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 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 fractions are absorbed at the same absorption site (i.e. a gut compartment).
- NONMEM V program (5) through Visual NM interface (6).

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.

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

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.

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

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

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.

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

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 points 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.

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 6: Typical posterior individual fittings. Curves represent the theoretical smooth curves and * and & represent observed concentrations.