Evaluation of body weight descriptors in modeling of cefoxitin and cefazolin pharmacokinetics in the normal and obese populations

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Objectives: The estimated prevalence of overweight and obese individuals >20 years in the US is 154.7 million (nearly double since the early 1960s). Our previous study and other works indicate that current antibiotic dosing strategies result in inadequate tissue concentration of antibiotics in obese patients.¹² The overall goal is to develop approaches for optimization of antibiotic dosing in the obese population. Specifically, we have investigated the relationship between the pharmacokinetic parameters of two cephalosporin antibiotics and several body weight descriptors of obese and normal-weight patients.

Methods: Plasma concentration-time profiles of cefoxitin and cefazolin in normal-weight, overweight, and obese subjects were extracted from published studies. Two- and three-compartment models were constructed and evaluated. The volume of the central compartment and the peripheral compartment(s) were expressed as a function of the total body weight (TBW), lean body weight (LBW), or extra fat (calculated as TBW-LBW). Mean data from different population were fitted simultaneously, and parameters were estimated using maximum likelihood method in Matlab.

Results: For both compounds, three-compartment model provided a good description of cefazolin and cefoxitin data sets. For each compound, the parameters were estimated with good precision. The best fit was obtained when volumes of the central and one of the peripheral compartments were set proportional to LBW, and the volume of the second peripheral compartment was set proportional to the size of the extra fat tissue (TBW-LBW).

Figure: Pharmacokinetic profiles of Cefoxitin

Conclusion: Biodisposition of antibiotics and other drugs can be significantly altered in obese subjects. The prevalence of obesity continues to increase and approaches for optimization of drug dosing in this population is urgently needed. Utility of indirect and direct measures of body size and body composition for describing drug pharmacokinetics should be evaluated in future studies.

References: