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Tacrolimus Pharmacokinetics in Living-Donor and Deceased-Donor Liver Transplant in Saudi Patients

Abou-Auda HS[1,*], Qaddour E[2], Alsisi H[3], Ajlan A[4] and Alsebayel M[5]

[1]College of Pharmacy, King Saud University, Riyadh, Saudi Arabia
[2]College of pharmacy, Riyadh Elm University, Riyadh, Saudi Arabia
[3]Liver Transplant Department, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia
[4]Solid organ Transplant, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia
[5]Liver Transplant Department, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia

***Correspondence**: Hisham S. Abou-Auda, College of Pharmacy, King Saud University, P.O.Box 2457, Riyadh 11454, Saudi Arabia, E-mail: hisham@ksu.edu.sa

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Abstract

Introduction: Tacrolimus is a macrolide immunosuppressant. It has a narrow therapeutic index and serious side effects which necessitate monitoring of tacrolimus blood concentration. The trough concentration of the drug may also differ based on the type of liver transplant. This study was conducted to investigate differences in pharmacokinetics between transplant types and to determine tacrolimus population pharmacokinetic in liver transplant recipients in Saudi Arabia.

Method: Patients on tacrolimus, as the main immunosuppressant, who underwent liver transplant throughout 2012-2014 were retrospectively studied. Demographic characteristic, tacrolimus blood trough concentrations, liver, renal, biochemistry, and hematology lab results were all collected. The pharmacokinetic parameters were estimated assuming one compartment model.

Results: Tacrolimus pharmacokinetic parameters were found to be as following; elimination rate constant ($\mathbf{k_{el}}$) 0.094 ± 0.0123 hr^{-1}, parent volume of distribution ($\mathbf{V_d/F}$) 112.48 ± 63.033 L/hr, elimination half-life ($\mathbf{t_{1/2}}$) 7.46 ± 1.01 hr and apparent total body clearance (**CL/F**) 10.27 ± 5.69 L/hr (mean ± SD). Statistically significant difference was found between living-donor and deceased-donor liver transplant with respect to apparent clearance and apparent volume of distribution. Living-donor liver transplant recipients have apparent volume of distribution of 97.39 ± 47.00 L (mean ± SD) and an apparent clearance of 8.89 ± 4.24 L/hr (mean ± SD). On the other hand, deceased-donor liver transplant has an apparent clearance of 12.97 ± 7.09 L/hr (mean ± SD) and an apparent volume of distribution of 142.17 ± 78.65 L (mean ± SD).

Conclusions: Tacrolimus pharmacokinetics parameters were accurately determined in liver transplant recipients in Saudi Arabia. The results of the present study can be clinically used in the therapeutic drug monitoring of tacrolimus in the individualization of drug dosage and taking the appropriate clinical decisions to prevent allograft rejection.

Keywords: Liver transplant, Tacrolimus, Pharmacokinetics, Saudi Arabia, Living donor, Deceased donor

Introduction

Rejection has been the most important issue after transplant but with the development of immunosuppressants, patients can overcome this problem. Tacrolimus, also known as FK506, is a macrolide antibiotic working as immunosuppressant by inhibiting calcineurin [1]. Due to the large variability in the rate

of absorption and absolute bioavailability in orally administered tacrolimusas [2] and the presence of some factors affecting its pharmacokinetic parameters [3] in addition of being a narrow therapeutic index drugs with a serious side effects [1,4,5,], Tacrolimus blood concentration should be monitored, and dose should be individualized based on patients-related factors to prevent rejection and serious side effects.

This study was conducted to identify the factors affecting pharmacokinetics of Tacrolimusas transplant type and to estimate pharmacokinetic parameters of Tacrolimus in Saudi liver transplant patients for better determination of the dose.

Methodology

Data of liver transplant patients, who underwent transplant between 2012-2014, were collected retrospectively during the year of 2015. 184 patients receiving Tacrolimus as their main immunosuppressant therapy, aged ≥ 16 years were enrolled in our study. Pregnant women and patient with another organ transplant were excluded.

Clinical data about participants (demographic characteristics, concomitant diseases and medications, Tacrolimus dose and trough levels, and biochemistry, hematology, renal and liver profile)were collected using a standardized data collection form (appendix 1).

Patients were categorized into groups based on BMI. In addition, BSA, using Mostellar [6] and Du Bois equations [7], IBW by Devine formula [8], and creatinine clearance by Cockcroft-Gault equations were all calculated for each patient [9].

Pharmacokinetic analysis

To determine pharmacokinetic parameters of Tacrolimus the data were fitted to the one-compartment steady state equation as follows:

$$C^{ss}_{min} = \frac{D \cdot e^{-k_d \cdot \tau}}{\left(V_d/F\right)\left(1 - e^{-k_d \cdot \tau}\right)} \qquad \text{eqn. (1) [10]}$$

Where D is tacrolimus daily dose,τ is the dosing interval, C^{ss}_{min} is the minimum tacrolimus concentration at steady state, (V_d/F) is the apparent volume of distribution, and k_d is the elimination rate constant.

The parameters will be determined by equation 1 using nonlinear regression.

The initial estimate for nonlinear regression were extracted from literature and confirmed by our preliminary calculations of pharmacokinetic parameters derived from our data. In this regard, the initial estimate of the elimination rate constant (k_{el}) was assumed to be 0.1 hr^{-1}, and the assumption of the apparent volume of distribution (V_d/F) was 200 L.

Based on the results from the previous step, the elimination half-life ($t_{1/2}$) was calculated using equation 2, as follows:

$$t_{1/2} = \frac{0.693}{k_{el}} \qquad \text{eqn. (2) [10]}$$

Where $t_{1/2}$ is the first order elimination half-life, and k_{el} is the elimination rate constant.

After that, the clearance was calculated for each level by equation 3 as follows:

$$CL/F = V_d/F \cdot k_d \qquad \text{eqn. (3) [10]}$$

Where **CL/F** is the apparent total body clearance, V_d/F is the apparent volume of distribution, and k_d is the elimination rate constant.

Statistical analysis performed using SPSS version 23 and appropriate statistical tests were applied when possible. Shapiro-Wilk test and Kolmogrov-Smirnov test were used to test normality, which was expressed using mean ± SD and any differences were analyzed using appropriate parametric tests. Non-normally distributed data was analyzed using Mann-Whitney test, Wilcoxon rank test, and Kruskal-Walis test based on the number of the groups. Chi square and Fisher's exact test were used for categorical variables. The level of significance for all test was 0.05.

Results

This study has involved 184 liver transplant patients who met the inclusion criteria and their data were analyzed. The demographic characteristics of the study sample are shown in table 1. The 184 liver transplant recipients have an age range between 16-80 years with an average age of 52.43 ± 14.06 years (mean ± SD). Females

comprise 41.3 % (*n*=76) of our sample of patients with an average age of 50.63 ± 15.30 years (mean ± SD), whereas males accounted for 58.7 % (*n*=108) of the sample of patients with an average age of 53.69 ± 13.03 years.

Females' mean height, weight, and ideal body weight (IBW) were 155.67 ± 6.71cm (mean ± SD), 70.40 ± 19.33 kg, and 48.80 ± 6.04 kg, respectively, which are lower than the corresponding mean height, weight, and IBW for males (167.32 ± 8.66 cm, 74 ± 18.65 kg, and 63.80 ± 7.80 kg, respectively).

A comparison between males and females with respect to their demographic data showed that there was no significant difference in age and weight between male and female (p>0.05). Whereas height, IBW, BMI and BSA showed that they were extremely statistically significant difference (p<0.05) (Table 1).

The clinical biochemical and hematological laboratory measurements were carried out for these patients and another statistically significant difference was found in MCHC, serum creatinine, and total protein between males and females (p<0.05) (Table 2).

In addition to their transplant crisis, patients were affected by other ailments and disease conditions. Almost three quarters of our sample suffered DM (135 patients). HTN, Hypothyroidism and CKD were found in 69, 33, and 18 patients consequently (Table 3). Among these diseases, only CKD found to affect the average Tacrolimus blood concentration (p<0.05). CKD reduces Tacrolimus blood concentration by 25%.

By identifying the reasons for liver transplant. We found that the most common reason for liver transplant is ESLD which comprises 69.6%. Hepatitis C was the second reason for transplant in about 34.2% compared to HBV which accounts for only 31 transplants. 57 patients suffered hepatocellular carcinoma, 47 patients cryptogenic liver cirrhosis, 25 patients with liver cirrhosis, 22 with autoimmune hepatitis, 16 patients with non-alcoholic steatohepatitis, and <10% causes for each of the following diseases: sclerosing cholangitis, Wilson disease, Biliary Cirrhosis, Budd Chiary Syndrome, bilharzial cirrhosis, Dubin Johnson Syndrome, Acute Liver failure, Focal nodular hyperplasia, alcoholic liver cirrhosis, schistosomia, Alagile Syndrome, liver tumor, and progressive familial intrahepatic cholestasis.

Table 4 shows the distribution of patients based on their type of transplant and gender. 37 males underwent deceased donor liver transplant whereas 71 had a living donor liver transplant. For females, 25 underwent deceased donor liver transplant and 51 females underwent living donor liver transplant. The comparison between living-donor and deceased-donor transplant recipients revealed a statistically significant difference in platelets (p=0.001), globulin (p=0.003), and alkaline phosphatase (p<0.001) (Table 5).

Determination of the pharmacokinetic parameters of Tacrolimus

10 post-transplant sampling periods were used to estimate the pharmacokinetic parameters for each sampling period and then the average parameters were calculated as shown in table 6.

The average parameter estimates for tacrolimus in a sample of 184 liver transplant recipients were found to be: Mean (± SD) elimination rate constant **(k_{el})** was 0.094 (± 0.0123) hr^{-1}. The volume of distribution **(V_d/F)** averaged 112.48 ± 63.033 L (mean ± SD). The elimination half-life of the drug **($t_{1/2}$)** was calculated using equation 1and averaged 7.46 ± 1.01hr (mean ± SD).

The total body clearance of tacrolimus **(CL/F)** was calculated from these data using cockroft-gault equation (9) and was found to be 10.27 ± 5.69 L/hr (mean ± SD) (Table 6).

Living donor vs. Cadaveric donor liver transplantation

A statistically significant difference (p<0.001) was found in average Tacrolimus volume of distribution and total body clearance between living-donor and cadaveric-donor liver transplant as shown in table 7. Average Tacrolimus volume of distribution was higher in deceased-donor (142.17 L) than in living-donor (97.39 L). As well as the total body clearance was higher in cadaveric donor (12.97 µg/L) than in living donor (8.89 µg/L) (Table 7).

Discussion

Tacrolimus trough levels for 184 adult liver transplant patients were extracted from the medical files of the studied patients, with other demographic characteristics, concurrent diseases, concomitant interacting drugs and important lab results.

Our sample showed a statistically significant difference

Table 1: Demographic characteristics of patients' sample as a function of genderin 184 liver transplant recipients.

	Mean ± SD (range)			P-value*
	Males	Females	Total	(sig)
	(n=108)	(n=76)	(n=184)	
Age (years)	53.69 ± 13.03	50.63 ± 15.30	52.43 ± 14.06	0.158
	(16-80)	(16-74)	(16-80)	
Weight (kg)	74 ± 18.65	70.40 ± 19.33	72.51 ± 18.97	0.206
	(24.8-122.6)	(44-131)	(24.8-131)	
Height (cm)	167.32 ± 8.66	155.67 ± 6.71	162.51 ± 9.77	0.000
	(132-191)	(140-173)	(132-191)	
IBW(kg)	63.80 ± 7.80	48.80 ± 6.04	57.60 ± 10.26	0.000
	(32-85.1)	(34.70-64.4)	(32-85.1)	
BMI(kg/m^2)	26.36 ± 6.10	29 ± 74.1	27.45 ± 6.79	0.009
	(8.10-43.06)	(17.19-49.57)	(8.10-49.51)	
BSA(m^2)	1.83 ± 0.25	1.71 ± 0.23	1.78 ± 0.25	0.001
	(1.02-2.44)	(1.37-2.37)	(1.02-2.44)	

* Student's t-test for independent samples (Normality test = Shapiro-Wilk's test)

IBW= ideal body weight, BMI= body mass index, BSA= body surface area

Table 2: Comparison between males and females in some clinical hematological and biochemical characteristics.

Test		Male (n=108)	Female (n=76)	p-value*
MCHC	(g/L)	341.74 ± 9.83	338.28 ± 9.27	0.031
BUN	(mmol/L)	8.66 ± 5.28	8.29 ± 5.26	0.675
Scr	(µmol/L)	103.91 ± 71.63	85.94 ± 65.91	0.047
CLcr	(mL/min)	93.98 ± 43.06	97.15 ± 45.65	0.442
Total Protein	(g/L)	51.36 ± 5.13	54.05 ± 6.83	0.002
Ammonia	(µg/L)	29.27 ± 19.57	32.47 ± 13.94	0.262

* Independent t-test (Normality by Shapiro-Wilk), MCHC=Mean Corpuscular Hemoglobin Content, BUN=blood urea nitrogen, Scr=serum creatinine, CLcr=creatinine clearance.

between males and females with regard to height, IBW, BMI and BSA. These differences are caused by higher muscle mass in males and greater bone density. These factors also contribute to the difference in serum creatinine, BUN and creatinine clearance between males and females.

The statistically significant difference between living-donor and deceased-donor liver transplant regarding platelets, globulin, and alkaline phosphatase may be caused by a difference in graft size.

CKD was found in only 18 patients but there was a statistically significant difference in the average tacrolimus blood concentration, where, concentrations were found to be lower in patients with chronic kidney disease. These differences might be due to hypoalbuminemia caused by kidney diseases. In which, there is increased albumin loss by glomerulus and increased degradation of the protein by the tubules. Our findings were contrary to the findings of C. Staatz et al (2004) where they concluded that tacrolimus clearance was the same in patients with severe renal dysfunction before transplant and in healthy volunteers [3].

Males and females showed statistically different values for MCHC, serum creatinine, and total protein. This difference may be attributed to different muscle mass

Table 3: The effect of disease state on the average Tacrolimus blood concentration in whole blood in 184 liver transplant recipients.

Disease	Blood Concentration (µg/L)		p-value*
	Mean ± SD		
	(n)		
	Disease	No Disease	
Diabetes	7.16 ± 1.74	6.71 ± 1.76	0.124
	-135	-49	
Hypertension	7.07 ± 1.79	7.03 ± 1.74	0.872
	-69	-115	
CKD	5.83 ± 1.53	7.17 ± 1.73	0.002
	-18	-166	
Hypothyroidism	7.15 ± 1.69	7.25 ± 2.08	0.814
	-33	-151	
Tuberculosis	7.57 ± 1.31	7.03 ± 1.77	0.495
	-5	-179	

* Independent sample t-test , NS = statistically not significant, S= statistically significant.

CKD= chronic kidney disease.

Table 4: The distribution of patients as a function of transplant type in 184 liver transplant recipients.

Transplant type	Number (%)		
	Male	Female	Total
Deceased Donor	37 (34.2)	25 (32.8)	62 (33.6)
Living Donor	71 (65.7)	51 (67.1)	122 (66.3)

** Chi-square

Table 5: Comparison between living-donor and deceased-donor transplant recipients in some clinical hematological and biochemical characteristics.

Test		Living-Donor	Deceased Donor	p-value*
		(n=122)	(n=62)	
Platelets	(103/µL)	100.12 ± 49.42	137.75 ± 79.81	0.001
Total protein	(g/L)	52.42 ± 6.27	53.853± 6.13	0.098
Globulin	(g/L)	16.31 ± 5.46	18.84 ± 5.39	0.003
Alkaline phosphatase	(U/L)	88.01 ± 59.97	152.87 ± 88.92	0

* Independent t-test (Normality by Shapiro-Wilk)

Table 6: Final pharmacokinetic parameter estimates of tacrolimus calculated usingnonlinear regression model.

Parameter	Estimate	
	Mean ± SD	Range
First order elimination rate constant (kel) (hr-1)	0.094 ± 0.0123	0.076-0.109
Half-Life (t1/2) (hr)	7.46 ± 1.01	6.36-9.12
Apparent volume of distribution (Vd/F) (L)	112.48 ± 63.033	19.49-433.91
Total body clearance (CL/F) (L/hr)	10.27 ± 5.69	1.82-39.62

Table7: Comparison of the apparent volume of distribution (Vd/F) and total body clearance (CL/F) between living-donor liver transplant recipients (n=122) and cadaveric-donor liver transplant recipients (n=62).

Parameter	Transplantation		p-value*
	Living-Donor	Deceased-Donor	
	Mean ± SD	Mean ± SD	
Vd/F (L)	97.39 ± 47.00	142.17 ± 78.65	0.000
Vd/F (L/kg)	1.44 ± 0.746	1.99 ± 1.27	0.003
CL/F (L/hr)	8.89 ± 4.24	12.97 ± 7.09	0.000
CL/F (L/hr/kg)	0.132 ± 0.067	0.182 ± 0.115	0.003

*Mann-Whitney U test/Wilcoxon rank sum W test
V_d/F = apparent value of distribution, CL/F = apparent total body clearence

between males and females.

The estimation of the pharmacokinetic parameters of tacrolimus was done by a nonlinear regression. Assuming that the drug is following a one compartment model, mean values for $\mathbf{k_{el}}$, $\mathbf{V_d}$, $\mathbf{t_{1/2}}$ and **CL/F** were found to be 0.094 ± 0.0123 hr^{-1}, 112.48 ± 63.033 L/kg, 7.46 ± 1.01 hr, and 10.27 ± 5.69 L/hr, respectively. The average dose was 5.35 ± 2.36 mg (mean ± SD) giving an average tacrolimus trough concentration 7.044 ± 1.76 ng/mL (mean ± SD). These results are comparable to the one found in Sam WJ et al (2006) were apparent clearance was found to be 14.1 L/hr and the apparent volume of distribution 217 L [11].

Our results differ from that of the Iranian liver transplant by Zahra Nassiri et al (2014), which had lower value for clearance (9.3 ± 0.96 L/hr, mean ± SD) and lower apparent volume of distribution (101 ± 29 L, mean ± SD) except for the elimination half-life (7.5 hr) which is the same [12].

The results of Zahir et al (2005) had greater values of the parameters. Where, the apparent clearance was 21.3 L/hr and the apparent volume of distribution was found to be 316.1 L [13].

17.6 L/hr, 225 L, and 4.48 hr^{-1} were the values found by Liqin Zhu et al (2015) for clearance, volume of distributions and absorption rate constant [14].

Cecile et al (2014) mentioned the determined values for the apparent clearance to be 17 L/hr, and the volume of distribution as 486 L, which was conducted in Paris. Still higher values than estimated in our study. All these differences could be attributed to ethnic differences in the pharmacokinetics of tacrolimus among these different populations of patients [15].

The findings in the present study revealed a statistically significant difference (p<0.001) in average Tacrolimus blood levels between living donor and deceased donor liver transplant and this is possibly due to reduced hepatic metabolism during liver regeneration following living donor transplantation [16]. These results agree with Tanaka et al (2005) [17].

About 45.89% increases in both the apparent volume of distribution **(V_d/F)** and the total body clearance **(CL/F)** of tacrolimus in cadaveric-donor liver transplant recipients compared to living-donor liver transplant recipients. The reasons for this increase can be attributed to the immature liver function in the living-donor liver transplant recipients and consequently, the lower metabolizing power of the living transplanted allograft.

Conclusion

This is a retrospective study conducted in Riyadh for the estimation of population pharmacokinetics of tacrolimus after liver transplant.

A nonlinear regression was used for the determination of the pharmacokinetic parameters, which were found to be as follows: elimination rate constant ($\mathbf{k_{el}}$) 0.094 ± 0.0123 hr^{-1}, apparent volume of distribution **(V_d/F)** 112.48 ± 63.033 L/hr, elimination half-life ($\mathbf{t_{1/2}}$) 7.46 ± 1.01 hr and apparent clearance **(CL/F)** 10.27 ± 5.69 mL/hr (mean ± SD).

Transplant type was also found to affect the clearance of the drug and the volume of distribution. Living-donor liver transplant recipients have lower clearance and volume of distribution than the deceased-donor liver transplant patients.

The effect of chronic kidney disease on the average tacrolimus trough concentration was found statistically

significant (p-value = 0.002).

Recommendation

Multicenter larger studies are still required to determine other factors affecting the trough concentrations of the drug and causing inter and intra patients' variability.

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