

Population pharmacokinetic model for protein binding and subcutaneous adipose tissue distribution of cefazolin in morbidly obese and non-obese patients

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OBJECTIVES

As morbidly obese patients are prone to surgical site infections, adequate blood and subcutaneous tissue concentrations of prophylactic antibiotic agent during surgery are imperative. In this study, we aimed to investigate the pharmacokinetics of cefazolin, in particular regarding protein binding and subcutaneous adipose tissue distribution in morbidly obese patients and non-obese patients.

Table 1 Patient characteristics, mean ± standard deviation and range.

	Morbidly obese	Range (min– max)	Non-obese	Range (min– max)
Male : Female	1/7		4/3	
Age (years)	40.1 ± 5.5	[32 -48]	53.7 ± 6.3	[42 - 61]
Body weight (kg)	140.4 ± 23	[107 -175]	86.2 ± 13	[72 - 109]
Lean body weight (kg)	75.2 ± 8.5	[64 - 89]	55.5 ± 5.7	[48 - 62]
BMI (kg/m2)	47.0 ± 5.8	[41 - 57]	28.2 ± 2.8	[24 - 31]
Duration surgery (min)	63.5 ± 12	[51 - 86]	59.6 ± 19	[39 - 92]

METHODS

Eight morbidly obese patients, of which seven were eligible for inclusion (body mass index [BMI] of 47 ± 6 kg/m2), and seven non-obese patients (BMI of 28 ± 3 kg/m2) received cefazolin 2 gram i.v. before surgery. Using microdialysis, interstitial space fluid (ISF) samples of the subcutaneous adipose tissue were collected until 240 minutes after dosing together with total and unbound serum cefazolin samples. Population pharmacokinetic modeling and covariate analysis characterizing the influence of body weight and other covariates was performed using NONMEM VI.

Table 2 Population pharmacokinetic parameters for the simple and final cefazolin pharmacokinetic model in morbidly obese and non-obese patients.

Parameters	Base model [CV%]	Final model [CV%]	Bootstrap [CV%]	Deviation [%]
CL= CL _{pop} * [AGE/47] ⁻¹				
CL _{pop} [L/min]	0.384 [7.5]	0.371 [5.7]	0.371 [5.5]	0.1
V1= V _{pop} * [1+Y* [TBW-109]]				
V _{pop}	8.79 [5.1]	8.94 [3.0]	8.97 [3.1]	-0.4
Y	-	0.0052 [18.0]	0.0051 [21.5]	2.4
V2 [L]	8.1 [8.9]	8.31 [7.8]	8.36 [7.6]	-0.6
Bmax [μM]	530 [7.8]	469 [7.3]	471 [7.6]	-0.3
Kd [μM]	81.2 [11.4]	71.3 [10.9]	71.7 [11.2]	-0.6
Gam= Gam _{pop} * [TBW/109] ²				
Gam _{pop} [or: Y _{pop}]	1 fixed	1 fixed	1 fixed	-
Z	-	-0.0946 [-27.6]	-0.0895 [-34.2]	5.4
Interindividual variability [%]				
CL	31.2 [28.1]	22.6 [31.6]	21.5 [32.9]	9.1
Bmax	20.6 [41.6]	11.6 [33.4]	10.8 [41.4]	13.3
Gamma	3.9 [28.9]	2.8 [50.4]	2.7 [53.2]	7.1
Proportional intraindividual error [%]				
Total and unbound serum	13.1 [18.2]	10.0 [22.2]	9.7 [22.1]	4.8
Subcutaneous ISF	16.5 [19.9]	17.0 [19.7]	16.7 [19.5]	3.5
OFV	1260.5	1166.5	1142.0 [9.7]	2.1

Bmax= maximal binding capacity, CL= Clearance [L/min], CV= coefficient of variation [%], Gam= gamma or Y factor on cefazolin amount going from central to subcutaneous compartment, Kd= dissociation constant for cefazolin protein binding to albumin, OFV= Objective function value (-2LL), TBW= total body weight, V1= central volume of distribution [L], V2= subcutaneous interstitial space fluid volume of distribution [L]

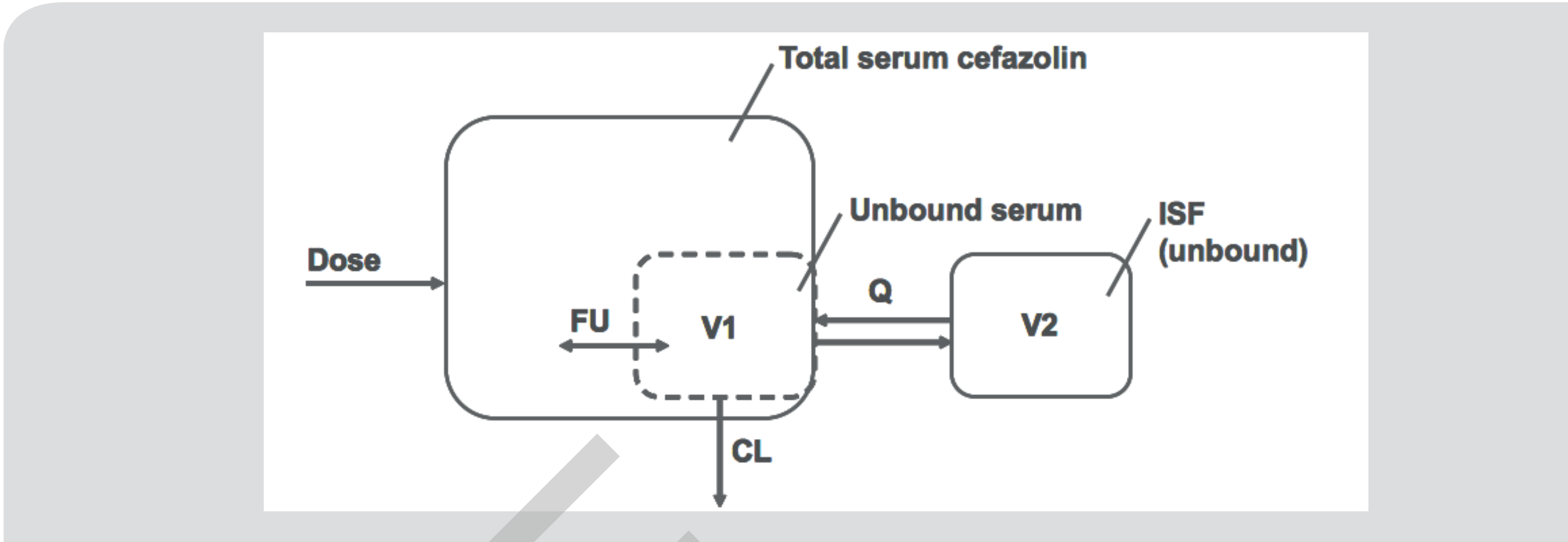


Figure 1. Schematic illustration of the population pharmacokinetic model of cefazolin. The lines indicate the type of observed data used for the compartment. CL= Clearance, FU= Fraction unbound (Bmax, Kd see equation 1), ISF= interstitial space fluid, Q= Intercompartmental clearance, V1= Volume of distribution of central compartment, V2= Volume of distribution of subcutaneous compartment.”

RESULTS

A two compartment model with saturable protein binding [equation 1] best described the data (Figure 1). Total body weight was a covariate for central volume of distribution, V1, [P<0.001] and cefazolin distribution to subcutaneous compartment, which was defined by a power factor (gamma, Y) on the cefazolin amount going from V1 to V2 [P<0.01, equation 2]. Goodness of fit plots showed equal distribution around the line of identity and no trends. Monte Carlo simulations illustrate the influence of body weight on cefazolin unbound serum and subcutaneous ISF concentrations (Figure 2).

$$FU = (C_{total} - Bmax - Kd) + \sqrt{(C_{total} - Bmax - Kd)^2 + 4 \cdot Kd \cdot C_{total}} \quad \text{(Equation 1)}$$

$$\Delta A1 / \Delta t = -k_{12} \cdot A1^Y \cdot FU - K_{10} \cdot A1 \cdot FU + K_{21} \cdot A2 \quad \text{(Equation 2)}$$

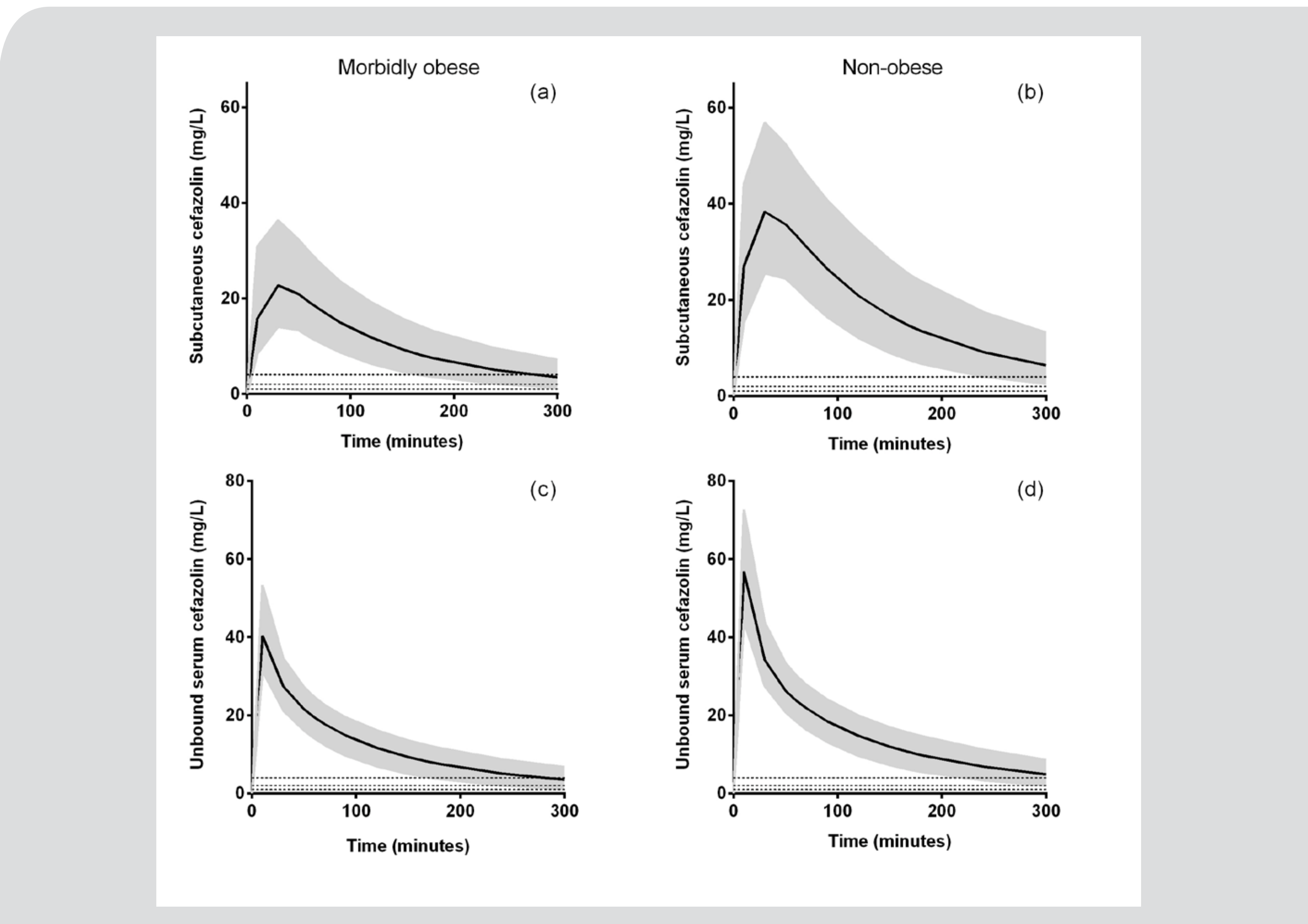


Figure 2. Mean and 90% confidence interval of unbound subcutaneous (a and b) and unbound serum concentrations (c and d) of 1000 Monte Carlo simulated morbidly obese (a and c) and 1000 non-obese patients (b and d).

CONCLUSIONS

A population pharmacokinetic model for cefazolin in morbidly obese and non obese patients was derived with a saturable protein binding model for cefazolin in serum and a body weight dependent distribution to the subcutaneous adipose tissue.