Population pharmacokinetic evaluation and optimisation of amikacin dosage regimens for the management of mycobacterial infections

[1,]Hinke SIEBINGA[1,2], Fiona ROBB[3], *Alison H THOMSON[1]

[1] Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK

[2] Department of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

[3] Pharmacy Department, Queen Elizabeth University Hospital, NHS Greater Glasgow and Clyde, Glasgow, UK

*Corresponding author

Fax: +44 141 552 2562

Tel: +44 141 548 4894

Email: Alison.h.thomson@strath.ac.uk

Short title: Amikacin in mycobacterial infection

[1]Current address Department of Pharmacy and Pharmacology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

SYNOPSIS

Background There is limited information on amikacin pharmacokinetics (PK) and dose requirements in patients with mycobacterial infections.

Objectives To conduct a population PK analysis of amikacin data from patients with mycobacterial infections and compare predicted concentrations from standard and modified dosage guidelines with recommended target ranges.

Methods A population PK model was developed using NONMEM. C_{max}, C_{min}, C1h post infusion (C_{1h}) and $AUC_{0\text{-}24}$ using 15 mg/kg daily (OD), the World Health Organisation (WHO) table, 25 mg/kg thrice weekly (TTW) and modified guidelines were compared using Monte Carlo simulations of 1000 patients.

Results Data were available from 124 patients (684 concentrations) aged 16 to 92 years. CL was 4.64 L/h per 100 mL/min CL_{CR}; V was 0.344 L/kg. With OD regimens, C_{max} was 35-45 mg/L in 30-35% of patients and 35-50 mg/L in 46-48%; C_{1h} was 25-40 mg/L in 53-59%. The WHO table produced high C_{max} values in patients <60 kg and low in patients >75 kg. With TTW dosing, around 30% of C_{max} were 65-80 mg/L, 40% were 60-80 mg/L and 48% of C_{1h} were 45-65 mg/L. Increasing the dosage interval for patients with CL_{CR} <50 mL/min reduced C_{min} values >2 mg/L from 34% to 25% for OD dosing and 18% to 13% for TTW. In patients whose C_{min} was <2 mg/L, 82% of $AUC_{0\text{-}24}$ were 100-300 mg.h/L.

Conclusions Standard amikacin dosing guidelines achieve low percentages of target concentrations for mycobacterial infections. Extending the dosing interval in renal impairment and widening target ranges would reduce the need for dose adjustment.

250 words

INTRODUCTION

Amikacin is currently used in the management of infections involving multi-drug resistant TB and non-TB mycobacteria.[1-4] However, there is limited evidence to define optimal amikacin dosage regimens and target concentrations for these indications. In Gram negative sepsis, recommended once daily (OD) doses range from 9 to 30 mg/kg and target C_{max} values from >40 to >64 mg/L.[5-8] OD (or 5 days per week) doses of 15 mg/kg are typically recommended for patients with mycobacterial infections[1,3,9] but three times weekly (TTW) doses of 10-30 mg/kg are also used.[2,3,9] Despite similarities in dosage regimens, associated C_{max} targets have been quoted as 20-30,[3] 25-35,[4] 35-45,[9,10] and 55-65 mg/L[11] for OD dosing and are typically 65-80 mg/L for TTW dosing.[4,9] C_{min} targets are generally <5 mg/L[3,5,7] but range from undetectable to <10 mg/L.[3,10]

High trough concentrations of amikacin have been linked to nephrotoxicity while ototoxicity has been associated with older age, duration of therapy and cumulative AUC.[9,12,13] Patients with mycobacterial infections are at particular risk of developing ototoxicity since they are often on prolonged courses of treatment[1] and long-term ototoxicity rates ranging from 7% to 62% have been reported in this patient group.[9,11,14-16] Although no clear association between toxicity and peak or trough concentrations has been identified, van Altena *et al*.[16] found that using therapeutic drug monitoring (TDM) to design dosage regimens that achieved a C_{max}/MIC ratio >20 led to lower doses, lower exposure and a low risk of ototoxicity with no evidence of treatment failure or relapse.

A recent review identified several studies describing the population pharmacokinetics (PopPK) of amikacin in adult patients with sepsis[17] but few have examined amikacin PK in

patients with mycobacterial infections.[11,18] The aims of the present study were to develop a PopPK model for amikacin using routine data collected from a large population of patients with mycobacterial infections then use Monte Carlo simulations to compare the concentrations achieved by internationally recognised amikacin dosage guidelines with their recommended target ranges and identify whether modifications to guidelines or target ranges would be helpful for this patient group.

METHODS

Patients and data

Retrospective data from patients treated with amikacin for mycobacterial infections (both TB and non-TB) were obtained from TDM files stored as hard copy or electronically in a MAP Bayesian package.[19] The study protocol was reviewed by the Ethics committee manager and the Caldicott Guardian. As the data had been generated in the course of routine TDM and fully anonymised, the study was judged a service evaluation for which patient consent and formal ethical approval were not required.

Data were collected between January 2002 and February 2018. Starting dosage regimens were initially 7.5 mg/kg twice daily but changed to 15 mg/kg OD and 25 mg/kg TTW in 2006, in line with the Peloquin guidelines.[9] Doses were administered over 30 min and samples for amikacin analysis were typically withdrawn 1-3 h after the start of the infusion and at the end of the dosage interval. Concentrations were measured by the local microbiology or biochemistry laboratory using a Fluorescence Polarisation Immunoassay (TDx, Abbott Laboratories) or a homogeneous particle-enhanced turbimetric inhibition assay (Architect, Abbott Laboratories). From 2006, doses were adjusted to achieve end of infusion C_{max} values

of 35-45 mg/L (OD) or 65-80 mg/L (TTW) according to the Peloquin guidelines.[9] Where necessary, dosage regimens were adjusted to maintain a C_{min} <2 mg/L.

The following data were extracted from TDM files: age, total body weight (TBW), sex, height, serum creatinine concentration(s), amikacin dose amounts, times, duration of infusion and amikacin concentrations and sampling times. Concentrations measured within 60 min of the start of the infusion, and likely to be sampled during distribution, were excluded. If height was available, ideal body weight (IBW)[20], fat free mass (FFM)[21] and adjusted body weight (AJBW = IBW + 0.4 x (TBW-IBW)) were also calculated. CL_{CR} was estimated using the Cockcroft-Gault equation[22] based on TBW, IBW, FFM and AJBW. If height was not available, TBW was used to estimate CL_{CR}.

Pharmacokinetic analysis

PopPK parameters were estimated on a Dell® XPS laptop with an Intel® Core™ i7 Processor using NONMEM 7.4.2 (Icon Development Solutions, Ellicott city, MD, USA) with a GNU FORTRAN complier 4.6.3 and first order conditional estimation and interaction. Bootstrap analysis was performed using Perl-Speaks-NONMEM[23] and graphical evaluation using Xpose version 4.3.5[24] implemented in R version 3.1.0.[25] Visual predictive checks were prepared using Wings for NONMEM version 743.[26]

Both one- and two-compartment structural models were explored. Between subject (BSV) and between occasion (BOV) variabilities in PK parameters were assumed to be log normally distributed; residual error was described by a combined error model. Patient age, sex, TBW, IBW, AJBW, FFM, allometric weight $(Weight/70)^{0.75}$ and CL_{CR} were evaluated as

covariates. Possible relationships between PK parameters and covariates were explored graphically and then, individually and in combination, by adding them to the basic model using a stepwise approach with a decrease in OFV of 3.84 ($p<0.05$) to identify significant covariates in the forward selection process and 6.63 ($p<0.01$) in the backward elimination process. Models were also compared using goodness of fit plots, visual predictive checks and by examining changes in BSV of CL and V. A nonparametric bootstrap of the final model was performed with 1000 replicates and a visual predictive check (VPC) with 1000 simulations.

Simulations

The final PopPK model was used with NONMEM to run Monte Carlo simulations of 1000 patients sampled from the patient data set to evaluate the Peloquin guidelines[9] (15 mg/kg OD and 25 mg/kg TTW) and the World Health Organisation (WHO) OD table[1] (Supplementary table 1). In addition, a modified table of weight banded doses based on the Peloquin guidelines[9] of 15 mg/kg OD and 25 mg/kg TTW was constructed (Table 1). This included a reduction in dose frequency to 48 hourly (OD) and twice weekly (TTW) for patients whose estimated CLCR was ≥30 and <50 mL/min. AJBW was used to determine the dose if TBW was >IBW. Dose administration times were 0, 24 and 48 h for the OD regimen and 0, 48 and 96 h for the TTW regimen. Infusions were set to run over 30 min and C_{max} (end of infusion), C at 1 h after the end of the infusion (C_{1h}) and C_{min} were determined for each regimen after the first dose and before and after the third dose. $AUC_{0\text{-}24}$ estimates were calculated from the total weekly dose/(7 x CL). The percentages of C_{max} in the ranges 35-45 mg/L (OD), 65-80 mg/L (TTW) and C_{min} values <5 mg/L and <2 mg/L were determined using

the standard and modified guidelines. Typical concentration ranges were identified for C_{1h} and percentages of concentrations within extended target ranges were also determined.

RESULTS

Patient data

Data were available from 124 patients (72 male) aged 16 to 92 years (median 49) and included 1624 amikacin doses and 684 concentrations (1-44 per patient, median 3). Clinical characteristics are summarised in Table 2. Sample times ranged from 1 to 97 h post infusion (median 2 h); 48% of samples were taken 1-2 h and 15% more than 12 h post infusion. Laboratory values for two samples (0.3%) below the limit of quantification were included in the data set. TBW exceeded IBW in 40 patients (32%) and was >20% above IBW in 22 patients (18%). CL_{CR} ranged from 18 – 184 mL/min (median 84). Severe renal impairment (CL_{CR} <30 mL/min) was present in 9 patients (7%) and CL_{CR} was <50 mL/min in 21 patients (17%). In accordance with routine clinical practice designed to avoid excessive estimates of CL_{CR},[27] some creatinine concentrations ≤60 µmol/L had been fixed to 60 µmol/L. The final data file contained 170 creatinine concentrations (10%) from 32 patients recorded as 60 µmol/L and 58 concentrations <60 µmol/L (13 patients).

Pharmacokinetic analysis

Data were adequately described by a one-compartment model. Although a two-compartment model produced a lower OFV, there was no improvement in diagnostic plots, volume of the peripheral compartment and intercompartmental clearance were poorly characterised and the bootstrap analysis indicated a lack of stability in these estimates. The base model had a typical CL of 3.38 L/h (BSV 72%) and a *V* of 21.0 L (BSV 32%). Addition of

BOV did not improve the fit of the data. In the forward selection process using individual clinical factors, sex, age, creatinine concentration and all weights influenced CL. Backward elimination removed sex from the full model but weight, age, and creatinine concentration remained significant. The lowest OFV values were obtained using FFM (3127) or AJBW (3129). Models that related CL to estimated CL_{CR} achieved similar fits to these more complex models. The best overall model (OFV 3132) was: CL (L/h) = 0.0464 x CL_{CR} (mL/min) based on AJBW; *V* = 0.344 L/kg AJBW. This resulted in a CL of 4.64 L/h for a patient with a CL_{CR} of 100 mL/min. This model reduced the OFV by 157 points from the base model, BSV in CL fell to 34% and in *V* to 23%. Using FFM or TBW to estimate CL_{CR} increased the OFV by 1.3 and 22, respectively. The parameters of the final model and the results of the bootstrap analysis are presented in Table 3. Differences between the bootstrap medians and PopPK model estimates were all <5%. Figure 1 shows the VPC and Supplementary figures 1 and 2 show additional goodness of fit plots. All indicate that the model described the data well.

Simulation results

Table 4 shows the percentages of simulated concentrations within the different target ranges based on the Peloquin[9], WHO[1] and modified guidelines. With both the Peloquin[9] and modified guidelines, only 35% of C_{max} were in the recommended target range of 35-45 mg/L; this increases to 48% if the upper limit is extended to 50 mg/L. The WHO guidelines[1] were slightly lower at 30% and 46% respectively. In all cases, more than 50% of C_{1h} lay between 25 and 40 mg/L. Figures 2a and 2b show the distributions of C_{max} and C_{1h} categorised according to weight: these demonstrate that, while the Peloquin[9] and modified guidelines achieved similar distributions across all weight ranges, the WHO table[1] resulted in higher concentrations at low weights and lower concentrations at high weights. Figure 3 shows

187 that the modified guidelines reduce the incidence of high troughs when CL_{CR} is <50 mL/min.
188 Overall, around 65% of C_{min} were <2 mg/L at 24 h with both the Peloquin[9] and WHO[1]
189 guidelines but this fell to only 18-20% in patients whose CL_{CR} was <50 mL/min. With the
190 modified guidelines, extending the dosage interval for patients whose CL_{CR} is <50 mL/min
191 increased the proportion of C_{min} values <2 mg/L to 75%. Although some accumulation was
192 observed in patients with renal impairment, the C_{max} and C_{min} values obtained at the third
193 dose were very similar to those after the first dose (data not shown).
194
195 The median $AUC_{0\text{-}24}$ with the OD Peloquin guidelines[9] was 227 mg.h/L (range 30-4423
196 mg.h/L); 65% were between 100 and 300 mg.h/L and 31% >300 mg.h/L. In patients whose
197 C_{min} was <2 mg/L, the median $AUC_{0\text{-}24}$ was 191 mg.h/L and 82% were between 100 and 300
198 mg.h/L. The WHO table[1] produced similar results with 62% of $AUC_{0\text{-}24}$ within 100-300 mg.h/L
199 and 35% >300 mg.h/L. With the modified guidelines, 73% and 22% of $AUC_{0\text{-}24}$, estimates
200 were within these ranges.
201
202 The WHO recommends the Peloquin guidelines of 25 mg/kg for TTW dosing.[1,9] With this
203 dosage regimen, around 30% of C_{max} were between 65 and 80 mg/L whereas 40% were
204 between 60 and 80 mg/L (Table 4). Around half of the C_{1h} predictions were between 45 and
205 65 mg/L. The modified guidelines achieved similar results. At 48 h, C_{min} was <2 mg/L in 82%
206 of patients with the Peloquin guidelines[9] and 87% with the modified guidelines. In patients
207 whose CR_{CL} was <50 mL/min, 47% had a C_{min} >2 mg/L with the Peloquin guidelines[9] and 13%
208 with the modified guidelines. $AUC_{0\text{-}24}$ estimates for 25 mg/kg TTW had a median of 161
209 mg.h/L (range 25 to 2936 mg.h/L). Overall, 68% of $AUC_{0\text{-}24}$ estimates were in the range 100–
210 300 mg.h/L with the Peloquin guidelines[9] and 77% with the modified guidelines.

DISCUSSION

This study determined the PopPK of amikacin from TDM data derived from patients with mycobacterial infections. Simple relationships between CL and CL_{CR} and *V* and weight adequately described the data; AJBW provided the best fit for obese patients. Monte Carlo simulations were used to examine the distributions of concentrations arising from the Peloquin,[9] WHO[1] and modified Peloquin guidelines. Based on these results, slightly modified doses and target ranges were proposed for back-extrapolated C_{max} and C_{1h} and a potential target $AUC_{0\text{-}24}$ range was identified.

PK parameters

Although previous studies have described amikacin using a two-compartment model,[28-31] a one-compartment model was adequate to describe the current data set. Both the median age (49 years) and weight (61 kg) of the population were similar to those reported in other PopPK studies of amikacin.[17,28,29] In common with most other studies, a simple model based on estimated CL_{CR} provided the best descriptor of CL[8,28-31] although a recent study found that the CKD-EPI and revised Lund-Malmo equations provided a better description of amikacin CL in a general population.[32] The results of the present study are also consistent with recommendations for amikacin dosing based on AJBW in patients with infections caused by non-TB mycobacteria.[4,10]

At 3.96 L/h, the median estimate of CL was lower than the value of 4.62 L/h reported by Dijkstra *et al*.[18] in 11 patients with multidrug-resistant TB (MDR-TB). However, their patients were younger (mean 26 years), which may explain this difference. Delattre *et al.*[30] reported

a typical CL of 2.21 L/h in 88 critically ill, septic patients within their first 24 h of treatment. Applying the present PopPK model to their median CL_{CR} of 55 mL/min gives 2.55 L/h, which is consistent with their results.

Pharmacodynamic relationships

Both C_{max}/MIC ratio and $AUC_{0\text{-}24}$/MIC ratio were identified as predictors of amikacin efficacy in a hollow fiber model of TB.[33] The authors found that a C_{max}/MIC ratio of 10 provided the best PK/PD outcome, and proposed a target serum C_{max}/MIC ratio of 70-90.[33] In clinical practice, targeting the C_{max}/MIC ratio has been found to reduce both the cumulative AUC and the average dose (to around 6.5 mg/kg).[16] While this may prove to be the optimal approach to maximise efficacy and reduce the risk of toxicity, MIC values are not currently available in most clinical settings. Consequently, standard dosage regimens and target concentration ranges are generally applied and in the absence of MIC values, the present study has focused on these doses and ranges.

Using the Peloquin guidelines[9], the median end of infusion C_{max} was 41 mg/L, which is consistent with the value of 39 mg/L reported by Donald *et al.*[34] after an intramuscular dose of 15 mg/kg. However, in the present study only 35% of C_{max} values were in the range 35-45 mg/L; 13% were 45-50 mg/L. This trend towards higher peaks is consistent with the Peloquin study,[9] which described a median peak of 46 mg/L with a dose of 15 mg/kg. These findings, together with the WHO recommendation of doses up to 20 mg/kg[1] and the C_{max} target of 55 – 65 mg/L defined by Lee *et al.*[11] for patients with *Mycobacterium abscessus*, suggest it might be reasonable to extend the upper limit to 50 mg/L. This would increase the

likelihood of initial doses achieving acceptable concentrations to nearly 50% and consequently reduce the need for dose modifications.

It is interesting to note that despite very similar dose recommendations, widely differing target ranges are recommended for TB and non-TB infections.[3,4,9,11,35] The present study has shown that 15 mg/kg will achieve concentrations well above the target of 25 – 35 mg/L recommended by the British Thoracic Society in the management of non-TB mycobacterial pulmonary disease[4] but below the C_{max} of 67 mg/L identified as predictive of serum conversion in patients with MDR-TB.[35] While different targets may reflect variability in MICs among different organisms, it would seem appropriate to devise dosage regimens that link more closely with the recommended target ranges. Nevertheless, whichever values are used, high inter-patient variability indicates that TDM is necessary to ensure that target concentrations are achieved.

A recurring problem in TDM is that duration of infusion and timing of the peak sample may influence the PK model, PK parameters and interpretation of concentration measurements, particularly if drug distribution is incomplete.[36] Although concentrations measured within 1 h post infusion were removed from the present study, some degree of distribution cannot be excluded. While a C_{1h} is commonly used as the C_{max} target for critically ill and septic patients,[7,8,28] it is commonly recommended for mycobacterial infections to back-extrapolate from concentrations measured 2 and 6 (or 10) h post dose to determine C_{max} at the end of the 30 min infusion.[4,9] This calculation is unlikely to define the true end of infusion concentration due to distribution and adds a complication that is perhaps unnecessary. The present study therefore examined both end of infusion and C_{1h} (post infusion)

concentrations. As illustrated in Figures 2a and b, a C_{1h} range of 25 – 40 mg/L is consistent with a C_{max} of 35 – 50 mg/L and could provide an alternative target range for use in clinical practice.

In addition to recommending doses of 15-20 mg/kg, the WHO provides a table of weight-related doses (Supplementary Table 1).[1] Although these doses achieved similar proportions of concentrations within the target ranges to the Peloquin[9] and modified guidelines, C_{max} was typically above the range in patients <60 kg and below the range in patients >75 kg. Furthermore, despite being challenged by Peloquin[9] in 2004, a maximum daily dose of 1000 mg is still recommended by the WHO, although higher doses may be used.[1] The present results confirm that applying this limit will underdose patients >75 kg: also it is inconsistent with the recommended dose of 15-20 mg/kg, since 1000 mg represents only 12.5 mg/kg for a patient weighing 80 kg. The modified guidelines contain a wider range of doses, achieved C_{max} equivalent to the Peloquin guidelines[9] and were consistent across the full weight range of the patient group.

Renal impairment

In clinical practice, questions often arise around dose adjustment for patients who are renally impaired. Guidance around the target C_{min} is also variable, ranging from undetectable to <10 mg/L.[3,4,9,10] The current study found that with OD dosing, C_{min} were consistently <2 mg/L in patients with normal renal function. Increasing the dosage interval to 48 h in patients whose CR_{CR} was 30-50 mL/min and analysing a 48 h trough to determine the dosage interval for patients whose CR_{CL} was <30 mL/min reduced the percentage of patients with troughs >2 mg/L from 34% to 25%, and >5 mg/L from 13% to 4%. This

approach is preferred to the dose reduction suggested by Shula *et al.*[10] since a lower dose would confound the interpretation of peak concentrations and potentially lead to high troughs if the dose is increased.

Modongo *et al*.[35] reported that a threshold C_{max} of 67 mg/L and an AUC_{0-24} of 568 mg.h/L predicted serum conversion in patients with MDR-TB. This AUC_{0-24} value seems high for their median dose of 17.3 mg/kg but their mean CL was only 1.47 L/h. The present study found that in patients whose troughs were <2 mg/L, the median AUC_{0-24} achieved with 15 mg/kg/day was 191 mg.h/L, only 6% were <100 mg.h/L and 88% were <300.mg.h/L. These values are consistent with the median AUC_{0-24} of 77 mg.h/L associated with 6.7 mg/kg[18] and a range of around 50 – 250 mg.h/L with doses averaging 6.5 mg/kg.[16] The present study therefore suggests that daily AUC_{0-24} values of 100–300 mg.h/L reflect target peak and trough concentrations.

Risk of toxicity

Reducing the frequency of administration to TTW has practical advantages and may reduce the risk of toxicity.[12] The present study found that in contrast to the OD regimen, TTW tended to achieve peaks lower than the target range, with 43% of concentrations <65 mg/L with the Peloquin guidelines[9] and 36% with the modified guidelines. Extending the range to 60–80 mg/L reduced the incidence of low peaks to 32% and 27%, respectively. Assuming these values still achieve satisfactory C_{max}/MIC ratios, this would reduce the need for dose adjustments. As previously observed with OD dosing, high troughs mainly occurred in patients with poor renal function. Reducing the frequency to twice weekly for patients with CL_{CR} 30-50 mL/min and checking the amikacin concentration in patients with a CL_{CR} <30

mL/min reduced the incidence of C_{min} values >2 mg/L from 18% to 13%. As the weekly dose was lower with TTW dosing, the corresponding AUC_{0-24} was also lower with a median of 161 mg.h/L overall and 152 mg.h/L in patients whose C_{min} was <2 mg/L. The modified guidelines reduced the incidence of AUC_{0-24} values >300 mg.h/L from 16% to 7%.

Study Limitations

This study has some limitations. The simulations were based on a relatively small number of patients and the value of including amikacin in the management of mycobacterial disease is still not clear.[1] Furthermore, the study focused on standard dosage guidelines and target concentrations, which may not be ideal. It has previously been shown that using a C_{max}/MIC target to guide therapy may improve outcome and lower the risk of toxicity.[16] However, as the present study used data generated during routine TDM where MICs are not routinely measured, C_{max}/MIC and AUC_{0-24}/MIC ratios could not be examined and neither efficacy nor toxicity could be assessed. Furthermore, the data set included patients with both TB and non-TB mycobacterial infections. While it is unlikely that this would have affected the PK parameters, it might influence the optimal target concentrations. However, in clinical practice the same dose guidelines and target concentrations are often used for both indications.

Conclusions

A PopPK model with CL based on CL_{CR} calculated using AJBW and V related to AJBW best described amikacin concentrations in patients with mycobacterial infections. Simulations based on this model found that standard guidelines[1,9] typically achieved C_{max} values of 35-50 mg/L for OD and 60–80 mg/L for TTW dosing and C_{1h} of 25–40 mg/L and 45-65 mg/L,

respectively. The WHO table[1] achieved higher concentrations in patients <60 kg and lower concentrations in patients >75 kg. In contrast, a modified, weight-banded table of doses, adjusted according to renal function, achieved similar peak concentrations to standard approaches but reduced the risk of C_{min} values >2 mg/L and high $AUC_{0\text{-}24}$ estimates.

Acknowledgements

The authors would like to thank University of Strathclyde MPharm students Tamara Cairney and Bao Lock for their help in compiling the data set and Professor Nick Holford, University of Auckland, New Zealand, for support with visual predictive checks.

Funding

This study was carried out as part of our routine work. HS was supported by a travelling grant from the Erasmus+ programme, the Jo Kolk study fund and the Royal Dutch Pharmacists Association stipend fund.

Transparency Declarations

All authors – none to declare.

REFERENCES

1. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2019. https://apps.who.int/iris/bitstream/handle/10665/311259/9789241550512-eng.pdf

2. Stout JE, Koh W-J, Yew WW. Update on pulmonary disease due to non-tuberculous mycobacteria. Int J Infect Dis 2016; 45: 123–134.

3. Floto RA, Olivier KN, Saiman L et al. US Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations for the management of non-tuberculous mycobacteria in individuals with cystic fibrosis. Thorax 2016; 71: i1-i22.

4. Haworth CS, Banks J, Capstick T et al. British Thoracic Society guidelines for the management of non-tuberculous mycobacterial pulmonary disease. Thorax 2017; 72: ii1-ii64.

5. Jenkins A, Thomson AH, Brown NM et al. Amikacin use and therapeutic drug monitoring in adults: do dose regimens and drug exposures affect either outcome or adverse events? A systematic review. J Antimicrob Chemother 2016; 71: 2754-9.

6. Roger C, Nucci B, Louart B et al. Impact of 30 mg/kg amikacin and 8 mg/kg gentamicin on serum concentrations in critically ill patients with severe sepsis. J Antimicrob Chemother 2016; 71: 208–12.

7. Gálvez R, Luengo C, Cornejo R et al. Higher than recommended amikacin loading doses achieve pharmacokinetic targets without associated toxicity. Int J Antimicrob Agents 2011; 38: 146-51.

8. Mahmoudi L, Mohammadpour AH, Ahmadi A et al. Influence of sepsis on higher daily dose of amikacin pharmacokinetics in critically ill patients. Eur Rev Med Pharmacol Sci 2013; 17: 285-91.

9. Peloquin CA, Berning SE, Nitta AT et al. Aminoglycoside toxicity: daily versus thrice-weekly dosing for treatment of mycobacterial diseases. Clin Infec Dis 2004; 38: 1538-44.

10. Shula JA, Escalante P, Wilson JW. Pharmacotherapy approaches in nontuberculous mycobacteria infections. Mayo Clin Proc 2019; 94: 1567-1581.

11. Lee H, Sohn YM, Ko JY et al. Once-daily dosing of amikacin for treatment of Mycobacterium abscessus lung disease. Int J Tuberc Lung Dis 2017; 21: 818-824.

12. Technical report on the pharmacokinetics and pharmacodynamics (PK/PD) of medicines used in the treatment of drug-resistant tuberculosis. Geneva: World Health Organization; 2018. https://apps.who.int/iris/handle/10665/260440

13. Modongo C, Pasipanodya JG, Zetola NM et al. Amikacin concentrations predictive of ototoxicity in multidrug-resistant tuberculosis patients. Antimicrob Agents Chemother 2015; 59: 6337-43.

14. Modongo C, Sobota RS, Kesenogile B et al. Successful MDR-TB treatment regimens including amikacin are associated with high rates of hearing loss. BMC Infect Dis 2014; 14: 542.

15. Ellender CM, Law DB, Thomson RM et al. Safety of IV amikacin in the treatment of pulmonary non-tuberculosis mycobacterial disease. Respirology 2016; 21: 357-362

16. Van Altena R, Dijkstra JA, van der Meer ME et al. Reduced chance of hearing loss associated with therapeutic drug monitoring of aminoglycosides in the treatment of multidrug-resistant tuberculosis. Antimicrob Agents Chemother 2017; 61: e01400-16.

17. Marsot A, Guilhaumou R, Riff C et al. Amikacin in critically ill patients: a review of population pharmacokinetic studies. Clin Pharmacokinet 2017; 56: 127-38.

18. Dijkstra JA, van Altena R, Akkerman OW et al. Limited sampling strategies for therapeutic drug monitoring of amikacin and kanamycin in patients with multidrug-resistant tuberculosis. Int J Antimicrob Agents 2015; 46: 332-7.

19. Kelman AW, Whiting B, Bryson SM. OPT: a package of computer programs for parameter optimisation in clinical pharmacokinetics. Br J Clin Pharmacol 1982; 14: 247-56.

20. Devine BJ. Gentamicin therapy. Drug Intel Clin Pharm 1974; 8: 650–655.

21. Janmahasatian S, Duffull SB, Ash S et al. Quantification of lean bodyweight. Clin Pharmacokinet 2005; 44: 1051–65.

22. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16: 31-41.

23. Lindbom L, Ribbing J, Jonsson EN. Perl-speaks-NONMEM (PsN)—a Perl module for NONMEM related programming. Comput Meth Prog Bio 2004; 75: 85-94.

24. Jonsson EN, Karlsson MO. Xpose—an S-PLUS based population pharmacokinetic/ pharmacodynamic model building aid for NONMEM. Comput Meth Prog Bio 1998; 58: 51-64.

25. R Development Core Team. A Language and Environment for Statistical Computing. Vienna, Austria;2011

26. Holford N. Wings for NONMEM. http://wfn.sourceforge.net/

27. Rosario M, Thomson AH, Jodrel DI et al. Population pharmacokinetics of gentamicin in patients with cancer. Br J Clin Pharmacol 1998: 46: 229-236.

28. Matar KM, Al-lanqawi Y, Abdul-Malek K et al. Amikacin population pharmacokinetics in critically ill Kuwaiti patients. Biomed Res Int. 2013; 202818.

29. Kato H, Hagihara M, Hirai J et al. Evaluation of amikacin pharmacokinetics and pharmacodynamics for optimal initial dosing regimen. Drugs in R&D. 2017; 17: 177-87.

30. Delattre I, Musuamba FT, Nyberg J et al. Population pharmacokinetic modeling and optimal sampling strategy for Bayesian estimation of amikacin exposure in critically ill septic patients. Ther Drug Monit. 2010; 32: 749-56.

31. Burdet C, Pajot O, Couffignal C et al. Population pharmacokinetics of single-dose amikacin in critically ill patients with suspected ventilator-associated pneumonia. Eur J Clin Pharmacol 2015; 71: 75-83.

32. Saez Fernandez EM, Perez-Blanco JS, Lanao JM et al. Evaluation of renal function equations to predict amikacin clearance. Expert Rev Clin Phar 2019;12: 805-813.

33. Srivastava S, Modongo C, Dona CWS et al. Amikacin optimal exposure targets in the hollow-fiber system model of tuberculosis. Antimicrob Agents Chemother. 2016: 60: 5922–5927.

34. Donald PR, Sirgel FA, Venter A et al. The early bactericidal activity of amikacin in pulmonary tuberculosis. Int J Tuberc Lung Dis 2001; 5: 533-538.

35. Modongo C, Pasipanodya JG, Magazi BT et al. Artificial intelligence and amikacin exposures predictive of outcome in multi-resistant tuberculosis patients. Antimicrob Agents Chemother 2016; 60: 5928-5932.

36. Sturkenboom MGG, Simbar N, Akkerman OW et al. Amikacin dosing for MDR tuberculosis: a systematic review to establish or revise the current recommended dose for tuberculous treatment. Clin Inf Dis 2018; Suppl 3: S303-S307.

Table 1 Modified, weight banded dosage guidelines based on the Peloquin[9] dose recommendations and adjusted for renal function

Weight (kg)	**< 40**	**40 – 44**	**45 – 49**	**50 – 54**	**55-59**	**60 – 64**	**65 – 69**	**70 – 74**	**75 – 79**	**80 – 89**	**≥ 90**
Once daily regimen											
Dose (mg)	**550**	**650**	**700**	**800**	**850**	**950**	**1000**	**1100**	**1150**	**1250**	**1350**
CL_{CR} ≥50 mL/min	24 hourly	24 hourly	24 hourly	24 hourly	24 hourly	24 hourly	24 hourly	24 hourly	24 hourly	24 hourly	24 hourly
CL_{CR} 30-50 mL/min	48 hourly	48 hourly	48 hourly	48 hourly	48 hourly	48 hourly	48 hourly	48 hourly	48 hourly	48 hourly	48 hourly
CL_{CR} <30 mL/min	Sample at 48 hours	Sample at 48 hours	Sample at 48 hours	Sample at 48 hours	Sample at 48 hours	Sample at 48 hours	Sample at 48 hours	Sample at 48 hours	Sample at 48 hours	Sample at 48 hours	Sample at 48 hours
Thrice weekly regimen											
Dose (mg)	**900**	**1000**	**1200**	**1300**	**1400**	**1600**	**1700**	**1800**	**1900**	**2000**	**2200**
CL_{CR} ≥50 mL/min	Thrice weekly	Thrice weekly	Thrice weekly	Thrice weekly	Thrice weekly	Thrice weekly	Thrice weekly	Thrice weekly	Thrice weekly	Thrice weekly	Thrice weekly
CL_{CR} 30-50 mL/min	Twice weekly	Twice weekly	Twice weekly	Twice weekly	Twice weekly	Twice weekly	Twice weekly	Twice weekly	Twice weekly	Twice weekly	Twice weekly
CL_{CR} <30 mL/min	sample at 72 hours	sample at 72 hours	sample at 72 hours	sample at 72 hours	sample at 72 hours	sample at 72 hours	sample at 72 hours	sample at 72 hours	sample at 72 hours	sample at 72 hours	sample at 72 hours

Key: CL_{CR} creatinine clearance. If total body weight (TBW) is >ideal body weight (IBW)[20], use IBW + 0.4(TBW-IBW) for dose weight and to calculate CL_{CR}[22]. Administer amikacin as an IV infusion over 30 minutes.

Table 2 Summary of the demographic and clinical characteristics of the 124 patients included in the dataset

Patient characteristic	**median**	**range**
Male/Female	72/52	
Age (years)	49	16 - 92
Weight (kg)	61.0	36.0 – 147.0
Ideal body weight (kg)	55.1	36.0 – 81.0
Adjusted body weight (kg)	58.4	36.0 – 92.2
Height (m)	1.68	1.46 - 1.93*
BMI (kg/m^2)	22.2	14.5 – 55.4*
Serum creatinine (µmol/L)	68	36 - 355
Creatinine clearance (mL/min)	84	18 - 184

Key: *n = 77, BMI – Body mass index

Table 3 Population pharmacokinetic parameter estimates for amikacin in patients with mycobacterial infections

Parameter	**Final estimate**	**RSE**	**Bootstrap median (5th and 95th percentiles)**
θ_{CL}	0.0464	3.6%	0.0463 (0.0436 – 0.0495)
θ_{V}	0.344	2.9%	0.344 (0.327 – 0.363)
BSV CL (CV%)	0.108 (33.8%)	15.6%	0.106 (0.0769 – 0.137)
Shrinkage ηCL	19.7%		
BSV *V* (CV%)	0.0501 (22.7%)	19.7%	0.0485 (0.0318 – 0.0683)
Shrinkage ηV	26.1%		
RUV – additive error (mg/L)	1.58	10.8%	1.568 (1.047 - 1.981)
RUV – proportional error (CV%)	16.5%	6.7%	0.165 (0.143 – 0.191)
Shrinkage RUV	11.0%		

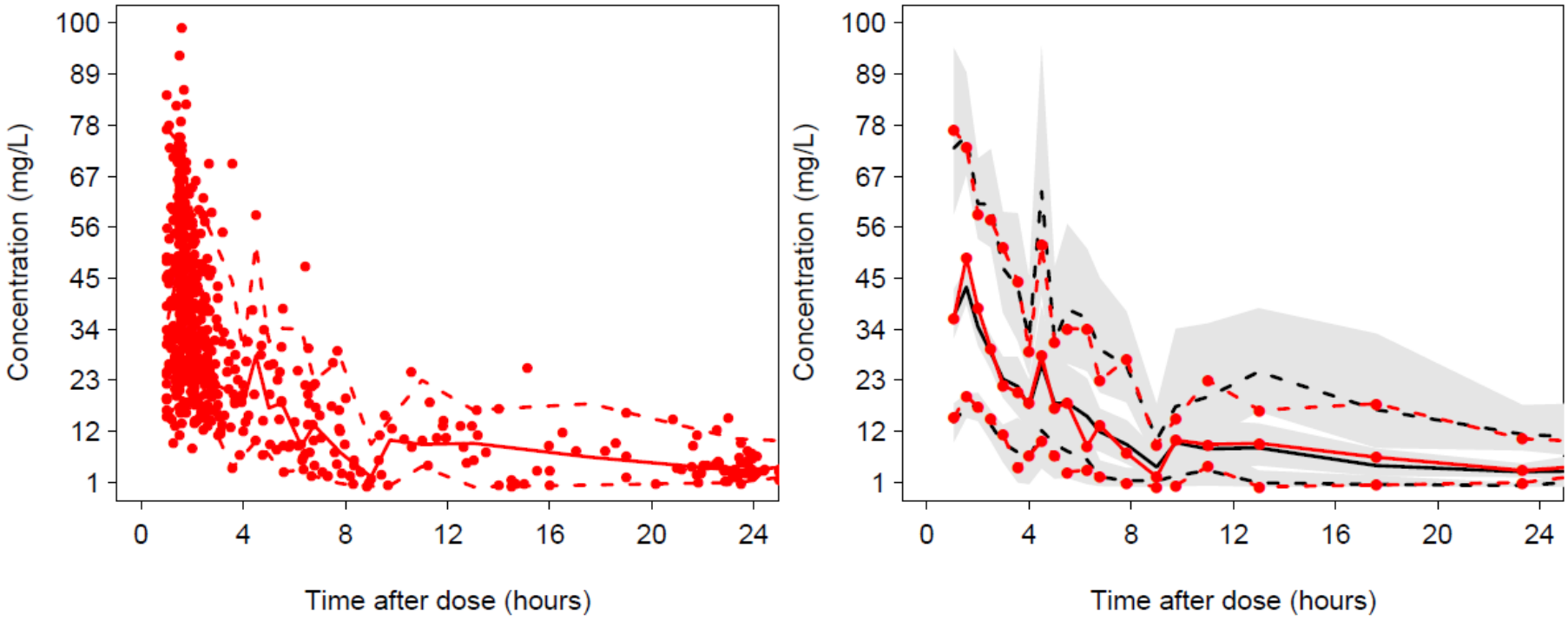
Key: CL = clearance; *V* = volume of distribution; BSV = between subject variability; ηCL = individual variation in CL, ηV = individual variation in *V*, RUV = residual unexplained variability; CV% = coefficient of variation expressed as a percentage; RSE = relative standard error. Model CL (L/h) = θ_{CL} x CL_{CR} (mL/min) based on the Cockcroft Gault equation[22], *V* (L) = θ_{V} x weight (kg). Adjusted body weight (Ideal body weight + 0.4 x (total body weight – ideal body weight)) was used in obese patients.

Table 4 Percentages of simulated amikacin concentrations within target concentration ranges for once-daily and three times weekly dosage regimens based on the Peloquin[9], WHO[1] and modified dosage guidelines.

Concentration range (mg/L)	Peloquin Guidelines[9]	WHO table[1]	Modified guidelines
Once daily dosing, end of the infusion (C_{max})			
<35	28	24	27
35 - 45	**35**	**30**	**35**
45 – 50	13	16	13
>50	24	32	24
Once daily dosing, 1 h after the end of the infusion (C_{1h})			
<25	17	15	16
25 - 40	**59**	**53**	**58**
>40	25	33	26
Once daily dosing C_{min}			
<2	66	65	75
<5	87	86	96
Three times weekly dosing, end of the infusion (C_{max})			
<60	32	NA	27
60-65	11	NA	10
65-80	**29**	**NA**	**30**
>80	28	NA	34
Three times weekly dosing, 1 h after the end of the infusion (C_{1h})			
<45	24	NA	20
45-65	**49**	**NA**	**48**
>65	27	NA	32
Three times weekly dosing C_{min}			
<2	82	NA	87
<5	96	NA	100

Note: the infusion time was set at 30 minutes. The Peloquin[9] target ranges for each sampling time are highlighted in bold. NA – not applicable

Figure 1 Visual predictive check of the final population model describing amikacin pharmacokinetic in patients with mycobacterial infections.



Key: Red and black lines represent the 5th, 50th and 95th percentiles of the observed data and predicted data, respectively. The shaded areas represent 95% CI for the percentiles of the predicted concentrations.

Figure 2a Distributions of simulated end of infusion amikacin concentrations based on the once daily Peloquin,[9] WHO[1] and modified dosing guidelines, categorised according to weight

Key: (a) Peloquin guidelines, (b) WHO guidelines, (c) Modified guidelines

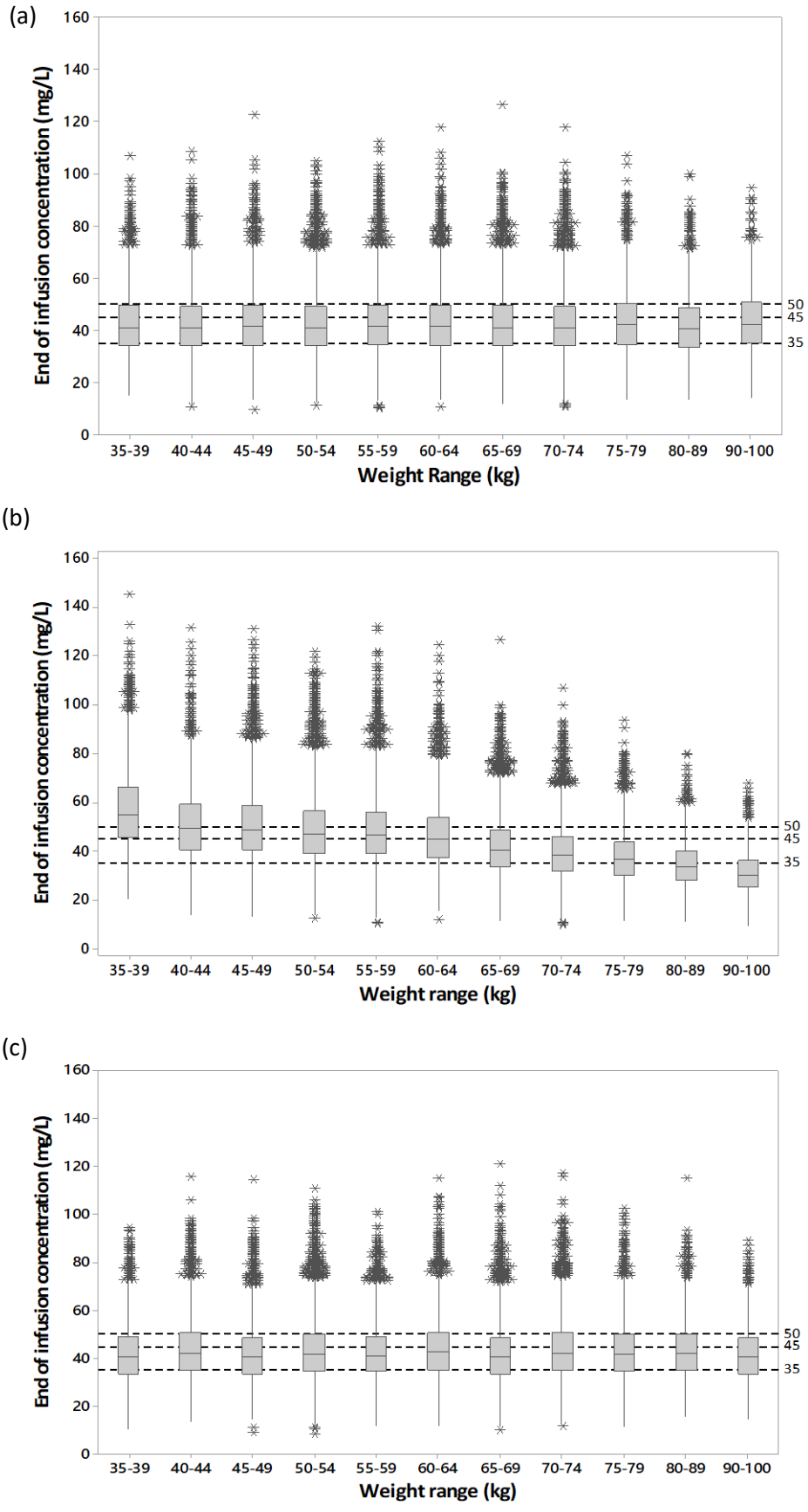


Figure 2b Distributions of simulated 1 hour post infusion amikacin concentrations based on the once daily Peloquin,[9] WHO[1] and modified dosing guidelines, categorised according to weight.

Key: (a) Peloquin guidelines, (b) WHO guidelines, (c) Modified guidelines

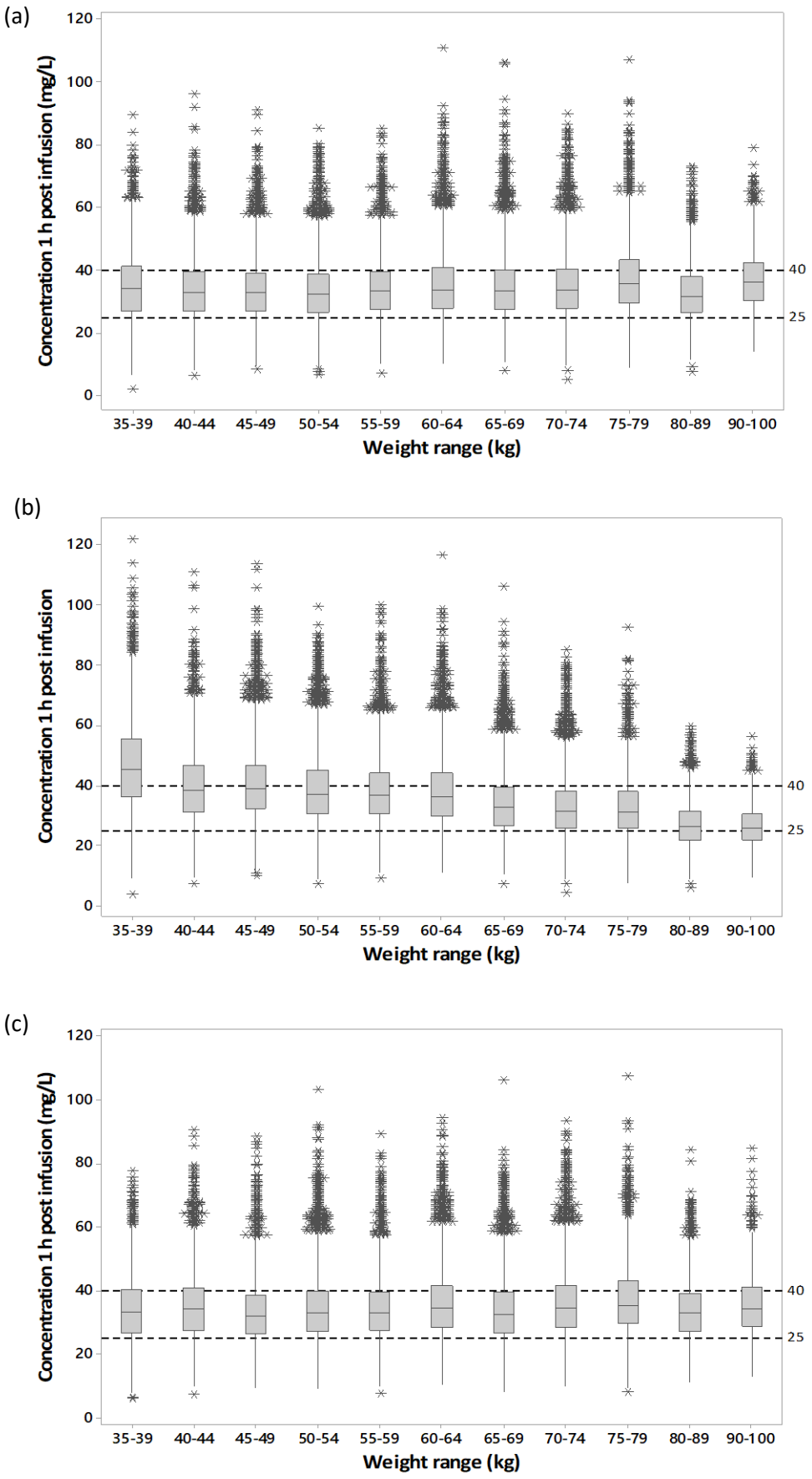
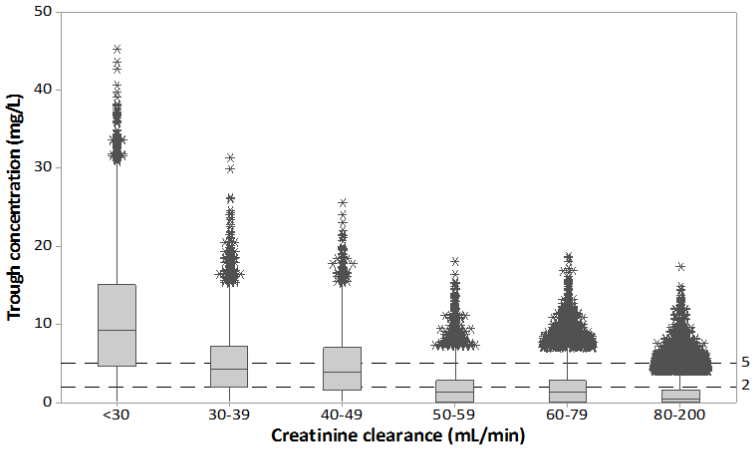


Figure 3 Distributions of simulated once daily trough amikacin concentrations based on the once daily Peloquin,[9] WHO[1] and modified dosing guidelines, categorised according to renal function.

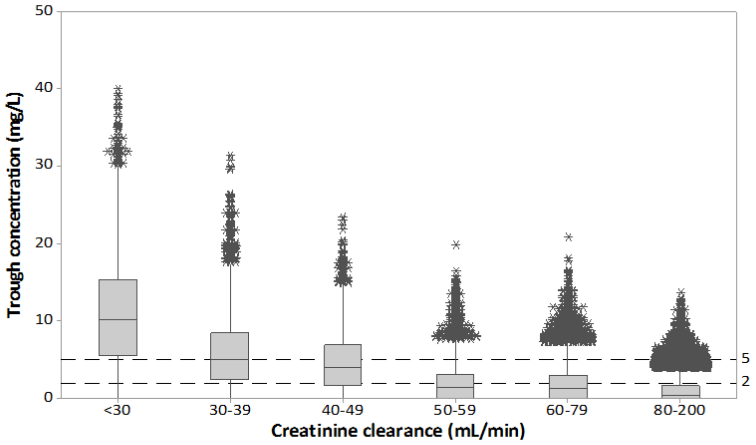
Key: (a) Peloquin guidelines, (b) WHO guidelines, (c) Modified guidelines

Note: the modified guidelines recommend analysing the amikacin concentration before the next dose if CL_{CR} is <30 mL/min)

(a)



(b)



(c)