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CLOMIPRAMINE IN RESISTANT OBSESSIVE COMPULSIVE DISORDER

SUMANT KHANNA [1]
P.N. RAJENDRA [2]
S.M. CHANNABASAVANNA [3]

SUMMARY

Twelve subjects with a diagnosis of Obsessive Compulsive Disorder who had not shown response to amitryptiline and imipramine/behaviour therapy underwent a cross over double blind trial with clomipramine and nortryptiline. Subjects who had earlier not shown response to the other drugs did not show response to clomipramine. The implications of these findings for clinical management are discussed.

Clomipramine has been widely recognised as the drug of choice for obsessive compulsive disorder (OCD) whose efficacy has been shown in various double blind studies (Thoren et al 1980, Marks et al 1980, Montgomery 1980, Ananth et al 1981, Insel et al 1983). However, it has been suggested that about one third of patients do not respond to pharmacotherapy (Insel 1985). Higher cerebrospinal fluid 5-hydroxy indole acetic acid has been shown to be related to clomipramine response (Thoren et al 1980b). Although various other drugs have been used (Insel & Murphy 1981), current interest has focussed mainly on drugs acting on the serotonergic system. Drugs which have been found efficacious include the serotonin precursor L-tryptophan (Yarvura-Tobias & Bhagavan 1977) and serotonergic uptake inhibitors like zimeldine (Fontaine et al 1985), trazodone (Prasad 1984) and Fluoxetine (Turner et al 1985). This interest mainly steps from the serotonergic hypothesis of obsessive compulsive disorder (Yarvura-Tobias et al 1977) which has recently been questioned (Insel et al 1985). At a more pragmatic clinical plane, various issues remain unanswered. Although clomipramine has been suggested to have specific anti-obsessional properties (Mavissakalian & Michelson 1983) it is not available in various countries, such as India and U.S.A. In the absence of this drug, authors have suggested the use of imipramine (Insel 1985) and amitryptiline (Snyder 1980) as the first line of therapy. Behaviour therapy has also got an established role in the therapy of OCD, although treatment failures here are also recognised (Steketee et al 1983). As such there remain a group of patients who do not respond to traditional tricyclic antidepressants and behaviour therapy. In this study we have tried to study the efficacy of clomipramine in subjects who are non-responsive to other forms of therapy, as defined here.

1. Lecturer
2. Junior Resident
3. Professor

Department of Psychiatry, National Institute of Mental Health and Neurosciences, Bangalore — 560 029.

Materials and Methods

The sample consisted of 18 subjects who had been followed up in the Psychiatry Out Patient Department at National Institute of Mental Health and Neurosciences, Bangalore. The diagnosis was made according to DSM III (American Psychiatric Association 1980). Subjects with depression were included in the OCD cohort provided (i) the depression was attributed by the subject as being secondary to the obsessive compulsive phenomenon (ii) there was a gap of atleast 2 months between the onset of obsession and depression, with the former occuring first and (iii) there was no history suggestive of melancholic or psychotic features (modified from Insel et al 1983). Non-responsiveness was defined as lack of significant response to (i) 300 mg. of amitrytptiline daily for 6 weeks or (ii) imipramine 300 mg. daily for 6 weeks.

The subjects were allotted double blind to clomipramine and nortryptieline initially (10 to clomipramine, 8 to nortryptiline). The drugs were administered in a dose of 50 mg/day for the first 3 days, with an increase of 50 mg/day every 3 days till the maximum tolerated dose or 200 mg/day was reached. All subjects had been free of all psychotropic drugs for a period of 4 weeks before the onset of the study, with a similar gap between the last session of behaviour therapy and the onset of this trial. All subjects were rated weekly from the onset of the trial on a Side effects check list, Maudsley Obsessive Compulsive Questionniare (Hodgson & Rachman 1977), Leyton's Obsessional Inventory (Cooper 1970) and Hamilton Depression Scale (Hamilton 1967). Each drug was given for a period of 6 weeks, with a cross over, with a drug free interval of 4 weeks. The blind was broken after the whole trial was over. Paired 't' test was used to compare groups before and after treatment.

Results

Out of the eighteen subjects with OCD, 8 completed the entire drug trial and 4 completed only one part of the trial. Of these 4, 3 completed the trial with clomipramine and 1 with nortryptilline. Six dropped out before finishing even one part of the trial. Thus 12 subjects received either drug for at least 6 weeks while 8 received both. There were 4 female and 8 male subjects. Two patients had only obsessions while the others also had compulsions. 4 of these latter subjects were checkers, 5 were washers and 1 had both checking and washing compulsions.

Pooling the data, 11 subjects received clomipramine and 9 nortryptiline. Seven of the subjects has received an adequate trail of amitryptiline (AMI) or imipramine (IMI). Nine of the 12 subjects received behaviour therapy (BT). Other interventions used included diazepam (DZM) and Electroconvulsive therapy (ECT). The average age of consultation was 30 years (SD=7.92) and the mean duration of illness was 10.08 years (SD=7.22). The patients were classified according to the predominant symptom cluster present.

There was no significant difference present between pre and post trial scores on the Leyton's Obsessional Inventory and Maudsley Obsessive Compulsive Questionnaire (Table 1). However there was a significant difference between the scores of Hamilton Depression Scale, but this did not differentiate between clomipramine and nortryptiline. Significant reduction of depressive symptoms was observed in both cases at 4 weeks. Only one of the 8 subjects who completed the whole trial reported subjective global improvement with clomipramine.

When considering the scores before administration of any drug, there was no significant difference between the two

Table 1

Changes in Depression and Obsessional Scores

	CLOMIPRAMINE				NORTRYPTILINE			
	Pre		Post		Pre		Post	
LOI : Symptom Score	28.7	(6.4)	25.4	(6.1)	31.3	(5.9)	27.8	(6.2)
Trait Score	13.2	(3.1)	12.9	(2.8)	12.4	(3.3)	12.5	(2.9)
Resistance Score	61.3	(18.4)	56.8	(19.2)	56.4	(19.8)	52.4	(16.4)
Interference Score	66.2	(23.1)	58.4	(26.1)	63.4	(21.8)	59.8	(19.6)
Maudsley Obsessional Questionnaire	18.2	(4.3)	18.4	(4.1)	17.4	(4.2)	17.1	(4.4)
Hamilton Depression Scale	18.9	(5.4)	12.6	(7.9) *	20.1	(6.5)	14.5	(9.2) *

* $P < .05$ Standard Deviations are given in brackets

groups who received nortryptiline (n=9) and clomipramaine (n=11); there was also no difference between the group which completed atleast one part of the trial (n=12) and the group which did not (n=6) and the group which completed only one half of the trial (n=4). There was no statistically significant difference when the antiobsessional effects of clomipramine and nortryptiline were compared, using either the 8 subjects who completed the whole trial or the 12 subjects who completed part of it. On the drug Side effects Check List, dryness of mouth was noted in 3 subjects who received clomipramine. Otherwise the drugs were well tolerated in the dosage regimen followed here.

Discussion

While clomipramine has been widely stated to be the drug of choice in OCD (Insel & Murphy 1981) there has been little stress on the drugs of choice where clomipramine is not available. While admitting that about one third of patients do not respond to clomipramine, Insel (1985) could not identify the non-responder group phenomenologically. He stated that the whole spectrum of obsessive compulsive disorders respond to clomipramine. Behaviour therapy is more beneficial when compulsions and avoiding are predominant (Insel 1985). Response to clomipramine therapy has few predictors except for cerebrospinal fluid 5-hydroxy indole acetic acid levels (Thoren et al. 1980b).

While amitryptiline has been found useful in OCD (Snyder 1980), some workers have proposed imipramine as the first drug of choice because of its structural similarity to clomipramine (Insel 1985). A recent double blind study did not find much difference in the antiobsessional effects of imipramine and clomipramine (Volavka et al 1985). However in another study clomipramine was found superior to amitryptiline (Ananth et al 1981).

The serotonergic hypothesis of OCD was initially proposed because of response to clomipramine, a serotonin uptake inhibitor, and L-tryptophan, a serotonin precursor (Yarvura-Tobias & Bhagavan 1977). Support also came from lower cerebrospinal fluid 5-hydroxy indole acetic acid levels found in OCD subjects (Thoren et al 1980b). More specific serotonin uptake inhibitors have also been found effective (Prasad 1984, Fontaine et al 1985, Turner et al 1985). This hypothesis stresses that decreased serotonin is the cause for OCD. However our study identifies a sub-

group of non-responders which apperantly does not have this biochemical abnormalty. Rather than disproving the serotonergic hypothesis our study stresses the need to study other neurotransmitter systems and points to the biochemical heterogenity of OCD.

On a more pragmatic plane, subject who do not respond to amitryptiline or imipramine in adequate doses, along with behaviour therapy, are unlikely to respond to clomipramine. One flaw in our study is the absence of plasma nor-tryptilline levels. With a maximum dose of 200 mg/day, some patients may have received doses outside the therapeutic window. There has been no study to the best of our knowledge where amitryptiline has been compared with imipramine. In a retrospective study where we studied sociodemographic and clinical factors (Khanna et al 1986a), improvement did not correlate with any specific modality of therapy. We are currently trying to develop alternate strategies of therapy of OCD. There is some suggestion that subjects with evidence of cerebral damage or malfunction respond best to amphetamine (Khanna & Janakiramaiah 1984, Khanna submitted). An attempt is also being made to define predictors of outcome and therapy response. This work is currently at a preliminary stage. However we have identified two large sub-groups of OCD probands. One consists of the young student, and the other a middle aged housewife (Khanna et al 1986b). We are trying to determine whether they have any preferred therapeutic responsiveness. Finally, with responses of OCD to a wide range of drugs (Turner et al 1985), the possibility has also to be kept in mind that OCD is a heterogenous group of illnesses and separate sub-groups respond better to specific therapies. Where anxiety is predominant alprazolam is effective (Tesar & Jenike 1984), while with panic attacks Monoamine Oxidase inhibitors may be the drug of choice (Jenike et al 1983). Some subjects who show ictal discharges respond to anti-epileptics (Jenike 1984) while ECT (Mellman & Groman 1984) and lithium (Stern & Jenike 1983) also have been found useful. Most of the studies which have shown response to antipsychotics have not had clearly defined patient populations (Jenike 1983).

Amitryptilline and imipramine when used in adequate doses for adequate periods of time most probably cover the therapeutic range for clomipramine, due to their serotonergic and noradronergic uptake inhibition. This study provides tentative evidence that an adequate trial of imipramine and amitryptiline should be given in all cases of OCD, and that if subjects do not respond to these two drugs, it is unlikely that they will show response to clomipramine.

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