TRICYCLIC ANTIDEPRESSANTS;
EFFICACY OF THE TREATMENT OF DEPRESSION, WITH AND WITHOUT THERAPEUTIC DRUG MONITORING; A COMPARATIVE STUDY

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ABSTRACT... Introduction: Despite advancements in the treatment of depression and availability of newer compounds, TCAs like amitriptyline remain to be the cornerstone of antidepressive therapy for more than three decades, however significantly more patients receiving a tricyclic withdraw from treatment mainly because of side effects. Higher response, lower incidence of side effects and improved compliance can be enhanced by the optimal use of Therapeutic Drug Monitoring (TDM). No research data is currently available on the therapeutic drug monitoring of TCAs in Pakistan. **Objectives:** To compare the relative efficacy of Tricyclic antidepressant in the treatment of depression, with and without Therapeutic Drug Monitoring **Main Outcome Measures:** Changes in HAMD scores in patients on TCAs. **Study Design:** A Quasi experimental study design was used. **Setting:** The study was conducted at Department of Psychiatry, Military Hospital Rawalpindi. **Subjects:** 34 patients completed the study in the monitored group (with TDM) and 33 in control group (without TDM). **Methods:** Serum TCA levels and HAMD scores at baseline and subsequently at sixth, eighth and tenth week of treatment were collected. In all the subjects, all the blood samples were drawn as a fasting sample in early morning. **Results:** The mean age of the monitored group was 31.97 years (SD=10.432) while that of the control group was 33.52 years (SD=9.385). in the monitored group 20 (58.82 %) of the patients were males while 14 (41.17%) were females, in the control group 22 (66.66%) were males and 11(33.33%) were female patients. A significant reduction in HAMD scores was noted at 8 weeks of treatment. The groups did not differ in terms of efficacy of TCAs, however the monitored group had fewer dropouts than the control group. **Conclusions:** Lower incidence of side effects and improved compliance can be enhanced by the optimal use of Therapeutic Drug Monitoring (TDM) of TCAs.

Key words: Tricyclic antidepressants (TCAs), Amitriptyline, Imipramine, Depression, Therapeutic Drug Monitoring (TDM).

INTRODUCTION

Therapeutic drug monitoring (TDM) of tricyclic antidepressants (TCA) is established in the treatment of depression to optimize outcome and safety[1].

Despite advancements in the treatment of depression and availability of newer compounds, TCAs like amitriptyline remain to be the cornerstone of antidepressive therapy for more than three decades[2].

It has been observed that patients with major depression are significantly more likely to receive TCAs, especially when antidepressant drugs are prescribed by psychiatrists[3], however significantly more patients receiving a tricyclic withdraw from treatment mainly because of side effects[4], in addition to this, nonresponse to tricyclic antidepressant (TCA) treatment is observed in about one-third of depressed patients.The cause(s) for nonresponse - apart from disease-specific effects - might be the failure to build up sufficiently high serum TCA levels due to noncompliance, substance abuse, rapid metabolism, or low dose[5].

No research data is currently available on the therapeutic drug monitoring of TCAs in Pakistan, which are the most cost effective antidepressants keeping in view the socioeconomic status of our patients. A few studies in India suggest that therapeutic drug monitoring (TDM) of antidepressants may be useful in special populations, such as in elderly patients, poor metabolizers, and patients with liver and kidney impairment[6].

The purpose of this study is to use therapeutic drug monitoring and see its effects on therapeutic efficacy of TCAs (Amitriptyline and Imipramine) in the local population.

PATIENTS AND METHODS

This quasi experimental study was carried out in the 'Department of Psychiatry' Military Hospital Rawalpindi

which is a tertiary care psychiatric unit and one of the largest inpatient mental health facilities in Pakistan. A total of 90 Patients diagnosed with depression, who met the inclusion criteria on ICD 10 and consented for participation in the study were assigned to two groups(40 in the monitored group A and 50 in the control group B) using convenience non probability sampling. The inclusion and exclusion criteria were:

1. Patients aged 18 to 60 years diagnosed as currently having depressive episode according to ICD10 criteria and having a total score of $\geqslant$07 on the Hamilton Depression Rating Scale (HAMD), who were drug naïve and hospitalized were included into the study.

2. Patients treated with any psychotropic medication in the last two weeks, an evidence of unstable physical or neurological illness, Risk of suicide, Necessity for electroconvulsive therapy, drug abuse, Refractory depression, Pregnancy or Puerperium, and patients with any other comorbid psychiatric illness were excluded.

Patients in both groups were prescribed with Amitriptyline (AT) or Imipramine (IM). They were evaluated before entering the study and after 6, 8 and 10 weeks of treatment, as follows:

1. Depression and its response to the drug was assessed using The 21-Items version of Hamilton Depression Rating Scale (HAMD), attached as annexure 1.

2. Serum drug concentrations were measured with "TDx TCA drug assay" which utilizes Fluorescence Polarization Immunoassay (FPIA) technology, only in group A with dose recommendations given in light of therapeutic drug levels, while in group B doses were titrated according to clinical judgment alone with no drug monitoring.

To measure TCA serum concentrations, the blood samples were drawn on the same day when clinical status of the patients was evaluated, at least 10 hours after administration of the drug.

Efficacy was defined as Improvements of $\geqslant$ 50 % in scores on Hamilton depression rating scale (7). All data collected was analysed through SPSS version 13.0. Descriptive statistics were used to calculate mean and standard deviation (SD) for age, serum levels of TCAs and scores on HAMD. Frequency as percentages was calculated for gender.

The HAMD scores were stratified as 'mild', 'moderate' and 'severe'. Values for HAMD score and serum TCA levels at 0, 6, 8 and 10 weeks were fed into SPSS 13. Mean values were compared using Student 't' test. A p value of $\leqslant$ 0.05 was taken as significant.

RESULTS

34 patients in the monitored group A and 33 patients in the control group B completed the study duration. The mean age of the monitored group was 31.97 years (SD=10.432) while that of the control group was 33.52 years(SD=9.385). 42 (62.68%) patients were men, and 25 (37.31%) were women.

Mean HAMD scores for the whole study population at base line was 23.25 as shown in table I. There was significant improvement in depressive symptoms (shown by 50 % or greater reduction in depression scale from baseline) at 8 weeks of treatment in the whole population (both groups) where the mean HAMD score was 10.23.For individual groups the base line HAMD scores for monitored and control groups were 22.58 and 23.93 respectively which reduced to 11.23 and 9.18 at 8 weeks and no significant differences were observed between the two groups in terms of efficacy.

50 patients were inducted into the control group out of which only 33 (66%) completed the trial, 17(34%) patients dropped out, due to intolerable side effects leading to change of antidepressant to SSRIs .Out of the 40 patients inducted in the monitored group 34 (85%) completed the study duration and there were 6 (15%) drop outs as depicted in table II.

The mean doses of TCAs received by the patients were

Table-I. Mean HAMD scores of whole study population at baseline, 6,8 and 10 weeks.

N=67	Baseline	6 weeks	8 weeks	10 weeks
Mean HAMD scores	23.253	15.806	10.223	7.343
Standard Deviation	6.911	5.957	5.364	4.617

Table-III. Mean TCA doses (mg/day) received by both groups at 6,8 and 10 weeks.

Group	Mean TCA doses mg/day			P
	6 weeks	8 weeks	10 weeks	
Group A	60.25 mg/d	82.54 mg/d	94.76 mg/d	0.04
Group B	79.67 mg/d	96.82 mg/d	118.50 mg/d	N.S

Table-II. Drop outs due to intolerable side effects in both groups

Total no. Of patients entering the study	No. of patients having intolerable side effects					Total drop outs	Total no. Of patients completing the study
	Dry mouth	constipation	Sedation	Blurred vision	Hypotension		
Group A (n=40)	2	3	-	-	1	6 (15%)	34
Group B (n=50)	4	8	2	2	1	17 (34%)	33

significantly lower in the monitored group as compared to the controls as shown in table III, where there was no monitoring of drug levels and clinical judgment alone determined the dose of TCAs. Lower doses used in the monitored group could have been the reason for fewer side effects and hence fewer drop out rates.

In the monitored group the mean TCA levels at 6, 8 and 10 weeks were 88.3 ng/ml, 133.74 ng/ml and 169.98 ng/ml respectively. It was observed that the best response in terms of reduction in HAMD scores was observed between 6 to 8 weeks corresponding to serum TCA levels in the range of 88.3 ng/ml and133.74 ng/ml. Further increases in serum TCA levels did not bring about any significant reduction in HAMD scores at 10 weeks.

DISCUSSION

The study concluded that the presence or absence of therapeutic drug monitoring did not bring about any statistically significant difference between the controlled and monitored groups, as far as the efficacy of TCAs is concerned. (Müller MJ et al 2003) investigated a TDM group (TDM) and a randomly assigned parallel group without TDM (no-TDM) while on TCA treatment. Serum levels were analyzed in both cohorts, but feedback and dose recommendation were only provided for the TDM group. The outcome was measured weekly using the Hamilton Depression Rating Scale (HAMD), the Clinical Global Impressions Scale (CGI), and the UKU side-effect scale. 84 patients with depressive disorder according to DSM-IV were recruited in three centers (TDM, n = 43; no-TDM, n = 41; mean age 49.9 +/- 13.2 years, 63.1 % female). Patients were treated with either amitriptyline (n = 69) or doxepin (n = 15). Both groups improved according to HAMD (from 25.2 +/- 8.4 at baseline to 12.0 +/- 7.4 at endpoint) and CGI scores (68 % responders). Moderately severe or severe side effects occurred in 16 % of patients. Adequate dose adjustment was significantly higher in the TDM group (60 % vs. 46 %, $p < 0.05$); this led to a significantly higher rate of therapeutic serum levels in the TDM group (58 % vs. 44 %, $p < 0.05$). Direct effects of TDM were not found for effectiveness however considerable side effects occurred significantly more often in the no TDM group, concluding that treating depression with TCA can be optimized by early TDM, which is superior to clinical judgment on its own[1]. The findings of our study showed similar results as significantly higher number of patients (34%) in the non TDM (control) group experienced intolerable side effects as compared to the monitored group (15%), whereas no difference was noted in efficacy between the two groups.

In our study, mean HAMD scores reduced from 23.25 at baseline to 10.23 at 8 weeks of treatment for the whole study population, with significant improvement in depressive symptoms (shown by 50 % or greater reduction in depression scale from baseline) for both groups. This finding is in keeping with international treatment guidelines which recommend that an antidepressant be continued for a period of 8 weeks before switching to another drug in case of non response, therefore it may be concluded that the best response for TCAs is achieved at 8 weeks[8,9].

The third important finding in our study was the difference between the two groups in terms of patient drop out rates. (34%) patients dropped out of the control group, due to intolerable side effects leading to change of antidepressant to SSRIs whereas (15%) patients dropped out of the monitored group.

The mean doses of TCAs received by the patients were significantly lower in the monitored group as compared to the controls, where there was no monitoring of drug levels and clinical judgment alone determined the dose of TCAs. Lower doses used in the monitored group could have been the reason for fewer side effects and hence fewer drop out rates. In a met analysis by (MacGillivray et al 2003), significantly more patients receiving a tricyclic withdrew from treatment (relative risk 0.78, 95% confidence interval 0.68 to 0.90; z=3.37, P < 0.0007) and withdrew specifically because of side effects (0.73, 0.60 to 0.88; z=3.24, P < 0.001)[4].

In another review (Arroll et al 2005) focusing only on primary care samples, found 12% dropout rates for TCAs, due to intolerable side effects which could be reduced by lowering doses[10].

Zaleska et al 2006 conclude that after applications of TCA, side effects can develop in 50% of patients, and in 10% then can reach the level of medical complications, they further add that Pharmacotherapy with TCAs might be comparably safe in young and elderly patient, if it is performed according to the rules of TDM[11].

It was observed that the best response in terms of reduction in HAMD scores was observed between 6 to 8 weeks corresponding to serum TCA levels in the range of 88.3 ng/ml and133.74 ng/ml. The American Psychiatric Association Task Force on the Use of Laboratory Tests in Psychiatry conclude that Studies of both nortriptyline (also an active metabolite of amitriptyline) and desipramine have, in general, demonstrated curvilinear concentration- response relationships, with optimum ranges of 50-150 ng ml and 100-160 ng ml , respectively.

Further increases in serum TCA levels did not bring about any significant reduction in HAMD scores at 10 weeks. Various studies also conclude that serum levels above those described above do not correspond with better outcomes, however the risk for adverse effects increases with increasing serum levels[12].

CONCLUSIONS

The findings of this study conclude that the presence or absence of therapeutic drug monitoring in the treatment of depression does not bring about any significant difference, as far as the efficacy of TCAs is concerned. How ever therapeutic drug monitoring of TCAs in acute treatment phase reduces frequency and severity of intolerable side effects and protects patients from receiving unnecessary high doses. This can help enhance treatment adherence to antidepressants and thus improve prognosis and outcome amongst patients of depression treated with TCAS.

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