

Olanzapine in the Treatment of Schizophrenia: An Open-Label Trial in Kuwait

Abdullah Fido

Kuwait University, Kuwait

Essam A. Al-Ansari

Psychological Medicine Hospital, Kuwait

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Olanzapine is a potential new “atypical” antipsychotic agent, which has been suggested to possess a superior clinical profile in the treatment of schizophrenia. The current prospective open-label trial was conducted on 10 male patients who met the *DSM-IV* diagnostic criteria for schizophrenia and had some residual symptoms (i.e., a global score of at least 24 on the Positive and Negative Syndrome Scale for schizophrenia, *PANSS*; Kay, Fiszbein, & Opler, 1987) for schizophrenia. After a washout period from previous medications (2-14 days), patients received olanzapine treatment (10-20 mg/day) dose for a 13-week period. Paired comparison of baseline and 13 weeks endpoints scores showed significant ($p = .0001$) improvement overtime for the negative symptoms subscale and global *PANSS* scores, and for the positive and general psychopathology subscale scores. Maximum efficacy of olanzapine was observed in the reduction of negative symptoms. There was no liver enzyme elevation or any other adverse serum chemistry changes resulted after treatment. There was no significant treatment-emergent EPS or dyskinetic symptoms side-effects observed. These findings support the expanded use of olanzapine in the treatment of patients with predominant negative symptoms of schizophrenia.

Keywords: Schizophrenia; Olanzapine; Atypical antipsychotics; Clinical trial; Kuwait.

Introduction

Schizophrenia, the most severe of the mental disorders, is frequently characterised by a chronic, recurrent course. With conventional antipsychotic agents, at least 30% of patients with schizophrenia do not show adequate response (Kane, 1989). Furthermore, 60% experience relapses within a year of therapy (Kane, 1966) and between 11 and 40 percent fail to comply with the treatment (Corrigan, Liberman, & Engel, 1990). This noncompliance is mainly attributable to the high incidence of drug-related side-effects (Fido & Razik, 1998; Weiden, Shaw, & Mann, 1986), espe-

cially extrapyramidal symptoms (EPS). Since the introduction of clozapine, the search for “atypical” or “novel” agents has led to a variety of investigational compounds exhibiting different pharmacologic profiles. Evidence of a low ESP risk within a therapeutic range has been a common defining criterion for “atypicality” (Meltzer, 1991). Based on studies using clozapine (e.g., Krupp & Barnes, 1992), the prototype of an atypical antipsychotic drug, it has been suggested that serotonin (5HT₂) receptor antagonism is a critical component for an atypical profile of lower motor side-effects and greater clinical efficacy. This theory has provided the impetus for the development of new antipsychotic drugs that possess a high degree of 5HT antagonism.

Olanzapine is a new antipsychotic agent that belongs chemically to the thienobenzodiazepine class. The compound has a high affinity for 5HT₂, 5HT₃, and dopamine receptors (Kinon & Lieberman, 1996; Moore, Calligaro, Wond, Bymaster, & Tye, 1993). An early study (Charles, Gary, & Pierre, 1997) revealed that

Correspondence concerning this article should be addressed to Abdullahi Fido, Department of Psychiatry, Faculty of Medicine, Kuwait University, P.O. Box 24923 Safat, Kuwait 13110. E-mail: fido@hsc.kuniv.edu.kw.

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olanzapine is effective in the control of psychotic symptoms, including both positive and negative symptoms. Although olanzapine was used for clinical trials elsewhere (Beasley, Sanger, Satterlee, Tollefson, Tran, & Hamilton, 1996), this drug has not been approved by the regulatory authority in Kuwait pending prior local clinical trial. For this purpose, an open-label trial was adopted to examine the clinical efficacy of olanzapine in a treatment resistant sample of schizophrenic patients.

Materials and Methods

Subjects were selected according to the *DSM-IV* criteria for the diagnosis of schizophrenia (American Psychiatric Association, 1994), as established by clinical interview and chart review. Patients were also required to have a history of partial responsiveness to conventional antipsychotic drugs, while further revealing residual positive symptoms (e.g., hallucinations and delusions), negative symptoms (e.g., apathy, avolition, and social isolation), or both. Patients could begin the study as inpatients or outpatients, and a change in hospitalization status during participation in the protocol was permissible. No comorbidity or other recent major Axis I disorder was allowed. Patients with serious medical illnesses which psychopharmacology posed a substantial risk or confounded diagnosis were excluded.

Symptoms of schizophrenia were assessed using the Positive and Negative Symptom Scale (*PANSS*; Kay, Fiszbein, & Opler, 1987). Each patient was rated by a staff psychiatrist who had experience with the *PANSS* rating instrument. Patients were only included if they had *PANSS* global scores of at least 24 at baseline. During entry, patients underwent psychiatric and physical investigations, including ECGs, chest X-rays, urinalysis, serum chemistry, haematology and hepatitis B-serology. The same investigations were repeated at week 13 of the study. Informed consent was obtained from all eligible patients after the procedure, and possible side-effects were explained. The trial consisted of two study periods: (a) a washout period from previous antipsychotics (2 to 9 days for oral antipsychotics and 14 days for depot-antipsychotic drugs, such as moderate); (b) an open-label therapy period in which patients started olanzapine therapy at 15 mg/day for the first seven days. Thereafter, investigators could adjust the daily dosage up or downwards by 5 mg within the approved range of 10-20 mg/day.

Assessment

Clinical assessments were carried out at the screening visit followed by a baseline assessment after the washout period. The efficacy measures included the *PANSS* total score and its subscales (positive, negative

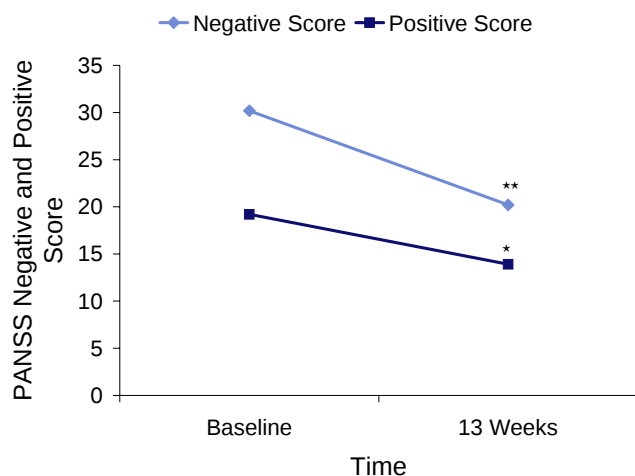


Figure 1. *PANSS* scores for negative and positive symptoms at baseline ($M = 30.20$, $SD = 1.50$; $M = 19.20$, $SD = 1.10$) and at 13 weeks into the study ($M = 20.20$, $SD = 0.50$; $M = 13.90$, $SD = 0.75$).

and general psychopathology scores). Side-effects such as EPS, akathisia and dyskinesia were further assessed using the Abnormal Involuntary Movement Scale (*AIMS*; Guy, 1976) at baseline and at 13 weeks. A designated measure of efficacy (25% reduction from baseline for global *PANSS* scores) was considered as a minimal criterion for efficacy. *t*-tests were used to compare the difference between the means of two continuous variables.

Results

Based on the recommendation of the manufacturer of olanzapine, Eli Lilly Pharmaceutical Co., a total of 10 patients were assigned to receive a 13-week open-label trial of olanzapine treatment (10-20 mg/day). The patient group were comparable with respect to demographic and illness characteristics. They were all men, mean age 35.2 years ($SD = 7.5$), with a mean age of illness onset of 23.7 years ($SD = 5.3$). Paired comparisons of baseline and 13-week endpoint scores showed significant improvements over time for the negative symptom subscale ($t = 5.96$, $p = .0001$), for the general psychopathology subscale ($t = 4.58$, $p = .001$), for the positive symptom subscale ($t = 4.44$, $p = .002$), and for global *PANSS* scores ($t = 5.66$, $p = .0001$; see Figure 1 and Figure 2). The proportion of patients with treatment-emergent EPS and dyskinetic symptoms assessed by *AIMS* were not significant, 3.0 ($SD = 0.5$) at baseline and 2.8 ($SD = 0.7$) at 13 weeks after treatment (Fisher Exact Test, $p = .35$). There was no hepatic enzyme elevation or any other serum chemistry changes observed after treatment.

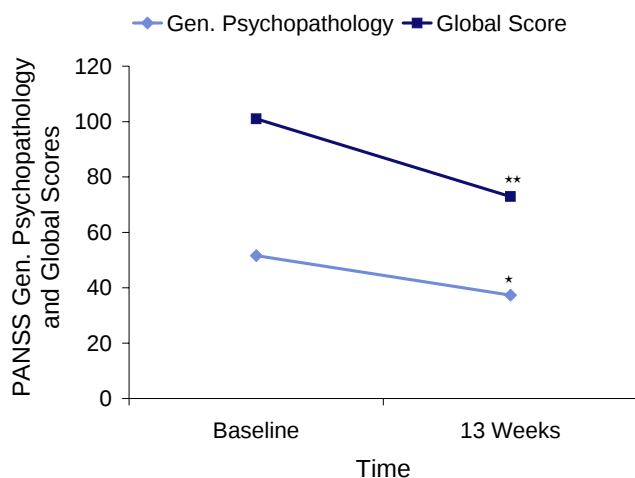


Figure 2. PANSS general psychopathology and global scores at baseline ($M = 51.60$, $SD = 4.70$; $M = 101.0$, $SD = 3.50$) and at 13 weeks into the study ($M = 37.30$, $SD = 2.50$; $M = 72.90$, $SD = 1.80$).

Discussion

The efficacy of olanzapine in the treatment schizophrenia has been assessed in a substantial number of studies, and comparison was made with placebo (Beasley et al., 1996), and a range of reference antipsychotic drugs under double-blind, randomized conditions (Tran et al., 1997). This study however, represents the first prospective trial of atypical antipsychotic drug efficacy in Kuwait.

The primary finding of the open-label trial presented here is that olanzapine is effective in the treatment of the overall psychopathology of schizophrenia as indicated by decrease in PANSS global scores, general psychopathology, positive and negative symptoms subscale scores. Dose titration occurred during the first week of treatment though; effective improvement was most marked with the highest dose of olanzapine (20 mg/day). While the general measure of efficacy (25% reduction in total PANSS score) after treatment indicated olanzapine effectiveness; this effect was mainly confined to improvement in negative symptoms. Caution must be exercised in drawing conclusions due to the small sample size and short treatment duration. A recent study (Chouinard et al., 1993) has shown that patients with a predominantly negative symptoms exhibited significant improvement after treatment with novel atypical antipsychotic drug risperidone. The analysis of this study however, would suggest that a high incidence of motor side-effects may be casually related to negative symptoms and that perhaps, the low side-effect profile of these new agents may have contributed to the improvement of negative symptoms. Since negative symptoms are present in

more than 50% of patients presented with schizophrenia (Schooler, 1994), the selection of an appropriate antipsychotic drug for such patients has to take into account the extent to which it has an activating characteristics.

Conclusion

Olanzapine has been studied in over 2500 schizophrenic patients worldwide (Tran et al., 1997). Safety evaluation in this significant database showed that olanzapine is generally well tolerated. It has been shown to be effective for the treatment of mainly negative and positive symptoms of schizophrenia and to have a mild side-effect profile. Its efficacy extends to patients who have prominent negative symptoms and whose disease process or age put them at increased risk for the serious side-effects of the conventional antipsychotic drugs, such as extrapyramidal symptoms and tardive dyskinesia. Olanzapine represents an important addition to the range of antipsychotic drugs currently available to the clinical psychiatrists.

References

- American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: American Psychiatric Association.
- Beasley, C. M., Sanger, T., Satterlee, W., Tollefson, G., Tran, P. & Hamilton, S. (1996). Olanzapine versus placebo: Results of a double-blind, fixed dose olanzapine trial. *Psychopharmacology*, 124, 159-167.
- Charles, M. B. Jr., Gary, D. T., & Pierre, V. T. (1997). Efficacy of olanzapine: An overview of pivotal clinical trials. *Journal of Clinical Psychiatry*, 58, 7-12.
- Chouinard, G., Jones, B., Remington, G., Bloom, D., Addington, D., MacEwan, G. W., et al. (1993). A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. *Journal of Clinical Psychopharmacology*, 13, 25-40.
- Corrigan, P. W., Liberman, R. P., & Engel, J. D. (1990). From noncompliance to collaboration in the treatment of schizophrenia. *Hospital & Community Psychiatry*, 41, 1203-1211.
- Fido, A., & Abdul Razik, M. (1998). Noncompliance with medication among psychiatric patients in Kuwait. *Medical Principles and Practice*, 7, 40-44.
- Guy, W. (1976). *ECDEU assessment manual for psychopharmacology* (rev. ed., pp. 534-537). Bethesda, MD: US Department of Health, Education and Welfare.
- Kane, J. M. S. (1966). Schizophrenia. *New England Journal of Medicine*, 334, 34-41.
- Kane, J. M. S. (1989). The current status of neuroleptics. *Journal of Clinical Psychiatry*, 50, 322-328.
- Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin*, 13, 261-276.

- Kinon, B. J., & Lieberman, J. A. (1996). Mechanisms of action of atypical antipsychotic drugs: A critical analysis. *Psychopharmacology*, 124, 2-34.
- Krupp, P., & Barnes, P. (1992). Clozapine-associated agranulocytosis: Risk and aetiology. *British Journal of Psychiatry*, 160, 38-40.
- Meltzer, H. Y. (1991). The mechanism of action of novel antipsychotic drugs. *Schizophrenia Bulletin*, 17, 263-287.
- Moore, N. A., Calligaro, D. O., Wond, T. D., Bymaster, F., & Tye, N. C. (1993). The pharmacology of olanzapine and other new antipsychotic agents. *Current Opinion in Investigational Drugs*, 2, 281-293.
- Tran, P. V., Hamilton, S. H., Kuntz, A. J., Potvin, J. H., Andersen, S. W., Beasley, C. Jr., et al. (1997). Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. *Journal of Clinical Psychopharmacology*, 17, 407-418.
- Schooler, N. R. (1994). Negative symptoms in schizophrenia: Assessment of the effect of risperidone. *Journal of Clinical Psychiatry*, 5, 22-28.
- Weiden, P. J., Shaw, E., & Mann, J. J. (1986). Causes of neuroleptic noncompliance. *Psychiatric Annals*, 16, 571-575.

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