INTENSIVE OBSERVATION OF TOXIC SIDE EFFECTS AFTER SEVERAL-YEAR OF CYCLOSPORIN TREATMENT IN KIDNEY TRANSPLANT PATIENT

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Abstract

In this work we are going to show results of intensive observation of adverse reactions of cyclosporine therapy during 18 months. The research was applied on 30 patients with kidney transplant. The medium time of kidney transplant survival was 9,7±2,3 years, with time span of 6 to 15 years. All the patients were subjects to several years' cyclosporine treatment, which was applied on a daily basis with a dosage of 2 to 5 mg/kg of body weight. The concentration of cyclosporine in blood was measured once a month. The concentration of cyclosporine in blood in 19 patients was in referent values of 122,50 nag/ml up to 280,50 nag/ml of blood. In 4 of the patients the concentration was heightened up to 370 to 538 nag/ml (X=766,37 nag/ml), and in 7 patients cyclosporine was below normal dosage down to 30,78 to 96,30 nag/ml in blood (x=77,12 nag/ml). We noticed these toxic side effects: increased values of systolic and diastolic arterial blood pressure in 5 patients, neurotoxic tremor effects in 4 patients, hyperplasia gingival and hirsute in 1 patient each.

KEY WORDS: concentration, cyclosporine, kidney transplant, toxic side effects

Introduction

Until 1945 the graft rejection was considered as a result of technical mistake in transplantation process. The same year Medawar diagnosed the rejection as a result of immunological reaction of human body to a foreign tissue. He proved that the homograft and the auto graft differed histological in rejection, i.e., homograft is being infiltrated by mononuclear leukocytes, vascular lesions and by degrading of histological architecture (1), while in auto graft this isn't the case (2).The transplanted tissue will be rejected as a foreign tissue in host (host versus graft reaction). The rejection is a result of cellular immunologic reaction that includes lymphocytes, and can be avoided by introduction of immunosuppressive medications. Nevertheless, there is no immunosuppressive medication that can be aimed to change immunologic reaction of rejection. Immune system is suppressed as a whole, so the patient is immune suppressed patient. The immunosuppressive treatment blocks all immune responses even to bacteria, fungi, even malign tumors. Some signs or symptoms of cyclosporine toxicity are: kidney damage, high blood pressure, tremors, bleeding, swelling, overgrowth of gums, extra hair growth (hirsute), and increased lipids in the blood (hyperlipidemia) (3).

Patient and Methods

The observation was done on 30 patients of both genders with average life span of 43,5±12,3 years who have had kidney transplants. The age of transplants was in average 9,7±2,3 years, with a year span of 6 to 15. The immunosuppressive therapy was conducted with cyclosporine with a daily dosage of 2 to 5 mg/kg of body weight. During the period of 18 months, dosage of cyclosporine of all the patients was measured once in a month. The level of cyclosporine in blood was determined by fluorescent polarization immunoassay on an ABBOTT TDx apparatus. The monoclonal testing was done on a whole blood. As a sample we used EDTA blood which was first treated with reagent for haemodialysis and precipitation and after that cyclosporine was measured in supernatant. The precision of the test is 25 nag of cyclosporine in 1 ml of blood.

Laboratory analysis	Referent values	Values in patients (M±SD)
Glomerular filtration (ml/min)	125	61,7 ± 22,5
Creatinin (A(μmol/l))	54 - 100	199 ± 205
Diuresys (l)	0,6 – 1,8	1,96 ± 0,47
Bilirubin (μmol/l)	2,8 – 9,8	11,0 ± 5,3
Bilirubin (μmol/l)	up to 21	16,9 ± 5,5
AST (nkat/l)	to 1200	366 ± 186
ALT (nkat/l)	to 1200	452 ± 345
Cy concentration in blood (nag/ml)	100-300	202,2 + 124,1

TABLE 1. Values of laboratory parameters

Results

All patients were optimally dosed in accordance with referent values of 2 to 5 mg/kg of body weight (medium value 2,41mg/kg of body weight). The concentration of cyclosporine in blood in 19 patients were in referent values of 122,50 to 280,50 nag/ml in blood. In 4 patients were above referent values, 370,00 to 538 hg/ml, and in seven patients the values were below referent and averaged between 30,78 to 98,00 mg/ml (Figure 1.). From laboratory results we monitored: glomerule filtration which was 16,7±12,5ml/min; creatinin 199±205μmol/l; AST 366±185nkat/l; ALT 452±345nkat/l (Table 1). Five patients were found with higher level of artery systolic and diastolic blood pressure, and the measured average level for systolic blood pressure was 160+18 mm Hg, and for diastolic 96+7 mm Hg (Figure 2.).

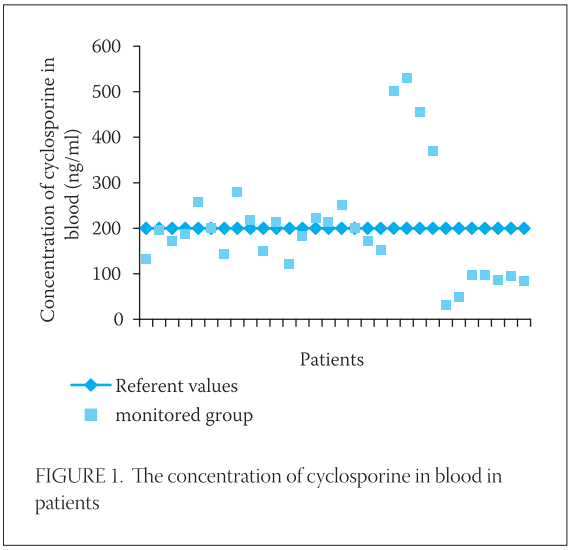

FIGURE 1. The concentration of cyclosporine in blood in patients

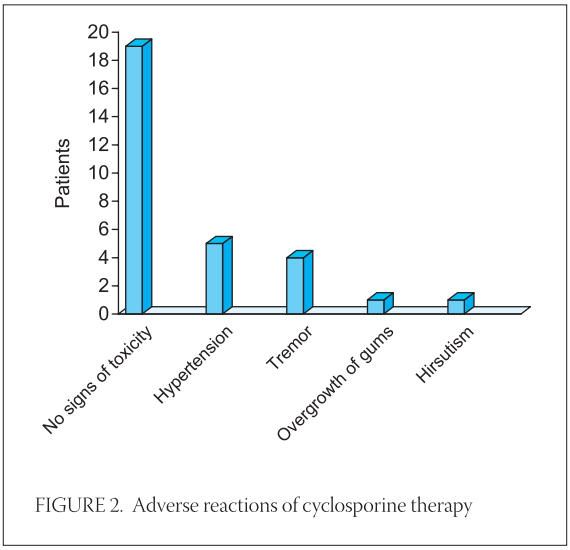

FIGURE 2. Adverse reactions of cyclosporine therapy

Considering other undesirable effects, four patients had neurotoxic effects, one patient had hyperplasia gingival and one had hirsute (Figure 2.).

Discussion

An important prerequisite for successful therapy by cyclosporine is keeping of the transplant function with occurrence of acceptable undesirable effects. Announced range of serum concentration in literature which is needed for kidney graft control (called optimal or therapy range) shows considerable variations for a particular patient (4). Considering nephrotoxicity of cyclosporine therapy and importance of its serum level, most of transplant centres adjust the dose based on the serum level concentration that is cautiously monitored (5). If the level of cyclosporine is being kept in referential limits, the undesirable effects are not noticed. Using dose optimising, the rejection of transplant is avoided on the one hand and toxicity on the other hand (6). Suboptimal dosing of cyclosporine is the most important cause of acute and by biopsy proved rejection (7). The stabile function of the graft after 10 years at optimal use of cyclosporine is described (8). Hypertension induced by cyclosporine is not done in correlation with vasoconstrictor effect but with making worse of endothelium dependent relaxation which is greatly done with prostacyclin. Cyclosporine decreases sodium-potassium pump activity which can be the cause of hypertension (9). The cause of renal vascular hypertension can be stenosys of proximal graft artery, the left joint iliac artery (10). If the person who is a kidney donor was hypertonic, hypertension can be expected after transplant of organs (11). Cyclosporine causes significance functional worse of renal perphusia and glomerular filtration. Nephrotoxicity induced by cyclosporine spreads over proximal tubular and distal segment (12). The values of serum creatinine were in limits where the graft function is still preserved. After cyclosporine withdrawal, the decreased values of serum creatinine (about 20%) were found after 4-6 months of stable function of kidney graft (13). A serious problem for clinicians is differential diagnose between cyclosporine toxicity and graft rejection. The characteristics of graft rejection are low concentration of cyclosporine in blood, fast increase of serum creatinine, the decrease of diuresis and blood circulation through glomerulus, and per vascular and periglomerular mononuclear cell infiltrates can be seen by biopsy. The level of cyclosporine in blood is high at cyclosporine nephrotoxicity. Also, the increase of creatinine is gradual and diuresis has been kept (14). The higher level of interleukin-2 in serum of the patient with kidney graft could contribute in differentiation of graft rejection from cyclosporine nephrotoxicity (15). Hepatoxicity of cyclosporine is one of the frequent undesirable effects. The most frequently it is expressed in the first month after transplant when cyclosporine is given in greater doses. Bioavailability of cyclosporine is has been increased by the time, so the lower concentration are needed for keeping of kidney graft. Hepatoxicity is reversible and the phenomenon dependent on dose. It is more frequent in persons with before diagnosed defect of liver function (16). Routine defining of cyclosporine concentration in blood has a great importance in therapy. It presents an important control of threatening toxic influence in the case of overdose. On the other hand, lower values lead to graft rejection. Therefore, it is necessary to keep the values in referential limits (17). Even though cyclosporine has selectivity on immune system, some examined persons had neurotoxic effects like tremor, hyperplasia gingival and hirsute. Cyclosporine toxicity is not marginal. Because of it, many recommend cyclosporine not to be used. It is published a metaanalysis where 64 publication examined different strategies for facultative withdrawal of cyclosporine are cited (18).

Conclusion

Cyclosporine monotherapy presents a good immunosuppressive therapy. To have the undesirable effect at minimum it is necessary to apply monitoring of cyclosporine concentration in blood. The test for cyclosporine is ordered to measure the amount of the drug in the blood to determine whether drug concentration have reached therapeutic levels and is not in a toxic range. In the case of kidney transplantation, blood levels may help to distinguish between kidney rejection and kidney damage due to high levels of cyclosporine. Cyclosporine is associated with several toxic side effects that can be avoided if blood levels are monitored and the dose adjusted if the level detected is too high.

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