OLANZAPINE INDUCED REDUCTIONS IN FRONTAL LOBE LACTATE LEVELS CORRELATE WITH TREATMENT RESPONSE IN FIRST EPISODE PSYCHOSIS

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Purpose: Typical and atypical antipsychotic medications differ in the extent to which they inhibit respiratory enzyme activity, with typical neuroleptics producing greater degrees of inhibition. Lactate is a neurochemical marker that increases with mitochondrial dysfunction and which can be detected using proton magnetic resonance spectroscopy (1H MRS). We hypothesized that olanzapine treatment would result in a greater reduction of brain lactate levels than haloperidol treatment in subjects with a first episode of psychosis. Design: Subjects with a first episode of psychosis (N = 263) were enrolled in a multi-site, double blind treatment trial of either olanzapine or haloperidol. Single voxel, 6 cm3, 1H MR spectra of the left frontal lobe (FC), basal ganglia (BG), and hippocampal (HC) regions were acquired both before and following 12 weeks of treatment for 156 subjects. The weak lactate doublet at 1.4 PPM was fit using an automated fitting method and the intensity of this resonance was normalized using a replacement phantom. Results: An acceptable fit of the lactate resonance was obtained on both occasions for approximately one fourth of the study subjects (N = 81). During 12 weeks of treatment, mean lactate reductions in the FC, BG, and HC were 12%, 18%, and 13% for the olanzapine cohort and 1%, 3%, and 8% for the haloperidol cohort. These differences did not reach statistical significance. However, reductions in frontal cortex lactate were strongly correlated with reductions in PANSS scores ($p = 0.0011$) and BPRS scores ($p = 0.0017$) for the entire subject population as well as for the olanzapine cohort ($p = 0.0035$ and $p = 0.017$, respectively; N = 42). These correlations were much weaker in the haloperidol cohort ($p = 0.17$ and $p = 0.043$, respectively; N = 39). Conclusions: Reductions in frontal cortex lactate during olanzapine treatment are strongly associated with resolution of psychotic symptoms. This relationship is weaker with haloperidol treatment, which has been associated with inhibition of complex 1. Lactate appears to be a chemical marker for the frontal hypometabolism that has been reported in prior studies; strategies to reduce brain lactate levels may present novel therapeutic opportunities for the treatment of schizophrenia. These findings are also consistent with the lower incidence of depression associated with olanzapine therapy, as we have recently observed elevated brain lactate levels in depressed, unmedicated bipolar subjects.

RECOVERY IN FIRST EPISODE SCHIZOPHRENIA

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Objective: Response criteria in schizophrenia studies are usually based upon change in a limited number of areas. This study examined recovery, an outcome criterion requiring sustained improvement in both symptoms and functioning. Methods: Patients with first episode schizophrenia or schizoaffective disorder were assessed at baseline and then treated according to a medication algorithm. Recovery criteria required: 1) remission of positive and negative symptoms and 2) sustained good social and vocational functioning (fulfillment of age-appropriate role expectations, performance of daily living tasks without supervision, and engagement in social interactions) for a 2 year period. Results: By five years after study entry, the cumulative percentage of subjects who achieved remission of positive and negative symptoms for 2 years was 47.2% (95% confidence interval [CI], 36.0%,58.4%). Improvement in functioning at the level specified by the recovery criteria was achieved by 25.5% (95% CI, 16.1%, 34.7%) of subjects. Only 13.7% (95% CI, 6.4%, 20.9%) of subjects met full recovery criteria based upon improvement in both symptoms and functioning. Conclusions: Patients with first episode schizophrenia can achieve sustained symptomatic and functional recovery, but the proportion who do so is small. Developing treatments to increase the rate of recovery, especially in terms of social and vocational functioning, should be an important goal for the field. This study was supported by grants MH41646, MH00537, MH60004 and MH41960 from the National Institute of Mental Health, Bethesda, MD., USA.

BENEFITS OF ADJUNCT MODAFINIL IN AN OPEN-LABEL, PILOT STUDY IN PATIENTS WITH SCHIZOPHRENIA

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To assess the efficacy and tolerability of modafinil (PROVIGIL), a novel wake-promoting agent, as an adjunct treatment for schizophrenia or schizoaffective disorder. This 4-week, open-label, single-center, pilot study included 11 patients with a diagnosis of schizophrenia or schizoaffective disorder. Patients received oral modafinil (100mg/day on Days 1-14, 100 or 200 mg/day on Days 15-28) in addition to ongoing treatment with antipsychotics/antidepressants. Treatment measures included the Global Assessment of Functioning (GAF), the Clinical Global Impression of Change(CGI-C), the Patient Global Impression of Change (PGI-C), the Positive and Negative Syndrome Scale (PANSS), the Letter-Number Sequencing Subtest of the Wechsler Adult Intelligence Scale (WAIS-III LNS), the Fatigue Severity Scale (FSS), and Heinrichs-Carpenter Quality of Life Scale (H-CQOL). Adverse events were monitored. All patients had at least 1 postbaseline assessment. Treatment with modafinil significantly improved patients' global functioning, as assessed by a blinded clinician (Weeks 2 and 4,$p < .05$ for the change from baseline) and the investigator (Week 3, $p < .05$ for the change from baseline) using the GAF. Modafinil significantly improved overall clinical condition at Week 4, with 7 of 11 patients (64%) and 9 of 11 patients (82%) rated by a blinded clinician and the investigator, respectively, as clinically improved (both $p=.001$ for the change from baseline) on the CGI-C. Most patients (89%) considered themselves to be clinically improved on the PGI-C at Week 4 ($p<.01$ for the change from baseline). There were no significant changes from baseline in mean PANSS negative-subscale scores. Modafinil tended to improve cognitive functioning (WAIS-III LNS) scores and significantly improved the mean fatigue (FSS) score (Week 3) and H-CQOL score (Week 2) (both $p < .05$ for the change from baseline). Control of PANSS positive symptoms was well maintained while patients were receiving modafinil. Treatment-emergent adverse events included dry mouth (n=2) and hallucinations (n=2). One patient discontinued treatment because of hallucinations that were considered by the investigator to be possibly related to inadequate antipsychotic therapy Modafinil was well tolerated with other medications. Modafinil may be an effective and well-tolerated adjunct treatment in patients with schizophrenia or schizoaffective disorder. Additional controlled studies in these patients are warranted.