Original Article

The investigation of correlation between Iminoral concentration and neurotoxic levels after kidney transplantation

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Abstract

Background: Neurotoxicity side effects related to cyclosporine kinetics could lead to dysfunction of kidney graft and patient outcome after transplantation. The aim of this study was evidence-based pharmacotherapy of kidney transplant recipients and to investigate neurotoxic levels of Iminoral.

Materials and Methods: The results of 2239 cyclosporine trough levels obtained from 743 patients were studied. Seventy-five adult kidney recipients who received Iminoral were studied for neurotoxicity symptoms. Demographic, clinical, hematology and biochemical data were recorded in d-base and analyzed using SPSS application for windows.

Results: The mean value related to cyclosporine C_0 was 246.3 μg/l. In the 48% the signs of neurotoxicity such as tremor and headache were noted, but only in 9% the levels of cyclosporine C_0 were >400 μg/l. Further studies on 75 patients showed that the incidence of neurotoxic side effects were as follows: Tremor in 35, headache in 24 and anxiety in 34 recipients of kidney. The prescribed drug regimens from the day of transplant in most patients were based on mycophenolic acid or cellcept, pulse therapy using methylprednisolone (daily from kidney transplant up to 3 days after transplant), cyclosporine or Iminoral plus other drugs related to each individual. Administrations of ganciclovir, thymoglobulin, clotrimazol and prednisolone were also distinguished with immunosuppressant-based therapy simultaneously.

Conclusion: Evidence-based study related to pharmacotherapy of Iminoral showed that clinical presentation related to neurotoxic side effects such as tremor, headache and anxiety might be due to many factors such as polypharmacy. Planning immunosuppression to individual patients based on programmed therapeutic Iminoral monitoring, avoiding polypharmacy in terms of removal or drug minimization and focusing on first week after transplant seem to be a realistic option.

Key Words: Cyclosporine, kidney, neurotoxicity, transplant

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INTRODUCTION

Transplantation is a well-established management for patients with mainly end-stage kidney diseases. Therefore, they require cautious management to prevent rejections (hyperacute-acute/chronic) or toxicity related to immunosuppression therapy. The inhibitor of calcineurin,

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cyclosporine is one of the main immunosuppressive drugs used after organ transplantation but the frequency of neurotoxicity from calcineurin inhibitors seems to be dissimilar. The slow and variable absorption of cyclosporine appears to be prejudiced by a series of issues such as, time after transplantation, presence of food and intestinal dysfunction. Inconsistencies in cyclosporine trough concentrations (C_0) are the result of marked disparities in the kinetic factors, such as clearance (CL) and bioavailability (F).[1-7] Previous publications reported that cyclosporine distribution could be affected by the lipoprotein concentration in plasma and hematocrit.[8,9] Cyclosporine is widely metabolized and hepatic metabolism is a main pathway of cyclosporine elimination. Inducers or inhibitors of cytochrome P450 (CYP450) could influence the metabolism of drug.[10,11] Adverse effects of cyclosporine are dose-related and therapeutic cyclosporine monitoring involves the use of C_0 measurements to individualize dosage regimens derived from kinetic values. Long period of cyclosporine exposure might induce renal dysfunction that results to nephrotoxicity.[12,13] Complexity related to central nervous system is numerous in recipients of kidneys and may mostly donate to morbidity and mortality. The post transplant neurological complications may be categorized as immunosuppressive medications, stroke, peripheral neuropathies, infection, and malignancies. Previous reports confirmed that immunosuppressive agents could cause neurotoxicity difficulties. Akinetic mutism, nephrotoxicity, hypertension, diabetes mellitus are some reported neurotoxic effects. A recent publication confirms that cyclosporine might induce neurotoxicity in spite of the low level in brain. The frequency of neurotoxic side effects related to cyclosporine is thought to be 10-25%. In solid-organ transplantation, neurotoxicity seems to occur more often with liver transplantation than with heart or renal transplantation. In most cases, neurologic signs and symptoms, such as seizures, confusion, or coma, occur within the first few days after transplantation. Mitochondria play a key role in cell death processes, notably through the opening of the permeability transition pore.[1,2,4,12] A recent publication confirmed that intensive immunosuppressive regimen might be accompanied with a higher risk for CMV infection.[14] Guillain–Barré syndrome may also expand, triggered in some cases by cytomegalovirus (CMV) or Campylobacter jejuni infection. Lymphomas are the most frequent brain tumors. They are typically connected to Epstein–Barr virus (EBV) infection and are more frequent in patients with vicious immunosuppressive prescriptions. Infection differentiates the most common neurological impediments. Acute meningitis typically founded by Listeria monocytogenes, subacute and chronic meningitis caused by *Cryptococcus neoformans,* focal brain infection by *Aspergillus fumigatus, Toxoplasma gondii* or *Nocardia asteroides,* and developing dementia explored by polyoma J virus or other viruses are the majority recurrent categories of neurological contaminations.[14-17] Iminoral which is a generic formulation of cyclosporine has been manufactured by Zahravi Pharmaceutical Company (Tabriz, Iran). As drug–drug interactions could influence the pharmacokinetics of immunosuppressant, therefore, to achieve an appropriate clinical management related to logical clinical pharmacotherapy, the aim of this study was evidence-based-Iminoral therapy after kidney transplantation in Isfahan/Iran.

MATERIALS AND METHODS

A total of 2239 results associated to cyclosporine trough concentrations (C_0) obtained from 743 kidney recipients with a mean age of 38 years comprised of 499 males and 244 females were studied. Seventy-five patients comprising of 28 females and 47 males, with a mean age of 40.6 years (ranged: 20-64 years old), were considered further to be studied for the presence or non-presence of tremor, anxiety, headache and sleep disorders. As the design of study was population-based, therefore, due to pharmacokinetic differences among adults and children, the only exclusion criteria were children. The study was conducted to Isfahan Neurosciences Research Centre (INRCC) and approved by research ethics committee (grant number 290295). All patients received cyclosporine orally twice a day. Because of wide inter- and intra- individual variability, recipients were required to meet the following inclusion criteria: Alive and age between 18 and 65 years. Other drugs such as ganciclovir, Anti-thymocyte globulin (ATG), mycophenolic acid or cellcept, tacrolimus, trimethoprim/sulfamethoxazole or co-trimoxazole, cyclosporine or Iminoral were noted from the medical records. Additional information including present and past clinical history, re-transplantation, hospital stay, presence of headache, tremor, anxiety, sleep disorder and other complications were recorded in Excel. Statistical analyses were performed using SPSS application for widows. Descriptive statistics such as means, median and range was calculated for variables of interest.

RESULTS

The mean value related to cyclosporine trough concentrations (C_0) was 246.3 μg/l (ranged; 16.5-1261 μg/l). As shown in Figure 1 in 51.3% cyclosporine whole blood levels with a value of <200 μg/l predict not to be essential to prevent graft rejection and in these recipients calcineurin phosphatase activity might be inhibited by <50% which leads to rejection.

The sings of toxicity including nephro- and neurotoxicity distinguished as 48%. In the 9% of

patients' cyclosporine blood levels were >400 μg/l on the day toxicities encountered. Seventy-five patients were studied further. As shown in Figure 2, 35% have showed evidence of rejection according to medical note.

Tremor, headache and anxiety were identified in 47%, 68% and 45% with suggestion of likely non-stable circumstance [Figure 3].

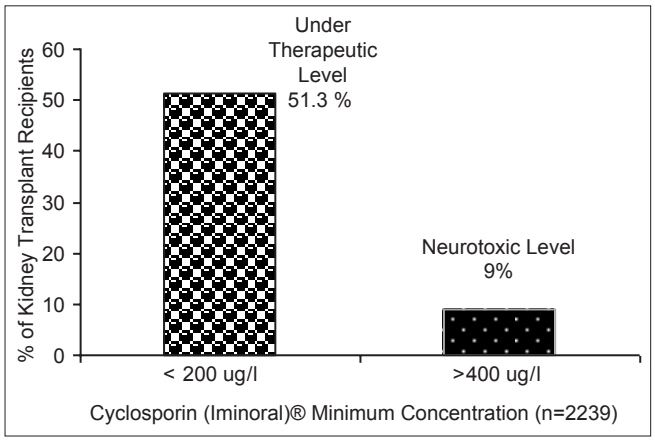

Figure 1: The % of cyclosporine C_0 associated to neurotoxic level after kidney transplantation

Table 1 shows evidence-based immunosuppressive therapy in kidney transplanted recipients. Prescriptions were based on administration of Iminoral at one dose before transplant and continues immunosuppressant in combination with other drugs. Kidney recipients in most cases received a combination of two immunosuppressant based on cyclosporine and mycophenolic acid plus pulse of methylprednisolone one dose before transplant and

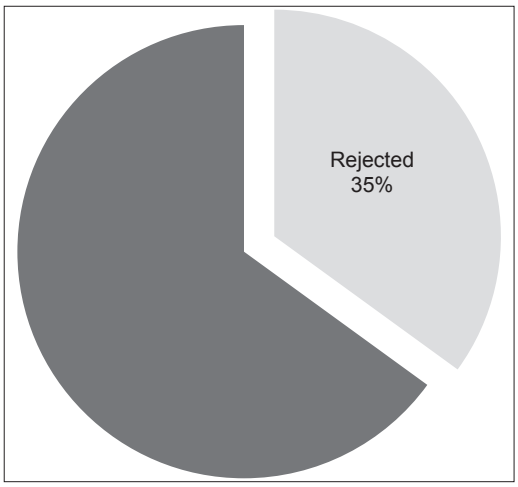

Figure 2: The % of rejected kidney recipients (n = 75)

Table 1: Evidence-based immunosuppressive-therapy using cyclosporine in kidney transplant recipients

Kidney recipient code no.	Varieties of drugs for each patient	Possible side effects[1-30]
2; 22-year-old lady was prescribed the following drugs: Ganciclovir, thymoglobulin, piperacillin/tazobactam or tazocin, minoxidil, losartan, cograft, pentoprazol, acetaminophen, cellcept, supp. clotrimazol, captopril, dilitiazem, metoral, prednisolone		
Ganciclovir; hematological adverse effects, elimination takes over 24 hours in end-stage renal disease		
Thymoglobulin, immunosuppression with rATG development immunological tolerance		
Tacrolimus or cograft, antifungals increase drug levels by competing for degradative enzymes		
Clotrimazole; specific inhibitor of CYP450 oxidase		
Cellcept, mycophenolic acid; invasive CMV infection, leuokopenia, gastrointestinal tract hemorrhage, headache		
Prednisolone; A lengthy course of prednisolone cause bloody or black tarry stools from bleeding into the stomach, osteoporosis, nervousness, depression, insomnia, memory loss		
5 26-year-old lady with a history of convulsion	Fluconazole, ofloxacin, citalopram Metoral, prednisolon, amlodipine, pentoprazol, cyclosporine, cellcept, dilitiazem, phenytoin, tab alprazolam	Fluconazole; contraindications with SSRIs, in this combination citalopram is a SSRIs Phenytoin; induce of CYP (3A4) and (2C19) Alprazolam; in a larger than normal dose cause deterioration in alertness
18 22-year-old male, showed signs of rejection 18 months after transplant due to not taking administered immunosuppressant	Eprex, prazosin, metoral, tacrolimus, cotrimoxazol- amlodipine, clonidine, prednisolone, cefixime	Co-trimoxazole or Trimethoprim/sulfamethoxazole; Stevens-Jonson syndrome, myelosuppression, mydriasis, sever liver damage, agranulococytosis Clonidine: Could cause hypotension and also due to peripheral α-agonist activity could lead to HTN
20 51-year-old male with positive history of MI; expired 1 month after transplant	Prednisolone, cotrimoxazol, plavix, cellcept, fursomide, atrovastatin, pentoprazole, carvedilol	Plavix or Clopidogrel; interacts with the inhibitor of CYP2C19 Atorvastatin; co-administration with cyclosporine could lead to myopathy and myoglobinuria ended to ARF
22 32-year-old male	Omeprazol, cellcept, methylprednisolon pulse therapy (3 days), amlodipine, Iminoral	Methylprednisolone; in combination with cellcept and cyclosporine could cause decreased resistance to infection
33 50-year-old male; rejected 2 months after transplant	Methylprednisolone pulse therapy, after pulse therapy tab prednisolone, cefazolin, Iminoral, isoniazid before operation), cellcept, dilitiazem	Isoniazid; abnormal liver functions tests, headache, poor memory and depression

rATG: Rabbit Anti-thymocyte globulin, CYP: Cytochrome P, CMV: Cytomegalovirus, SSRIs: Selective serotonin re-uptake inhibitors, HTN: Hypertensionj, ARF: Acute renal failure, CNS: Central nervous system

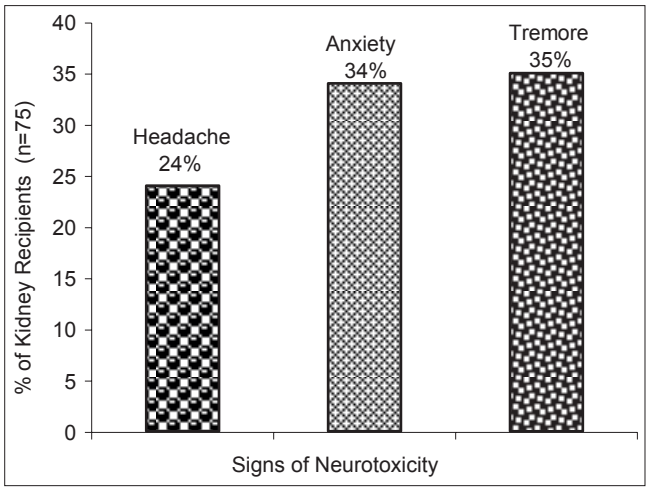

Figure 3: The incidence of the signs related to neurotoxicity in kidney recipients (*n* = 75)

maintains dose for three days after transplant. A scenario related to prescribe drugs could be discussed against individual cases. The drug regimens in a twenty-two years old lady with code no 2 on day of transplant were as follows: Amp ganciclovir -amp hydrocortisone- amp tymoglubuline- amp tazocin- tab minoxidil (6 days after operation)-tab clonidin (3 days after operation)- cap cograft (7 days after operation)- tab pentoprazol (1 day after operation)- tab acetaminophen (1 day before operation)- cap cellcept (1 day before operation)- supp clotrimazol (five days after operation)- tab captopril- tab dilitiazem (day of operation)- tab prednisolone. Prescriptions at the time of discharge from the hospital in a 60-year-old lady with code no. 23 were based on coadministration of sandimmune, rocatrol, leveotiroxin, cellcept, amitriptyline, gabapentin and amlodipine. The level of cyclosporine noted as 289 μg/l. On the day of transplant for this patient the drug regimen were as follows: Cap Iminoral- tab cellcept- spray serotide- methylprednisolone- amp cefazolin- cap omeprazol - tab levothyroxine- spray atrovent-spray salmeterol-tab co-trimoxazole- aciclovir (1 day before transplant). In a 51-year-old male with code no. 20, the prescribed drug regime for discharge from the hospital was as follows: Tab prednisolone- tab cotrimoxazole- tab plavix- tab digestive- tab cellcept- tab folic acid- tab fursomide- tab atrovastatine- tab pentoprasol- tabcarvedilol. Cyclosporine trough concentrations (C_0) stated as 146 μg/l. In another 55-year-old male patient with code no. 22, cyclosporine trough concentrations (C_0) stated 122 μg/l. This patient discharged from hospital with a combination of drugs based on Iminoral, cellcept and prednisolone.

DISCUSSION

In kidney transplant recipients drug–drug interactions owing to polypharmacy could cause the increased incidence of either rejection or neuro- and nephrotoxicity. Since the year 1936 in which the first human cadaveric renal transplant performed by Voronoy in Russia, progress in the field of transplantation continues all over of the world and also in Iran. Medawar was the first to declare that rejection was an immunological response, with the inflammatory reaction due to lymphocyte infiltration. The major advance in clinical immunosuppression eventually arrived in 1983 with the introduction of cyclosporine. Cyclosporine or Zahvir's Iminoral with a narrow therapeutic index is an immunosuppressant used in Iranian kidney transplantation. The drug mainly eliminated via biotransformation by CYP450 3A in the gut wall and liver. In addition, P-glycoprotein situated in the gastrointestinal epithelium can influence cyclosporine C_0 after oral administration, most probably by transporting the drug from the systemic circulation back into the gastrointestinal lumen. As cyclosporine is a substrate of both CYP3A and P-glycoprotein, therefore polypharmacy could have significant side effects related to rejection or neurotoxicity.[4,12,13]

Judgment associated with immunosuppressive neurotoxicity may be realized by the grouping of new-onset neurological shortfalls, current beginning of a new treatment drug and characteristic results on magnetic resonance imaging.[14-18] Neurological adverse effects associated with post-transplant immunosuppression most commonly develop during the high levels of cyclosporine 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. Co-administration of cyclosporine, cellcept and pulsetherapy using methylprednisolone seems to be routine regimen for nearly all kidney recipients immediately after transplant. Previous publication reported that combination of cyclosporine with high doses of methylprednisolone, in a 33-year-old male with cystic fibrosis, caused severe neurotoxic signs tended to coma.[19] Out of 75 kidney transplant recipients, tremor, headache and anxiety were identified in 47%, 68% and 45%. This is in agreement with previous publication in which it was reported that calcineurin inhibitors may cause mild symptoms, such as tremors and paresthesia, or severe symptoms, such as disabling pain syndrome and leukoencephalopathy.[14,19-22] ABCB1 polymorphisms may be supportive in estimating convinced cyclosporine-linked adverse effects in renal transplant recipients.[23] Cyclosporine is metabolized by intestinal and hepatic CYP3A4/3A5 and transported across the cell membrane by P-glycoprotein. Drug interactions with mycophenolic

acid occur mainly through inhibition of their enterohepatic recirculation, either by interference with the intestinal flora (antibacterials) or by limiting drug absorption (resins and binders). Cyclosporine inhibits the enterohepatic recirculation of mycophenolic acid, resulting in significantly lower concentrations and therefore risk of underexposure. Studies performed by de Jonge in 2011 confirmed that *in vivo* hepatic and first-pass CYP3A activities are considerably poorer in patients getting cyclosporine than tacrolimus.[12,24-30] Finally, reduction in the number of medication could help to decrease adverse effects related to polypharmacy. To avoid drug-related side effects such as nephro- and neurotoxicity, acute or chronic rejections, more clinical studies related to Iminoral seem to be useful.

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