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CASE REPORT

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Fatality from Olanzapine Induced Hyperglycemia

ABSTRACT: A case history of a 31-year-old male schizophrenic patient is presented. The man was treated with olanzapine for three weeks before he died. After one week on a 10 mg daily dose of olanzapine, his fasting blood glucose was elevated to 11.3 mmol/L (203 mg/dL). In order to treat more aggressively his psychosis, the olanzapine dose was raised to 20 mg daily resulting in his fasting blood glucose climbing to 15.8 mmol/L (284 mg/dL). On the days preceding his death, he became progressively weaker, and developed polydipsia with polyuria. He had no personal or family history of diabetes mellitus and he was on no other medication at the time of his death.

Postmortem blood, vitreous humor, and urine glucose concentrations were 53 mmol/L (954 mg/dL), 49 mmol/L (882 mg/dL), and 329 mmol/L (5922 mg/dL), respectively. Drug screen on urine and blood indicated only a small amount or olanzapine and no alcohols. Peripheral blood olanzapine concentration was within therapeutic limits, 45 ng/mL.

Analysis of vitreous humor and urine revealed severe dehydration with small amounts of ketones. Death was attributed to hyperosmolar nonketotic diabetic coma, and olanzapine was felt most likely to be the cause.

Another atypical neuroleptic, clozapine, has also been associated with the development and exacerbation of diabetes mellitus or diabetic ketoacidosis. We recommend including vitreous glucose and β-hydroxybutyrate analysis as part of postmortem toxicology work up when the drug screen reveals the presence of either olanzapine or clozapine.

KEYWORDS: forensic science, olanzapine, hyperglycemia, diabetes, fatality, adverse reaction

Olanzapine and clozapine are termed atypical neuroleptic drugs. They are popular treatment choices for schizophrenia because they show fewer of the extrapyramidal side effects commonly encountered with the traditional neuroleptics such as chlorpromazine and thioridazine (1). Recently, however, there are literature reports of patients who have developed diabetes mellitus or diabetic ketoacidosis after starting olanzapine or clozapine treatment (2,3). The onset of symptoms occurred a few weeks to several months after beginning drug therapy. There are no reports relating to risperidone, sertindole or amisulpride (2), and just one report implicating hyperglycemia with the initiation of quetiapine therapy (4).

The following case report describes the clinical course of a schizophrenic patient who developed hyperglycemia and died from hyperosmolar nonketotic diabetic coma. His postmortem blood olanzapine concentration was therapeutic.

Case Report

The decedent, a 31-year-old man, had a history of paranoid schizophrenia with a complex set of bizarre delusions, as well as alcohol and recreational drug abuse. There was no personal or family history of diabetes mellitus. He was poorly compliant with his medication and had a number of involuntary admissions to psychiatric facilities in the years prior to his death. Treatment at these admissions included haloperidol and risperidone. Eight months prior to his death he was admitted for more than three weeks and treated this time with olanzapine, 10 mg per day. He showed significant improvement during his stay, and was eventually discharged on the same prescription.

The patient reportedly took his medication regularly for several weeks before deciding he no longer required it. A five month period of noncompliance followed, culminating in his involuntary admission with frank psychosis just one month before his death. At this time his body weight was 81 kg (178 lb); he had gained 12 kg while refraining from taking his olanzapine. A random blood glucose level measured in the emergency room was acceptably low, 7.2 mmol/L (130 mg/dL). He was again started on a 10 mg daily dose of olanzapine. One week later, his fasting blood glucose was elevated to 11.3 mmol/L (203 mg/dL). His olanzapine dose was further increased to 20 mg. His psychosis steadily improved. However, after a week at this dosage, his fasting blood glucose had climbed to 15.8 mmol/L (284 mg/dL). He was discharged two days later with a prescription for olanzapine, 20 mg daily. He resided with his brother. According to his brother, he took his medication regularly, but developed abdominal discomfort and loss of appetite with progressive polydypsia and polyuria in the week following his discharge. The day before his death, he was reportedly so weak that he needed assistance to go to the bathroom. He was found dead in bed. A pill count was consistent with his prescribed usage.

An autopsy conducted the following morning revealed no anatomical cause of death. The pancreas showed no evidence of any pathological abnormality. The decedent's body weight was 82 kg (180 lb), and he had a body mass index of 29 kg/sqm (normal male <27). Toxicological analysis of body fluids revealed the findings illustrated in Table 1. These findings support the diagnosis of uncontrolled diabetes mellitus with terminal dehydration. Death

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TABLE 1—*Findings of toxicological analysis of body fluid.*

		Blood	Vitreous	Urine
Olanzapine	ng/mL	45	115	205
Glucose	mmol/L	53 ↑	49 ↑	329 ↑
	mg/dL	954	882	5922
HbA1c	%	12.3 ↑	na	na
β-hydroxybutyrate	mmol/L	0.4 ↑	1.6 ↑	0.5 ↑
Acetone	mmol/L	0†	0.9 ↑	0†
	mg/dL		5.2	
Na	mmol/L	nd	174 ↑	30 ↓
K	mmol/L	nd	14.3 ↑	27 ↓
Cl	mmol/L	nd	139 ↑	33 ↓
Urea	mmol/L	nd	18.3 ↑	57 ↓
	mg/dL		51*	159*
Creatinine	μmol/L	nd	74	2500 ↓
	mg/dL		0.83	28.2

NOTE:
na: not applicable.
nd: not done.
↑ above normal reference range.
↓ below normal reference range.
† LoQ = 0.8 mmol/L (4.6 mg/dL).
* mg/dL as nitrogen.

was attributed to complications of diabetes mellitus (hyperosmolar nonketotic diabetic coma).

Methods

Peripheral blood, urine, and vitreous humor were submitted for toxicology work-up. Urine was screened by GC-MS for basic, acid, and neutral drugs. Basic drugs were detected using a modified method of Foerster et al. (5), whereas acid and neutral drugs were detected using the method described by Meatherall (6) for barbiturate analysis. Drugs of abuse testing was performed on the urine sample by Hitachi 717 analyzer (Roche Diagnostics, Laval, QC) using CEDIA (Microgenics, Freemont, CA) for the benzodiazepines and EMIT II Plus (Syva, Palo Alto, CA) for all others. Alcohols, including acetone, were screened by gas chromatography on a 1.83 m Carbopack B column coated with 5% Carbowax 20M (7). Direct injection (8) was used for sample introduction.

Pure olanzapine and its ethyl analogue LY170222 were received from Eli Lilly and Company (Indianapolis, IN). Structures of these two compounds are depicted in the article by Catlow et al. (9) who describe an analytical method for olanzapine in plasma by HPLC. The primary metabolites, N-desmethylolanzapine and 2-hydroxymethylolanzapine were not available. Stock standards were prepared at 1 mg/mL in acetonitrile. A substock olanzapine standard, 10 μg/mL in acetonitrile, was used to prepare standards in biological fluids between 0 and 500 ng/mL. The internal standard diluted to 10 μg/mL in acetonitrile was used in sample preparation.

After the addition of ascorbic acid to standards and case samples, the olanzapine was analyzed by solvent extraction and GC-MS. The ascorbic acid prevents olanzapine oxidation during sample preparation (9,10) and reduces any of the previously oxidized drug that could be present in the case samples (10). The dramatic in vitro olanzapine reduction that can occur in postmortem samples over just a few weeks has been reported by Anderson (11) and Levine (12). Oxidation of olanzapine to olanzapine-S-oxide (13) is analogous to the oxidation of some phenothiazines such as chlorpromazine and perphenazine (12).

The following were pipetted into 20 mL glass extraction tubes: 1 mL of blood, urine or vitreous, 30 μL of internal standard, 100 μL of 2% ascorbic acid, 0.8 mL of 1 mol/L (pH 9) bicarbonate buffer, 4 mL of methyl-t-butyl-ether and 2 mL of methylene chloride. The tubes were sealed with teflon lined caps and mixed by inversion for 15 min. After centrifugation, the organic layer was transferred to a 5 mL conical tube containing 100 μL of 0.1 mol/L HCl. The organic layer was evaporated under a stream of nitrogen at room temperature. The HCl layer was washed with hexane to remove lipids, then aspirated to waste. After alkalinizing with 100 μL of 1 mol/L (pH 9) bicarbonate buffer, the aqueous layer was extracted into 2 mL of methylene chloride. The phases were separated by centrifugation; the aqueous portion was aspirated to waste. The methylene chloride was evaporated under a nitrogen stream. The residue was reconstituted in 30 μL of acetonitrile and 1 μL injected into the mass spectrometer. The GC-MS was an ITS40 ion trap running Magnum software (Thermoquest Finnigan, San Jose, CA). Separation was performed with a DB-1, 15 m × 0.25 mm, 0.25 μm film methyl silicone capillary column. A 1 m × 0.52 mm retention gap deactivated with 5% phenyl methyl silicone connected the analytical column to the temperature programmable injector. Helium carrier gas flowed at 45 cm/s. The oven was initially held at 80°C for 1 min, then programmed at 10°C to a final temperature of 290°C where it was held for 5 min. The temperature programmable injector was ramped from 85°C to 290°C at 13°C. Electron impact mass spectra were collected in full scan from 44 to 650 amu at 1 scan/s. Under these conditions, olanzapine and the internal standard eluted at 1015 and 1048 s, respectively. Mass spectral fits to olanzapine were greater than 900 of a possible 1000. The quantitation ions were the base peak ions, 242 and 256 amu. Linear regression of the calibration standards and interpolation of the case samples was handled by the Magnum software.

Glucose in postmortem blood was measured by the AccuSoft glucose meter (Roche). Urine and vitreous glucose were measured by the hexokinase method on the Hitachi 717 analyzer (Roche) after appropriate dilutions. Electrolytes, urea, creatinine and β-hydroxybutyrate were measured using standard methods on the Hitachi 717 analyzer. Hemoglobin A1c was measured on a Hitachi 917 by the Tina-quant (Roche) method.

Results

Only olanzapine was detected in the urine GC-MS drug screen. Drugs of abuse testing were negative. No alcohols were present.

A portion of the total ion chromatogram of the case blood extract is shown in Fig 1. The extracted ion chromatogram for m/z = 242 and 256, corresponding to the base peaks for olanzapine and the internal standard mass spectra are displayed below the total ion chromatogram. These two ions were used to calculate olanzapine concentrations in the case fluids. The blood concentration was therapeutic, 45 ng/mL. The corresponding mass spectra of these two compounds are inlays on the extracted ion chromatograms. The parent molecular ions, m/z = 312 and 326 are prominent ions in the respective mass spectra.

A summary of analytical results appears in Table 1. Postmortem glucose concentrations in all three fluids were extremely high. Normal fasting serum glucose is 3.6–6.1 mmol/L (64–110 mg/dL). The blood glucose, 53 mmol/L (954 mg/dL), and the vitreous glucose, 49 mmol/L (882 mg/dL) agree with each other. The urine dipstick showed positive results for glucose (>2%), protein (1 g/L) and blood (250/μL) and normal results for specific gravity (1.010), pH (7.0), leucocytes (negative), bacterial nitrites (negative), ketones (negative), urobilinogen (negative), bilirubin (negative). The positive protein was likely due to the urine specimen being contaminated with blood. Glucose was analyzed on an aliquot of di-

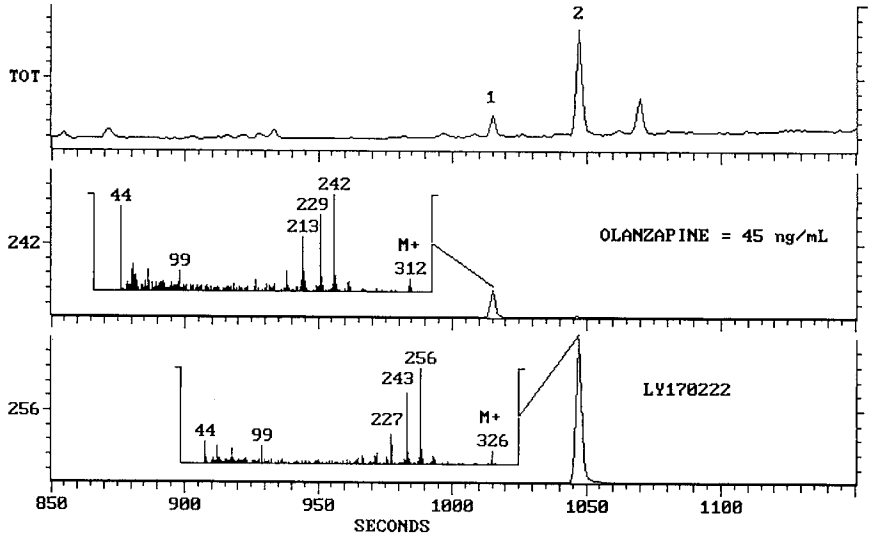

FIG. 1—*Total ion current (m/z = 44–650) and extracted ion chromatograms for olanzapine (m/z = 242) and the internal standard LY170222 (m/z = 256) over a portion of the chromatogram. Case blood olanzapine concentration = 45 ng/mL. Peak 1, olanzapine; peak 2, internal standard.*

luted urine by the hexokinase method and found to be extremely elevated, 329 mmol/L (5922 mg/dL).

Hemoglobin A1c was 12.3% (normal 4.8–6.0%) supporting the likelihood of a prevailing elevated blood glucose in the preceding weeks. As shown by Hindle et al. (14), glycated hemoglobin is far less susceptible than glucose to changes in postmortem blood. The β-hydroxybutyrate was only slightly elevated in the urine, 0.5 mmol/L and in the vitreous humor, 1.6 mmol/L. Likewise, acetone was only slightly elevated in the vitreous humor, 0.9 mmol/L (5.2 mg/dL) and undetected in the blood and urine.

The elevated vitreous sodium and chloride suggest dehydration. The elevated vitreous potassium is a result of both dehydration and postmortem interval. The elevated vitreous urea with normal creatinine suggests pre-renal failure. All of the urinary electrolytes, urea, and creatinine are abnormally low because of the osmotic diuresis caused by his elevated blood glucose.

Discussion

Olanzapine concentrations were 45, 115, and 205 ng/mL in the blood, vitreous humor, and urine, respectively. These concentrations are in line with 39 previously published postmortem cases in which olanzapine was present but was not considered to be the cause of death (11,12). Anderson et al. (11) summarized 34 cases and Levine et al. (12) summarized five cases. Causes of death were varied and not necessarily toxicology related. Catlow (9) reported plasma olanzapine in the 4–55 ng/mL range for patients being treated with 2.5 to 17.5 mg of drug daily. Similar findings were published by Aravagiri et al. (15). Olesen (16) recommended a steady state target serum concentration of 7.8–46.8 ng/mL (25–150 nmol/L). His recommendation was based on the clinical response of schizophrenic patients who were given standard 5 to 20 mg daily doses. Robertson et al. (17) reviewed olanzapine concentrations in 1653 random clinical serum specimens and 58 postmortem blood specimens. Of the clinical specimens, 85% had olanzapine concentrations between 5 and 75 ng/mL. The authors conclude that toxicity primarily due to olanzapine should be considered when the blood concentration exceeds 160 ng/mL. For our case, there is no reason to suspect an acute overdose. The 45 ng/mL blood concentration is within the expected therapeutic range and is in keeping with his prescribed dose, 20 mg per day over the previous two weeks.

Olanzapine stability in biological fluids has confounded the development of distinct reference ranges. The accuracy of existing reference ranges is in question. Oxidation of olanzapine in serum samples refrigerated for one and two weeks resulted in recoveries of 45% and 13%, respectively (10). Immediate analysis resulted in 86% recovery; the loss occurred in the extraction process during analysis. The amount of oxidative loss when specimens are frozen is unknown. Both Anderson et al. (11) and Levine et al. (12) have commented on the dramatic reduction in olanzapine postmortem blood concentrations within one month. The addition of ascorbic acid to the biological fluid reverses the oxidative losses (10), and should be included in all analytical methods. Reported olanzapine concentrations could easily be falsely lowered to a point where an original toxic blood concentration is measured and reported as therapeutic. The apparent overlap of therapeutic and toxic blood concentrations reported by Robertson et al. (17) may, at least in part, be due to olanzapine instability. The authors were aware of olanzapine instability in blood and suggest it as a possible explanation for their observations. Ascorbic acid was not included in their gas chromatographic method.

Prior to June 2000, there were 15 case reports of impaired glucose tolerance in patients taking olanzapine. The same cases were summarized in two review articles (2,3). The onset of symptoms varied from a few weeks to several months after starting olanzapine. The major adverse effect was hyperglycemia in ten patients and ketoacidosis in five patients. There was no correlation to age, sex, ethnic background, or family history as predisposing factors. Clozapine, a structurally related antipsychotic, has resulted in a similar incidence of impaired glucose tolerance and the literature cases are summarized in the same two reviews (2,3). The authors recommend glucose and hemoglobin A1c monitoring for patients on olanzapine or clozapine therapy. Patients were treated by diet intervention, oral hypoglycemic agents and insulin. Most patients became normoglycemic after a week of discontinuing olanzapine or clozapine treatment. A few patients were rechallenged with the same antipsychotic and again became hyperglycemic.

Weight gain has been associated with olanzapine and clozapine therapies as a common side effect (18). There is no association of moderate weight gain with the development of diabetes although it is tempting to speculate about a common biochemical mechanism. Patients who have had large weight gain on treatment with these newer antipsychotics have often become diabetics (19). Obesity is a risk factor in developing non-insulin dependent diabetes, and thus patients taking olanzapine or clozapine could exacerbate the onset of diabetes.

Recently, Roefaro and Mukherjee (20) published an olanzapine case report of a 51-year-old man whose clinical course closely paralleled that of our case but who survived. The man presented to the emergency department with a blood glucose of 1596 mg/dL, polydipsia, polyuria and hallucinations. He developed hyperglycemic nonketotic coma which was treated with intravenous fluids and insulin. His coma resolved within 24 h. Supplemental insulin was not required eight days after discontinuing olanzapine. His fasting glucose normalized without any glucose lowering agents 16 days after discontinuing olanzapine.

The mechanism by which olanzapine provokes hyperglycemia appears to be through insulin resistance rather than through decreased pancreatic insulin secretion. Melkersson et al. (21) showed that olanzapine treatment was associated with elevated serum insulin, leptin, cholesterol, and triglycerides. The authors theorize that enhanced pancreatic insulin secretion occurs as a secondary response to insulin resistance. Leptin production is stimulated by insulin at the adipocytes (22) and has been associated with insulin resistance. Of the 14 study patients, three developed diabetes. Serum olanzapine concentrations ranged between 19–87 ng/mL (61–280 nmol/L). There was no correlation between drug concentration and any of the biochemical markers. The decedent in our case became hyperglycemic within one week of resuming his olanzapine. We hypothesize that he was sensitized to insulin resistance during his initial olanzapine treatment eight months prior. Mir and Taylor (2) in their review note that hyperglycemia returned eight days after a patient was rechallenged with olanzapine. Also, in two patients rechallenged with clozapine, hyperglycemia returned within three days.

Conclusion

When investigating postmortem cases with positive findings for the atypical neuroleptics—olanzapine, clozapine and quetiapine, glucose and β-hydroxybutyrate should then be measured in vitreous humor. Therapy with these atypical neuroleptics can cause diabetes mellitus with or without associated ketosis. Symptoms can occur even though the drug is administered in therapeutic doses and blood concentrations are within therapeutic limits.

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