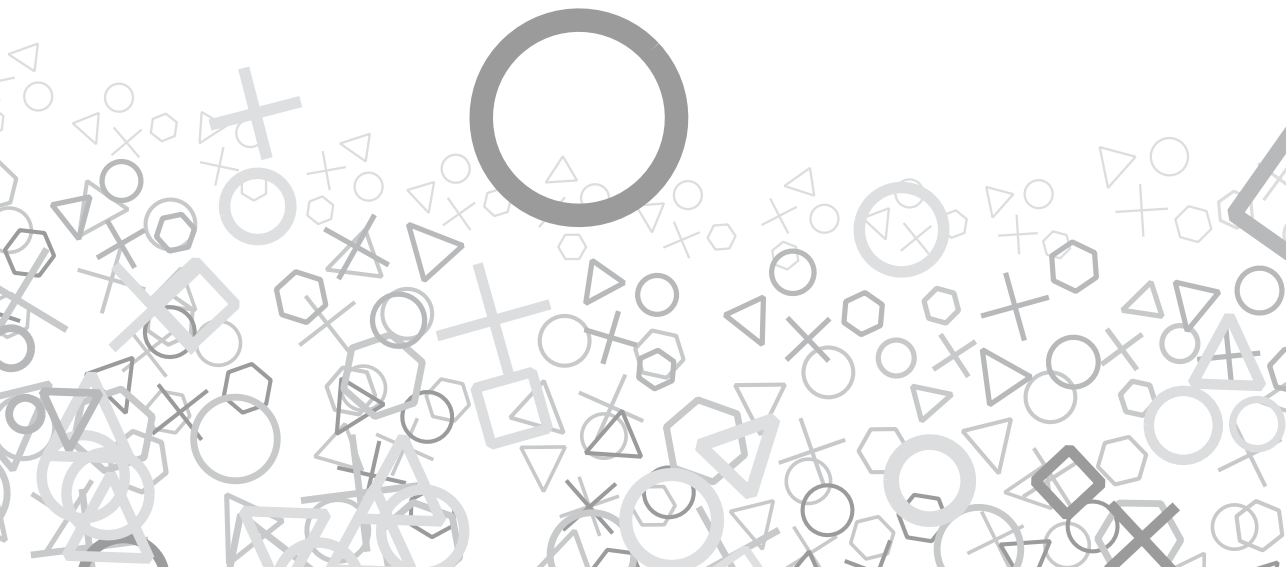
APPENDIX I

Evidence-based dosing recommendations



Based on the results of the studies in this thesis together with other relevant studies currently available in the literature, evidence-based dosing guidelines for morbidly obese patients and in case of midazolam also for bariatric patients can be composed. A dosing advice monograph consists of a discussion of the relevant available literature (evidence) and a proposed dosing advice. Then, these monographs should be discussed by an expert panel consisting of clinical pharmacologists, hospital pharmacists and medical specialists (expert opinion). After finishing this process, the final dosing advice can be included in the Informatorium Medicamentorum of the knowledge center of the Royal Dutch Society for Pharmacy (KNMP), which can be accessed by Dutch pharmacists and physicians. For the drugs studied in this thesis, monographs were prepared and are presented below in a summarized version.

I.1 CEFAZOLIN IN MORBIDLY OBESE PATIENTS

Advice

For prophylaxis in morbidly obese patients (BMI>40 kg/m^2) in the Netherlands, 2 grams of cefazolin will lead to adequate subcutaneous ISF levels for a minimal inhibitory concentration (MIC) of 1 mg/L. Repeat this dose after 4 hours in case the surgical procedures lasts longer than 4 hours. This dosing advice is based on patients with a body weight range of 107 kg tot 175 kg (BMI 40 kg/m^2 tot 57 kg/m^2) [1].

Discussion

This advice is based on Chapter 4 and three other studies on the pharmacokinetics and/or pharmacodynamics of cefazolin in (morbidly) obese patients [1-4]. To evaluate the influence of morbid obesity on cefazolin target site concentrations in Chapter 4 unbound cefazolin concentrations at the interstitial space fluid (ISF) of the subcutaneous adipose tissue were measured using microdialysis. It was found that cefazolin subcutaneous tissue penetration is reduced in morbidly obese patients in comparison to non-obese patients. Using Monte Carlo simulations it was shown that unbound ISF cefazolin will remain above 1 mg/L until 120 minutes post dose in morbidly obese patients (see Figure 4 in Chapter 4). However, in case higher MIC values apply (2 or 4 mg/L), unbound ISF cefazolin concentrations will drop below the MIC values faster than in non-obese patients and redosing or increasing the initial cefazolin dose may be necessary [1].

While it has been suggested before that a dose of 1 gram cefazolin as prophylaxis is inadequate for the prevention of surgical site infections in morbidly obese patients [4], Edmiston *et al.* measured active cefazolin concentrations in 3 patient groups (A=BMI 40-50; B=BMI50-60 en C=BMI>60 kg/m^2) after a cefazolin 2 gram intravenous dose and an additional dose after 3 hours in tissue biopsies at closure of the surgical wound. They

reported that 48.1%, 28.6% en 10.2% of the active cefazolin concentrations of Group A, B and C, respectively, reached an MIC > 8 µg/mg [3]. However, these results cannot be easily extrapolated to the Dutch (and European) situation, while in the Netherlands generally an MIC_{90} of 1 mg/L is considered (MIC at which 90% of all *s. aureus* species is susceptible to cefazolin 1 mg/L). In addition, the American guideline advises a prophylactic cefazolin dose of 2 gram for patients >80 kg and 3 grams for patients >120 kg [5]. This advice is mainly supported by studies applying MIC values of 4 and 8 mg/L and the consideration that cefazolin is inexpensive and well-tolerated. As mentioned before, due to the different MIC values applied, this advice may not be applicable for the Dutch (and European) situation.

In conclusion, based on these studies a 2 gram cefazolin prophylactic dose is sufficient for morbidly obese patients in the Netherlands in case of an MIC of 1 mg/L. As these studies predominantly involved morbidly obese patients, it remains unclear how cefazolin should be dosed in overweight and obese patients.

I.2 MIDAZOLAM IN OBESE AND MORBIDLY OBESE PATIENTS

Advice based on pharmacokinetic considerations only

First of all, midazolam half-life in (morbidly) obese patients strongly increases with body weight, which may cause midazolam effect to last longer. This is particularly important to consider for intravenous administration of midazolam.

- Oral dose administration: Same dose as in non-obese adults (Figure 4 of Chapter 5).
- Intravenous bolus dose: To reach the same maximum concentration as in non-obese health volunteers, for (morbidly) obese patients total body weight should be used (calculate dose based on mg/kg dose * total body weight) for a mg/kg dose that would be used in a non-obese patient, see Figure 1a
- Intravenous continuous infusion: For a morbidly obese patient the body weight of a non-obese individual (i.e. 75 kg) can be used for an mg/kg dose that would be used for non-obese patients. To reach steady state concentration with in approximately 1 hour, higher infusion rates should be applied, see Figure 1b.

Discussion

In addition to the study of Chapter 5, one other study evaluated the pharmacokinetics of midazolam in (morbidly) obese patients after both oral and intravenous administration [7]. In both studies parameters estimates for the obese and non-obese study population, for midazolam central volume of distribution (mean of 44 L *vs* 21 L in Brill *et al.* and 58 L vs 38 L in Greenblatt *et al.*, respectively), total volume of distribution (322 L versus 78 L [6] and 311 L vs 114 L[7]) and systemic clearance (0.36 vs 0.36 L/min [6] and 0.47 vs 0.53 L/

min [7]) were in good agreement. However, the estimates for oral bioavailability (F) differed between the studies. Brill *et al.* found an oral bioavailability of 60% versus 28% ($p<0.001$) and Greenblatt *et al.* of 42% versus 40% ($p>0.05$). This difference may be explained by the studied population, i.e. the mean body weight of the obese population of Greenblatt *et al.* was 117 ± 8 kg (n=20) in comparison to 144 ± 22 kg (n=20) for Brill *et al.*

Due to the substantial increase of volume of distribution with body weight, one should consider a strong increase in the midazolam half-life in (morbidly) obese patients which may cause midazolam effects to last longer than in non-obese patients. The increased half-life also significantly prolongs the time to reach the steady state concentration in (morbidly) obese patients. For this reason, for midazolam continuous infusion, initially higher infusion rates are advised based on dose simulations. For a 145 kg patient, higher infusion rates for a period of 8 hours are proposed to reach the steady state concentration with 1 hour (Figure 1). For non-obese healthy volunteers, a higher infusion rate for the duration of 2 hours is needed to reach steady state concentration within 1 hour.

Finally, it should be noted that the midazolam dosing advice is based on midazolam concentration-time data, while midazolam effects (sedation) have not been included in these studies. Although, no studies have looked into the concentration-effect relationship for midazolam in (morbidly) obese patients, a clear concentration effect relationship has been shown for the general adult and pediatric population [8-9].

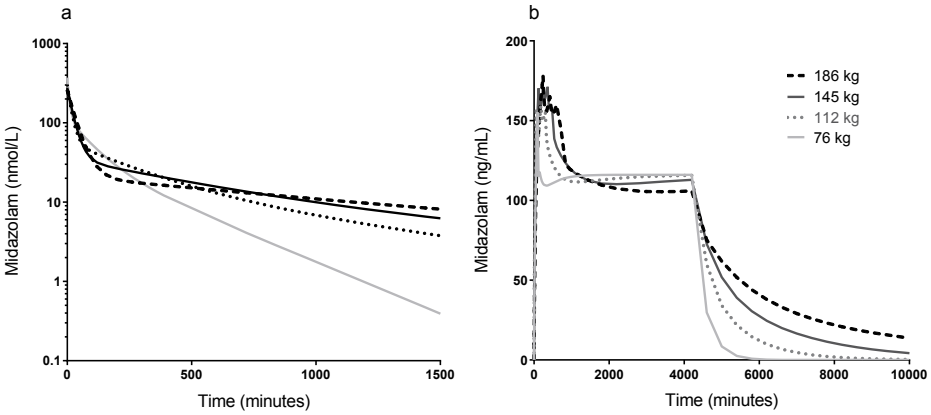


Figure 1 Simulated midazolam concentration time profiles for three morbidly obese patients of 112, 145 and 186 kg and one non-obese healthy volunteer of 76 kg after receiving:
(a) a 0.1 mg/kg total body weight (TBW) intravenous bolus dose (the concentration at T=5 minutes is 247 ng/ml for 76 kg; 236 ng/ml for 112 kg; 233 ng/ml for 145 kg; 229 ng/ml for 186 kg), (b) a continuous intravenous infusion of 2.5 mg/h (0,033 mg/kg/h*75kg) for the duration of 72 hours + a temporarily higher infusion rate to reach the steady state concentration within 1 hour (*76 kg:* 1h 7.5 mg/h, 1h 5 mg/h, 70h 2.5 mg/h; *112 kg*: 1h 15 mg/h, 2h 7.5 mg/h, 2h 5 mg/h, 67h 2.5 mg/h; *145 kg:* 2h 15 mg/h, 2h 10 mg/h, 2h 7.5 mg/h, 2h 5 mg/h, 64h 2.5 mg/h, *186 kg:* 4h 15 mg/h, 3h 10 mg/h, 3h 7.5 mg/h, 2h 5 mg/h, 60h 2.5 mg/h). The simulations have be executed based on the population pharmacokinetic model by Brill *et al.*[6]

I.3 MIDAZOLAM IN GASTRIC BYPASS PATIENTS

Advice based on pharmacokinetic considerations only

- Oral dose administration: The same total dose in mg as in non-obese adults. Be aware of a decreased time to maximum concentration (T_{max}) and increased maximum concentration (C_{max}) in comparison to morbidly obese and matched control patients. In addition, midazolam effect will have shorter duration due to increased midazolam systemic clearance of which the clinical relevance is unclear (see Figure 3 of Chapter 6).
- Intravenous bolus dose: Dose based on mg/kg total body weight (TBW). Be aware of more rapid decrease in effect due to increased midazolam systemic clearance in gastric bypass patients, see Figure 2a.
- Intravenous continuous infusion: To reach a similar steady state concentration as in morbidly obese patients, a higher infusion rate should be applied since the level of the steady state concentration is determined by midazolam clearance (which is increased). In gastric bypass patients midazolam clearance was 1.68 times higher in comparison to morbidly obese and control patients (therefore, calculate the dose based on: mg/kg* 75 kg/hour *1.68), see Figure 2b.

Discussion

Clinical studies into the PK of midazolam show that after a gastric bypass, oral absorption rate is increased, oral bioavailability is similar and systemic clearance substantially increases in comparison to morbidly obese and matched control patients [10-12]. Based on these studies the above midazolam dosing advice is defined. There are several important factors which need to be considered when adjusting the midazolam dose for gastric bypass patients. Firstly, it is important to know exactly what type of bariatric surgery a patient underwent. There are several types of bariatric surgery (as described in the introduction of this thesis) of which each may have a different effect on the PK of midazolam (and thus a different consequence for dosing). The advice defined here is based on studies which predominantly included patients after a Roux- and Y gastric bypass (RYGB). In the study described in Chapter 6 also two gastric sleeve patients were included [10], and therefore potentially, for this group the same midazolam dosing advice may be applied. Secondly, it should be noted that it remains unclear how the pharmacokinetics of midazolam changes over the course of time after a gastric bypass procedure. Possibly, there is a difference in midazolam PK in patients shortly after versus 10 year after a gastric bypass procedure, because some sort of adaption may occur. The studies included in this monograph investigated patients on average 1-1.9 year after a gastric bypass and no further studies are currently available. Finally, this midazolam dosing advice is based on two studies in which midazolam PK was compared with morbidly

obese patients before the surgery [10] and matched control individuals [11]. Until now, no studies have directly compared midazolam PK in gastric bypass patients with non-obese patients or healthy volunteers.

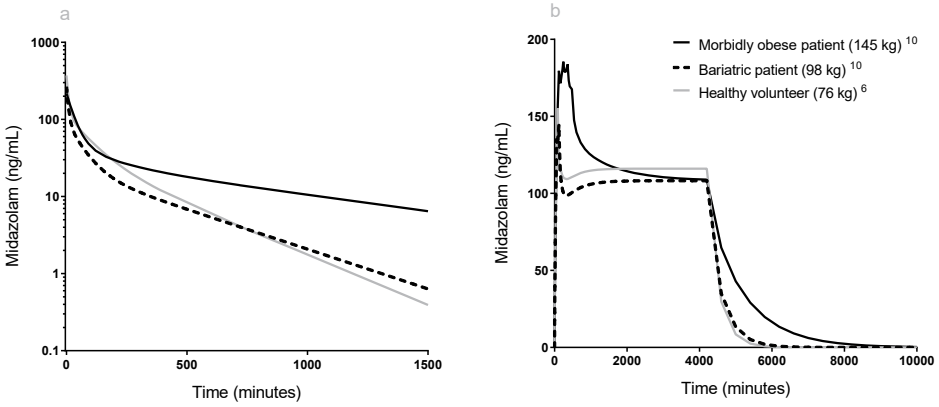


Figure 2 Simulated midazolam concentration-time profiles in a patient after a bariatric surgery, a 145 kg morbidly obese patients [10] and a healthy volunteer (76 kg) [6] after:
(a) an intravenous bolus dose of 0.1 mg/kg (7.5 mg for a healthy volunteer, 14.5 mg for a morbidly obese patients of 145 kg and 9.8 mg/kg for a bariatric patients of 98 kg). At T=5 minutes post dose midazolam concentrations are: 247 ng/ml, 194 ng/ml en 175 ng/ml, respectively. (b) a continuous intravenous infusion during 72 hours with temporarily higher infusion rates to quickly reach steady state concentration. (Bariatric patient: 1h 15 mg/h, 1h 10 mg/h, 70h 4.2 mg/h; healthy volunteer of 76 kg: 1h 7.5 mg/h, 1h 5 mg/h, 70h 2.5 mg/h; morbidly obese patient of 145 kg: 2h 15 mg/h, 2h 10 mg/h, 2h 7.5 mg/h, 2h 5 mg/h, 64h 2.5 mg/h). Simulations have been executed based on the population PK models from Brill *et al.* [6, 10].

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