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

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Part IV

Main findings, considerations and perspectives

8

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MAIN FINDINGS

Although it is well known that (patho)physiological changes in obese patients can influence the pharmacokinetics (PK) and pharmacodynamics (PD) of drugs implying adjusted doses, there is still a need for specific dose guidelines for many classes of drugs [1]. This is exemplified by aminoglycosides (such as gentamicin or tobramycin) and vancomycin, which are renally cleared antibiotics that are commonly used for severe bloodstream infections. Despite being rather old drugs, discovered during the 'Golden Age' of antibiotic discovery in the 1950's and 1960's, there is still much debate on how these drugs should be dosed in real-world (morbidly) obese patients, and specifically how clearance or volume of distribution are influenced by a combination of excessive overweight, renal impairment and/or critical illness in this population. Specifically in children, maturation of renal clearance processes are an additional factor influencing the pharmacokinetics. Gaining more quantitative knowledge on these influences is of utmost importance since the efficacy of these drugs closely relates to blood concentrations and therefore should be dosed sufficiently high [2,3]. On the other hand, aminoglycosides and vancomycin are known to be nephrotoxic when blood concentrations surpass a certain toxic threshold [4,5]. Knowledge on the pharmacokinetics in these vulnerable populations is of eminent importance to safeguard adequate therapy. However, given the lack of high-quality evidence on the changes in pharmacokinetics of these drugs in the (morbidly) obese population, both in adults and children, we still remain in the dark as to how the gentamicin, tobramycin or vancomycin dose should be adapted in (morbidly) obese individuals with or without renal dysfunction and critical illness. This exposes this population to an increased risk of either underdosing, and therefore less effective treatment of severe infections, or overdosing, leading to more toxicity. In this thesis we aimed to characterize the pharmacokinetics of gentamicin, tobramycin and vancomycin in morbidly obese patients and to provide practical dose recommendations that lead to an effective and safe antibiotic treatment for obese children, adolescents and adults.

As an introduction, in **Chapter 2**, we presented a comprehensive overview of the (patho) physiological changes that occur with obesity, and how these changes may influence the pharmacokinetics and pharmacodynamics of drugs. Additionally, body size descriptors that are commonly used to guide drug dosing were discussed. Although this topic has been increasingly studied over the recent years, we identified several gaps in our current knowledge, particularly regarding the influence of obesity on drug absorption and clearance, both major pharmacokinetic parameters driving exposure. An example of such a knowledge gap is the influence of obesity on hepatically cleared drugs. Although it is known that inflammatory processes associated with obesity may hamper CYP3A4 activity, clearance of the CYP3A4-metabolized drug midazolam was shown not to be decreased in obese individuals. This result may be explained by the different influence of obesity on the parameters that determine a

drug's clearance (liver blood flow and intrinsic clearance), with increases in one parameter (liver flow) being compensated by decreases in the other (intrinsic clearance). A second example is the obesity-related change in renal clearance. While glomerular filtration rate (GFR) in general appears to increase with obesity, this does not necessarily mean that all renally excreted drugs have a higher clearance in obesity, which we exemplified in Chapter 2 with data from cefazoline and fluconazole. Moreover, over time, renal function might actually decrease, since obesity is also an important risk factor for developing chronic kidney disease. Additionally, many renally excreted drugs also undergo active tubular secretion which might be separately influenced by obesity. We identified an urgent need for more studies that further unveil the exact influence of obesity on renal clearance. Lastly, we discussed in Chapter 2 the common assumption that drug distribution can be well predicted using a drug's lipophilic properties with lipophilic drugs diffusing into adipose tissue more easily. We have presented several examples from the literature that show that not all drugs behave accordingly, as drug properties other than lipophilicity play a role in drug distribution.

In the next chapters, we studied the pharmacokinetics of several renally cleared antibiotics, i.e. gentamicin, tobramycin and vancomycin, in non-obese and (morbidly) obese adult but otherwise healthy individuals. In **Chapter 3**, we characterized the pharmacokinetics of gentamicin across body weights using a prospective rich sampling study design where we included morbidly obese patients undergoing bariatric surgery (n = 20) with body weights up to 221 kg and non-obese healthy volunteers (n = 8). We found that total body weight (TBW) predicted gentamicin clearance (using a power equation with exponent 0.73) and volume of distribution of the central compartment (using a power equation with exponent 1.25). To obtain similar exposure across body weights in this population with a normal renal function, we presented a dose nomogram based on a 'dose weight', calculated as $70 \times (TBW/70)^{0.73}$.

In **Chapter 4,** we studied the pharmacokinetics of tobramycin in both morbidly obese individuals undergoing bariatric surgery (n = 20) and non-obese healthy volunteers (n = 8). We found that with body weights up to 194 kg, volume of distribution increases linearly with body weight. In contrast to gentamicin, we found that tobramycin clearance could be best predicted by a serum creatinine-based renal function estimate, namely de-indexed Modification of Diet in Renal Disease (MDRD), expressed in ml/min. Although by de-indexation body weight is indirectly introduced in this covariate through body surface area, this result points out that TBW is less predictive for tobramycin clearance than for gentamicin clearance in the obese population with normal renal function. For gentamicin, we found no significant relation between renal function and clearance. This might be explained by subtle differences in renal clearance routes. We proposed a hypothesis that gentamicin clearance, compared to tobramycin, might be more relying on OCT2-mediated active renal transport. OCT2 appears to be induced by body weight in obesity, based on data from both a preclinical obese mouse model [6] and human

clinical studies with metformin, a known OCT2 substrate [7]. Also, tobramycin was reported to accumulate less in the kidney and therefore is potentially less nephrotoxic, indicating less dependency upon OCT2-mediated renal uptake [8]. Since this hypothesis has not been properly studied so far, further research is warranted to clarify these differences between tobramycin and gentamicin. At the end of chapter 5, we have presented a dose nomogram based on de-indexed MDRD that is expected to result in similar, less variable exposure in (morbidly) obese individuals with normal renal function compared to lean individuals receiving the standard dose of 5 mg/kg TBW.

In **Chapter 5** we studied the glycopeptide antibiotic vancomycin. In a prospective pharmacokinetic study in morbidly obese patients undergoing bariatric surgery (n = 20) and non-obese healthy volunteers (n = 8), with body weights from 60 – 235 kg, we found that vancomycin clearance increased with body weight following the equation CL = 5.72 x $(TBW/70)^{0.535}$. In a three-compartment model, volume of distribution of the second compartment (V2) increased with linearly with body weight, whereas age also had a small influence on the central compartment (V1) and V2. This model was externally validated using earlier published data from six obese and four non-obese individuals [9]. Using Monte Carlo simulations we showed that we could maximize the portion of individuals within the target exposure (24-h area under the curve (AUC_{24h}) of 400 – 700 mg*h/L) by dosing 35 mg/kg/day (maximized at 5500 mg/day). The FDA drug label fixed dose of 1000 mg twice daily [10] leads to unacceptable underexposure while another often recommended dosage of 45 mg/kg/day [3] leads to an unacceptable risk of toxicity. In addition, to aid in therapeutic drug monitoring (TDM) in obese patients, our study showed that for obese patients, a target AUC_{24h} of 400 – 700 mg*h/L corresponds to steady state trough concentrations between 5.7 – 14.6 mg/L. This is much lower than what is recommended as a target trough concentration in leading guidelines (15 – 20 mg/L) [3]. Therefore, clinicians should be aware that in obese individuals, below target trough concentrations do not necessarily correspond with subtherapeutic exposure and as such we advise to estimate the individual's AUC using TDM with Bayesian forecasting software.

In the previous chapters, the influence of weight was characterised while keeping other covariates such as renal function within normal limits. Thereto, these studies were done with individuals who were obese, but otherwise relatively healthy. Yet, obesity is not the sole factor introducing variability in clearance and volume of distribution. For the studied drugs it is known that both renal function and critical illness are important determinants for clearance in non-obese adults. For this reason, in **Chapter 6** we further characterized the pharmacokinetics of gentamicin by combining the prospectively collected data in obese and non-obese individuals with a large retrospectively collected dataset derived from (critically ill) obese individuals with and without impaired renal function (n = 542). Here we found

that a combination of TBW and renal function (estimated using the serum creatinine based Chronic Kidney Disease Epidemiology equation [CKD-EPI]) could well describe the changes in gentamicin clearance in the real-world population. These two covariates were combined in the de-indexed CKD-EPI, which equals CKD-EPI (expressed as ml/min/1.73 m^2) multiplied by body surface area (BSA)/1.73. Additionally, we found that patients admitted to the ICU had an almost 25% lower clearance, independent of renal function. With some other studies also reporting critical illness as a separate predictor for gentamicin clearance [11,12], this finding might be a result of serum creatinine lagging behind as marker for renal impairment. Using the final model, which was externally validated in a second dataset with similar patient characteristics (n = 208), we designed an easy-to-use dose nomogram for obese individuals that incorporated both body weight and renal function. In this nomogram, a mg/kg dose should be reduced with decreasing CKD-EPI values, and the dosing interval extended beyond 24h when CKD-EPI drops below 50 ml/min/1.73 m^2. Earlier, in Chapter 4, we proposed a dose nomogram for tobramycin on basis of a study in obese adults with a normal renal function, that uses de-indexed MDRD. Figure 1 illustrates that this nomogram results in similar doses compared to the dose nomogram we propose for gentamicin in Chapter 6 that uses CDK-EPI and body weight, with the exception of a subgroup of patients with CKD-EPI <50 ml/min/1.73 m^2. This particular group of patients with renal impairment was not included in the tobramycin study. As such, it appears feasible to use an overarching model and dosing guideline incorporating both weight and renal function like the one presented in Chapter 6 to predict exposure of tobramycin and gentamicin as exemplified in Figure 1. Such a combined approach remains to be validated for tobramycin but seems a practical uniform tactic.

In the second real-world study, **Chapter 7** describes the results of a pharmacokinetic study on vancomycin in a large obese and non-obese paediatric population consisting of 1892 children and adolescents aged 1 – 18 years. We extracted data on vancomycin administrations, serum concentrations and covariates from 21 hospitals in the Utah area in the USA. The dataset consisted of both a wide age range, as well as a large distribution of overweight (body weight up to 188 kg, with 13% and 16% of patients being overweight and obese, respectively) and renal function (lowest estimated creatinine clearance 8.6 ml/min/1.73 m^2). Moreover, the range in sampling time after dose varied largely which provides optimal information for population pharmacokinetic modelling. In this population, vancomycin clearance could be predicted using a relatively simple covariate model with body weight and renal function, depicted by the bedside Schwartz formula (SCHW): $CL = 2.12 \times (TBW/22.1)^{0.745} \times (SCHW/100)$. This model outperformed more sophisticated models such as one that separately characterizes the influence of weight for age and weight excess or one that employs a body size dependent exponent for the influence of body weight that accounts for maturation. Such a body size dependent exponent model was originally developed to be able to distinguish between the influence of increasing weight resulting from growth and maturation versus the influence of

weight from obesity. Ultimately, we proposed a straightforward dose regimen that bridges the existing IDSA recommendations for non-obese children (15 mg/kg four times daily without specific recommendations for obesity or renal function) and the in Chapter 5 proposed dosing strategy for obese adults, with adaptions for renal impairment and overweight. Using this dosing strategy, we demonstrated that on target exposure on day 3 (AUC_{24h} between 400 and 700 mg*h/L) can be expected throughout the entire population for any given weight and renal function. One limitation in the study was the relatively low number of included individuals with a renal function <30 ml/min/1.73 m^2 (n = 12). As such, extra caution should be put in place when our dose recommendations are used in this paediatric subpopulation. Similar to what we found in the adult population, we noticed that there is large variability in obtained vancomycin trough concentrations, with trough concentrations varying between 6.9 – 21.5 mg/L in several typical individuals, despite being within the exposure (AUC_{24h}) target. This again underlines estimation of the patient's vancomycin AUC using a limited sampling strategy in conjunction with Bayesian forecasting software as a preferred method above targeting trough concentrations.

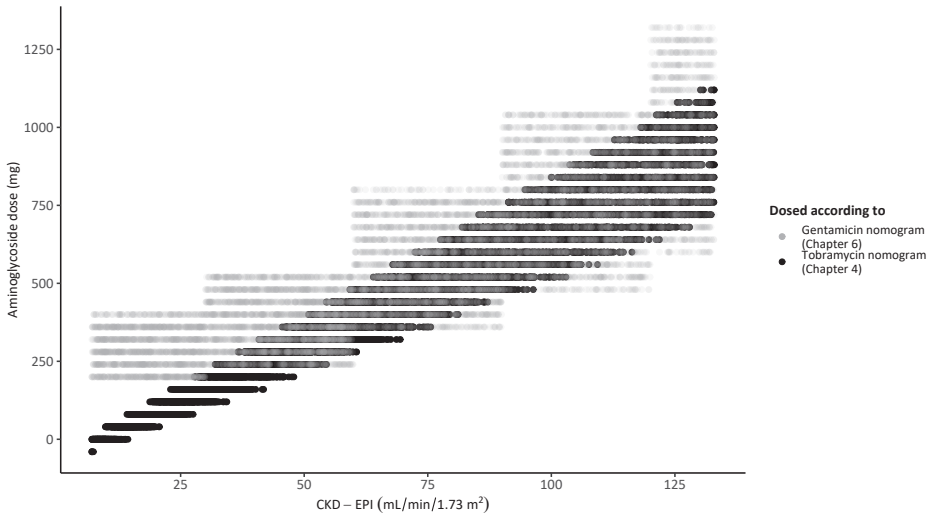

Figure 1. Comparison of the aminoglycoside dose (rounded to nearest multiple of 40 mg) versus CKD-EPI (in ml/min/1.73 m^2) according to the dose nomogram proposed for gentamicin based on the study in a real world population in Chapter 6 (with doses based on CKD-EPI and body weight) and according to the dose nomogram proposed for tobramycin in obese individuals in Chapter 4 (with dose based on de-indexed MDRD). Each dot represents one individual. The population consists of 10.000 subjects with body weights from 100 – 220 kg, with randomly assigned CKD-EPI values varying from 7 – 133 ml/min/1.73 m^2. For the tobramycin nomogram, we assumed that each individual's MDRD was the same as the CKD-EPI, after which this was de-indexed by multiplying by BSA/1.73. For calculating each BSA, height was imputed as 180 cm (for males) or 167 cm (for females) and gender allocated randomly. *CKD-EPI* Chronic Kidney Disease Epidemiology equation.

CONSIDERATIONS AND PERSPECTIVES

In this section we will discuss the results that were obtained in this thesis from a broader perspective. First, we will reflect on the methodological approach that we chose for our studies. Second, we will evaluate what the results can teach us on how pharmacokinetics change in the obese population, with a focus on the prediction of volume of distribution and clearance in obese individuals. Lastly, we will discuss how the clinical use of the obtained knowledge can be maximized.

METHODOLOGICAL APPROACH

To get to dose recommendations for obese patients in the 'real-world' or daily clinical practice, we first characterized the influence of obesity using a prospective, rich sampling pharmacokinetic study design in non-obese and (morbidly) obese, but otherwise healthy individuals without severe organ dysfunction. The (morbidly) obese individuals were included during their admission for a bariatric operation (Chapters 3,4 and 5). Next, we conducted an extension study in real-world patients combining the prospective data with retrospectively collected data from clinical patients with and without renal dysfunction or critical illness (gentamicin, Chapter 6). In the past, pharmacokinetic studies were conducted either in a prospective, rich sampling design in obese healthy volunteers [13], or by means of a retrospective, sparse (therapeutic drug monitoring) design with peak and trough concentrations only [14]. Our approach combines both designs, which has several benefits. First, the prospective design in obese healthy individuals provides us with the opportunity to include patients with a wide range of body weights, with weights varying between 53 and 235 kg in the studies presented in this thesis. Besides being obese, participants were otherwise healthy and as such, by keeping all other variables like renal function or critical illness constant except weight, this allowed us to specifically characterize the influence of body weight on drug pharmacokinetics. Second, because of the planned surgery, the obese study participants are all admitted to the hospital for at least two days, receive a venous catheter and are monitored closely during the admission. As such, we can limit the study related burden for participants. The impact of surgery on PK is considered negligible as surgery is performed laparoscopically in a short procedure (around 45 minutes) with minimal blood loss (usually <50 mL). Third, over the years we have established a consortium of closely collaborating departments involved in these studies (surgery, anesthesiology and clinical pharmacy). This strongly increases the feasibility of conducting such studies. The biggest benefit of our approach however comes from combining the prospective, rich data from healthy obese volunteers with TDM data collected in the real-world clinical setting. This is a valuable model development strategy, since it provides us with the opportunity to simultaneously study a wide variety of covariates: In prospectively

collected data in obese healthy individuals there is a large variability in body weight as a result of the study design, while in the retrospectively collected TDM data, there is usually a large variability in covariates such as renal function and critical illness. Both datasets separately would most likely not have sufficient information to develop a robust pharmacokinetic model and dose recommendations. Similar efforts to extent the developed models for tobramycin and vancomycin in real-world clinical obese populations are currently under way.

PREDICTABILITY OF VOLUME OF DISTRIBUTION IN OBESE INDIVIDUALS

For all drugs studied within this thesis (gentamicin, tobramycin and vancomycin) we have separately identified total body weight as the most predictive covariate for volume of distribution. As discussed in Chapter 2, it is often assumed that a drug's lipophilicity or hydrophilicity determines how and whether the volume of distribution changes. All three studied drugs are considered hydrophilic (Log P values of -3.1 (gentamicin), -5.8 (tobramycin) and -3.1 (vancomycin) [15]), so one might expect that obesity may not influence the volume of distribution. Our results show that volume of distribution for these drugs increases linearly with TBW, following the equation $CL = CL_{70kg} \times (TBW/70)$, where CL_{70kg} is the typical clearance for an individual weighing 70 kg. In Chapter 3, where we studied the pharmacokinetics of gentamicin in obese and non-obese healthy individuals, we identified a model where the factor TBW/70 was scaled with an exponent of 1.25. However, in the extension study to real-world patients (Chapter 6), a model with an exponent fixed to 1 led to the best fit. This points towards a similar drug penetration into adipose tissue as in normal, lean tissue. Although other explanations for this linear increase of volume of distribution such as alterations in protein or tissue binding cannot be excluded, these are less likely given the low protein binding of the studied drugs [16,17]. Our findings are in line with what has been reported for several other drugs and has been described by Jain et al. in a review paper on this topic [18]. For example, the highly lipophilic anaesthetic propofol, shows no change in volume of distribution in obese individuals, while the volume of distribution of similarly lipophilic drugs such as midazolam or diazepam strongly increase with increasing body weight [19–21]. In conclusion, our results show that alterations in volume of distribution in obesity cannot be predicted by lipophilicity alone.

BODY SIZE DESCRIPTORS FOR PREDICTING DRUG CLEARANCE IN THE OBESE POPULATION

Over the years, many researchers have tried to identify an optimal body size descriptor as an alternative for total body weight to guide drug dosing in obesity. One reason to investigate alternative body size descriptors is that drug excretion may be correlated with lean tissue as adipose tissue may be considered 'inactive', and therefore might not increase linearly with total body weight [22]. Several body size descriptors have been described for specific drugs or drug categories, for example pharmacokinetic mass (PM) for fentanyl [23] and adjusted body weight (ABW) for aminoglycosides [24]. Ideal body weight (IBW) is often recommended for drugs that show no change in pharmacokinetics in obese individuals compared to non-obese individuals, as has been found for certain muscle relaxants [25]. BSA is predominantly used in chemotherapy, for non-obese as well as obese patients [26]. Since the introduction of this spectrum of body size descriptors, several efforts have been undertaken in determining a *universal* body size descriptor that predicts pharmacokinetics in obesity regardless of the drug at hand. The most important candidate in this light is Lean Body Weight (LBW), as described by Janmahasatian et al. in 2005 [22,27,28]. This body size descriptor predicts the Fat Free Mass (FFM) using a complex formula including TBW, height and gender [27]. Technically, FFM consists of all body tissue without fat, where LBW in its original meaning comprises all lean tissue (organs, blood, water), including a small portion of fatty tissue in the organs [29]. Since this portion is very small (less than 5% [29]), it is generally accepted that LBW and FFM are used interchangeably in drug pharmacokinetics.

Several papers have advocated the use of LBW as body size descriptor for predicting drug clearance in obese individuals [22,28]. The basis for using LBW was given by a study in 2008, where in 17 individuals (9 obese and 8 lean) with normal renal function, GFR normalized for LBW was found to be similar between obese and non-obese individuals, although a trend towards a lower normalized clearance was visible in the obese group [30]. The theoretical concept here is that the mass of organs involved in drug clearance (kidney's and liver) is better represented by LBW than TBW. Indeed, LBW was found to be a better predictor compared to TBW for clearance of acetaminophen, a hepatically cleared drug in 28 obese and non-obese patients [31]. In contrast, in this thesis we show that there are no large differences between LBW or TBW for predicting vancomycin clearance (Chapter 5), or in the case of gentamicin, TBW even outperformed LBW in predicted clearance in obese patients with a normal renal function (Chapter 4). This shows that LBW cannot be used as a *universal* body size descriptor for drug clearance. In addition, our results pointed out some features of LBW that are crucial when LBW is used as a covariate in a pharmacometrics analysis or as a basis for drug dosing. In this section, we will address these aspects of LBW in more detail.

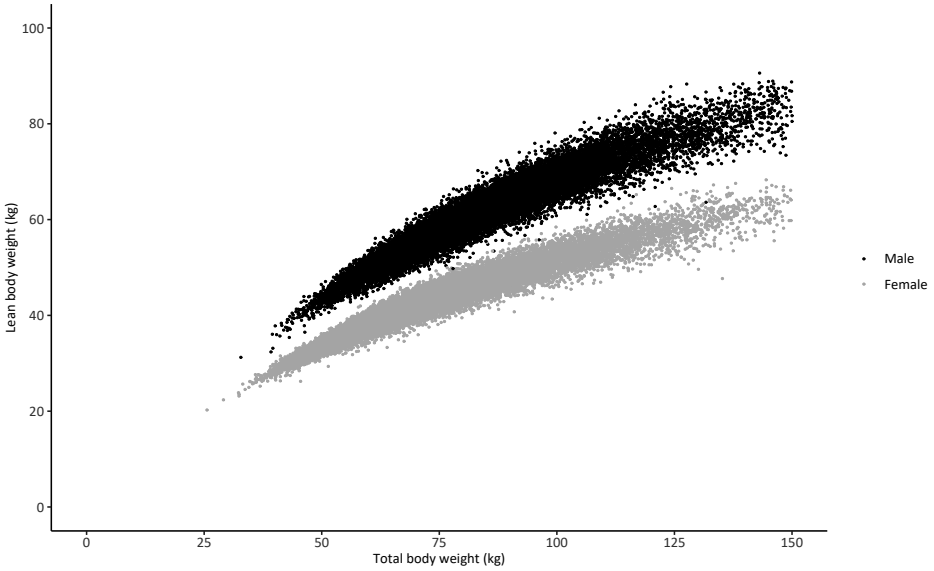

Figure 2. Lean body weight (kg) versus total body weight (kg) derived from data from the NHANES dataset [32] coloured by gender (males as black dots, females as grey dots, n = 48.348).

One of the variables in the LBW-equation as proposed by Janmahasatian et al. is gender [27]. To illustrate the large impact of gender on LBW, we show the LBW in Figure 2 for 48.348 individuals derived from the National Health and Nutrition Examination Survey (NHANES) database, which is a large database consisting of representative data from adults from the USA gathered between 1999 to 2016 [32]. As can be seen in the figure, LBW is approximately 25% lower in females compared with males. This has some major implications for drug dosing: when dosed on LBW, females receive lower doses as compared to males with the same body weight, which is especially of relevance for obese individuals. For example, it was demonstrated in Chapter 3 that for obese individuals >100 kg, a gentamicin dose of 8 mg/kg LBW results in similar exposure compared to the proposed dose nomogram with TBW as basis (3.5 – 5 mg/kg TBW) for the whole population (Chapter 3, Figure 4). However, when these results are split by gender, large differences can be observed, with females receiving 8 mg/kg LBW having considerably lower exposure compared to males receiving 8 mg/kg LBW (Figure 3).

From the observations illustrated in Figure 3, it can be concluded that the use of LBW for dosing may have important implications for the exposure in males versus females. Therefore, close inspection of gender differences is important when investigating LBW as a covariate. Typically, when screening for a possible influence of covariates, the first step is to inspect the individual (post-hoc) clearances versus covariate plots. In order to further illustrate the relevance of gender in covariate model building with LBW, plots for drug clearance versus

TBW and LBW are shown in Figure 4 for the studies from Chapters 3 and 5 (gentamicin and vancomycin, respectively) and for the earlier mentioned study with acetaminophen (data derived from the study by Van Rongen et al. [31]). In this figure, it is visible that for gentamicin, TBW outperforms LBW in predicting clearance, whereas for acetaminophen LBW shows a better fit than TBW. More specifically, for gentamicin, when using LBW (Figure 4a) obese females and males of the same LBW have substantially different clearance values, whereas for TBW (Figure 4b), male and female individuals of the same TBW have similar clearances. In other words, when using LBW (Figure 4a), two parallel lines can be identified, one of females and one for males, implying that when using LBW, gender is another covariate. In contrast, the acetaminophen data illustrate that for individuals with the same TBW (Figure 4f), gender is an additional factor influencing acetaminophen clearance. This is resolved when using LBW and as such, it is for acetaminophen justified to use LBW as a covariate. These differences between TBW and LBW are less clear for vancomycin (Figure 4c and 4d), where both covariates result in a similar goodness-of-fit and objective function value. Upon close inspection, it is visible that around a LBW of 50 – 75 kg, introduction of LBW might result in a gender difference, as obese females still show a lower clearance compared to non-obese males (with the same TBW), albeit not as clearly as seen for gentamicin. There are insufficient data points to state this with certainty. For now, this might be a reason to not include LBW in the vancomycin model, although there were no large differences between LBW and TBW with regard to OFV and goodness-of-fit. This demonstrates the added value of critically assessing covariate plots, such as those presented in Figure 4 and inter-individual variability-versus-gender plots made before and after introduction of LBW as a covariate. These findings also show that the importance of including both genders with a sufficient range in bodyweights in a pharmacokinetic study when investigating LBW as a possible covariate.

To conclude, there is insufficient evidence to use LBW as a *universal* body size descriptor to predict drug clearance in obese individuals. Additionally, the importance of gender when investigating LBW as a covariate in pharmacokinetics in general deserves more attention. It is important to realize that when a drug is dosed using LBW, females receive a lower dose compared to males with the same body weight, increasing the risk of underexposure in females, or overexposure in males. We have shown that, depending on the drug, this may occur (gentamicin) or not (acetaminophen), where we demonstrate the importance of assessing covariate plots such as shown in Figure 4.

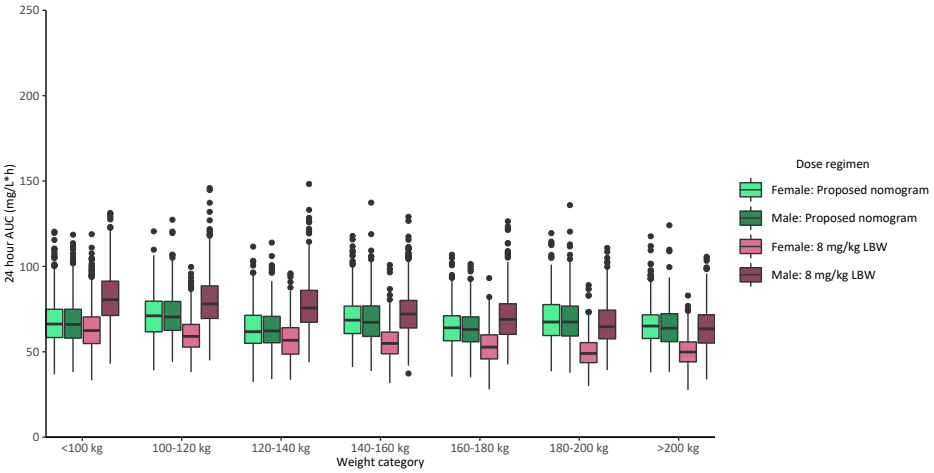

Figure 3. Boxplots (median and 95% confidence interval) representing gentamicin AUC_{24} for different weight categories upon the proposed nomogram (based on a 'dose weight' calculated as $70 \times (TBW/70)^{0.73}$, Chapter 3) (green) or 8 mg/kg LBW (red) on the basis of the pharmacokinetic model as presented in Chapter 3, split for gender (females and males light and dark, respectively). Results are based on Monte-Carlo simulations (n = 10.000 subjects per dose regimen with weight ranging 50 – 215 kg), similar to Figure 4 in Chapter 3. *LBW* lean body weight, *TBW* total body weight.

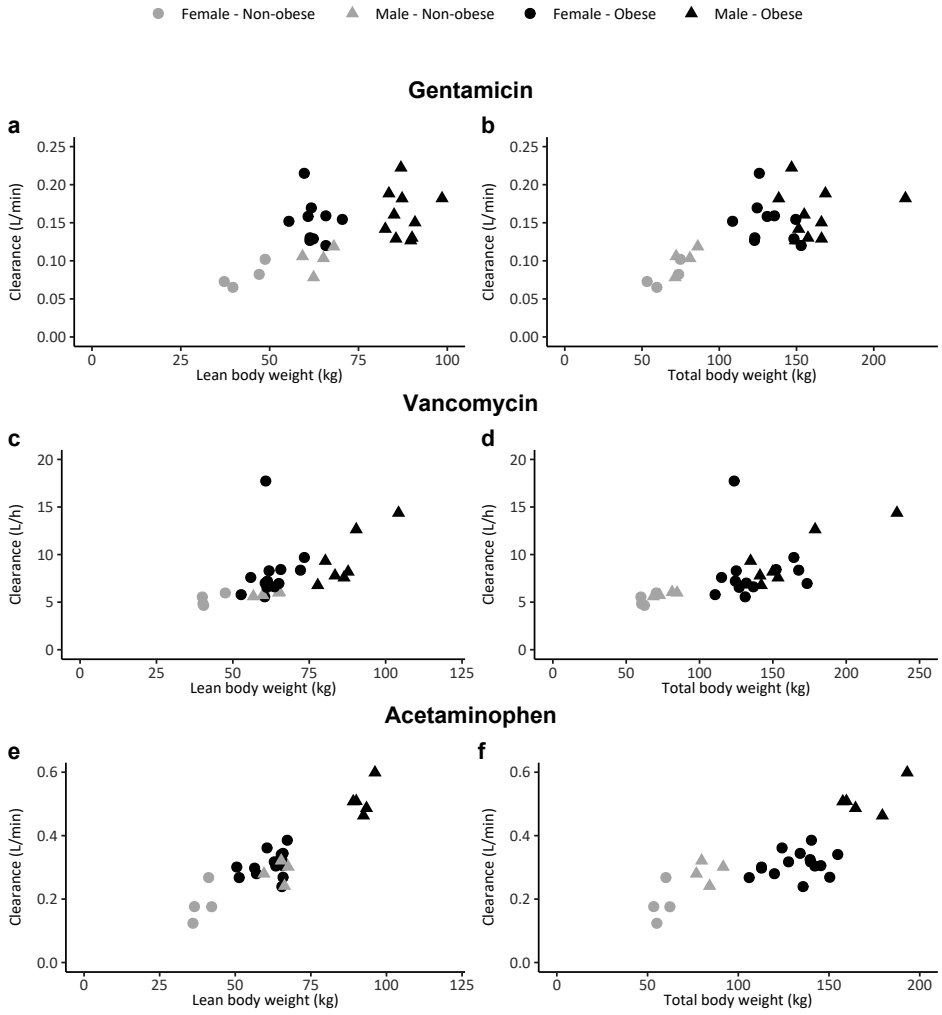

Figure 4. Clearance of gentamicin (Chapter 3), vancomycin (Chapter 5) or acetaminophen (data obtained by Van Rongen et al. [31], with permission) versus lean body weight (a, c, e) or total body weight (b, d, f) for non-obese (grey figures) and morbidly obese individuals (black figures). Females and males are shown in circles and triangles, respectively.

PREDICTING DRUG CLEARANCE OF RENALLY CLEARED DRUGS IN OBESE ADULTS

In clinical practice, assessment of renal function is usually done by estimating glomerular filtration rate (GFR) using serum creatinine-based estimations such as the MDRD [33], CKD-EPI [34] or, in children, the Schwartz equation [35]. These equations produce an estimate of GFR indexed for a standard BSA of 1.73 m^2 to allow for comparison between individuals. In contrast to lean individuals, where this 'indexed' and de-indexed (or absolute) measurements of GFR are not very different [36], indexation in the obese population leads to a significant underestimation of the 'true' value (measured using an isotopic method) [36]. The Cockcroft-Gault (CG) formula, which strictly speaking estimates creatinine clearance instead of GFR, is commonly used in the USA to guide drug dosing. This equation uses total body weight and is expressed as absolute clearance in ml/min, in contrast to CKD-EPI and MDRD. However, also CG was originally developed in a lean population, and was reported to overestimate GFR in obese individuals [37,38]. Over the years, there has been much debate what might be the most accurate method for estimation of renal function in the obese population. Some have advocated de-indexing MDRD or CKD-EPI equations [39–41], while others propose to use CG with a different body size descriptor such as LBW [37,42]. The latter seems the most rational, since serum creatinine is primarily related to muscle mass which, in obesity, might be best described by LBW [30].

Another approach to estimate GFR in obese individuals is by assessing clearance of renally excreted drugs, which is an approach that has been applied before in children and critically ill adults [43–45]. However, many renally excreted drugs are not only cleared trough glomerular filtration, but also undergo active tubular secretion. It is likely that tubular processes are also to a certain extent involved for gentamicin, tobramycin and vancomycin. Therefore, the best method for estimating GFR in the obese may or may not be by estimating clearance of these drugs. Vice-versa, it is not necessarily the 'best' predictor for estimating GFR that can best predict drug clearance in obesity. For this reason, we chose an empirical approach in this thesis for estimating the drug clearance, which is to evaluate several methods, such as using MDRD or CKD-EPI with de-indexation, CG with LBW or by using the measured 24-hour creatinine clearance.

We found for tobramycin (Chapter 5) and gentamicin (Chapter 6) that de-indexed MDRD or CKD outperformed their non-indexed counterparts or the CG equation with LBW. Although CG with LBW might be a good predictor for GFR in obese individuals [37,42], this shows that it is the best predictor for clearance in the renally cleared drugs studied here. One explanation could be that drug clearance might be larger than GFR due to active (renal) processes that are influenced by body weight and resembles the BSA-correction in

de-indexation of MDRD or CKD. This is the most pronounced for gentamicin, based on the fact that for this drug, we found body weight to be best predictive in obese individuals without renal impairment (Chapter 3), which is possibly due to a body weight dependent influence of the renal drug transporter OCT2. Interestingly, a better performance of MDRD or CKD-EPI over CG with LBW in predicting aminoglycoside clearance in an obese population was reported before [14]. In conclusion, the most suitable estimate for renal function to guide drug dosing of renally excreted drugs in obese individuals seems dependent on the drug's particular renal clearance route (passive and/or active). Although we have undertaken the first steps in this thesis in clarifying how the renal clearance route exactly translates to changes in drug clearance with obesity this needs to be further clarified in future studies.

MODEL INFORMED PRECISION DOSING: IMPLEMENTATION OF PHARMACOKINETIC MODELS IN CLINICAL PRACTICE

In this thesis, we characterized the pharmacokinetics of gentamicin, tobramycin and vancomycin in non-obese and morbidly obese healthy volunteers and, for gentamicin and vancomycin, have extended these results to clinical populations of obese adult patients (gentamicin) or obese children and adolescents (vancomycin), with and without renal impairment. With the developed pharmacokinetic models, we have established dose recommendations that can be implemented in daily practice. The next step is the use of this information to support precision dosing in daily clinical practice, a concept known as model-informed precision dosing (MIPD). Recently, an interesting overview of the lessons learned from over 50 years of MIPD was published by many key opinion leaders [46]. In this paper, several challenges regarding adoption of MIPD in healthcare were identified, of which some can be considered relevant for the models developed in this thesis. Here, we will discuss how integration of the results of this thesis in MIPD can be facilitated, what steps were done and where we should focus on in the future.

Within a MIPD framework, the developed pharmacokinetic models can be directly used in daily clinical practice. In this setting, information from real-time monitoring, for example via TDM, is used in conjunction with a population pharmacokinetic model to estimate or forecast individual PK parameters (mostly using Bayesian statistical methods) and aid in optimizing the dose for the individual patient [46]. To facilitate the use of our models in this way, we have collaborated with the developers of the software package MwPharm++ (Mediware a.s, Prague, Czech Republic), to readily include the developed population pharmacokinetic models

in their software. This software package is widely used for MIPD, especially in The Netherlands. However, by publication of the raw model structure in international, peer-reviewed journals, we have ensured that virtually any MIPD software package can implement the developed population PK models.

Another aspects that aids the adoption of the models is an external validation of our results. This means that the predictive performance of the models are tested in a population sample different than the one used for model development and is considered imperative in light of rigor and reproducible science [46]. In this thesis, we have used different sources of data for an external validation. For vancomycin, we have included an external validation using previously published raw data from a different obese population (Chapter 5) [9]. For gentamicin, the performance of the developed model was validated using independent data from a similar population provided by a second hospital (Chapter 6). These validations further strengthen confidence in the obtained results and dose recommendations. For the tobramycin (Chapter 4) and vancomycin (Chapter 5) models, external validations are currently in preparation. An important remark here is that while an external validation is important, dose recommendations or models based on well-designed PK studies that show a substantial, clinically relevant covariate effect but lack an external validation, should still be implemented in clinical practice.

A crucial step in the implementation of study results is the integration of the dose recommendations in leading guidelines. To facilitate this, we have closely collaborated with associations that are responsible for developing guidelines since the first stages of study design. These include the Royal Dutch Society for Pharmacy (KNMP), the Dutch Working Party on Antibiotic Policy (SWAB) and the Dutch Society of Hospital Pharmacists (NVZA). After publication of the results in international peer reviewed journals, the dose recommendations for gentamicin, tobramycin and vancomycin for the adult obese patients have been implemented in the *Informatorium Medicamentorum*, a major knowledge database under redaction of the KNMP which forms the primary source for drug dosing information and medication monitoring for Dutch (hospital) pharmacists and general practitioners. Additional implementation of our recommendations in other leading national and international guidelines will remain a priority in the nearby future.

CONCLUSIONS

The prevalence of obesity in adults and children has dramatically increased over the last decades. It is known that obesity can significantly alter pharmacokinetics of many drugs and as clinicians will increasingly be treating obese patients with antibiotic therapy, we have tried to close some knowledge gaps that exist regarding the pharmacokinetics of three frequently used antibiotics in the obese population. For these drugs, namely gentamicin, tobramycin and vancomycin, we have developed population pharmacokinetic models and proposed straightforward dose recommendations to be used in the obese population. For gentamicin and vancomycin, we have extended these dose recommendations towards the clinical, real-world population of obese adult (gentamicin) and paediatric and adolescent (vancomycin) patients with and without renal impairment.

With the work presented in this thesis we show that the pharmacokinetics of these antibiotics are significantly impacted by obesity. For gentamicin, which we studied in both non-obese, healthy and hospitalized obese individuals with and without renal impairment, we found that clearance increased with body weight and renal function (combined using de-indexed CKD-EPI), and was lower in patients admitted to the ICU. Tobramycin clearance correlated strongest with de-indexed MDRD in (morbidly) obese healthy volunteers with normal renal function. Compared to gentamicin, body weight seems to be of a lesser impact on tobramycin clearance, since we could not identify total body weight as a covariate for clearance in the tobramycin study. The pharmacokinetics of vancomycin were characterized in two special populations, namely morbidly obese and non-obese adults (with normal renal function), and second in lean, overweight and obese hospitalized children and adolescents aged 1 – 18 year with and without renal impairment. For both populations we found that clearance can be predicted using a combination of body weight and renal function. For all studied drugs, volume of distribution consequently increased linearly with total body weight.

Based on these studies we have designed several straightforward dose recommendations to be used in the obese adult, paediatric and adolescent populations. In addition, the studies from this thesis have provided us with some insights regarding pharmacokinetics in obesity. First, our results showed that volume of distribution of the three drugs increases linearly with TBW, which points towards a similar contribution of adipose tissue and lean tissue to drug distribution. Considering that all studied drugs are hydrophilic, our results showed that alterations in volume of distribution in obesity cannot be predicted by lipophilicity alone. Secondly, we discussed the importance of gender when using lean body weight (LBW) as a covariate in pharmacokinetic analyses or as a basis for drug dosing. Thirdly, we have shown that the methods that appear suitable in estimating glomerular filtration in obesity, such as the Cockcroft-Gault equation with LBW, are not necessary the best predictors for clearance of renally cleared drugs.

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