation of the CL_{CR}, especially if CL_{CG} is used. All seven studies that included CL_{CG} in their final PopPK model used TBW in the CG equation [7][9][10][40][13][17][41]. For studies that included impaired renal patients, each study retained a bodyweight parameter in one of the two parameters their final model [8][10][12][15]. Indeed, the inclusion of a bodyweight parameter is expected in this population considering that bodyweight is used in order to determine dialysate or ultrafiltration flow rate for renal replacement therapy (RRT) [8][12][40][15].

For body size parameters, only body surface area (BSA), lean body mass according to the equation of Chennavasin (LBMc), and free fat mass (FFM) were retained covariates in amikacin, gentamicin, and tobramycin models, respectively [7][16][18]. In fact, these three covariates were retained in the estimation of aminoglycoside Vd. Although BSA has rarely been mentioned as a covariate influencing aminoglycoside PK, it was suggested by Boidin et al. that the use of BSA might lower the risk of exposure in overweight patients [7][42]. In fact, BSA considers both the bodyweight and height, where the latter is much less variable than bodyweight in ICU adult patients [43]. Recent studies did suggest dose recommendations based on height (mg/cm) instead of bodyweight for tobramycin in cystic fibrosis patients [44][45].

Although the inclusion of parameters related to bodyweight or body size in the final model of most studies allowed a reduction in IIV, the latter remains relatively high across studies. This variability could be explained by the inaccuracy and variability of the estimation of TBW or actual bodyweight of ICU patients [46][47].

2.2. External Validation and Application

External validation is one of the strictest approaches in model testing and consists of applying a new dataset within a final model to determine the accuracy and reproducibility of the model and in which conditions it would be applicable. Different strategies and steps are possible in order to adequately evaluate models from the literature.

The conception of a meta-model for each aminoglycoside may also be feasible by including the characteristics (covariates, error models, initial estimates) from the best-performing models following external validation with an independent dataset. The development of this meta-model is, therefore, derived from the independent dataset while also being based on previously published PK models.

2.3. Simulation of Dosing Regimens

Firstly, amikacin dosing recommendations in critically ill patients without RRT were simulated in two articles [7][10]. In Boidin et al., an optimal initial amikacin dose of 3.5 g showed a better PTA for $C_{max} \geq 64$ mg/L and $AUC_{0-24} \geq 600$ mg*h/L compared to the conventional 30 mg/kg of corrected bodyweight (CBW), considering an MIC of 8 mg/L [7]. It was suggested that an increase in the dosing interval up to 36 or 48 h might be feasible in critically ill patients with normal to moderate renal function. In fact, several recommendations were simulated on the basis of different values of the two significant covariates in their respective PopPK model, CL_{CG} (10 mL/min to 250 mL/min), and BSA (1.5 m^2 to 2.5 m^2). As for Aréchiga-Alvarado et al., different daily dosing recommendations were simulated on the basis of three different MICs (4 mg/L, 8 mg/L, and 16 mg/L) and CL_{CR} ranging from 60 mL/min to 200 mL/min [10]. Considering an MIC of 8 mg/L, a 30 mg/kg daily dose would be able to show a TAR over 80% and 75% for patients with CL_{CR} lower than 140 mL/min and greater than 140 mL/min, respectively. As for amikacin dosing recommendations in critically ill patients RRT, two studies showed similar results in terms of optimal dosing regimens. In fact, Roger et al. and Carrié et al. suggested, respectively, that a dose of 25 mg/kg every 48 h and a dose ranging from 25 mg/kg and 30 mg/kg every 36 to 48 h were the most appropriate in order to maximize TAR for C_{max}/MIC ≥ 8 and $AUC_{0-24} \geq 70$ or $AUC_{0-24} \geq 75$ with an MIC of 8 mg/L [8][9].

Secondly, gentamicin and tobramycin dosing recommendations in critically ill patients without RRT were simulated in five different articles [25][13][17][41][18]. Three out of the five studies established similar dosing recommendations with an initial starting dose of 6 to 7 mg/kg or a daily dose of 7 mg/kg [25][13][14]. The other study from Conil et al. provided a graphical representation of TAR for $C_{max} > 10$ mg/L, $C_{trough\ at\ 24h} < 1$ mg/L, and AUC between 80 and 125 mg*h/L according to different fixed dose regimens [17]. Their main takeaway was that these targets were not reached simultaneously in more than 45% of patients. Furthermore, only half of the population was able to attain the target for AUC with daily fixed dosages of 375 and 400 mg. The other study from Aarons et al. simulated dosing regimens on the basis of CL_{CR} values [41]. All dosing regimens proposed were presented as a sequence: a fixed dose administered for the first 48 h with a dosing interval ranging from 8 h to 24 h depending on the CL_{CR}. Following the first 48 h, a maintenance dose was to be

administered as per the same dosing interval. The first period of 48 h was chosen according to the authors' assumption that aminoglycoside concentration was to be detectable and, thus, have the possibility of dose adaptation [41]. As for patients under RRT, Teigen et al. demonstrated that, on the basis of PK/PD targets of C_{max} ≥ 8 mg/L and AUC_{48} between 140 and 24 0 mg·h/L, three fixed starting doses (300 mg, 240 mg, 220 mg) prior to dialysis are related to a better TAR compared to post-dialysis administration [40]. Furthermore, Roberts et al. showed that a dosing of gentamicin 6 mg/kg every 48 h and administered 30 min prior to RRT (EDD-f in this situation) was able to achieve PK/PD targets compared to daily 7 mg/kg administration [15].

Results from simulations based on inter- and extrapolation should be interpreted cautiously considering the high variability observed in the estimation of PK parameters for all aminoglycosides.

3. Conclusions

Although many PopPK models for aminoglycosides exist in the literature, important variability remains. Despite multiple covariates being tested across all studies, the significant covariates would still be creatinine clearance and bodyweight for aminoglycoside clearance and volume of distribution, respectively. Moreover, considering that aminoglycoside-induced toxicity is reported to be more frequent amongst individuals with mitochondrial DNA mutations, such as m.1555A>G and m.1494C>T in the 12S rRNA gene [48], pharmacogenetics should be taken into account in future PopPK models. Several limitations are to be considered; seven study populations had fewer than 30 subjects, and more than half of the articles had retrospective designs with few aminoglycoside samples.

Although simulations have been carried out and help us to suggest optimal dosages, it should not be forgotten that many models were not evaluated externally and, therefore, may not be generalizable. Moreover, these dosing regimens were taken from a small sample size of studies, and additional research on simulated dosing regimens based on specific subpopulations should be necessary to optimize aminoglycoside individualized dosing. TDM remains essential in the ICU population to achieve therapeutic success while minimizing the likelihood of toxicity.

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