One size does not fit all: how to adjust the dose of anidulafungin in obese patients

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Background: In 2025 approximately one in five individuals will be obese. Physiological changes associated with obesity may influence the pharmacokinetics (PK) of drugs. We previously demonstrated lower exposure to anidulafungin in morbidly obese subjects. A direct comparison with non-obese was lacking. Likewise it is unknown which PK parameters are impacted by obesity. We combined data from obese with data from two trials in non-obese. Population-PK modeling and simulation were used to determine an optimal dosing regimen for in obese.

Material/methods: Twenty adult individuals, of which twelve were normal-weight healthy volunteers (median [range] weight of 67.7kg [60.5-93.6]) and eight morbidly obese patients undergoing bariatric surgery (BMI > 40kg/m²; 149.7kg [124.1-166.5]) were included. Subjects received a single dose of 100mg anidulafungin i.v. over 90 minutes and were sampled up to 168 hours for non-obese and 48 hours for obese. PK analysis was performed by means of non-linear mixed effects modeling. Several body size descriptors were investigated as covariates, using linear or allometric functions with fixed or estimated allometric exponents. Covariates were added stepwise with forward inclusion (p<0.005) backward elimination (p<0.001). The final model was selected by objective-function-value, goodness-of-fit plots and ETA-plots. Internal model validation was performed with prediction-corrected visual-predictive-checks and non-parametric bootstrap. Monte Carlo simulations with 5000 subjects per 10kg weight bands (range:60-170kg) were defined to simulate three dosing regimens: 1) licensed dose (200mg loading/ 100mg maintenance); 2) 25% higher dose (250mg/125mg) and; 3) 50% higher dose (300mg/150mg).
Results: A 3-compartment model with a proportional error and equal volumes of distribution (Vd) described the data best. Clearance and Vd were 1.00L/h (95% confidence interval [CI] 0.9-1.1) and 16.6L (95%CI 15.6-17.6) for a 70kg individual, respectively. Both were found to change with TBW using an allometric function with an empirically estimated exponent of 0.322 (95%CI 0.17-0.50) and 0.631 (95%CI 0.39-0.83), respectively. Inter-compartmental clearances between central and peripheral compartments were 0.15L/h (95%CI 0.13-0.18) and 14.1L/h (95%CI 12.2-16.0), respectively. Inter-individual variability of clearance and central Vd were 12.5% (95%CI 4.5-17.7%) and 10.1% (95%CI 5.5-14.2%). We predicted that >85% of patients with a weight above 100kg will be exposed to an AUC$_{0-24}$ lower than 100mg*h/L (reference of normal weight individuals) due to higher clearance. Besides clearance, Vd was 25% higher compared to normal weight individuals. To compensate these changes, a 25% increase in dose is needed in patients >100kg.

Conclusions: We constructed a PK-model for obese subjects to determine the effect of weight on PK parameters. Our investigations illustrate to what extend overweight influences both Vd and clearance and therefore overweight patients will have a lower exposure to anidulafungin. As a result, a 25% increase in both loading and maintenance dose should be considered in patients >100kg. Both model and suggested dose increase need external validation.