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THERAPEUTIC DRUG MONITORING (TDM) OF LITHIUM AT TERTIARY CARE CENTRE IN KASHMIR: A RETROSPECTIVE AUDIT OF 10 YEARS SERVICE

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ABSTRACT

Lithium remains a mainstay of treatment for bipolar disorders but dose individualization, measured of serum drug concentrations and monitoring for adverse drug reactions are vital in order to maximize therapeutic response as the patient has to take the drug for rest of his life for treatment and prophylaxes. Lithium has a narrow therapeutic index (0.4-1.2meq/L) and drug interactions, changes in diet and fluid intake, illness and compliance can all markedly affect serum drug concentrations, reducing therapeutic response or causing toxicity. The method of estimation is simple and accurate by flame photometry. The study was carried out from the sample of 16,679 consisting of 6,989 males (41.9%) and 9690 (58.09%). This data shows that physicians prescribe medicines about which they should know that narrow therapeutic index drug needs vigilance and optimizations while titrating the dose as per the levels so that the level is maintained within the therapeutic range.

Keywords: Lithium, Therapeutic drug monitoring, Manic depressive psychosis, Milli equivalent per litre, Optimization.

INTRODUCTION

Lithium is a drug of choice for bipolar disorders. It has a narrow therapeutic index so needs serum monitoring in the laboratory so as to correlate its concentration with the therapeutic effect [1]. Its therapeutic level is important as individual variation, poor compliance, renal disease, seasonal variation are important reasons to individualize the TDM, so as to optimize the dosage regimen. Therapeutic Drug Monitoring is an important tool to optimize the therapy for safety reasons having narrow therapeutic index [2]. Therapeutic Drug Monitoring is a complete system where there is a need of education from hospital personnel on appropriateness of serum sample collection, interpretation and proper use of serum drug levels in quantitative analysis. In clinical decisions, TDM has a role like it needs correct requisition form and correct sampling, patient compliance makes a success in optimization and reduces unnecessary costs [3]. Regular lithium level monitoring, helps in better clinical management in poor compliance. It has been observed that 12% requisition forms were incomplete and therefore could not be analyzed [(4)]. TDM is subsequently interpreted to individualize and optimize patient's dosage regimen and therapeutic outcome by maintaining drug concentration within a target therapeutic window [5]. Serum lithium concentration should be measured at least every 3-6 months after achieving stable therapeutic concentration. The lithium still remains a very useful drug in the treatment of manic-psychosis (MDP), irrespective of the recent advances in the field of psychiatry [6]. Lithium, because of its narrow therapeutic index and marked inter-

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individual variation, requires TDM in those patients who are on prophylaxis [7].

Variability in lithium levels has to be viewed with caution since it can affect the efficacy and safety in the patient. Seasonal variation in lithium levels have been reported in the literature from Italy, the Netherlands and the United States [8]. Seasonal variation in the incidence of psychotropic illness, like bipolar disorder, mania, depression and schizophrenia have been observed and its potential relation to temperature variation has been suggested [9]. Lithium concentration varies widely during a dosing interval representative single time point for serum monitoring was established for standardization. Although some how, arbitrary, the 12 hour post-dose time point was selected for this purpose because it avoids the highly variable absorption and distribution phases. The usual practice is to obtain the sample before the first lithium dose and 12 hours after the previous evening dose [10].

MATERIAL AND METHODS

The aim of this study was to evaluate the pattern of TDM of lithium in a tertiary care and compare the results as per season, sex at different concentrations. From the archived data in the Department of Clinical Pharmacology, SKIMS, Srinagar for a period of 10 years from 2003-2004 to 2012-2013, a total of 16,679 samples were analyzed, values were found normal in 11079 (66,5%) therapeutic, low in 4143 (24.8%) sub-therapeutic, toxic in 553 (8.2%) and outliers 90 (0.5%). Females 6429 (58.03%) were in therapeutic range but 2589 (62.50%) were in sub-therapeutic range. Toxic levels are detected in 347 (21.3%) out of 1629 samples in the age range of (61-70) yrs. Sub-therapeutic levels are detected in 1930 (41.8%) out of 4617 in the age range of (51-60) yrs. Maximum samples were obtained in autumn/winter season 8974 (53.80%). A sub-therapeutic level was obtained in this season and in females. Samples were analyzed on flame photometer, a simple and accurate method in serum from the trough levels.

The study was conducted in the department of Clinical Pharmacology, SKIMS, Srinagar a tertiary care centre in Jammu and Kashmir. Records were obtained of blood samples received and analyzed from March 2003-2004 to September 2012-2013 from archived databank. Serum lithium < 0.40meq/L, 0.4–1.2 and >1.2meq/L were considered sub-therapeutic (low), therapeutic (normal) and toxic (high) respectively. One more group was formed during the compilation of data named as outliers. This group consisted of those levels which were not fitted in the groups mentioned above. The trend of serum lithium levels was calculated as percentage of patients in each of the four categories over the ten year period.

TDM of lithium was carried out by simple and accurate method on digital flame photometer (129 Systronics). Standard solution of 0.2 meq/L against reagent blank was adjusted as 20 on digital reading. The blank contains all electrolytes except Lithium. The serum sample 0.5 ml was diluted with distil water (0.5 ml serum+4.5 ml distil water) dilution of 1:10. The blood sample was centrifuged at 3000 rpm for 15 min for serum separation and was done on the same day after collection the sample. The flame photometer is still a gold standard for estimation of lithium and electrolytes.

RESULTS

Among the 16,679 samples analyzed over a period of ten years, values were normal in 11,079 (66.5%), low in 4.143 (24.8%), toxic in1367 (8.2%) and outliers 90 (0.5%) as in (Table 1) which depicted the male and female percentage in this study as well.

Table 1. Yearly distribution of samples in two different seasons

Year	Apr. to Sept. (with percentage)	Oct. to Mar. (with percentage)	Total
2003-2004	408 (40.00)	612 (60%)	1020
2004-2005	710 (63.33)	411 (36.67)	1121
2005-2006	300 (27.88)	776 (72.12)	1076
2006-2007	800 (46.79)	910 (53.21)	1710
2007-2008	900 (47.12)	1010 (52.88)	1910
2008-2009	800 (45.71)	950 (54.29)	1750
20009-2010	900 (46.00)	1050 (54.00)	1915
2010-2011	1050 (47.20)	1175 (52.80)	2225
2011-2012	817 (44.71)	1010 (55.29)	1827
2012-2013	1020 (48.00)	1105 (52.00)	2125
Total	**7705 (46.20)**	**8974 (53.80)**	**16679**

Patients were sub-classified as per age from 20-70 yrs. 4671 comprised of highest group in the age group of 51-60 yrs with male (44.25%) and (55.5%) females and 1629 patients were lowest in the age group of 61- 70 yrs comprising (40.27%) male and (59.28%) females (Table 2).

Table 2. Age distribution in both genders

Age (years)	Total	Male (percent)	Female (percent)
20-30	2804	1214 (43.30)	1590 (56.70)
31-40	3790	1734 (45.75)	2056 (54.25)
41-50	3839	1333 (34.72)	2506 (65.28)
51-60	4617	2043 (44.25)	2574 (55.75)
61-70	1629	656 (40.27)	973 (59.28)
Total	**16679**	**6980 (41.85)**	**9699 (58.15)**

Distribution of different levels depicted in Table 3 shows the percentage of therapeutic levels is 66.5% while as the level of outliers comprising of 90 is only 0.5% and the toxic level being 8.2%.

Table 3. Distribution of different levels in both genders

Different Levels	Male (%)	Female (%)	Overall %age
Level-1(therapeutic) 11079	4650 (41.97)	6429 (58.03)	66.5
Level-2(subtherapeutic)4143	1554 (37.50)	2589 (62.50)	24.8
Level-3 (toxic)1367	553 (40.40)	814 (59.60)	8.2
Level-4 (outliers)90	22 (24.44)	68 (75.56)	0.5

Highest normal or therapeutic levels were from the age group of 20-30 years (80.74%), low or sub-therapeutic levels were from 51-60 years (47.7%) and toxic or highest levels were in the age group of 61-70 years (21.3%). The outliers group was represented by those samples which were inconclusive in interpreting the results comprised of 61-70 years of 29 (1.8%) (Table4).

Table 4. Distribution of different levels visi-a-vis age

Age (yrs.)	Total	Therapeutic level-1 (%)	Subtherapeutic Level-2 (%)	Toxic level-3 (%)	Outliers level-4 (%)
20-30	2804	2264 (80.7)	415 (14.8)	110 (3.9)	15 (0.5)
31-40	3790	2705 (71.3)	925 (24.4)	150 (4.0)	10 (0.3)
41-50	3839	3110 (81.0)	420 (10.9)	290 (7.6)	19 (0.5)
51-60	4617	2200 (47.7)	1930 (41.8)	470 (10.1)	17 (0.4)

Yearly distribution of samples in two different seasons viz. April to September and October to March (Table. 1) showed the trend of TDM of lithium increased from 2003-2004 to 2012-2013 with maximum in 2010-2011 of 2225 samples (47.20%) in spring/ summer and (52.80%) in autumn/winter. The lowest representation of samples were in 2003-2004 with a total of 1020 (48.0%) in spring summer. Overall samples received in these ten years in spring/ summer were 7705 (46.20%) and 8974(53.80%) in autumn/winter (Table.1).

DISCUSSION

Analysis showed (66.5%) of samples in normal range, (24.8%) sub-therapeutic, (8.2%) toxic and (0.5%) outliers. Normal range samples were not satisfactorily represented as there is a lack of awareness in physician community about the TDM programme. Subtherapeutic level is represented by large number of samples so the need is to increase the dosage to obtain the therapeutic level but to ensure that the level is maintained within the therapeutic level. Other studies have shown 6.8% of patients in toxic range [11] and 50% having low level of serum level [12]. In our study women had more toxic levels and sub- therapeutic levels as well. However, only 27.8% of patients with excessive levels had signs and symptoms of toxicity and women were significantly more likely to have higher plasma levels [12]. Our study also showed almost the same results. Contrary to these findings there was no predisposition to lithium toxicity for either males or females. Coefficient of variation of our Na/K/Li analyzer was 1-2% which is in the acceptable range. Caution is needed in elderly patients who showed more toxic levels as the creatinine level increase with age and the drug is excreted unchanged through kidneys. At the therapeutically effective limits, lithium increases urine output and decreases creatinine clearance in men with decrease in renal concentrating ability and can alter calcium homeostasis. Non-compliance with lithium therapy can lead to relapse of the patient. It shows genetic variability in pharmacokinetics, drug-drug interactions, and high levels can lead to adverse effects like long term neurotoxicity following poisoning [13,14,15]. Patients with nephrogenic diabetes inspedious, older age, abnormal thyroid function are susceptible to toxicity. This drug has its hazardous in pregnancy leading to increased rates of cardiovascular malformations and perinatal death [16]. This stresses the need of therapeutic drug monitoring of lithium. Unfortunately there is a un-necessary practice of TDM in some situations so is the need of awareness of physicians about this programme. Salivary lithium levels were tried for the TDM but there is a wide variation in

these levels because of adrenocortical and psychosomatic influences vary the results of estimations [17]. This could solve the problem of taking the sample without any problems.

TDM programme is a vital process to optimize the dosage in order to get the therapeutic accurate levels in patients. Awareness and knowledge of this programme is needed in order to keep the patients and physicians aware as to how to draw the samples for TDM. The outliers which are 0.5%, is because of wrong methods of taking samples from the patients. As the trough level is needed for optimizing the routine analysis of lithium.

Thus monitoring of serum drug concentration of lithium indicates a pattern of awareness when using a drug having narrow therapeutic range. TDM assisted psychiatric treatment is potentially useful and cost-effective in decreasing adverse drug reactions and preventing lack of response (sub-therapeutic). Drug level monitoring and oral dose adjustment are required to avoid significant variation in serum lithium levels that can otherwise lead to toxicity or lack of efficacy due to seasonality, sex and age.

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