Pharmacokinetics of tacrolimus (FK 506) in children and adolescents with renal transplants

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Abstract

Background. Only few data exist on pharmacokinetics of tacrolimus in children.

Patients. In 1995 and 1996, 14 children (mean age 13 years, range 5–23 years) received tacrolimus after renal transplantation; 10 of these after biopsy-proven steroid-resistant rejection (2 with vascular rejection), two for cyclosporin A (CsA)-induced severe nephrotoxicity, one for untreated gingival hyperplasia on CsA, and one child was treated primarily after transplantation because of severe liver involvement in nephronophthisis. Pharmacokinetic investigations were performed after establishing a stable maintenance dose with trough levels in the desired window of 5–12 ng/ml.

Results. Mean follow-up time was 6 months (range 3–25 months). Eleven patients are still on tacrolimus. Two were discontinued because of severe aggravation of chronic persistent hepatitis C (one of them also developed diabetes mellitus), and one patient was subsequently switched to conventional immunosuppression because of tacrolimus-associated nephrotoxicity. All tacrolimus levels were measured by a modified assay (MEIA, Tacrolimus, Abbott) with improved sensitivity. At the time of switch, median serum creatinine was 234 ± 82 µmol/l and 6 months after switch 201 ± 99 µmol/l. All grafts are still functioning. Mean FK-506 dose was 0.16 mg/kg body weight/day (range 0.036–0.30 mg/kg). Mean trough level was 7.1 ± 2.6 ng/ml in the morning and 6.5 ± 2.0 ng/ml in the evening. Median time of maximum concentration (t_{max}) was 120 min after application, and the mean maximum concentration (C_{max}) was 15.2 ± 6.7 ng/ml. Mean area under the curve (AUC) was 104 ± 33 ng * h/ml, with a range from 65 to 169 ng * h/ml. No patient had unsatisfactorily low trough levels during the study. There was only a weak but significant (P < 0.05) correlation between dose per kg body weight and AUC and, as expected, an excellent correlation (r² = 0.73, P < 0.001) between AUC and trough level.

Conclusion. Because of interindividual variation between patients, therapeutic drug monitoring of tacrolimus is mandatory. In this study, a daily dose of 0.15 mg/kg was sufficient in most patients. We recommend the performance of at least one pharmacokinetic study after establishing stable FK 506 trough levels to ascertain a safe profile.

Key words: renal transplantation; rescue therapy; tacrolimus; tacrolimus pharmacokinetics

Introduction

Tacrolimus (FK 506) is a new powerful macrolide immunosuppressant. Tacrolimus has shown notable efficacy as a rescue or primary immunosuppressant therapy when combined with corticosteroids in adult and paediatric recipients following liver or kidney transplantation. Like cyclosporin (CsA), tacrolimus demonstrates considerable interindividual variation in its pharmacokinetic profile. This has caused difficulty in defining the optimum dosage regimen and has highlighted the usefulness of therapeutic drug monitoring [1]. In most respects, however, the tolerability profile of tacrolimus appears to be broadly similar to that of CsA. Recently, evidence has been presented that CsA profiles provide more useful information in the management of renal transplant recipients than CsA trough levels alone [2]. Here we present our data on FK 506 profiles in children and adolescents with a renal transplant.

Subjects and methods

Fourteen patients were treated with tacrolimus since January 1995. They were transplanted between June 1986 and November 1995. Age at end-stage renal failure was 9.1 ± 3.7 years, and mean age at time of transplantation was 10.8 ± 3.5
years. Mean waiting time was 1.7 ± 1.7 years. One graft in patient JK was a maternal graft, all others were cadaveric grafts. Details on patients, underlying disease and the outcome are listed in Table 1. In cases of significant tacrolimus treatment, the latest serum creatinine is noted. Table 1 also states the reason for commencement of tacrolimus treatment. One patient with Caroli syndrome and nephronophthisis was treated immediately after transplantation because of anticipated CsA absorption problems due to chronic liver failure.

Tacrolimus levels were measured by IMx and with a newly developed modification of the Tacrolimus assay (Abbott) with improved sensitivity (min 1.5 ng/ml) [3]. From the previous experience of both paediatric liver transplant recipients and our own experience a tacrolimus trough level was targeted at 5–11 ng/ml; however, dose adjustments were only made in the context of clinical signs or clinical chemistry parameters, and not in isolation. All pharmacokinetic profiles were obtained when the patients were on stable doses for at least 4 days and stable trough levels. In the majority of cases patients took their tacrolimus as two equal daily doses 1 h before or 2 h after meal. For the profiles, blood samples were taken before, and at 30, 60, 90, and 120 min, and 3, 4, 6, 8 and 12 h after the dose, with the 12-h sample being the evening pre-dose sample. \( C_{\text{max}} \) was taken from the results of the profiles. The AUC in h × ng/ml for each profile was calculated from a plot of tacrolimus concentrations versus time from 0 to 12 h using the trapezoid rule (TopFit pharmacokinetic program [4]).

**Results**

Mean age at the time of start of tacrolimus was 14.0 ± 4.2 years with a range from 5.1 to 22.4 years. The switch from CsA to tacrolimus was performed at a mean of 3.3 ± 2.8 years after transplantation, with a range from 5 days to 9 years.

Probability of event-free survival (no adverse events) is shown in Figure 1. Two patients were discontinued because of aggravation of hepatitis C, and one patient also developed transient diabetes mellitus, when she had tacrolimus trough levels of more than 25 ng/ml [5]. Patient SFA was discontinued because he showed the same signs of toxicity in the graft whilst being on CsA (see Table 1). No other adverse events occurred, in particular there was no haemolytic-uraemic syndrome, no post-transplant lymphoproliferative disease (PTLD) or thyroid or other overt neurotoxicity or liver toxicity. Time sequelae of serum creatinine of the patients is summarized in Figure 2. In the follow-up period there was no acute rejection episode.

Two patients were treated early after transplantation, one starting on day 1 and one starting on day 5. Both patients received a starting dose between 0.12 and 0.14 mg/kg/day and were adjusted to 0.22 and 0.32 mg/kg/day after 1 month. Mean FK-506 dose was 0.16 mg/kg body weight/day (range 0.036–0.30 mg/kg). The data are summarized in Figure 3. Mean trough level was 7.1 ± 2.6 ng/ml (range 3.3–10.1 ng/ml) in the morning and 6.5 ± 2.0 ng/ml (range 3.3–10.7 ng/ml) in the evening. Median time of peak whole blood levels was 120 min after application, and the mean peak level was 15.2 ± 6.7 ng/ml (range 7.7–30.7 ng/ml). Figure 4 summarizes the tacrolimus blood levels with regard to time. The individual pharmacokinetic profiles are demonstrated in Figure 5. Mean AUC was 104 ± 33 ng × h/ml, with a range from 65 to 169 ng × h/ml. No patient had unsatisfactorily low trough levels during the study. There was only a weak but significant \( r^2 = 0.3176, P < 0.05 \) correlation between dose per kilogram body-weight and AUC, and, as expected, an excellent correlation \( r^2 = 0.7316, P < 0.001 \) between AUC and trough level (Figure 6).
Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Underlying diagnosis</th>
<th>Indication (and additional immunosuppressive treatment if appropriate)</th>
<th>Duration of tacrolimus use (days)</th>
<th>Outcome and/or serum creatinine values</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS</td>
<td>12.3</td>
<td>HUS</td>
<td>Steroid-resistant rejection</td>
<td>268</td>
<td>331 µmol/l</td>
</tr>
<tr>
<td>RH</td>
<td>17.0</td>
<td>Dysplasia</td>
<td>Steroid-resistant rejection</td>
<td>275</td>
<td>127 µmol/l</td>
</tr>
<tr>
<td>JS</td>
<td>22.4</td>
<td>Cystinosis</td>
<td>Steroid-resistant rejection</td>
<td>272</td>
<td>155 µmol/l</td>
</tr>
<tr>
<td>SFA</td>
<td>17.8</td>
<td>Dysplasia</td>
<td>CsA toxicity</td>
<td>31</td>
<td>FK 506 toxicity, well-functioning graft on AZA and steroids</td>
</tr>
<tr>
<td>MR</td>
<td>17.4</td>
<td>FSGS</td>
<td>Steroid-resistant rejection</td>
<td>229</td>
<td>304 µmol/l</td>
</tr>
<tr>
<td>KS</td>
<td>17.5</td>
<td>Dysplasia</td>
<td>Steroid-resistant rejection</td>
<td>282</td>
<td>220 µmol/l</td>
</tr>
<tr>
<td>JK</td>
<td>13.1</td>
<td>Xanthogranulomatous pyelonephritis</td>
<td>Steroid-resistant rejection</td>
<td>58</td>
<td>Transient diabetes mellitus, exacerbation of chronic aggressive hepatitis C, functioning graft on CsA 35 µmol/l</td>
</tr>
<tr>
<td>AP</td>
<td>5.1</td>
<td>Caroli syndrome</td>
<td>Caroli syndrome, primary FK 506 therapy</td>
<td>180</td>
<td></td>
</tr>
<tr>
<td>AS</td>
<td>13.0</td>
<td>Senior Loken syndrome</td>
<td>Steroid-resistant rejection, vascular, MMF therapy</td>
<td>92</td>
<td>120 µmol/l</td>
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<tr>
<td>JH</td>
<td>10.3</td>
<td>Congenital nephrotic syndrome</td>
<td>Severe gingival hyperplasia, following 4th gingivectomy</td>
<td>23</td>
<td>Exacerbation of chronic aggressive hepatitis C, functioning graft on CsA 221 µmol/l</td>
</tr>
<tr>
<td>SB</td>
<td>14.9</td>
<td>HUS</td>
<td>Steroid-resistant rejection, vascular, MMF therapy</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>OB</td>
<td>9.0</td>
<td>HUS</td>
<td>Steroid-resistant rejection</td>
<td>461</td>
<td>250 µmol/l</td>
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<tr>
<td>MB</td>
<td>11.9</td>
<td>Anti-basal membrane glomerulonephritis</td>
<td>Steroid-resistant rejection</td>
<td>176</td>
<td>133 µmol/l</td>
</tr>
<tr>
<td>KT</td>
<td>13.8</td>
<td>Nephronophthisis</td>
<td>Steroid-resistant rejection</td>
<td>44</td>
<td>186 µmol/l</td>
</tr>
</tbody>
</table>

Fig. 4. Tacrolimus trough levels after start of the drug. The mean is plotted as a straight line.

Fig. 5. Tacrolimus profiles in 14 paediatric renal transplant recipients.

Fig. 6. Correlation between area under the curve (AUC) and trough levels in 14 paediatric renal transplant recipients.

Discussion

The recommended starting dose for adult primary kidney transplant recipients is 0.10–0.40 mg/kg/day (product information guide), and the results of both the two patients who were started early after transplantation as well as data from all children indicated that children obviously do not require a higher dose. By contrast, there is evidence from the published literature that paediatric liver transplant recipients need higher doses compared to the corresponding adult patient population [6]. In a previous study Ellis et al. [7] also needed higher doses in paediatric renal transplant recipients compared to adults; however, he started tacrolimus intravenously. We felt very reluctant to use tacrolimus intravenously because of a risk of anaphylactic reactions to cremophores (vehicles for
intravenous delivery of hydrophobic drugs) such as HCO-60. [8] The lower doses in this study could be attributable to the additional liver disease in three patients, particularly when considering pathological cytochrome C3A4 activity in patient AS. However, recalculation of mean dose per kilogram without the three patients with additional liver disease resulted in only minor changes of the average dose of tacrolimus per kilogram body-weight and day: instead of 0.16 it was 0.17 mg/kg body-weight/day. We would like to point out that because of the considerable interindividual variation between patients, dose adjustment according to trough concentrations are more important, and dose recommendations should be restricted to a starting dose.

Only few data on AUCs are available from paediatric renal transplant recipients with stable graft functions. Mekki et al. [9] reported pharmacokinetics of tacrolimus in kidney transplant recipients. Compared to results the AUCs of the patients presented by us are in his lower range. This did not lead to an increase of rejection in our patients. Possibly the doses of tacrolimus used in previous studies were unnecessarily high and a dosing with an AUC around 100 h × ng/ml may be more advisable to minimize adverse events.

We feel that it is important to have at least one pharmacokinetic study after establishing stable trough levels despite of the good correlation between AUC and trough level. In patients with a high $C_{\text{max}}$, the dosage was adjusted in order to minimize toxicity although the trough levels was in the desired window of 5–11 ng/ml.

Conclusions

Because of considerable interindividual variation of tacrolimus bioavailability between patients, therapeutic drug monitoring of tacrolimus is mandatory. In this study, a daily tacrolimus maintenance dose of 0.15 mg/kg was sufficient in most paediatric renal transplant recipients to prevent rejection. At least one pharmacokinetic study should be performed to ascertain a safe profile without toxicity.

References


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