

Fatal Olanzapine-Induced Ketoacidosis

TO THE EDITOR: Recently 24 deaths have been reported in association with olanzapine-induced ketoacidosis. Koller and Doraiswamy (1) reported 23 deaths among 289 cases of hyperglycemia, and Meatherall and Younes (2) added another. We wish to report an additional case resulting in death.

Mr. A, a 45-year-old man with a 29-year history of bipolar disorder with psychotic features, polysubstance abuse, and no history of diabetes, died in December 2001. The cause of death was ascertained to be diabetic ketoacidosis; the postmortem vitreous glucose level was 743 mg/dl, and the blood was positive for acetone (concentration, 0.03%). Mr. A was 72 inches tall and weighed 214 lb. He was of mixed race, part African American. Treatment with olanzapine, 30 mg/day, had been restarted 1 month before Mr. A's death. He had been treated with it on two previous occasions for less than 2 weeks; each time, treatment ended because of noncompliance. At the time olanzapine treatment was restarted, routine testing showed his blood sugar level to be normal. At the time of death he had also received prescriptions for risperidone (6 mg/day), lithium (1800 mg/day), fluoxetine (20 mg/day), and bupropion (400 mg/day). He was living with family members who insisted that he take his medication, and he had not been seen psychiatrically since restarting olanzapine treatment. The family did not observe warning signs of ketoacidosis. He had a history of alcohol, crystal methamphetamine, and occasional cocaine abuse, but postmortem toxicology studies were negative for all three substances.

This case, like most of the other 24 reported cases of fatal ketoacidosis associated with olanzapine, progressed to death within a relatively short time. Recently, Wilson et al. (3) reported five additional patients with nonfatal ketoacidosis, two of whom were taking olanzapine, two clozapine (augmented with risperidone in one case), and one quetiapine, thus raising the issue of whether ketoacidosis is also associated with other second-generation antipsychotics or combinations of medications. Alternatively, ketoacidosis may occur in genetically predisposed individuals, such as those with the polymorphism recently described as being associated with clozapine-induced weight gain (4). The fact that African Americans were disproportionately represented in previous reports (1, 3, 5) and an African American was involved in this case is consistent with that hypothesis.

It appears that hyperglycemia leading to ketoacidosis is an important side effect of olanzapine, and possibly other second-generation antipsychotics, and may have a fatal outcome. Its incidence is not known, but Wilson et al. (3) reported it as occurring in 4% (five of 126) of individuals treated with these antipsychotics. It is suggested that all individuals who start treatment with this drug, but especially African Americans, receive weekly monitoring of their blood sugar levels for the first 6 months.

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Deaths From Diabetic Ketoacidosis After Long-Term Clozapine Treatment

TO THE EDITOR: There is strong evidence that clozapine is associated with new-onset type 2 diabetes mellitus and diabetic ketoacidosis. In fact, between clozapine's introduction and June of 2000 there were eight spontaneous reports of diabetic ketoacidosis during clozapine treatment in patients with no documented history of diabetes mellitus or hyperglycemia. In these cases, diabetic ketoacidosis occurred approximately 5.8 weeks (range=2-20 weeks) after the beginning of clozapine treatment in patients with a mean age of 36.4 years (range=30-46 years) (1). Others report that people developing diabetic ketoacidosis during antipsychotic treatment are significantly younger and less overweight than those developing diabetes mellitus alone (2).

In Maryland, 2,046 people were treated with clozapine through Medicaid or the Maryland Pharmacy Assistance Program between 1990 and 2000 and were registered with the Clozapine Authorization and Monitoring Program. Three cases of lethal diabetic ketoacidosis occurred during clozapine treatment (0.15%), as noted by death certificates. Two of the three patients were male, and the mean age at death was 38.0 years (SD=6.1). All three people had schizophrenia and were being treated in outpatient settings. Concomitant psychiatric medications included sertraline, divalproex, fluoxetine, and methylphenidate. None of the patients had a diagnosis of diabetes mellitus or was being treated for this disorder. Weight, smoking status, and family history were unknown. All had been taking clozapine for over 1 year before death (25.5 months, 14.5 months, and 59.5 months; mean=33.2 months). To our knowledge, this is the first report of lethal diabetic ketoacidosis during long-term clozapine treatment.

A recent consensus conference recommended that glucose levels be monitored at baseline and then annually if weight gain is more than 7% of body weight (3) in people treated with any of the atypical antipsychotics. More careful attention, however, may need to be paid to both the short- and long-term risk of diabetes mellitus or diabetic ketoacidosis, especially with antipsychotics implicated in causing diabetes mellitus. While most cases do occur in the short term, there have been reports of diabetic ketoacidosis or diabetes mellitus worsening during long-term treatment with olanzapine. In recent cases, diabetic ketoacidosis occurred 17 months (4)

and 24 months (5) after the start of olanzapine treatment. Another report noted dramatic worsening of diabetes mellitus after 3 years of olanzapine treatment (6). Other cases of diabetic ketoacidosis from olanzapine and clozapine may go unreported because of no apparent temporal relationship.

The mechanism by which clozapine causes diabetes mellitus is not clear but could involve insulin resistance, suppression of insulin release, or impairments in glucose utilization. Hyperglycemia has been noted to occur in over 50% of people receiving long-term clozapine treatment, and the elevated risk of developing diabetes may continue as long as the treatment (7). These authors recommend measurement of fasting blood glucose every 6 months during clozapine treatment. The discrepancy in monitoring recommendations underscores the need for greater attention to this topic. Health care professionals should be aware of the links of clozapine to diabetes mellitus and diabetic ketoacidosis and the potential for delayed recognition of complications associated with diabetes mellitus, especially in people who suffer from schizophrenia.

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Lethal Gastroenteritis Associated With Clozapine and Loperamide

TO THE EDITOR: Clozapine is an effective and widely used antipsychotic medicine in the United States and elsewhere. Furthermore, loperamide is a common antimotility drug, usually considered quite safe. Here we describe a case of fatal gastroenteritis associated with the simultaneous use of clozapine and loperamide.

In Niuvanniemi State Mental Hospital in Kuopio, Finland, an unexpected, extensive epidemic of intestinal dis-

ease broke out; within 24 hours 85 patients and 26 employees suffered diarrhea, abdominal cramps, and vomiting. There were no local neurological symptoms or fever. Most cases were mild, but six people, all patients, were hospitalized. One of these patients later died, despite previous physical good health and an age of 36. This man died on the operating table after about 16 hours of symptoms. The autopsy revealed toxic megacolon as the immediate cause of death and acute gastroenteritis as the basic cause. He had received 500 mg of clozapine daily and, after the diarrhea, 6 mg of loperamide. He received no other drugs.

Standard analyses of all known food sources as well as samples of feces and vomitus revealed no significant causes of the epidemic. This process led to preparation of a fresh batch of vanilla sauce like that served before the epidemic.

An epidemiological questionnaire, the foodstuff analyses, temperatures of the replicated vanilla sauce, and the microbiological results all confirmed the vanilla sauce as the cause. The pathogen was determined to be either *Bacillus licheniformis* alone or concurrent with *B. cereus*. Toxin-producing strains of *B. licheniformis* have been previously reported (1) and, together with *B. cereus* (2), have been known to cause food poisoning.

The most seriously affected people in the hospital were patients, not personnel. Furthermore, the diarrhea was generally followed by some deceleration of intestinal function and abdominal distension. The issue of pharmaceutical influences surfaced. Some patients had received loperamide, an antimotility drug, for relief of symptoms. The deceased patient received loperamide and clozapine. According to the literature, loperamide should not produce pharmacokinetic interactions with clozapine or other antipsychotics, which are also antimotility agents. Pharmacodynamically, however, this intestinal deceleration was relevant. We performed a search using PubMed, available through the National Center for Biotechnology Information Entrez retrieval system (3), and also requested reports from the databases of the Finnish National Agency for Medicines, Novartis (clozapine), and Orion Pharma Finland (loperamide). There were no reports of similar cases specifically involving psychiatric patients. However, antimotility agents have previously been identified in fatal *Campylobacter jejuni* infections (4). It can be reasonably concluded that the simultaneous use of clozapine, or other antipsychotics with anticholinergic properties causing constipation, and antimotility drugs may expose patients to serious intestinal infections. The results may not be as serious when loperamide is combined with antipsychotics lacking these properties. This should be considered when treating gastroenteritis in psychiatric patients.

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Symptomatic Bradycardia Secondary to Risperidone

TO THE EDITOR: Risperidone, a selective monoaminergic serotonin and dopaminergic antagonist, is known to cause orthostatic hypotension and tachycardia. To our knowledge, sinus pauses with bradycardia secondary to risperidone have not been previously reported. We describe a young man with schizophrenia without any prior cardiac history who developed symptomatic sinus bradycardia with pauses after an increase in the dose of risperidone. The bradyarrhythmias resolved after discontinuation of risperidone, implicating it in the pathogenesis of this patient's arrhythmia.

Mr. A, a 40-year-old man with a history of schizoaffective disorder and alcoholism, came to the emergency room with nausea, vomiting, and abdominal pain. He had been taking paroxetine, 10 mg/day, and risperidone, 2 mg/day. He denied any history of heart illness. Mr. A appeared diaphoretic and tremulous, was tachycardic with a heart rate of 102 bpm, and had a low-grade fever with a temperature of 99.8°F. Laboratory evaluation revealed a creatinine phosphokinase level of 2949 IU/liter with a normal MB fraction and a troponin-I concentration of 0.4 µg/liter. A 12-lead ECG showed sinus tachycardia, nonspecific ST-T abnormalities, and a QTc interval of 400 msec. Mr. A was admitted to a telemetry unit for alcohol withdrawal, mild rhabdomyolysis, and alcohol gastritis. Intravenous fluids, multivitamins, and lorazepam were administered. Subsequent creatinine phosphokinase and troponin levels showed substantial decreases. Because of worsening psychosis, the risperidone dose was increased to 6 mg/day on the second day of hospitalization. On the third day, Mr. A developed sinus bradycardia with 38 bpm and had several episodes of sinus pauses lasting 2.0 to 3.0 seconds associated with lightheadedness without hypotension. At this time the QTc interval was 410 msec. The results of a two-dimensional ECG were normal. Because of the temporal relationship of the bradyarrhythmias with the increase in the risperidone dose, risperidone treatment was discontinued. Over the next 48 hours of telemetry monitoring, there were no further sinus pauses and the sinus bradycardia resolved completely. Mr. A's heart rate at the time of discharge was 78 bpm.

Risperidone is a selective monoaminergic antagonist with no known affinity for cholinergic muscarinic or β_1 and β_2 adrenergic receptors. The strong temporal relationship between the occurrence of bradyarrhythmia and risperidone therapy in this case points to risperidone as the cause of this adverse event. The bradyarrhythmic potential of risperidone appears to be dose related and reversible. Recent experimental work has suggested that risperidone has electrophysiological properties similar to those of class III antiarrhythmics (1) like sotalol and amiodarone, both of which can cause sinus brady-

cardia and sinus pauses. Like class III antiarrhythmics, risperidone causes concentration-dependent block of the rapid component of the delayed rectifier K^+ current (I_{Kr}) in voltage-clamped canine ventricular myocytes (1). We believe that risperidone should be included in the ever-growing list of drugs that induce bradyarrhythmias.

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Antipsychotic-Induced Paroxysmal Perceptual Alteration

TO THE EDITOR: Antipsychotics have sometimes been reported to induce brief and recurrent episodes characterized by hypersensitivity of visual perception (1, 2). However, some researchers still believe that this paroxysmal perceptual alteration is a schizophrenic symptom because the patients with paroxysmal perceptual alteration were diagnosed with schizophrenia. We report on a nonschizophrenic patient who experienced paroxysmal perceptual alteration only during exposure to antipsychotics.

Ms. A, a 49-year-old woman with a 2-year history of generalized anxiety disorder, had suffered from dizziness, anxiety, and syrigmus. Ophthalmologic, otolaryngological, and neurological examinations showed no abnormality, including cataract, and she had good vision and did not wear glasses. Her symptoms did not respond to antidepressants or anxiolytics. Haloperidol, 0.5 mg b.i.d., was added to her regular regimen of alprazolam, 1.2 mg t.i.d., because she became obsessed with her symptoms. Two days after haloperidol treatment was started, the following symptoms occurred: "The fine pattern of the wall and ceiling seems more vivid than usual. I have also noticed that outlines of papers and tiny objects such as dust seem more prominent. These symptoms occur suddenly like an 'attack' almost every afternoon and last an hour."

These symptoms disappeared 2 days after haloperidol treatment was discontinued. Although Ms. A subsequently tried various antidepressants and anxiolytics, none of them ameliorated her original symptoms. Then we prescribed methotrimeprazine (levomepromazine) alone, 10 mg at bedtime, and on the second day she experienced the same symptoms as those induced by haloperidol: "I am having the same 'attacks.' Light seems much brighter than usual. Tiny objects like dust and stains seem to be emphasized for a couple of hours every night."

The bizarre symptoms disappeared soon after we switched the methotrimeprazine to vitamin E, 150 IU/day, as she requested. Her medication regimen has remained the same ever since.

To our knowledge, this is the first report of a nonschizophrenic patient whose exposure to antipsychotics led to paroxysmal perceptual alteration twice. This case shows that this phenomenon can occur in patients treated with antipsychotics regardless of their diagnosis. The evening appearance of this phenomenon might be explained by the circadian pat-

tern of antipsychotic-induced side effects (3). Dopamine receptor antagonists can induce dopamine deficiency in the retina and the visual cortex, which is known to modulate visual processing, including contrast sensitivity (4, 5). The altered visual processing might lead to paroxysmal perceptual alteration. Physicians prescribing antipsychotics should be alert to this potentially important side effect.

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