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SHORT REPORT

A pilot trial of quetiapine for the treatment of patients with delirium

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Twenty-two Korean inpatients with delirium were administered prospectively a flexible dose of quetiapine. The delirium rating scale-revised-severity 98 (DRS-R-98) and clinical global impression scale-severity (CGI-s) scores were assessed at the time of pre- and post-treatment. The DRS-R-98 and CGI-s scores were significantly reduced by 57.3% and 55.1%, respectively. Quetiapine was effective and safe for the treatment of patients with delirium, and could be a useful alternative agent to classical antipsychotics in the treatment of delirium. Copyright © 2004 John Wiley & Sons, Ltd.

KEY WORDS — quetiapine; delirium; delirium rating scale-revised-98; clinical global impression scale; Korean

INTRODUCTION

Delirium is an organic neuropsychiatric syndrome that is characterized by a cognitive impairment, changed consciousness, altered perception and behavioural disturbances (Schwartz and Masand, 2002).

Typical antipsychotics have been used as the first line therapy for treating delirium. However, these are also known to cause extrapyramidal symptoms (EPS), particularly in those vulnerable patients with medicosurgically complicated conditions (Schwartz and Masand, 2002).

Atypical antipsychotics have a much lower incidence of EPS, suggesting their favourable application for treating delirium. Recently, several studies using both prospective (Horikawa *et al.*, 2003; Kim *et al.*, 2001; Breitbart *et al.*, 2002) and retrospective methods (Sipahimalani and Masand, 1998) demonstrated that risperidone and olanzapine, which have superior pharmacological profiles in lowering the EPS via a simultaneous blockade of the serotonin and dopamine receptors, could be alternative agents to typical antipsychotics in the treatment of delirium. The efficacy and safety of quetiapine for treating delirium was also examined in case reports (Al-Samarrai *et al.*, 2003; Torres *et al.*, 2001), a retrospective chart review (Schwartz and Masand, 2000) and an open trial with a small sample (Kim *et al.*, 2003). The unique pharmacological profile of quetiapine such as a relatively short half life (3–6 h) enables the drug to be discontinued if adverse effects appear, which suggests that this medication could be a promising agent in this field (Torres *et al.*, 2001).

Therefore, this study investigated the efficacy and tolerability of quetiapine as a prospective treatment for delirium using a relatively larger sample.

METHODS

Kangnam St Mary's Hospital is a 850-bed tertiary care general hospital that primarily covers the metropolitan city of Seoul with a population of approximately 9 800 000 (www.nso.go.kr/cgi-bin). Twenty-two patients were enrolled in this open label study. They were recruited from the departments of neurosurgery, orthopaedic surgery and oncology due to their

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delirious behaviour that occurred during hospitalization as a result of multiple medico-surgical conditions. The Psychiatric Consultation Service of Kangnam St Mary's Hospital—The Catholic University of Korea consisted of two board-certified psychiatrists, three psychiatric residents and one psychologist. All the patients were classified by the DSM-IV criteria for delirium (American Psychiatric Association, 1994), with a physical examination, laboratory findings, clinical course and combined medications. Subjects who were likely to resolve spontaneously (e.g. those who immediately recovered after a major operation) were excluded.

All the subjects were given quetiapine, with a flexible dose according to the clinicians' experiences and preferences where needed until the maximum clinical benefit was achieved. Quetiapine was administered orally and any other oral or parenteral agents of antipsychotics or benzodiazepines were prohibited. Quetiapine was terminated as the clinical global impression-global improvement scale (CGI, Guy, 1976) had reached 2 or less.

The efficacy of quetiapine was evaluated according to the delirium rating scale-revised-98-severity (Trzepacz *et al.*, 2001, DRS-R-98) and CGI-s (severity) scores, which were rated by a board-certified psychiatrist (C.U.P.) at the time of pre- and post-treatment.

Written informed consent was obtained from the primary relatives of the subjects. All adverse events were reported and all patients could withdraw from the study at any time for any reason.

Statistical analysis was performed using the SPSS 10.0 for Windows (SPSS Inc., Chicago, USA) program. All the subjects ($n = 22$) were included for the data analysis on the efficacy and tolerability. The Kolmogorov–Smirnov test showed a skewing of the data from normality. Therefore, a nonparametric analysis—Wilcoxon signed rank test and descriptive statistics were performed to analyse the efficacy measure or frequency of adverse events. The statistical significance was two-tailed and set at $p < 0.05$.

RESULTS

The subjects consisted of 13 males and 9 females. The mean age of subjects was 69.1 ± 9.8 years ranging from 48 to 85 years. The medical diagnoses of the subjects were as follows: dementia (seven cases), lung cancer (five cases), intra-cranial haemorrhage (ICH, five cases), cerebrovascular attack (two cases), femur neck fracture (two cases) and acquired immune deficiency syndrome (AIDS, one cases).

The mean daily dose was 127.1 ± 72.2 mg. The mean initial dose was 37.5 ± 12.8 mg/day and the mean maximal dose was 177.3 ± 121.0 mg/day. The mean duration of the quetiapine treatment was 8.5 ± 4.5 days. Using the cutoff score on the DRS-R-98 of 15, the mean day that the DRS-R-98 decreased by 15 or less was 7.1 ± 3.9 days.

The DRS-R-98 scores were significantly reduced from 21.8 ± 3.2 at the time of pre-treatment to 9.3 ± 3.8 at the time of post-treatment ($p < 0.0001$). A significant reduction in CGI-s was also observed, from 4.9 ± 0.8 to 2.1 ± 1.1 ($p < 0.0001$). Nineteen (86.3%) and 17 (77.3%) of the 22 patients showed a reduction in the DRS-R-98 and CGI-s scores, more than 50%, respectively, after the quetiapine treatment. One patient with ICH showed an increased DRS-R-98 score, from 19 to 21, at day 6.

Serious adverse events including EPS such as dyskinesia and dystonia were not observed. Twenty patients completed this trial. Only two patients had to stop quetiapine due to sedation on day 5 and a lack of efficacy on day 6. The others completed this trial without any serious adverse events. None showed EPS, and two subjects with ICH and the one subject with AIDS showed mild sedation.

DISCUSSION

This study showed that quetiapine might be effective and tolerable for treating patients with delirium and who are also prone to developing EPS and other side effects. The main strength of this study includes: the prospective design, the first report using an Asian sample that replicated the results of Western studies and a relatively larger sample size compared with other studies.

Compared with previous studies, the mean daily dose (127.1 mg/day) of quetiapine was in a similar range; from 93.8 mg/day to 211.4 mg/day (Kim *et al.*, 2003; Schwartz and Masand, 2000). The correlation of the mean daily dose of quetiapine and the change in the DRS-R-98 score was not significant in this study ($p = 0.336$), which is similar to that reported previously ($p = 0.618$, Schwartz and Masand, 2000), indicating that the effect of quetiapine for treating delirium is not associated with a dose increment.

In this study, the mean change in the DRS-R-98 score was 57.3% and the frequency of those with a 50% or more decrease in the DRS-R-98 score was 19 after the quetiapine treatment. This showed a similar trend toward the efficacy compared with previous studies. In addition, past reports showed that the peak clinical response day was approximately 6 to 7 days,

and this study also showed a similar time (7.1 days) using a cutoff DRS-R-98 score (Kim *et al.*, 2003; Schwartz and Masand, 2000).

This study also revealed that quetiapine is a safe agent, with no EPS or serious adverse events. In line with other studies (Kim *et al.*, 2003; Schwartz and Masand, 2000; Torres *et al.*, 2001), the most common side effect was sedation. However, a worsening of the delirium and excessive sedation was observed in one patient. Sim *et al.* (2000) reported acute confusion after initiating quetiapine treatment of 300 mg/day for 3 days during the first week. Another study also showed that the sedation might be a side-effect indicating that some caution should be taken when quetiapine is prescribed to patients suffering from delirium (Kim *et al.*, 2003; Schwartz and Masand, 2000). In particular, these findings may draw clinicians' attention to the fact that quetiapine should be carefully monitored when given to subjects who are vulnerable to the unwanted side effects.

This study has some critical drawbacks. First, although the number of subjects were extended to 22, the small sample size, the lack of randomization and a control group, which might represent a type I error such as symptom improvement as to the natural course of delirium. For any new drug that is proposed as a therapeutic, double-blind case controlled studies are crucial. Finally, this study only assessed the prevalence of side effects without any objective measures.

In summary, this small open study indicates that low-dose quetiapine is effective in reducing the behavioural disturbances and symptoms in delirium and is well tolerated in delirious patients, although further systematic controlled studies are warranted.

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