Modelling Tacrolimus AUC in Acute and Chronic Liver Disease Immediately after Transplant

**Objectives:** To optimize therapy with tacrolimus the measurement of its concentration in blood is an integral part of the recipients care. The aim of this study was predicting area under the time-concentration curve (AUC) in acute and chronic liver disease immediately after liver transplant.

**Methods:** Pharmacokinetic profiles for a period of 10 h, were obtained from seventy five adult liver recipients (30 acute liver failure and 45 chronic liver disease). Tacrolimus whole blood samples were analyzed using IMx analyzer. Statistical analyses were performed using SPSS for windows.

**Results:** After subdividing patients on the basis of acute and chronic presentation examination of relationships between tacrolimus exposure and clinical biochemical markers showed that significant correlations existed only in the acutely presenting cases and there were associations between AUC (dose corrected) and serum albumin ($r = -0.586$, $p = 0.0001$) and total protein ($r = -0.544$, $p = 0.002$).

**Conclusion:** By incorporating variables influencing tacrolimus exposure immediately after transplant derived AUC in acutely presenting cases could be modeled with reasonable precision ($r = 0.857$) as: $AUC=- (1.20 \times \text{Alb}) + (9.57 \times \text{PO}_4) – (0.98 \times \text{Prot}) + (1.05 \times \text{Urea}) + 84.7$.

**Key words:** tacrolimus, AUC prediction, acute and chronic liver disease
Markern, dass signifikante Korrelationen nur in den akuten Fällen vorhanden waren und dass Verbindungen zwischen AUC (dosisbe-reinigt) und Serumalbumin (r = -.586, p = 0.0001) sowie Gesamtpro-tein (r = -.544, p = 0.002) bestanden.

Schlussfolgerung: Durch die Einbeziehung von Variablen, die die Tacrolimus-Exposition unmittelbar nach Transplantation beein-flussen, konnte die abgeleitete AUC bei den akuten Fällen mit annehmbarer Genauigkeit (r = 0.857) folgendermaßen modelliert werden: AUC = -(1.20 x Alb) + (957 x PO4) – (0.98 x Prot) + (1.05 x Harnstoff) + 84.7.

Schlüsselwörter:
Tacrolimus, Vorhersage von AUC, akute und chronische Leberer-krankung

Introduction
Immunosuppressive therapy aims to protect transplanted organs from host immune responses (1). Requirements for monitoring tacrolimus originate both from its narrow therapeutic range and the inter-individual variability in its pharmacokinetics and efficacy (2). Differences in absorption and clearance of tacrolimus largely determine pharmacokinetic variability and result both from genetic determinants and clinical status. To overcome this variability, an alternative approach could be made base on modelling AUC (3,4). The aim of this study was to investigate the contribution of several clinical variables relating to the indication for transplant and therefore, predicting AUC in patients transplanted for acute and chronic liver disease.

Patients and Methods
Patients: Seventy five adult liver recipients of median age 49 years (range 15 to 64 years) and median weight 80 kg (range 48 to 128 kg) were studied. Thirty had been transplanted for acute liver failure and forty five patients for chronic liver disease. Clinical biochemistry and haematological results were retrieved from the patients’ records. The median starting dose of tacrolimus was 0.07 mg/kg body weight (range 0.02-0.11 mg/kg). Tacrolimus concentrations were analysed in whole blood by the first generation, tacrolimus microparticle enzyme immunoassay. Comparison between groups was made using the non-parametric Mann-Whitney U-test. Correlations between variables were determined by Spearman Rank order and Pearson regression analyses. Multiple regression analysis was performed by step-wise treatment of independent variables.

Results
The profile of blood levels observed was shown to be influenced by a number of static indicators such as the indication for transplantation (acute and chronic), retransplantation, the age and gender of the patient and dynamic indicators such as several clinical biochemical and haematological indicators. By incorporating these variables into a regression equation it proved possible to predict drug exposure in patients transplanted for acute and chronic presentation with reasonable precision. In order to address whether the Non-Gaussian distribution of the observed AUC affected their correlation with predicted values (i.e. derived), Spearman Rank Order correlation analysis was performed and data are presented in Table 1. Comparison between true and predicted values of AUC in twenty nine acutely presenting cases is shown in Figure 1.

Tab. 1: Derived equation for predicting AUC/mg dose in patients transplanted for acute and chronic liver disease immediately after transplant.

<table>
<thead>
<tr>
<th>AUC per mg dose</th>
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<tr>
<td>Acute Cases</td>
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<td>Including Retransplants (n = 29)</td>
<td>-(1.20x Alb) + (9.57 x PO4) – (0.98 x Prot) + (1.05 x Urea) + 84.7</td>
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<td></td>
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<tr>
<td>Including Retransplants (n = 45)</td>
<td>+(0.007 x AST) + 39.7</td>
<td>0.279</td>
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<tr>
<td>Excluding Retransplants (n = 17)</td>
<td>+(442.5 x Dose) – (14.0 x Sex) + (14.2 x K) – 48.5</td>
<td>0.515</td>
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One case with PGNF and urea of 209 mmol/L was excluded from the analysis.

Abbreviations for contributing variables (Var): Alb, Albumin; AST, Aspartate aminotransferase; Dose, Tacrolimus dose (mg/kg body weight); K, Potassium; Na, Sodium; PO4, Phosphate; T.Prot, Total protein; ReT, Retransplantation; Sex, Female gender; (+) or (-): positive or negative correlation; r, Correlation coefficient

Correlation coefficients (r) and corresponding p values were derived by multiple regression analysis.

Conclusion
The wide range of exposure in pharmacokinetic variables obtained during tacrolimus therapy has been obvious since early publication (3). Identified among possible contributory factors to inconsistencies in the oral bioavailability of tacrolimus (4-6) immediately post transplantation were a number of static variables including retransplantation, age, gender and indication for operation (7-9). Higher values of median AUC observed in retransplanted patients most likely reflected existing saturation of the compartments into which tacrolimus is distributed. The negative contributions of serum albumin and total protein to AUC may be related to the supraphysiologial ranges of serum albumin and total protein concentrations observed in

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these patients. Two specific factors emerging additionally from these analyses were the influence of presenting aetiology and serological and haematological indicators of liver, kidney and clinical dysfunction (10). The arbitrary inclusion of many of these latter variables in regression models can be criticised on the basis that there is little known of their ability to effect the pharmacokinetics of tacrolimus but the same arguments might have excluded presenting aetiology from the modelling process so the approach appears justifiable. Several of these variables which appeared in predictive models for AUC developed here may be applicable to setting tacrolimus dosage immediately after transplantation, particularly in those patients transplanted for acute liver failure.

References


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