Shaping the pharmacokinetic landscape for renally cleared antibiotics in obesity: Studies in adults, adolescents and children

Smit, C.

Part V

Appendices

Dose recommendations presented in this thesis

DOSE RECOMMENDATIONS PRESENTED IN THIS THESIS

Throughout this thesis, dose recommendations have been proposed for gentamicin, tobramycin and vancomycin based on studies in adult obese individuals with and without renal impairment (gentamicin) or without renal impairment (tobramycin and vancomycin), and in obese and non-obese children and adolescents with and without renal impairment (vancomycin). These dose recommendations are summarized in this appendix together with a short description of their applicability.

Gentamicin dose recommendations for adult obese individuals

Dose recommendations for gentamicin are based on studies in obese and non-obese healthy volunteers (Chapter 3) combined with a real-world population of obese individuals with and without renal dysfunction (Chapter 6). The final dose recommendation as presented in Chapter 6 are shown in Table 1. Included patients (n = 524) had a total body weight (TBW) between 53 and 221 kg and renal functions based on the Chronic Kidney Disease Epidemiology equation (CKD-EPI) between 5.1 and 141.7 mL/min/1.73 m^2. The developed pharmacokinetic model was externally validated in an additional dataset from a second hospital with similar weight and renal function ranges (n = 321, total body weight 69 – 180 kg, CKD-EPI 5.3 – 130.0 mL/min/1.73 m^2). With this data we designed dose recommendations in which mg/kg dose reductions and interval extensions were incorporated based on the renal function measured with CKD-EPI (Table 1). Monte Carlo simulations showed that using the dose recommendations from Table 1, similar exposure compared to lean individuals, receiving the EUCAST recommended dose of 6 mg/kg total body weight, is expected for all obese individuals regardless of renal function (Chapter 6, Figure 2).

Table 1. CKD-EPI based dosing for gentamicin in obese individuals with varying renal function (expressed as CKD-EPI), relative to standard dose of 6 mg/kg TBW for lean individuals with a normal renal function (> 60 mL/min/1.73 m^2). This table is also shown in Chapter 6, Table 3.

	Obese individuals >100 kg (non-ICU patients)[a]					Lean individuals <100 kg (reference)
CKD-EPI (mL/min/1.73 m^2)	>120	90 – 120	60 – 90	30 – 60	<30	>60
Gentamicin dose, mg/kg (based on TBW in kg)	6 (100 %)	4.8 (80 %)	3.6 (60 %)	2.4 (40 %)	1.8 (30 %)	6 (100 %)
Dose interval (h)[b]	24	24	24	24 – 36	36 – 48	24

[a] Consider 25% dose reduction in ICU patients for all CKD-EPI groups.

[b] Based on time to reach the target trough concentration (<1 mg/L). We recommend to individualize dosing using therapeutic drug monitoring

CKD-EPI Chronic Kidney Disease Epidemiology, *TBW t*otal body weight.

Tobramycin dose recommendations for adult obese individuals

Dose recommendations for tobramycin presented in this thesis are based on studies in non-obese and obese healthy volunteers (Chapter 4). Using a pharmacokinetic model that was developed using prospectively collected data from 28 individuals (TBW 57-194 with an estimated renal function >60 ml/min, using the Modification of Diet in Renal Disease [MDRD, non-obese] or LBW in the Cockcroft Gault formula [obese]) a dosing nomogram was developed (Figure 1). In this nomogram, the tobramycin dose was based on the de-indexed MDRD, where the individual's MDRD is multiplied by the body surface area (BSA)/1.73, while targeting an AUC_{24h} of 75 mg*h/L. This target has been proposed for tobramycin in treating pathogens with a MIC of 0.25 – 1 mg/L, as it has shown to have the best balance between effectiveness and toxicity. When this dose strategy is employed in the obese, a stable median AUC_{24} up to 190 kg without trends can be expected with outer ranges lying around ~75% to ~125% relative to the target of 75 mg*h/L (Chapter 4, Figure 4). Some remarks should be made regarding the dose nomogram. First, the tobramycin dose nomogram shows dose recommendations for de-indexed MDRD values between 30-250 mL/min. However, the model is based on a dataset with MDRD values of 77 to 171 mL/min and as such, dose recommendations outside of this MDRD-range (depicted with grey area's in the figure) should be interpreted with caution. Second, we have shown in the discussion (Chapter 8) that both the dosing guidelines from Table 1 (proposed for gentamicin based on individuals with and without renal impairment) and Figure 1 (proposed for tobramycin based on individuals without renal impairment) lead to similar doses with the exception of a subgroup of patients with CKD-EPI <50 ml/min/1.73 m^2, based on simulations in a population of 10.000 subjects with body weights from 100 – 220 kg, and randomly assigned CKD-EPI values varying from 7 – 133 ml/min/1.73 m^2. As such, it appears feasible to also use the gentamicin recommendations (Table 1) for tobramycin as well. However, this remains to be prospectively evaluated in future research.

Vancomycin dose recommendations for adult obese individuals

In Chapter 5, we present dose recommendations for vancomycin for adult obese individuals. These recommendations are based on a prospective study in non-obese and obese healthy volunteers (n = 28, TBW 60 – 235 kg). All individuals had an estimated renal function > 60 ml/min, calculated using the Cockcroft-Gault (CG) formula with lean body weight (LBW) for obese or with TBW for non-obese. With a population pharmacokinetic model based on this data we explored several dosing strategies, where best results (highest probability of having a AUC_{24h} between 400 – 700 mg*h/L on day 3) were obtained using a dose of 35 mg/kg TBW (maximized at 5500 mg/day) (Chapter 5, Figure 3). As these dose recommendations only apply to individuals without renal impairment, and they were based on single dose pharmacokinetics, the model could benefit from addition of TDM data from clinical practice similar to gentamicin.

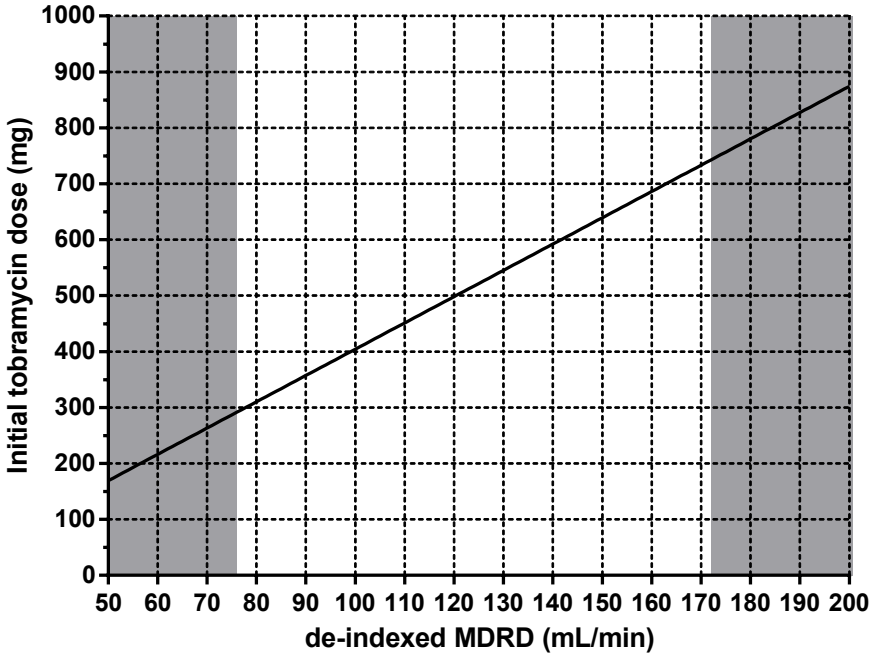

Figure 1. Dosing nomogram for tobramycin dose (in mg) based on the final tobramycin population PK model in non-obese and obese patients with body weights ranging from 57–194 kg and de-indexed MDRD values (calculated as MDRD * body surface area (BSA)/1.73) ranging from 77 to 171 mL/min, aiming for an AUC_{24} of 75 mg*h/L. The recommended tobramycin dose is calculated using equation: Dose (mg) = $AUC_{24, target}$ * 6.33 * (1 + 0.099 * [MDRD – 115]), where $AUC_{24, target}$ is the target AUC_{24} in mg*h/L of 75 and MDRD represents the de-indexed MDRD in mL/min. Since the PK data consists of MDRD values from 77 to 171 mL/min, dose recommendations extrapolation to values outside these should be interpreted with caution (grey area in the nomogram). This figure is also shown in Chapter 4, Figure 5. *MDRD* Modification of Diet in Renal Disease.

Vancomycin dose recommendations for non-obese and obese children and adolescents with and without renal impairment

A dosing guideline for vancomycin that can be used for all children and adolescents aged 1 – 18 years was presented in Chapter 7. For these recommendations a pharmacokinetic study was conducted using retrospectively collected data in 1892 children aged 1 – 18 years who were treated with vancomycin. This resulted in a population with a wide age and weight range, i.e. TBW between 6 – 188 kg, in which 13% and 16% was overweight or obese, respectively, and estimated creatinine clearance (based on the bedside Schwartz equation) was as low as 8.6 ml/min/1.73m^2. A dosing guideline was designed that bridges existing guidelines for non-obese children without renal impairment (i.e. the paediatric IDSA guideline recommending 15 mg/kg four times daily) and our earlier developed recommendations for obese adults without

renal impairment as presented in Chapter 5 (i.e. 35 mg/kg per day maximized at 3500 mg/day), with dose adaptations for renal impairment and obesity. The proposed guideline is shown in Table 2. Using this dosing strategy, we demonstrated that target exposure (AUC_{24h} 400 – 700 mg*h/L on day 3) can be expected throughout the entire population for any given weight and renal function (Chapter 7, Figure 5). One remark here is that in this study we included a relatively low number of individuals with renal functions <30 ml/min/1.73 m^2 (n = 12). As such, extra caution is necessary when the dose recommendations are used in this subpopulation.

Table 2. Dosing guideline for intermittent dosing of vancomycin in children and adolescents aged 1 – 18-years based on total body weight and renal function according to bedside Schwartz. This table is also shown in Chapter 7, Table 3.

Schwartz creatinine clearance (mL/min/1.73 m^2)	Total body weight (kg)			Relative daily dose (%)
	<30	30 – 70	>70	
>90	15 mg/kg every 6 h	15 mg/kg every 8 h	18 mg/kg every 12 h	100%
50 – 90	11 mg/kg every 6 h[a]	11 mg/kg every 8 h[a]	12 mg/kg every 12 h[a]	70%
30 – 50	5 mg/kg every 6 h[a]	5 mg/kg every 8 h[a]	6 mg/kg every 12 h[a]	35%
10 – 30	5 mg/kg every 12 h[a]	3 mg/kg every 12 h[a]	3 mg/kg every 12 h[a]	15%

[a] First dose is 15 mg/kg.

Curriculum vitae

CURRICULUM VITAE

Cornelis Smit was born in Menaldum, The Netherlands in 1988. After finishing secondary school at the Christelijk Gymnasium Beyers Naudé in Leeuwarden in 2006, he studied Pharmacy at the University of Groningen. During a research internship in 2010 at the Max-Planck-Institut für Molekulare Physiologie in Dortmund, Germany in 2010, he developed a special interest in conducting scientific research. After graduating as a PharmD cum laude in 2012 he started a residency in hospital pharmacy at the St. Antonius Hospital in Nieuwegein, The Netherlands, under mentorship of drs. M.M. Tjoeng, dr. E.M.W. van de Garde and Prof. dr. C.A.J. Knibbe. He combined this traineeship with a PhD research project, carried out at the St. Antonius Hospital, Radboudumc and Leiden University, supervised by Prof. dr. C.A.J. Knibbe, dr. H.P.A. van Dongen and dr. R.J.M. Brüggemann. Cornelis registered as a hospital pharmacist in 2017 and, following a traineeship under supervision of Prof. Dr. C.A.J. Knibbe, as a clinical pharmacologist in 2019. He currently holds a position as postdoctoral researcher and clinical pharmacologist at the University Children's Hospital (UKBB) in Basel, Switzerland, where he lives together with his wife Harriëtte and two children, Yfke and Karsjen.

List of publications

LIST OF PUBLICATIONS

Smit C, van Schip AM, van Dongen EPA, Brüggemann RJM, Becker ML, Knibbe CAJ. Dose recommendations for gentamicin in the real-world obese population with varying body weight and renal (dys)function. *Journal of Antimicrobial Chemotherapy* 2020; 75:3286–3292.

Smit C, Peeters MYM, van den Anker JN, Knibbe CAJ. Chloroquine for SARS-CoV-2: Implications of Its Unique Pharmacokinetic and Safety Properties. *Clinical Pharmacokinetics* 2020; 59:659–669.

Wasmann RE, Smit C, van Donselaar MH, van Dongen EPH, Wiezer RMJ, Verweij PE, Burger DM, Knibbe CAJ, Brüggemann RJM. Implications for IV posaconazole dosing in the era of obesity? *Journal of Antimicrobial Chemotherapy* 2020, 75(4): 1006–1013.

Smit, C., Wasmann, R.E., Goulooze, S.C., Wiezer, R.M.J., Van Dongen, H.P.A., Mouton, J. W., Brüggemann, R.J.M., Knibbe, C.A.J. Population pharmacokinetics of vancomycin in obesity: finding the optimal dose for (morbidly) obese individuals. *British Journal of Clinical Pharmacology* 2020, 86(2):303-317.

Wasmann RE, Smit C, van Dongen EPH, Wiezer RMJ, Adler-Moore J, de Beer YM, Burger DM, Knibbe CAJ, Brüggemann RJM. Fixed Dosing of Liposomal Amphotericin B in Morbidly Obese Individuals. *Clinical Infectious Diseases* 2019, 70(10):2213-2215.

C. Smit, R. E. Wasmann, M.J. Wiezer, H. P.A. van Dongen, J. W. Mouton, R. J.M. Brüggemann, C. A.J. Knibbe. Tobramycin Clearance Is Best Described by Renal Function Estimates in Obese and Non-obese Individuals: Results of a Prospective Rich Sampling Pharmacokinetic Study. *Pharmaceutical Research* 2019, 36(8):112.

C. Smit, R. E. Wasmann, S. C. Goulooze, E. J. Hazebroek, E. P.A. van Dongen, D. M.T. Burgers, J. W. Mouton, R. J.M. Brüggemann, C. A.J. Knibbe. A prospective clinical study characterizing the influence of morbid obesity on the pharmacokinetics of gentamicin: towards individualized dosing in obese patients. *Clinical Pharmacokinetics* 2019, 58(10):1333-1343.

Wasmann RE, Smit C, Ter Heine R, Koele SE, van Dongen EPH, Wiezer RMJ, Burger DM, Knibbe CAJ, Brüggemann RJM.Pharmacokinetics and probability of target attainment for micafungin in normal-weight and morbidly obese adults. *Journal of Antimicrobial Chemotherapy* 2019, 74(4):978-985.

Smit, C., Wiertz-Arts, K., Van de Garde, E.M.W. (2018) Intravitreal aflibercept versus ranibizumab in age-related macular degeneration: a comparative effectiveness study. *Journal of Clinical Effectiveness Research* 2018, 7(6): 561-567.

Smit, C., De Hoogd, S., Brüggemann, R. J. M., & Knibbe, C. A. J. (2018). Obesity and drug pharmacology: a review of the influence of obesity on pharmacokinetic and pharmacodynamic parameters. *Expert Opinion on Drug Metabolism & Toxicology* 2018, 14(3): 275–285.

Smit C, Blümer J, Eerland MF, Albers MF, Müller MP, Goody RS, Itzen A, Hedberg C. Efficient synthesis and applications of peptides containing adenylylated tyrosine residues. *Angewandte Chemie International Edition* 2011, 50(39):9200-4.

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