A Retrospective Study of the Safety of Intramuscular Ziprasidone in Agitated Elderly Patients

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Objective: Authors evaluated the safety of intramuscular ziprasidone for use in acute agitation in an elderly population.

Method: Medical records were reviewed retrospectively to identify consecutive patients who were admitted to our neuropsychiatry service with the presenting complaint of dementia (DSM-IV) with agitation and who were given intramuscular ziprasidone and then administered an electrocardiogram (ECG) (N = 23). Some patients also had a baseline ECG (N = 14). QTc intervals were recorded, and significance was defined as a QTc of ≥ 450 ms or a 10% prolongation from baseline. A paired-samples t test was performed to compare the baseline and postmedication QTc intervals. Confounding factors were examined, and cardiac events (torsades de pointes, cardiac arrest) were recorded.

Results: There was no significant difference in the QTc interval between the baseline and the post-ziprasidone values. One patient had a QTc greater than 500 ms and 25% over baseline, and therefore the medication was discontinued. The mean prolongation of the QTc interval was only 0.5 ms. There were no episodes of torsades de pointes. Other medications that the patients were taking did not appear to affect the QTc interval in an expected manner.

Conclusion: Larger studies need to be done to evaluate the safety of intramuscular ziprasidone in agitated elderly patients, a population with an increased risk of QT prolongation and torsades de pointes because of their age, comorbid conditions, and concomitant use of multiple medications.

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Several antipsychotics are associated with a prolonged QTc interval on electrocardiogram (ECG). Prolongation of the QTc interval is a risk factor for the development of torsades de pointes, a potentially fatal arrhythmia.[1–3] Two of the currently available intramuscular antipsychotics are associated with QTc prolongation. Haloperidol is associated with QT prolongation, torsades de pointes, and sudden death (A. Loebel, M.D.; C. O. Siu, Ph.D.; S. Romano, M.D.; data on file, Pfizer Inc, New York, N.Y.). Ziprasidone is associated with QTc prolongation and with torsades de pointes.[4–7] Several studies have shown ziprasidone to be safe, but these have focused on patients aged 18 to 65 years. Few data are available about ziprasidone's effect on the QTc interval in the elderly.[5] This is a retrospective chart review study of acutely admitted demented, agitated geriatric patients, investigating potential QTc changes after intramuscular injection of ziprasidone.

METHOD

Following Emory University Institutional Review Board approval to conduct this retrospective chart review, hospital records from 23 consecutive patients who were admitted to our neuropsychiatry service (Wesley Woods Center at Emory University) with the presenting complaint of dementia with agitation (DSM-IV) and who had received intramuscular ziprasidone for acute agitation were reviewed. Ziprasidone was administered as needed for agitation and, as a safety precaution, an ECG was obtained approximately 2 hours later. Because of concerns about QTc interval changes, 2-hour postinjection ECGs were required as a part of institutional (hospital pharmacy and therapeutics committee) evaluation of safety in this population. This time interval was chosen after a review of limited data in elderly patients provided by the manufacturer (A. Loebel, M.D.; C. O. Siu, Ph.D.; S. Romano, M.D.; data on file, Pfizer Inc, New York, N.Y.). None of the patients was in a formal clinical trial involving ziprasidone. In 14 of these patients, the post-ziprasidone ECG was compared to a baseline ECG prior to the first intramuscular injection. The QTc was determined from automated calculations. A significant QTc interval was defined either as greater than or equal to 450 ms or as a 10% prolongation of the QTc interval as compared to the base-

Table 1. QTc Intervals of Agitated Elderly Patients Prior to and Following Intramuscular (IM) Ziprasidone Administration

Patient	Baseline QTc, ms	2-h Post-Ziprasidone QTc, ms	Percent Change
1	406	391	–4
2	418	399	–5
3[a]	441	445	1
4	437	411	–6
5[a,b]	413	517	25
6[a]	443	464	5
7	424	405	–5
8[a]	408	424	4
9[c]	471	445	–6
10	443	375	–15
11[a]	406	425	5
12[a]	423	440	4
13	431	428	–1
14[a]	414	447	8
Mean QTc	427.00	427.54	0.13*

[a]Increase in QTc interval following IM ziprasidone administration.
[b]Significant QTc interval and/or percent change from baseline following IM ziprasidone administration.
[c]Baseline QTc > 450 ms.
*p = .960.

line ECG. A paired-samples t test was performed to compare the baseline and postmedication QTc intervals.

RESULTS

The mean patient age was 74 years (range, 59–95). The population was 74% white and 70% female. All patients suffered from dementia with agitation, with Alzheimer's disease being the most common diagnosis. Patients had a variety of comorbid illnesses including risk factors for QT prolongation. These included diabetes (N = 7, 32%), stroke (N = 4, 18%), congestive heart failure (N = 4, 18%), and coronary artery disease (N = 3, 14%). Comorbid arrhythmias included bradycardia (N = 3), tachycardia (N = 2), atrial fibrillation (N = 2), premature atrial contractions (N = 2), and ectopic atrial rhythm (N = 1). One patient had a baseline QTc of greater than 450 ms. Data from these 23 patients were examined to determine if any of the patients had a QTc interval greater than 450 ms following intramuscular injection. Five had QTc intervals greater than 450 ms (range, 455–517).

Fourteen patients had a baseline ECG performed before receiving any intramuscular ziprasidone. In the paired-samples t test of the data for these patients, there was no significant difference in the QTc interval between the baseline and the post-ziprasidone values (Table 1). Eight patients had repeat doses of intramuscular ziprasidone with repeat ECGs at 2 hours following injection. Two of these patients had a QTc interval greater than 450 ms after receiving intramuscular ziprasidone. One of these patients had a QTc greater than 500 ms (a greater than 25% increase over baseline), and ziprasidone was discontinued. Her sex, age, diabetes, bradycardia, left ventricular hypertrophy, and history of stroke may have contributed to the QTc prolongation. She had taken no other QTc-prolonging medications. There were no episodes of torsades de pointes in any patients.

DISCUSSION

Our study shows no greater risk of QTc changes for intramuscular ziprasidone when compared to intramuscular haloperidol. One limitation of this study is that we investigated the immediate effect of a single injection of intramuscular ziprasidone. Also, ziprasidone was used only on an as-needed basis for agitation in patients with a variety of diagnoses. All were taking scheduled doses of other antipsychotic medications, including 3 patients who received oral ziprasidone. However, the population in this study was older and had more medical comorbidity than did those in prior studies. This study identified 1 patient with a significant prolongation of the QTc interval requiring discontinuation of the medication. This study did not detect a difference between the QTc interval before or after ziprasidone. The average prolongation of the QTc interval was only 0.5 ms. None of the medications expected to confound the results of this study seemed to affect the QT interval in the expected manner. Larger studies need to be done to evaluate the confounding effect of other antipsychotic medications and to determine the safety of intramuscular ziprasidone in agitated elderly patients.

Drug names: haloperidol (Haldol and others), ziprasidone (Geodon).

REFERENCES

1. Al-Khatib SM, LaPointe NM, Kramer JM, et al. What clinicians should know about the QT interval. JAMA 2003;289:2120–2127
2. Crouch MA, Limon L, Cassano AT. Clinical relevance and management of drug-related QT interval prolongation. Pharmacotherapy 2003;223: 881–908
3. Geodon [package insert]. New York, NY: Pfizer, Inc; 2002
4. Glassman AH, Bigger JT. Antipsychotic drugs: prolonged QTc interval, torsade de pointes, and sudden death. Am J Psychiatry 2001;158: 1774–1782
5. Roe CM, Odell KW, Henderson RR. Concomitant use of antipsychotics and drugs that may prolong the QT interval. J Clin Psychopharmacol 2003;23:197–200
6. Brook S. A pilot study of intramuscular ziprasidone in the short-term treatment of patients with acute exacerbation of schizophrenia. Hum Psychopharmacol 2000;15:521–524
7. Sharma ND, Rosman HS, Padhi ID, et al. Torsades de pointes associated with intravenous haloperidol in critically ill patients. Am J Cardiol 1998; 81:238–240