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Pharmacokinetics and/or pharmacodynamics of propofol, atracurium and cefazolin in morbidly obese patients

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Chapter 2

**Scope and intent of
the investigations**

The prevalence of obesity is escalating worldwide with percentages for obesity of approximately 35% and for morbid obesity (body mass index (BMI) $\geq 40 \text{ kg m}^{-2}$) as high as 2.8% in men and 6.9% in women [1, 2]. One of the strategies to treat morbid obesity is weight-reducing surgery such as laparoscopic adjustable gastric banding or gastric bypass surgery [112, 113]. During anaesthesia for this type of surgery, morbidly obese patients are administered several drugs peri-operatively as propofol, atracurium and cefazolin. However, it is unknown to what extent the pharmacokinetics and/or -dynamics of these drugs are affected as a result of the physiological changes associated with morbid obesity. In addition, it is unknown at what body weight these changes become relevant, thereby necessitating the need for studies in morbidly obese patients. Particularly in view of the increasing body weights in this special patient group, evidence-based dosing schedules for these drugs in morbidly obese patients should be developed.

Based on the available literature, it can be concluded that limited information is available on peri-operative drugs in morbidly obese patients. The impact of excess body fat on the pharmacokinetics and pharmacodynamics of peri-operative medication is still not quantified. While the degree of obesity varies within the described studies, in general, the studied patients are less obese compared to the population that is currently undergoing bariatric surgery. It is therefore important to evaluate the pharmacokinetics and pharmacodynamics of commonly used drugs during bariatric surgery in order to develop rational dosing guidelines for this special population. Ultimately, these studies will demonstrate if and how the dosage of routinely used drugs peri-operatively should be adjusted in morbidly obese patients.

One of the goals in this thesis was to develop a population pharmacokinetic and pharmacodynamic model of propofol in morbidly obese patients when used for induction and maintenance of anaesthesia administered in combination with remifentanyl. By comparing propofol-remifentanyl anaesthesia with propofol-epidural anaesthesia another aim of this thesis was to evaluate and compare the amounts of propofol necessary to maintain anaesthesia in morbidly obese patients undergoing bariatric surgery.

Another goal of this thesis was to study atracurium when used as neuromuscular blocking agent during induction of anaesthesia in morbidly obese patients by comparing the train-of-four response after two different doses of atracurium, one based on total body weight and the other based on ideal body weight. The time course of atracurium effect and the need to antagonize with neostigmine was evaluated.

Finally, a study was performed to evaluate the pharmacokinetics and protein binding of cefazolin in morbidly obese patients undergoing bariatric surgery, to evaluate the influence of bodyweight measures and age on pharmacokinetic parameters and to evaluate unbound cefazolin concentrations over time in this population. The results of this study can be used – together with local information on the MIC₉₀ of cefazolin for *S. Aureus* – to define what dose of cefazolin is needed for prophylaxis of wound infections in morbidly obese patients.

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