The influence of morbid obesity on the pharmacokinetics and pharmacodynamics of drugs in adolescents and adults

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Summary

Introduction

For most commonly used drugs in morbidly obese patients evidence based dosing guidelines are not available. Therefore, current dosing is based on experience of the prescriber rather than on clinical evidence. Pharmacokinetic and pharmacodynamics data in non-obese patients are extrapolated without proper exploration of influence of overweight on the dose-exposure-effect relationship.

The research described in this thesis focused on two commonly used drugs, propofol and the low-molecular-weight heparin (LMWH) nadroparin with the aim to develop weight appropriate dosing algorithms for these drugs in morbidly obese patients based on population pharmacokinetic and pharmacodynamics analysis. As an introduction to this thesis, in **Chapter 2**, a comprehensive overview is presented of clinical studies that reported on drug clearance estimates in both obese and non-obese patients. Most drug clearance values in obese patients were increased compared to non-obese patients, while clearance values of cytochrome P450 (CYP) 3A4 substrates were lower in obese as compared with non-obese patients. Very limited information was available in obese children.

The influence of morbidly obesity on the pharmacokinetics and pharmacodynamics of propofol in adults, adolescents and children

In **Chapter 3** we described that propofol clearance in morbidly obese adults can be predicted based on total body weight in an allometric function. The clearance of propofol could be predicted for a wide range of total body weights from 55 kg to 167 kg. The scaling factor of 0.72 did not change when the data in morbidly obese patients were combined with data of non-obese adults and proved to be in accordance with results from previous studies in non-obese patients (1, 2). Another aim was to explore the influence of excessive body weight on the pharmacodynamics of propofol anaesthesia

using the Bispectral index (BIS) as pharmacodynamic endpoint. A two-compartment biophase-distribution pharmacodynamic model, similar to a model described in non-obese patients (3-5), described our data well. Redistribution of propofol within the central nervous system was considered the most likely explanation for the observed biphasic distribution process. While the impact of obesity on pharmacodynamics parameters is rather unexplored, there are indications that obesity and related comorbidities can alter the pharmacodynamic response to drugs. For instance, obese patients showed an increased pain sensation as compared to non-obese patients (6). For propofol, we could not show a relationship between obesity and pharmacodynamic effect as none of the tested covariates in our morbidly obese patients significantly improved the pharmacodynamic model fit. The obtained pharmacodynamic parameters in morbidly obese patients were in accordance with previously reported pharmacodynamic parameter estimates of propofol in non-obese patients (3, 7). Therefore, our study provided the first preliminary data to suggest that there are no apparent differences between morbidly obese and non-obese patients in propofol effects as measured by the BIS. Of course, this finding has to be confirmed in a larger cohort and by analysing obese and non-obese pharmacodynamic patient data simultaneously. With the large between and within patient variability and the targeted BIS between 40 and 60 in morbidly obese patients, it is possible that more patient data covering a wider BIS range are needed to capture any influence of excessive body weight on the pharmacodynamics of propofol using the BIS. Based on the final propofol pharmacokinetic pharmacodynamic model, we derived a dosing algorithm for propofol-remifentanil anaesthesia targeting a BIS value of 40. In this model-based dosing algorithm, propofol infusion rates (in mg per kg per hour) are based on the adjusted body weight (according to ABW = 70 kg * (total body weight/70 kg)$^{0.72}$).

In addition to these results, in **Chapter 4** we showed that there are no differences in the individual pharmacokinetic or pharmacodynamic parameter estimates of propofol in morbidly obese patients receiving maintenance propofol-remifentanil or propofol-epidural anaesthesia using BIS values as pharmacodynamic endpoint. For non-obese patients, study results of the influence of remifentanil on propofol requirements are conflicting (8, 9). It cannot be excluded, however, that the exact influence of remifentanil on the level of anaesthesia may not be captured by the BIS. As the pharmacokinetic and pharmacodynamic study described in Chapter 4 was a pilot study in only six morbidly obese patients receiving epidural anaesthesia, the results have to be confirmed in a larger population.

In **Chapter 5** the model based dosing algorithm developed in Chapter 3 was prospectively evaluated in two different hospitals using BIS values as pharmacodynamic endpoint. To our knowledge this is the first study prospectively evaluating a model based dosing algorithm in morbidly obese patients. Fifty-one morbidly obese patients ranging in total body weight from 95 kg to 210 kg received stable and effective maintenance anaesthesia on the basis of BIS, blood pressure and heart rate. However, there were still concerns during the first twenty minutes after the propofol bolus dose as mean blood pressure then dropped more than 30% from pre-operative baseline values. In the study all patients received a fixed bolus dose of 350 mg propofol whereas individualisation of the induction dose might have alleviated some of these concerns. Recently, lean body weight has been suggested as a more appropriate dosing scalar to calculate propofol induction dose for morbidly obese patients and should therefore be considered instead of dose capping (10). Volumes of distribution are often used to calculate the loading dose of a drug resulting in a larger loading dose for a larger volume of distribution. In the pharmacokinetic and pharmacodynamic model derived in Chapter 3, there were no significant covariates to predict the central volume of distribution (V1), as V1 was 4.51 L (SD 13.0) when analysed in morbidly obese patients versus 3.10 L (SD 8.3) when analysed in both non-obese and morbidly obese patients. In our view, this non-significant increase in V1 may be seen as a partial explanation for the drop in blood pressures during the first twenty minutes of anaesthesia described in Chapter 5. However, the concept of a loading dose for drugs that exhibit multi-compartmental pharmacokinetics even in non-obese patients is complex, and therefore the use of V1 as the major determinant of the loading dose may not be justified. Therefore, a well-designed study is needed to determine factors predicting the optimal propofol induction dose in combination with the propofol-remifentanil maintenance dose as described in Chapter 3.

In **Chapter 6** we described the effect of excessive weight on the pharmacokinetics of propofol in children and adolescents. While the prevalence of childhood obesity increased to 17% in 2008 in the US (11), studies providing adequate pharmacokinetic and pharmacodynamic data in these patients are lacking. In accordance with the effect of morbid obesity on the pharmacokinetics of propofol in adults as described in Chapter 3, propofol clearance in morbidly obese children and adolescents proved to scale best with total body weight using an allometric function with an estimated scaling factor of 0.80. These unique results were in accordance with the observed non-linear increase of propofol clearance with total body weight in non-obese children (1, 2, 12). Based on these results, propofol maintenance dose may be based on this non-linear relationship using total body weight. This finding will have to be confirmed using a pharmacodynamic endpoint such as the BIS.

In order to fully characterize the influence of obesity and age, we performed in **Chapter 7** a population pharmacokinetic meta-analysis for propofol on the basis of data from morbidly obese adults, adolescents and children and their non-obese controls. This model was based on data with a wide total body weight range of 37 – 184 kg and an age range of 9 – 79 years. The results showed that total body weight was the most predictive covariate for propofol clearance across all patients when implemented as a power function with a scaling factor of 0.77. Increased blood volume and cardiac output in obese patients may increase liver blood flow (13) and this may explain the observed increase of both propofol clearance and other high extraction drug clearance values such as paclitaxel (14). In addition, age was identified as a significant covariate using a bilinear function with two distinct slopes, reflecting an initial increase and subsequent decrease in clearance depending on age. The potential generalizability of this pharmacokinetic model with total body weight and age as covariates of propofol clearance may increase the applicability of this type of models to scale clearance of other drugs over wide total body weight and age ranges.

Conclusions and recommendations

- The increase in propofol clearance due to obesity in adults, adolescents and children can be described using total body weight as the body size descriptor using an allometric function with a scaling factor of 0.77.
- The pharmacodynamics of propofol as measured by the BIS did not show an effect of excessive body weight in morbidly obese adults. This finding should be confirmed in a combined analysis of data obtained from both non-obese and (morbidly) obese adults, adolescents and children.
- A model based dosing algorithm using an adjusted dosing weight for propofol maintenance infusion was successfully evaluated in a prospective study in morbidly obese adults and can therefore be implemented in daily practice.
- The pharmacokinetic meta-analysis suggests to use a lower propofol maintenance dose in morbidly obese adolescents with the same body weight as morbidly obese adults.

The influence of morbidly obesity on the pharmacodynamics of low molecular weight heparins

As up to now, no dosing guidelines for low-molecular-weight heparins (LMWH) in morbidly obese patients are available, it is recommended to dose adjust based on anticoagulant effect using anti-Xa levels (15). In **Chapter 8** we showed in a morbidly obese patient with pulmonary embolism weighing 252 kg, that effective anti-thrombotic therapy can be achieved using a lower dose based on anti-Xa levels as opposed to the recommended standard units per total body weight dose. The results suggested that the pharmacodynamics of LMWH are influenced by extreme overweight and therefore we investigated current dosing strategies for LMWH dosing and monitoring for (morbidly) obese patients.

We conducted an online and telephone survey as described in **Chapter 9** among Dutch hospitals. Dosing adjustments in obese patients in Dutch hospital were found to differ widely. In the majority of the hospitals, LMWH dose was increased by body weight to a maximum dose based on a cut-off weight value (dosing cap). These cut-off weight values differed widely per institution and were based either on total body weight or BMI. Importantly, monitoring of the LMWH anticoagulant effect in morbidly obese patients using anti-Xa levels was not standard practice in any of the hospitals.

In order to determine the most appropriate dose for LMWH in morbidly obese patients, we investigated the influence of excessive body weight on the nadroparin effect following a bolus dose as described in **Chapter 10**. In morbidly obese patients anti-Xa levels four hours after drug administration strongly correlated with lean body weight. Lean body weight has been proposed previously to estimate the therapeutic dose of enoxaparin another LMWH, in patients weighing more than 100 kg (16). In accordance with the present results, it has been reported that an increase in nadroparin dose did not result in a linear increase in maximum anti-Xa levels four hours after administration in obese patients (17). We showed that lean body weight based dosing correlates well with anti-Xa levels four hours after administration in morbidly obese patients and this method therefore is suggested as a suitable dosing scalar for nadroparin dosing.

In order to fully characterize the influence of excessive body weight on the pharmacodynamics of nadroparin we also measured anti-Xa levels after a bolus dose nadroparin in non-obese patients. Population pharmacodynamic modeling was used to describe the influence of body weight on each individual PD parameter in the model in order to develop a model-based dosing algorithm. In the final pharmacodynamic model for nadroparin described in **Chapter 11** and in accordance with Chapter 10, we showed that in both non-obese and morbidly obese patients lean body weight was the best body size descriptor for the central volume of distribution. In addition, 31% of the variability of clearance between patients could be explained with total body weight as body size descriptor. The pharmacodynamic model was based on a rich anti-Xa sampling schedule in patients over a wide total body weight range from 72 kg to 252 kg. Previous reports on the influence of excessive weight on the pharmacodynamics of other LMWH (enoxaparin,

tinzaparin and dalteparin) showed that obese patients have much higher total drug clearances than non-obese patients (18). For some other renally cleared drugs such as vancomycin, daptomycin and carboplatin it is known that clearance is increased, related to higher glomerular filtration rates in obese patients as described in Chapter 2 (19-21). Renal function is affected by excessive body weight as it has been shown that obese patients have a 62% increase in estimated glomerular filtration rate (22). Therefore, the observed increased clearance values and their association with total body weight are likely due to increased glomerular filtration in (morbidly) obese patients. For LMWH, the central volume of distribution is the parameter of interest as this parameter predominantly determines the maximum anti-Xa level, which is reached around four hours after administration, and for which a therapeutic target for prophylaxis has been defined in non-obese patients (18). LMWH are assumed to mainly distribute over blood and vascular tissues, and plasma volume is known to increase in a non-linear fashion with total body weight (23) and most probably also with lean body weight. Therefore, it has been suggested to guide safe and effective dosing of a LMWH on the basis of lean body weight (16). Although the prophylactic anti-Xa target range is established for non-obese patients and not for morbidly obese patients, this model can be used as a clinically useful starting point until future research identifies alternate anti-Xa targets for safe and effective thromboprophylaxis in this special patient population.

Conclusions and recommendations

- There are large differences in the practice of thromboprophylaxis in morbidly obese surgical patients in Dutch hospitals, and current guidelines lack evidence-based dosing recommendations.
- The central volume of distribution and peak anti-Xa levels correlate with lean body weight, suggesting that lean body weight is clinically useful for nadroparin dosing.
- The developed pharmacodynamic model for nadroparin in non-obese and morbidly obese patients can be used as a starting point to further identify the appropriate anti-Xa targets in morbidly obese patients.

Perspectives

In this thesis the focus was on studying the influence of morbid obesity on the pharmacokinetics and pharmacodynamics of propofol and nadroparin with the goal to develop safe and evidence-based dosing strategies. A non-linear relationship was found between propofol clearance and total body weight in both morbidly obese and non-obese adults, adolescents and children. Furthermore, the influence of age on propofol clearance was described using a bilinear function. For nadroparin in both morbidly obese and non-obese patients, total body clearance increased linearly with total body weight whereas the central of volume distribution increased linearly with lean body weight.

As there is still an unmet clinical need for evidence based dosing algorithms for many commonly used drugs in morbidly obese patients, it should be emphasized that pharmaceutical companies need to be encouraged to start including (morbidly) obese patients in their clinical trials to identify the influence of excessive weight on the pharmacokinetics and pharmacodynamics of drugs and as part of the (early) phases of drug development. In the meantime, continued pharmacokinetic and pharmacodynamics research is desperately needed for most commonly used drugs in the morbidly obese population. These studies should focus on describing the influence of excessive overweight on the pharmacokinetic and pharmacodynamics parameters and include testing of all available body size descriptors. In this thesis, all available body size descriptors were tested and the most statistically significant covariates were incorporated into the final models. These empirical functions were based on model fit of the observed concentrations and observed effects. An alternative way to describe the influence of excessive body weight on pharmacokinetics has been proposed and entails the incorporation of lean body weight for all clearance values of all drugs using one allometric exponent of 0.66 (24). This proposal was based on a meta-analysis of covariate relationships between clearance and body size of a series of different drugs (24). This suggestion is in line with the allometric scaling principles (25). The theory of allometry is based on the empirical observation that over a wide weight range, metabolic rates in animal species increase with body weight to the power of 0.75 (26). While this empirical allometric exponent has no obvious biological or physiological meaning and even for scaling between species, the existence of one unique value for the allometric clearance exponent is widely disputed (27-30). In spite of this, allometry has gained popularity for scaling 'within' a population of a single species, i.e. the human range (25). As obesity is related to body composition and the accumulation of excess body fat, we think that one should be careful in applying the theory of allometry or to use one body size descriptor for all drugs in (morbidly) obese patients. As shown in Chapter 2 of this thesis, not all metabolic activity is increasing with body weight as for instance CYP3A mediated clearance seems to decrease. In order to develop evidence based dosing guidelines for drugs in morbidly obese patients the influence of body weight on each of the pharmacokinetic and pharmacodynamic parameter should be characterized

by testing all available obesity and body size descriptors and be based on the characteristics of a drug. Instead of the common a priori use of total body weight for dosing guidelines, detailed information on pharmacokinetics and potentially also the pharmacodynamics needs to be considered in order to define effective and safe dosing regimens over a large body weight range.
Beside the identification of predictive body size descriptors for variability pharmacokinetic and pharmacodynamic parameters, the final covariate model should be validated and prospectively be evaluated. Before the final model based dosing algorithm is prospectively tested for accuracy as described in Chapter 5, a framework for model evaluation should be used. As shown by a literature review, most pharmacokinetic and pharmacodynamic modeling papers do not adequately describe all available evaluation steps (31). Model misspecification leads to poor predictive performance and could have far-reaching consequences when such pharmacokinetic and pharmacodynamic models are used as a basis for dosing algorithms in obese patients. Therefore, the accuracy of the covariate relationships across the entire range of covariate values should be evaluated during model building. Six evaluation criteria are suggested to be performed and reported during model building using data of (morbidly) obese patients and this is adapted from guidelines for pharmacokinetic and pharmacodynamic modeling in children (32). First, the influence of each covariate on the parameters is examined separately by implementing into exploratory covariate models which are compared with the simple base model (no covariates) using the objective function value. In addition, goodness-of-fit plots are used to evaluate if the model is able to describe the data accurately and without bias. If different data sets are combined, for example non-obese and obese data, goodness-of-fit plots should be generated for each data set separately in order to evaluate if the final covariate model is able to describe the data for the different (sub)groups (33). In order to judge the accuracy of the estimated parameters, confidence intervals or standard errors should be reported. Incorporated covariates need to describe the relationship with the parameter across the entire range of covariate values. Therefore, the eta distribution of the parameter with covariates should be plotted against this covariate. Finally, at least two internal validation steps should be used, e.g. bootstrap (34), visual predictive check (35) and/or normalised prediction distribution errors (36).
The question remains how to further investigate drug dosing in obese patients in the future. As the prevalence of obesity and total body weights of both children and adults are still increasing and as this trend will persist, future studies assessing the impact of morbid obesity on specific drug elimination pathways in both children and adults are warranted. In the traditional pharmacokinetic and pharmacodynamics modeling approaches rather empirical models such as the Hill equation are used to describe in vivo dose-concentration-effect relationships. These equations do not provide insight into physiology or factors determining the concentration-effect relationship. In theory, the relationship between drug concentration and biological response depends on drug and biological system specific factors (37). The classical modeling can ultimately lead to physiological based pharmacokinetic modeling as can be done using software such as the Simcyp software (Simcyp Ltd, UK) (38, 39). Using this software the obesity related (patho)-physiological changes such as for example blood volume, liver blood flow, kidney function and metabolic processes can be incorporated in the model. Furthermore, physicochemical drug properties like the molecular mass, the octanol/water partition coefficient (logP) and the acid dissociation constant (pKa) are taken into account. As data of specific (patho)-physiological processes in (morbidly) obese patients may not all be available, these models currently also rely on assumptions and on in vitro parameters. Therefore, information generated using traditional pharmacokinetic and pharmacodynamic modeling may be of added value to obtain evidence based dosing guidelines and to gain information about the influence of excessive body weight on the pharmacokinetics and pharmacodynamics. However, it is unlikely that thoroughly validated pharmacokinetic covariate models will be developed for every existing drug prescribed for (morbidly) obese patients across the entire weight range. Therefore, more efficient approaches have to be set up to develop safe and effective dosing regimens for this special group of patients. In Chapter 2, we described the current knowledge of the impact of obesity on drug metabolism and elimination and how it differs per drug based on metabolic or elimination pathway. This implies that covariate relationships describing the influence of obesity on the clearance of a specific drug may be extrapolated to other drugs if cleared through the same pathway, which has been described before in children (40, 41). The extrapolation of covariate models between drugs would expedite the development of obesity pharmacokinetic and pharmacodynamics models, which in its turn could help with the individualization of drug dosing in first-in-obese studies and in facilitating the development of evidence-based dosing recommendations for obese patients.

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