

Dissolution Profile, Tolerability, and Acceptability of the Orally Disintegrating Olanzapine Tablet in Patients With Schizophrenia

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Objectives: This pilot study investigates the dissolution profile, tolerability, and acceptability of an orally disintegrating olanzapine tablet in patients with schizophrenia.

Method: Eleven patients with schizophrenia stabilized on oral olanzapine (mean dosage 12.7 mg daily [SD5.2]) were given an orally disintegrating olanzapine tablet, rather than their usual tablet, daily for 7 days. At each visit, visual assessments were made for elapsed time to initial disintegration (every 15 seconds) and complete disintegration (every 1 minute). At the end of the study, patients completed a drug-acceptance questionnaire.

Results: The mean time to initial disintegration was 15.78 seconds, and mean time to complete disintegration was 0.97 minutes. All patients found the orally disintegrating tablet acceptable and expressed positive comments. Nonserious clinically significant adverse events, asthenia, purpuric rash, headache, depression, and insomnia (preexisting, except for asthenia and insomnia) were reported in 3 patients.

Conclusion: The orally disintegrating olanzapine tablet disintegrates rapidly and is a well-tolerated and acceptable alternative to standard olanzapine tablets in patients with schizophrenia.

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See page 773 for funding support and author affiliations.

Clinical Implications

- This is the first study of a rapidly disintegrating oral antipsychotic medication completed in patients with schizophrenia.
- This formulation may be clinically useful in patients who cannot swallow tablets or who cheek (spit out) medication.
- Medication adherence may be improved in some patients through use of this formulation.

Limitations

- The sample size was small.
- This was an open-label, single-site study.
- There was no control group.

Key Words: *olanzapine, orally disintegrating tablet, schizophrenia*

A choice of formulations of antipsychotic medications provides valuable options for treating patients with schizophrenia. Intramuscular injectable antipsychotics offer advantages over traditional oral tablets in the emergency treatment of the acute phase of schizophrenia, and long-acting de-

pot formulations are useful in the stable phase, particularly when adherence problems exist. However, situations occur wherein patients have difficulty swallowing traditional oral tablets, or may spit out liquid medication, or for whom an injectable formulation is contraindicated or unacceptable. Like-

wise, there are patients who appear to comply with tablet ingestion but instead conceal the medication between their gums and cheek and subsequently spit it out (“cheeking”). This may lead the clinician to wrongly conclude that the medication is ineffective, prompting either a premature discontinuation of an effective treatment or an inappropriate increase in dosage. To address these problems that are common in real-life clinical settings, an oral lyophilisate, or orally disintegrating tablet, was developed for olanzapine. Unlike conventional tablets that must be taken with liquid and swallowed, this formulation begins to disintegrate when placed on the tongue and may therefore enhance drug adherence in patients who are less than optimally compliant. Although liquid formulations may offer similar advantages in this patient population, the orally disintegrating tablet is more convenient and easy to store and does not require measurement to ensure proper dosage.

This 7-day, open-label pilot study assessed the dissolution profile, tolerability, and acceptability of once-daily orally disintegrating olanzapine tablets in schizophrenia patients who were previously stabilized on oral olanzapine tablets (1).

Methods

In this single-site, open-label study, outpatients meeting DSM-IV criteria for schizophrenia (2) who were stable on monoantipsychotic therapy with oral olanzapine (5, 10, 15, or 20 mg daily) for a minimum of 7 days were switched to the same dosage of orally disintegrating tablet (supplied by Eli Lilly) for 7 days. Patients signed written informed consent documents after the procedures and possible side effects had been fully explained. The site’s ethical review board approved the study protocol. A physical examination and laboratory investigations were completed at screening, including complete blood count (CBC) with differential thyroid stimulating hormone (TSH), hepatitis panel, and liver function tests (LFTs). For female patients, a serum beta human chorionic gonadotrophin (β -HCG) level was also obtained. CBC and LFTs were repeated upon completion of the study. Erect and supine blood

pressure and pulse were monitored at each visit, 30 minutes postdose.

At each daily visit, an orally disintegrating olanzapine tablet was placed into the patient’s mouth following a drink of water. Patients opened their mouths every 15 seconds for visual assessment of elapsed time between administration and the start of disintegration. Once disintegration began, patients opened their mouths every minute to determine when disintegration was complete. The same observer administered the tablet and monitored the tablet dissolution for every patient and dose. The times to initial and complete disintegration of the orally disintegrating olanzapine tablet were summarized, using the mean and standard deviation of the times measured. Adverse events were elicited at each visit postdose. At the last visit, the observer administered a patient-acceptance questionnaire that was specifically developed for the study. Patients were asked if this was an acceptable way of taking their medication and what they had liked about this new type of tablet.

Results

All 11 patients (6 men, 5 women; 82% white; mean age 32.5 years) completed the study. Mean duration of illness was 9.8 years, and mean duration of olanzapine therapy was 9.3 months. The mean and mean modal dosages of the orally disintegrating olanzapine tablet were 12.7 mg daily (SD5.2) and 15.0 mg daily, respectively.

In nearly all cases, the tablet began to dissolve by 15 seconds, with an overall mean time to initial disintegration of 15.78 seconds (Table 1).

The amount of time for the tablet to completely disappear ranged from 15 seconds to 5 minutes, with an overall mean elapsed time of 0.97 minutes. There was a decreasing trend of mean disintegration times across days of treatment.

There were no serious adverse events. Of the patients, 3 reported nonserious clinically significant adverse events. Purpuric rash (2 patients) and headache and depression (1 patient) were reported—but were preexisting—whereas asthenia (1

Table 1 Time to initial and complete disintegration of olanzapine orally disintegrating tablet (n = 11)

Day of treatment	Mean (SD) time to initial disintegration (seconds)	Mean (SD) time to complete disintegration (minutes)
1	16.36 (4.52)	1.27 (0.65)
2	17.73 (6.07)	1.30 (1.25)
3	16.36 (4.52)	1.16 (1.07)
4	15.00 (0.00)	0.84 (0.67)
5	15.00 (0.00)	0.86 (1.10)
6	15.00 (0.00)	0.68 (0.57)
7	15.00 (0.00)	0.66 (0.39)
Overall	15.78 (3.35)	0.97 (0.87)

patient) and insomnia (1 patient) were new. None of the reported adverse events led to withdrawal from the study, dosage reduction, or institution of concomitant therapy. No abnormalities in vital signs nor changes in laboratory values occurred during the course of the study.

All 11 patients reported that the orally disintegrating tablet was an acceptable way of taking medication; subjective comments were all positive, ranging from ease of use to pleasant taste of the tablet.

Discussion

This study found that the orally disintegrating olanzapine tablet is acceptable to patients with schizophrenia. Rapid disintegration of the tablet occurs when it comes into contact with saliva. For this reason, the formulation may be an effective option for overcoming noncompliance due to cheeking. It may also be useful for patients who have difficulty swallowing, for whom an injectable medication is not feasible, or for covertly nonadherent patients. Medication noncompliance may account for up to 55% of relapse in schizophrenia (3), which may be a function of the drug administration route, its ease of use, and tolerability (4). In addition, many patients with schizophrenia do not adhere to prescribed medication because of a refusal to acknowledge that they are ill (lack of insight). Clearly, nonadherence with treatment has multiple determinants (5), but an oral medication wherein the clinician is assured of delivery may be part of an overall strategy to improve the care of schizophrenia patients.

The tolerability of an antipsychotic agent is another factor that may contribute to nonadherence (6). One patient experienced asthenia (described as fatigue approximately 3 to 4 hours after ingestion of the orally disintegrating olanzapine tablet); this may have related to the study drug according to the clinical investigator. Although, in this case, the asthenia was temporally associated with olanzapine treatment, in other large-scale clinical studies, the incidence of asthenia did not differ from placebo or haloperidol (7). One patient experienced insomnia. It is possible that, in these 2 patients, the regular supervised ingestion of their medication represented a change in total weekly dosages of olanzapine, despite no change in the dosage strength during the study. Most adverse events were pre-existing and thus do not appear to represent formulation-related adverse events.

Unpublished data from previous Phase 1 clinical trials in healthy volunteers demonstrated that standard olanzapine tablets and orally disintegrating olanzapine tablets were bioequivalent, according to standard bioequivalence criteria (data on file, Eli Lilly and Company). Consequently, the onset of action of orally disintegrating olanzapine tablets is not faster

than in standard oral olanzapine tablets, despite rapid disappearance from the mouth, because buccal absorption does not appear to occur to any measurable extent. Pharmacokinetic data were not collected, given that this was an early pilot study involving the first exposure of the orally disintegrating olanzapine tablet in patients with schizophrenia, with the primary objectives of examining practicality and tolerability in this patient population.

Due to the small patient sample size and open-label study design, limited conclusions can be drawn from this pilot trial. Randomized and controlled larger-scale studies with therapeutic blood monitoring would be useful to determine longer-term compliance and tolerability with orally disintegrating olanzapine tablets, compared with standard tablets. Similarly, to assess the utility and acceptability of this formulation in more severely ill patients, studies that involve patients in inpatient and emergency settings are desirable.

The results of the present study suggest that orally disintegrating olanzapine tablets have a dissolution profile that is practical for use in patients with schizophrenia and is well tolerated and accepted with no additional safety concerns.

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Résumé : Une recherche du profil de dissolution, de la tolérabilité et de l'acceptabilité d'un comprimé d'olanzapine à désintégration orale chez des patients souffrant de schizophrénie

Objectifs : Cette étude pilote examine le profil de dissolution, la tolérabilité et l'acceptabilité d'un comprimé d'olanzapine à désintégration orale chez des patients souffrant de schizophrénie.

Méthode : On a donné à 11 patients souffrant de schizophrénie stabilisés à l'aide d'olanzapine orale (dose moyenne = $12,7 \pm 5,2$ mg par jour) un comprimé d'olanzapine à désintégration orale plutôt que leur comprimé habituel, chaque jour pendant 7 jours. À chaque visite, on a évalué visuellement le temps que prenaient la désintégration initiale (toutes les 15 secondes) et la désintégration complète (toutes les minutes). À la fin de l'étude, les patients ont rempli un questionnaire sur l'acceptation du médicament.

Résultats : Le temps moyen de la désintégration initiale était de 15,78 secondes, et celui de la désintégration complète, de 0,97 minute. Tous les patients ont jugé acceptable le comprimé à désintégration orale et exprimé des commentaires favorables. Des effets indésirables cliniquement significatifs et non sérieux comme l'asthénie, l'angiodermite purpurique, le mal de tête, la dépression et l'insomnie (pré-existants sauf l'asthénie et l'insomnie) ont été déclarés chez 3 patients.

Conclusion : Le comprimé d'olanzapine à désintégration orale se désintègre rapidement et constitue une solution acceptable et bien tolérée aux comprimés d'olanzapine réguliers chez les patients souffrant de schizophrénie.