JOP. J Pancreas (Online) 2004; 5(5):388-391.

CASE REPORT

Olanzapine-Induced Pancreatitis: A Case Report

Christian Waage[1], Hans Carlsson[2], Erik Waage Nielsen[1,3]

[1]Department of Anesthesiology and [2]Department of Medicine, Nordland Hospital. Bodo, Norway. [3]University of Tromso. Tromso, Norway

ABSTRACT

Context The antipsychotic agent clozapine has been linked to several cases of pancreatitis. The newer, but related, olanzapine was believed to have fewer side effects.

Case report A 42-year-old man in good physical condition gradually developed hypertriglyceridemia, hypercholesterolemia, elevated alanine aminotransferase, diabetes and, ultimately, acute pancreatitis after 19 months of olanzapine monotherapy. Due to multiorgan failure, he was in the intensive care unit and surgical ward for 29 days. He made a full recovery. The olanzapine was discontinued. Glucose, triglyceride and cholesterol levels normalized as did pancreas and liver function.

Conclusions We report olanzapine as the probable cause of acute pancreatitis in a patient without any known predisposing factors. Olanzapine-treated patients should be monitored with glucose, lipid, pancreatic function and liver function tests, and the olanzapine should be discontinued if the results of these tests worsen.

INTRODUCTION

Olanzapine (Zyprexa™, Eli Lilly and Company, Indianapolis, Indiana, USA) has become a commonly prescribed antipsychotic drug because of its assumed low association with dystonia and other extrapyramidal side effects. With sales of 4 billion US dollars, Zyprexa™ was the fourth leading pharmaceutical on the global market in 2002 [1].

Olanzapine is a thienobenzodiazepine, structurally related to the older dibenzodiazepine clozapine. Clozapine has been associated with the induction of diabetes mellitus and several cases of acute pancreatitis [2, 3, 4, 5]. Recently, new-onset diabetes, ketoacidosis and some cases of pancreatitis have also been linked to olanzapine treatment [3, 6]. We report on a case of olanzapine-induced pancreatitis in a man who had always been in good physical health.

CASE REPORT

A 42-year-old male with paranoid psychosis was treated with the antipsychotic drug olanzapine 10 mg od. Extensive blood tests prior to beginning the olanzapine therapy were normal, including alanine aminotransferase (ALAT) of 39 IU/L (reference range: 0-50 IU/L), non-fasting blood glucose of 5.9 mmol/L (reference range: 3.0-5.0 mmol/L) and total cholesterol of 4.9 mmol/L (reference range: 3.9-8.6 mmol/L). He did not use alcohol, narcotics or other medication. He was 170 cm tall and weighed 79 kg (body mass index: 27.3 kg/cm^2). After 7 months of monotherapy with olanzapine, the fasting glucose level was 8.8

mmol/L (reference range: 3.7-6.0 mmol/L), ALAT was 110 IU/L and total cholesterol was 7.3 mmol/L.

After 19 months of olanzapine monotherapy he was admitted to the local tertiary level hospital in poor physical condition. Two days prior to admission, he suffered from polydypsia and polyuria. His fasting glucose concentration was greater than 60 mmol/L and he had ketoacidosis with urinary glucose greater than 250 mmol/L (reference range: 0-1.5 mmol/L). The glycosylated hemoglobin A1c test was 12.4% (reference range: 4.5-6.0%), C-reactive protein (CRP) was 407 mg/L (reference range: 0-10 mg/L), amylase was 2,663 IU/L (reference range: 0-120 IU/L), ionized calcium was 1.08 mmol/L (reference range: 1.13-1.32 mmol/L), triglycerides were 23.1 mmol/L (reference range: 0.6-3.9 mmol/L), leukocytes were 15.6 10^9/L (reference range: 3.5-11.0 10^9/L) and total cholesterol was 14.3 mmol/L. Lipase was not measured.

On the second day of his hospital stay, the patient developed acute abdominal pain, followed by respiratory and circulatory failure. He needed a respirator and vasopressors. An abdominal CT scan was performed without contrast due to rapidly developing renal failure. The pancreas was enlarged with poorly defined borders. There were signs of peripancreatic inflammation and fluid was visible around the liver, spleen, small intestines and in the pelvis. The abdomen was firm, distended and board-like with extensive guarding. Bowel sounds were absent. An explorative laparotomy showed an edematous pancreas with yellow plaques and nodules on the duodenum and in the infracolic space and excessive ascites. The gallbladder was normal. He was treated with the antibiotic imipenem. The patient developed acute renal failure with creatinine values over 700 μmol/L. After three days in the local tertiary hospital, he was transferred to the intensive care unit (ICU) in the primary level hospital for hemodiafiltration. His antibiotic was changed to meropenem. Amylase and CRP gradually declined. Vasopressors were reduced and respirator weaning was started. The patient was transferred to the ICU in a secondary level hospital on day 10 for continued hemodiafiltration. He was treated for invasive candida infection with fluconazole. The patient was extubated on day 14. Dialysis treatment ended on day 16. An ultrasound on day 16 confirmed the previous finding of a normal gallbladder. The patient was transferred to the local third level hospital on day 18. A CT scan of the abdomen on day 28 showed signs of pancreatic pseudocysts, but no abscesses. He was discharged on day 29 in good physical condition. On day 53, amylase, triglyceride and blood glucose levels were normal. Insulin was discontinued.

DISCUSSION

Olanzapine is believed to exert its pharmacological action by transiently occupying dopamine D2 receptors and then rapidly dissociating to allow normal dopamine neurotransmission. This would keep prolactin levels normal, maintain cognitive attitudes, and reduce extrapyramidal symptoms as compared to the older anti-psychotics [7]. This last effect has recently been questioned though [8].

According to the manufacturer's data sheet, the common adverse effects of olanzapine (i.e. with a frequency greater than 10%) include sedation, weight gain and hyperprolactinemia [9]. Among the common adverse effects (frequency: 1-10%), transient elevations in liver transaminases were also seen. Reports of diabetic coma, diabetic ketoacidosis and pancreatitis were rare (less than 0.01%). A recent review of studies and case reports showed that hyperglycemia, diabetes mellitus type II and diabetic ketoacidosis were more frequently reported in patients receiving clozapine and olanzapine as compared to conventional antipsychotics [10]. The mechanism is unclear, but insulin and leptin may play a role as may triglycerides and the weight-inducing effect of atypical antipsychotics [10, 11]. However, olanzapine may also affect glucose metabolism in the absence of weight gain [12]. Even though primary damage to the pancreatic islet cells

and/or sympathetic dysregulation has been mentioned, the most probable explanation is that the pancreatic toxicity of olanzapine is mediated by the metabolic effects of the drug [6].

Some few cases of olanzapine-induced pancreatitis have been published since 2000 [13, 14]. Of the reports reviewed by the Food and Drug Administration's MedWatch, 39% dealt with clozapine, 33% olanzapine, 16% risperidone and 12% haloperidol [3]. Although psychiatric patients may have had complicating substance abuse and alcohol consumption, it was not present in all the reports. This was also the case in our patient where the common causes of acute pancreatitis, e.g. trauma, cholelithiasis, ethanol, hypercalcemia and other drugs, were ruled out as the source of the acute pancreatitis.

Our patient had used olanzapine for 19 months. In most reported cases, pancreatitis occurred within six months after administration [3]. In one case, however, diabetes and acute pancreatitis presented after more than 12 months of olanzapine use [15].

Considering the aforementioned points discussed and the rapid and sustained normalization of lipids and blood glucose which our patient experienced upon olanzapine discontinuation, we believe that olanzapine was the probable cause of the pancreatitis.

Owing to its potential for fatal clinical deterioration and chronic complications, and because pancreatitis may improve upon discontinuation of olanzapine, clinicians and psychiatrists should be alert to its possible adverse effect.

Received July 6th, 2004 - Accepted July 16th, 2004

Keywords Antipsychotic Agents /adverse effects; Diabetes Mellitus; Pancreatitis

Abbreviations ALAT: alanine amino-transferase; ICU: intensive care unit

Correspondence
Erik Waage Nielsen
Department of Anesthesiology
Nordland Hospital
8092 Bodo
Norway
Phone: +47-7555.34000
Fax: +47-8503.1206
E-mail address: erikwn@fagmed.uit.no

References

1. Medicines and Health Care. Oslo, Norway: Norwegian Association of Pharmaceutical Manufacturers, 2004. Page 86. [ISSN 1503-352X]

2. Wehring H, Alexander B, Perry PJ. Diabetes mellitus associated with clozapine therapy. Pharmacotherapy 2000; 20:844-7. [PMID 10907975]

3. Koller EA, Cross JT, Doraiswamy PM, Malozowski SN. Pancreatitis associated with atypical antipsychotics: from the Food and Drug Administration's MedWatch surveillance system and published reports. Pharmacotherapy 2003; 23:1123-30. [PMID 14524644]

4. Popli AP, Konicki PE, Jurjus GJ, Fuller MA, Jaskiw GE. Clozapine and associated diabetes mellitus. J Clin Psychiatry 1997; 58:108-11. [PMID 9108812]

5. Cerulli TR. Clozapine-associated pancreatitis. Harv Rev Psychiatry 1999; 7:61-3. [PMID 10439307]

6. Goldstein LE, Sporn J, Brown S, Kim H, Finkelstein J, Gaffey GK, et al. New-onset diabetes mellitus and diabetic ketoacidosis associated with olanzapine treatment. Psychosomatics 1999; 40:438-43. [PMID 10479950]

7. Seeman P. Atypical antipsychotics: mechanism of action. Can J Psychiatry 2002; 47:27-38. [PMID 11873706]

8. Leucht S, Wahlbeck K, Hamann J, Kissling W. New generation antipsychotics versus low-potency conventional antipsychotics: a systematic review and meta-analysis. Lancet 2003; 361:1581-9. [PMID 12747876]

9. Eli Lilly. Data Sheet. ZYPREXA™ & ZYPREXA ZYDIS™ Olanzapine tablets 2.5 mg, 5 mg, 10 mg. Olanzapine wafers 5 mg, 10 mg. Information for Health Proffesionals. Auckland, New Zealand: Eli Lilly and Company (NZ) Limited, 2004.

10. Wetterling T. Diabetes Mellitus Type II - Induced by 'Atypical' Neuroleptics? Fortschr Neurol Psychiatr 2003; 71:312-22. [PMID 12796851]

11. Melkersson KI, Hulting AL, Brismar KE. Elevated levels of insulin, leptin, and blood lipids in olanzapine-

treated patients with schizophrenia or related psychoses. J Clin Psychiatry 2000; 61:742-9. [PMID 11078035]

12. Ramankutty G. Olanzapine-induced destabilization of diabetes in the absence of weight gain. Acta Psychiatr Scand 2002; 105:235-6. [PMID 11939979]

13. Doucette DE, Grenier JP, Robertson PS. Olanzapine-induced acute pancreatitis. Ann Pharmacother 2000; 34:1128-31. [PMID 11054978]

14. Hagger R, Brown C, Hurley P. Olanzapine and pancreatitis. Br J Psychiatry 2000; 177:567. [PMID 11102343]

15. Ragucci KR, Wells BJ. Olanzapine-induced diabetic ketoacidosis. Ann Pharmacother 2001; 35:1556-8. [PMID 11793618]