Modeling the complex pharmacokinetic profiles of cyclosporin and of mycophenolate observed in the early post-transplantation period

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BACKGROUND

- In the early post-grafting period, the pharmacokinetic profiles of immunosuppressive drugs are complex.

- The time-blood concentration curves of cyclosporin (CsA) frequently exhibit delayed absorption and secondary peaks. Complex absorption profiles and time-dependent clearance were reported for mycophenolate (MPA) and pharmacokinetic profiles frequently exhibit multiple peaks (1).

- Clinical evidence advocates for the rapid achievement of sufficient and stable exposure of these drugs in the early post-transplantation period, which may require dose adjustment based on pharmacokinetic modeling.

OBJECTIVES

- To develop a pharmacokinetic (PK) model able to fit the complex pharmacokinetic profiles of CsA (Neoral®) and MPA (Cellcept®) in the very early post-grafting period.

METHODS

PATIENTS DATA

- Pharmacokinetic analysis was performed in 20 renal transplant patients on day 3 post-transplantation. All patients received an immunosuppressive therapy including CsA and MPA twice daily and corticosteroids. Eleven blood samples were collected, immediately before (T0) the morning dose and 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 9 and 12 hours after dosing.

- CsA blood concentrations were measured using EMIT immuno-assay (Dade-Behring Diagnostics). MPA plasma concentrations were quantified with a validated LC/MS/MS method (2)

MODEL BUILDING

- The model used took into account a discontinuous absorption in order to describe the concentration-time profiles with two peaks (3,4). It assumed :

  - ➢ absorption from the stomach is negligible
  - ➢a given oral dose is absorbed sequentially in two fractions,
  - ➢the two portions are absorbed at the same absorption site (i.e. a gut compartment).

- NONMEM V program (5) through Visual NM interface (6).
- ADVAN 6, FOCE INTERACTION

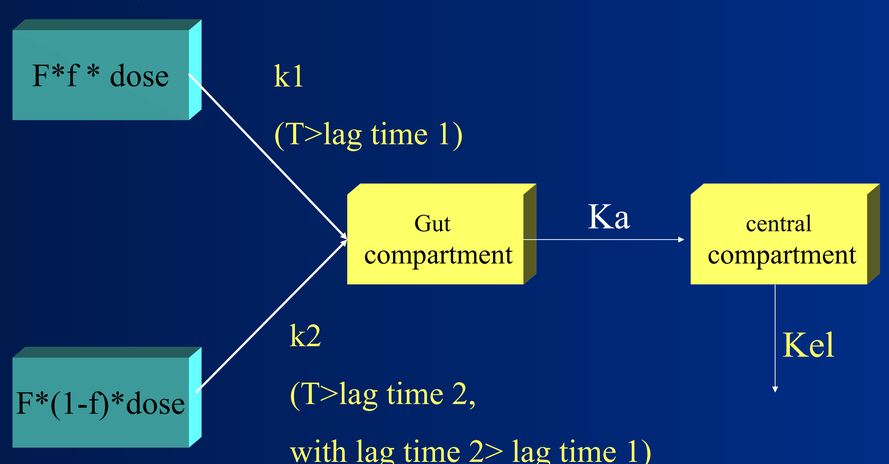

Figure 1: graphical representation of the model for CsA. f and (1-f) = first and second fraction of dose, k1 and k2 = first-order transfer rate constants, Ka= first-order absorption rate constant, Kel first-order elimination rate from central compartment.

The model used for MPA included additionally, a peripheral compartment.

RESULTS

Cyclosporin:

- 6 CsA Pk profiles exhibited two peaks while 14 CsA curves had apparently a single , sometimes delayed and wide peak. As examples, the Figure 2 presents 3 profiles.

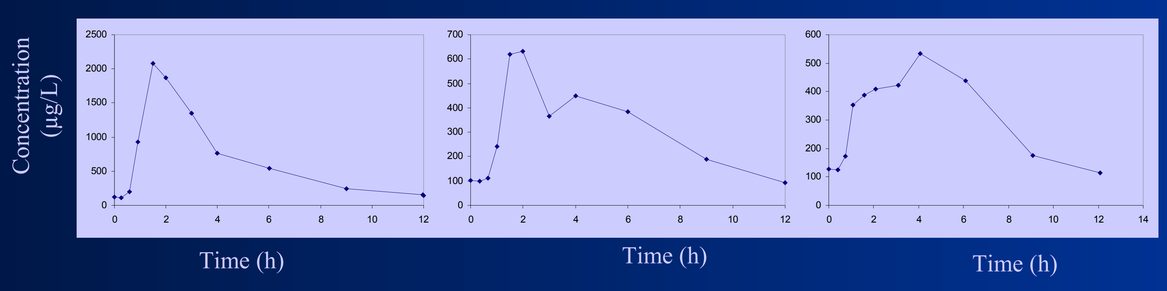

Figure 2: CsA concentration-time curves observed in 3 patients.

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4. Rousseau A and Marquet P. Clin Pharmacokinet (under press)
5. Beal SL, Sheiner LB, NONMEM User's Guide. (I-VIII). Hanover, Maryland, GloboMax, 1989-1998.
6. Gomeni R, Visual-NM User's Manual. R.D.P.P., Montpellier, France.

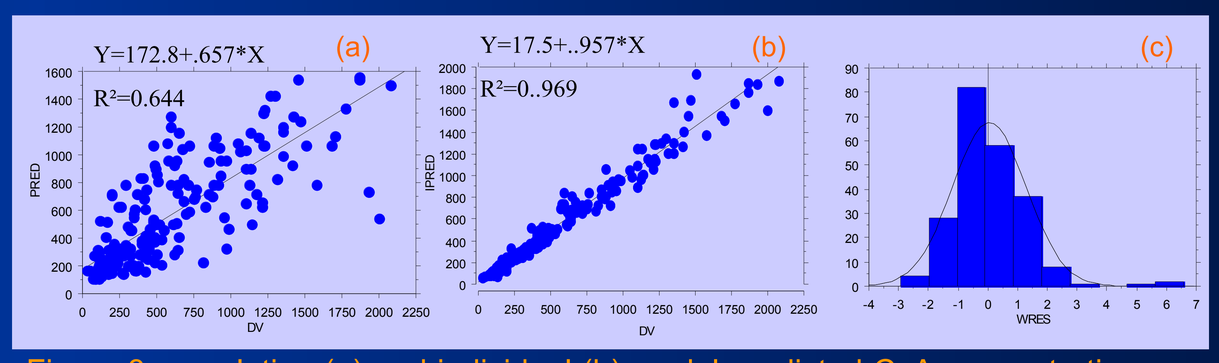


Figure 3: population (a) and individual (b) model-predicted CsA concentrations versus observed concentrations (µg/L). Frequency distribution of the weighted residuals (c). Residual variability consisted in a combined additional (21 µg/L) and proportional (13.1%) error model.

The population mean (CV%) values for K1, K2, lag1, lag2, Kel, Vc/F, KA and f were 3.65 h^{-1} (161), 0.097 h^{-1} (77), 0.44 h (51), 3.70 h (42), 1.23 h^{-1}(23), 36.1L (24.5), 0.71h^{-1} (29), 0.58 (13) respectively.

Mycophenolate:

- Examination of the observed concentration-time curves showed complex and highly variable profiles. As examples, the Figure 4 presents 3 profiles.

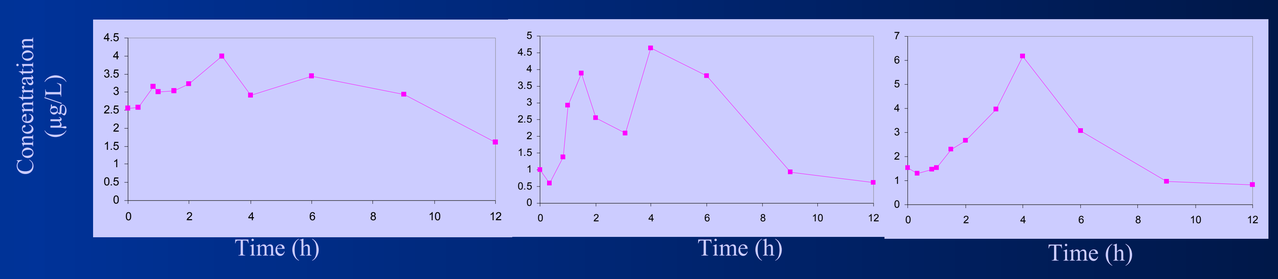


Figure 4: MPA concentration-time curves observed in 3 patients.

- FO method was used because FOCE with interaction did not run successfully.

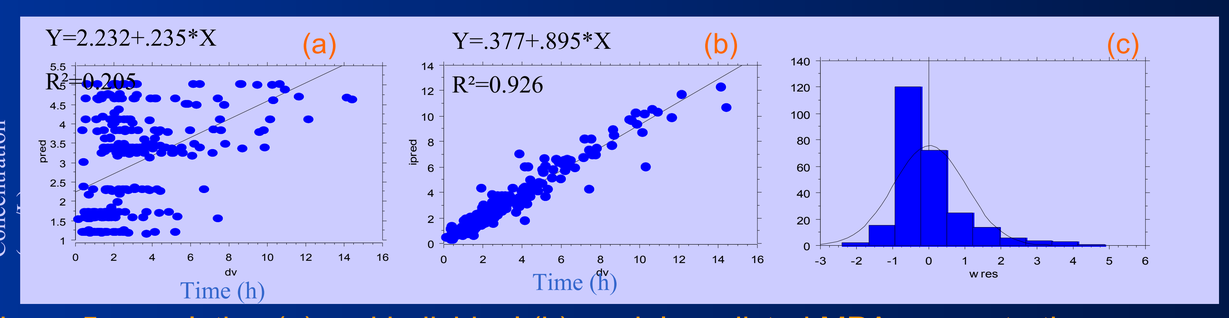


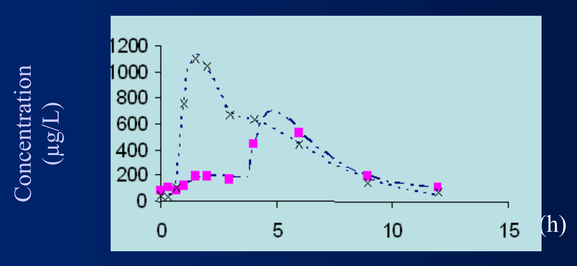
Figure 5: population (a) and individual (b) model-predicted MPA concentrations versus observed concentrations. Frequency distribution of the weighted residuals (c). Residual variability consisted in a combined additional (0.60 mg/L) and proportional (18%) error model.

DISCUSSION

Cyclosporin:

- A one-compartment model associated with this double absorption model reliably described the pharmacokinetic profiles observed at day 3 post-transplantation whether a double peak was present or not on the concentration-time curves. Interestingly, with this model, the objective function was at least 113 point less than with models based on zero- or first-order absorption with lag-time. The short time delay between the two estimated time-lag (median 2.49 h, IQR 0.56h) support the hypothesis of discontinuous absorption.

Figure 6: Typical posterior individual fittings. Curves represent the theoretical smooth curves and ■ and ✕ represent observed concentrations

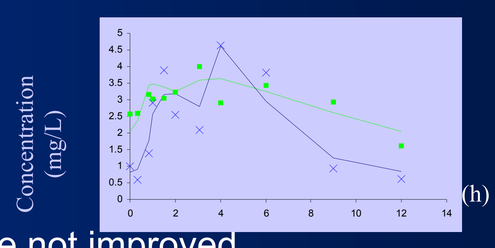


Mycophenolate

-A two-compartment model associated with the double absorption model studied here led to a decrease of 10 of the objective function compared with the same absorption model associated with a one compartment model.

With this 2 compartment model, the objective function was at least 52 points less than with models based on zero- or first-order absorption with lag-time.

Figure 7: Typical posterior individual fittings. Curves represent the theoretical smooth curves and ■ and ✕ represent observed concentrations



-Other models were tested but the results were not improved.

- for absorption: models based on Weibull or Erlang distribution, double sequential Weibull or Erlang absorption process, a double absorption process combining both a first-order process and a Michaelis-Menten absorption
- models accounting for non linear elimination
- a model accounting for enterohepatic recirculation

Previously, only one study (1) concerned pharmacokinetic modeling of MPA in the early post-transplantation period: the observed profiles were similar to the profiles obtained herein and the tested models accounting for complex absorption process, enterohepatic recirculation and time-dependent clearance did not improve the fit over a two-compartment model with first order absorption with lag time.

CONCLUSION

The double sequential absorption model proposed herein is suitable for the analysis of CsA population pharmacokinetic in the first days after renal transplantation. The profiles of MPA observed in the early post-grafting period are very complex; the present absorption model provided a better fit than the other tested models but improvement is still needed.