Switching to quetiapine in patients with acute mania who were intolerant to risperidone

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This study evaluated the overall efficacy and tolerability of quetiapine in the treatment of inpatients with acute mania who are intolerant to risperidone in combination with a mood stabilizer. Eighteen patients completed this 3-week trial. The efficacy and tolerability was assessed upon admission, at baseline, and 1 and 3 weeks later. The Young mania rating scale (YMRS) and clinical global impression-severity (CGI-s) scores from the baseline to the endpoint, decreased by 39.8% and 40.0%, respectively. Fifteen (78.9%) and 18 (94.7%) patients exhibited at least a 50% improvement in the YMRS and CGI-s scores by the end of the trial. Measurements taken through the Barnes akathisia rating scale (BARS), the Simpson-Angus rating scale (SARS) and the drug attitude inventory shortened version-10 (DAI-10) also showed significant improvement.

This study suggests that quetiapine may hold promise as an alternative regimen that does not worsen the psychopathology, particularly for those vulnerable to the side effects of drugs, including atypical agents such as risperidone, in naturalistic treatment settings. Copyright © 2004 John Wiley & Sons, Ltd.

KEY WORDS — quetiapine; risperidone; switch; mania

INTRODUCTION

Antipsychotics, such as the typical and atypical agents, are widely prescribed to patients with bipolar disorder, particularly to control the manic symptoms in acute episodes (Brambilla *et al.*, 2003).

Risperidone, an atypical antipsychotic, has proven efficacy as a monotherapy or in combination with mood stabilizers (MS) in controlling acute symptoms in patients with acute mania as evidenced by the results of a large number of uncontrolled (Jacobsen, 1995; Sajatovic *et al.*, 1996; Licht *et al.*, 2001; Vieta *et al.*, 2002a[Q2]; Yatham *et al.*, 2003a) and controlled clinical trials (Sachs *et al.*, 2002; Segal *et al.*, 1998; Yatham *et al.*, 2003b). Brambilla *et al.* (2003) in their review conclude that risperidone showed a 75% anti-

manic response with a mean dose of 3.4 mg/day in uncontrolled trials and 83% with a mean dose of 5.4 mg/day in controlled trials. These findings suggest that risperidone is effective in controlling manic symptoms in acute mania patients.

However, although some studies reported no significant association between risperidone and the extrapyramidal symptoms (EPS) (Sachs *et al.*, 2002; Vieta *et al.*, 2002a), EPS are frequently observed in clinical practice. Licht *et al.* (2001) reported that 64.3% of patients experienced EPS at least once, while Sajatovic *et al.* (1996) reported that 33.3% of patients discontinued risperidone as a result of EPS. Similar findings have been reported in controlled trials. Yatham *et al.* (2003b) reported that 16 (23.2%) of 69 patients suffered EPS, and showed that there were statistical differences compared with a placebo group. The EPS of both the risperidone- and haloperidol-treated group increased during the 4 weeks of a double blind trial with no significant difference (Segal *et al.*, 1998) between the two groups. Although the inconsistent findings of the incidence of EPS from risperidone use in patients with acute

mania may be due to differences in the study methodologies, such as a different sample size and the characteristics of the subjects, it can be assumed that patients with acute mania may be vulnerable to antipsychotic induced-EPS (Licht *et al.*, 2001). Therefore, the individual susceptibility should be considered when commencing an antipsychotic treatment for manic patients (Lerer *et al.*, 2002). Moreover, although there is continuing debate about the long term use of antipsychotic agents for bipolar patients, the long-term adjunctive use of antipsychotics in bipolar patients is common and is widely accepted by clinicians. A combination of antipsychotics and MS may also increase the risk of movement disorders (Brambilla *et al.*, 2003).

Therefore, this study assessed the efficacy and tolerability of a non-tapered switch to quetiapine in a naturalistic setting in patients with acute mania who were intolerant to risperidone in combination with MS.

METHODS

This study was a prospective and non-comparative trial conducted in a naturalistic setting, at Kangnam St Mary's Hospital, Seoul, Korea.

Subjects

The eligibility and exclusion criteria for this study were as follows: (1) inpatients aged 18–65 years, with a diagnosis of bipolar I disorder—acute manic episode, with or without psychotic features according to the DSM-IV criteria (American Psychiatric Association, 1994), which was diagnosed by the consensus of two board-certified psychiatrists (C.U.P.; I.H.P.) based on the clinical assessment and the administration of the MINI (Sheehan *et al.*, 1998); (2) patients were treated with risperidone exclusively from the time of admission and maintained this medication until they switched to quetiapine (baseline day), as a combination agent with one MS; (3) the patients must be intolerant of risperidone, with symptoms such as akathisia and dystonia (intolerance was defined based on the patients' subjective complaint and clinicians' observation as well as assessments using the Barnes akathisia rating scale (BARS, Barnes, 1989) and Simpson-Angus rating scale (SARS, Simpson and Angus, 1970); (4) patients should not have participated in any other clinical trials within 6 months before being enrolled in this study; (5) patients should provide written informed consent; (6) patients having other major psychiatric comorbidities other than that mentioned in item (1) were excluded; (7) patients with

organic mental disorders and serious medical illness, such as arrythmia, or patients with QTc > 500 msec were excluded; (8) patients with a history of quetiapine and risperidone sensitivity were excluded; (9) patients on MS with two or more agents were also excluded. The patients were recruited between June 2002 and January 2003. Of the 21 patients who met the criteria, 19 gave written informed consent.

Medication

The dose schedules of MS and risperidone were made according to the patients' response and the clinicians' preference from the time of admission. When the patients became intolerant to risperidone, as defined above, they were switched to quetiapine with a flexible dose schedule according to the clinicians' experience and preferences based on the clinical response and tolerability throughout the study period.

Only MS, antiparkinsonian drugs and benzodiazepines were allowed. Benzodiazepines were maintained at the same dose from the time of the switch throughout the study period.

Assessment of efficacy and tolerability

In order to evaluate the efficacy, the Young mania rating scale (Young *et al.*, 1978, YMRS) and clinical global impression scale-severity (CGI-s, Guy, 1976) scores were measured upon admission, at baseline, and after 1 and 3 weeks. The primary measurement of the efficacy was the mean change in the YMRS from the baseline to the endpoint with the last observation carried forward (LOCF).

In order to assess the tolerability, the BARS, the SARS and the drug attitude inventory short version-10 (DAI-10, Hogan *et al.*, 1983) scores were administered at each period. All adverse events were collected. A complete blood count, blood chemistry, urinalysis and electrocardiogram (ECG) were also assessed at the time of admission, the baseline and the endpoint.

Data analysis

Statistical analysis was performed using Windows SPSS 10.0 (SPSS Inc., Chicago, USA). All the data were analysed in the intent-to-treat (ITT) sample using the last observation carried forward (LOCF) method. Repeated measures analysis of the variance (ANOVA), a Mann–Whitney test, a Wilcoxon signed rank test and the descriptive statistics were used according to the characteristics of the data, and comparisons made where appropriate. A two tailed p value < 0.05 was considered significant.

RESULTS

Characteristics of patients

The detailed characteristics of the patients are shown in Table 1. Of the 19 patients, 11 (57.9%) were male and 8 (42.1%) were female. Four (21.1%) patients had the first onset, i.e. they were drug naïve, and four patients (21.1%) exhibited psychotic features. One patient (male) discontinued the trial due to excessive sedation, and 18 patients completed this trial.

Eight patients had been prescribed risperidone prior to admission, but it was only taken intermittently due to poor compliance. Two had been on risperidone with a dose of 2 mg/day before admission. Five patients had taken chlorpromazine prior to admission. The mean risperidone dose was 2.0 ($\pm$0.7) mg/day at the time of admission and 3.8 ($\pm$0.9) mg/day at baseline.

As for MSs, they were not changed to a different class at the time of admission and were maintained until the endpoint with the exception of flexible dosing. The MSs were lithium, valproate and carbamazepine in eight (42.1%), nine (47.4%) and two (10.5%) subjects, respectively, at the baseline. Twelve patients (63.2%) were on benzodiazepine at the baseline. All the patients were given benztropine as an antiparkinsonian drug at baseline.

Outcome measures

The YMRS and CGI-s scores decreased significantly from the time of admission to the endpoint as shown in Figure 1. YMRS and CGI-s scores also decreased significantly from admission to the baseline (termination of risperidone and commencement of quetiapine), by 28.7% (8.5 $\pm$ 3.4) and 29.4% (1.5 $\pm$ 0.8), respectively ($p < 0.001$; $p < 0.001$). The YMRS and CGI-s scores from the baseline to the endpoint decreased

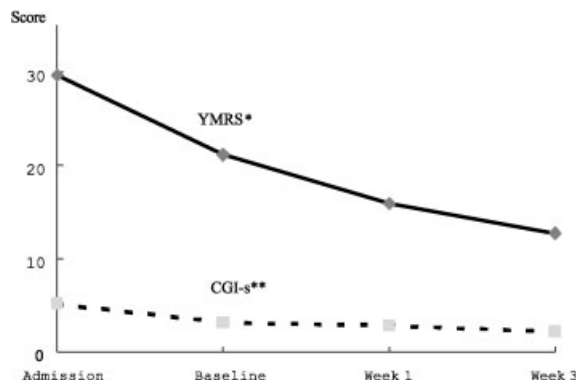

Figure 1. Changes in the outcome scales throughout the study. YMRS, Young mania rating scale; CGI-s, clinical global impression-severity; *,**Admission to endpoint: $F = 219.7, p < 0.001$, and $F = 175.4, p < 0.001$, repeated measure ANOVA

by 39.8% (8.4 $\pm$ 2.1) and 40.0% (1.4 $\pm$ 0.5), respectively ($p < 0.001$; $p < 0.001$. Compared with the scores upon admission, 15 (78.9%) and 18 (94.7%) patients showed at least a 50% improvement on the YMRS and CGI-s scores, respectively, at the endpoint. Compared with the baseline, 4 (21.1%) and 7 (36.8%) patients showed at least a 50% improvement on the YMRS and CGI-s scores, respectively, at the endpoint. In the subgroup analyses, the YMRS and CGI-s scores from the baseline to the endpoint significantly decreased by 38.2% (8.6 $\pm$ 2.8, $p < 0.001$) and 42.1% (1.6 $\pm$ 0.5, $p < 0.001$), respectively, in the lithium subgroup ($n = 8$). In the valproate subgroup, the YMRS and CGI-s scores from the baseline to the endpoint decreased by 40.0% (8.0 $\pm$ 2.0, $p < 0.001$) and 36.4% (1.2 $\pm$ 0.4, $p < 0.001$), respectively, showing no significant differences between the two groups (YMRS, $p = 0.582$; CGI-s, $p = 0.108$).

Tolerability and side effects

The SARS and BARS scores at the time of the baseline were significantly higher than at admission, by a mean of 1.8 $\pm$ 0.8 ($p < 0.001$) and 1.3 $\pm$ 0.7 ($p < 0.001$), respectively. The mean DAI-10 score at baseline was significantly different compared with that upon admission (-0.4 ± 1.4 vs -1.7 ± 0.7, $p = 0.003$).

The SARS and BARS scores improved significantly at the endpoint compared with the base line, by a mean change of 75% (1.8 $\pm$ 0.9, $p < 0.001$) and 77.8% (1.4 $\pm$ 0.8, $p < 0.001$), respectively. The DAI-10 scores also changed to a positive response with statistical significance from the baseline to the endpoint (-1.7 ± 0.7 vs 0.8 ± 0.9, $p < 0.001$). Furthermore, the

Table 1. Clinical parameters of the patients

Parameter	Value
Age	31.1 $\pm$ 8.1
Duration of illness (year)	3.8 $\pm$ 3.6
Number of past admissions	1.6 $\pm$ 1.4
Dose of initial quetiapine (mg/day)	160.5 $\pm$ 56.7
Daily dose of quetiapine throughout the study (mg/day)	221.1 $\pm$ 55.1
Dose of quetiapine at endpoint (mg/day)	231.6 $\pm$ 71.1
Duration on quetiapine (days)	20.4 $\pm$ 2.5
Dose of benztropine on baseline (mg/day)	1.3 $\pm$ 0.5
Duration of benztropine before baseline (days)	4.7 $\pm$ 2.1
Dose of lorazepam equivalent dose on baseline (mg/day)	1.1 $\pm$ 0.9

Values represent mean (SD).

benztropine dose decreased significantly from the baseline to the endpoint (mean change of 0.8 ± 0.6, $p < 0.001$).

The side effects observed in this study ($n = 19$) included sedation in 11 patients (57.9%), gastrointestinal irritation in eight patients (42.1%), dizziness in six patients (31.6%), headache in four patients (21.1%), a dry mouth in four patients (26.7%) and postural hypotension in two (11.1%) patients; one patient (male) discontinued the trial due to excessive somnolence. However, of the 18 subjects who completed the trial, none had clinically significant abnormalities on the laboratory findings, including ECG. The mean weight of the subjects increased significantly from the baseline to endpoint (2.4 ± 1.2 kg, $p < 0.001$).

The SARS and BARS scores improved significantly at the endpoint compared with the baseline, by a mean change of 76% ($p < 0.001$) and 93.3% ($p < 0.001$), respectively, in the lithium subgroup. In the valproate subgroup, the SARS and BARS scores had improved significantly at the endpoint compared with the baseline, by a mean change of 78.3% ($p < 0.001$) and 81.3% ($p < 0.001$), respectively. However, there were no statistical differences between the two groups (SARS, $p = 0.793$; BARS, $p = 0.916$). The final benztropine dose in the two groups was similar ($p = 0.823$). The mean weight increase from the baseline to the endpoint in the lithium subgroup was 2.1 ± 1.3 kg, while it was 2.8 ± 1.2 kg in the valproate subgroup, but there was no significant difference ($p = 0.291$).The frequencies of the other side-effects in the two groups were similar.

DISCUSSION

The results in this study are in line with those of open or controlled studies regarding the efficacy and safety of quetiapine for treating patients with bipolar disorder (Sajatovic *et al.* 2001; Brown *et al.*, 2002; Delbello *et al.*, 2002; Vieta *et al.*, 2002b). Recent reports have suggested that quetiapine might be beneficial in treating patients with mania based on the data of uncontrolled studies, indicating an antimanic response of 67% at a mean dose of 217 mg/day (Brambilla *et al.*, 2003). The mean daily dose of quetiapine in this trial (221.1 mg) was similar to that used in other studies (Brambilla *et al.*, 2003). The most frequent side effect was sedation and others were not different from those of other studies (Sajatovic *et al.* 2001; Brown *et al.*, 2002; Delbello *et al.*, 2002; Vieta *et al.*, 2002b). Consistent with our hypothesis, quetiapine led to a significant improvement in the manic

symptoms as well as the EPS, as indicated by the significant reductions in the YMRS, CGI, SARS and BARS, without causing any significant laboratory abnormalities or other side effects. Only one patient discontinued the trial as a result of excessive sedation.

Interestingly, this study found that risperidone also significantly decreased the YMRS and CGI within 10 days of administration, which is consistent with the results reported in the literature (Yatham *et al.*, 2003a; Yatham *et al.*, 2003b; Sachs *et al.*, 2002; Vieta *et al.*, 2002a). A consecutive switch to quetiapine further decreased both the YMRS and CGI scores by approximately 40%. The overall changes in the YMRS and CGI scores from admission to the endpoint were comparable to other studies in terms of the efficacy of risperidone in patients suffering from mania (Yatham *et al.*, 2003a; Yatham *et al.*, 2003b; Sachs *et al.*, 2002; Vieta *et al.*, 2002a). Overall, it would appear that switching from risperidone to quetiapine, in the treatment of patients who are intolerant of the unexpected side effects such as EPS, can be an effective strategy for some patients without compromising the efficacy.

These findings will provide clinicians with promising data for the use of quetiapine as an add-on therapy in patients with bipolar disorder, although controlled trials should be conducted in order to obtain more objective data. In addition, subgroup analyses according to the combined MSs showed that there were no significant differences in the efficacy and tolerability. This is in line with other studies using risperidone as an add-on therapy (Sachs *et al.*, 2002; Yatham, 2003b), which showed no significant differences in efficacy and tolerability measures among different MS subgroup.

It should be noted that this study has several limitations. This study was an open design without a control group and the sample size was small. Power analysis of this study showed that the effect size was 0.68, which corresponds to a difference in the YMRS of approximately 3 points, with 80% power. Although naturalistic open studies make it difficult to draw a definite conclusion, it helps in collecting data on the efficacy. Most other open data reported support these results. The dosing schedule in this study was dependent on the clinicians' experience. However, the mean dose was similar to that used in previous studies, suggesting the flexible and easy implementation of quetiapine in clinical practice, particularly the switching aspect. A non-tapered switch to quetiapine may overlap with the effect of risperidone. Meanwhile, the mean initial dose of quetiapine was relatively high compared with

the conventional dosing schedule, while the exit dose was not high enough. It is believed this would be caused from the direct switch to quetiapine from the risperidone at the time of baseline. Currently, there is no proven dose titration in switching from risperidone to quetiapine, which will require further controlled studies. Concomitant drugs may confound the effect of quetiapine, although concomitant drug doses were relatively stable and no other psychotropic medication other than MSs and antiparkinsonian medication were used. It is also important to remember that quetiapine is metabolized by cytochrome (CYP) 3A4 (Prior and Baker, 2003). Carbamazepine is a known inducer of CYP 3A4. Therefore, patients on carbamazepine will require a higher dose of quetiapine. The two patients treated with carbamazepine were on a higher mean daily dose of quetiapine throughout the study (327.5 mg/day) when compared with those on lithium (201.7 mg) or valproate (233.3 mg). However, there were only two patients and the clinical data on the potential drug–drug interactions regarding CYP are lacking. Finally, the sample involved only inpatients. Therefore, this study was not fully representative of all clinical groups.

In conclusion, quetiapine was found to be an efficacious and tolerable switching option for patients with acute mania, who are vulnerable to the side-effects of risperidone. The results in this study complement previous data reported in western countries regarding the effect of quetiapine for bipolar patients.

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