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ARTICLE

Olanzapine orally disintegrating tablets in the treatment of acutely ill non-compliant patients with schizophrenia

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Abstract

The objective of this study was to determine if the orally disintegrating tablet formulation of olanzapine, Zyprexa® Zydis®, would facilitate antipsychotic medication compliance in acutely ill, non-compliant patients. Eighty-five acutely ill patients with schizophrenia or schizoaffective disorder who met medication non-compliance criteria received open-label olanzapine orally disintegrating tablets (10–20 mg/d) for up to 6 wk. Improvement in medication compliance was assessed using various rating scales to measure changes in psychopathology, medication-taking and compliance attitudes, and nursing care burden. Safety variables were also measured. Significant improvement from baseline was demonstrated in the Positive and Negative Syndrome Scale total score at Week 1 and subsequently ($p < 0.001$). Significant improvement from baseline was also seen in various scales measuring medication compliance, attitude, and nursing care burden ($p < 0.05$). Olanzapine orally disintegrating tablets were well-tolerated. Olanzapine orally disintegrating tablets may benefit acutely ill, non-compliant schizophrenic patients by facilitating acceptance of active antipsychotic drug therapy.

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Key words: Acute, non-compliance, olanzapine, schizophrenia, Zyprexa Zydis.

Introduction

Medication non-compliance is a significant concern in the acute care of psychiatric patients and is closely linked to treatment failure. Studies indicate rates of medication non-compliance of 20% in schizophrenic in-patients and between 40 and 50% for schizophrenic outpatients (Soskis, 1978). Overall, 42% of patients prescribed antipsychotic medications are reportedly non-compliant, with 63% of these patients labeled as 'wilfully non-compliant'. Wilful non-compliance may be due to social stigmas, medication side-effects, or symptoms of the psychiatric illness such as hostility and negativism or lack of judgement and insight. All of these factors may result in overt refusal of medications or surreptitious non-compliance behaviours characterized as a failure to swallow pills (i.e. 'cheeking') and then expulsion of pills (i.e. 'spitting') in an in-patient setting, as well as chronic outpatient non-compliance (Kinon, 2001). Patients who discontinue their medications have been found to experience a monthly relapse rate of 11%, compared to that of 3.5% per month for patients who continue on maintenance conventional antipsychotic drugs (Weiden and Olfson, 1995).

Dosage forms other than tablets or capsules have been used to treat these non-compliant patients in an attempt to more reliably deliver medication. In the outpatient setting, depot formulations of typical antipsychotics are commonly used. In the in-patient setting, liquid formulations can be used for patients with questionable compliance, although liquid doses can also be cheeked and spat out. The currently available injectable or liquid formulations of typical antipsychotics carry very real liabilities (e.g. tardive dyskinesia, hyperprolactinaemia) and questionable incremental improvement in compliance (Schooler et al., 1980). As atypical antipsychotic medications are not yet widely available in parenteral forms, restriction of therapy to medications that are available in an injectable or liquid form has the disadvantage of significantly narrowing therapeutic options.

The orally disintegrating tablet formulation of olanzapine, an atypical antipsychotic, may provide an alternative method of treating non-compliant patients.

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Table 1. Criteria for medication non-compliance[a]

I	In-patients or outpatients demonstrating ⩾2 episodes within the past 72 h of: Active or passive refusal of prescribed antipsychotic medication Direct evidence, or suspicion of cheeking or spitting prescribed antipsychotic medication Display of significant ambivalence toward taking prescribed antipsychotic medication
II	Newly admitted in-patients with a recent history of outpatient non-compliance as evidenced by at least 7 d of antipsychotic medication non-compliance within the past month
III	Outpatients with a recent history strongly suggestive of non-compliance such that the clinical decision has been made to place the patient on supervised medication within the past month
IV	In-patients who claim that they cannot swallow antipsychotic medication despite the absence of any obvious physical condition that would impede swallowing of medications

[a] Patients needed to meet at least one of the aforementioned criteria to be considered non-compliant.

The orally disintegrating tablet is designed to dissolve upon contact with saliva. In a trial of schizophrenic patients ($n=11$) the mean disintegration time of the olanzapine orally disintegrating tablet was 15.8 s (Chue et al., 2001). Additional studies in healthy subjects have noted that removal of the disintegrating tablet from the tongue would be difficult because it forms an amorphous residue that can only be removed by scraping the tongue (Lilly, data on file). Trials in normal, healthy subjects have also shown that the olanzapine orally disintegrating tablet has a similar pharmacokinetic profile to olanzapine tablets and no difference in tolerability (Lilly, data on file).

An open-label, multicentre study was conducted to explore the strategy of initiating therapy with the olanzapine orally disintegrating tablet in acutely ill non-compliant patients with schizophrenia. We hypothesized that this novel formulation of olanzapine would facilitate a successful therapeutic outcome in psychotic symptoms, compliance attitudes and health-seeking behaviours during acute treatment.

Methods

Patient population

Male or female in-patients or outpatients, aged 18–55 yr, meeting DSM-IV criteria for schizophrenia, schizoaffective disorder, or schizophreniform disorder as defined in DSM-IV (APA, 1994), were screened for inclusion into this study. Eligible patients demonstrated a threshold level of psychosis of at least 42 on the Brief Psychiatric Rating Scale ($BPRS_{1\text{-}7}$, extracted from the PANSS), as well as a CGI-Severity score of at least 4 (moderate). Patients were also required to meet study-specific medication non-compliance criteria (Table 1). Written informed consent was obtained from all participants, and institutional review board approval was given at each of the 13 study sites.

Study design

This study was a single arm, open-label study. Medical and psychiatric histories were taken, and a physical examination was performed at study entry. During the first week of the study, all patients were required to receive study medication within a supervised medication programme (i.e. in-patient unit, day hospital programme, or group home). After week 1, patients could be released from supervised care if clinically indicated.

All patients began therapy on study day 1 with the orally disintegrating tablet formulation of olanzapine (10 mg/d). Dosage increases were allowed in 5 mg increments up to a maximum of 20 mg/d. The first increase could occur as early as day 3 of the study, with subsequent increases occurring on a weekly basis. If a physician felt that a patient had shown significant improvement in psychosis and medication compliance, then the physician could switch the patient from orally disintegrating tablets to standard oral tablets (after week 1) on a direct milligram-for-milligram basis. This switch was allowed to determine if patients who showed an initial robust response to the orally disintegrating tablets would subsequently accept and adhere to treatment with the standard oral tablets. The use of benzodiazepines and antiparkinsonian medications was permitted during the study, although the

Table 2. Nursing Assessment of Medication Assessment (NAMA) scale

Item	Title	Description
1	Attitude	Patient has a positive attitude towards prescribed medication
2	Compliance	Patient is compliant with medication
3	Ingestion	Patient ingests medication
4	Nursing effort	No more nursing effort than usual was required to medicate this patient

[a] Items are scored from 1 to 5 (1 = strongly agree, 2 = agree, 3 = undecided, 4 = disagree, 5 = strongly disagree).

dose was limited. The use of antiparkinsonian drugs for prophylaxis of extrapyramidal symptoms was not allowed.

Assessments

The primary efficacy measure was the Positive and Negative Syndrome Scale (PANSS) total score (Kay et al., 1987). Other efficacy measures included the Clinical Global Impression (CGI) Severity and Improvement scales (Guy, 1976). Medication compliance and acceptance were measured with the Rating of Medication Influences (ROMI) (Weiden et al., 1994), and Treatment Compliance Interview (TCI) (Weiden et al., 1995). In addition, we included a new rating scale developed by Lilly, Nursing Assessment of Medication Acceptance (NAMA), to assess medication compliance and acceptance as well as nursing care burden (Table 2). We also analysed the Patient Global Impression scale (PGI) assessing how the patient felt overall about the medication [e.g. 'I like it very much' (score 1) to 'I dislike it very much' (score 7)].

Ratings on the CGI Severity and NAMA scales, as well as ratings on the CGI Improvement and PGI scales after the first day of treatment, were performed daily throughout week 1, with subsequent ratings occurring after weeks 2, 4 and 6 of treatment. After the first week, ratings on the NAMA scale occurred only for those patients receiving supervised care. Ratings on the PANSS, ROMI, TCI and all safety scales were performed at the start of the study, and then after weeks 1, 2, 4 and 6 of treatment.

Trough plasma concentrations were collected as a proxy measure of medication compliance. Olanzapine concentrations above the minimum effective level of 9 ng/ml inferred adequate ingestion of study medication (Perry et al., 1997). This assumption is limited by known inter-patient variability in olanzapine metabolism and was not treated as an absolute measure of compliance.

Safety was evaluated throughout the study via weekly ratings of the modified Simpson–Angus Scale (Simpson and Angus, 1970) and the Barnes Akathisia Scale (Barnes, 1989), as well as by assessments of dyskinetic movements via the Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976). Vital signs, weight, and treatment-emergent adverse events were collected.

Statistical methods

Analyses were performed on an intent-to-treat basis. All total scores from rating scales and subscales were derived from individual items. If any of the individual items were missing, the total score was treated as missing. For continuous variables, the change from baseline-to-endpoint [last observation carried forward (LOCF)] as well as from baseline to visit-wise observations [observed case (OC)] was tested for significance using the Signed Rank test. Categorical variables were analysed using the Fisher's Exact test. All statistical tests were performed at a two-sided α-level of 0.05.

Results

Patient demographics and disposition

A total of 85 acutely ill, non-compliant patients were enrolled in the study. There were 59 male patients and 26 female patients, with an overall mean age of 40.35 ($\pm$9.55) yr. The primary diagnosis was schizophrenia (n = 63) for a mean duration of 15.58 ($\pm$10.61) yr, followed by schizoaffective disorder (n = 22) for a mean duration of 16.70 ($\pm$11.83) yr.

Sixty-four (75.3%) patients completed the 6-wk study. One (1.2%) patient discontinued due to an adverse event of atrial flutter, five (5.9%) were lost to follow-up, six (7.1%) did not meet enrolment criteria or were non-compliant with study procedures and nine (10.6%) discontinued due to a patient, sponsor, or physician decision. Per protocol, patients were not to be discontinued due to medication non-compliance during the study.

Mean daily dose of orally disintegrating olanzapine at the end of week 1 was 13.09 $\pm$ 3.00 mg/d (n = 68). For patients who stayed on the orally disintegrating

Table 3. Treatment outcomes for efficacy, compliance and safety variables (OC)

Scale	Baseline	Day 2/ week 1[a]	*p* value	Final endpoint[b]	*p* value
Efficacy measures					
PANSS total	97.53	81.68	<0.001	70.89	<0.001
CGI Improvement	–	3.82	<0.001	2.74	<0.001
Compliance measures					
NAMA total	10.54	8.11	<0.001	6.66	<0.001
NAMA item 1 (attitude)	3.07	2.59	<0.001	1.72	<0.001
NAMA item 2 (compliance)	2.75	2.00	<0.001	1.68	<0.001
NAMA item 3 (ingestion)	1.99	1.49	<0.001	1.55	0.007
NAMA item 4 (nursing burden)	2.73	2.02	<0.001	1.70	<0.001
ROMI Compliance	15.86	17.10	0.081	17.23	0.062
ROMI Non-compliance	16.38	13.44	<0.001	12.84	<0.001
TCI total	6.29	5.84	0.092	4.73	<0.001

[a] The first post-baseline time-point measured was day 2 for CGI Improvement and NAMA, and week 1 for PANSS, ROMI Compliance and Non-compliance, and TCI. The range of observations included for each scale: CGI Improvement and NAMA ($n=84$–85), PANSS and TCI total ($n=73$–74), ROMI Compliance ($n=50$), ROMI Non-compliance ($n=39$).
[b] The range of observations included for each scale: CGI Improvement, PANSS and TCI total ($n=64$–66), NAMA ($n=47$), ROMI Compliance ($n=43$), ROMI Non-compliance ($n=37$).

tablet formulation of olanzapine throughout their participation in the study, the mean daily dose at endpoint (LOCF from weeks 1–6) was 14.80 ± 4.20 mg/d ($n=49$). For patients who switched to standard olanzapine tablets ($n=24$), the mean daily dose of the orally disintegrating tablets at the time of switch was 14.58 ± 3.27 mg/d and the mean daily dose of oral tablets at endpoint (LOCF) was 17.08 ± 3.27 mg/d.

Efficacy

Patients showed significant improvement in overall psychopathology as measured by a reduction of -24.41 (± 22.61) in the PANSS total score (LOCF; $p<0.001$) during the 6-wk study. Visit-wise comparisons revealed significant improvement from baseline in the PANSS total score as early as week 1 (first post-baseline time-point measured), which continued throughout the study (OC; $p<0.001$ for all measured time-points) (Table 3).

Improvement of 20% or greater in the PANSS total score was set a priori as a measure of clinical response. By the end of week 1, 32% of patients showed a 20% or greater reduction in the PANSS total score. By week 6, 60% of patients demonstrated this degree of improvement.

Significant improvement in clinical symptoms was also evident in the physician-rated CGI Improvement scale with improvement occurring as early as day 2 (OC; $p<0.001$), and continuing throughout the remainder of the study (OC; $p<0.001$ for all measured time-points) (Table 3).

Medication compliance

Significant improvement in medication compliance was observed with baseline-to-endpoint increases in ROMI Compliance score (LOCF; $p=0.031$) and decreases in the ROMI Non-compliance score (LOCF; $p<0.001$). Visit-wise comparisons revealed significant improvement in ROMI Non-compliance score as early as week 1 and subsequently ($p<0.001$) (Table 3), with a trend for improvement in the ROMI Compliance. Improvement in medication compliance, attitude and nursing care burden was also observed with significant baseline-to-endpoint reductions in the TCI total score and in the NAMA total score including each item of the NAMA rating scale (LOCF; $p<0.001$). Visit-wise comparisons revealed significant improvement in the NAMA rating scale as early as day 2 ($p<0.001$) (Table 3). In addition, corroborating the findings on attitude, patient-rated feelings about the medication showed positive acceptance at all measured time-points (OC; range of PGI scores, 2.01–2.74).

Plasma concentrations

Between 80 and 90% of patients had olanzapine plasma concentrations above the recognized minimum effective level of 9 ng/ml at weeks 1, 2, 4 and 6.

Safety

There was no significant increase in extrapyramidal symptoms during treatment with olanzapine. In fact, the Modified Simpson–Angus scale showed a significant decrease of -1.14 from baseline to endpoint (LOCF; $p<0.001$) while the Barnes Akathisia and AIMS scales showed numerical, but not statistical improvement over baseline (Barnes mean change $=-0.06$, $p=0.594$; AIMS mean change $=-0.32$, $p=0.894$).

Treatment-emergent adverse events reported by at least 10% patients during the study were agitation, anxiety, dry mouth, headache, insomnia, somnolence, and weight gain. No clinically significant change over baseline was seen in laboratory analytes or vital signs other than a mean weight gain of 2.96 ± 3.62 kg.

Discussion

The orally disintegrating tablet formulation of olanzapine was effective in getting patients with a history of medication non-compliance to begin active antipsychotic drug therapy. Within 1 wk of treatment with the orally disintegrating tablets, a significant reduction in the PANSS total score was observed. This improvement in psychopathology was corroborated by a significant improvement in the physician-rated CGI Improvement scale. Continued improvement in schizophrenia symptoms was observed throughout the 6-wk study (during treatment with either orally disintegrating tablets or the standard oral tablets), with 60% of patients achieving at least a 20% reduction in PANSS total score by week 6.

Olanzapine was also effective in improving compliance attitudes and behaviours. A majority (75.3%) of patients who were non-compliant toward their antipsychotic medication at baseline completed the 6-wk study and held a positive opinion about taking olanzapine throughout the course of the study. Significant improvement was observed in all measures of patient attitude and behaviours towards taking medication. Of particular note, significant improvement was observed not only in the ROMI Compliance and Non-compliance scales, but also in the NAMA suggesting that this newly developed scale may be beneficial in assessing improvement in patient's attitude, medication compliance, and nursing care burden. A large proportion of patients had olanzapine plasma concentrations above the minimum effective level further substantiating that these previously non-compliant patients were now taking their antipsychotic medication.

One factor that may be critical for a successful therapeutic outcome is the initial acceptance of medication during the acute phase of illness. Patients are more willing to accept medication if they perceive the medicine as helping them and not harming them (i.e. effective control of psychotic symptoms with minimal adverse side-effects). Acceptance of medication differs from the depot strategy of simply ensuring that the antipsychotic drug gets on board. While the conventional depot antipsychotics provide initial insured drug delivery, they generally do not foster subjective acceptance of the medication (Kinon, 2001). The olanzapine orally disintegrating tablets may enhance the acceptance of medication in two ways: (1) providing a drug formulation that is easy to take and not easy to discard, and (2) providing a method of delivering olanzapine, an atypical antipsychotic, that offers clear control of psychotic symptoms with minimal adverse side-effects. The concurrent improvement in psychotic symptoms and medication compliance along with improvement in extrapyramidal symptoms would lend support to this basic argument. Of interest, in the United Kingdom, following availability of orally disintegrating olanzapine tablets (Velotab™), a significant inverse correlation between the use of orally disintegrating tablets and depot medication has been reported (Johnson et al., 2002).

There are two main limitations to the present study. First, the design of this study was open-label and uncontrolled, not allowing for direct comparisons among different treatment methods in acutely ill, non-compliant patients. A second limitation is the extent to which patients are truly 'non-compliant'. The fact that patients were willing to sign an informed consent form might suggest the inclusion of relatively 'more compliant' patients among a group of difficult-to-treat patients. Further clinical studies are needed to understand the potential significance of the olanzapine orally disintegrating tablets in facilitating medication compliance.

Conclusion

The orally disintegrating tablet formulation of olanzapine was effective in rapidly reducing psychopathology while improving medication compliance attitudes and behaviours. The initial improvements in schizophrenia symptoms and medication compliance observed within the first week of treatment was sustained throughout the 6-wk study in patients who either continued on the orally disintegrating tablets or who were switched to standard oral tablets. This new

formulation of olanzapine may offer an alternative strategy in the treatment of acutely ill, non-compliant schizophrenia patients.

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