# LIMITED SAMPLING STRATEGY FOR THE AREA UNDER CONCENTRATION-TIME CURVE ESTIMATION IN CHILDREN WITH NEPHROTIC SYNDROME TREATED WITH MYCOPHENOLATE MOFETIL

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## Introduction and Objectives

Mycophenolate mofetil (MMF) is an ester pro-drug of mycophenolic acid (MPA). MPA is a selective, noncompetitive and reversible inhibitor of inosine 5'-monophosphate dehydrogenase. MPA is used mainly after solid organ transplantation and also in the treatment of some autoimmune diseases like lupus erythematosus or nephrotic syndrome with different etiologies. Due to MPA complicated pharmacokinetics, resulting from enterohepatic recirculation, and significant intra- and interindividual variability of MPA pharmacokinetic parameters, therapeutic drug monitoring (TDM) is recommended for MMF. Limited sampling strategy (LSS) is the TDM method which is both precise and relatively convenient to the patient [1, 2].

The objective of the study was to develop a LSS that could be used to monitor plasma concentration of MPA in paediatric patients with nephrotic syndrome treated with MMF.

## Methods

The total of 40 MPA pharmacokinetic profiles from 33 children (14 boys and 19 girls) were used. The profiles were developed based on MPA plasma concentrations determined using HPLC-UV method. Blood samples were collected immediately before and 1, 2, 3, 4, 6 and 12 hours after MMF administration.

Test group consisted of 19 children, while validation group consisted of 14 children. In the case of 7 children, whose MPA profiles were estimated twice, the second estimation was included in the validation group.

**Table 1. Comparison between test group and validation group characteristics**

| | Test group | Validation group | p |
|---|---|---|---|
| Age [years] | 9.5 ± 4.5 | 10.9 ± 4.2 | 0.317 |
| Daily dose [mg] | 947 ± 319 | 1140 ± 355 | 0.100 |
| $AUC_{0-12}$ [µg/ml·h] | 42.58 ± 22.83 | 52.08 ± 15.90 | 0.139 |

Multilinear regression method was used to develop the LSS. The MPA area under the time-concentration curve ($AUC_{0-12}$), calculated using linear trapezoidal rule, was considered as the dependent variable, while MPA plasma concentrations at each sampling time-point were the independent variables. Firstly, the correlations between MPA plasma concentrations from single time points and $AUC_{0-12}$ were verified. Secondly, the equations based on samples collected during the first 6 hours after MMF administration were developed using stepwise regression with backward elimination. Finally, the equations based on samples collected during the first 3 hours after drug administration were developed manually. Statistica 10.0 software was used for the calculations.

Each developed equation was used for calculating $AUC_{0-12}$ for children in the validation group. The results were compared with the $AUC_{0-12}$ calculated previously using trapezoidal rule ($r^2$). The bias and precision for predicting $AUC_{0-12}$ were assessed basing on mean prediction error (%MPE) and mean absolute error (%MAE), respectively. The accepted values for %MPE and %MAE were ±15% and ±10%, respectively [3].

## Results

MPA concentrations versus time for children included in the test group are presented on Fig. 1.

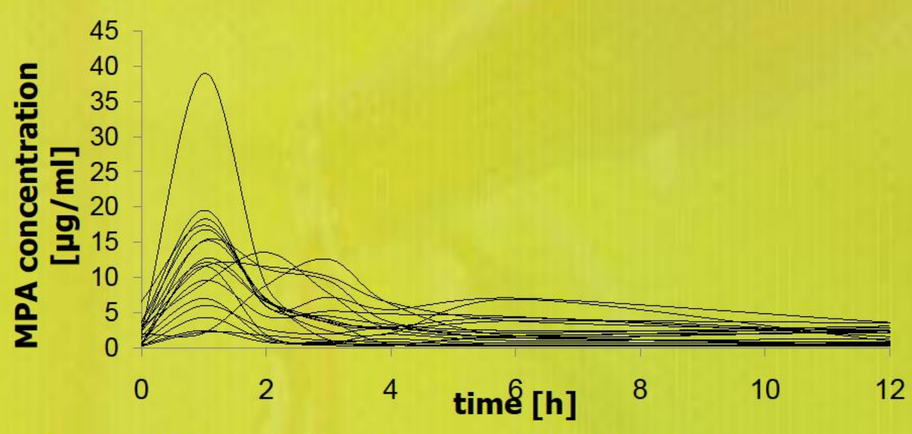


**Fig. 1. MPA concentrations profiles for the test group.**

Single time-points concentrations and the equations based on samples collected during the first 3 hours after MMF administration did not correlate with MPA $AUC_{0-12}$ sufficiently to be used in clinical practice.

**Table 2. The validation results of the developed equations**

| Time-points included in the equation | $r^2$ | %MPE [mean ± SD] | %MAE [mean ± SD] |
|---|---|---|---|
| $C_0$ | 0.1982 | 13.51 ± 49.83 | 35.23 ± 37.00 |
| $C_1$ | 0.6240 | 2.60 ± 30.88 | 22.64 ± 20.53 |
| $C_2$ | 0.6055 | -0.02 ± 28.45 | 24.34 ± 13.21 |
| $C_3$ | 0.4579 | -9.01 ± 29.92 | 26.07 ± 16.29 |
| $C_4$ | 0.4731 | -1.53 ± 29.69 | 23.83 ± 16.92 |
| $C_6$ | 0.5793 | -4.16 ± 28.85 | 23.7 ± 16.10 |
| $C_{12}$ | 0.5451 | -0.48 ± 33.77 | 26.68 . 19,79 |
| $C_0$, $C_1$, $C_3$, $C_4$, $C_6$ | 0,9274 | 0.93 ± 4.08 | 3.52 ± 2.12 |
| $C_0$, $C_1$, $C_3$, $C_6$ | 0.9564 | 0.67 ± 7.90 | 6.0. ± 4,93 |
| $C_1$, $C_3$, $C_6$ | 0.8802 | -1.04 ± 8.86 | 7.17 ± 5.07 |
| $C_0$, $C_1$, $C_2$, $C_3$ | 0.5801 | 1.57 ± 20.53 | 16.54 ± 11.66 |
| $C_0$, $C_1$, $C_3$ | 0.6695 | 4.44 ± 19.96 | 15.72 ± 12.61 |
| $C_0$, $C_1$, $C_2$ | 0.6956 | 10.20 ± 20.66 | 16.11 ± 16.22 |
| $C_0$, $C_1$ | 0.4092 | 12.46 ± 30.59 | 23.66 ± 22.59 |

From all developed equations, only two were adequately precise and accurate, namely:

- $AUC_{0-12} = 2.39 + 1.82 \cdot C_0 + 1.29 \cdot C_1 + 2.86 \cdot C_3 + 3.61 \cdot C_6$
- $AUC_{0-12} = 2.80 + 1.28 \cdot C_1 + 2.96 \cdot C_3 + 4.70 \cdot C_6$

## Conclusion

The proposed equations are important and useful implement which can be used in of MPA in children with nephrotic syndrome treated with MMF. Still, it is important to remember that properly validated LSS should be used only in population for which it was developed.

**References**

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