

BEHAVIOURAL EFFECTS OF IV MCPP IN SCHIZOPHRENIA

Sally Szymanski*, David Mayerhoff, Amy Koreen, Carmen Lemus, Jose Alvir, Anthony Loebel, Raphael Munne, Daniel Umbricht, Steven Sobel, Jeffrey Lieberman

Hillside Hospital, Psychiatry Research, P.O. Box 38, Glen Oaks, NY 11004, USA

The effect of the serotonergic system on psychotic behaviour and schizophrenia has been recently studied. Meta-chlorophenylpiperazine (MCP) is a direct-acting 5HT receptor agonist which has been shown to have both neurochemical and behavioural effects in schizophrenic subjects. In this study, we report the behavioural effect of I.V. MCP administration in a cohort of new-onset and chronic schizophrenics.

Seventeen drug free schizophrenic subjects (RDC), (47% new-onset) received intravenous (0.1 mg/kg) MCP and evaluated behavioural response at pre and post infusion. An increase in agitation, bizarre behaviour, anxiety, thought disorder, with no significant change in depression, irritability, grandiosity, distrustfulness, impaired understandability or in overall severity of delusions or hallucinations was observed. Multiple side effects of MCP were seen with the sensation of warmth and chills being the most common.

Although all increase in psychotic symptoms has been reported in schizophrenic patients following an MCP infusion, in this sample, no change in psychotic symptoms, other than thought disorder, was noted. An increase in agitation was reported which may in part be due to increased motoric restlessness secondary to anxiety. The results suggest that MCP may produce its behavioural responses in schizophrenia patients through nonspecific effects on psychopathology as well as through reactions to side effects. These and other findings will be presented and discussed.

THE DOPAMINE-SEROTONIN RELATIONSHIP IN CLOZAPINE RESPONSE

Sally Szymanski*, Simcha Pollack, Tom Cooper, Allan Safferman, Raphael Munne, Daniel Umbricht, Jeffrey Lieberman, Michael Kronig

Hillside Hospital, Psychiatry Research, P.O. Box 38, Glen Oaks, NY 11004, USA

Clozapine's atypical antipsychotic properties, e.g. superior efficacy, fewer extrapyramidal effects, and a reduced likelihood of producing tardive dyskinesia, have been reported. A stronger ability to block serotonin vs dopamine receptors has been proposed as the underlying mechanism of drug action. Consequently, the purpose of this study was to determine the effect of clozapine both dopamine and serotonin indices.

Nineteen treatment refractory and intolerant schizophrenic and schizoaffective disorder patients underwent a six week open

clozapine trial. Patients were rated for the presence of psychopathological and tardive dyskinesia at regular intervals. Plasma and cerebrospinal fluid homovanillic acid (pHVA, CSF HVA) and cerebrospinal 5-hydroxyindoleacetic acid (CSF 5HIAA) levels were collected at baseline and treatment week 3.

Data from 19 DSM III schizophrenic and schizoaffective disorder patients were examined. The sample was 68% male, 88% treatment refractory, 53% had tardive dyskinesia and the mean age was 29.5±6.3 years. Dividing the sample into clozapine responders vs nonresponders showed that the responders had both a lower baseline CSF HVA levels ($p<.08$) and a CSF HVA/5HIAA ratio ($p<.04$). Plasma HVA levels were not associated with CSF HVA values but with CSF 5HIAA levels.

These results suggest that the dopamine-serotonin relationship is important in determining response to clozapine. These and other findings will be presented and discussed.

CHOLINERGIC MECHANISMS IN SCHIZOPHRENIA: RELATIONSHIP TO SLEEP-EEG ABNORMALITIES AND POSITIVE/NEGATIVE SYMPTOMS

Rajiv Tandon*, James E. Shipley, JoAnn Goodson, John F. Greden

University of Michigan Schizophrenia Program, Ann Arbor, MI 48109-0120, USA

Considerable evidence suggests that ACh mechanisms may play a significant role in schizophrenic pathophysiology. Based on various data (Tandon and Greden, Arch Gen Psychiatry, 1989, 46: 745-753), we proposed the following model of dopaminergic (DA)/ACh interactions in schizophrenia: (i) disruption of DA/ACh balance is important in schizophrenic pathophysiology; (ii) ACh activity increases to maintain this balance in the face of increasing DA activity that occurs in the psychotic phase of the illness; (iii) this increased ACh activity exerts a damping effect on the production of positive symptoms associated with DA hyperactivity; and (iv) this compensatory increase in ACh activity is, in turn, accompanied by an increase in nonenduring negative symptoms. To test predictions of this model, we studied the effects of biperiden (a relatively selective M-1 anticholinergic agent) on positive/negative symptoms and polysomnographic measures in drug-free schizophrenic patients. Employing a double-blind, placebo-crossover design, we observed that biperiden (in comparison to glycopyrrolate) increased positive symptoms and decreased negative symptoms in drug-free schizophrenic patients. At baseline, schizophrenic patients showed impaired sleep continuity, and shortened REM latency in comparison to normal controls. Biperiden increased REM latency in a dose-dependent manner in both groups; it decreased REM density to a significantly greater extent in the schizophrenic group. These findings are consistent with the hypothesized concomitant increases in DA and ACh activity in schizophrenia. Our findings further implicate the cholinergic system in schizophrenic pathophysiology and suggest a role for dopaminergic/ACh interactions at least in the

production of sleep abnormalities and expression of positive and negative symptoms. These data indicate the need for systematic trials of cholinergic and anticholinergic agents in the treatment of positive and negative symptoms of schizophrenia, respectively.

COVARIANCE OF POSITIVE AND NEGATIVE SYMPTOMS DURING TREATMENT WITH TYPICAL NEUROLEPTICS AND CLOZAPINE

Rajiv Tandon,* Saulo CM Ribeiro, Melinda Perez, John F. Greden

University of Michigan Schizophrenia Program, Ann Arbor, MI 48109-0120, USA

Although poor response to neuroleptics has traditionally been considered a characteristic feature of negative schizophrenic symptoms, several recent studies have documented significant improvement in negative symptoms in schizophrenic patients treated with neuroleptics. The question of whether neuroleptic-induced improvement in negative symptoms is linked to concomitant improvement in positive symptoms or occurs independently of such improvement is unresolved; it is also unclear if this profile is similar during treatment with clozapine and typical neuroleptics. To address these issues, we studied 120 RDC/DSM-III-R schizophrenic inpatients at drug-free baseline and after 3-4 weeks of treatment with clinically-determined doses of typical neuroleptics. We also studied 40 RDC/DSM-III-R schizophrenic patients before a trial of clozapine and after 4-6 weeks of initiating clozapine treatment. Positive and negative symptoms were assessed by the BPRS "THOT" factor and the SANS sum of global scores, respectively. During treatment with typical neuroleptics, there was significant improvement in both positive symptoms (15.6 ± 2.9 to 10.2 ± 3.2) and negative symptoms (12.5 ± 4.2 to 8.6 ± 3.4); the change in positive symptoms was highly correlated to the change in negative symptoms ($r=0.60$; $p<0.001$). During treatment with clozapine, both positive symptoms (from 16.0 ± 3.6 to 12.4 ± 3.5) and negative symptoms (from 13.8 ± 4.5 to 10.5 ± 4.1) improved significantly; change in positive symptoms was again significantly correlated to change in negative symptoms ($r=0.63$; $p<0.01$). Although there are sample differences between the two groups making comparisons difficult, these data indicate that negative symptoms improve along with positive symptoms in the course of initial neuroleptic treatment, both with typical neuroleptics and clozapine. Clozapine's apparent greater efficacy on negative symptoms may be related to its greater efficacy on positive symptoms (in otherwise treatment-refractory patients) and its lower propensity to cause EPS.

A HIGH CONCENTRATION OF PLASMA INTERLEUKIN-6 IN SCHIZOPHRENIC PATIENTS TREATED WITH NEUROLEPTIC DRUGS

J. Wei*, H-M. Xu, G.P. Hemmings

Institute of Biological Psychiatry, SAGB, Bangor, Gwynedd LL57 2UW, UK

In a previous study, we found a low concentration of plasma interleukin (IL)-1 α in neuroleptic-free patients with schizophrenia. In view of the considerable overlap in the cellular sources and biological activity of IL-1, IL-6 and tumor necrosis factor (TNF), it was thought necessary to examine all three of the relevant cytokines in schizophrenic patients. This study demonstrated that the concentration of plasma IL-6 was significantly higher in the patients taking neuroleptic drugs (5.95 ± 1.20 pmol/L, $n=32$) than in those not taking neuroleptic drugs (4.81 ± 1.13 pmol/L, $n=13$, $p<0.01$), but was not significantly higher than in normal control subjects (5.04 ± 1.78 pmol/L, $n=9$, $p>0.05$). Kruskal-Wallis analysis of variance revealed a significant difference in the concentration of plasma IL-6 among the patients taking neuroleptic drugs, those not taking neuroleptic drugs and normal control subjects ($H=7.1$, $df=2$, $p<0.05$). The increased plasma IL-6 was not related to the clinical state of the patients taking neuroleptic drugs. No significant differences of plasma IL-1 β and TNF- α were found between the three groups. These results suggest that neuroleptic treatment may increase only IL-6 production, and that the low concentration of plasma IL- α found in our previous study may be peculiar to schizophrenia.

CLINICAL REVIEW OF CLOZAPINE TREATMENT IN A STATE HOSPITAL

W. H. Wilson*

Department of Psychiatry, Oregon Health Sciences University, Portland, OR 97201-3098, USA

We recently reported on a review of the medical records of the first 37 patients to begin clozapine treatment at a state hospital in Oregon. Records were reviewed for the six months before clozapine treatment and six months after. Patients had a long history of schizophrenia and had responded poorly to antipsychotic medication. Clozapine treatment was generally well tolerated, although the rate of seizures (8%) was slightly higher than expected. Psychotic symptoms decreased as measured by the Brief Psychiatric Rating Scale, as did symptoms of tardive dyskinesia, as measured by the Abnormal Involuntary Movement Scale. Thirty-four patients remained hospitalized after six months of treatment. However, indicators of social function (hospital privilege level, community passes, violent episodes, and episodes of seclusion and restraint) all showed that patients improved markedly after receiving clozapine. We will present data extending this analysis to include a six month follow-up of 100 patients, with 68 of the patients followed for eighteen months.