Preliminary Report

An Open-Label Study of Quetiapine for Delirium

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Objective: *To evaluate the effects of quetiapine treatment in patients with delirium.*
Material and Method: *All patients with delirium were assessed. The diagnosis of delirium was confirmed by using the Confusion Assessment Method (CAM). Quetiapine at the dose between 25 and 100 mg /day was given for 7 days. The efficacy of quetiapine on delirium was evaluated by using the Delirium Rating Scale (DRS) and the Clinical Global Impression-Severity scale (CGI-S). The extrapyramidal side effects were assessed by using the Modified (9-item) Simpson-Angus Scale (MSAS).*
Results: *Twenty-two patients had delirium. Seventeen (10 males and 7 females) subjects with a mean age (SD) of 55.6 (18.6) years were included in the present study. Means (SDs) dose and duration (SD) of quetiapine treatment were 45.7 (28.7) mg/day and 6.5 (2.0) days, respectively. The DRS and CGI-S scores of days 2-7 were significantly lower than those of day 0 ($p < 0.001$) for all comparisons). Only two subjects were shown to have mild tremor.*
Conclusion: *Quetiapine within the range of 25-100 mg/day improves delirious condition within 24 hours of treatment. It is well-tolerated and has a very low propensity to induce extrapyramidal side effects. Further randomized, placebo-controlled trials are warranted.*

Keywords: *Delirium, Quetiapine, Extrapyramidal side effects, Treatment outcome*

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Delirium is a common neuropsychiatric syndrome with a prevalence of 10% to 20% among hospitalized patients in medical and surgical wards[1]. Its symptoms include disturbances of consciousness, attention, cognition, and perception. This condition develops over a short period of time and tends to fluctuate during the course of the day, and it is caused by one or more physical conditions[2]. Delirium is traditionally considered as a transient syndrome that ends in recovery after 10-12 days[3]. Disorganized behavior in delirious patients, such as aggression, agitation, restlessness, insomnia, liability of mood, and delusion usually disturb treatment settings and may be dangerous to patients and others. In addition, hospital mortality estimates range from 10% to 65%[4].

Management of delirium includes early detection, environmental manipulation, and treatment for the underlying physical conditions contributing to delirium. However, psychopharmacological treatment is a major component of all interventions for moderate to severe cases. As a condition that impairs global cerebral function and decreases function of the cholinergic system[5], any medications with considerable anticholinergic effect, such as low-potency, conventional antipsychotics, should be avoided[6]. Due to their less anticholinergic effects, high-potency, conventional antipsychotics (e.g., haloperidol) have been used as first-line treatment for the neuropsychiatric symptoms of delirium[7]. However, these medications are also frequently associated with extrapyramidal side effects (EPS).

Atypical antipsychotic medications, which are less likely to induce EPS, may be an alternative to high-potency conventional antipsychotics for the treatment of delirium. Recently, several lines of evidence have shown that risperidone and olanzapine are effective and safe for patients with delirium[8].

In schizophrenic patients, quetiapine is an atypical antipsychotic with a very low propensity to induce EPS[9]. Due to its relatively low affinity to

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muscarinic (M1) receptors[10], quetiapine may be less likely to worsen the delirious condition. Due to the above-mentioned safety profile, a number of quetiapine studies have been carried out in patients with delirium. Although most study findings suggest that quetiapine is effective and safe in this population, none of the studies used an objective measure to examine antipsychotic-induced EPS, which may be the main benefit of this medication.

The present study aimed to examine the therapeutic effects and adverse events, in particular EPS, of quetiapine in patients with delirium.

Material and Method

This 7-day prospective study of quetiapine was carried out in physically ill patients admitted to Chiang Mai University Hospital, a tertiary care setting in northern Thailand. The research proposal was approved by the Ethics Committee of the Faculty of Medicine, Chiang Mai University. Prior to the study participation, written informed consent was obtained from a 1st degree relative of each subject after the study details had been fully explained.

Subjects

All physically ill in-patients, whose primary physicians consulted the psychiatrists for assessing and treating delirium, were considered as potential subjects. The inclusion criteria for the subjects were: i) physically ill patients meeting the DSM-IV diagnostic criteria of delirium, due to a medical condition, or delirium due to multiple etiologies and ii) male or female patients aged 18 years old or more. The diagnosis of delirium was reconfirmed by use of the Confusion Assessment Method (CAM)[11]. The exclusion criteria were: i) delirium tremens, ii) history of psychotic disorders, iii) being on narcotic medications, and iv) pregnant and nursing women. To ensure that the process of consent obtained would not be a cause of treatment delay, the authors also excluded patients who were not accompanied by a 1st degree relative during the first psychiatric assessment.

Procedures

The patients were given quetiapine at doses between 25 and 100 mg/day. Patients received quetiapine once (bedtime) or twice a day (morning and bedtime). Quetiapine dosage was assessed after the present study had ended, the primary physician made a decision about the appropriate antipsychotic to use for each patient. During the present study, lorazepam at the maximum dose of 2 mg/day was an additional medication that could be used if needed. The patients were not allowed to receive other psychotropic medications, including antidepressants, mood stabilizers, other anxiolytics/hypnotics, or other antipsychotic medications.

Clinical measures and safety assessment

The authors assessed the severity of delirium by using the Delirium Rating Scale (DRS), which has a maximum score of 32 points[12] and the Clinical Global Impression-Severity scale (CGI-S) which comprises 7 score[13]. Clinically significant improvement was defined as a DRS score reduction of 50% or more. The authors assessed the EPS by using the Modified (9-item) Simpson-Angus Scale (MSAS)[14]. The MSAS is a 5-point scale of 9 items (arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head dropping, glabellar tap, tremor, and salivation). Score 0 = normal, 1 = slightly, 2 = moderate, 3 = marked, 4 = extreme, and 9 = not ratable, which has a maximum score of 81 points. The item of gait stability was excluded because the patients might not cooperate properly or have injuries during the assessment. All measures were applied at baseline (day 0, prior to the commencement of quetiapine treatment) and daily throughout the present study (days 1-7).The higher the score, the greater the functional impairment.

Statistical analysis

Data were expressed as number, present, mean, and standard deviation (SD). The DRS and CGI-S scores measured on day 0 were compared with those assessed on days 1-7 by the use of repeated measurement ANOVA of. All p-values of less than.05 were considered as significant differences. The data analyses were performed on an intention-to-treatment basis by the use of last-observation-carried-forward analysis. A p-value of less than 0.05 was considered statistical significance.

Results

From June to December 2005, 22 delirious patients were consulted for psychiatric assessment and treatment. Of those, five did not meet the inclusion/exclusion criteria or gave written informed consent. Seventeen patients (10 males and 7 females) with DSM-IV delirium participated in the present study. None of them had a history of psychiatric illness. Their mean (SD) age was 55.6 (18.6) years old. Mean (SD) duration of delirium before treatment were 7.9 (7.2) days. Most subjects had varies diagnoses and multiple etiologies

of delirium. One patient had about six (1.4) causes of delirium. (Table 1). No patient received lorazepam (the rescue medication). The mean (SD) of quetiapine doses was 45.7 (28.7) mg/day.

Efficacy and adverse events

Five patients who had much improvement were discharged before the present study ended. However, these patients accepted to continue the same dosage of quetiapine at home until 8 days. Two patients discontinued quetiapine within 3 and 6 days of treatment respectively. One subject (multiple myeloma) refused to take medication after the 6th day of treatment. The authors discontinued quetiapine in one patient with dilated cardiomyopathy with sepsis due to hypotension.

Of 17 subjects participating in the present study, 15 (88.2%) had clinically significant improvement ($\geq$ 50% reduction of the DRS scores). The mean (SD) days of treatment until improvement was 3.9 (2.1). A mean (SD) DRS score of 24.5 (3.2) at baseline (day 0) was decreased to a mean (SD) of 9.6 (6.0) on day 7. All DRS scores obtained on days 1-7 were significantly lower than those at day 0 (Table 2). A mean (SD) CGI-S score of 4.9 (0.9) at baseline (day 0) was lowered to a mean (SD) of 1.6 (1.3) on day 7. All CGI-S score assessed at days 1-7 were significantly lower than those of day 0 (Table 2). DRS and CGI-S scores were decreased by time (Fig. 1).

Of all subjects, only two had MSAS scores of 1 on the item of tremor. The first one was a 33-year-old woman with seizures, due to neuropsychiatric complications of systemic lupus erythematosus. Valproate-induced tremor was suspected because her tremor was found on day 0 (prior to the start of quetiapine) and subsided on day 6 after the discontinuation of valproate. The second participant was a 68 years old man with dilated cardiomyopathy who also had multiples organ failure, sepsis, and cerebral infarct. Right hand tremor of this patient was increased from 0 to 1 during the present study. Other adverse effects found during treatment are shown in Table 3.

Table 1. Patients details characteristics

Characteristic	
Mean age (years) (SD)	55.6 (18.6)
Gender	
Male	10 (58.8%)
Female	7 (41.2%)
Physical disease (n = 17)	
Dilated cardiomyopathy	2 (11.8%)
SLE	3 (17.6%)
Multiple sclerosis	1 (5.9%)
Acquired immune deficiency syndrome	1 (5.9%)
Carcinoma	4 (23.5%)
Fracture or head injury	5 (29.4%)
DKA	1 (5.9%)
Causes of delirium (n = 17)	
Infection	11 (64.7%)
Acute metabolic	12 (70.6%)
Trauma*	7 (41.1%)
CNS pathology	14 (82.4%)
Hypoxia	11 (64.7%)
Malnutrition	11 (64.7%)
Toxin or drug intoxication	12 (70.6%)
Others	8 (47.1%)
Dosages	
Starting dose (mg/day)	36.8 (24.8)
Mean dose (mg/day) (n = 17)	45.7 (28.7)
Mean dose daytime (n = 10)	15.0 (5.5)
Mean dose bedtime (n = 17)	35.0 (21.9)
Mean dose prn agitation (n = 9)	6.6 (4.3)

Data are n (%) or mean (SD)

* Fracture femur (n = 1), subtrochanteric fracture (n = 1), intertrochanteric fracture (n = 1), postoperative trauma (n = 1), C-spine injury (n = 1) and closed head injury (n = 2)

Discussion

The present study findings showed that quetiapine at a mean dose of 45.7 mg/day may rapidly decrease neuropsychiatric symptoms of delirium. Quetiapine treatment is well-tolerated by patients with delirium. By the use of a standard measure, the comprehensive physical examination for EPS could find only mild tremor in two patients.

Table 2. Delirium rating scales (DRS)

Scale	Baseline (d0)	d1	d2	d3	d4	d5	d6	d7
DRS	24.5 (3.2)	18.2 (5.7)*	14.6(6.3)**	12.6 (6.5)**	11.7 (7.0)**	10.7 (6.3)**	10.5 (6.0)**	9.6 (6.0)**
CGI-S	4.9 (0.9)	2.9 (0.8)*	2.6 (0.9)**	2.2 (1.1)**	2.2 (1.7) **	1.9 (1.4)**	1.9 (1.3)**	1.6 (1.3)**

Data are expressed as mean (SD)

* $p < .01$, ** $p < .001$ based on within-treatment changes

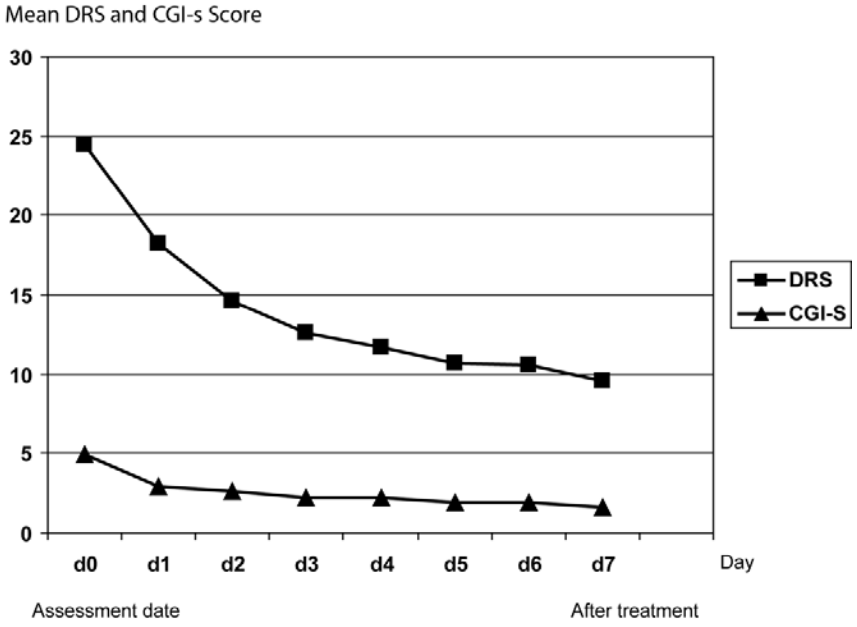

Fig. 1 Mean of DRS and CGI-S scores from day 0 to day 7 in 17 patients with DSM-IV delirium (n = 17)
Abbreviation: DRS = Delirium rating scale; CGI-S = Clinical global impression-severity scale

Table 3. Adverse effects of quetiapine

Adverse effects	n = 17
Extrapyramidal side effect	
Tremor	2 (11.8)
Other adverse effect[+]	
Hypotension	2 (11.8)
Daytime sleepiness	13 (76.5)
Nightmare	3 (17.6)
Dry mouth	2 (11.8)
Nausea	1 (5.9)

Data are n (%)
[+] One case with more than one adverse effect

The results of the present study confirm the previous findings that quetiapine is effective and safe for individuals with delirium. The mean daily dose of quetiapine in the present study (45.7 mg/day) was relatively lower than those in previous ones (93.8-211.4 mg/day)[15-18]. It is possible that the metabolism of Thai patients was slower than those of Caucasian[15] and Asian subjects[16-18]. The correlation of the mean daily dose of quetiapine and the change in the DRS score was not significant in our study ($p = 0.667$), which is similar to that of previous studies ($p = 0.618$ and $p = 0.336$)[15,17], indicating that the effect of quetiapine for treating delirium is not associated with a dose increment.

To the authors' knowledge, this is the first study of quetiapine to use a low dose of medication in patients with delirium. However, there were some limitations. The open-label study design may be prone to bias. Because delirium is self-limited in most patients, self-improvement cannot be ruled out. The small sample size was also another important limitation.

In conclusion, quetiapine treatment may rapidly decrease neuropsychiatric symptoms of delirium. It is well tolerated and has a very low propensity to induce EPS in patients with delirium. Further randomized, placebo-controlled trials with large sample sizes are warranted.

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การศึกษาแบบเปิดฉลากของ quetiapine สำหรับภาวะเพ้อ

เบญจลักษณ์ มณีทอน, ณรงค์ มณีทอน, มานิต ศรีสุรภานนท์

วัตถุประสงค์: *เพื่อประเมินประสิทธิภาพของยาคิวไทอาปีน ในการรักษาผู้ป่วยที่มีภาวะเพ้อ*

วัสดุและวิธีการ: *ทำการศึกษาในผู้ป่วยที่มีภาวะเพ้อ ตามเกณฑ์วินิจฉัยแบบ diagnostic และ statistical manual of mental disorders, fourth edition diagnosis (DSM-IV) โดยยืนยันการวินิจฉัยด้วยเครื่องมือ the confusion assessment method (CAM) ผู้รายงานได้ให้ยาคิวไทอาปีนขนาด 25-100 มิลลิกรัมต่อวัน เป็นเวลาประมาณ 7 วัน แก่ผู้ป่วยที่มีภาวะเพ้อและประเมินประสิทธิภาพในการรักษาด้วยเครื่องมือ the delirium rating scale (DRS) และ the clinical global impression-severity scale (CGI-S) นอกจากนี้ยังประเมินผลข้างเคียงชนิด extrapyramidal ด้วยเครื่องมือ the modified (9-item) Simpson-Angus scale (MSAS)*

ผลการศึกษา: *มีผู้ป่วยจำนวน 22 ราย ที่ได้รับการวินิจฉัยว่ามีภาวะเพ้อ โดยมีผู้ป่วยจำนวน 17 รายเข้าร่วมการศึกษา เป็นเพศชาย 10 รายและเพศหญิง 7 ราย มีอายุเฉลี่ย (ค่าเบี่ยงเบนมาตรฐาน) เท่ากับ 55.6 (18.6) ปี ผู้ป่วยกลุ่มนี้ได้รับยาเฉลี่ย (ค่าเบี่ยงเบนมาตรฐาน) เท่ากับ 47.0 (27.3) มิลลิกรัมต่อวัน เป็นเวลาเฉลี่ย (ค่าเบี่ยงเบนมาตรฐาน) เท่ากับ 6.5 (2.0) วัน พบว่าผู้ป่วยมีการตอบสนองต่อยาดี โดยคะแนน DRS และ CGI-S มีค่าลดลงเมื่อเทียบกับคะแนนก่อนการรักษาในวันที่ 2 หลังการรักษาเป็นต้นไป อย่างมีนัยสำคัญ ($p < 0.001$) นอกจากนี้พบว่าผู้ป่วย 2 ราย มีอาการมือสั่นเพียงเล็กน้อย*

สรุป: *ยาคิวไทอาปีนขนาด 25-100 มิลลิกรัมต่อวัน สามารถช่วยรักษาภาวะเพ้อได้ดีภายในเวลา 24 ชั่วโมง หลังเริ่มรักษา ทั้งยังทำให้เกิดผลข้างเคียงในกลุ่ม extrapyramidal ค่อนข้างน้อย อย่างไรก็ตามควรมีการศึกษาเพิ่มเติมโดยใช้กลุ่มควบคุมต่อไป*