



THERAPEUTIC DRUG MONITORING OF TACROLIMUS AND CYCLOSPORINE, PHENYTOIN AND VALPROIC ACID

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ABSTRACT

Therapeutic drug monitoring is the measurement of specific drugs at intervals in order to maintain a relatively constant concentration of the medication in the bloodstream. The aim of the present study is to determine the therapeutic drug monitoring of Cyclosporine, Tacrolimus, Phenytoin, Valproic Acid in a multi-specialty hospital. The study period was between November 2009 to April 2010. A total of 56 patients were enrolled from both genders, aged 3-75 years over a period of 6 months. In these 56 patients 36 were under tacrolimus treatment, in that 23 were males, 13 were females, 7 patients were under cyclosporine treatment, in that 4 males, 3 females. As well as in anti-epileptics group 7 were under phenytoin treatment (4 males, 3 females), 6 were under valproic acid treatment (5 males, 1 females). In the tacrolimus group (36 patients) 28 were therapeutic range in that 16 were males, 12 were females, and in cyclosporine group (7 patients) 5 were therapeutic range in that 3 were males, 2 females. In tacrolimus group 1 were sub therapeutic range that is also female. In cyclosporine group also 1 (female) patient under the therapeutic range. In toxic levels, tacrolimus group were having 7 patients all that patients are males. In cyclosporine group only 1 patient was above therapeutic range. In conclusion this study reveals the wide interpatient variation of blood and plasma drug levels and the usefulness of carrying out therapeutic drug monitoring of Tacrolimus, cyclosporine and of Phenytoin and valproic acid in renal transplant and epileptic patients respectively.

Key Words: Therapeutic Drug Monitoring, Monitoring, Pharmacist.

INTRODUCTION:

Therapeutic drug monitoring is used in pharmaceutical services to enhance patient care. It was first introduced to the clinical practice in the early 1970s. Since the initiation of this service, different studies evaluating Therapeutic Drug Monitoring laboratory activities, studying the impact of the service on patient outcome, surrogate endpoints, and pharmacoeconomic evaluations have been done worldwide

Therapeutic drug monitoring is the measurement of specific drugs at intervals in order to maintain a relatively constant concentration of the medication in the bloodstream. Drugs that are monitored tend to have a narrow “therapeutic range” – the quantity required to be effective is not far removed from the quantity that causes significant side effects and/or signs of toxicity¹. Maintaining this steady state is not as simple as giving a standard dose of medication. Each person will absorb, metabolize, utilize, and eliminate drugs at a different rate based upon their age, general state of health, genetic makeup, and the interference of other medications that they are taking. This rate may change over time and vary from day to day¹².

METHODOLOGY

The present study was carried out in APOLLO HOSPITALS, Hyderabad, during the period of Nov-2009 to April 2010. It is a patient data observational study. In this study 56 patients were enrolled from both genders the males are denoted as M, females are denoted as F, aged 3-75 years over a period of 6 months who are satisfied the exclusion and inclusion criteria. The main indications for carrying out Therapeutic Drug Monitoring in these renal transplant¹⁷ recipients were to avoid kidney rejection². In the epileptic patients were uncontrolled seizures, symptoms and signs of over dosage toxicity or suspected non-compliance. For renal transplant recipients the tacrolimus¹⁵ dose was started according to their body weight and disease condition

Tacrolimus: 0.2 – 0.3 mg/kg/day (per oral), 0.05 – 0.1 mg/kg/day (IV)

Cyclosporine 10 – 15 mg/kg/day (per oral), 5 – 6 mg/kg/day (IV)

Similarly for epileptic patients also started according to their body weight and severity of the disease.

Phenytoin: 3 -4 mg/kg/day (per oral), 10 – 15 mg/kg/day (IV)

Valproic acid: 10 -15 mg/kg/day (per oral), 20 – 30 mg/kg/day (IV)

The whole blood samples was assayed for Tacrolimus and cyclosporine in the department of bio-chemistry using Antibody conjugated magnetic immunoassay (for Tacrolimus¹⁶) and Fluorescence Polarization Immuno Assay (for cyclosporine¹) techniques. The blood samples were collected from patients as soon as cyclosporine therapy begins, usually daily or depending up on concentration levels of the drugs. For Tacrolimus, whole blood samples, as soon as Tacrolimus therapy begins, frequently at first then at regular intervals to monitor concentration overtime. The plasma is to assay for phenytoin, Valproate in department of bio-chemistry using Chemiluminescence technique. The blood samples were collected from patients in the morning just before the next dose was due (trough concentration); lowest detectable limit for phenytoin was 0.1 µg/mL. For the purpose of analysis, the patients were placed in to four groups i.e. Tacrolimus (36 patients), cyclosporine (7 patients), phenytoin (7 patients) and Valproate (6 patients). They are further categorized depending up on the plasma concentration of the drugs⁴.

Therapeutic: The plasma levels within normal therapeutic range (1st month- 1700, 2nd - 1500, 3rd-4th - 1200, 5th-6th- 1000, 7th above- 800 µg/mL cyclosporine⁹, 5-20 ng/ml for tacrolimus, 10-20 micro gram/ml for Phenytoin¹¹, 50-100 mg/l for sodium Valproate¹¹).

Sub therapeutic: The plasma levels below the minimum value of range i.e. below 1st month- 1700, 2nd - 1500, 3rd-4th - 1200, 5th-6th- 1000, 7th above- 800 µg/mL for cyclosporine, below 5 ng/ml for tacrolimus, below 10 micro gram/ml for Phenytoin, <50 mg/l for sodium Valproate.

Toxic: The plasma levels more than the maximum value of normal ranges i.e. more than 1st month- 1700, 2nd - 1500, 3rd- 4th - 1200, 5th-6th- 1000, 7th above- 800 µg/mL for cyclosporine, 20 ng/ml tacrolimus, 20 micro gram/ml for Phenytoin and >100 mg/l for sodium Valproate.

Not detectable: No levels could be detected in the plasma or blood.

Clinical records of the patients are examined for the follow up action taken based up on the Therapeutic Drug Monitoring reports.

RESULTS

Tacrolimus, Cyclosporine, Phenytoin, Valproic acid blood and plasma levels of 56 patients in the period between Nov-2009 and April-2010, were analyzed. In which Total no. of patients were 56 in that Tacrolimus group containing 36 members (M – 23, F – 13), Cyclosporine group – 7 (M– 4, F– 3), Phenytoin group – 7 (M– 4, F – 3) and Valproic acid group – 6 (M– 5, F– 1). In these 56 patients 36 were under tacrolimus treatment, in that 23 were males, 13 were females, 7 patients were under cyclosporine treatment, in that 4 males, 3 females. As well as in anti-epileptics group 7 were under phenytoin treatment (4 M, 3 F), 6 were under valproic acid treatment (5 M, 1 F). In the tacrolimus group (36 patients) 28 were therapeutic range in that 16 were males, 12 were females, and in cyclosporine group (7 patients) 5 were therapeutic range in that 3 were males, 2 F. In tacrolimus group 1 were sub therapeutic range that is also female. In cyclosporine group also 1(F) patient under the therapeutic range. In toxic levels, tacrolimus group were having 7 patients all that patients are males. In cyclosporine group only 1 patient was above therapeutic range. In anti-epileptic group, patients who are treating with phenytoin, 1 patient in therapeutic range, 6 patients are sub therapeutic range (3 males, 3 females). In valproic acid group 3 were therapeutic range (2 males, 1 female), 3 patients were sub therapeutic range (3 males). No toxic levels found in anti-epileptics category.

Side effects were found in tacrolimus therapy are Post transplant Diabetes Mellitus, hyperglycemia, fever, vomiting and head ache in 6 patients. In cyclosporine group fever and dysuria observed in only one patient. In patients who are treating with phenytoin Erythematous rash on face in one patient. In valproate group no side effects was observed. Drug interactions were observed and noted down of above studying drugs.

The follow up action was taken in patients those who are having toxic or sub therapeutic levels of concentration in the blood. For the patients with sub therapeutic levels, dose was increased for better response or drugs which are decreasing the levels of above studying drugs by interacting with them; they are stopped for better results, if that drug was not necessary and changed to another regimen. Similarly dose was reduced in patients of all groups, presenting with toxicity.

DISCUSSION

The results revealed that 1 (14.2%) patient receiving cyclosporine, 1 (2.7%) patient receiving Tacrolimus, 6 (85.7%) patients receiving Phenytoin and 3 (50%) patients receiving Valproate treatment had sub therapeutic levels of these drugs. In tacrolimus therapy one patient have sub therapeutic levels, due to the low dose of tacrolimus (0.5). But concomitantly mycophenolate mofetil used to obtain better result. But that patient was liver transplant recipient in other hospital. Due to this reason first the treatment started with 0.5 mg. After concentration levels monitored the dose

was increased (to 1 mg), then the concentration levels are at normal range. In patients those who are treated with cyclosporine two patients had sub therapeutic levels, due to poor bioavailability of drug in those patients. These patients have relevant diseases like persistent klebsiella, Urinary Tract Infections, Type- II Diabetes Mellitus, nephropathy and Coronary Artery Disease. Due to this diseases absorption decreased, thus occurs poor bioavailability. In phenytoin group patients those who are in sub therapeutic levels, they treated with low doses of phenytoin, and concomitantly they are treated with valproic acid to obtain better seizure control. Generally valproate decreases concentration of phenytoin by displaced phenytoin from protein binding sites. In valproic acid group three patients are in sub therapeutic levels. In that two were due to phenytoin. Phenytoin decreases valproate levels in plasma up to 50%. But in remained one patient it is due to low dose of valproate, further increased the dose. The toxic levels are found in seven patients, this is due to the concomitant use of clonidine, nifedipine, fluconazole and diltiazem. These drugs may interact with tacrolimus. These drugs increase its concentration. Fluconazole may inhibit the metabolism of tacrolimus by Cytochrome P450-3A4 in the intestine and the liver. Concurrent administration of fluconazole increases tacrolimus oral bioavailability by 114%, oral tacrolimus clearance decreases by 65.6%. In some patients diltiazem, nifedipine increases tacrolimus concentration by inhibits the metabolism of tacrolimus by Cytochrome P450-3A4. It may increases tacrolimus concentration up to 26 to 67%. In cyclosporine group, one patient had above the therapeutic range due to nifedipine and over dose of Pannimune (259 mg). Nifedipine may increases the levels or effect of cyclosporine by affecting hepatic/intestinal enzyme Cytochrome P3A4 metabolism. The side effects were found and noted down. In patients treating with tacrolimus, experienced post transplant Diabetes Mellitus in two patients. It is common side effect with tacrolimus. In remained patients hyperglycemia, fever, vomiting and head ache were observed. In cyclosporine group fever and dysuria observed in only one patient. In patients who are treated with phenytoin experienced Erythematous rash on face in one patient. In valproate group no side effects were observed. Therapeutic levels were achieved in immunosuppressant drugs are had lower proportion of patients (71.4%) in cyclosporine, than (77.7%) in Tacrolimus categories. Therapeutic levels were achieved in a much higher proportion of patients (50%) on valproic acid treatment as compared to only 14.2 % patients on Phenytoin therapy. This is due to the low doses of phenytoin prescribed. Concomitantly valproic acid was used to obtain better seizures control. This valproic acid also decreasing the plasma levels of phenytoin. The overall skews towards sub therapeutic levels is to be expected as requests for Therapeutic Drug Monitoring were in patients having uncontrolled seizures. Knowledge of concentration levels of Tacrolimus, cyclosporine, Phenytoin and valproic acid was put to for avoid acute rejection of kidney in immunosuppressant's group and for better management of epileptic patients. The ability to monitor blood concentrations of immunosuppressant drugs has been shown to help in the avoidance of acute rejection of kidney. Similarly the ability to monitor plasma concentration of anti epileptic drugs has been shown to help in the control of epileptic seizures. Patients suspected to be noncompliant were not detected by Therapeutic Drug Monitoring in this study.

CONCLUSION

In conclusion this study reveals the wide interpatient variation of blood and plasma drug levels and the usefulness of carrying out therapeutic drug monitoring of Tacrolimus, cyclosporine and of Phenytoin and valproic acid in renal transplant and epileptic patients respectively. The findings suggests that the dose of tacrolimus or cyclosporine should be reduced when Fluconazole, Nifedipine, Diltiazem and Clonidine therapy is started and that plasma levels of the immunosuppressant's should be monitored during and at the discontinuation of these drugs therapy. So those dosages are adjusted accordingly. This recommendation is consistent with current standard of care for patients receiving cyclosporine or tacrolimus with concomitantazole anti fungal and calcium channel blockers therapy. Similarly the findings suggest in the ant-epileptic group phenytoin dosage should be maintained low when valproic acid using concomitantly. Valproic acid increases phenytoin levels in plasma in low doses of phenytoin, but it gives better seizure control.

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FIGURE 1: OUTCOMES OF THE THERAPEUTIC DRUG MONITORING

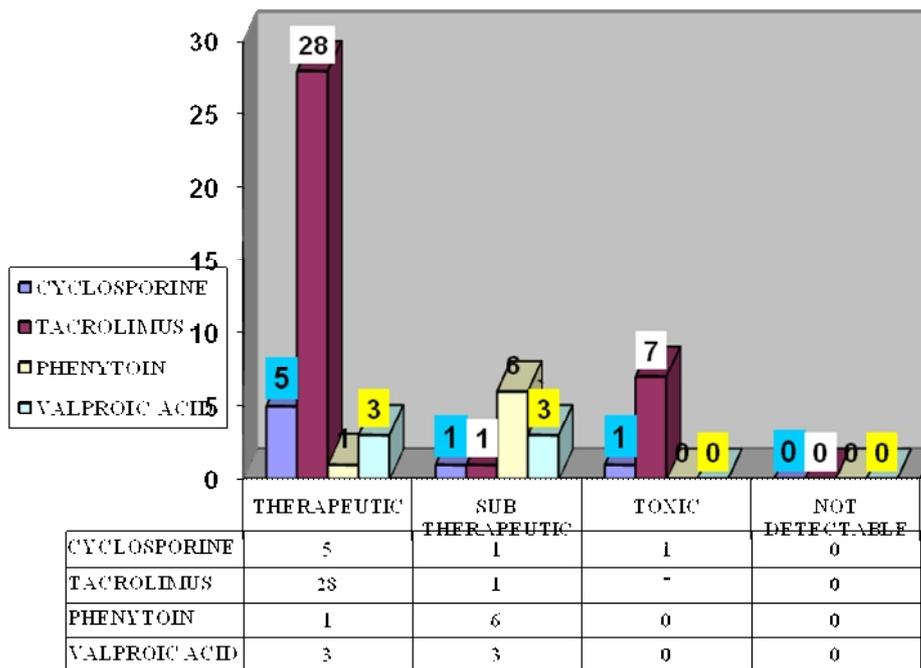


FIGURE 2: DEMOGRAPHICS OF THE TACROLIMUS GROUP PATIENT ACCORDING TO CONC. LEVELS

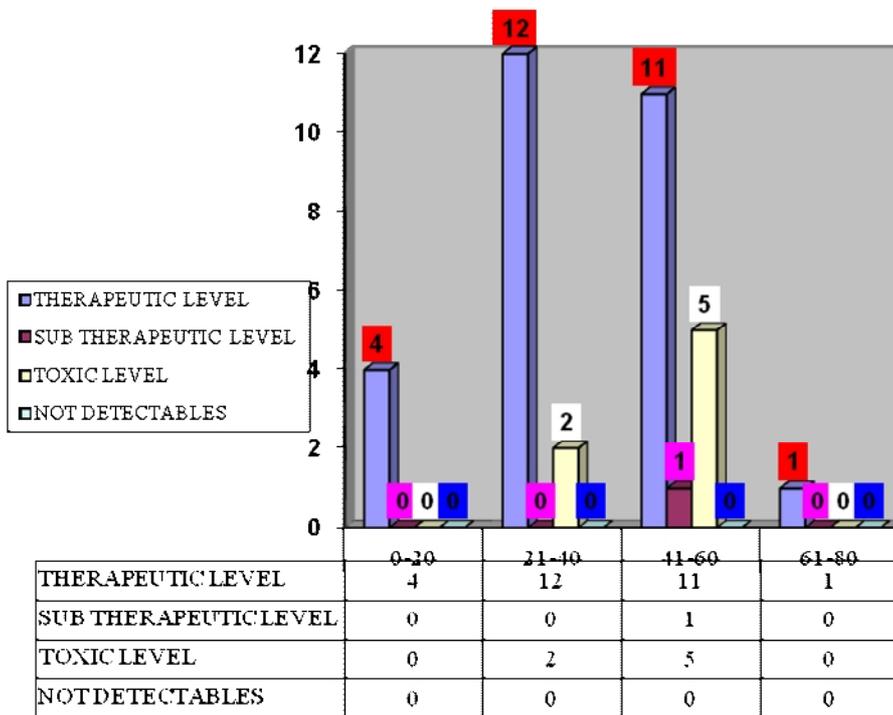


FIGURE 3: DEMOGRAPHICS OF THE CYCLOSPORINE GROUP PATIENTS ACCORDING TO CONC. LEVELS

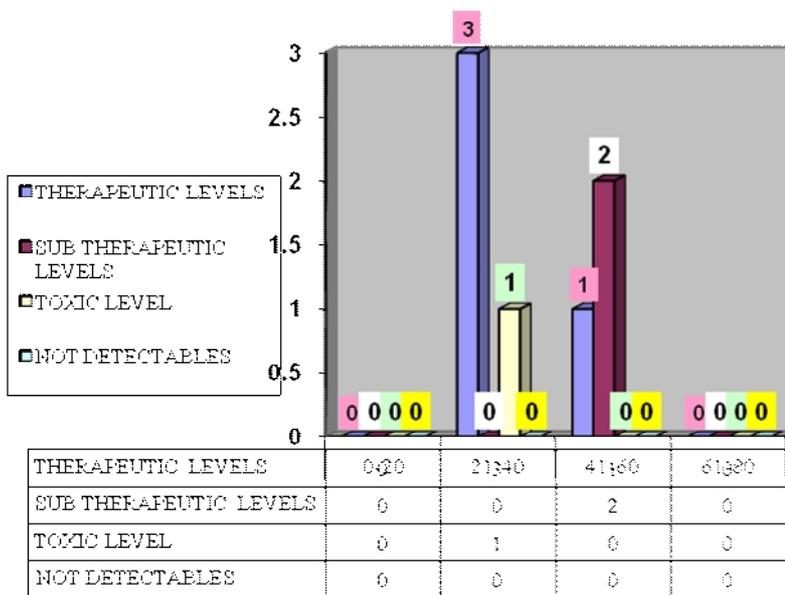
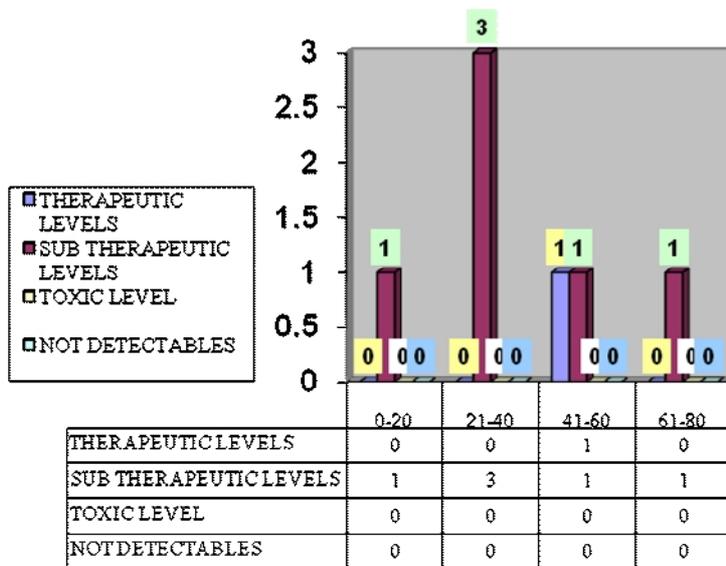


FIGURE 4: DEMOGRAPHICS OF THE PHENYTOIN GROUP PATIENTS ACCORDING TO CONC. LEVELS



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