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A 3-Week, Open Label Study to Evaluate The Efficacy and Safety of Extended Release Quetiapine Fumarate in The Treatment of Agitation in Patients with Schizophrenia

Koh Ong Hui[1], Ahmad Hatim Sulaiman[1], Jesjeet Singh Gill[1], Subash Kumar Pillai[1], Stephen Thevanathan Jambunathan[1], Rusdi Abdul Rashid[2]

ÖZET:

Şizofreni hastalarında ajitasyonun tedavisinde uzamış salınımlı ketiyapin fumarat'ın etkinlik ve güvenliği: 3 haftalık, açık etiketli bir çalışma

Amaç: Bu çalışmada, akut şizofreni hastalarında ajitasyonun tedavisinde uzamış salınımlı ketiyapin fumarat'ın (XR) etkinliğini değerlendirmek amaçlandı.
Yöntem: Üç haftalık açık etiketli olarak tasarlanan bu çalışmaya yatan veya ayaktan şizofreni hastaları dahil edildi. Ketiyapin XR 1. gün 300 mg, 2. gün 600 mg ve 3. günden itibaren araştırmacının takdirine göre 400-800 mg/gün dozunda uygulandı. Birincil sonlanım noktası olarak bazal Pozitif ve Negatif Semptom Skalasının Eksite Bileşeni (PANSS-EC) puanındaki değişim alındı. İkincil sonlanım noktası olarak bazal PANSS-Pozitif, PANSS-Negatif, PANSS-Genel Psikopatoloji (PANSS-G) alt ölçek skorları ile toplam PANSS skoru, PANSS agresyon, hostilite ve depresyon skorları, CGI-Hastalık Şiddeti (CGI-S) ve CGI-İyileşme (CGI-I) puanlarındaki değişim esas alındı. Tolerabilitenin değerlendirmesi amacıyla bildirilen yan etkiler (YE), Simpson-Angus Ölçeği (SAÖ), Barnes Akatizi Derecelendirme Ölçeği (BADÖ), laboratuvar ölçümleri ve elektrokardiyogram (EKG) kullanıldı.
Sonuç: Çalışmaya alınan 40 hastadan 35'i çalışmayı tamamlamıştır. Yirmi birinci günde birincil ve ikincil sonlanım noktası değerlendirmelerinde başlangıca göre istatistiksel olarak anlamlı değişme gözlendi. YE insidansı düşüktü ve tüm yan etkiler hafif orta şiddetteydi. SAÖ ve BADÖ ile yapılan değerlendirmeye göre hiç ekstrapiramidal semptom (EPS) saptanmadı ve tedavi iyi tolere edildi. Bir hastada psikozun relapsı nedeniyle hospitalizasyon gerekti, ancak bu durumun tedaviyle ilişkisi olmadığı değerlendirildi.
Sonuç: Günde tek doz ketiyapin fumarat akut şizofreni semptomlarının ve ajitasyonun azaltılmasında etkilidir. Bu çalışmada, hızlı doz titrasyonuna rağmen tedavi genel olarak iyi tolere edilmiştir.

Anahtar sözcükler: Antipsikotik ajanlar, şizofreni, psikomotor ajitasyon, tedavi

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ABSTRACT:

A 3-week, open label study to evaluate the efficacy and safety of extended release quetiapine fumarate in the treatment of agitation in patients with schizophrenia

Objective: To evaluate the efficacy of extended-release quetiapine fumarate (XR) monotherapy once daily, in the treatment of patients with acute episodes of schizophrenia and agitation.
Method: Our study was a 3-week open-label study conducted in adult in- or outpatients with schizophrenia. Quetiapine XR was initiated at 300 mg on day 1, 600 mg on day 2, and 400-800 mg (at the investigator's discretion) on day 3 and onwards. The primary endpoint was the change from baseline in the Positive and Negative Syndrome Scale Excited Component (PANSS-EC) score. Secondary endpoints included change from baseline in PANSS-Positive, PANSS-Negative, PANSS-General Psychopathological (PANSS-G) subscale scores, total PANSS score, PANSS aggression, hostility and depression cluster scores, CGI-Severity of illness (CGI-S) and the absolute CGI-Improvement (CGI-I) scales. Tolerability was assessed based on reported adverse events (AEs), the Simpson-Angus Scale (SAS) and Barnes Akathisia Rating Scale (BARS) scores, laboratory measurements and electrocardiograms (ECGs).
Results: Of 40 patients enrolled, 35 completed the study. At day 21, statistically significant improvements versus baseline were seen for the primary and all secondary endpoints assessed. The incidence of AEs was low, and all were mild to moderate in severity. No extrapyramidal symptoms (EPS) as measured by the SAS and BARS were reported, indicating that the treatment was well tolerated. Hospitalization was required in one out-patient due to a relapse of psychosis, but was not considered to be treatment related.
Conclusion: Once-daily quetiapine fumarate XR (400-800 mg/day) was effective in reducing agitation and a broad range of symptoms in acute schizophrenia. Treatment, including rapid dose escalation, was generally well tolerated in this study.

Key words: Antipsychotic agents, quetiapine, schizophrenia, psychomotor agitation, treatment

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[1]Assoc. Prof., Department of Psychological Medicine, Faculty of Medicine, University of Malaya - Malaysia
[2]Dr., Department of Psychological Medicine, Faculty of Medicine, University of Malaya - Malaysia

Yazışma Adresi / Address reprint requests to: Associate Professor Koh Ong Hui University of Malaya Faculty of Medicine Building, Department of Psychological Medicine 50603, Kuala Lumpur, Malaysia

Elektronik posta adresi / E-mail address: kohong@um.edu.my

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INTRODUCTION

Immediate release quetiapine (IR) is an atypical antipsychotic used as first-line treatment for patients with schizophrenia. It is effective against positive and negative symptoms whilst exhibiting a good tolerability profile in long term treatment, with placebo-like incidence of extrapyramidal symptoms (EPS), e.g. akathisia, parkinsonism or dystonia, and is associated with minimal weight gain (1). It is usually administered twice daily and requires dose titration over 4 days to reach the target therapeutic dose (Seroquel XR® Prescribing Information).

Extended release quetiapine fumarate (quetiapine XR) is a new formulation of quetiapine, developed to provide sustained exposure to the drug when administered once daily, at therapeutically effective doses reached from day 2 (2).

In Malaysia, many schizophrenic patients still delay seeking treatment (3). Most families opt for alternative treatment methods, such as traditional healers (4). Only when the person becomes aggressive will he/she be brought in to psychiatric services. Hence, most patients will require an effective treatment method to control their agitation upon admission. Furthermore, in patients with psychotic disorders, compliance is especially important and problematic and provides a strong rationale for reducing the frequency of administration and simplifying the dose-titration regimen (5-7).

A recent study has demonstrated the safety and tolerability of quetiapine XR once daily (400-800mg/day) versus placebo in patients with acute schizophrenia (2). Treatment including rapid dose escalation was well tolerated. The improvement, expressed as the change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score and Clinical Global Impression-Improvement (CGI-I) response rates, was significantly larger than that observed for placebo. Evidence from several small studies has suggested that a more rapid dose initiation, allowing for a dose of up to 800 mg/day by day 4, might be a generally well tolerated and effective treatment for patients with acute schizophrenia (8-10).

Patients with schizophrenia accompanied with acute psychotic symptoms often display signs of aggression and hostility, which can lead to a challenge for psychiatrists in terms of treatment and diagnosis. One of the preferential aims of treatment in schizophrenia is to rapidly resolve psychotic symptoms that often manifest as aggression and hostility to prevent harm to the patient and to others. On many occasions, practitioners have resorted to polypharmacy in an attempt to control these symptoms. Several studies have shown the efficacy of quetiapine in the acute setting (11-15) with significant improvements in aggressive symptoms observed within 24h in a naturalistic uncontrolled trial (9).

The objective of this present study was to assess the effectiveness of quetiapine fumarate XR in controlling agitation for patients with acute schizophrenia. Safety and tolerability were also evaluated.

PATIENTS AND METHODS

Study Design

This was a 3-week open-label study (Study D1444C00146, ClinicalTrials.gov Identifier: NCT00954122), conducted at 2 centers in Johor and Kuala Lumpur, respectively, from September 2009 to April 2010. There were 7 investigators in total from both sites, all of whom were qualified psychiatrists. They were not blinded to the study objectives. All of them had received the required training during the investigators' meeting and all of the investigators demonstrated high inter-rater reliability.

The study was performed in accordance with the Declaration of Helsinki and the International Conference on Harmonization and Good Clinical Practice guidelines. Written informed consent was obtained from all patients, and approvals of the local institutional review boards/ethics committees were obtained from each study center. All patients were equally familiar with the language in which the study was conducted and the informed consent forms were available in the 3 main languages in Malaysia namely Bahasa Malaysia, English and Mandarin.

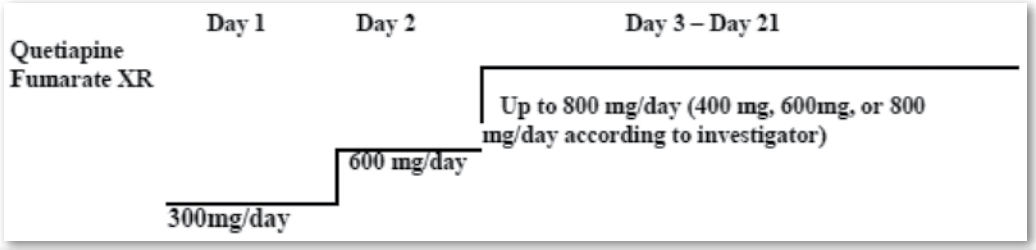

Figure 1: Flow chart of study design

Patients

The study included male and female patients, aged 18-65 years, with a Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) diagnosis of schizophrenia (1st episode/relapse). Key inclusion criteria were a PANSS total score of ≥ 75; a PANSS-Excited Component (PANSS-EC) score of ≥ 14; a severity score of at least 4 on at least one of the five PANSS-EC items (P4 – Excitement, P7- Hostility, G4 – Tension, G8 – Uncooperativeness, or G14 – Poor Impulse Control) and a Clinical Global Impression (CGI) score ≥4. The patients were recruited from the acute inpatient wards or from the outpatient clinics after they were screened thoroughly according to the inclusion/exclusion criteria stated in the study protocol.

Key exclusion criteria included any other Axis I diagnosis (DSM-IV) not defined in the inclusion criteria; patients who posed an imminent risk of suicide or danger to self or others (in the opinion of the investigator); pregnancy or lactation; unstable or inadequately treated medical illness (e.g. congestive heart failure, angina pectoris, hypertension); substance abuse or alcohol dependence at enrolment as defined by DSM-IV criteria; unstable diabetes mellitus; an absolute neutrophil count (ANC) of ≤ 1.5 x 109 per liter; abnormal ECG or participation in another drug trial within 4 weeks prior to enrolment.

In order to exclude treatment-resistant patients, the following groups were also excluded: patients with a known intolerance or lack of response to quetiapine fumarate as judged by the investigator; patients with a known lack of response to 2 or more antipsychotics with adequate doses given for at least 4 weeks; patients who required clozapine treatment for symptom control and patients treated with clozapine within 1 month prior to enrolment. The patients were hospitalized if required for treatment and assessment based on the investigator's judgment. If the patient was hospitalized, he/she could be discharged from the hospital if the investigator believed that it was clinically appropriate, and the patient could reasonably be expected to continue in the study on an outpatient basis.

Treatment

Eligible patients enrolled on day 1 were treated with quetiapine fumarate XR for 21 days. Quetiapine fumarate XR was administered orally, once daily. The initial dose was given when the patient entered treatment; morning doses were preferred to give maximum drug concentration during daytime. The initial dose was 300 mg; the dose on day 2 was 600 mg; from Day 3 to Day 21, the dose of quetiapine fumarate XR could be adjusted to 400 mg/day, 600 mg/day, or 800 mg/day (Figure 1) at the investigator's discretion based on the subject's clinical response and tolerance.

Lorazepam could be administered to treat agitation and anxiety, up to 6 mg/day, but was not given in the morning before scheduled assessments. Zolpidem tartrate (up 10 mg/day), zaleplon (up to 20 mg/day) and zopiclone (up to 7.5 mg/day) were permitted to treat sleep disturbances throughout the study; all other sleep medications were prohibited. Antidepressants (serotonin-norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors), mood stabilizers lithium and divalproex were allowed if the patient had been on a stable dose of the medication for at least 14 days before

enrolment. Anticholinergics could be used to treat emergent EPS but prophylactic use was not permitted.

The introduction of antidepressants, anxiolytics, mood stabilizers, hypnotics, sedative medications or other antipsychotic or psychoactive drugs during the study was prohibited, and was discontinued at least 1 week before day 1. Use of drugs that induce or inhibit the hepatic drug metabolizing cytochrome P450 3A4 enzymes were also not permitted from 14 days prior to day 1 until the end of the treatment period. Depot and long-lasting antipsychotics must have been stopped within at least two and preferably three dosing intervals prior to day 1 and were prohibited during the treatment period.

Study Objectives

Primary Objective

The primary objective was to evaluate the efficacy of quetiapine fumarate XR monotherapy, once daily, in the treatment of agitation in patients with acute episodes of schizophrenia. The primary outcome variable was the change from baseline in the PANSS-Excited Component (PANSS-EC) score.

Secondary objectives

Efficacy

The secondary efficacy objectives were to evaluate (i) the efficacy of quetiapine fumarate XR in reducing the positive, negative and general psychopathological symptoms, and aggression, hostility, and depression in the treatment of acute schizophrenia; (ii) the efficacy of quetiapine fumarate XR in improving the overall clinical status of patients with acute schizophrenia and (iii) the safety and tolerability of quetiapine fumarate XR in the treatment of patients with acute schizophrenia. The variables used to evaluate the secondary outcomes were: (i) change from baseline in the PANSS-Positive (PANSS-P), PANSS-Negative (PANSS-N), and PANSS-General Psychopathological (PANSS-G) subscale scores at the end of treatment; (ii) change from baseline in total the PANSS score; (iii) change from baseline in the PANSS aggression, hostility and depression clusters scores at the end of treatment; and (iv) change from baseline in CGI-Severity of illness (CGI-S) and absolute CGI-Improvement (CGI-I) scales.

Safety And Tolerability

The tolerability of quetiapine XR was assessed by monitoring the number and severity of adverse events (AEs) and withdrawals throughout the study period. Laboratory measurements including hematology and clinical chemistry, as well as electrocardiograms were performed at enrolment and week 12. Vital signs (blood pressure and pulse rate) and changes in body weight were assessed at every visit until the end of the study.

Assessments

Following enrolment (Visit 1), study visits were scheduled for days 1, 2, 4, 7, 14 and 21 (Table 1). The first dose of study medication was dispensed on Visit 1 or Visit 2, depending on whether assessment results could be obtained on the day of enrolment (Visit 1).

Statistical Analysis

Due to the exploratory nature of this study, the sample size was not based on any statistical calculations.

Data analyses were based on 2 patient populations: intention-to-treat (ITT) and safety. The ITT population consisted of all patients who were given quetiapine fumarate XR and who had a baseline value and at least 1 set of valid post-baseline PANSS assessments. The safety population consisted of all patients given at least one dose of the study medication.

The changes in PANSS total and subscales scores were analyzed using the T-test under the null hypothesis of no change in the scores from baseline. The mean value and a two-sided 95% confidence interval (CI) were calculated for each change.

The CGI-S assessment was based upon the subject's symptoms during the previous week.

The T-test was used to analyze the significant of

Table 1: Study plan

Visit Visit Description	1 Enrolment + Treatment[b]	2 Treatment	3	4	5	6	7[a] Final visit
Day	**< Up to – 1 day**	**1**	**2**	**4**	**7**	**14**	**21**
Visit Window (± No. Days)					± 1	± 3	± 3
Informed consent	X						
Medical history	X						
Inclusion/Exclusion criteria	X	X					
Physical examination	X						X
Vital signs/Weight	X	X	X	X	X	X	X
ECG	X						X
Clinical chemistry/Haematology	X						X
Urinalysis/Pregnancy	X						
PANSS	X	X	X	X	X	X	X
CGI-S and CGI-I	X[c]	X	X	X	X	X	X
SAS		X	X	X	X	X	X
BARS		X	X	X	X	X	X
Dispense study medication		X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X

a Day 21 assessments was performed at the end of treatment for all patients including those who withdrew early.
b Study medication was started if result could be obtained on the same day as enrolment, visits 1 & 2 combined visit.
c At visit 1, only CGI-S was performed.

the change in the CGI-S score from baseline, with reference to the null hypothesis of no change in the CGI-S score from baseline.

A paired T-test was used to compare the pre and post CGI-I score at each visit under the null hypothesis that the mean scores of the pre and post CGI-I scales are even.

RESULTS

Patients

In total, 40 patients were enrolled. Of these, 35 (87.5%) were eligible and proceeded to receive the study medication, and these subjects comprised both the ITT and safety populations. Out of the 5 patients who failed screening and were excluded from the study, 3 patients did not fulfill the eligibility criteria (1 had diabetes and 2 had positive urine tests for cannabis), while 2 patients experienced AEs (1 with abnormal ECG with a corrected QT interval of 541 milliseconds, and 1 with high blood pressure and elevated creatine kinase).

Out of the 35 patients receiving the study medication, 7 (17.5%) discontinued treatment early due to voluntary discontinuation (n=5), AE (n=1) and for safety reason (n=1). The AE reported was hospitalization due to relapse of psychosis, while the safety reason was worsening of psychotic symptoms in the patient (Table 2). Twenty-eight patients completed the study. All patients who withdrew early from the study returned on Day 21 to have assessments performed at the end of the study period. There were more male than female patients in the study (24 vs. 11); Malay and Chinese patients accounted for more than 70% of the subject population. The other 30% of the subjects were made up of Indians and 1 Pakistani patient. The mean age of the patients was 38.3±11 (SD) years.

Based on the DSM-IV Diagnostic Criteria, the predominant type of schizophrenia among the patients was paranoid schizophrenia (71.4%), followed by undifferentiated schizophrenia (17.1%) and disorganized schizophrenia (11.4%). Most of the patients (n=27) had a psychiatric history. The number of lifetime hospitalization for schizophrenia among the patients ranged from 0 to 31 times, with an average of 3 (±5.2 SD). The mean age at which the patients first received treatment for psychiatric illness was 29.3 (±6.8 SD) years.

Four patients (11.4%) had a medical history; three had been treated in the past for childhood asthma, tuberculosis and hepatitis B (carrier), respectively, and one was receiving current

Table 2: Disposition of patients

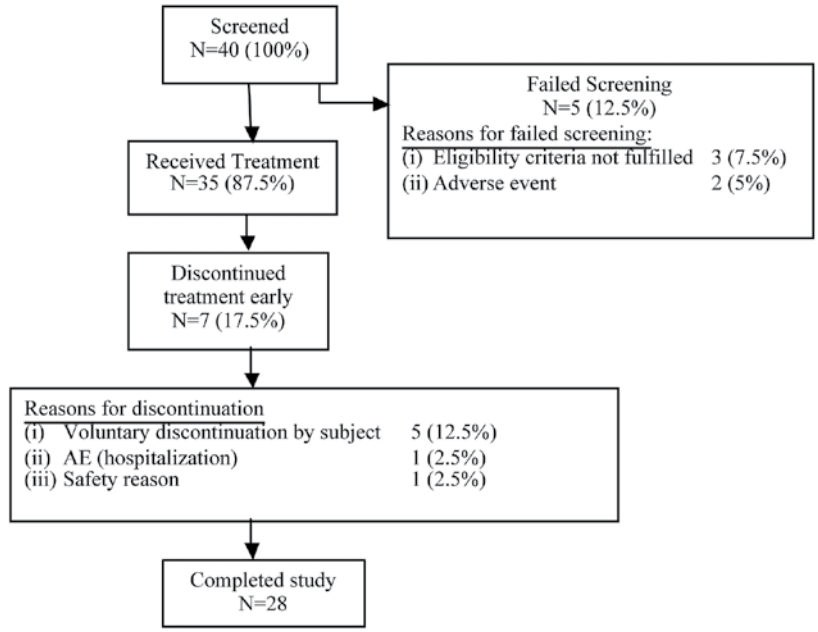

Table 3: Demographic and baseline characteristic of subjects (ITT population)

Population	**Subjects (N=35)**
Demographic characteristics	
Sex, n (%)	
Male	24 (68.6%)
Female	11 (31.4%)
Age, years (SD)	38.3 (11)
Race, n (%)	
Malay	12 (34.3%)
Chinese	13 (37.1%)
Indian	9 (25.7%)
Others (Pakistani)	1 (2.9%)
Height, cm (SD)	165.1 (6.9)
Baseline characteristics	
Subjects with:	
Medical history	4 (11.4%)
Surgical history	2 (5.7%)
Psychiatric history	27 (77.1%)
Subjects with schizophrenia (based on DSM-IV Diagnosis criteria)	
Disorganized type	4 (11.4%)
Paranoid type	25 (71.4%)
Undifferentiated type	6 (17.1%)
Baseline efficacy measurements, mean (SD)	
PANSS-EC score	17.8 (2.7)
PANSS-P score	26.6 (4)
PANSS-N score	25 (5.4)
PANNS-General psychopathological score	51.3 (7.6)
PANSS total score	110.8 (15.7)
CGI-S	4.6 (0.5)
CGI-I	3.9 (0.4)
Baseline EPS symptoms	
SAS score	0
BARS score	0.1 (0.5)

Baseline values for efficacy measurements and SAS and BARS scores were values at visit 2.

Table 4: Concomitant Medications Patients Received During the Study

	All Patients (N=35)
Any concomitant treatment	22 (62.9%)
Type of medication	
Magnesium compounds (for acid-related disorder)	1 (2.9%)
Propulsives (for functional gastrointestinal disorder)	1 (2.9%)
Contact laxatives	1 (2.9%)
Potassium supplement	1 (2.9%)
Tertiary amines (for anti-Parkinson)	1 (2.9%)
Psycholeptics	21 (60%)
Butyrophenone derivatives	2 (5.7%)
Diazepines, oxazepines, thiazepines and oxepines	1 (2.9%)
Other antipsychotics	3 (8.6%)
Benzodiazepine derivatives	20 (57.1%)
Benzodiazepine- related drugs	1 (2.9%)
Substituted alkylamines (antihistamines for systemic use)	1 (2.9%)

medication for the condition of periodic paralysis. Two patients (5.7%) had a surgical history in the past but were not currently taking medication. The demographic and key baseline characteristics, including baseline measurements of the PANSS scores, CGI scores and EPS symptom scores, of the study subjects are summarized in Table 3.

A total of 30 (85.7%) patients received medication prior to the study. A majority of them (n=29, 82.9%) were on psycholeptic treatment. The most common psycholeptics used were benzodiazepine derivatives

Table 5: Primary and secondary efficacy variables - Changes from baseline at Day 21*

Variables	Mean±SD	95% Confidence interval	T-test
Primary efficacy			
PANSS-EC	-7.5±4	-8.842,-6.072	p<0.001
Secondary efficacy			
PANSS-P	-9.3±5.5	-11.192,-7.379	p<0.001
PANSS-N	-5.7±4.9	-7.336,-3.979	p<0.001
PANSS-G	-15.2±10.5	-18.853,-11.605	p<0.001
PANSS total	-33.2±21.3	-40.502,-25.841	p<0.001
Aggression & hostility cluster score	-5.6±3.3	-6.705,-4.437	p<0.001
Depression cluster score	-3.1±2.5	-3.957,-2.214	p<0.001
CGI-S	-1.2 ±0.9	-1.541,-0.916	p<0.001
	Baseline score±SD	**Day 21 score±SD**	**Paired T-test**
CGI-I	3.9±0.4	2.4±1.2¥	p<0.001

(n=18, 51.4%), followed by other antipsychotics (n=16, 45.7%) and butyrophenone derivatives (n=12, 34.3%).

A total of 22 (62.9%) patients received concomitant therapies during the study. A majority of them (n=21, 60.0%) were given concomitant psycholeptic treatment. The most common class of psycholeptic used was benzodiazepine derivatives (n=20, 57.1%). All concomitant medications patients received during the study are shown in Table 4.

Table 6: Number (%) of Patients reporting Adverse Events – Safety Population

	All Subjects (N=35)
Study exposure, mean (days)	16.7 (9,21)
Number of patients experienced AE, n (%)	3 (8.6%)
ADVERSE EVENT, n (%)	**5 (14.3%)**
Dry mouth[1]	1 (2.9%)
Sedation[1]	1 (2.9%)
Vomiting[2]	1 (2.9%)
Hospitalization	1 (2.9%)
Gastritis[2]	1 (2.9%)
MAX INTENSITY, n (%)	**5 (14.3%)**
2 - Moderate: Discomfort sufficient to cause interference with normal activities	3 (8.6%)
1 - Mild: Awareness of sign or symptom, but easily tolerated	2 (5.7%)

[1]Dry mouth and sedation occurring in one patient.
[2]Vomiting and gastritis occurring in one patient.

Efficacy

Efficacy analyses were based on the ITT population.

Primary Efficacy Variable

The primary variable was the change from baseline in PANSS-EC score to the end of treatment (day 21) where baseline was defined as the day the subject first received study medication (day 1, Visit 2). Results showed that there was a steady decline in the mean PANSS-EC score over the course of the study, with a mean reduction of 7.5±4 points from baseline at day 21 (Table 4), thus indicating a statistically significant improvement (p<0.001) in patients after receiving quetiapine fumarate XR.

Secondary Efficacy Variables

Results showed that there were reductions across the various PANSS subscales scores over the 3-week study period, indicating treatment with quetiapine fumarate XR led to improvement in the overall clinical status in patients with acute schizophrenia. Changes from baseline at each visit were statistically significant (p<0.001) for all the PANSS subscale variables and were evident from Visit 3 onwards up till the end of the study (Visit 7).

Table 5 shows the mean reduction from baseline for both primary and secondary efficacy variables.

Safety and Tolerability

Safety evaluation was performed in the safety population.

Adverse Events

Quetiapine fumarate XR was generally well tolerated during the study. Adverse events were reported in 3 (8.6%) patients in the safety population during the study period, after 16 days of study exposure. All AEs were mild to moderate in intensity (Table 6).

The reported AEs were dry mouth, sedation, vomiting, gastritis and hospitalization. Hospitalization due to relapse of psychosis occurred in one patient after 9 days of study exposure, and was considered as a serious AE that led to the patient's early withdrawal from the treatment. Even though the patient was compliant with the study drug, the reason for the relapse was attributed to unresolved psychosocial stressors to which that the particular subject was exposed. Only dry mouth and sedation were judged by the investigators to be treatment-related. No deaths occurred during the study period.

Laboratory Evaluations and Vital Signs

The laboratory evaluations included hematological parameters (i.e. red blood cells, white blood cells, hemoglobin, platelets, hematocrit and neutrophils) and clinical chemistry parameters (i.e. HbA1c, glucose, prolactin, triglycerides, cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol). Vital signs measured were weight, pulse, systolic blood pressure and diastolic blood pressure; ECGs were examined.

Overall, there were no individual clinically important abnormalities observed in the various safety evaluation parameters among the patients. Mean changes in the laboratory parameters at the end of the treatment were small and statistically and clinically insignificant, except for the levels of prolactin (-444.4±835.7 uIU/ml; p=0.005), triglycerides (0.4±0.9 mmol/L, p=0.008) and cholesterol (0.3±0.8 mmol/L; p=0.03). These changes were not considered by the investigators to be clinically important.

There were no significant changes in the hematology parameters, ECG and vital signs. There was, however, a small but statistically significant 1.1±1.8 kg increase in body weight observed from baseline to day 21. There were no significant changes observed in EPS over time.

DISCUSSION

The aim of this 3-week, open label, single-arm study was to evaluate the efficacy in agitation and safety of quetiapine fumarate XR monotherapy, given once-daily, in treating patients with acute schizophrenia. Results from this study have indicated that once-daily quetiapine fumarate XR (400 mg, 600 mg, and 800 mg) was effective for the management of agitation in acute schizophrenia.

In our study, the inclusion criteria for PANSS-EC was a score of >14. The mean baseline PANSS-EC score was 17.8, which was higher than that set for inclusion, indicating that the patients enrolled into this study had high scores of agitation at baseline. The reduction of 7.5 points in PANSS-EC score from baseline in this study was statistically significant, suggesting that the once-daily quetiapine fumarate XR used was effective in treating agitation in schizophrenia.

Our result is in line with that reported for the benefits of quetiapine in a post-hoc analysis by Chengappa et al. (2003) (14). Their study has suggested that quetiapine treatment had effects on agitation, as assessed by the Brief Psychiatric Rating Scale, that were independent of improvements in the overall psychology.

The CGI inclusion criteria for this study was set at >4, meaning that patients in our study were all at least moderately ill. A total PANSS score of 110.8 at baseline also showed that they had high scores for overall psychotic symptoms. The efficacy of once-daily quetiapine fumarate XR in this patient population was supported by the statistically significant improvement observed in the secondary efficacy variables, i.e. PANSS-P, PANSS-N and PANSS-G subscales, total PANSS, as well as PANSS aggression, hostility and depression clusters. Significant improvement was also noted in the CGI-I and CGI-S scales. These results suggest that

quetiapine fumarate XR was effective against a broad range of symptoms in schizophrenia.

Quetiapine fumarate XR was generally well tolerated, in agreement with the good tolerability profile reported in other studies (2,16). The incidence of AEs and serious AEs was low, with most of the incidences mild to moderate in intensity. Only dry mouth and sedation were considered to be treatment related. The effect of treatment on EPS, prolactin, glucose parameters and lipids is consistent with the results of randomized, placebo-controlled studies of quetiapine IR.

No incidence of EPS was reported during the study; most patients showed no change in SAS and BARS scores. This was consistent with the known tolerability profile of quetiapine IR. The study withdrawal rate due to AE was low—one patient discontinued treatment due to hospitalization for relapse of psychosis, but this was not considered to be treatment-related. This indicated that the rapid initiation of quetiapine fumarate XR, reaching 600 mg by day 2 and possibly 800 mg by day 3, in this patient population was both efficacious and generally well tolerated.

The use of concomitant medications is standard in clinical practice for patients with severe agitation. Our study tried to mimic normal clinical practice by allowing the usage of benzodiazepines. Furthermore, the patients that were recruited for the study had moderate to severe illness at baseline (PANSS total score of 110 and CGI score of 4.6). However, the usage of benzodiazepines might have an impact on the results, and this was one of the limitations of this study.

As illustrated in Table 4, 60% of the subjects received psycholeptics as concomitant medication. These included the antipsychotics they received before rapid titration of quetiapine was commenced. This was not a violation of the protocol since they received these medications prior to day 1, but after informed consent was obtained. Hence, they were recorded as 'concomitant medications'. Similarly, it was noted that butyrophenone derivatives were received by 2 subjects, where both of them received an injection of intramuscular haloperidol, to control agitation, prior to day 1.

The design of our study might also be limited by the absence of a control arm, the small sample size and the short study duration. These limitations may have introduced bias associated with the non-comparative design and not provided information on the magnitude of any non-treatment-related response to the intervention. However, the efficacy of quetiapine XR has been earlier established in a placebo-controlled study (2) and an open-label study (16) and our study further supported the reported favorable efficacy and safety profile of quetiapine XR in the treatment of acute schizophrenia.

Non-compliance is a major issue in patients with schizophrenia, and has been associated with treatment failure, relapse, and serious consequences, such as hospitalization or suicide (5-7). Side effects of treatment and the complexity of dosing regimens are some of the factors that can affect patients' adherence to a treatment (17,19), thus providing a strong rationale for reduced administration frequency and a simplified dose-escalation regimen.

The simplified dose-escalation regimen used in this study allowed physicians to administer quetiapine once-daily to reach an effective dose earlier, since patients with acute schizophrenia require a more rapid resolution of their symptoms. The good tolerability profile of quetiapine fumarate XR made it a more acceptable treatment choice for patients, encouraging patient adherence, a significant factor in improving long-term prognosis.

CONCLUSION

The efficacy of quetiapine fumarate XR in reducing agitation as well as a broad range of symptom domains in acute schizophrenia was evident in this study, as reflected in the primary and secondary efficacy variables measured. The drug was generally well tolerated using rapid dose escalation (300 mg on day 1, 600 mg on day 2, and 400-800 mg on day 3) in patients with acute schizophrenia treated for a period of up to 3 weeks. To better demonstrate the efficacy of quetiapine fumarate XR for this indication, further research should be considered to enhance our findings.

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