AN IMMUNOMODULATOR IN THE TREATMENT OF SCHIZOPHRENIA : A DOUBLE-BLIND STUDY

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In a double blind study, the immunomodulator drug levamisole was administered along with chloropromazine to 18 schizophrenic patients, and efficiency of the combination was compared to that of chloropromazine along with placebo administered to 16 schizophrenic patients. The decrease in T suppressor cell count found in both groups at benchmark was found to be corrected in the patients receiving levamisole and this increase in T suppressor cell count was significantly correlated with the improvemnt in psychosis. The findings provide evidence in favour of the autoimmune hypothesis of schizophrenia.

Though a considerable amount of research has been done in relation to the autoimmune hypothesis, it continues to be controversial (Ganguli et al., 1987; Koljaskine and Prilipko, 1988). Vartanian and Koljaskine (1987) found a hyperactive B-cell response (resulting in increased immunoglobulins) in schizophrenic patients, associated with altered T suppressor cell functioning. Based on this observation, these authors studied the therapeutic effect of correcting T suppressor cell functioning using an immunomodulator, levamisole, and reported encouraging positive results in some schizophrenics. The present study was carried out to study the therapeutic efficacy of levamisole as an adjunct to chlorpromazine employing a more rigours study design.

MATERIAL AND METHODS

34 male schizophrenics fulfilling Research Diagnostic Criteria for Schizophrenia (Spitzer et al. 1978), and a set of predefined inclusion and exclusion criteria were selected for the study. Patients were thoroughly investigated to exclude any physical disease. The baseline (day 0) psychiatric assessment was done on Modofied Brief Psychiatric Rating Scale (MBPRS; Overall and Gorham, 1962) and on the sign and symptoms scale for Neuroleptics (WHO, 1986) within three days of hospitalization, and subsequently on days 21 and 42 of the study. Patients were randomly assigned to either chlorpromazine with levamisole group (Group 1; N = 18) or to chlorpromazine and placebo group (Group 2; N = 16). Levamisole or placebo, respectively, were administered on a double-blind basis. Chlorpromazine was administered in doses of 15 mg/kg body weight per day through the study period (6 weeks) and levamisole in doses 150mg at bedtime twice a week. Estimations of T and B lymphocytes were done employing the technique developed by Kapoor et al.(1980) which is a modification of Coulson and Chalmers' (1964) technique, on day 0, 21 & 42. The T suppressor lymphocytes on these days were estimated by the technique of Gupta et al.(1983). The data was statistically analysed employing the student's 't' test and Pearsons' correlation coefficient.

OBSERVATIONS AND RESULTS

Both groups of patients were comparable for age and body weight. There was no significant difference between the two groups

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Table 1 - Illness Characteristics Of Sample

Illness variables	Experimental Group (N = 18)	Control Group (N = 16)

Age of onset
    upto 20 years
    > 20 Years
	5
	13
	$X^2 = 0.049$, d.f. = 1, N.S.
		5
		11

Duration
    upto 2 years
    2 years
	9
	9
	$X^2 = 0.54$, d.f. = 1, N.S.
		6
		10

No. of episodes
    upto 2 episodes
    2 episodes
	11
	7
	$X^2 = 0.08$, d.f. = 1, N.S.
		9
		7

Table 2- MBPRS scores and lymphocyte counts in Exp. and Control groups

	Experimental group (N = 18)			Control group (N = 16)		
	Day 0 (a)	Day 21(b)	Day 42 (c)	Day 0 (d)	Day 21 (e)	Day 42 (f)
MBPRS Scores	31.0	15.5	2.4	30.1	16.2	5.8
	a vs. b: $p < 0.01$; a vs. c: $p < 0.001$; d vs. e: $p < 0.001$; d vs. f: $p < 0.001$ a vs. d: N.S.; b vs. e: N.S.; c vs. f: $p < 0.05$					
T lymphocytes Count (in %)	31.2	30.9	31.1	30.2	30.2	30.4
	All comparisons are not significant					
T lymphocytes Count (in %)	58.2	58.5	58.7	58.2	58.4	58.7
	All significants are not significant					
T suppressor lymphocyte	17.8	19.0	21.1	16.9	17.1	17.2
	a vs. b: $p < 0.01$; a vs. c: $p < 0.001$; d vs. e: N.S.; d vs. f: N.S. a vs. d: N.S.; b vs. e: $p < 0.01$; c vs. f: $p < 0.01$					

Table 3- Coefficient of correlation between the changes in MBPRS scores and lymphocytes in the two groups

Correlation between changes from baseline in MBPRS scores with	On day 21		On day 42	
	Experimental group	Control group	Experimental group	Control group
B Cells	+0.06	-0.09	-0.26	-0.13
T Cells	-0.37	-0.06	-0.04	-0.06
T suppressor cells	-0.11	-0.33	-0.70**	-0.48

** $p < 0.01$

Table 4- T-Suppressor lymphocyte counts in experimental and control groups

Experimental group (N = 18)					
Non-chronic (N = 9)			Chronic (N = 9)		
Day 0 (a)	Day 21 (b)	Day 42 (c)	Day 0 (d)	Day 21 (e)	Day 42 (f)
19.9	19.8	20.0	15.6	18.7	20.1
a vs. d: $p < 0.001$; (a-b) vs. (d-e): $p < 0.001$; (a-c) vs. (d-f): $p < 0.001$					
Control group (N = 16)					
Non-chronic (N = 9)			Chronic (N = 9)		
Day 0 (a)	Day 21 (b)	Day 42 (c)	Day 0 (d)	Day 21 (e)	Day 42 (f)
19.8	20.0	20.0	15.2	15.3	15.5
a vs. d: p; < 0.05 (a-b) vs. (d-e): N,S.; (a-c) vs. (d-f): N.S.					

on variables such as age of onset, total duration of illness, and number of episodes(Table- 1).

The corrected mean MBPRS scores and lymphocytes counts on baseline, on day 21 and on day 42 in the experimental and control groups are shown in Table 2. Patients in both the groups showed significant improvement (p < 0.001) on day 21 and at the end of the study when compared to the base line. Patients reciving levamisole (Group 1) had significantly lower scores on MBPRS than the placebo (Group 2) at the end of the study (p < 0.05).

B & T lymphocytes counts remained almost similar throughout the study in both the groups, whereas T suppressor lymphocyte count showed significant increase on day 21 and on day 42 from baseline (P < 0.01 & p < 0.001, respectively) in the exsperimental group, but not in the control group, it was found that the increment in T suppressor cells was statistically significant in the experimental group on days 21 and 42 (P < 0.01). The coeficient of correlation between the changes in MBPRS and the lymphocytes revealed that the increments in T suppressor cells were significantly correlated with the reductions in MBPRS scores in the experimental group (P < 0.01) at the end of the study (Table 3). There was no change in T & B lymphocytes.

When nonchronic and chronic subgroups were compared, levamisole was not found to exert any beneficial effect either on mean MBPRS scores or on lymphocyte counts in the nonchronic subgroups of experimental patients, both on Student's 't' test and coefficient of correlation. However, in the chronic subgroup of schizophrenics, levamisole was found to be an effective adjunct both in terms of incresing T suppressor lymphocytes counts and in reducing the mean MBPRS scores at statistically significant levels, on both Student's 't' test (P < 0.001) and on ceofficient of correlation (P < 0.005).

When MBPRS score and lymphocyte counts of the chronic and nonchronic subgroups of schizophrenics were compared in the experimental and control groups it emerged that the difference in the MBPRS scores as well as T & B lymphocytes counts at baseline were nonsignificant in the experimental and control groups, but the T suppresor lymphocyte count was significantlu lower in the chronic subgroup in comparison to nonchronic subgroup of the experimental (P < 0.001) and control groups (P < 0.05) (Table 4). Further, in the experimental group, the T suppresor lymphocytes increased gradually with treatment in the chronic subgroup and became almost equal to those of the non- chronic subgroup, while in the control group there was no change in the T suppressor cell lymphocyte count. All the side-effects noted were those of chlorpromazine and none were attributable to levamisole.

DISCUSSION

This is the first attempt inour country to study the role of an immunomodulator, levamisole, as an adjunct in the treatment of schizophrenia. The results of the study indicate the beneficial effects of levamisole as an adjunct to chlorpromazine, atleast in schizophrenics having total duration of illness more than two years (chronic). The beneficial effects of levamisole were manifest in marked reduction of MBPRS mean scores and increments in T-suppressor lymphocytes. Previous studies of this therapeutic modality, limited to the USSR, showed similar results (Vertanian and Koljaskina, 1987; Mikheva et al., 1987). However, the sample size, was small in both the studies.

The results of the study also provide indirect evidence in favour of the autoimmune hypothesis of schizophrenia. Immunological parameters of diagnostic importance in autoimmune diseases include autoantibodies, immune complexes, and immunoglobuline in the serum

which are elevated and serum complements and T suppressor cells is an important diagnostic indicator which was found to be decreased in the present study. However, the other parameters such as immunoglobuline (IgG, IgA & IgM), and complement (C_3 & C_4) which were also investigated, did not show any difference (Agarwal, 1990) Thus, not all the findings expected on the basis of the autoimmune hypothesis of schizophrenia have been found, and further research with a larger sample, homogenous for chronicity, is indicated.

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