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MONITORING OF ORGAN (KIDNEY TRANSPLANT) TRANSPLANT DRUG (TACROLIMUS) CONCENTRATIONS AND ANALYSIS OF INDIVIDUALIZED DOSING

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Abstract: Objective: To explore the influence of patient's gender, age and combination of drugs on FK506 blood concentration after organ transplantation (kidney transplantation), monitor and analyze the whole blood trough concentration of tacrolimus in patients after kidney transplantation, and evaluate the effectiveness and safety of tacrolimus treatment by referring to the effective target concentration range of the guidelines and the influence of patients' combination of drugs. Methods: 138 patients after kidney transplantation were collected, and FK506 blood concentration at different time after kidney transplantation was retrospectively analyzed. Statistical analysis was carried out according to gender, age and other groups, and the blood concentration of tacrolimus, intra individual fluctuations of blood concentration and related drugs were analyzed. Results: One month after operation, the FK506 blood concentration gradually decreased with the prolongation of postoperative time. During the same period, there was no significant difference in FK506 plasma concentration between male and female patients of different sexes ($P<0.05$). Within 3 months after kidney transplantation, the blood concentration of female patients was slightly higher than that of male patients. Three months after operation, the FK506 blood concentration, dosage and blood concentration in the elderly group were significantly lower than those in the young group and the middle-aged group ($P<0.05$). The immunosuppressive regimen after transplantation was tacrolimus+mycophenolate mofetil+methylprednisolone. Proton pump inhibitors, calcium antagonists and Bailing capsules were commonly used after transplantation; The target blood concentration of tacrolimus was 5.1~6.1 ng · mL －; At 12 months after transplantation, 47%, 47% and 8% of the patients had in vivo coefficient of variation of tacrolimus blood concentration<20%, 20.1% - 35% and>35%, respectively. Conclusion: Gender, age, combined medication and other factors have a certain impact on the pharmacokinetics of FK506 in vivo. It is necessary to strengthen the evaluation of treatment plans and pharmaceutical monitoring after transplantation, adopt individualized drug delivery plans and timely adjust them, keep the blood concentration of tacrolimus in a reasonable range and reduce fluctuations, and effectively optimize the anti rejection effect.
Keywords: Renal transplantation; Tacrolimus; Blood drug concentration; Medication analysis

1 INTRODUCTION

Tacrolimus (also known as FK506) is a macrolide immunosuppressive drug. It has good clinical effect on immunosuppression after organ transplantation [1] . It was originally extracted from the fermentation broth of soil fungi, and is a calcineurin inhibitor. As a classical immunosuppressive drug that must be used by kidney transplant patients, it is a first-line drug [2-3] to prevent and treat acute rejection after transplantation. As early as 1989, it was found that tacrolimus was applied to clinical transplantation rejection treatment, and the rejection of the recipient to the transplanted organ was well controlled [4-5] . Subsequently, the role of tacrolimus in preventing immune rejection after different organ transplantation and bone marrow transplantation was accepted clinically. However, due to its narrow therapeutic window and large individual difference in pharmacokinetic/pharmacodynamic characteristics, its clinical application cannot be widely used. When renal transplant patients use tacrolimus, the survival rate of recipient kidney transplantation is low due to the occurrence of serious adverse events [6] . Therefore, it is necessary to monitor the blood concentration of FK506 to achieve individualized medication and ensure safe and effective medication. The blood drug concentration of oral tacrolimus varies greatly among individuals, the therapeutic window is narrow, the therapeutic dose is very close to the toxic dose, and the effective blood drug concentration of tacrolimus is closely related to the renal function and rejection after transplantation. Therefore, it is necessary to conduct routine blood drug concentration monitoring and individualized dose adjustment for the drug.

This paper retrospectively analyzed the postoperative tacrolimus blood concentration in 138 patients who underwent allogeneic renal transplantation in a tertiary hospital, aiming to explore the range of efficacy and safety of the anti-rejection therapy of tacrolimus after renal transplantation, and to provide a reference for further implementation of the medication guidance, and to effectively improve the level of clinical treatment of tacrolimus.

2 INFORMATION AND METHODS

2.1 Case Information

The cases were derived from 138 post renal transplantation patients (75 males, 63 females) totaling 1309 cases, aged between 18 ~65 years, with a mean of (37.3+8.6) years, who underwent tacrolimus blood concentration monitoring at the author's hospital from 2019.05 to 2020.12 .
Inclusion criteria: the postoperative time is not less than 3 months, and the postoperative follow-up data is ≥ 90 days. The follow-up indicators include the blood concentration of tacrolimus, serum creatinine (Scr) and glomerular filtration rate. All patients have clear research content and signed an informed consent form.
Exclusion criteria: recipients with acute rejection and acute infection; Have used drugs that affect tacrolimus metabolism due to infection and other factors, such as macrolide antibiotics, ketoconazole, fluconazole, clotrimazole and rifampicin; Patients who take grapefruit juice, diltiazem and other foods or drugs that can increase the blood concentration of tacrolimus. There were liver diseases before and after the operation (that is, ALT and AST increased more than twice the normal value during the study period); Take tacrolimus for at least 3 months.

2.2 Combined Medication Programs

After kidney transplantation, the patient directly adopted the scheme of tacrolimus+mycophenolic acid+prednisone. He began to take tacrolimus orally 24 hours after the operation, with the initial dose of 0.10~0.25 mg/kg · d, once for 12 hours, for 4 consecutive days or once a day for rabbit anti human thymocyte immunoglobulin, and for 3 consecutive days, he received immunosuppressive induction treatment. The dose was adjusted in time according to the monitoring of tacrolimus blood concentration and clinical conditions. Mycophenolate mofetil 1.5-2.0 g/d, taken twice, starting at 8:00 p.m. on the first day before operation; After operation, methylprednisolone 500mg was given intravenously once a day for 5 days, and then oral prednisolone 16mg was taken and gradually reduced to the maintenance dose.
Antibacterial drugs: intravenous drip of antibacterial drugs was started 30 minutes before the routine operation to prevent infection. On the day after the operation, the antifungal drug micafen was used for net intravenous drip to prevent fungal infection. The dual antibacterial drugs were used for 10-15 days of prophylactic treatment, and then the drugs were stopped, other antibacterial drugs were changed or antiviral drugs were added as needed.
Proton pump inhibitors: Intravenous proton pump inhibitors are routinely started on the day of surgery, with omeprazole, lansoprazole and pantoprazole being the most commonly used.
Other medications include calcium antagonists, atorvastatin calcium, Berin capsules, and berberine hydrochloride.

2.3 Blood Sample Collection

The whole blood tacrolimus trough concentration should be monitored from 1 week after surgery, 1-2 times/week in 1 month, 1 time/week in 1~3 months, 1 time/month in 3~6 months, and irregular blood collection after 6 months. When dosage adjustment or combination of drugs may affect the blood concentration of tacrolimus, increase the frequency of measurement to keep the blood concentration in the appropriate range. The fluctuation of tacrolimus concentration within 12 months after transplantation was observed to evaluate the prognosis of the transplanted kidney. For the evaluation of blood creatinine and glomerular filtration rate, blood creatinine and glomerular filtration rate at 1, 3, 6 and 12 months after transplantation were observed to evaluate the post-transplant renal function.
All patients strictly followed the standard medication and blood collection time. They took tacrolimus at 20:00 in the evening one day before blood collection, and took 2 ml of venous blood within 1 hour before taking the drug at 8:00 in the morning of the next day. They were placed in an EDTA-K2 anticoagulant tube and measured on the same day.

2.4 Monitoring of Wole Blood FK506 Concentration

2.4.1 Instruments and reagents
Instrument: American ABBOTT Tacrolimus Monoclonal Antibody Kit and Particle Immunoanalyzer (IMX), high efficiency centrifuge.
Tacrolimus capsule, specification: 0.5 mg per capsule, produced by Asterai Pharmaceutical Co., Ltd; Tacrolimus capsule, specification: 1mg per capsule, 0.5mg per capsule, produced by Hangzhou Zhongmei Huadong Pharmaceutical Co., Ltd.
2.4.2 Measurement methods
Microparticle immunoassay (MEIA) was used. The main steps of the determination are: accurately suck 150ul of the blood sample to be tested or the standard blood sample or the quality control blood sample, add 150ul of the whole blood protein precipitant, swirl for 30s, centrifugate at 10000r/min for 5min, suck 150ul of the supernatant after centrifugation and put it into the IMX analyzer, which will automatically detect and print the results, and it takes about 60 minutes to get the results.

2.5 Statistical Treatment

SPSS19.0 was used to sort out and analyze the data, which was expressed by counting data ($x \pm s$). $P<0.05$ was statistically significant.

3 RESULTS AND DISCUSSION

3.1 General Information about the Patients

Table 1 General Information about the Patients

Group	Data
Sex (m/f)	75/63
Age (years)	18-65
Weight (kg)	63±11
Number of days of hospitalization (days)	41±12.8
Number of days of hospitalization after transplantation (days)	28±9

3.2 Results of Whole Blood Tacrolimus Concentration Measurements at Different Times Postoperatively

1309 times of whole blood tacrolimus trough concentration of 138 renal transplant patients were compared according to different time after operation. The results are shown in Table 1. The mean whole blood trough concentration of tacrolimus gradually decreased with the time after transplantation. It was ≤ 5.07~15.17 μ g/L in one month, 5.31~11.73 μ g/L in one to three months, 4.96~10.74 μ g/L in three to six months, 4.04~8.57 μ g/L in six to twelve months, and 2.88~7.84 μ g/L in more than 12 months.

Table 2 Determination Results of Whole Blood Tacrolimus Concentration at Different Times after Operation (x ± s)

Postoperative time (months)	Example	Blood concentration (ug/L)
≤1	546	10.12±5.05
1<n≤3	398	8.52±3.21
3<n≤6	189	7.85±2.89
6<n≤12	103	6.34±2.23
>12	73	5.36±2.48

3.3 Relationship between FK506 Blood Concentration and Gender of Renal Transplant Patients

The measured values of 1309 whole blood tacrolimus valley concentrations in 138 renal transplant patients were compared according to gender groups, as shown in Table 3. During the same period, there was no statistically significant difference in FK506 plasma concentration between male and female patients of different gender groups (P>0.05). Within 3 months after kidney transplantation, the blood concentration of female patients was slightly higher than that of male patients.

Table 3 Relationship between FK506 Blood Concentration and Gender and Dose of Renal Transplant Patients (x ± s)

Duration (months)	male		female	
	Example	Blood concentration (ug/L)	Example	Blood concentration (ug/L)
≤1	327	9.82±4.75	219	10.35±4.82
1<n≤3	227	8.13±2.82	171	8.62±3.11
3<n≤6	107	7.89±2.85	82	7.138±2.82
6<n≤12	68	6.16±2.12	35	6.31±2.26
>12	41	5.36±2.48	32	5.04±2.16

3.4 Relationship between FK506 Blood Concentration and Age of Renal Transplant Patients

138 patients were divided into three age groups according to their age. They were young people (19~45 years old). 897 cases were followed up; Middle aged people (45-59 years old) were followed up for 294 times; The elderly (⩾ 60

years old) group was followed up for 118 times. The dosage and blood concentration of FK506 in three patients of different ages showed a downward trend with the increase of age, as shown in Table 4. Three months after operation, the FK506 blood drug concentration, dosage and blood drug concentration of the elderly group were significantly lower than those of the young group and the middle-aged group (P<0.05).

Table 4 Relationship between FK-506 Blood Concentration and Age of Renal Transplant patients (x ± s)

Duration (months)	19-45 years old		45-59 years old		≧60 years old	
≤1	374	9.83±4.76	122	10.23±4.94	50	10.06±4.62
1<n≤3	272	8.10±2.79	90	7.89±2.34	36	9.02±2.63
3<n≤6	130	7.82±2.92	42	7.52±2.54	17	7.13±2.17
6<n≤12	71	6.82±1.75	23	6.54±2.03	9	6.12±1.92
>12	50	5.76±2.08	17	4.89±2.18	6	4.08±1.2

3.5 The medication treatment of the perioperative period of kidney transplant patients.

Table 5 List of Combination Medications for Renal Transplantation Patients During the Perioperative Period

Category	Drugs	mode of administration	Quantity
Antimicrobials	piperacillin tazobactam	Oral	65
	Cefoperazone; Sulbactam sodium	Oral	2
	ceftazidime	Oral	1
	Sulbenicillin sodium	Oral	1
Antifungals	micafungin sodium	Oral	67
proton pump inhibitors	Lansoprazole	Oral	22
	Omeprazole	Oral	28
	pantoprazole	Oral	23
calcium antagonists	Nifedipine	intramuscular injection	11
	Amlodipine	intramuscular injection	36
	Nicardipine	intramuscular injection	1
	Felodipine	intramuscular injection	1
other relevant drugs	Atorvastatin calcium tablets	intramuscular injection	57
	Aspirin enteric-coated tablets	intramuscular injection	45
	Bai Ling Capsules	intramuscular injection	69
	Berberine hydrochloride tablets	intramuscular injection	2

3.6 Tacrolimus Blood Concentrations after Transplantation

There were 138 subjects in this study, and the blood drug concentration of tacrolimus was grouped into<5,5.1~6.1,6 1~10,10. 1~15 and>15 ng • mL-1, according to the proportion and percentage, the blood concentration of tacrolimus at 1,3,6 and 12 months after transplantation is shown in Table 6.

Table 6 Blood Concentration of Tacrolimus after Transplantation (n,%)

Concentration (ng/ml)	January	March	June	December
≤5	56(40.7)	60(44)	54(44)	40(49)
5.1-6.1	44(32)	47(34)	37(29.8)	30（37）

6.1-10	34(25)	33(24)	31(26)	12(15)
>10	4(3)	0	0	0

3.7 Blood Creatinine and Glomerular Filtration Rate

Table 7 shows that with the combination of drugs, blood creatinine and glomerular filtration rate change for the better, which can indicate that the post-transplantation renal function recovery is good, but with the combination of drugs for a longer period of time, to 6 months, not all people blood creatinine and glomerular filtration rate will be better, the combination of drugs to 12 months, the number of patients who improve on the number of patients is reduced, but still more than half of the people appeared to be in good condition. This shows that, because of individual differences, for different patients still need to carry out postoperative blood concentration test to achieve the best results.

Table 7 Comparison of Serum Creatinine and Glomerular Filtration Rate before and after Transplantation (c,%)

Time (months) Number of persons	Preoperatively		Postoperative	
	Creatinine	glomerular filtration rate	Creatinine	glomerular filtration rate
January (138)	(935±292)μmo/L	(5. 8±2. 3) %	(125±292)μmol/L	(77±2. 38) %
March (138)			(103±23.6)μmol/L	(80.9±21) %
June (122)			(108.6±35)μmol/L	(77±21) %
December (88)			(105±23. 1)μmol/L	(79±16) %

4 DISCUSSION

The results of this study show that the FK506 dose and blood concentration within one month after operation are lower than those within one to three months after operation, which may be related to the fact that the renal function of renal transplant patients is still in the clinical recovery stage. One month after operation, the FK506 dose and blood concentration gradually decrease with the extension of the postoperative time. During the same period, there was no significant difference in FK506 plasma concentration between male and female patients of different sexes (P>0.05). Within 3 months after kidney transplantation, the blood concentration of female patients was slightly higher than that of male patients, which may be related to the slower recovery of female patients' physique, renal function and metabolic elimination. The dosage and blood concentration of FK506 in three patients of different ages decreased with the increase of age. Three months after operation, the FK506 blood concentration, dosage and blood concentration in the elderly group were significantly lower than those in the young group and the middle-aged group (P<0.05), which may be related to the changes of P-glycoprotein and cytochrome P4603A (CYP3A) activity in the elderly patients [7-9] . According to the literature, the ideal therapeutic window range of whole blood trough concentration is 10~15 μ g/L ≤ 1 month, 9~12 μ g/L 2-3 months, 7~10 μ g/L 4-6 months, and 5~8 μ g/L ≥ 7 months. Thereafter, the maintenance valley concentration of tacrolimus was 5~8 μ g/L [10-12] . The therapeutic window obtained in this trial is basically consistent with the reference therapeutic window. In addition, gender, age and other factors have a certain impact on the pharmacokinetics of FK506 in vivo. When taking FK506 orally, these factors should also be paid attention to, so as to make immunosuppressive treatment more reasonable.

It was reported in the literature [13-14] that when the concentration of tacrolimus was lower than the lower limit of the target concentration, the risk of acute rejection increased significantly for every 1 ng • mL-1 decrease in the concentration of tacrolimus. In this study, the target concentration of tacrolimus was set at 5.1~6.1 ng • mL-1. Some patients did not reach the target concentration. Although no obvious acute rejection reaction occurred, doctors and pharmacists were still recommended to fully evaluate the patients and formulate more reasonable dose and concentration range according to the guidelines. Clinicians and pharmacists should carry out necessary medication education for renal transplant patients, provide appropriate pharmaceutical care and individualized medication guidance, and inform patients that proton pump inhibitors, calcium antagonists, berberine hydrochloride [15] related drugs may interact with tacrolimus to affect the blood concentration of tacrolimus. When the blood concentration fluctuates abnormally, the monitoring frequency should be increased appropriately. Therefore, it is suggested that when using tacrolimus, the dosage should be adjusted according to the physiological and pathological status of the patient, so as to keep the blood concentration of tacrolimus in a more reasonable range and reduce fluctuations, and promote the long-term survival of the transplanted kidney.

There are some differences between the treatment windows obtained in this group of trials and the reference treatment windows in the literature, which may be related to the individual renal transplant patients, measurement methods and clinical factors, but the therapeutic effects are relatively good. Table 7 shows that the improvement of blood creatinine and glomerular filtration rate with the combination of drugs can indicate that the combination of drugs is effective, but with the combination of drugs for a longer period of time, the number of patients who improved decreased, but still more than half of the patients showed improvement. This may be due to the fact that the body functions have not returned to normal and that the combination of drugs has a large number of effects on each other. Therefore, monitoring the blood concentration of tacrolimus in the postoperative period and establishing the ideal concentration in the therapeutic window are of great importance in guiding the rational use of immunosuppressants in the clinic.

In a word, tacrolimus is a powerful immunosuppressant with great potential and is gradually replacing cyclosporine A as the first choice of immunosuppressive drugs. Since tacrolimus varies greatly among individuals and the therapeutic window is narrow, the whole blood tacrolimus valley concentration should be dynamically monitored during treatment to establish an ideal therapeutic window concentration and adjust medication according to it. Therefore, it is necessary to integrate various influencing factors and formulate individualized medication programs to achieve ideal therapeutic effects.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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