Population pharmacokinetics of cefazolin in morbidly obese patients upon a prophylactic dose of 2 gram for weight reducing surgery

Margreke J.E. Brill[1], Simone van Kralingen[2], Eric P.A. van Dongen[2], René J. Wiezer[3], Bert van Ramshorst[3], Catherijne A.J. Knibbe[1,4]

[1] Department of Clinical Pharmacy; [2] Department of Anaesthesiology and Intensive Care; [3] Department of Surgery, St. Antonius Hospital, Nieuwegein, The Netherlands; [4] Division of Pharmacology, Leiden/ Amsterdam Center for Drug Research, Leiden University, Leiden, The Netherlands.

OBJECTIVES

Morbid obesity is an independent risk factor for the development of surgical site infections. Before weight reducing surgery an i.v. dose of cefazolin 2 gram is given for prophylaxis of surgical site infections. In this study we aimed to investigate the population pharmacokinetics of cefazolin in morbidly obese patients undergoing weight reducing surgery.

METHODS

At induction of anesthesia morbidly obese patients received an i.v. dose of cefazolin 2 gram. Blood samples were drawn at T=0, 5, 10, 30, 60, 120, 180 and 240 min after dosing and were analyzed using HPLC-UV. Cefazolin plasma concentrations were modelled using NONMEM VI and S-PLUS. A step-wise covariate analysis was performed to identify the influence of total body weight, lean body weight, ideal body weight, body mass index (BMI), age, sex, creatinine and bilirubin on the pharmacokinetics of cefazolin.

Table 1 Step-wise covariate analysis.

Model	Model definition	Objective function	Parameters (n)	Drop in OBF	Inter-individual variability V1 (%)	Inter-individual variability CL (%)
Simple	V1, V2, CL, Q, η(V1), η(CL)	809.7	6	-	21.7	28.4
LBW on CL	CL= θ(3)*(1+ θ(5)*(BW-66.5))	808.4	7	-1.3*	21.7	27.4
TBW on CL	CL= θ(3)*(1+ θ(5)*(TBW-144))	807.3	7	-2.4*	21.7	26.6
AGE op CL	CL= θ(3)*(1+ θ(5)*(AGE-48))	802.8	7	-6.9*	21.6	23.6
CREAT on CL	CL= θ(3)*(1+ θ(5)*(CREAT-63))	800.9	7	-8.8*	21.6	22.4
BMI on V1	V1= θ(1)*(BMI/45.7)$^{\theta(5)}$	802.3	7	-7.4*	17.3	28.4
LBW on V1	V1= θ(1)*(LBW/66.5)$^{\theta(5)}$	799.2	7	-10.5*	15.8	28.4
TBW on V1	**V1= θ(1)*(1+θ(5)*(TBW-144))**	**792.4**	**7**	**-17.3***	**12.4**	**28.3**
TBW on V1 and CREAT on CL	V1= θ(1)* (1+ θ(5)*(WT-144)) CL= θ(3)*(1+ θ(6)*(CREAT-63))	783.4	8	-26.3*	12.2	22.2
TBW on V1 and AGE on CL	**V1= θ(1)* (1+ θ(5)*(WT-144)) CL= θ(3)*(1+ θ(6)*(AGE-48))**	**785.3**	**8**	**-24.3***	**12.3**	**23.4**

*TBW= Total body weight (kg), LBW= lean body weight (kg), BMI= body mass index (kg/m2), CREAT= creatinine (mol/L), AGE= age (years), V1= volume of distribution of central compartment (L), CL= clearance (L/min), OBF= Objective function (-2 Log Likelihood). * Compared to simple model.*

Figure 1 Posthoc central volume of distribution values versus total body weight (A), body mass index (B), lean body weight (C), and posthoc clearance values versus age (D), creatinine (E) and total body weight (F) for the simple two compartment pharmacokinetic model for cefazolin concentrations in 20 morbidly obese patients.

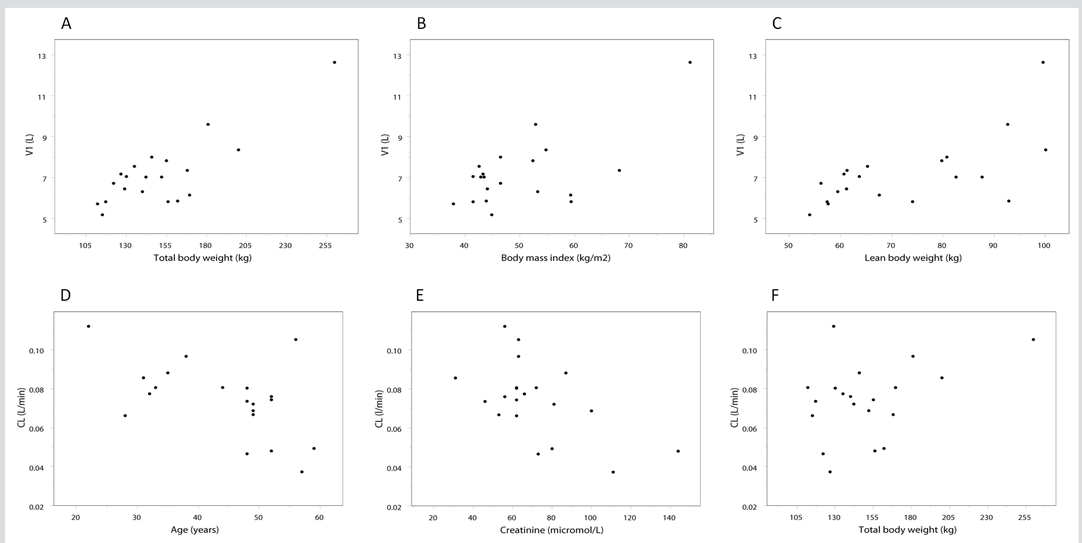

Figure 2 Diagnostic plots of the final two compartment model of cefazolin in morbidly obese patients: individual predicted concentrations versus observed concentrations (A), population predicted concentrations versus observed concentrations (B), time versus conditional weighted residuals (C) and population predicted concentrations versus conditional weighted residuals (D).

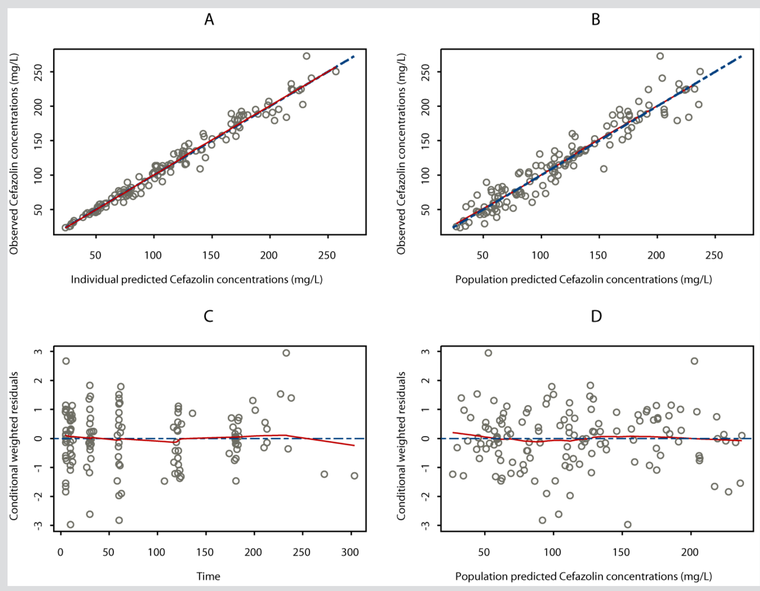

Table 2 Population pharmacokinetic parameters and their bootstrap values for the simple and final pharmacokinetic model for cefazolin in twenty morbidly obese patients.

Parameter	Simple model estimates (CV%)	Final model estimates (CV%)	Bootstrap final model estimates (stability %) (500/500 successful)
Fixed effects			
V1 (L)	7.03 (7.8)	6.84 (9.1)	6.80 (100)
V2 (L)	5.76 (10.9)	5.78 (10.4)	5.81 (99)
Cl (mL/min)	76.1 (6.6)	68.0 (6.5)	68.3 (100)
Q (mL/min)	449 (17.7)	450 (16.3)	450 (100)
Θ(5)*	-	0.0058 (24.5)	0.0055 (105)
Θ(6)*	-	-0.017 (43.5)	-0.017 (99)
Inter-individual variability			
V1 (%)	21.7 (58.3)	12.3 (42.3)	12.2 (102)
CL (%)	28.4 (35.8)	23.4 (37.8)	22.1 (112)
Residual proportional error			
σ (%)	8.4 (16.2)	8.5 (16.2)	8.3 (103)
Objective function (-2LL)	809.7	785.3	775.4 (101)

CV= coefficient of variation, -2LL= -2 log likelihood, V1= volume of distribution of central compartment (L), CL= clearance (L/min), Θ(5)= linear scaling factor for total body weight on V1, Θ(6)= linear scaling factor for age on CL.

RESULTS

Twenty morbidly obese patients with a median total body weight of 144 kg (range 112-252), a median BMI of 51 kg/m2 (range 38-79), a median age of 48 years (range 22-59) and a median creatinine of 63 mol/L (range 31-144) were included in the study. In a two compartment model (ADVAN 3 TRANS 4) total body weight proved the most predictive covariate for central volume of distribution (linearly centred) with inter-individual variability decreasing from 21.7% to 12.4% ($p < 0.001$, Table 1). Age or creatinine as a covariate for clearance implemented in a linear fashion further improved the model and reduced inter-individual variability for clearance from 28.4% to 23.4% ($p < 0.01$) or 22.4% ($p < 0.01$), respectively (Table 1 and Figure 1). Final results are shown in Table 2 and Figure 2.

CONCLUSION

We developed a two compartment pharmacokinetic model for cefazolin in morbidly obese patients in which total body weight and age or creatinine proved to be the major determinants for respectively central volume of distribution and clearance. Plasma concentrations profiles in lean patients are awaited to confirm the currently observed covariate relations for the pharmacokinetic parameters of cefazolin.