

Development Of A Limited Sampling Strategy For Mycophenolate Mofetil In Adult Patients With Lupus Nephritis

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Background: - Mycophenolate Mofetil (MMF), the immunosuppressive agent, is commonly used to treat renal transplant patients and patients with other autoimmune diseases such as Systemic Lupus Erythematosus (SLE). Due to the high inter-dose, inter-patient variability in drug exposure, therapeutic drug monitoring (TDM) has proved extremely beneficial in individualizing the MMF therapy.(1,2)

Aim: To develop a robust limited sampling strategy (LSS) to measure MPA $AUC_{0-12 \text{ hr}}$ (Area under the concentration-time curve) in patients with lupus nephritis.

Methods: MPA plasma specimens from 30 patients were prospectively collected at time points 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8 and 12 hours after patients had taken the Mycept brand (Panacea Biotec, New Delhi) of mycophenolate mofetil (MMF) for lupus nephritis. The measurement of MPA is based on a previous publication using HPLC with UV detection.(3) Limited sampling strategies with acceptable correlation coefficients (R^2), bias and precision were developed by stepwise multiple regression analysis using MPA concentrations at time points 0, 0.5, 1, 1.5, 2, 2.5, 3, 4 and 6 hours post dose. The predictive performance of the LSS was validated using bootstrap validation.

Results: The observed MPA $AUC_{0-12 \text{ hr}}$ ranged from 19.52 to 67.67 mg.h/L with a mean of 45.12 mg.h/L. The mean dose per Kg body weight of MMF prescribed was 26.47 mg/kg. The serum creatinine values in these patients ranged from 0.46 to 3.15 mg/dl. The Spearman correlation between the MPA $AUC_{0-12 \text{ hr}}$ and the pre-dose concentration in this study was 0.63. Three LSS models were chosen with a multiple $R^2 > 0.87$ which included 3 different combinations of concentrations at time points 0, 1, 2, 4 and 6. The best model included concentrations at time points 0, 1, 2 and 4 (multiple $R^2 = 0.926$). The final model validated post bootstrap is as follows:

$$\text{MPA } AUC_{0-12\text{Hr}} = 12.3376 + (2.9013 \times C_0) + (0.8305 \times C_1) + (0.7945 \times C_2) + (4.5156 \times C_4).$$

Here, C_0 , C_1 , C_2 , C_4 refer to the MPA concentrations at that particular time point. No statistical or clinical difference was found between the two methods (observed and LSS predicted) of MPA measurement (paired t-test t-value=0.705; Intraclass correlation=0.981; 95 % confidence interval (0.960-0.991)). Calculated bias and imprecision were -0.13 and 7.09 % respectively.

Conclusion: For patients on Mycept for lupus nephritis, this 4 point LSS is an accurate measure of the full 12-hour AUC with favourable bias and imprecision.

References:

- (1) Neumann I et al. J Am Soc Nephrol JASN; 14(3):721–7.
- (2) Rahman ANA et al, Clin Pharmacokinet; 52(5):303–31.
- (3) Fleming DH et al, J Postgrad Med; 52(4):248–52.