

A CLINICAL TRIAL OF ADJUNCTIVE CYPROHEPTADINE IN THE TREATMENT OF AUTISTIC DISORDER: A DOUBLE-BLIND AND PLACEBO CONTROLLED TRIAL

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Autism is a severe neurodevelopmental disorder characterized by qualitative impairment before the age of 3 in verbal and nonverbal communication, in addition to a markedly restricted repertoire of activities and interests. The primary goal of treatment interventions is to reduce maladaptive behaviours, improve language acquisition or facilitate communication via sign language or other strategies, and improve social responsiveness (Hunsinger *et al*, 2000). The involvement of neurotransmitters such as 5-HT has been suggested in neuropsychiatric disorders and particularly in autistic disorder. Increased platelet 5-HT levels were found in 40% of the autistic population, suggesting that hyperserotonemia may be a pathologic factor in infantile autism. Therefore, it is of interest to assess the efficacy of cyproheptadine, a 5-HT₂ antagonist in the treatment of autistic disorder (Herault *et al*, 1996). In this 8-week double blind, placebo controlled-trial, we assessed the effects of cyproheptadine plus haloperidol in the treatment of autistic disorder.

Children between the ages 3 and 11 years (inclusive) with a DSM IV clinically diagnosis of autism were outpatients from a specialty clinic for children at Roozbeh Psychiatric Teaching Hospital. The children presented with a chief complaint of severely disruptive symptoms related to autistic disorder. Patients were randomly allocated 20 to cyproheptadine + haloperidol (Group A) and haloperidol + placebo (Group B) for an 8-week, double-blind, placebo-controlled study. All patients completed the trial. The dose of haloperidol and cyproheptadine was titrated up to 0.05 mg/kg per day and 0.2 mg/kg per day respectively. Patients were assessed by a third year resident of psychiatry at baseline and after 2, 4, 6 and 8 weeks after the medication started. The primary measure of the outcome was the Aberrant Behaviour Checklist- Community and the

secondary measure of the outcome was the Childhood Autism Rating Scale (relating to people and verbal communication). Extrapyrimal symptoms were systematically recorded throughout the study and were assessed using Extrapyrimal Symptoms Rating Scale, administered by a resident of psychiatry on week 1, 2, 4, 6 and 8. A two-way repeated measures analysis of variance (time- treatment interaction) was used. The two groups as a between-subjects factor (group) and the five measurements during treatment as the within-subjects factor (time) were considered. In addition, a one-way repeated measures analysis of variance with a two-tailed post-hoc Tukey mean comparison test were performed in the change from baseline in each group. To compare the two groups at baseline and the outcome of two groups at the end of the trial, an unpaired Student's t-test with a two-sided P value was used. To compare the demographic data, Fisher's exact test was performed.

The Aberrant Behaviour Checklist- Community and the Childhood Autism Rating Scale scores improved with cyproheptadine. The behaviour of the two treatments was not homogeneous across the time (groups-by-time interaction, Greenhouse-Geisser correction; F=7.30, d.f.=1.68, P=0.002; F=8.21, d.f.=1.19, P=0.004 respectively). The difference between the two protocols was significant as indicated by the effect of group, the between-subjects factor (F = 4.17, d.f.=1, P = 0.048; F = 4.29, d.f.=1, P = 0.045 respectively). The changes at the endpoint compared with baseline were (mean ± SD): -10.90 ± 7.19 and -1.85 ± 2.08; -0.37 ± 0.48 for groups A and B respectively. No significant difference was observed between the two groups in terms of extrapyramidal symptoms (P=0.23).

The results demonstrate that the combination of cyproheptadine with a conventional antipsychotic was superior to conventional antipsychotic alone for the rapid reduction of autistic symptoms.