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CLINICAL EFFICACY OF CENTPROPAZINE - A NEW ANTIDEPRESSANT

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Efficacy of centpropazine, a new antidepressant, has been evaluated in forty two patients of endogenous depression. The 4 week open trial was carried out in a dose-range of 40 to 120mg per day. A significant lowering of Hamilton Depression Rating Scale (HDRS) score was observed in 34 patient. The antidepressant effect could be detected in 9 patients within one week, in 28 cases in two weeks and in all the 34 patients by third week. Giddiness, headache, dryness of mouth and weakness were reported by 11 patients.

Centpropazine [1-propionyl-phenoxy)-3-(N^4-phenyl-piperazinyl)propane-2-Ol] is a new antidepressant with minimal autonomic effects in animals (Prasad *et al.*, 1969). This compound counteracts reserpine induced hypothermia, ptosis and sedation and potentiates amphetamine induced hyperactivity in mice. Centpropazine does not antagonize the pilocarpine induced salivation and its antitremorine activity is weaker than that of imipramine. The receptor binding studies have shown that centpropazine decreases 5-HT receptor density in cortical region (Hussain *et al.*, 1988). The study on noradrenergic receptors has shown it to have a greater affinity with alpha receptors and modulatory effect on second messanger system (Dikshit *et al.*, 1992). It has been found to be safe in chronic toxicological evaluation including teratogenicity and mutagenicity studies (unpublished data). Phase I clinical trial with this potential drug were undertaken succesfully in normal male subjects and was found to be safe upto a dose of 200mg in single dose studies and upto 80mg per day in multiple dose studies (Gupta *et al.*, 1989). The aim of phase-II clinical trial was to evaluate centpropazine for antidepressant effect and nature of side effectes in patients suffering from depression.

METHODS

The trial was conducted at the following centres in collaboration with Central Drug Research Institute, Lucknow.

Deptt. of Psychiatry	Seth G.S. Medical College, Bombay.
„	Ram Manohar Lohia Hospital, New Delhi.
„	K.G.'s Medical College, Lucknow.
„	Govt. Medical College, Patiala.

Patients of either sex suffering from major depressive disorder (endogenous depression) were recruited for the study. The diagnosis was made in accordance with Research Diagnostic Criteria (Spitzer *et al.*, 1978). All patients were admitted in the hospital and were subjected to a thorough clinical examination and biochemical laboratory investigations to rule out any hepatic, renal, cardiac or organic brain disease. An informed consent was obtained from the patients or his/her guardians. The initial dose was 40 mg per day and it was increased upto 120 mg in two weeks and continued on this dose upto 4 weeks. Patients receiving any other psychotropic drugs before

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entering the trial underwent 2 weeks placebo washout period before inclusion. Each patient was evaluated on Hamilton Depression Rating Scale (HDRS) and Side Effect Symptom Check List (SESCL) on day 0, 7, 14, 21 and 28 of the trial. The criterian for onset of antidepressant effect was 25 percent reduction in HDRS score of the individual patient. Clinical global impression scale was used for final mental status evaluation at the end of the trial. The clinical examination and laboratory investigations were repeated at the end of the trial. The data has been presented as mean ±SD and analysed by paired 't' test for statistical significance.

RESULTS

In the present study 42 patients (30 males and 12 females) with mean age of 38.6±11.0 years suffering from depression completed the 4 week trial. The results have been presented for each centre separately.

BOMBAY CENTRE

Eleven patients (8 males and 3 females) aged 28 to 54 years (mean 41.3±8.4) were included in the trial. One patient was withdrawn from the study because of increased severity of illness and one patient dropped due to his inability to come for follow up visit. The mean HDRS score at intervals show a steady and statistically significant decrease (Table 1). After one week of therapy with centpropazine onset of effect was observed in 3 cases, 3 cases showed improvemnt at 2 weeks and 2 cases had signs of improvemnt after 3 weeks. At the end of 4 week therapy final evaluation on Clinical Global Impression Scale (CGIS) revealed that two patients were very much improved, 6 patients showed mild to moderate improvemnt and 1 case had no improvemnt.

DELHI CENTRE

Seven patients (4 male and 3 female) aged 22 to 65 years (mean 43.33±16.48) were included in the trial. One patient was lost to follow up. However, 6 patients completed the study. The fall in mean HDRS scores at weekly intervals was found to be statistically significant in these patients (Table). Onset of antidepressive effect was noticed in 2 pateints at 1 week, 3 patient at 2 week and in 1 pateint at 3 weeks of centpropazine therapy. The evaluation on CGIS at the end of trial showed that 2 patients were very much improved and 4 pateints experienced mild to moderate improvemnt.

LUCKNOW CENTRE

The study was initiated on 24 patients (16 male and 8 female) aged 24 to 57 years (mean 42.81±9.5 years). Five patients dropped during their follow up visits. However, 19 patients completed the study. A statistically significant decrease in mean HDRS scores was observed after 2 weeks of drug therapy (Table). Three pateints started improving as early as 1 week, 8 patients showed improvemnt at 2 week and 1 patient experienced improvemnt at 3 weeks. The final evaluation on CGIS revealed a mild to moderate improvement in 12 patients whereas no change was observed in 7 patients.

PATIALA CENTRE

Ten patients (7 male, 3 female) aged 28 to 55 years (mean 38.8±14 years) were included. Two patients were dropped as they could not come for follow up. Eight patients completed the trial. The mean HDRS scores at weekly intervals have shown a steady fall which was found to be statistically significant (Table). The antidepressant effect was noticed in one

patient at 1 week, 5 started improving at 2 week and 2 showed improvement at 3 weeks. The final clinical evaluation on CGIS revealed that 4 patients were very much improved. 3 patients showed mild to moderate improvemet and 1 case showed no change.

The final clinical assessment at the endof the trial from the 4 centres revealed that 8 patients were very much improved, 26 patients showed a mild to moderate improvemet while 8 patients remained unchanged. The analysis of side effects (SESCL) has shown that eleven patients complained of giddiness, headache, dryness of mouth and weakness. These were transient and did not interfere in day to day routine of the patient or the treatment schedule. No drug effect were observed on clinical examintion and laboratory parameters.

Table 1: Showing pre- and post-drug HDRS scores (Values expressed as mean ±SD)

Centre	Day 0	±1 wk	±2 wk	±3 wk	±4wk
Bombay (n = 9)	32.11 ±6.17	24.11** ±4.19	19.33** ±7.36	15.11** ±7.52	12.66** ±7.01
Delhi (n = 6)	39.66 ±5.35	31.83* ±10.06	23* ±11.29	19.83* ±15.72	12.83* ±11.32
Lucknow (n = 19)	31.52 ±6.71	28.63 ±6.85	24.73** ±7.63	22.31** ±8.41	18.63** ±7.68
Patiala (n = 8)	35.37 ±8.39	28.25** ±7.38	17.5** ±7.31	11.37** ±7.63	7.12** ±4.22

(* $p < 0.05$, ** $p < 0.01$)

DISCUSSION

The present communication reports the findings of multicentric clinical trials carried out with centpropazine in patients of depression at four centres in India in collaboration with Central Drug Research Institute, Lucknow.

The study has shown antidepressant response in 80.9% patients at the end of 4 weeks medication with centpropazine. The antidepressant effect was present in 9 patients after one week, in 28 patient after 2 weeks and in 34 patients after 3 weeks of therapy. Centpropazine has also shown a wider safety margin in acute toxicity studies as compared to imipramine and could be safer than tricylics in overdosage by suicidal patients, a persistent risk in severely depressed pateints. The side effects were also mild and were transient.

The preliminary studies have, therefore, revealed that centpropazine has antidepressant effect with safer profile in a small population of 42 patients. The drug is currently undergoing a double blind phase III clinical trial.

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