OBSESSIVE COMPULSIVE NEUROSIS: CLOMIPRAMINE, PROLACTIN AND THERAPEUTIC RESPONSE
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ABSTRACT
This study was designed to assess the relationship between psychopathology and serotonin generated prolactin response to clomipramine and to assess the relationship between improvement in psychopathology and prolactin levels. The experimental sample consisted of 15 patients in the drug and 12 patients in the placebo groups. Blood samples for prolactin levels were drawn at baseline, and at the end of 4, 8, and 12 weeks. There were statistically significant differences in prolactin increase between the drug and the placebo groups at 4 but not at 12 weeks following treatment. When the four least improved and a similar number of the most improved patients were compared, the least improved patients had the most increase in prolactin and the most improved had the least increase.

Key Words: Clomipramine, obsessive compulsive neurosis, prolactin response to clomipramine

The unique symptomatology and manifestations of obsessive compulsive disorder (OCD) as well as recent technological advances have allowed researchers to gain insight into the pathophysiology of this disorder. Serotonin (5HT) dysregulation is implicated in OCD (Murphy et al., 1989). The implication of serotonin dysregulation in OCD is based on the indirect evidence that clomipramine, a potent serotonin uptake inhibitor, has been found to be useful in treating OCD (Ananth, 1985; Clomipramine Collaborative Study Group, 1991; Thoren et al., 1980a; Zohar et al., 1987a; Grist et al., 1995a). Usefulness of other selective serotonin inhibitors (SSRI) such as fluvoxamine (Goodman et al., 1990; Mallaya et al., 1992; Freeman et al., 1994; Greist 1995b), fluoxetine (Pigott et al., 1990; Montgomery et al., 1993; Tollefson et al., 1994), sertraline (Chouinard, 1992; Jenike et al., 1990; Greist et al., 1995c) in the treatment of OCD provides further credence for serotonin involvement. Administration of pharmacological probes including tryptophan, a serotonin precursor (Charney et al., 1988), fenfluramine a 5HT releaser (Hollander et al., 1988), metergoline a 5HT antagonist (Pigott et al., 1991; Pigott et al., 1993) and meta-chlorophenylpiperazine (mCPP) (Barr et al., 1992; Zohar and Insel, 1987; Zohar et al., 1987; Hollander et al., 1988; Charney et al., 1988; Pigott et al., 1991; Pigott et al., 1993; Goodman et al., 1995; Hollander et al., 1992) did not yield consistent and replicable response.

There are multiple serotonin receptors (5-HT1 to 5-HT7) cloned and subtyped (Lucki, 1996; Hoyer et al., 1994; Kreiss and Lucki, 1994). The list is never complete as the classification is ongoing with identification of new receptors. Genes are identified for the 5-HT1a, 5-HT1b, 5HT1d, 5HT1e, 5HT1f, 5HT2a, 5HT2b,
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5HT_2c, 5HT_3, 5HT_5a, 5HT_5b, 5HT_6 and 5HT_7 (Dubovsky & Thomas, 1995; Lovenberg et al., 1993; Meltzer, 1990). To assign particular psychopathology to a particular receptor is not possible for a number of reasons: a) many of the drugs that are employed act on multiple receptors; b) interact and influence each other; c) it is unlikely that particular subtypes are involved in each psychiatric illness; d) OCD may be a heterogeneous group and thus different subtypes of 5HT receptors might be involved in different patients, and that OCD may be due to the generalized dysfunction of the 5HT system.

There is evidence that 5HT regulates the secretion of prolactin (Coven et al., 1990; Lopez et al., 1987; Ben-Jonathan et al., 1989). An enhanced prolactin level after administration of clomipramine has been reported (Anderson & Coven, 1989; Hanna et al., 1991; Zohar et al., 1988). A problem in interpreting these data includes the variance of physiologic, pathologic and pharmacologic factors that affect prolactin secretion. In addition, sensitivity of serotonergic system in OCD patients may differ from that in normal. Currently, the relationship between clomipramine administration and prolactin levels as well as psychopathology has not been definitively established. Therefore, this study was designed to assess the relationship between psychopathology and prolactin response to clomipramine; and to ascertain the relationship between improvement in psychopathology and prolactin levels.

MATERIAL AND METHOD

Patients were diagnosed on the basis of a clinical interview and rating on the Yale Brown Obsessive Compulsive Rating Scale (YBOCS). Inclusion criteria was a diagnosis of OCD on the basis of SCID, of at least one year duration, a score of 20 or more on the YBOCS, and age range between 18 and 65 years, good physical health as well as normal electrocardiogram, biochemical tests, chest X-ray and eye tension. Exclusion criteria were the presence of physical illness, primary depression, epilepsy, history of head injury, thyroid disease, schizoid personality disorder based on SCID, drug and alcohol abuse, and/or anyone on concomitant medication. The exclusion of schizoid personality is based on the finding of nonresponsiveness of these patients to clomipramine treatment (Baer and Jenike, 1989).

The experimental sample consisted of 13 males and 14 females with a mean age of 35.8 years and a range between 19 and 64 years. The placebo group consisted of 4 males and 8 females with a mean age of 36.6 years, and a range between 19 and 64 years. Similarly, the drug treated group consisted of 9 males and 6 females with a mean age of 35 years and a range between 22 and 51 years.

All selected patients were on placebo for one week, and during that week all investigations including a detailed physical examination, glaucoma test, chest X-ray, electrocardiogram and a battery of biochemical examination were conducted. According to a precoded design, only those with normal results were randomly assigned to either placebo or drug treatment. Half the patients were given placebo and the other half received gradually increasing doses of clomipramine up to 250 mg daily. Blood for prolactin levels were drawn at baseline, and at the end of 4, 8 and 12 weeks on the same day as the clinical assessment. Each patient had four prolactin samples and there were no drop-out in either group. On the day of the sample collection for prolactin estimation, patients were clinically interviewed on the basis of which the Yale Brown Obsessive Compulsive Scale was completed. There were no dropouts in either group. Blood was drawn between 8:00 and 8:30 A.M. in all patients, and in females blood was drawn a week after the menstrual cycle. Data was analysed using multiple correlation coefficient. Serum sample were analysed for prolactin by radio-immune assay with reagents obtained from the National Pituitary Agency (Poland & Robin, 1981). As determined by multiple high, medium, and low
serum pool replicates; maximum inter-and intra-assay variability was 13%. The lower limit of sensitivity using 50ng/ml.

RESULTS

a) Prolactin levels: In the clomipramine group, mean prolactin level of 7.79 ng/ml change to 14.36ng/ml at the end of 4 weeks, to 12.60 ng/ml at the end of eight weeks and to 11.34 ng/ml at the termination. However, there was a significant change in prolactin levels across trials in this group (p<0.001). The change in prolactin level from 6.9 ng/ml at baseline to 7.25 ng/ml at the end of 4 weeks, 7.35 ng/ml at the end of 8 weeks to 7.8 ng/ml at termination. There was no significant change in the prolactin level for patients on placebo across trials. Between the placebo and the drug groups at the end of 4 and 8 weeks (t=2.81, df=25, p<.006, respectively) but not at the end of 12 weeks of the study, there were statistically significant difference in the mean prolactin level (Table). These prolactin levels did not correlate with gender for either group at any week of treatment except for the drug group at week 4 (t=2.27, p<.041) with females having significantly higher levels of prolactin. There was a statistically significant correlation between total YBOCS scores and the baseline prolactin level in the female population as a whole (r=.54 p<0.001).

Dosage of medication insignificantly correlated with prolactin level at the end of 4 weeks (r=.279) with a mean daily dose of 210 mg, 8 weeks (r=.353) with a mean daily dose of 230 mg, and 12 weeks (r=.152) with a mean daily dose of 210 mg.

b) Psychopathology: In the clomipramine group, the base-line YBOCS score of 28.1 changes to 19 at the end of 4 weeks, 15.3 at the end of 8 weeks and 13.2 at the end of 12 weeks and in the placebo group the baseline YBOCS scores of 27.9 changed to 26.9 at the end of 4 weeks, 25.2 at the end of 8 weeks and 25.7 at the end of 12 weeks. There was a statistically significant 52.8% improvement in the drug group and 10% in the placebo group at termination. The improvement in the clomipramine group at 4,8 and 12 weeks of treatment (p<0.001) and the difference between the two groups (p<0.001) was statistically significant. Male patients improved better than the females (78% vs.51%) which was statistically significant (p<0.001).

| Patients on placebo | WK 0 | WK 4 | WK 8 | WK 12 | Patients on clomipramine | WK 0 | WK 4 | WK 8 | WK 12 |
|---------------------|------|------|------|-------|--------------------------|------|------|------|-------|
| 1M                  | 7.5  | 11.4 | 8.7  | 11.4  | 1M                       | 4.9  | 13.1 | 12.3 | 11.0  |
| 2M                  | 3.9  | 3.9  | 6.1  | 5.6   | 2M                       | 8.8  | 13.0 | 5.9  | 7.8   |
| 3M                  | 6.6  | 6.6  | 7.0  | 7.5   | 3M                       | 8.6  | 8.4  | 9.9  | 9.1   |
| 4M                  | 8.1  | 5.6  | 8.5  | 7.2   | 4M                       | 9.6  | 10.4 | 11.0 | 11.0  |
| 5F                  | 7.6  | 6.5  | 7.6  | 7.6   | 5F                       | 7.2  | 12.9 | 13.4 | 13.9  |
| 6F                  | 8.9  | 8.9  | 8.5  | 7.3   | 6F                       | 4.8  | 9.9  | 9.4  | 4.1   |
| 7F                  | 8.0  | 4.4  | 6.7  | 8.1   | 7F                       | 8.3  | 13.2 | 13.2 | 13.1  |
| 8F                  | 7.8  | 8.5  | 7.3  | 8.2   | 8F                       | 6.5  | 8.4  | 8.3  | 9.2   |
| 9F                  | 6.0  | 13.0 | 7.6  | 7.6   | 9F                       | 5.7  | 8.4  | 9.2  | 2.5   |
| 10F                 | 5.0  | 5.0  | 6.5  | 6.5   | 10F                      | 5.7  | 14.0 | 12.7 | 6.1   |
| 11F                 | 5.3  | 5.3  | 7.4  | 10.9  | 11F                      | 9.3  | 15.5 | 10.8 | 9.5   |
| 12F                 | 8.1  | 8.0  | 6.3  | 6.5   | 12F                      | 9.6  | 12.5 | 13.4 | 13.4  |
| 13                  | -    | -    | -    | -     | 13F                      | 4.0  | 7.4  | 8.2  | 7.0   |
| 14                  | -    | -    | -    | -     | 14F                      | 15.5 | 35.5 | 21.1 | 13.7  |
| 15                  | -    | -    | -    | -     | 15F                      | 8.6  | 32.5 | 30.3 | 39.0  |
c) Psychopathology and prolactin level interactions: There was a significant negative correlation between YBOCS scores and serum prolactin levels ($r = -0.50$, $p<0.05$) for the entire group at the end of four weeks and no other significant correlation was noted. There was essentially no correlation between psychopathology and prolactin level for those on drug at baseline ($r = -0.18$) and throughout week 8 ($r = -0.05$ $r = -0.08$), and only a modest correlation at 12 week ($r = 0.36$).

d) The best and the worst responders: The four most improved patients were compared with the four least improved ones. The total YOBCS score of the four with least improvement changed from 104 to 99 and that of most improved changed from 116 to 23 ($p<0.001$). The total prolactin level of the least improved group changed from an initial level of 33 to a final level of 72 with an average daily dose of 250 mg of clomipramine (Table). On the other hand, the prolactin level of the most improved group did not change throughout the study. The differences in prolactin increase between the two groups was significant ($p<0.001$). In fact, the resistant group had a higher increase in prolactin levels.

DISCUSSION

In the total population of 27 patients, initial prolactin levels correlated significantly ($r = -0.4$, $p>0.01$) with the total YOBCS scores in females and not in males. There were statistically significant differences in prolactin increase between the drug (15 patients) and the placebo (12 patients) groups at 4 but not at 12 weeks following treatment. These levels were not significantly related to drug dosage, psychopathology, age or gender. When the four least improved and a similar number of the most improved patients were compared, the least improved patients had the most increase in prolactin and the most improved had the least increase.

These findings lend themselves to a number of interpretations: 1) optimal prolactin response occurs at four weeks and no later, and a correlation of YBOCS scores and prolactin increase exists at four weeks only; 2) serotonin increase as reflected by increase in prolactin may not be the mechanism of action of clomipramine in OCD; and 3) prolactin may not be an adequate marker for serotonin function; 4) the findings may be a chance factor due to the small sample size.

However, the finding that the most improved had the least increase in prolactin, provides evidence for the down regulation of the postsynaptic serotonin receptors. Delay in onset of action on obsessive compulsive symptoms noted in many of the studies supports this down regulation indirectly. To prove these intricate relationships, it is important to carry out a study with a large number of patients and normal controls.

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