Kidney transplant recipients and the incidence of adverse reactions to cyclosporin

Zahra Tolou-Ghamari, PhD, Abbas-Ali Palizban, PhD.

Cyclosporin monitoring of blood concentration measurements is recognized as an important part of a transplant patient receiving the drug. The quantitation of cyclosporin in biological fluids is essential for several reasons, 1) wide inter and intra-individual variability in pharmacokinetic standard; 2) low blood concentrations due to poor drug absorption or rapid elimination; 3) high blood concentrations; 4) patient compliance with the medication regimen.

Among the most important side effects of the immunosuppressant cyclosporin are nephrotoxicity, neurotoxicity and hypertension. Neurological adverse effects associated with post-transplant immunosuppression most commonly develop during the high levels of cyclosporin and can be categorized as a major (expressive aphasia, seizures, confusion, psychosis, encephalopathy, persistent coma) or a minor (tremors, headache, sleep disturbances, nightmares, dysesthesias, photophobia) neurotoxicity. It has been consistently documented that cyclosporin causes a reversible, dose-related renal vasoconstriction and a reduction in the glomerular filtration rate and may precipitate systemic hypertension. Hypertension is often observed in allograft recipients. In those who were previously normotensive, this may be due to excessive water volume, intrinsic renal damage or increased vasomotor tone. Use of corticosteroids may also lead to retention of excess water. There are drug interactions that may affect the levels of cyclosporin. Drugs that induce or interfere with the hepatic CYP3A4 enzyme pathway may cause significant change in cyclosporin levels leading to either toxicity or sub-therapeutic levels. Rifampicin, phenytoin and phenobarbitone are potent CYP3A4 inducers, which may reduce blood levels progressively within a few days of commencing therapy. Less potent enzyme inducers include carbamazepine, isoniazid and possibly low-dose glucocorticoids used for supplemental immunosuppression. High doses of cyclosporin have been associated with toxic reactions. These are believed to be due to the occurrence of extremely high blood levels, which to date have not been adequately explained. These toxic reactions considerably complicate clinical management. Adverse reaction to cyclosporin seems to be dependent on the individual susceptibility of the recipient. The purpose of the present study was to retrospectively evaluate the incidence of adverse reaction to cyclosporin after kidney transplantation in Isfahan, Iran.

Four hundred and thirty (341 males and 89 females), renal transplant patients (mean age 40 years, range 25-69) who were given cyclosporin approximately 8.5 mg/kg/day (range 3.2-10.7) were included in this study. Cyclosporin pre-dose blood samples were assayed using a radioimmunoassay technique. All patients received cyclosporin and prednisone as immunosuppressive maintenance treatment. The study was conducted one month to 5 years after transplantation. For combination therapy, other drugs that were used for clinical management after kidney transplantation such as; Lovastatin, Ciprofloxacine, Insuline, Ranitidine, Adalat, Folic Acid, Imuran, Captopril, Digoxin and Gentamicin were also noted. Information were gathered from the clinical record of the patients. Neurological or renal complication (fits or delirium, increase in serum creatinine, serum urea and reduced urine output) was accepted as signs of cyclosporin toxicity. Patients with or without toxicity were compared by means of the Mann-Whitney U-test, p value of less than 0.05 was considered statistically significant.

After kidney transplantation the administered dosage of cyclosporin, produced widely variable whole blood through concentrations (C\textsubscript{w}) in different studied patients. It seems that the upper therapeutic concentration incidences of life threatening opportunistic adverse reaction when whole blood trough concentrations as measured by radioimmunoassay exceed 400 µg/L. Toxicity occurred in 234 patients after kidney transplantation. Neurological problems were encountered in approximately 35% of patients mainly fits and confusional states. Of these patients 130 had high cyclosporin blood levels (more than 400 µg/L) on the day complications occurred, and 16 patients had normal therapeutic levels (150-250 µg/L). The 4 patients exhibited delirium 2 days after withdrawal of cyclosporin. All neurological complications disappeared when cyclosporin dosage was reduced or stopped. Twenty-five percent of patients had evidence of renal toxicity. Nephrotoxicity, which associated from therapy, occurred in patients when cyclosporin was administered at dosage of 4.3-10.9 mg/kg. All patients exhibited high serum creatinine levels, which resolved with a reduction in cyclosporin dosage. Mild nephrotoxicity responding to dose reduction occurred in 10-15 kidney transplant recipients. In some patients with renal impairment, cyclosporin trough whole blood concentration was less than 100µg/L. These findings indicate that renal toxicity may occur with cyclosporin even if such concentrations are maintained at low levels. Infection complications occurred in some patients.

Drug interactions were seen in some patients as the manipulating the dose of cyclosporin in response to quadruple therapy, therefore, the relevance of is used alone or as part of dual, triple or even cyclosporin could be largely affected by whether it 6 drugs are being administered.

Immunosuppression with cyclosporin is what other relevant issues on the dose of baseline 5 prophylaxis, prevent cyclosporin nephrotoxicity is cyclosporin renal damage. Therefore, one potential approach to Toxic levels of cyclosporin may also cause chronic reversible, dose-related renal vasoconstriction. Therefore, for routine clinical monitoring of cyclosporin, targeting at therapeutic mean levels within an organized immunosuppressive monitoring program may improve outcome after kidney transplantation in Isfahan, Iran.

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From the Department of Pharmaceutics (Tolou-Ghamari), and the Department of Clinical Biochemistry (Palizban), Faculty of Pharmacy, University of Medical Sciences and Health Services, Isfahan, Iran. Address correspondence and reprint request to Dr. Zahra Tolou-Ghamari, Assistant Professor, Faculty of Pharmacy, Isfahan University of Medical Sciences, PO Box 81746-73461, Isfahan, Iran. Tel. +98 (311) 7922632. Fax. +98 (311) 6680011. E-mail. z_tolou_ghamari@hotmail.com

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