Indian Journal of Psychiatry, 1999, 41 (3),249-253

MULTICENTRIC EFFICACY STUDY OF CENTPROPAZINE AND IMIPRAMINE IN DEPRESSED PATIENTS

J.S. SRIVASTAVA, O.P. ASTHANA, H. SINGH, A.K. AGARWAL, L.P. SHAH, K.C. SHARMA, P.S.GOPINATH & R.C. SRIMAL

ABSTRACT

Centpropazine is a new antidepressant with minimal anticholinergic effects in preclinical animal models. In this study centpropazine has been compared with imipramine in a double blind randomised multicentric study. A total of 159 patients of major depressive disorder (79 in centpropazine group and 80 in imipramine group) from four centres were included in this trial. Each patient was randomised to receive either centpropazine in a dose of 40 to 120 mg per day or imipramine in a dose of 50 to 150 mg per day for a period of six weeks. The antidepressant efficacy of centpropazine was comparable to imipramine but anticholinergic side effects were four times less than imipramine. This establishes centpropazine as an effective antidepressant with remarkably safer tolerability profile.

Key words : Centpropazine antidepressants depression.

One of the still unmet needs in the treatment of depression is the availability of antidepressants with better tolerability profile despite claims made by most of them. Centpropazine, 1-(p-propionyl phenoxy)-3(N4-phenylpiperazinyl)-propane-2-ol, is a new antidepressant belonging to aryloxypropanolamine series of compounds (Rastogi et al., 1972). Pharmacologically it has shown antidepressant activity in preclinical screening tests for evaluating an antidepressant (Prasad et al.,1967). These include antagonism of reserpine induced ptosis, hypotension, sedation and potentiation of amphetamine induced hyperactivity in mice. Centpropazine does not antagonize the pilocarpine induced salivation and its antitremorine activity is weaker than imipramine. Neurochemically it decreased the density of $5HT_1$ and $5HT_2$ receptors in the cortical regions following prolonged administration in rats whereas ß receptor down regulation was not observed (Hussain et al.,1988). In another study it was found that centpropazine has an affinity with alpha 1-adrenoceptor but the affinity is two times lower than that of imipramine (Dikshit et al.,1993). Centpropazine inhibited inositol phosphate but cyclic AMP accumulation in rat brain was not altered. In normal male volunteers centpropazine was well tolerated in single and multiple doses (Gupta et al.,1989). The efficacy studies in patients of depression revealed its therapeutic activity in 80% patients (Srivastava et al.,1992). We report here in this communication results of multicentric double blind randomized Phase III clinical trial.

MATERIAL & METHOD

The study was a double blind parallel trial comparing centpropazine with imipramine at following centres in India.

Deptt.of Psychiatry	K.G.Medical College, Lucknow
Deptt. of Psychiatry	National Institute of Mental Health & Neurosciences,

Bangalore.
Deptt. of Psychiatry Seth G.S. Medical College, Bombay.
Deptt. of Psychiatry Govt. Medical College, Patiala.

Patients of either sex diagnosed to be suffering from Major Depressive Disorder in accordance with DSM-III R (Diagnostic and Statistical Manual of Mental Disorders Ed.III Revised) were included at each centre. The protocol was approved by Institutional Ethics Committees following permission from The Drugs Controller General of India. An informed consent was obtained from each patient or a near relative if the patient was unable to execute such a consent. Patients below 18 years or above 55 years and/or patients with a history of depression lasting for more than 2 years or with severe depression requiring electroconvulsive therapy or other forms of therapy and patients with renal, hepatic, cardiac or respiratory diseases were excluded from the trial. Selected patients underwent a 7 day placebo period after evaluation on 24 item Hamilton Depression Rating Scale (HDRS) and Rating Scale for Side Effects (Asberg). Any patient showing a decrease of 25% or more on HDRS was excluded from the study at the end of placebo period. Patients were now assigned to either receive centpropazine or imipramine on the basis of randomization chart supplied to the centre from Central Drug Research Institute, Lucknow. Subsequently each patient was evaluated on HDRS and ASES scales at weekly intervals upto six weeks. Every patient was also assessed on Clinical Global Impression Scale (CGIS). The patients received either centpropazine (40 to 120 mg/day) or imipramine(50 to 150 mg/day) in two divided doses for a duration of six weeks. The maximum dose was achieved within a period of one week. During this period of 6 weeks each patient was required to stay in the hospital. Complete haemogram,serum biochemical investigations and electrocardiogram were done before (0 week) and after (+6 weeks) the trial.

The predrug and postdrug mean HDRS scores at weekly intervals were statistically analysed using t-test.

RESULTS

A total of 159 patients (40 patients from each centre) suffering from major depressive disorder were included in the study. Out of 40 patients twenty patients each received centpropazine and imipramine at individual centre according to randomization chart. The data from each centre was analysed separately and then pooled for the purposes of presentation.

Centpropazine Group

Seventy nine patients received six week treatment with centpropazine. Out of these 40 were males and 39 were females. The age of these patients ranged between 20 to 55 years (mean 35.2 ± 9. 8). Fiftyfive patients (38 males, 17 females) completed the six week study and remaining 24 patients dropped out due to factors unrelated to the drug (unwilligness to stay in the hospital/ physical illness) The mean HDRS scores were significantly reduced from second week onward and this lowering, was maintained till the end of the study at each centre. The mean HDRS score decreased from 25.3±2.4 (initial) to 8.2±6.3(final) after the centpropazine therapy. The initial and final (i.e. at the end of 6weeks of therapy) mean HDRS scores of depressed patients at each centre have been depicted in Figure 1. The percentage lowering of more than 75 % was observed in 27 patients, between 50 to 74 % in 17 patients, between 25 to 49% in 9 patients and less than 25% in 2 patients (Table1). The side effect analysis showed that side effects were present in only 10 patients which included presence of dryness (5), giddiness (3), headache (2), tremor(l) and constipation(l). They have been depicted in Figure 3. On Clinical Global Impression Scale (CGIS) it was found that 28 patients were very much improved, 18 patients improved moderately, 8 patients experienced mild improvement and one patient did not show any response (Table 2).

Imipramine Group

Out of 80 patients who were treated with imipramine, 41 were males and 39 were females. The age of these patients ranged between 18 to 55 years (mean 36.14 ± 9.37). Fiftyfive patients

TABLE 1
SHOWING PERCENTAGE REDUCTION IN HDRS SCORE WITH CENTPROPAZINE AND IMIPRAMINE THERAPY

Group	>75%	50-74%	25-49%	<24%
Centpropazine (n=55)	27	17	9	2
Imipramine (n=54)	30	14	9	1

TABLE 2
ASSESSMENT ON CLINICAL GLOBAL IMPRESSION SCALE AFTER CENTPROPAZINE AND IMIPRAMINE THERAPY

Group	Very Much Improved	Moderate Improve-ment	Mild Improve-ment	No Improve-ment
Centpropazine (n=55)	28	18	8	1
Imipramine (n=54)	29	18	6	1

completed the study. Remaining 26 patients dropped out during the course of study. Major reason of dropout was their unwillingness to stay in the hospital except in three patients where it was due to development of severe anticholinergic side effects. The mean HDRS scores decreased from 25.2 ± 3.9 (initial) to 7,4 ± 5.3 (final) after six week therapy with imipramine. The initial and final (i.e. at the end of 6weeks of therapy) mean HDRS scores of depressed patients at each centre have been depicted in Figure 2. The mean HDRS scores were significantly decreased second week onwards. The percentage lowering in individual HDRS scores was more than 75% in 30 patients and between 50 to 74% in 14 patients following imipramine therapy (Table 1). The anticholinergic side effects (Figure 3) were present in 40 patients and these include dryness of mouth (33), constipation (16), palpitation (10), tremor (9), dizziness (6), perspiration (4), physical tiredness (4), orthostatic symptoms(4), drowsiness (4), sexual symptoms (2) and headaches). On clinical Global Impression Scale (CGIS) 29 patients were very much improved, 18 patients improved moderately whereas 6 patients showed mild improvement and one patient did not improve (Table 2). Four patients developed orthostatic symptoms and out of these 3 dropped out from the study within first two weeks as mentioned above.

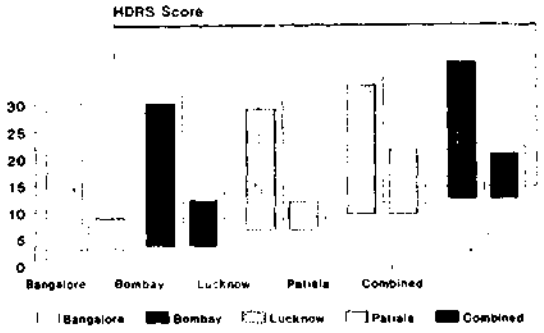

Fig.1 Initial and final mean HDRS scores following Centpropazine Therapy

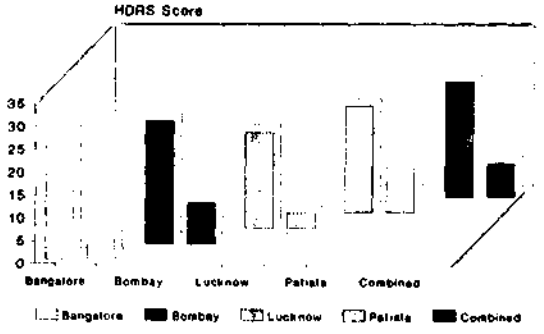

Fig.2: Initial and final mean HDRS scores following Imipramine Therapy

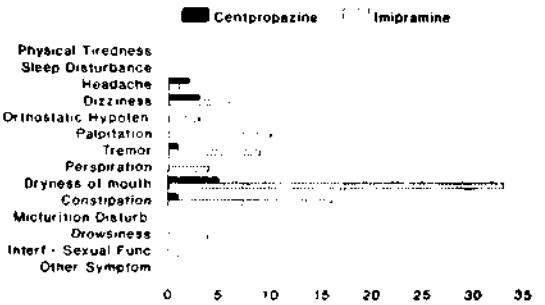

Fig. 3: Comparative incidence of side effects with Centpropazine & Imipramine during the study

DISCUSSION

This multicentric, double blind, randomised and parallel study suggests that the efficacy of centpropazine is comparable with that of a standard drug imipramine. The advantage of centpropazine over imipramine is clearly evident due to its better tolerability profile. This will allow clinicians to use a higher dose without the risk of unpleasurable anticholinergic side effects and will provide an edge over conventional tricyclic antidepressants in elderly de pressed patients and in patients with suicidal intent owing to its wider therapeutic margin. The dropout rate was marginally less with centpropazine (30%) than with imipramine (33%) as three patients in imipramine group dropped early in the study and were due to anticholinergic side effects. As far as incidence of anticholinergic side effects is concerned they are present in 40/80 (50%) cases with imipramine as compared to only 10/79 (12.7%) cases in centpropazine group. However in none of patients these were severe enough to stop or reduce the dosage.

The antidepressant drugs have been mainly classified into tricyclics and specific serotonin reuptake inhibitors. The third group of monoamine oxidase inhibitors may have serious interactions with certain foodstuffs containing tyramine. The tricyclic antidepressants have been shown to produce anticholinergic, cardiac and serious overdosage effects especially in elderly depressed patients (Blackwell,1981). A search for safer and more effective antidepressants continues. This has resulted in newer tricyclic drug like amoxapine, dothiepin and maprotiline, tetracyclic compounds like mianserin and mirtazapine and specific serotonin reuptake inhibitors like fluoxetine, sertraline, paroxetine and citalopram. The development of centpropazine is also a step in the same direction. It has shown a wider safety margin as compared to imipramine in acute toxicity studies and could be safer than tricyclics in accidental overdosage by suicidal patients which is a persistent risk in patients with suicidal intent.

It has been claimed that newer antidepressant drugs lack anticholinergic effects, produce less cardiotoxicity and are safer in overdose. Amoxapine and maprotiline are toxic as well as epileptogenic in overdosage (Kulig et al.,1982; Knudsen & Heath,1984). However, amoxapine induces no cardiotoxicity but maprotiline is equally if not greater than currently used TCAs. Mirtazapine, a tetracyclic compound caused somnolence, weight gain and amblyopia in some cases (Smith et al.,1990). Mianserin another tetracyclic drug has been associated with agranulocytosis and aplastic anemia. Zimelidine, though introduced enthusiastically, had to be withdrawn from market following reports of Guillain - Barre Syndrome (Martindale,1989). Viloxazine caused nausea, vomiting, weight loss and may precipitate migraine (Blackwell,1981). Trazodone aggravated the ventricular arrhythmias in patients with preexisting cardiac disease (Janowsky et al.,1983). This drug also produced severe priapism in several cases (Scher et al.,1983). Nomifensin has been associated with massive intravascular haemolysis (Lylloff et al.,1982). Fluoxetine, a prototype of serotonin reuptake inhibitors, has been associated with gastrointestinal side effects such as anorexia and insomnia (Nelson,1997). In comparison to above mentioned newer antidepressants, centpropazine has shown a remarkably safer profile in depressed patients. The Drugs Controller General of India has granted marketing permission and it has been licensed for marketing to a pharmaceutical company recently.

ACKNOWLEDGEMENT

Authors express gratitude to Dr.C.M. Gupta, Director, CDRI, Lucknow and Dr. V.P. Kamboj, Former Director, CDRI, Lucknow for constant encouragement and guidance through the development of this manuscript. We are also thankful to Mr. Shyam Lal and Mr. J.A. Zaidi, CDRI, Lucknow for computerisation of the manuscript.

REFERENCES

Blackwell, B. (1981) Adverse effects of antidepressant drugs Part 1: Monoamine oxidase

inhibitors and tricyclics. Part 2: Second generation antidepressants and rational decision making in antidepressant therapy. *Drugs*, 21, 201-219 & 273-282.

Dikshit, M., Chalecka-Franaszek, E. & Nalepa, I. (1993) Centpropazine affinity to cortical noradrenegic receptors and their effect on their responsiveness. *Journal of Pharmacy & Pharmacology* 45, 228-230.

Gupta, P.P., Asthana, O.P., Tangri, A.N. & Dhawan, B.N. (1989) Clinical Pharmacological Studies on Centpropazine - A new antidepressant compound. *Indian Journal of Medical Research*, 90, 360-362.

Hussain, G., Gulati, A. & Srimal, R.C. (1988) Effect of centpropazine, a new anti depressant on the central serotonin and beta adrenergic receptors. Proceedings of VIIth annual Conference of Academy of Neurosciences at IICB, Calcutta.

Janowsky, D., Curtis, G., Zirook, S., Kuhn, K., Kesovsky, K. & Le Winter, M. (1983) Ventricular arrhythmias possibly aggravated by trazodone. *American Journal Psychiatry*, 140, 796-797.

Knudsen, K. & Heath, A. (1984) Effects of self poisoning with maprotiline. *British Medical Journal*, 288, 601-603.

Kulig, K., Rumack, B.H., Sullivan, J.B., Bradt, H., Daniel, A., Spiker, D.A., Duffy, J.P. & Shipe, J.R. (1982) Amoxapine overdose: Coma and seizures without cardiotoxic effects. *Journal of American Medical Association*, 248, 1092-1094.

Lylloff, K., Jersild, C., Backer, T. & Slot, O. (1982) Massive intravascular haemolysis during treatment with nomifensin. *Lancet*, 2, 41.

Martindale (1989) *The Extra Pharmacopoeia*. Edn.29 (Ed.) Reynolds, J.E.F., pp. 385, London : Pharmaceutical Press.

Nelson, J.C. (1997) Safety and tolerability of new antidepressants. *Journal of Clinical Psychiatry*, 58, 26-31.

Prasad, C.R., Sharma, J.N. & Dhawan, B.N. (1969) A preliminary report on the pharmacological activity of a new anti-depressant. *Indian Journal of Physiology Pharmacology*, 13, 28-31.

Rastogi, S.N., Anand, N. & Prasad, C.R. (1972) Agents acting on the central nervous system- a new class of antidepressants. *Journal of Medicinal Chemistry*, 286-291.

Scher, M., Krieger, J.N. & Juergens, S. (1983) Trazodone and priapism. *American Journal of Psychiatry*, 140, 1362-1364.

Smith, W.T., Glandin, V., Panadiges, J. & Gilvary, E.(1990) Mirtazapine versus amitriptyline versus placebo in the treatment of major depressive disorder. *Psychopharmacology Bulletin*, 26, 191-195.

Srivastava, J.S., Gupta, P.P., Asthana, O.P., Nityanand, S., Devi, S., Doongaji, D.R., Sethi, B.B., Singh, G., Srimal, R.C., & Dhawan, B.N. (1992) Clinical efficacy of centpropazine - a new antidepressant. *Indian Journal of Psychiatry*, 34, 3, 260-263.

J.S.SRIVASTAVA,MD,DM, O.P.ASTHANA,MD,DCH, R.C.SRIMAL,MD, Division of Clinical & Experimental Medicine, Central Drug Research Institute, Lucknow, H.SINGH,MD, A.K.AGARWAL,MD,DPM, Department of Psychiatry, K.G. Medical College, Lucknow, L. P. SHAH, MD,DPM,FRC Psych., Department of Psychiatry, Seth G.S.Medical College, Bombay, K. C. SHARMA,MD, Department of Psychiatry, Govt. Medical College, Patiala, P.S.GOPINATH, MD,Department of Psychiatry, National Institute of Mental Health and Neurosciences, Bangalore (*Division of Clinical & Experimental Medicine, Central Drug Research Institute, Chattar Manzil Palace, Post Box No.173 Lucknow-226 001, CDRI Communication No. 5855)*

***Correspondence**