29th ECCMID Amsterdam, Netherlands 13 – 16 April 2019

The congress of ESCMID

O1164 Dosing of tobramycin in (morbidly) obese patients should be based on renal function rather than weight

Cornelis Smit*[1,2], Roeland Wasmann[3], Rene Wiezer[4], Eric Van Dongen[5], Johan W. Mouton[6], Roger Brüggemann[3], Catherijne Knibbe[1,2]

[1] St. Antonius Hospital, Dept. of Clinical Pharmacy, Nieuwegein, Netherlands, [2] Leiden University, Division of Systems Biomedicine and Pharmacology, Leiden Academic Centre for Drug Research, Leiden, Netherlands, [3] Radboud University Medical Center, Dept. of Pharmacy, Radboud Institute for Health Sciences, Nijmegen, Netherlands, [4] St. Antonius Hospital, Dept. of Surgery, Nieuwegein, Netherlands, [5] St. Antonius Hospital, Dept. of Anesthesiology, Nieuwegein, Netherlands, [6] Erasmus MC, Dept. of Medical Microbiology and Infectious Diseases, Rotterdam, Netherlands

Background: Tobramycin is an aminoglycoside antibiotic that is commonly used for severe infections. Although the prevalence of obesity increased tremendously over the last years, there is still no consensus on how to adjust the dose of aminoglycosides in obese individuals, where use of adjusted body weight (ABW), or, more recently, lean body weight (LBW) have been proposed. Recently, we have shown that dosing of the aminoglycoside gentamicin should be based on total body weight (TBW) [1]. In this study we characterize the pharmacokinetics of tobramycin in morbidly obese and non-obese individuals to develop dosing guidelines for tobramycin in the obese population.

Materials/methods: Morbidly obese subjects undergoing bariatric surgery (n=20) and non-obese healthy volunteers (n=8) received an IV dose of tobramycin (obese: 5 mg/kg LBW, non-obese: 5 mg/kg TBW) with plasma concentrations measured over 24 hours. Considered covariates were TBW, LBW, ABW, Glomerular Filtration Rate (GFR) based on 24h-urine collection and estimated GFR using non-indexed Modification of Diet in Renal Disease (MDRD x BSA/1.73) or Cockroft-Gault using LBW. Statistical analysis and population pharmacokinetic modelling was performed using R and NONMEM 7.3.

Results: Obese individuals (median [range] TBW 137.8 [103-194] kg) receiving 5 mg/kg LBW showed a substantially lower tobramycin AUC_{0-24} and C_{max} compared to non-obese individuals (median [range] TBW 66.3 [57-91] kg) receiving 5 mg/kg TBW (AUC_{0-24} (mean ±SD): 56.1 ±16.3 vs. 70.0 ±12.0 mg*h/L, respectively, p=0.039. C_{max}: 11.8 ±2.8 vs 18.3 ±2.7 mg/L, respectively, p<0.001). In a two compartment model, clearance was best described using non-indexed MDRD (CL (ml/min) = 0.105 [95% CI: 0.100-0.105] x (1 + 0.0099 [0.0078-0.012] x (MDRD (ml/min) - 114.9). For V_c, TBW was the most predictive covariate (both p<0.001).

Conclusions: In morbidly obese and non-obese individuals, renal function appeared a more important driver for tobramycin exposure than body weight derived parameters. As such, to ensure similar exposure in obese patients compared to non-obese individuals, we recommend tobramycin dosing to be based on renal function rather than weight.

[1] Smit, C, et al. A novel dosing algorithm for gentamicin dosing in (morbidly) obese patients. ECCMID 2018, ACCP 2018

Funded by ZonMW under grant 836041004