PHARMACOKINETIC-PHARMACODYNAMIC ANALYSIS OF WEIGHT AND HEIGHT SCALED TOBRAMYCIN DOSAGE REGIMENS FOR PATIENTS WITH CYSTIC FIBROSIS

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Running title: PKPD analysis of tobramycin doses for adults with CF

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ABSTRACT (258 words) if Cmax and AUC targets are removed = 250 words

Objectives: To determine tobramycin pharmacokinetic/pharmacodynamic (PK/PD) breakpoints for weight (WT) and height (HT) based dosing regimens for patients with cystic fibrosis (CF).

Methods: A simulated data set of 5000 patients based on 331 patients with CF was created using NONMEM. PK parameters were derived for each patient from a published population model using Monte Carlo simulation. The abilities of 10 and 12 mg/kg/day and 3 and 4 mg/cm/day to achieve standard and extended C_{max} (20-30 and 20-40 mg/L) and AUC_{0-24} (80-120 and 80-150 mg.h/L) target ranges were evaluated. PK/PD limits for a C_{max}/MIC ratio ≥10 and AUC_{0-24}/MIC ≥110 for a range of MIC values and cumulative fraction of response (CFR) for *Pseudomonas aeruginosa* were also determined.

Results: Higher proportion of patients achieved standard C_{max} and AUC_{0-24} targets with 3 mg/cm/day (64% and 62%, respectively) than with 10 mg/kg/day (43% and 48%, respectively). AUC_{0-24} estimates >120 mg.h/L were more common with WT-based dosing. With higher doses and targets, 72% achieved target peaks with 4 mg/cm/day and 65% with 12 mg/kg/day. The PK/PD limits for a C_{max}/MIC ratio ≥10 was 2 mg/L for lower doses and 2.5 mg/L for higher doses and for an AUC_{0-24}/MIC ≥110 was 0.5 mg/L for all regimens. The CFR for all regimens was >90% for C_{max} targets and 66% to 79% for AUC_{0-24} targets.

Conclusions: Using a tobramycin dose of 3 mg/cm/day rather than 10 mg/kg/day achieved similar PK/PD outcomes but dose and AUC_{0-24} ranges were narrower and the incidence of high AUC_{0-24} values was lower. HT-based doses should therefore be considered for patients with CF.

INTRODUCTION (3355 words)

Cystic fibrosis (CF) is an inherited autosomal recessive disorder characterised by frequent lung infections. This results in repeated courses of antibiotics, particularly tobramycin. Recommended doses of tobramycin range from 10 - 15 mg/kg/day[1-3] and aim to achieve concentrations likely to be effective against *Pseudomonas aeruginosa (P. aeruginosa),* which accounts for 44.5% of infections in UK adults with CF.[4] Optimising both C_{max}/MIC and daily area under the curve to MIC (AUC_{0-24}/MIC) ratios has been found to correlate with measures of clinical efficacy, including forced expiratory volume in one second (FEV_1), and forced vital capacity (FVC).[1,2] Although nephrotoxicity had traditionally been associated with high trough concentrations, AUC_{0-24} has been suggested as a better predictor of nephrotoxicity, particularly when once daily dosing regimens are used.[5]

For patients with CF, current tobramycin monitoring approaches include measuring C_{max} (target 20 - 30 mg/L, 30 min after a 30-min infusion)[6] and trough concentrations (target ≤1 mg/L). "Troughs" are often measured 18 hours after the dose since concentrations are usually undetectable at 24 hours.[7,8] In Australia and New Zealand, AUC_{0-24} is used to monitor once daily aminoglycoside therapy,[8] with a recommended target range of 90 – 110 mg.h/L.[9]

Although total body weight,[3] body surface area[10] and lean body weight[11,12] have been used to individualise aminoglycoside doses, a large population study[13] found that weight (WT) had no influence on clearance whereas including height (HT) in the model led to a small

reduction in between patient variability. These results suggested that aminoglycoside doses for patients with CF might be better calculated from HT rather than WT.

The aims of the current study were to use Monte Carlo simulations to compare the ability of three WT and two HT scaled tobramycin dosage regimens to achieve target C_{max} and AUC_{0-24} ranges and to determine the PTA and cumulative fraction of response (CFR) against *P. aeruginosa*.

METHODS

Dosage regimens and targets

A simulated data set of 5000 patients was created using NONMEM Version 7.1.[14] The distributions of clinical characteristics in these simulated patients were based on observed values from 331 patients with CF whose data were analysed in a previous study.[13] The patient characteristics from this data set are summarised in Supplementary Table 1. Data were restricted to the following ranges: weight 30 – 108 kg; height 139 – 194 cm; age 14 – 88 years, serum creatinine 60 – 209 µmol/L; creatinine clearance 26 - 181 mL/min. These restrictions ensured that the clinical characteristics of the simulated patients were consistent with the original data set. Renal impairment (a creatinine clearance <50 ml/min) was present in 1% of the original data set and 4% of the simulated patient data. WT-based tobramycin doses were calculated for each patient as follows: 10 mg/kg/day to a maximum of 660 mg;[6] 10 mg/kg/day with no upper limit; and 12 mg/kg/day, based on the recommendation of VandenBussche *et al*.[15] Two new dosage regimens based on HT, 3 mg/cm/day and 4 mg/cm/day, were also tested. The lower dose was calculated from an

AUC_{0-24} of 106 mg.h/L multiplied by the median clearance (CL) estimate from the population pharmacokinetic model and scaled by dividing by the median HT.[13] A higher target AUC_{0-24} of 120 mg.h/L was used to determine the higher dose. All doses were administered over 30 min. Individual pharmacokinetic (PK) parameters were then simulated for each patient using NONMEM and a published population model[13] and used to predict C_{max} (30 min after the end of the infusion) and AUC_{0-24} estimates arising from these dosage regimens.

Two target ranges for C_{max} were defined: the standard range of 20-30 mg/L was based on the TOPIC study[6]; the extended range of 20–40 mg/L was based on Staubes *et al*.[16] An initial target AUC_{0-24} of 106 mg.h/L was calculated from the 10 mg/kg/day dose and PK parameters reported in the TOPIC study. [17] The AUC_{0-24} target range was then derived by examining C_{max} concentrations, CL and AUC_{0-24} (daily dose/CL) estimates from the 77 patients (135 courses) within a previous population[13] who received once daily tobramycin. Since AUC_{0-24} estimates in patients who achieved C_{max} values of 20-30 mg/L were typically ≥85 mg.h/L, the lower limit of the range was defined as 80 mg.h/L. It was difficult to identify an upper AUC_{0-24} limit since only 3 trough concentrations were above 1 mg/L. However, as 89% of the AUC_{0-24} values in patients whose predicted troughs were <1 mg/L were <120 mg.h/L, this was set as the standard upper limit. The target AUC_{0-24} was then modified to the midpoint of this range (100 mg.h/L) in line with the recommendations of Couthard *et al*.[18] The extended AUC_{0-24} range was 80 – 150 mg.h/L, an increase of 25%.

Pharmacokinetic/Pharmacodynamic (PK/PD) analysis

PK/PD analyses were conducted using all five dosage regimens. Targets were set at a C_{max}/MIC ratio ≥10, as recommended by Kashuba *et al*[19] and an AUC_{0-24}/MIC ratio ≥110,[20] and were calculated for each simulated patient at MICs ranging from 0.5 to 8 mg/L. For each regimen, the highest MIC at which the regimen achieved a PTA ≥90% was defined as the PK/PD susceptibility limit. CFR was estimated using tobramycin MIC distributions against *P. aeruginosa* obtained from the EUCAST website.[21] The fraction of patients who were expected to achieve the target PK/PD index was multiplied by the fraction of the organism distribution at a particular MIC. The CFR was then calculated as the sum of all fraction products at each MIC value.[22]

RESULTS

Pharmacokinetic data

Table 1 summarises the distributions of doses, C_{max} and AUC_{0-24} values arising from the five sets of WT and HT scaled doses. In all cases, the ranges were narrower when doses were scaled according to HT rather than WT. When the 10 mg/kg dose was unrestricted, 20% of the simulated patients received doses above 660 mg (range 661 to 1054 mg). Table 2 shows that restricting the 10 mg/kg dose had little effect on the distribution of C_{max}, and slightly increased the percentage of AUC_{0-24} values within the target range, mainly by reducing the percentages >120 mg.h/L and >150 mg.h/L. The 3 mg/cm/day dosage regimen achieved both a higher percentage of C_{max} and AUC_{0-24} estimates within their standard target ranges (64% versus 43% and 62% versus 51%, respectively) and lower percentages of high values (31% versus 50% and 27% versus 39%, respectively) when compared to the restricted 10

mg/kg/day regimen. With the higher doses of 12 mg/kg/day and 4 mg/cm/day, although the percentage of C_{max} values within the extended range was higher with the HT-based regimen (72% versus 65%), the AUC_{0-24} results were similar (63% versus 61% within and 36% versus 37% above the range).

Figure 1 shows the dose, C_{max} and AUC_{0-24} distributions for each simulated dosage regimen, stratified according to BMI. The percentage of simulated patients in each BMI category was as follow; underweight 35%, normal weight 54%; overweight 10%, and obese 1%. With WT-based dosage regimens, both C_{max} and AUC_{0-24} increased with increasing BMI. Patients whose BMIs were <18.5 kg/m^2 typically achieved predictions within C_{max} and AUC_{0-24} target ranges while patients whose BMIs were ≥30 kg/m^2 achieved values above the ranges. In contrast, HT-based dosage regimens produced a flat distribution across all BMI categories.

Figure 2 shows the C_{max} and AUC_{0-24} distributions for each simulated dosage regimen, stratified according to renal function. No difference was observed in achieving peak and AUC_{0-24} targets in HT vs WT based doses in patients with normal renal function and renal impairment. However, there was tendency for those with renal impairment to have lower peak concentrations and $AUCs_{0-24}$ compared with normal renal function group in all WT based dosage regimens. On the other hand, the peak concentrations and $AUCs_{0-24}$ were higher for those with renal impairment compared with no impairment for the HT based doses. The difference was highest with $AUCs_{0-24}$ values than for peak concentrations.

PK/PD analysis

Figure 3 shows the PTA results for each tobramycin dosage regimen against a range of MICs. For a C_{max}/MIC ratio ≥10, the PK/PD susceptibility limit was 2 mg/L for doses of 10 mg/kg/day and 3 mg/cm/day, and 2.5 mg/L for 12 mg/kg/day and 4 mg/cm/day. For an AUC_{0-24}/MIC ratio ≥110, the limit for all dosage regimens was 0.5 mg/L.

All dosage regimens were predicted to achieve a CFR >90% against *P. aeruginosa* for a C_{max}/MIC ratio ≥10 (91 % for 10 mg/kg/day and 3 mg/cm/day and 92% for 12 mg/kg/day and 4 mg/cm/day). For a target AUC_{0-24}/MIC ratio ≥110, the results with 10 mg/kg/day and 3 mg/cm/day were similar (70% and 66%, respectively), increasing to 78% with a dose of 12 mg/kg/day and 79% with 4 mg/cm/day.

DISCUSSION

This study used the clinical characteristics and population PK parameters of tobramycin derived from adult patients with CF to compare the abilities of a range of tobramycin dosage regimens to achieve C_{max}, AUC_{0-24} and PK/PD targets. Doses based on HT achieved PK targets more consistently and with less variability than WT based dosage regimens but PTA and CFR results were similar. This might be explained by being height was less variable between patients and had a narrow range. In addition, tobramycin is a water soluble drug it distributes mainly into plasma and not to any great extent into fat.

Target tobramycin C_{max} values 30 min after a 30 min infusion for patients with CF are based on a C_{max}/MIC ratio of 8-10, which results in a range of 20 – 30 mg/L for MICs of 2-3 mg/L, as used in the TOPIC study.[6] As the EUCAST and BSAC breakpoint for *Pseudomonas aeruginosa* is 4 mg/L, Staubes and colleagues initially proposed a target of 30 to 50 mg/L for concentrations back-extrapolated to the end of a 1 h infusion.[16] However, they revised this range to 20-40 mg/L after finding that 91% of local isolates of *P. aeruginosa* had an MIC $\leq$3 mg/L. Differences in the duration of infusion, which can range from 5 mins to 1 hour, and in the definition of C_{max}, make it difficult to compare studies directly.[16,23,24] Nevertheless, the current study was consistent with the findings of Staubes *et al*[16] as both found that >70% of C_{max} values would be within 20-40 mg/L with a dose of 10 mg/kg/day. A target C_{max} of up to 35 mg/L was suggested by VandenBussche *et al*,[15] who recommended a tobramycin dose of 12 mg/kg/day, while a dose of 11 mg/kg/day was identified as optimal by Hennig *et al*.[11] To cover these varying recommendations, the present study examined both standard and extended target ranges and two sets of dosage guidelines. The results demonstrated that a HT based dose of 3 mg/cm/day achieved the target C_{max} for both the standard and extended ranges more consistently than WT based doses, which were more likely to achieve high concentrations. There was no advantage in increasing the dose to 4 mg/cm/day as the results were similar to those obtained with 12 mg/kg/day.

Target C_{max} ranges generally focus on efficacy and there is little information on tobramycin concentration-toxicity relationships in patients with CF. Previous studies have claimed that doses up to 15 mg/kg/day and C_{max} values up to 56 mg/L were well tolerated.[16,24-26] Bragonier *et al*[24] reported no nephrotoxicity in 7 pediatric patients given 15 mg/kg/day for

10 to 14 days, although one patient complained of transient dizziness. Master and colleagues reported a mean C_{max} (1 h post dose) of 41 mg/L in 23 pediatric patients treated with 13 mg/kg/day over 15 mins for 10 days and found no evidence of nephrotoxicity or ototoxicity.[25] Similar C_{max} values at 1 h post infusion were found by Vic *et al*[26] following 15 mg/kg/day over 30 min for 14 days to 12 pediatric patients; they reported that all patients had a normal audiogram on day 14 and no evidence of nephrotoxicity. It is not clear whether these small, paediatric studies can be extrapolated to an adult population. Using RIFLE (Risk, Injury, Failure, Loss, and End-stage kidney disease) criteria, Staubes *et al*[16] found a 10% incidence of nephrotoxicity in 179 patient encounters; ototoxicity was not assessed.

Although tobramycin monitoring guidelines currently recommend a pre-dose concentration <1 mg/L,[6] 24 hour troughs are typically below quantification limits.[7, 8] Furthermore, there is evidence that this target is unable to detect patients at risk of underdosing or overdosing and that a target $AUC_{0\text{-}24}$ of 100 mg.h/L provides a better indicator of dose requirements.[18] The target $AUC_{0\text{-}24}$ chosen for the present study is consistent with this value and the Australia Antimicrobial Therapeutic Guideline,[9] while the lower limit of 80 mg.h/L is similar to previously reported values from clinical and survey studies.[25,27] As no specific data on toxicity were available, the upper limit of 120 mg.h/L was based on typical $AUC_{0\text{-}24}$ values and previously reported ranges.[25,27] Master *et al* reported a mean $AUC_{0\text{-}24}$ of 104 ± 19 mg.h/L with an average dose of 13 mg/kg/day, which was well tolerated and associated with around 10% improvement in lung function on day 10 of therapy compared with admission.[25] The predicted $AUC_{0\text{-}24}$ for 10 mg/kg/day, based on the average PK values from the study by Staubes *et al* ,[16] was 119 mg.h/L, which is consistent with the limit set in the current study. The extended range of up to 150 mg.h/L, represents a relatively conservative increase of

25%. Although there is little evidence to support this value, it does not seem excessive; Murry *et al* reported a 7.5% nephrotoxicity rate with aminoglycoside $AUC_{0\text{-}24}$ values of up to 200 mg.h/L.[28]

The present study found that a fixed dose of 10 mg/kg/day resulted in a wide range of dose amounts and $AUC_{0\text{-}24}$ estimates. In all cases, the incidence of $AUC_{0\text{-}24}$ estimates below 80 mg.h/L was low (1%-11%) and high $AUC_{0\text{-}24}$ values were common. Restricting the maximum dose to 660 mg, as recommended in the TOPIC study,[6] produced only a small reduction in the risk of excessive $AUC_{0\text{-}24}$ values as most doses were <660 mg. In contrast, 3 mg/cm/day produced a narrower range of doses, required no restrictions and only 27% of $AUC_{0\text{-}24}$ values were >120 mg.h/L. With 12 mg/kg/day, 69% of $AUC_{0\text{-}24}$ estimates were >120 mg.h/L and, as illustrated in Figure 1, several were above 300 mg.h/L. Such high exposure is likely to increase the risk of nephrotoxicity. Although 4 mg/cm/day did not achieve such high values, 74% of estimates were >120 mg.h/L and 36% >150 mg.h/L. This suggests that 4 mg/cm/day is too high and that 3 mg/cm/day is preferred to meet these targets.

Although 62% of the patients in the original data set[13] had a normal BMI, 34% were underweight and 2 were obese. It was interesting to examine the impact of BMI on C_{max} and $AUC_{0\text{-}24}$ predictions as Staubes *et al* found that patients whose BMIs were 18.5 – 24.9 kg/m^2 achieved higher C_{max} values than patients with BMIs <18.5 kg/m^2.[16] The present study was consistent with these findings as there was a clear link between increasing C_{max} and increasing BMI. In contrast to the findings with WT scaled doses, no trend was observed

238 with HT based doses, C_{max} or AUC_{0-24} estimates across the different BMI categories. When
239 stratified based on renal function, AUC_{0-24} were lower for those with renal impairment for all
240 WT scaled doses, while AUC_{0-24} tended to be higher with HT scaled doses. This indicates that
241 with using HT, the impact of renal function on tobramycin dosing requirement is much
242 apparent than with WT scaled doses.

243

244 As AUC_{0-24}/MIC and C_{max}/MIC ratios have been found to correlate with lung function in
245 patients with CF[1,2] both were used in the present study to assess the PTA and CFR. The MIC
246 breakpoints of 2 – 2.5 mg/L identified for the C_{max} target are below the EUCAST and BSAC
247 sensitivity breakpoints against *P. aeruginosa* of 4 mg/L[20,29] but consistent with Sherwin *et*
248 *al*,[30] who reported that 10 mg/kg/day achieved a C_{max}/MIC target >10 for most paediatric
249 patients if the MIC was <2 mg/L.

250

251 The results for the AUC_{0-24}/MIC target of >110 identified an MIC limit of 0.5 mg/L for all
252 dosage regimens. These results differ from those of Butterfield *et al*[31] whose simulation
253 study identified an MIC limit of 1 mg/L with a dose of 10 mg/kg/day. However, their
254 simulations were based on a sample size of only 9 patients, and their mean tobramycin CL
255 (3.83 L/h) was lower than the value of 4.92 L/h in the original study of 331 patients.[13]
256 Butterfield *et al*[31] recommended increasing the dose to 15 to 20 mg/kg/day if MICs were 2
257 to 4 mg/L despite achieving AUC_{0-24} values >200 mg.h/L. The authors assumed these values
258 to be safe, as Drusano and Louie[32] had reported that AUCs up to 600 mg.h/L are not

associated with nephrotoxicity. However, these were both simulation studies and it is unlikely that such high exposures would be accepted as safe in routine clinical practice.

Analysis of the CFR identified a success rate >90% for all regimens for a C_{max}/MIC ratio ≥10 using the EUCAST MIC distribution for *P. aeruginosa*. This was not surprising since 83% of isolates had an MIC <1 mg/L against tobramycin.[20] At an AUC_{0-24}/MIC ratio ≥110, the CFR ranged from 66-70% with the lower dosage regimens and increased to 78% and 79% with 12 mg/kg/day and 4 mg/cm/day. These results are in agreement with Butterfield *et al*,[31] who found that the probability of treatment success was >80% for a dose of 10 mg/kg/day and isolates with an MIC ≤1 mg/L.

Overall, the present study suggests that if the MIC of *P. aeruginosa* is <2 mg/L, doses of 10 mg/kg/day or 3 mg/cm/day are sufficient to achieve C_{max}/MIC targets but higher doses (12 mg/kg/day or 4 mg/cm/day) would be required for pathogens with MICs up to 2.5 mg/L. However, none of the dosage regimens achieved the target AUC_{0-24}/MIC ratio for pathogens with an MIC >0.5 mg/L. The current study indicated that all tested doses will not achieve MIC target of 3 or 4 mg/L and higher doses are required. However, the increase in dose will result in excess exposure and would be on the price of toxicity. Further studies are needed to establish which PK/PD parameter and target gives the best prediction for efficacy to manage *P. aeruginosa* infections in patients with CF. In addition, clinical studies are urgently needed to assess the safety of high tobramycin AUC_{0-24}.

The study has some limitations. Lack of clinical outcome data in the original data set meant that it was not possible to link the simulation results directly with efficacy or to define safe upper limits for C_{max} and AUC_{0-24}. Consequently, the values used in the simulations reflected previous publications or typical exposures. Although renal function was generally good in the original population and obesity was rare (1% of patients had a CrCL <50 mL/min and <1% were obese), AUC_{0-24} values >150 mg.h/L and high C_{max} predictions typically occurred in patients whose simulated CL was low and/or who had BMIs above 30 kg/m^2. It is clear that a lower dose or longer dosage interval would be required for patients with renal impairment. The value of using an adjusted body weight to determine dose has been reported elsewhere[16,23] and might be more appropriate than using actual WT for obese patients. The TOPIC study[6] addressed this issue to some extent by restricting the maximum dose to 660 mg/day. However, this approach only limits the dose for patients weighing more than 66 kg, does not address the issue of small, overweight patients and may risk underdosing patients whose ideal weight is >66 kg. Furthermore, the present study showed that while the restriction reduced the risk of excessive concentrations, the overall results were similar to those with the unrestricted dose. Problems related to obesity did not arise with HT-scaled dosing.

Conclusions

This simulation study based on data from a large population of patients with CF has demonstrated that a HT-based dosage regimen of 3 mg/cm/day produced a narrower range of doses, C_{max} and AUC_{0-24} estimates than WT-based dosage regimens, higher percentages of concentrations and exposures within target ranges and a lower incidence of excessive exposure. All dosage regimens achieved C_{max}/MIC ratios >10 for pathogens with an MIC $\leq$2

mg/L but AUC_{0-24}/MIC ratios >110 could only be achieved if the MIC was ≤0.5 mg/L. These results suggest that HT rather than WT-based dosing should be considered for patients with CF who are undergoing treatment with intravenous tobramycin.

ACKNOWLEDGMENTS

Part of this work has been presented in poster format at the Population Approach Group in Europe meeting, June 2011 (PAGE 20 (2011) Abstr 2077 [www.page-meeting.org/?abstract=2077]), and as oral presentation at the Pharmacokinetics UK meeting in November 2012.

FUNDING

This study was supported by a grant from Kuwait University, Kuwait City, Kuwait.

TRANSPARENCY DECLARATIONS

None to declare. SA conducted the study and wrote the first draft of the manuscript. AHT supervised the study and edited the manuscript. DJT contributed to the study analysis and interpretation and provided editorial input to the manuscript.

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Table 1 Median and range of daily doses, C_{max} and AUC_{0-24} for a range of weight and height scaled tobramycin dosage regimens for patients with cystic fibrosis

	10 mg/kg/day (max 660 mg)	10 mg/kg/day	12 mg/kg/day	3 mg/cm/day	4 mg/cm/day
Daily Dose (mg/day)	550 (300-660)	550 (300–1054)	656 (365-1296)	498 (418-581)	664 (556–776)
C_{max} (mg/L)	30.0 (9.7-79.3)	30.0 (9.7–79.3)	35.6 (9.6-98.3)	27.2 (11.8-52.1)	36.2 (14.5-68.7)
AUC_{0-24} (mg.h/L)	112 (45-260)	114 (45–291)	137 (54-410)	104 (48-227)	139 (60-303)

Table 2 The percentages of simulated patients whose C_{max} and AUC_{0-24} estimates were below, within and above target ranges with a range of weight and height scaled dosage regimens

Dosage regimen	10 mg/kg/day (max 660 mg)	10 mg/kg/day	12 mg/kg/day	3 mg/cm/day	4 mg/cm/day
C_{max} (mg/L)					
<20	7	7	1.5	5	0.2
20 - 30	43	43	25	64	20.4
>30	50	50	73	31	79.4
30 - 40	37	37	40	29	52.0
>40	13	13	33	2	27.4
AUC_{0-24} (mg.h/L)					
< 80	10	9	2	11	1
80 – 120	51	48	29	62	25
>120	39	43	69	27	74
120 - 150	27	27	32	22	38
>150	12	16	37	5	36

Key:AUC_{0-24}-daily area under the curve

Figure Legends

Figure 1 The distribution of daily doses, predicted C_{max} and AUC_{0-24} using a range of weight and height-based tobramycin dosage regimens

Key: BMI = body mass index where 1 = <18.5, 2 = 18.5-24.99, 3 = 25-29.99, 4 = ≥30 kg/m^2.

The solid black lines represent the target C_{max} and AUC_{0-24} ranges

Figure 2 The distribution of predicted C_{max} and AUC_{0-24} using a range of weight and height-based tobramycin dosage regimens

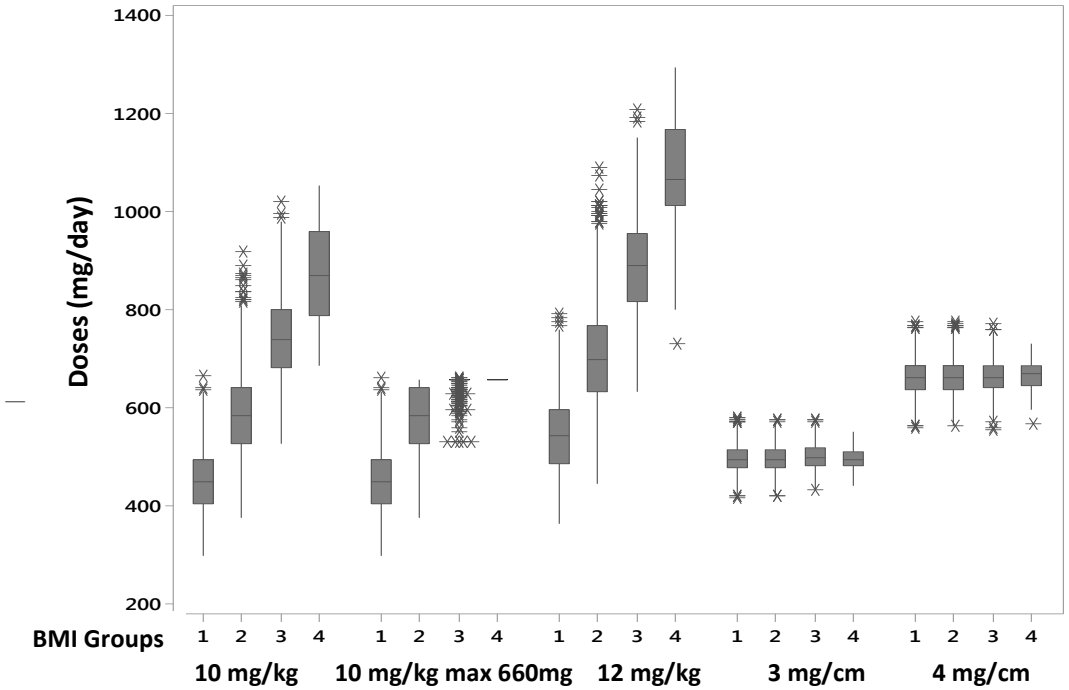
Key: CrCL = creatinine clearance where 1 = < 50 mL/min, 0 = > 50 mL/min.

The solid black lines represent the target C_{max} and AUC_{0-24} ranges

Figure 3 Percentage probability of achieving a target (a) C_{max}/MIC ratio ≥10 and (b) AUC_{0-24}/MIC ratios ≥110 with weight (10 and 12 mg/kg/day) and height (3 and 4 mg/cm/day) scaled doses over a range of MIC values.

Key: The black solid line and closed circle (—●—) represents the 10 mg/kg/day dose (max 660 mg/day); the solid black line and open circle (—○—) represents the 12 mg/kg/day dose; the grey solid line and closed square (—■—) represents the 3 mg/cm/day dose; the grey solid line and open square (—□—) represents the 4 mg/cm/day dose.

435 **Figure 1**



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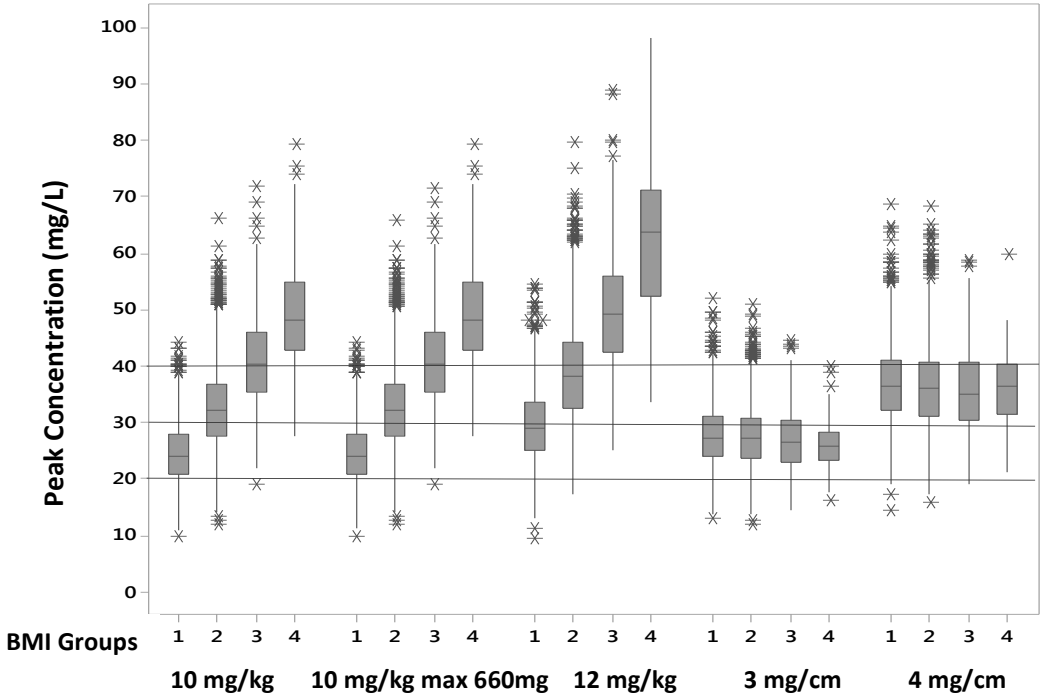

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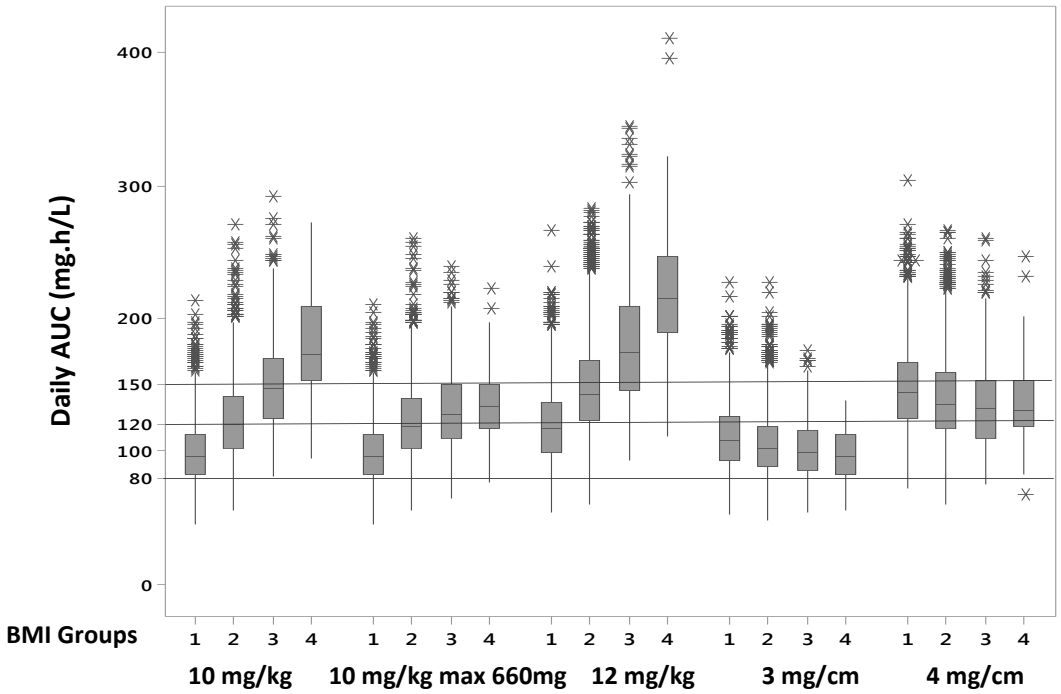
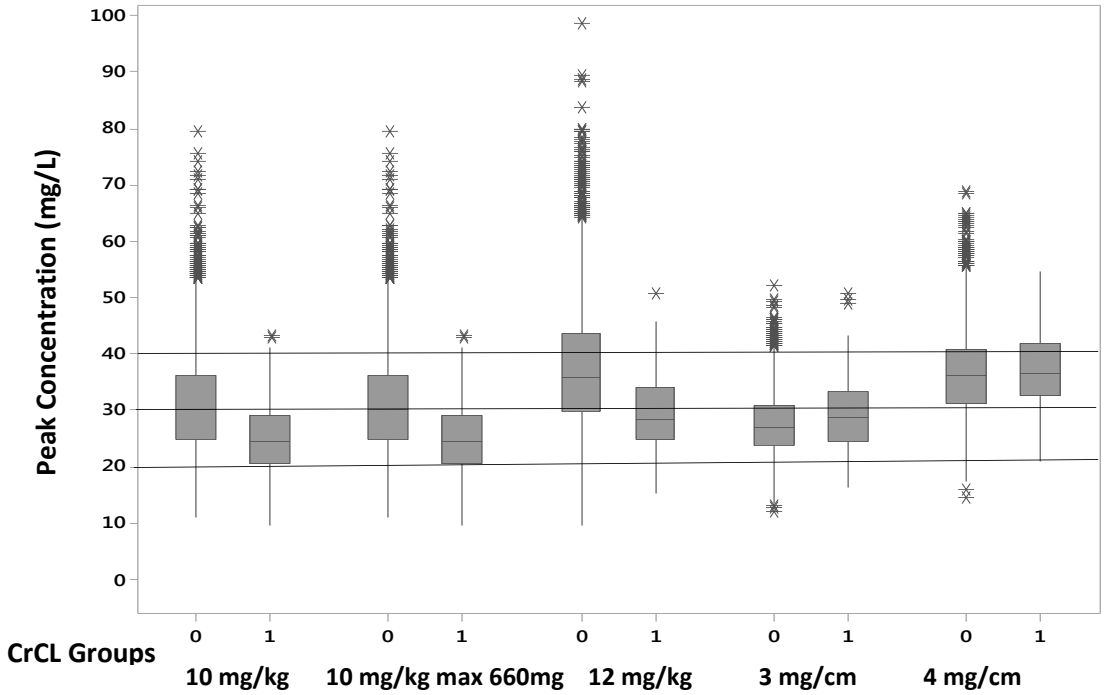

Daily AUC (mg.h/L)
400
300
200
150
120
100
80
0
BMI Groups
1 2 3 4 1 2 3 4 1 2 3 4 1 2 3 4 1 2 3 4
10 mg/kg
10 mg/kg max 660mg
12 mg/kg
3 mg/cm
4 mg/cm

440

441 **Figure 2**



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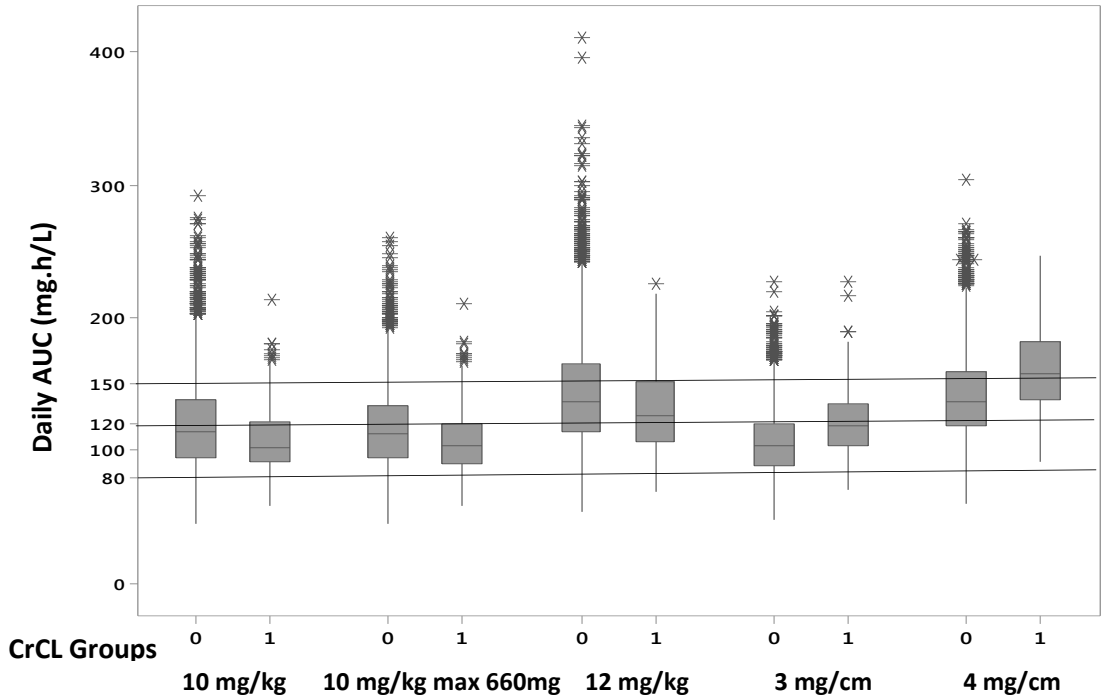
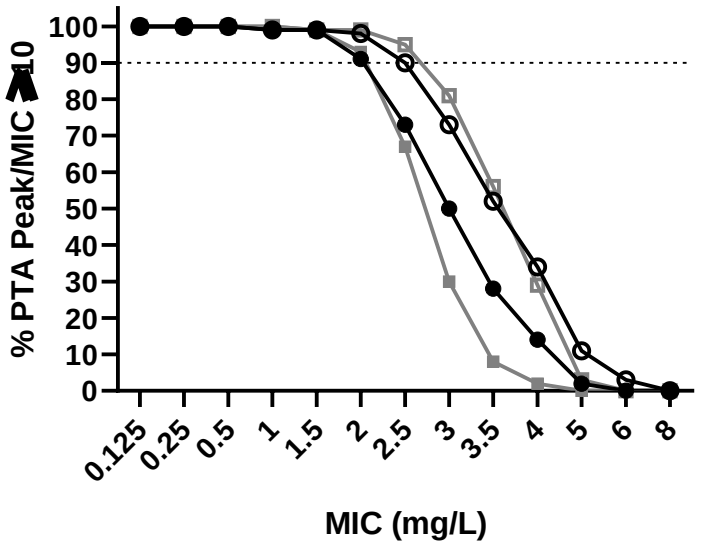


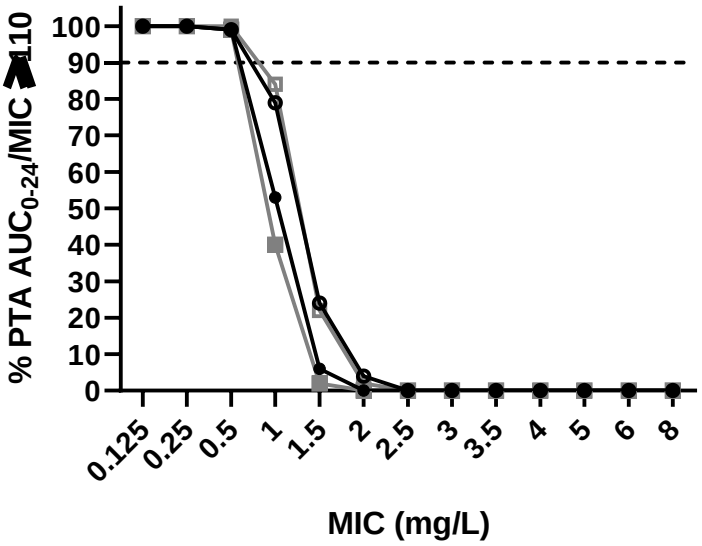
443

Figure 3

a)


% PTA Peak/MIC ≥10
100
90
80
70
60
50
40
30
20
10
0
0.125
0.25
0.5
1
1.5
2
2.5
3
3.5
4
5
6
8
MIC (mg/L)

b)


% PTA AUC0-24/MIC ≥110
100
90
80
70
60
50
40
30
20
10
0
0.125
0.25
0.5
1
1.5
2
2.5
3
3.5
4
5
6
8
MIC (mg/L)

Supplementary Table 1 Median and ranges for original data set patients' characteristics.

Variable	Median (ranges)
Age (years)	24.6 (14 – 88.4)
Weight (kg)	53 (30 – 108)
Height (cm)	166 (139-194)
Serum Creatinine (μmol/L)	70 (19 – 209)
Creatinine Clearance (mL/min)	94 (26 – 181)