UNIVERSITEIT GENT

FACULTEIT FARMACEUTISCHE WETENSCHAPPEN

MOXIFLOXACIN DOSING IN POST-BARIATRIC SURGERY PATIENTS: ANOTHER NAIL IN THE COFFIN OF THE "ONE DOSE FITS ALL PARADIGM".

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1. Introduction & Objectives

Roux-en-Y gastric bypass surgery is the most commonly performed procedure for the treatment of morbid obesity. This anatomical alteration may affect the absorption and, consequently, the pharmacokinetic profile of oral drugs, possibly hampering **therapeutic efficacy**.

This study aims to (i) describe the **pharmacokinetic variability** of **moxifloxacin** concentrations in this cohort of healthy volunteers who have undergone gastric bypass using a **population pharmacokinetic model** and (ii) to assess the expected **probability of target attainment** (PTA) by MIC against a hypothetical ***Streptococcus pneumonia*** infection.

2. Patients & Methods

In this modelling and simulation study we used data from a randomized cross-over trial on moxifloxacin pharmacokinetics previously published[1]. In this trial, twelve volunteers, who had previously undergone bariatric surgery, received **2 single standard doses** (intravenous and oral) of **400mg moxifloxacin** administered on 2 occasions separated by a washout period of 1 week. Serial venous **blood samples** were drawn up to 72h after dosing and moxifloxacin plasma levels were measured by a validated high performance liquid chromatographic method with fluorescence detection. Population compartmental modelling and PK-PD simulations were performed using **NONMEM®**.

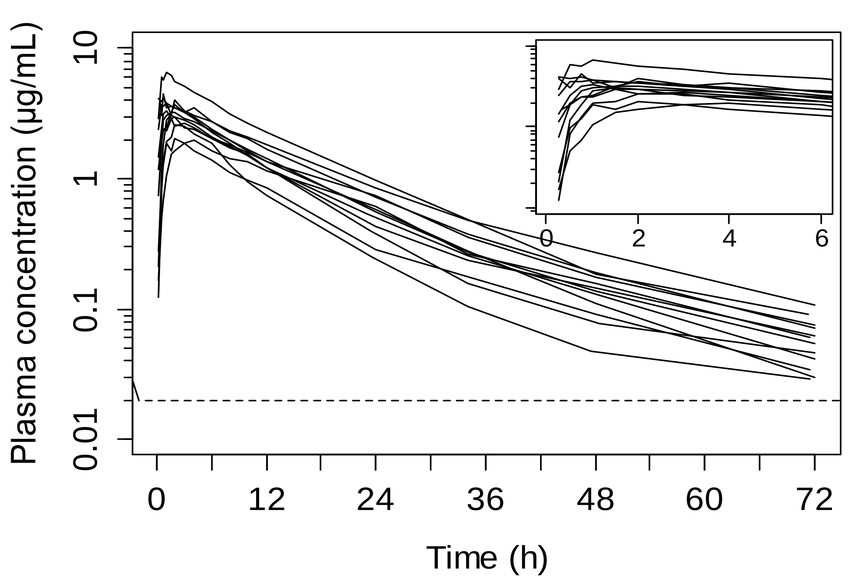

Figure 1: Observed moxifloxacin plasma-concentration time profiles after oral dosing.

3. Results (Pop-PK model)

Parameter	Final pharmacokinetic model
Fixed effects	
k_a (h^{-1})	0.95 [0.72 – 1.21]
$V_1 \times (\frac{LBM}{60})^1$ (L)	47.7 [31.6 – 78.6]
$Cl \times (\frac{LBM}{60})^{0.75}$ (L/h)	8.60 [7.80 – 9.70]
$V_2 \times (\frac{LBM}{60})^1$ (L)	61.5 [37.6 – 75.7]
$Q_2 \times (\frac{LBM}{60})^{0.75}$ (L/h)	105.3 [55.2 – 140.0]
$V_3 \times (\frac{LBM}{60})^1$ (L)	48.4 [34.4 – 92.9]
$Q_3 \times (\frac{LBM}{60})^{0.75}$ (L/h)	1.35 [1.23 – 1.56]
Inter-individual variability	
ω^2 (k_a)	0.24
ω^2 (V_1)	0.14
ω^2 (Cl)	0.04
Residual error	
σ^2 (Proportional)	0.03

Table 1: Population parameter estimates of the final pharmacokinetic model and the associated 95% bootstrap confidence intervals calculated on 100 bootstrap samples. All model parameters except ka were centered for a typical subject with a LBM of 60 kg.

3. Results (PK-PD simulation)

$$AUIC = \frac{Area\ under\ the\ plasma\ concentration\ time\ curve\ (AUC)}{MIC_{invading\ pathogen}}$$

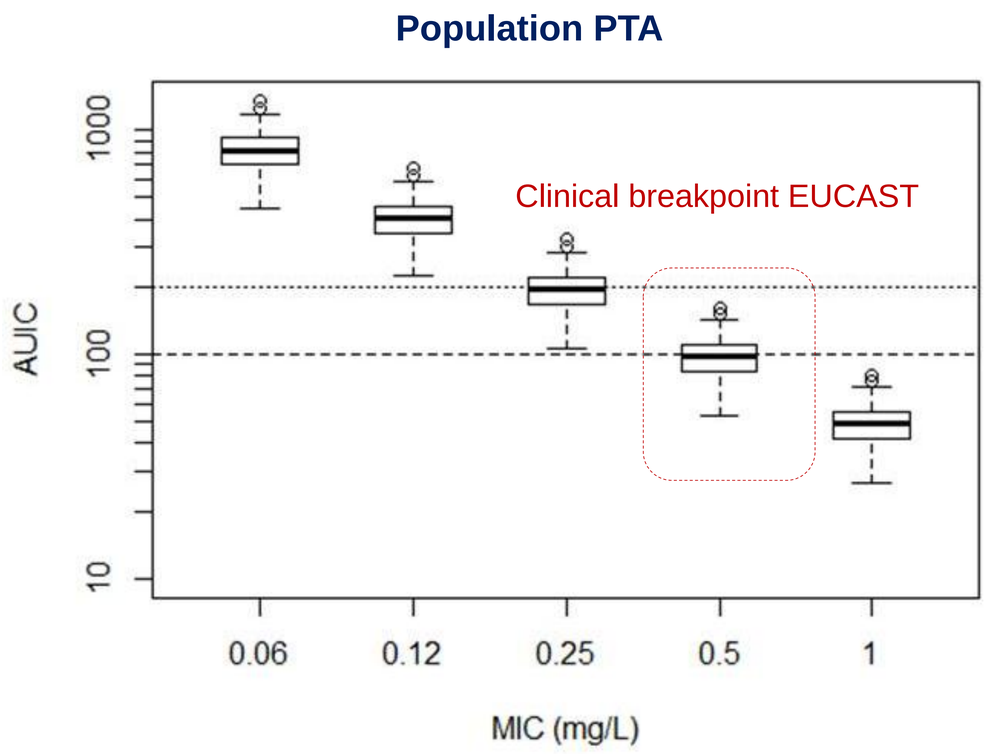

Figure 2: Predicted AUIC values after a standard 400mg oral dose versus the theoretical Streptococcus pneumonia MIC-values.

Simultaneously the AUIC cut-off values as proposed in literature are shown.
***long dashes**: $AUIC_{Total}$ = 100 target for bacterial eradication*
***short dashed lines**: $AUIC_{Unbound}$ = 100; target for suppression of bacterial resistance formation.*

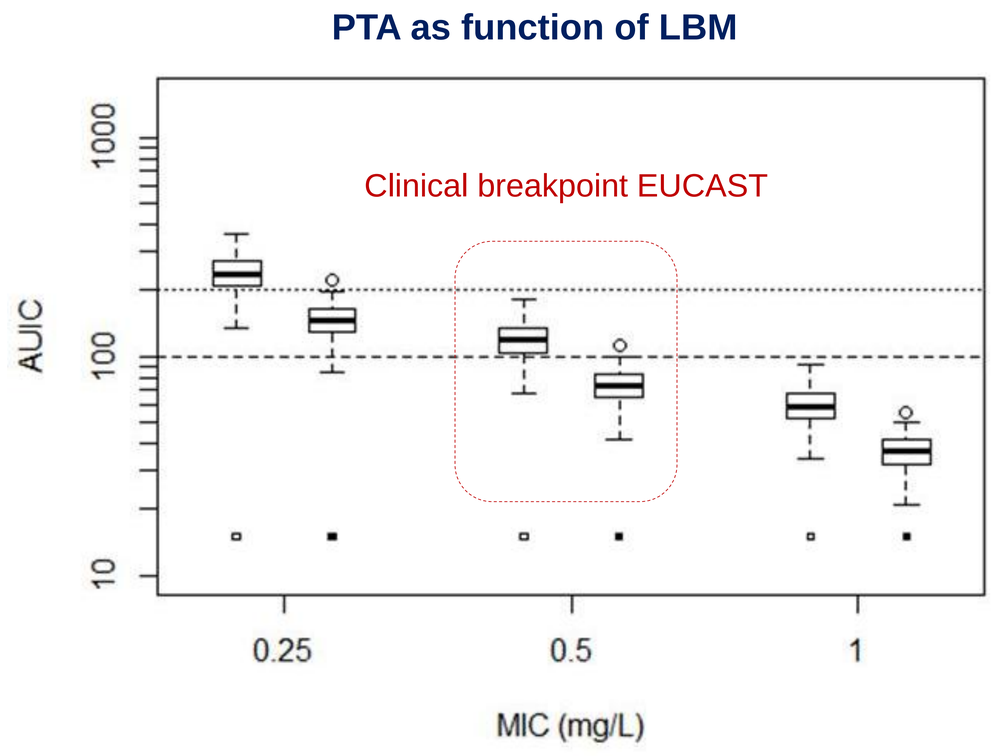

Figure 3: Predicted AUIC values for subjects with a LBM of 42 kg (open squares) and 78 kg (solid squares) after a standard 400mg oral dose versus the theoretical Streptococcus pneumonia MIC-values.

4. Conclusion

Our study clearly emphasises the need for an **individualized dosing** of moxifloxacin in this patient population. Furthermore, throughout our PK-PD simulation study it became apparent that the development of a model based dosing regimen for moxifloxacin is hampered by the current **discussion on which PK-PD target value** to pursue when optimizing patient moxifloxacin therapy.

[1]*De Smet J, Colin P, De Paepe P, et al. Oral bioavailability of moxifloxacin after Roux-en-Y gastric bypass surgery. J Antimicrob Chemother 2012; 67: 226-9.*

Reference: Colin P, Eleveld D.J., Struys M.M.R.F, et al. Moxifloxacin dosing in post-bariatric surgery patients: another nail in the coffin of the "one dose fits all paradigm". J Antimicrob Chemother Under review