New-Onset Diabetes Mellitus Among Parkinsonian Patients Treated with Long-term Quetiapine

Hubert H. Fernandez[1], Katie M. McCown[1], Janet Romrell[1], Martha E. Trieschmann[2], Joseph H. Friedman[2], Charles E. Jacobson IV[1] and Michael S. Okun[1]

[1]Dept. of Neurology, University of Florida, Gainesville, FL. [2]Dept. of Clinical Neurosciences, Brown University, Providence, RI.

Abstract: Atypical antipsychotics (AA) are commonly used to manage drug-induced psychosis (DIP) in parkinsonian patients. In the treatment of schizophrenia, AA's have been associated with increasing reports of new-onset diabetes mellitus (DM). This study examined the risk of developing new-onset DM among parkinsonian patients on long-term, low dose quetiapine. Fifty-three parkinsonian subjects (mean age: 71.3 years) taking an average quetiapine dose of 70.5 mg/day (range: 12.5–350 mg/day) for a mean duration of 21.3 months (range 3–61 months) were reviewed. Eight out of 53 subjects carried a diagnosis of DM prior to quetiapine treatment. Four out of 45 patients (8.9%) met criteria for new diagnosis of DM, giving a total prevalence rate of 22.6% (12 out of 53). This prevalence rate of 22.6% was slightly higher than that reported in the aged-matched general population (year 2003 DM prevalence = 17.3% for 65–74 years) but methodological differences could explain the difference. Larger epidemiologic studies will be needed to confirm these results as they could potentially impact a significant number of patients.

Keywords: quetiapine, diabetes, atypical antipsychotic, parkinson's disease

Introduction

Atypical antipsychotics (AAs) have become first line treatment in the management of drug-induced psychosis (DIP) in patients with parkinsonian diseases. They are considered first line because of their lower risk of extrapyramidal side effects (EPS) when compared to conventional neuroleptics [1]. Currently, clozapine is considered the most efficacious and perhaps best AA for parkinsonism [1–3]. However, its use is limited by the rare associated risk of agranulocytosis, and consequent weekly blood draws as well as intensive monitoring. Quetiapine is the closest AA to clozapine in terms of efficacy in parkinsonism, and is currently the most employed alternative to clozapine by movement disorder specialists [4]. Given its low EPS profile and lack of hematologic risk, many authors consider quetiapine to now be the first line treatment of DIP in parkinsonism [4].

Several of the AAs, most notably olanzapine and clozapine, have been associated with the development of diabetes mellitus (DM) when used to treat schizophrenia [5,6]. Though rare, there are also case reports of new-onset DM associated with quetiapine use in schizophrenia [5–7]. In the setting of parkinsonism, the association with DM is unclear and has not been carefully investigated. Previously we described a lower incidence of DM with clozapine in the parkinsonian population when compared to age-matched controls [8]. Although published reports indicate no dose relationship between clozapine and glucose tolerance, most studies involve schizophrenia patients who are typically on 200–800 mg/day of clozapine. Since the average dose of clozapine was lower in parkinsonism than in schizophrenia, we hypothesized that perhaps the risk of DM could be dose-related.

Since quetiapine is the 'practical first line treatment' for DIP in parkinsonism, and because the published mean daily dose of quetiapine in the parkinsonian population is slightly higher compared to that reported for clozapine [1,4], we sought to study the prevalence of newly-diagnosed DM among parkinsonian patients on long-term quetiapine.

Method

We reviewed the medical records of all quetiapine-treated parkinsonian patients actively followed at two Movement Disorder Centers, Brown University and the University of Florida. Patients were excluded

Correspondence: Hubert H. Fernandez, M.D., Department of Neurology/McKnight Brain Institute. University of Florida, PO Box 100236, Gainesville, Florida 32610. Fax: (352) 273 5575; Email: fernandez@neurology.ufl.edu

if they had been on quetiapine for less than three months or were no longer taking the agent. To determine true prevalence, patients with previous and recent diagnoses of DM, and/or use of hypoglycemic agents prior to quetiapine initiation were included. The dose and duration of quetiapine use were recorded, as well as the patient's age and sex. A fasting blood glucose (FBG) was obtained on all non-diabetic patients taking quetiapine. The diagnosis of new-onset DM while on quetiapine was determined by (1) a diagnosis made by the patient's primary care physician, (2) the initiation of oral hypoglycemic agents or insulin by their primary care physician after initiation of quetiapine, (3) or a FBS greater than or equal to 126 mg/dl which is the 'gold standard' level warranting a diagnosis of DM [9].

The prevalence of DM in this cohort was then compared to the latest reported prevalence (year 2000) of DM in the (age-matched) general population [10]. The prevalence of DM in the general population was taken from the National Health and Nutrition Examination Survey (NHANES) based on a house to house survey.

Results

Fifty-three parkinsonian subjects (36 males, 17 females) with a mean: age of 71.3 years (range: 51–91 years), quetiapine dose of 70.5 mg/day (range: 12.5–350 mg/day), and treatment duration of 21.3 months (range 3–61 months) were identified. Nine out of the 53 subjects resided in long-term care facilities. Because quetiapine was the first line treatment for psychosis in both participating institutions, none of the subjects were previously exposed to other antipsychotic agents.

Eight out of 53 patients carried a prior diagnosis of DM prior to quetiapine initiation. Among those without a prior diagnosis of DM, three undiagnosed patients had FBG $\geq$126 mg/dl, and a fourth patient was started on a hypoglycemic agent (after obtaining a FBG $>$126 mg/dl by the primary care physician) while taking quetiapine (total: 4/45; 8.9%). Therefore, the prevalence of DM in our cohort was 22.6% (12/53). This rate was slightly higher than that reported in the age-matched general population (year 2003 DM prevalence = 17.3% for ages 65–74 years [10]). However, if 3 of the newly diagnosed DM cases based on "active diagnostic intervention" were excluded, and only known/recorded cases of DM (before and after quetiapine treatment) were included, then our cohort would have a "natural" prevalence rate of 16.9% (9/53).

Discussion

This is, to our knowledge, the first study to evaluate the prevalence of DM among parkinsonian patients on quetiapine. How quetiapine and other AAs are related to DM remains unclear. Quetiapine has been associated with weight gain [12], and this increase in body weight may at least in part be responsible for the slightly higher increased risk of new-onset DM. The AA drugs have also been linked to hypertriglyceridemia [13]. Increased appetite, insulin resistance, and other endocrine changes may also play a role [12,14].

Although this study found a slightly higher rate of DM in parkinsonian patients taking quetiapine than in the age-matched general population, there were several weaknesses in this study. The sample size was small making it difficult to draw firm conclusions from the data. Ideal body weights versus actual body weights were not calculated, and therefore we cannot carefully account for who was at risk for type II DM. Additionally, in this study there was no screening for DM with FBG prior to quetiapine initiation, and no careful screening for endocrinopathies was performed. A repeat FBG was not drawn in the three patients who were high ($\geq$126 mg/dl). In addition, FBG may be a less stringent criteria for diagnosing DM than is post-prandial blood glucose which was not measured in this study. Post prandial blood glucose is an independent risk factor for mortality in patients with new-onset DM, while FBG is not [15]. These study weaknesses could have led to an overestimation of the prevalence of DM in this cohort.

Also of note was that this study utilized age-matched historical controls. The prevalence rate of DM at the NHANES study was determined from a "naturalistic" survey (i.e. based on know/recorded diagnosis of DM) without active diagnostic intervention; whereas the overall prevalence rate of DM in our cohort was calculated from a combination of data recording/inquiry and active diagnostic intervention. Thus, employing the same method used at the NHANES study would yield a prevalence rate of 16.9%, but including newly diagnosed DM cases from mandatory blood testing of patients without a prior diagnosis would yield a higher prevalence rate.

We included only patients who were taking quetiapine for 3 months or more. Most studies on the prevalence of diabetes in the schizophrenia population required 2–3 months of antipsychotic exposure prior to inclusion in their cohort. However, in schizophrenia, there are conflicting reports as to whether duration of disease is a significant risk factor for DM development. Two reports found no association [16,17], while one found a significant association with olanzapine, clozapine and conventional antipsychotic agents [18]. No association with duration of disease was found in our cohort.

Larger epidemiologic studies are needed to better assess, and verify, these preliminary findings for the risk of new-onset DM associated with quetiapine. Neurologists, psychiatrists and primary care physicians should be aware of this potential slight increased risk of DM related to quetiapine and be cautious.

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