



Universiteit  
Leiden  
The Netherlands

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

Kralingen, S. van

### **Citation**

Kralingen, S. van. (2011, June 23). *Pharmacokinetics and/or pharmacodynamics of propofol, atracurium and cefazolin in morbidly obese patients*. Retrieved from <https://hdl.handle.net/1887/17732>

Version: Corrected Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/17732>

**Note:** To cite this publication please use the final published version (if applicable).

# 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)  $\geq 40$  kg m<sup>-2</sup>) 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 MIC<sub>90</sub> of cefazolin for *S. Aureus* – to define what dose of cefazolin is needed for prophylaxis of wound infections in morbidly obese patients.

## References

1. Mathus-Vliegen, E.M., [*Overweight. I. Prevalence and trends*]. Ned Tijdschr Geneeskd, 1998. **142**(36): p. 1982-9.
2. Ogden CL, C.M., Curtin LR, et al., *Prevalence of overweight and obesity in the United States, 1999-2004*. Jama, 2006. **295**: p. 1549-55.
3. Buchwald, H., et al., *Bariatric surgery: a systematic review and meta-analysis*. Jama, 2004. **292**(14): p. 1724-37.
4. Cheymol, G., *Clinical pharmacokinetics of drugs in obesity. An update*. Clin Pharmacokinet, 1993. **25**(2): p. 103-14.
5. Cheymol, G., *Effects of obesity on pharmacokinetics implications for drug therapy*. Clin Pharmacokinet, 2000. **39**(3): p. 215-31.
6. Alexander JK, D.E., Smith WG., *Blood volume, cardiac output and distribution of systemic blood flow in extreme obesity*. Cardiovasc Res Cent Bull, 1962-1963. **1**: p. 39-44.
7. Licata, G., et al., *Effect of obesity on left ventricular function studied by radionuclide angiocardiology*. Int J Obes, 1991. **15**(4): p. 295-302.
8. Herrera, M.F. and M. Deitel, *Cardiac function in massively obese patients and the effect of weight loss*. Can J Surg, 1991. **34**(5): p. 431-4.
9. Lemmens, H.J., D.P. Bernstein, and J.B. Brodsky, *Estimating blood volume in obese and morbidly obese patients*. Obes Surg, 2006. **16**(6): p. 773-6.
10. Crocker, D.W., *Lipomatous infiltrates of the heart*. Arch Pathol Lab Med, 1978. **102**(2): p. 69-72.
11. Bharati, S. and M. Lev, *Cardiac conduction system involvement in sudden death of obese young people*. Am Heart J, 1995. **129**(2): p. 273-81.
12. Yao, A., *Anesthesiology*. 2008: p. 1260.
13. Guzzaloni, G., et al., *Liver steatosis in juvenile obesity: correlations with lipid profile, hepatic biochemical parameters and glycemic and insulinemic responses to an oral glucose tolerance test*. Int J Obes Relat Metab Disord, 2000. **24**(6): p. 772-6.
14. Moretto, M., et al., *Hepatic steatosis in patients undergoing bariatric surgery and its relationship to body mass index and co-morbidities*. Obes Surg, 2003. **13**(4): p. 622-4.
15. Ijaz, S., et al., *Impairment of hepatic microcirculation in fatty liver*. Microcirculation, 2003. **10**(6): p. 447-56.

16. Farrell, G.C., N.C. Teoh, and R.S. McCuskey, *Hepatic microcirculation in fatty liver disease*. Anat Rec (Hoboken), 2008. **291**(6): p. 684-92.
17. Casati, A. and M. Putzu, *Anesthesia in the obese patient: pharmacokinetic considerations*. J Clin Anesth, 2005. **17**(2): p. 134-45.
18. Ribstein, J., G. du Cailar, and A. Mimran, *Combined renal effects of overweight and hypertension*. Hypertension, 1995. **26**(4): p. 610-5.
19. Marik P, V.J., *The obese patient in the ICU*. Chest, 1998. **113**: p. 492-8.
20. Bosma, R.J., et al., *Obesity and renal hemodynamics*. Contrib Nephrol, 2006. **151**: p. 184-202.
21. Snider, R.D., et al., *Accuracy of estimated creatinine clearance in obese patients with stable renal function in the intensive care unit*. Pharmacotherapy, 1995. **15**(6): p. 747-53.
22. O'Donnell, M.P., et al., *Effects of genetic obesity on renal structure and function in the Zucker rat. II. Micropuncture studies*. J Lab Clin Med, 1985. **106**(5): p. 605-10.
23. Kasiske, B.L., et al., *Effects of genetic obesity on renal structure and function in the Zucker rat*. J Lab Clin Med, 1985. **106**(5): p. 598-604.
24. Schmitz, P.G., et al., *Renal injury in obese Zucker rats: glomerular hemodynamic alterations and effects of enalapril*. Am J Physiol, 1992. **263**(3 Pt 2): p. F496-502.
25. Kasiske, B.L. and J.T. Crosson, *Renal disease in patients with massive obesity*. Arch Intern Med, 1986. **146**(6): p. 1105-9.
26. Yao, A., *Anesthesiology*. 2008: p. 1264-1265.
27. Spector, D. and S. Shikora, *Neuro-modulation and bariatric surgery for type 2 diabetes mellitus*. Int J Clin Pract Suppl, (166): p. 53-8.
28. Pories, W.J., et al., *Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus*. Ann Surg, 1995. **222**(3): p. 339-50; discussion 350-2.
29. Schauer, P.R., et al., *Effect of laparoscopic Roux-en Y gastric bypass on type 2 diabetes mellitus*. Ann Surg, 2003. **238**(4): p. 467-84; discussion 84-5.
30. Rubino, F., et al., *The early effect of the Roux-en-Y gastric bypass on hormones involved in body weight regulation and glucose metabolism*. Ann Surg, 2004. **240**(2): p. 236-42.
31. Rubino, F., et al., *The mechanism of diabetes control after gastrointestinal bypass surgery reveals a role of the proximal small intestine in the pathophysiology of type 2 diabetes*. Ann Surg, 2006. **244**(5): p. 741-9.

32. Choban, P.S., et al., *Increased incidence of nosocomial infections in obese surgical patients.* Am Surg, 1995. **61**(11): p. 1001-5.
33. Lesser, G.T. and S. Deutsch, *Measurement of adipose tissue blood flow and perfusion in man by uptake of <sup>85</sup>Kr.* J Appl Physiol, 1967. **23**(5): p. 621-30.
34. Canturk, Z., et al., *Nosocomial infections and obesity in surgical patients.* Obes Res, 2003. **11**(6): p. 769-75.
35. Fleischmann, E., et al., *Tissue oxygenation in obese and non-obese patients during laparoscopy.* Obes Surg, 2005. **15**(6): p. 813-9.
36. Herwaldt, L.A., et al., *Preoperative risk factors for nasal carriage of Staphylococcus aureus.* Infect Control Hosp Epidemiol, 2004. **25**(6): p. 481-4.
37. Fantuzzi, G., *Adipose tissue, adipokines, and inflammation.* J Allergy Clin Immunol, 2005. **115**(5): p. 911-9; quiz 920.
38. Wolf, A.M., et al., *Adiponectin induces the anti-inflammatory cytokines IL-10 and IL-1RA in human leukocytes.* Biochem Biophys Res Commun, 2004. **323**(2): p. 630-5.
39. Wasan, K.M. and G. Lopez-Berestein, *The influence of serum lipoproteins on the pharmacokinetics and pharmacodynamics of lipophilic drugs and drug carriers.* Arch Med Res, 1993. **24**(4): p. 395-401.
40. Derry, C.L., et al., *Pharmacokinetics and pharmacodynamics of triazolam after two intermittent doses in obese and normal-weight men.* J Clin Psychopharmacol, 1995. **15**(3): p. 197-205.
41. Abernethy, D.R., et al., *The influence of obesity on the pharmacokinetics of oral alprazolam and triazolam.* Clin Pharmacokinet, 1984. **9**(2): p. 177-83.
42. Abernethy, D.R. and D.J. Greenblatt, *Phenytoin disposition in obesity. Determination of loading dose.* Arch Neurol, 1985. **42**(5): p. 468-71.
43. Abernethy, D.R. and D.J. Greenblatt, *Pharmacokinetics of drugs in obesity.* Clin Pharmacokinet, 1982. **7**(2): p. 108-24.
44. Abernethy, D.R. and D.J. Greenblatt, *Drug disposition in obese humans. An update.* Clin Pharmacokinet, 1986. **11**(3): p. 199-213.
45. Blouin, R.A., J.H. Kolpek, and H.J. Mann, *Influence of obesity on drug disposition.* Clin Pharm, 1987. **6**(9): p. 706-14.
46. Jung, D., et al., *Thiopental disposition in lean and obese patients undergoing surgery.* Anesthesiology, 1982. **56**(4): p. 269-74.

47. Blouin, R.A. and G.W. Warren, *Pharmacokinetic considerations in obesity*. J Pharm Sci, 1999. **88**(1): p. 1-7.
48. Abernethy, D.R., et al., *Prolonged accumulation of diazepam in obesity*. J Clin Pharmacol, 1983. **23**(8-9): p. 369-76.
49. Abernethy, D.R., D.J. Greenblatt, and T.W. Smith, *Digoxin disposition in obesity: clinical pharmacokinetic investigation*. Am Heart J, 1981. **102**(4): p. 740-4.
50. Christoff, P.B., et al., *Procainamide disposition in obesity*. Drug Intell Clin Pharm, 1983. **17**(7-8): p. 516-22.
51. Benedek, I.H., R.A. Blouin, and P.J. McNamara, *Serum protein binding and the role of increased alpha 1-acid glycoprotein in moderately obese male subjects*. Br J Clin Pharmacol, 1984. **18**(6): p. 941-6.
52. Sneyd, J.R., et al., *A meta-analysis of nausea and vomiting following maintenance of anaesthesia with propofol or inhalational agents*. Eur J Anaesthesiol, 1998. **15**(4): p. 433-45.
53. Longnecker DE, B.D., Newman MF, Zapol WM, *Anesthesiology*. p. 856-9.
54. Morgan EG, M.M., Murray MJ, *clinical anesthesiology*. 2006(4th edition): p. 199.
55. Gin, T., et al., *Pharmacokinetics of propofol in women undergoing elective caesarean section*. Br J Anaesth, 1990. **64**(2): p. 148-53.
56. Cockshott, I.D., et al., *Pharmacokinetics of propofol in female patients. Studies using single bolus injections*. Br J Anaesth, 1987. **59**(9): p. 1103-10.
57. Kay, N.H., et al., *Disposition of propofol in patients undergoing surgery. A comparison in men and women*. Br J Anaesth, 1986. **58**(10): p. 1075-9.
58. Shafer, A., et al., *Pharmacokinetics and pharmacodynamics of propofol infusions during general anesthesia*. Anesthesiology, 1988. **69**(3): p. 348-56.
59. Gepts, E., et al., *Disposition of propofol administered as constant rate intravenous infusions in humans*. Anesth Analg, 1987. **66**(12): p. 1256-63.
60. Schuttler, J. and H. Ihmsen, *Population pharmacokinetics of propofol: a multicenter study*. Anesthesiology, 2000. **92**(3): p. 727-38.
61. Schnider, T.W., et al., *The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers*. Anesthesiology, 1998. **88**(5): p. 1170-82.
62. Dawidowicz, A.L., et al., *The role of human lungs in the biotransformation of propofol*. Anesthesiology, 2000. **93**(4): p. 992-7.

63. [http://www.medscape.com/viewarticle/410903\\_3](http://www.medscape.com/viewarticle/410903_3).
64. Simons, P.J., et al., *Disposition in male volunteers of a subanaesthetic intravenous dose of an oil in water emulsion of <sup>14</sup>C-propofol*. *Xenobiotica*, 1988. **18**(4): p. 429-40.
65. Bryson, H.M., B.R. Fulton, and D. Faulds, *Propofol. An update of its use in anaesthesia and conscious sedation*. *Drugs*, 1995. **50**(3): p. 513-59.
66. Gillies, G.W. and N.W. Lees, *The effects of speed of injection on induction with propofol. A comparison with etomidate*. *Anaesthesia*, 1989. **44**(5): p. 386-8.
67. Kobayashi, Y., et al., *[Effects of speed of injection on anesthesia induction with propofol and fentanyl]*. *Masui*, 1999. **48**(8): p. 847-51.
68. Rolly, G., et al., *Effect of speed of injection on induction of anaesthesia using propofol*. *Br J Anaesth*, 1985. **57**(8): p. 743-6.
69. Peduto, V.A., et al., *Biochemical and electrophysiologic evidence that propofol enhances GABAergic transmission in the rat brain*. *Anesthesiology*, 1991. **75**(6): p. 1000-9.
70. Frenkel, C. and B.W. Urban, *Human brain sodium channels as one of the molecular target sites for the new intravenous anaesthetic propofol (2,6-diisopropylphenol)*. *Eur J Pharmacol*, 1991. **208**(1): p. 75-9.
71. Ickx, B., et al., *Propofol infusion for induction and maintenance of anaesthesia in patients with end-stage renal disease*. *Br J Anaesth*, 1998. **81**(6): p. 854-60.
72. Nathan, N., et al., *Pharmacokinetics of propofol and its conjugates after continuous infusion in normal and in renal failure patients: a preliminary study*. *Acta Anaesthesiol Belg*, 1993. **44**(3): p. 77-85.
73. Grounds, R.M., et al., *The haemodynamic effects of intravenous induction. Comparison of the effects of thiopentone and propofol*. *Anaesthesia*, 1985. **40**(8): p. 735-40.
74. Aitkenhead, A.R., et al., *Comparison of propofol and midazolam for sedation in critically ill patients*. *Lancet*, 1989. **2**(8665): p. 704-9.
75. Ronan, K.P., et al., *Comparison of propofol and midazolam for sedation in intensive care unit patients*. *Crit Care Med*, 1995. **23**(2): p. 286-93.
76. Schnider, T.W., et al., *The influence of age on propofol pharmacodynamics*. *Anesthesiology*, 1999. **90**(6): p. 1502-16.
77. Peeters, M.Y., et al., *Disease severity is a major determinant for the pharmacodynamics of propofol in critically ill patients*. *Clin Pharmacol Ther*, 2008. **83**(3): p. 443-51.

78. Bouillon, T.W., et al., *Pharmacodynamic interaction between propofol and remifentanyl regarding hypnosis, tolerance of laryngoscopy, bispectral index, and electroencephalographic approximate entropy*. *Anesthesiology*, 2004. **100**(6): p. 1353-72.
79. Bouillon, T., et al., *Non-steady state analysis of the pharmacokinetic interaction between propofol and remifentanyl*. *Anesthesiology*, 2002. **97**(6): p. 1350-62.
80. Strachan, A.N. and N.D. Edwards, *Randomized placebo-controlled trial to assess the effect of remifentanyl and propofol on bispectral index and sedation*. *Br J Anaesth*, 2000. **84**(4): p. 489-90.
81. Koitabashi, T., J.W. Johansen, and P.S. Sebel, *Remifentanyl dose/electroencephalogram bispectral response during combined propofol/regional anesthesia*. *Anesth Analg*, 2002. **94**(6): p. 1530-3, table of contents.
82. Ferreira, D.A., et al., *The effect of a remifentanyl bolus on the bispectral index of the EEG (BIS) in anaesthetized patients independently from intubation and surgical stimuli*. *Eur J Anaesthesiol*, 2006. **23**(4): p. 305-10.
83. Guignard, B., et al., *The effect of remifentanyl on the bispectral index change and hemodynamic responses after orotracheal intubation*. *Anesth Analg*, 2000. **90**(1): p. 161-7.
84. Wang, L.P., et al., *Low and moderate remifentanyl infusion rates do not alter target-controlled infusion propofol concentrations necessary to maintain anesthesia as assessed by bispectral index monitoring*. *Anesth Analg*, 2007. **104**(2): p. 325-31.
85. Lysakowski, C., et al., *Effects of fentanyl, alfentanil, remifentanyl and sufentanil on loss of consciousness and bispectral index during propofol induction of anaesthesia*. *Br J Anaesth*, 2001. **86**(4): p. 523-7.
86. de Baerdemaeker LEC, M.E., Struys MMRF, *Pharmacokinetics in obese patients. Continuing education in anaesthesia, critical care and pain*. 2004. **4**(5).
87. Kanto, J. and E. Gepts, *Pharmacokinetic implications for the clinical use of propofol*. *Clin Pharmacokinet*, 1989. **17**(5): p. 308-26.
88. Kurita, T., et al., *Influence of cardiac output on plasma propofol concentrations during constant infusion in swine*. *Anesthesiology*, 2002. **96**(6): p. 1498-503.
89. Lemmens, H.J. and J.B. Brodsky, *Anesthetic drugs and bariatric surgery*. *Expert Rev Neurother*, 2006. **6**(7): p. 1107-13.
90. Servin, F., et al., *Propofol infusion for maintenance of anesthesia in morbidly obese patients receiving nitrous oxide. A clinical and pharmacokinetic study*. *Anesthesiology*, 1993. **78**(4): p. 657-65.

91. Albertin, A., et al., *Predictive performance of 'Servin's formula' during BIS-guided propofol-remifentanyl target-controlled infusion in morbidly obese patients*. Br J Anaesth, 2007. **98**(1): p. 66-75.
92. La Colla, L., et al., *No adjustment vs. adjustment formula as input weight for propofol target-controlled infusion in morbidly obese patients*. Eur J Anaesthesiol, 2009. **26**(5): p. 362-9.
93. Hughes, R. and D.J. Chapple, *The pharmacology of atracurium: a new competitive neuromuscular blocking agent*. Br J Anaesth, 1981. **53**(1): p. 31-44.
94. <http://db.cbg-meb.nl/IB-teksten/h16532.pdf>. IB-tekst.
95. Scott, R.P., et al., *Atracurium: clinical strategies for preventing histamine release and attenuating the haemodynamic response*. Br J Anaesth, 1985. **57**(6): p. 550-3.
96. Ogunnaike, B.O., et al., *Anesthetic considerations for bariatric surgery*. Anesth Analg, 2002. **95**(6): p. 1793-805.
97. Beemer, G.H., A.R. Bjorksten, and D.P. Crankshaw, *Effect of body build on the clearance of atracurium: implication for drug dosing*. Anesth Analg, 1993. **76**(6): p. 1296-303.
98. Varin, F., et al., *Influence of extreme obesity on the body disposition and neuromuscular blocking effect of atracurium*. Clin Pharmacol Ther, 1990. **48**(1): p. 18-25.
99. Kirkegaard-Nielsen, H., et al., *Anthropometric variables as predictors for duration of action of atracurium-induced neuromuscular block*. Anesth Analg, 1996. **83**(5): p. 1076-80.
100. Weinstein, J.A., et al., *Pharmacodynamics of vecuronium and atracurium in the obese surgical patient*. Anesth Analg, 1988. **67**(12): p. 1149-53.
101. [www.fk.cvz.nl](http://www.fk.cvz.nl). farmacotherapeutisch Kompas.
102. Kahlmeter G, B.D., Canton R, et al.; EUCAST. *The European committee on antimicrobial susceptibility testing*. Available online at: <https://www.eucast.org>. Assessed July 10th, 2010.
103. Pories, W.J., et al., *Prophylactic cefazolin in gastric bypass surgery*. Surgery, 1981. **90**(2): p. 426-32.
104. Forse, R.A., et al., *Antibiotic prophylaxis for surgery in morbidly obese patients*. Surgery, 1989. **106**(4): p. 750-6; discussion 756-7.
105. Edmiston, C.E., et al., *Perioperative antibiotic prophylaxis in the gastric bypass patient: do we achieve therapeutic levels?* Surgery, 2004. **136**(4): p. 738-47.
106. Falagas, M.E. and D.E. Karageorgopoulos, *Adjustment of dosing of antimicrobial agents for bodyweight in adults*. Lancet. **375**(9710): p. 248-51.

107. Hollenstein, U.M., et al., *Soft tissue concentrations of ciprofloxacin in obese and lean subjects following weight-adjusted dosing*. *Int J Obes Relat Metab Disord*, 2001. **25**(3): p. 354-8.
108. Bergan, T., A. Engeset, and W. Olszewski, *Does serum protein binding inhibit tissue penetration of antibiotics?* *Rev Infect Dis*, 1987. **9**(4): p. 713-8.
109. Foord, R.D., *Cefuroxime: human pharmacokinetics*. *Antimicrob Agents Chemother*, 1976. **9**(5): p. 741-7.
110. Lister, P.D. and C.C. Sanders, *Pharmacodynamics of trovafloxacin, ofloxacin, and ciprofloxacin against Streptococcus pneumoniae in an in vitro pharmacokinetic model*. *Antimicrob Agents Chemother*, 1999. **43**(5): p. 1118-23.
111. Singhvi, S.M., et al., *Human serum protein binding of cephalosporin antibiotics in vitro*. *J Lab Clin Med*, 1977. **89**(2): p. 414-20.
112. Greve, J.W., I.M. Janssen, and B. van Ramshorst, *[Gastric reduction in morbidly obese adults in the Netherlands]*. *Ned Tijdschr Geneeskd*, 2007. **151**(20): p. 1116-20.
113. DeMaria, E.J., *Bariatric surgery for morbid obesity*. *N Engl J Med*, 2007. **356**(21): p. 2176-83.

