Treatment of Delirium in Older Adults with Quetiapine

Kye Y. Kim, Geoffrey M. Bader, Victor Kotlyar and Debra Gropper

J Geriatr Psychiatry Neurol 2003 16: 29
DOI: 10.1177/0891988702250533

Treatment of Delirium in Older Adults With Quetiapine

Kye Y. Kim, MD, Geoffrey M. Bader, MD, Victor Kotlyar, MD, and Debra Gropper, PharmD

ABSTRACT

Delirium is a neuropsychiatric syndrome characterized by impairment of consciousness, changes in cognition, or perceptual disturbances. In addition, delirium is often accompanied by delusions, hallucinations, and agitation. In this study, 12 older patients with delirium were treated for neuropsychiatric symptoms with quetiapine. The mean duration for stabilization was 5.91 ± 2.22 days, and the mean dose was 93.75 ± 23.31 mg/day. None of the 12 patients developed extrapyramidal symptoms. There were significant improvements on all measures used in this study. Interestingly, the Delirium Rating Scale scores along with scores of the Mini-Mental State Examination and Clock Drawing Test continued to improve throughout the 3-month study period. In our study, we found that quetiapine was a safe and effective treatment in hospitalized older patients with delirium. (*J Geriatr Psychiatry Neurol* 2003; 16:29–31)

Keywords: delirium; older adults; quetiapine; behavioral symptoms

Delirium is a syndrome of disturbed consciousness, cognition, and perception that develops over a short period of time and tends to fluctuate during the course of the day, and it is caused by 1 or more physical conditions.[1] Although delirium is significantly common among people of all ages, older adults are more prone to develop this syndrome because they are at higher risk for underlying brain disease.[2] The prevalence of delirium has been estimated from 10% to 40% among hospitalized elderly patients on medical and surgical wards.[3] Also, hospital mortality estimates range from 10% to 65%.[4]

Delirium is traditionally considered a transient syndrome that ends in recovery after several days to weeks in most cases.[3] This notion tends to lead most clinicians' psychopharmacological interventions to a brief one as long as the underlying causes of delirium are identified and resolved. Interestingly, Levkoff and her colleagues[2] in their prospective study demonstrated that many patients still had 1 or more symptoms as long as 6 months after hospital discharge. Older adults with delirium can present with a wide variety of neuropsychiatric symptoms.[5] The principal treatment of delirium is still the diagnosis and treatment of the underlying physical conditions contributing to delirium. However, psychopharmacological intervention is a major component of all interventions for delirium. Typically, high-potency neuroleptic agents such as haloperidol have been used as first-line treatment for neuropsychiatric symptoms of patients with delirium.[6] However, they are frequently associated with extrapyramidal symptoms (EPS), particularly in older adults. Recently, there have been several reports of use of the atypical antipsychotic agents, risperidone and olanzapine.[7-10]

Quetiapine is an atypical neuroleptic agent and dibenzothiazepine derivative structurally related to clozapine and olanzapine.[11] Quetiapine is well tolerated and associated with improvement in psychotic symptoms, although it demonstrates lack of EPS and minimal sedative, hypotensive, and anticholinergic side effects in the dose range used in older adults.[12,13] This study was designed to determine the efficacy and safety of open-label quetiapine treatment in patients with delirium over a period of 3 months.

METHODS

All patients were enrolled from the acute medical units of Salem Veterans Affairs Medical Center, a 271-bed, general and teaching hospital for the University of Virginia, School of Medicine. The hospital's Human Studies Subcommittee

Received March 25, 2002. Received revised April 29, 2002. Accepted for publication April 30, 2002.

From Salem Veterans Affairs Medical Center, Department of Psychiatric Medicine, School of Medicine, University of Virginia (Drs. Kim and Bader), Institute of Living, Hartford, CT (Dr. Kotlyar), and Perry Point Veterans Affairs Medical Center, Perry Point, MD (Dr. Gropper).

This study was conducted at Veterans Affairs Medical Center, Salem, Virginia, and supported by a grant from AstraZeneca.

Reprint requests: Kye Y. Kim, MD, Psychiatry Service, Veterans Affairs Medical Center, Salem, VA 24153; e-mail: kye.kim@med.va.gov.

DOI: 10.1177/0891988702250533

Table 1. Clinical Characteristics of Patients

Patient Number	*Age (years)*	*Gender*	*Medical Diagnosis*	*Dose (mg) at T_1*	*Time to Stabilization (days)*	*Adverse Reactions*
1	80	Male	DM, CRI[a], hypertension, hypothyroidism, dementia	50 mg bid	6	None
2	64	Male	UTI, delirium tremens[a]	75 mg bid	8	None
3	68	Male	S/P laryngectomy, hypertension, hypothyroidism, UTI[a]	50 mg bid	5	None
4	70	Male	DM, S/P hip hemiarthroplasty[a], BPH	50 mg bid	10	None
5	82	Male	CRI[a], CHF, hypertension, DM, BPH	25 mg qam 75 mg ghs	4	None
6	79	Male	GI bleeding[a], DM, chronic anemia, dementia	50 mg ghs	6	None
7	75	Male	CHF[a], hypertension, BPH, sleep apnea	50 mg bid	8	Vivid dreams, drowsiness
8	67	Male	S/P coronary bypass[a], hypertension, DM, chronic anemia	50 mg bid	8	None
9	71	Male	MI[a], cardiomyopathy, hypertension, DM	25 mg bid	4	None
10	77	Male	UTI, dehydration[a]	25 mg bid	3	None
11	74	Male	Pneumonia[a], PE, duodenal ulcer, esophageal stricture	25 mg qam, 50 mg ghs	4	None
12	88	Male	GI bleeding[a], glaucoma, BPH	50 mg qam, 100 mg ghs	5	Drowsiness

DM = diabetes mellitus; CRI = chronic renal insufficiency; UTI = urinary tract infection; BPH = benign prostatic hypertrophy; GI = gastrointestinal; MI = myocardial infarction; PE = pulmonary embolism.

a. Main cause of delirium.

and Research and Development Committee approved the study protocol. Informed consent was required for participation in this study. All patients were referred to Consultation-Liaison Psychiatry Service for evaluation of mental status changes. Patients who had known histories of psychotic disorders and were treated with neuroleptic agents within the previous 4 weeks prior to the enrollment were excluded from this study. They were required to be at least 60 years old. Patients provided written informed consent before admission to the study. When they did not have a capacity to consent due to significant changes in mental status, the consent was sought from their next of kin. All patients enrolled in this study met *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.) criteria for delirium.[1] They were administered the Mini-Mental State Examination (MMSE),[14] Delirium Rating Scale (DRS),[15] Clock Drawing Test (CDT),[16] and Clinical Global Impression (CGI).[17] At their admission to the study (T_0), they were administered the MMSE, the DRS, and the CGI. When an attending psychiatrist determined that patients were in need of antipsychotic treatment based on clinical grounds, they were given a starting dose of quetiapine 25 mg twice a day. The dosages were then increased by 25 mg every 2 days until patients were maximally stabilized (T_1). When patients required an adjunctive psychotropic therapy for acute symptoms, they were given oxazepam or lorazepam by mouth or by intramuscular injection as needed. At stabilization, patients were again given the above-mentioned measures and discharged on the stabilizing dose of quetiapine. All patients had follow-up visits at the first month of therapy (T_2) and third month of therapy (T_3). At the first-month visit, the quetiapine was tapered off by 25 mg every 3 days when they were considered stable. At each follow-up visit, they were given the same measurements. The efficacy of quetiapine was evaluated using responder analyses and paired *t* tests. Side effects were assessed with clinically oriented, open-ended questions.

RESULTS

Eleven of the 12 patients completed the study to T_3. One patient was started on quetiapine and followed at T_1, but he died of acute myocardial infarction a few days later. This patient had preexisting cardiac conditions, and his death was unrelated to the study drug. All 12 patients were considered evaluable (Table 1). There were no dropouts due to side effects. The age (mean ± SD) of patients was 74 ± 7 years, and all of them were male. None of the 12 patients had prior history of psychiatric treatment. Two patients had a diagnosis of early dementia, but they had no behavioral symptoms prior to the development of delirium. Only 1 patient required a one-time dose of lorazepam (1 mg) administered intramuscularly. The mean ± SD dose of quetiapine at T_1 was 93.75 ± 23.31 mg/day. The mean duration for stabilization at T_1 was 5.91 ± 2.22 days. None of the 12 patients developed EPS, and rates of other side effects were considered minimal (sedation in 2 patients and vivid dreams in 1). Average scores on the efficacy measures at T_0 through T_3 are reported in Table 2. All *t* tests were highly significant, indicating that there were significant improvements on all measures used in this study. Interestingly, the DRS scores along with scores of MMSE and CDT continued to improve during the study period from T_0 to T_3. Although a monitoring of the patient's blood pressure was not one of the measurements in this study, there was no indication of any significant changes in blood pressure secondary to quetiapine use.

Table 2. Paired *t* Tests Comparing Scores on the MMSE, DRS, CDT, and CGI Across Time Periods

Measure	T_0	T_1	T_2	T_3
MMSE				
Mean	14.50	21.17	24.27	25.18
SD	5.90	4.55	4.86	4.45
N	12	12	11	11
t[a]		4.07		
t[b]			3.96	
t[c]				1.99
P		.002	.003	*ns*
DRS				
Mean	18.25	8.00	2.27	0.63
SD	6.05	2.34	2.28	1.21
n	12	12	11	11
t[a]		5.60		
t[b]			7.88	
t[c]				2.57
P		.0002	.0001	.03
CDT				
Mean	3.25	6.25	7.91	8.09
SD	2.77	4.07	3.45	3.21
n	12	12	11	11
t[a]		3.35		
t[b]			3.46	
t[c]				1.00
P		.007	.006	*ns*
CGI-S				
Mean		3.00	1.91	1.36
SD		0.43	0.83	0.67
n		12	11	11
t[b]			–5.16	
t[c]				–2.63
P			.0004	.03

MMSE = Mini-Mental State Examination; DRS = Delirium Rating Scale; CDT = Clock Drawing Test; CGI-S = Clinical Global Impressions–Severity.

a. Paired *t* test between T_0 and T_1.

b. Paired *t* test between T_1 and T_2.

c. Paired *t* test between T_2 and T_3.

DISCUSSION

Since this was a small, open-label study with no control group, our findings are certainly limited for generalization. This study was also limited in that all subjects were male. All patients had multiple physical disorders. They were also taking various drugs for their medical conditions. However, all patients were free of previous psychiatric diagnosis and were not on any type of psychotropic agents for at least 4 weeks prior to admission to this study; thus, it was an appropriate group of patients for a psychotropic drug study.

Quetiapine was well tolerated by all patients in this study. Vivid dreams and sedation were reported, but no patients developed EPS. Peak response times were comparable to what has been reported for olanzapine and haloperidol.[10] In addition, it was of clinical interest that the main measure in this study, the DRS, continued to improve across time periods. This finding might have some implication for the duration of intervention, especially pharmacotherapeutic treatment. In our study, we found that quetiapine was a safe and effective treatment in hospitalized older patients with delirium. However, it will be difficult to absolutely determine whether the neuropsychiatric symptoms improved because of quetiapine, resolution of the underlying medical conditions, or a combination of the two. Larger controlled studies are needed to further explore these preliminary findings and conclusions.

References

1. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 4th ed. Washington, DC: American Psychiatric Association, 1994.
2. Levkoff SE, Evans DA, Lipzin B, et al. Delirium: the occurrence and persistence of symptoms among elderly hospitalized patients. *Arch Inter Med* 1992; 152:334-340.
3. Lipowski ZJ. Delirium (acute confusional state). *JAMA* 1987; 258:1789-1792.
4. Inouye SK. Delirium in hospitalized elderly patients: recognition, evaluation, and management. *CT Med* 1993; 57:309-315.
5. Sandberg O, Gustafson Y, Braennstroem B, Bucht G. Clinical profile of delirium in older patients. *JAGS* 1999; 47:1300-1306.
6. Shapiro BA, Warren J, Egol AB, et al. Practice parameters for intravenous analgesia and sedation for adult patients in the intensive care unit: an executive summary. *Crit Care Med* 1995; 23:1596-1600.
7. Sipahimalani A, Masand PS. Use of risperidone in delirium: case reports. *Ann Clin Psychiatry* 1997; 9:105-107.
8. Ravona-Springer R, Dolberg OT, Hirschmann S, Grunhaus L. Delirium in elderly patients treated with risperidone: a report of three cases. *J Clin Psychopharmacol* 1998; 18:171-172.
9. Sipahimalani A, Sime RM, Masand PS. Treatment of delirium with risperidone. *Int J Geriatric Psychopharmacology* 1997; 1:24-26.
10. Sipahimalani A, Masand PS. Olanzapine in the treatment of delirium. *Psychosomatics* 1998; 39:422-430.
11. Goren JL, Levin GM. Quetiapine, an atypical antipsychotic. *Pharmacotherapy* 1998; 18:1183-1194.
12. McManus DQ, Arvanitis LA, Kowalcyk BB. Quetiapine, a novel antipsychotic: experience in elderly patients with psychotic disorders. *J Clin Psychiatry* 1999; 60:292-298.
13. Madhusoodanam S, Brenner R, Alcantra A. Clinical experience with quetiapine in elderly patients with psychotic disorders. *J Geriatr Psychiatry Neurol* 2000; 13:28-32.
14. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12:189-198.
15. Trzepacz PT, Baker RW, Greenhouse J. A rating scale for delirium. *Psychiatry Res* 1988; 23:89-97.
16. Wolf-Klein GP, Silverstone FA, Levy AP, et al. Screening for Alzheimer's disease by clock drawing. *J Am Geriatr Soc* 1989; 37:730-734.
17. Guy W. *ECDEU assessment manual for psychopharmacology–revised* (DHEW Publ No ADM 76-338). Rockville, MD: U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, NIMH Psychopharmacolgy Research Branch, Division of Extramural Research Program, 1976:218-222.