Midazolam pharmacokinetics following oral and intravenous administration in morbidly obese patients before and 1 year after gastric bypass/sleeve surgery

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INTRODUCTION

• Gastric bypass/sleeve surgery or bariatric surgery is the most successful treatment for morbid obesity (body mass index >40 kg/m^2).
• Both surgery induced weight loss and gastro-intestinal alterations may influence a drugs pharmacokinetics.
• We aimed to quantify the influence of bariatric surgery on oral and intravenous pharmacokinetics of the CYP3A substrate midazolam in patients before and 1 year post bariatric surgery.

METHODS

• 20 morbidly obese patients participated before bariatric surgery and 18 patients [-44.5 kg (21-58 kg)] returned 52 ± 2 weeks post gastric bypass/sleeve surgery (16/2).
• On both occasions, patients received 7.5 mg oral and 5 mg i.v. midazolam separated by 160 ± 50 minutes and 21-23 blood samples per patient were collected until 9-11 h post oral dose.
• Population pharmacokinetic modeling using NONMEM.

Table 1 Patient characteristics

	Morbidly obese Patients (n=20) (range)		Post bariatric surgery patients (n=18) (range)	
Female/Male	12/8		11/7	
Age (years)	43.6 ± 7.6	26 – 57	45.5 ± 7.4	27 – 58
Body weight (kg)	144.4 ± 21.7	112 – 186	98.3 ± 18.0	62 – 138
LBW (kg)*	71.5 ± 11.9	53 – 95	59.5 ± 10.0	39 – 73
BMI (kg/m^2)	47.1 ± 6.5	40 – 68	31.9 ± 5.9	24 – 50

**Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. Quantification of lean bodyweight. Clin Pharmacokinet. 2005;44(10)*

RESULTS

• A three-compartment model with equalized peripheral volumes and a transit absorption model for absorption with transit rates set equal to the absorption rate (Ka=Ktr) was identified.
• Post bariatric surgery, population mean midazolam oral absorption rate and clearance increased substantially, while central and peripheral volume of distribution decreased and oral bioavailability remained unchanged (Fig. 1) in comparison to morbidly obese patients before surgery.
• Midazolam pharmacokinetic parameters from 12 healthy volunteers were added in Figure 1 to facilitate a comparison with patients studied here *(Brill et al. ASCPT PI-115 CPT 95 suppl 1 Mar 2014)*
• Fig. 2 shows dose simulations of the final pharmacokinetic model.

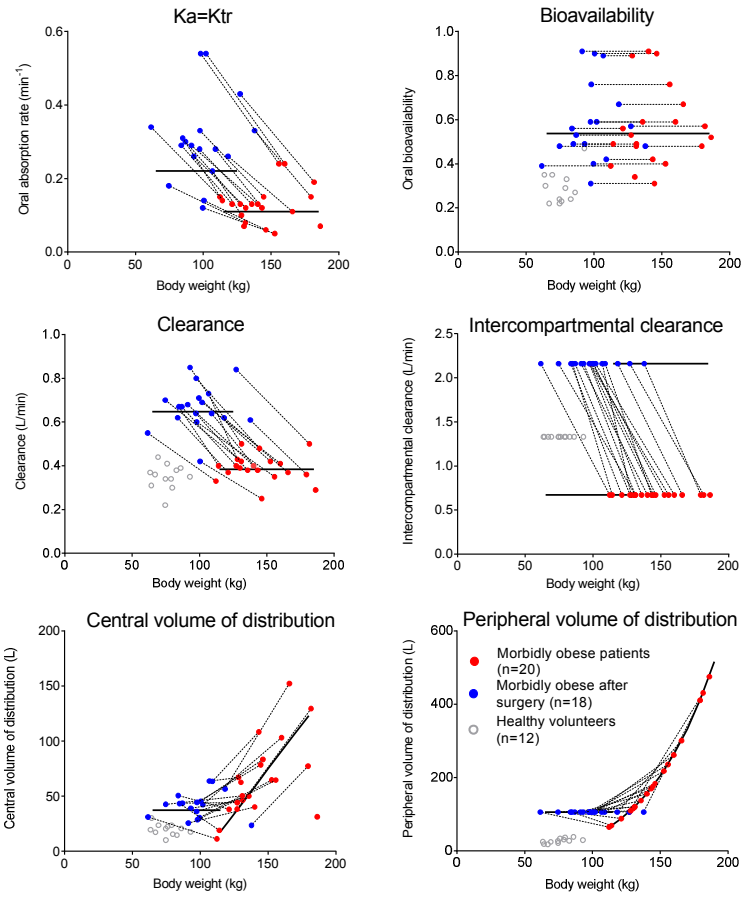

Figure1 Empirical bayes estimates and population parameter values versus body weight (kg) of 20 morbidly obese patients and 18 bariatric patients. In addition, parameter values of 12 healthy volunteers were added for comparison (Brill et al. ASCPT PI-115 Clin Pharmacol Ther 95 suppl 1 Mar 2014).

CONCLUSION

• Oral and i.v. midazolam pharmacokinetics in post bariatric patients revealed higher clearance compared to before bariatric surgery, while oral bioavailability remained unchanged.
• Except for central volume of distribution, midazolam pharmacokinetic parameters found for bariatric patients do not seem to change back to baseline values in healthy volunteers.

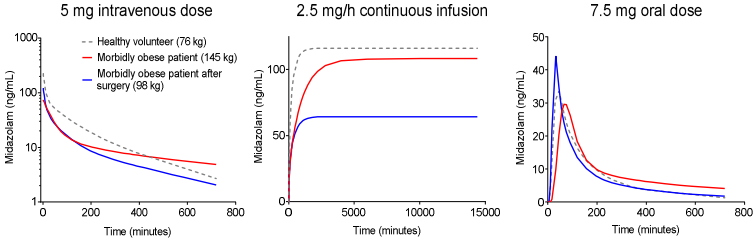

Figure 2 Model-based midazolam concentrations (ng/mL) over time after a 5 mg intravenous bolus dose, a 2.5 mg/h continuous infusion and a 7.5 mg oral dose in a typical morbidly obese patient before and1 year after surgery and of a healthy volunteer (Brill et al. ASCPT PI-115 Clin Pharmacol Ther 95 suppl 1 Mar 2014).

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