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Pharmacokinetics of tacrolimus (FK506) in paediatric liver transplant recipients

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SUMMARY

The pharmacokinetics of intravenous and oral tacrolimus was assessed in paediatric liver transplant patients at two centers in Europe. Sixteen patients, age 0.7 to 13 years, participated in the study; 12 patients were evaluable for intravenous pharmacokinetics, and 16 for oral. Intravenous tacrolimus was given as a continuous 24 h infusion (mean 0.037 ± 0.013 mg/kg/day), and oral tacrolimus was given in 2 doses per day (mean 0.152 ± 0.015 mg/kg). Whole blood samples for the intravenous pharmacokinetic profile were taken before initiation of the first infusion, 4, 8, 12 and 24 h post-infusion, and every 24 h thereafter until intravenous administration was discontinued. During the 12 h wash-out period between intravenous and oral administration, samples were taken every 3 h. Samples for the oral pharmacokinetic profile were taken immediately before the first oral dose and 0.5, 0.75, 1, 2, 2.5, 3, 4, 6, 8, 10 and 12 h post-administration. Non-compartmental procedures were used to characterise the pharmacokinetic parameters. Mean estimates for clearance and terminal half-life were 2.3 ± 1.2 ml/min/kg and 11.5 ± 3.8 h, respectively, following intravenous tacrolimus. The mean bioavailability of oral tacrolimus was 25 ± 20%. A strong correlation was observed between AUC and trough whole blood levels of tacrolimus (r = 0.90). The clearance was approximately 2-fold higher than that previously observed in adults; this could explain the higher dosage requirements in children.

INTRODUCTION

Tacrolimus (FK506) is an established, well-tolerated, and potent primary immunosuppressant in paediatric liver transplantation (1,2). Studies comparing tacrolimus with cyclosporin have shown a reduced incidence of rejection in patients receiving tacrolimus therapy, a similar spectrum of side effects, and lower corticosteroid requirements (3,4). The pharmacokinetics of tacrolimus has been characterised in adult liver transplant recipients (5,6). This paper reports the pharmacokinetics of intravenous and oral tacrolimus

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from 16 paediatric liver transplant patients assessed in the context of a pilot efficacy study.

MATERIALS AND METHODS

Patient selection

Male and female patients, up to 18 years of age, who were scheduled to undergo primary liver transplantation were eligible for entry. Patients were excluded if they were to undergo a second transplant or a multiple-organ transplant, or if they were to receive a liver allograft from a living donor. Other grounds for exclusion were renal impairment, neoplastic disease, uncontrolled and severe infection, HIV or hepatitis B infection, active collagen-vascular disease, and stage IVb hepatic encephalopathy.

Dosing

Intravenous therapy was carried out as a continuous 24 h infusion; the recommended dosage was 0.03–0.10 mg/kg/day. The recommended oral daily dosage of tacrolimus was 0.3–0.6 mg/kg/day administered as a suspension (1 mg/ml) or capsule (1 mg or 5 mg) and divided into two doses per day. The choice of formulation was left to the discretion of the investigator.

Sample collection

Whole blood samples for the intravenous pharmacokinetic profile were taken before initiation of the first infusion, 4, 8, 12 and 24 h after beginning the infusion, and every 24 h thereafter until intravenous administration was discontinued. During the 12 h wash-out phase between the last intravenous dose and the first oral dose, samples were taken every 3 h. Samples for the oral tacrolimus pharmacokinetic profile were taken immediately before the first oral dose and 0.5, 0.75, 1, 2, 2.5, 3, 4, 6, 8, 10 and 12 h post-administration.

Measurement of tacrolimus concentrations

Tacrolimus concentrations were measured by an enzyme-linked immunosorbent assay (7) at a central laboratory (BCO Centre for Research, Breda, The Netherlands) according to the standards of OECD-GLP (Organisation for Economic Corporation Development – Good Laboratory Practice). The assay has a lower limit of quantification of 0.5 ng/ml.

Pharmacokinetic data evaluation and statistics

Intravenous and oral tacrolimus pharmacokinetic parameters were assessed for each patient. Non-compartmental procedures were used to characterise pharmacokinetic parameters using the TopFit 2.0 computer program (8). The area under the concentration–time profile (AUC) was estimated using linear trapezoidal methods from the start of the particular profile to the last data point (AUC_{0-T}). Total body clearance was estimated as:

$$Cl = \frac{Dose_{(intravenous)}}{AUC_{0-T\,(intravenous)}} \qquad \text{Eq. 1}$$

Absolute oral bioavailability (F) was calculated as a percentage with the equation:

$$F = \frac{AUC_{0-T\,(oral)} \times dose_{(intavenous)}}{AUC_{0-T\,(intravenous)} \times dose_{(oral)}} \times 100 \qquad \text{Eq. 2}$$

Statistical calculations were carried out with the functions of MS-Excel 4.0a (mean, median, SD, minimum and maximum) and the related analysis tools package. All calculations were performed at the Pharmacokinetic Department of Fujisawa GmbH.

Ethics

This study was conducted in accordance with the Declaration of Helsinki and the principles laid down in the Good Clinical Practice (GCP) Guidelines in the European Community.

RESULTS

Sixteen patients, 9 female and 7 male, were recruited. Ages ranged from 0.7 to 13 years. The main reason for transplantation was biliary atresia (85%).

Twelve patients' data were evaluable for intravenous pharmacokinetics and 16 for oral pharmacokinetics. The mean daily intravenous dose was 0.037 mg/kg (SD 0.013 mg/kg; range 0.030–0.049 mg/kg/day) with a mean total dose of 2.34 mg/kg and mean total infusion period 103 h. The mean dose for oral tacrolimus was 0.152 mg/kg (SD 0.015 mg/kg; range 0.123–0.183 mg/kg); 7 patients received suspension (mostly infants) and 9 received capsules.

Pharmacokinetic parameters for intravenous and oral tacrolimus are presented in Table I. Mean

Table I : Pharmacokinetic parameters following intravenous and oral administration of tacrolimus.

		Intravenous infusion (n = 12)		First oral dose (n = 16)	
		Mean	SD	Mean	SD
$AUC_{(0-n)}$	(ng.h/ml)	1278.4	1931.0	252.4	167.4
CL	(ml/min/kg)	2.3	1.2	na	na
$t_{1/2}$	(h)	11.5	3.8	12.4	4.4
Vz	(l/kg)	2.6	2.1	9.0	11.1
C_{max}	(ng/ml)	na	na	37.0	26.5
t_{max}	(h)	na	na	2.1	1.3
F	(%)	na	na	25	20

Where CL is the total body clearance, $AUC_{(0-n)}$ is area under the time curve from the initial to subsequent dose, $t_{1/2}$ is the terminal half-life, V_z the volume of distribution, C_{max} is the peak concentration, t_{max} the time to peak concentration and F the absolute oral bioavailability; na = not applicable.

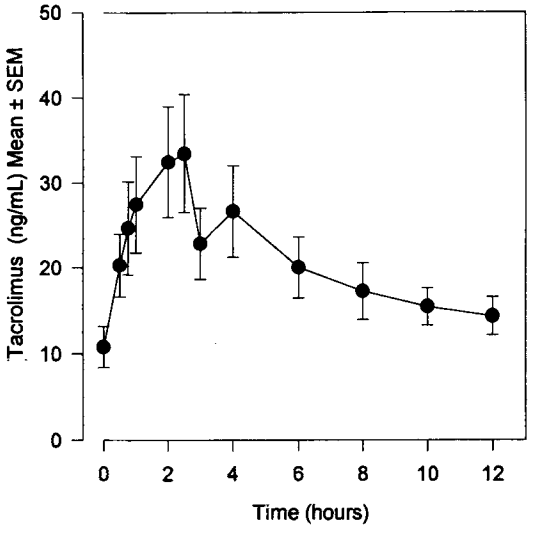

Fig. 1 : Mean pharmacokinetic profile after the first oral dose.

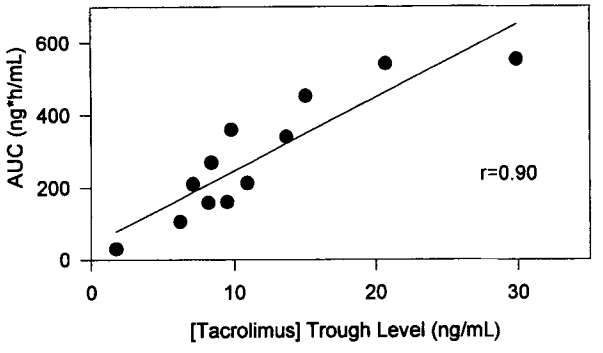

Fig. 2 : AUC values versus whole blood trough concentrations of tacrolimus.

terminal half-life ($t_{1/2}$) estimates were similar for intravenous and oral tacrolimus. Interpatient variability was high. The mean pharmacokinetic profile for the first oral dose is shown in Figure 1.

A strong correlation was observed between AUC and trough whole blood levels of tacrolimus after the first oral dose of tacrolimus ($r = 0.90$; Fig. 2).

DISCUSSION

Since the intravenous pharmacokinetic estimates were derived, in many instances, from only three data points and some of the profiles did not have data points within the terminal portion of the elimination period, clearance rather than the terminal half-life is a more accurate estimate of the elimination of tacrolimus. The accuracy of the oral tacrolimus half-life estimate is limited by the period in which the data were collected. The sampling period was approximately the same as the estimated half-life (approximately 12 h). The profile could not be extended beyond 12 h because oral tacrolimus had to be given twice daily to ensure sufficient immunosuppression. Overall, the reliability of the pharmacokinetic estimates is limited by the low patient number and the high interpatient variability.

The mean intravenous clearance of 2.3 ml/min/kg estimated in this paediatric population is about twice as high as the mean clearance previously estimated in adult liver transplant recipients (0.88 ml/min/kg or 4.1 l/h) (5). The faster clearance in children observed in the present study could account for their higher dosage requirements (9,10). The mean oral bioavailability in the present study is similar to that estimated in adult liver transplant recipients (5).

The high correlation between AUC values and trough whole blood concentrations after oral administration of tacrolimus suggests that the trough concentration is a reliable measure of systemic exposure.

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REFERENCES

1. Tzakis A.G., Reyes J., Todo S. et al. (1993) : Two-year experience with FK 506 in pediatric patients. Transplant. Proc., 25, 619-621.
2. Inomata Y., Tanaka K., Egawa H. et al. (1996) : The evolution of immunosuppression with FK506 in pediatric living-related liver transplantation. Transplantation, 61, 247-252.
3. Tzakis A.G., Reyes J., Todo S. et al. (1991) : FK 506 versus cyclosporine in pediatric liver transplantation. Transplant. Proc., 23, 3010-3015.
4. McDiarmid S.V., Busuttil R.W., Ascher N.L. et al. (1995) : FK506 (tacrolimus) compared with cyclosporine for primary immunosuppression after pediatric liver transplantation. Results from the US multicenter trial. Transplantation, 59, 530-536.
5. Lee C., Jusko W., Shaefer M. et al. (1993) : Pharmacokinetics of tacrolimus FK506 in transplant patients. Clin. Pharmacol. Ther., 53, 181.
6. Undre N., Möller A., the FK 506 European Study Group. (1994) : Pharmacokinetic interpretation of FK 506 levels in blood and in plasma during a European randomised study in primary liver transplant patients. Transplant. Int., 7 (Suppl.1), S15-S21.
7. Kobayashi M., Tamura K., Katayama N. et al. (1991) : FK 506 assay past and present characteristics of FK 506 ELISA. Transplant. Proc., 3, 2725-2729.
8. Heinzel G., Woloszczak R., Thomann P. (1993) : TopFit: 2.0; pharmacokinetic and pharmacodynamic data analysis system for the PC. Berlin: Gustav Fischer, ISBN 3-437-11486-7.
9. Jain A.B., Fung J.J., Tzakis A.G. et al. (1991) : Comparative study of cyclosporine and FK 506 dosage requirements in adult and pediatric orthotopic liver transplant patients. Transplant. Proc., 23, 2763-2766.
10. McDiarmid S.V., Colonna J.O., Shaked A. et al. (1993) : Differences in oral FK506 dose requirements between adult and pediatric liver transplant patients. Transplantation, 55, 1328-1332.