

EARLY EXPERIENCE WITH FLUOXETINE

Pages with reference to book, From 275 To 277

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ABSTRACT

A new antidepressant Fluoxetine, a serotonin re-uptake inhibitor, was tried on 26 resistant depressed patients. There were four drop out due to severe side effects. Improvement was noticeable soon after the first week and was maximum within 3 weeks of medication in 14 (63.6%) patients while in 8 (36.4%) patients it was as late as 6-12 weeks. The decline in improvement after three weeks in 7(31.8%) patients, needs attention in future studies. Bradycardia in 2 patients above the age of sixty indicate that the drug should be used with caution in elderly. GIT disturbance, insomnia, anorexia, restlessness and lethargy were common side effects. A well planned double blind study is recommended before its place is assigned in our patient population (JPMA 41: 275, 1991).

INTRODUCTION

Fluoxetine (Prozac) is a new antidepressant which provides an interesting model for examining the possible selective advantages of serotonin (5-HT) re-uptake inhibitor. The chemical structure of Fluoxetine differs from other tricyclic antidepressants (TCAs) by lacking three fused ring system¹. All presently available antidepressants have some draw backs. Since TCAs, are associated with unpleasant and sometimes dangerous side effects they reduce the compliance. In this process tetracyclic antidepressants (Mianserine) was introduced but the search for new and those with minimum side effects and greater efficacy is still an important goal. The place of serotonin system in depression has now been appreciated². Disturbance of serotonin in depressed patient is measured by taking levels of serotonin metabolites i.e., 5-Hydroxy Indole Acetic Acid (5-HIAA) in cerebrospinal fluid. Low level of 5-HIAA in CSF, is associated with suicidal behaviour or aggression.^{3,4} It is observed that serotonin may be involved in impulsive behaviour, fear, worrying and obsession.^{5,6} Hisrich and Bennet⁷ have shown that fluoxetine is as effective as tricyclics. It resembles the TCAs in efficacy with better compliance and low dropout rate⁸. Fluoxetine is recommended both in unipolar and bipolar depression and also in obsessive compulsive disorders⁹. It is a specific inhibitor of serotonin. The site of action is at serotonin re-uptake pump rather than specific neurotransmitter receptors. It is well absorbed by oral route and equally distributed in central nervous system following administration of single dose of 20 mg within one hour and 94% binds with plasma protein. Three fourth is excreted in urine and 15% in faeces^{10,11}.

PATIENTS AND METHOD

The selection of patients was guided by resistance in improvement by available antidepressants. All the patients procured Fluoxetine themselves. The limitation in number of patients is because of high cost of drug. The cost of four week course was approximately Rs. 1500/- on current exchange rate. Following criteria were observed for selection: Treatment resistant depression; severe side effects with tricyclic antidepressants; resourcefulness of patients to procure drug; no associated organicity; all age groups and meeting the criteria of Diagnostic and Statistical Manual, Third edition, Revised (DSM III-R) for major depressive disorder (code 296.3) and bipolar affective disorder (code 296.5). For clinical

impression, we rated the patients on seven points clinical global impression scale (CGI). Fluoxetine was commenced as a single morning dose of 20 mg/day. Only one patient received upto 40 mg/day in 3rd and 4th week of treatment. The duration of treatment was 3 weeks . Due to late onset of response in certain patients within three weeks, it was decided to follow those patients who could procure medicine for three months. Physical examination and base-line laboratory investigations (complete blood picture, blood sugar and urea) were carried out to exclude any organicity. Assessments were made every week. For tabulation 3rd, 6th, 8th and 12th weeks records are used. Concomitant therapy given to few patients was benzodiazepines for anxiety and insomnia. Side effects were recorded as reported spontaneously and upon questioning.

RESULTS

A total of 26 depressed patients (both bipolar and unipolar) were included in the study on the basis of defined criteria and ability to procure the drug. Age, sex, diagnosis, duration of illness and previous treatment is shown in Table 1.

TABLE I. Demographic Characteristics N = 26.

Age	Mean age 39.34 years (range 20-70 years)	
Sex	Male 18, Female 8	
Socioeconomic status	Upper middle class	
Diagnosis	- Major unipolar depression	19
	- Bipolar affective disorder (Currently depressed)	7
Duration of illness	Mean 6.69 months (Range 2.5 months - > 1 year)	
Previous drug treatment	All available anti-depressants	18
	Anti-psychotics and anti-depressants	7
	None	1

On clinical global impression, two were mildly depressed, seven moderate, thirteen marked and four were in the severe category. Four patients dropped out leaving twenty two who completed varying period of three to twelve weeks (depending on the availability of drug, 2 patients took the drug for three weeks, 2 for four weeks, 11 for six weeks, 2 for eight weeks and 5 for twelve weeks). Among the dropout one was 65 years old male with major depression who developed severe bradycardia on the third day of treatment and needed emergency treatment. The second was again a 70 year old male with major depression who complained of insomnia not responding to hypnotics. The pulse rate dropped to 60 per minute as recorded on fifth day. The drug was withdrawn on the eighth day and the pulse rate improved on the second day. The third patient was 20 year old female with major depression and marked obsessional features who had to be taken off drug on the third day due to increase in obsessive symptoms, insomnia and suicidal ideas. The fourth patient was 51 year old physician with major depression who stopped medication on fourth day due to severe gastric upset. The progress at the end of three weeks (22 patients), six weeks (18 patients), eight weeks (7 patients) and twelve weeks (5 patients) is recorded in Table II.

TABLE II. Clinical Global Impression Rating of patients who completed 3-12 weeks of treatment (three weeks 22, six weeks 18, eight weeks 7 and twelve weeks 5).

No.	Base Line	Week 1	Week 3	Week 6	Week 8	Week 12	Comments
1	3	2	3	6	-	-	Worse in 6 weeks
2	5	4	3	5	4	3	Became manic
3	5	5	4	4	2	2	Better
4	6	6	5	6	6	-	Stopped after 8 weeks
5	4	4	3	2	3	1	Improved after 12 weeks
6	6	6	6	6	-	-	No improvement
7	6	6	6	6	-	-	No improvement
8	6	5	2	5	-	-	Good early response
9	5	4	2	5	2	1	Later relapsed
10	4	4	4	-	-	-	Stopped after 3 weeks
11	4	4	3	3	-	-	Stopped after 6 weeks
12	5	5	4	3	3	4	Minimal improvement
13	4	4	4	4	6	-	Worse after 8 weeks
14	5	5	4	5	-	-	40 mg/day for 2 weeks
15	4	4	4	3	-	-	Improvement in 6 weeks
16	3	3	4	4	-	-	Worse after 6 weeks
17	5	3	1	-	-	-	Improved
18	4	3	2	1	-	-	Improved
19	5	5	2	-	-	-	Stopped after 3 weeks
20	5	4	2	2	-	-	Improved
21	5	3	4	-	-	-	Later relapsed
22	5	5	3	3	-	-	Became manic
Total Score	104	94	75	The score between base line and third week is statistically significant (P < 0.001).			

Fourteen (63.6%) patients showed considerable improvement in first three weeks while eight (36.4%) took 6-12 weeks. Decline in the improvement in seven (31.8%) patients after three weeks inspite of continuation of medication remains unexplained. The baseline total scores of 22 patients when compared at the end of three weeks was statistically significant. There was a significant difference in the CGI rating between baseline and third week with difference of mean and standard error of difference of means as -1.32 ± 0.34 with $p < 0.001$ level of significance i.e., CGI decreased by -1.32 after three weeks from baseline. The side effects experienced by twenty two patients (excluding drop out) is given in Table III.

TABLE III. Side effects observed N = 22.

Side effects	No. of Patients
GIT disturbance (Nausea, vomiting, loose motion, abdominal pain and constipation)	19
Insomnia	11
Anorexia	10
Restlessness/irritability/agitation	8
Lethargy and weakness	6
Weight loss	2
Tremor	3
Dryness of mouth	2
Skin rashes/fall of hairs	1
Severe pain in calf and foot	3
Psychomotor excitation	3
Toxic confusional state	1
Headache	2
Stammering	1
Vertigo	1
Smacking oral movement	1

DISCUSSION

Being fair to this new compound it must be stated that the patients included were resistant to all available antidepressants. The real efficacy can only be judged by double blind trial and random selection. Three of the 26 patients stopped medication within a week due to intolerance and one after second week. Two of them were above 60 years who developed bradycardia. Among the 22 patients who completed treatment for 3 weeks or more, the drug was discontinued due to varying reasons like 'became worse' (five patients), 'manic' (two patients), 'no improvement' (four patients) while others stopped due to 'non availability' of the drug. Fourteen of the 22 patients who continued therapy for 3 weeks or more had shown very encouraging result in the first three weeks of treatment. Seven of them remained better upto six weeks or more while seven^{1,2,4,5,8,9,11}, of them slipped later. In remaining eight patients (out of twenty two), three did not respond at all or became worse after six weeks and stopped medication. Five patients showed remarkable improvement during six to twelve weeks of treatment (responded later than expected three weeks). The usual side effects shown by tricyclics were not experienced, which is a great advantage. The common side effects were insomnia, anorexia, restlessness, irritability, lethargy and G.I.T. disturbance (nausea, vomiting, loose motion and abdominal pain). Two patients had shown quick weight loss after two weeks. Mi available antidepressants are known to cause increase in weight which is the most undesirable side effect. Two patients (case No. 2 and 22) with bipolar depression developed mania after twelve and five weeks respectively. In one patient drug had to be stopped after fourteen weeks due to mild pontine leak, confirmed by C.T. scan

and angiography. Relationship with drug has not been confirmed. Fluoxetine appears to be potent antidepressant. In view of the limited experience in the West and use and abuse of antidepressants in our country great caution in prescribing this costly compound is suggested. Carefully planned double blind studies in our patient population is recommended.

REFERENCES

1. Schmidt, M.J., Fuller, R.W. and Wong, D.T. Fluoxetine, a highly selective serotonin reuptake inhibitor. A review of preclinical studies. Br. J. Psychiatry, 1988; 153 (Suppl. 3):40.
2. Montgomery, S.A. The benefits and risk of 5-HT uptake inhibitor in depression. Br. J. Psychiatry, 1988;153(Suppl. 3):7.
3. Traskman, L, Asberg, M., Bertilsson, L. and Sjostrand, L Monoamine metabolites in CSF and suicidal behaviour. Arch. Gen. Psychiatry, 1988;38:631.
4. Lopez-Ibor, Jr., Juan, S. The involvement of serotonin in psychiatric disorder and behaviour. Br. J. Psychiatry, 1988:153 (Suppl. 3):26.
5. Linnoila, M., Virkkunen, M.S. and Scheinin, M. Low, C.S.F., 5HIAA concentration differentiate impulsive from nonimpulsive violent behaviour. Life Sciences, 1989;33:2609-2614. cited by Br. J. Psychiatry, 1988:153 (Suppl. 3):7.
6. Ballenger, J.C., Goodwin, F.K., Major, L.F. and Brown, G.L. Alcohol and central serotonin metabolism in man. Arch. Gen. Psychiatry, 1979;36:244.
7. Hisrich, K.R., Bennet, J.A. Journal of Pharma Tech., 1987; 219-222 cited by Fluoxetine drug evaluation, D.Petty, Pharmacist, Drug Information Centre, March, 1989.
8. Lader, M. Fluoxetine efficacy vs comparative drugs: an overview. Br. J. Psychiatry, 1988;153 (Suppl. 3):51.
9. Turner, S.M. Journal of Psychopharmacology, 1984; 5: 207 cited by Fluoxetine drug evaluation, D. Petty, Pharmacist, Drug Information Centre, March, 1989.
10. Bergstrom, R.F., Lemberger, L., Farid, N.A. and Wolen, R.L. Clinical pharmacology and pharmacokinetics of Fluoxelinc, a review. Br.J. Psychiatry, 1988;153 (Suppl. 3):47.
11. Aronoff, G.R., Bergstrom, R.F., Pottratz, S.T., Sloan, R.S., Wolen, R.L and Lamberger, L. Fluoxetine Kinetics and protein binding in normal and impaired renal function. Clin.Pharmacol. Therapeutics, 1984;36:138.