OMCR

Oxford Medical Case Reports, 2019;3, 117–119

doi: 10.1093/omcr/omz012
Case Report

CASE REPORT

Muscle relaxant induced pancreatitis leading to hyperosmolar hyperglycemic state

Yicheng K. Bao[1,*], Vishwanath C. Ganesan[1], Winston Jiang[2], Lydia Lin[3], Norwood R. Brown[1], Kristy E. Steigerwalt[1] and Amy Z. Yu[4]

[1]Department of Medicine, University of Missouri–Kansas City School of Medicine, Kansas City, USA, [2]Brown University Alpert School of Medicine, Providence, USA, [3]Department of Biomedical Engineering, McKelvey School of Engineering and Applied Science, Washington University, St. Louis, USA, and [4]Little Rock Diagnostic Clinic, CHI St. Vincent, Little Rock, USA

*Correspondence address. University of Missouri–Kansas City School of Medicine, 2411 Holmes Street, Kansas City, MO 64108, USA. Tel: +1-501-349-7721; E-mail: ybao@umkc.edu

Abstract

Muscle relaxants are commonly prescribed in the United States but may have deleterious side effects that are unrecognized by physicians. Here, we report a 55-year-old Caucasian man who developed pancreatitis and a subsequent hyperosmolar hyperglycemic state after being prescribed tizanidine. The patient had untreated hypertriglyceridemia, unbeknownst to the prescribing physician. While hypertriglyceridemia is a widely understood risk factor for pancreatitis, its incidence with tizanidine is not. As an alpha-2 agonist, tizanidine slows gastrointestinal motility by inhibiting gastrointestinal smooth muscle contraction, which could lead to ileus which occurred in this patient. Alpha-2 agonists further contract the hepatopancreatic sphincter, which may result in obstruction of pancreatic enzyme flow via the pancreatic duct. This patient's case of pancreatitis was precipitated by 2 factors: (i) his use of tizanidine and (ii) hypertriglyceridemia. This case demonstrates that patients presenting with severe hypertriglyceridemia, or other potential risk factors for pancreatitis, should not be prescribed tizanidine.

CASE REPORT

A 55-year-old Caucasian male with a past medical history of hypertension and hyperlipidemia presented to the emergency department with nausea, vomiting and mental status changes. Patient history revealed an injury to his back after lifting heavy objects a few days prior. This injury prompted a visit to his primary care physician who prescribed the muscle relaxant tizanidine hydrochloride (Zanaflex®), without baseline laboratory testing. Preceding this visit, he had not followed up with his primary care provider for 2 years, was taking no medications for his hypertension or hyperlipidemia, nor was he taking any additional prescribed medications or over the counter supplements. After ingesting tizanidine, the patient became excessively drowsy. The following day, he became delirious, could not be roused by his family, and was subsequently brought to the emergency department.

On review of systems, the patient reported that he had been recently experiencing fatigue, polyuria and polydipsia, as well as 20 pound weight loss over the past 3 months. On physical examination, he was comatose, febrile at 101.2 °F, and his systolic blood pressure was 60 mmHg. Laboratory data is displayed in Table 1. Notably, labs showed glucose was 1811 mg/dL

Received: September 18, 2018. **Revised:** November 26, 2018. **Accepted:** January 25, 2019

Table 1: Laboratory findings for this patient

Laboratory test	Serum levels
Glucose (80–107 mg/dL)	1811 mg/dL
Na+ (136–146 mg/dL)	129.2 mEq/L
K+ (3.50–5.50 mEq/L)	6.86 mEq/L
Cl– (98–107 mEq/L)	94.09 mEq/L
Creatinine (0.6–1.2 mg/dL)	2.0 mg/dL
Ca2+ (8.2–10.8 mg/dL)	11.2 mg/dL
Phosphate (2.3–4.7 mg/dL)	0.7 mg/dL
Mg (1.56–2.52 mg/dL)	1.86 mg/dL
Alanine aminotransferase (10–40 U/L)	418 U/L
Aspartate aminotransferase (8–48 U/L)	975 U/L
Lipase (8–78 U/L)	106 U/L
Amylase (25–125 U/L)	339 U/L
Alkaline phosphatase (80–150 U/L)	92 U/L
pH (7.350–7.450)	7.396
pO2 (80–100 mmHg)	74.00 mmHg
pCO2 (25–45 mmHg)	29.9 mmHg
HCO3 (22–26 mEq/L)	17.9 mEq/L
Total cholesterol (0–200 mg/dL)	196 mg/dL
Triglycerides (0–150 mg/dL)	352 mg/dL
HDL (15–100 mg/dL)	38 mg/dL
LDL (<99 mg/dL)	88 mg/dL

(80–107 mg/dL), creatinine 2.0 mg/dL (0.6–1.2 mg/dL), and WBC count 9300 with a left shift. Alanine aminotransferase (ALT) (10–40 U/L) and aspartate aminotransferase (AST) (8–48 U/L) were elevated at 418 and 975 U/L, respectively; lipase 106 U/L (8–78 U/L) and amylase 339 U/L (25–125 U/L) were as well. Alkaline phosphatase was 92 U/L (80–150 U/L). The metabolic panel included hyponatremia, hyperkalemia, hypochloridemia, hyperkalcemia, elevated creatinine, hypophosphatemia, etc. pH was 7.396 (7.350–7.450), pO2 74.0 mmHg (80–100 mmHg), pCO2 29.9 mmHg (35–45 mmHg) and HCO3 17.9 mEq/L (22–26 mEq/dL). A fasting lipid profile obtained 2 years prior by the primary care provider indicated a history of hyperlipidemia: total cholesterol 196 mg/dL (0–200 mg/dL), triglycerides 352 mg/dL (0–150 mg/dL), HDL 38 mg/dL (15–100 mg/dL) and LDL 88 mg/dL (<99 mg/dL). A lipid profile obtained in the emergency department indicated hyperlipidemia: total cholesterol 380 mg/dL, triglycerides 1125 mg/dL and HDL 9 mg/dL. Abdominal CT showed proximal small bowel thickening with mesenteric edema. In addition, there was increased fluid signal, and swelling of the pancreatic head with fluid in the pararenal spaces. No peripancreatic pseudocyst was identified. His liver showed significant steatosis. Due to his severely increased liver enzymes and acute pancreatitis, MRI ERCP was performed the next day. No evidence of cholelithiasis or choledocholithiasis was found, nor were biliary stones or masses visible.

The patient was intubated for airway protection, treated with insulin drip, intravenous fluids and required vasopressor support. Tizanidine was discontinued. The patient's osmolar status resolved and he regained consciousness 2 days after discontinuation. After three days of intravenous fluid, insulin drip and fasting, the patient's hypertriglyceridemia decreased to 437 mg/dL. The patient was then extubated. He was discharged on Day 7 with normalized electrolytes. His diabetes was initially managed with insulin.

On follow-up, his diabetes was under moderate control with Metformin 1 g two times a day, and insulin was discontinued. Triglycerides were below 300 mg/dL following a regimen of diet and exercise. He was started on Atorvastatin 20 mg daily for his cholesterol and Lisinopril 10 mg daily for his hypertension. He had no complaints of pancreatitis. His liver enzymes were slightly elevated due to persistent fatty liver. He was subsequently able to follow a low-carbohydrate, low-fat diet which resulted in continued weight loss.

DISCUSSION

In summary, this patient presented with undiagnosed type 2 diabetes, severe hypertriglyceridemia, and oral tizanidine use which we suspect caused acute pancreatitis and mental status changes. Acute pancreatitis further precipitated a hyperglycemic hyperosmolar event that resulted in this patient's comatose state.

This episode of acute pancreatitis was potentially precipitated by two factors: (i) use of tizanidine and (ii) hypertriglyceridemia. Tizanidine, an alpha-2 adrenergic agonist [1], is a commonly used muscle relaxant that is used to treat muscle tightness, cramping and spasms. While many complications of this drug are well documented, the effects of using this drug in patients with severe hypertriglyceridemia, to our knowledge, have not been reported in the literature.

Hypertriglyceridemia is a well-documented cause of acute pancreatitis [2]. Chylomicrons are the largest transporter of triglycerides, up to 600 nm in width [3]; it is postulated that these large particles obstruct the pancreatic vasculature and cause ischemia and infarction distal to the blockage, leading to acute pancreatitis. Additionally, lipase within the pancreas may be exposed to fatty acid contained within the chylomicron, resulting in excess fatty acid release, which ultimately may trigger activation of pancreatic lipases.

Alpha-2 agonists are commonly prescribed in the USA as muscle relaxants. Tizanidine is an alpha-2 receptor agonist which potentially influenced this patient's episode of acute pancreatitis. The alpha-2 adrenergic receptor is a G-protein coupled receptor (GPCR) present in a wide variety of tissues, such as vascular smooth muscle, coronary arteries, salivary glands and the gastrointestinal tract. Its specific actions on the gastrointestinal tract include contraction of sphincters and decreased motility of the smooth muscle within the gastrointestinal tract [4, 5]. Activation of the alpha-2 receptor causes contraction of the hepato-pancreatic sphincter (sphincter of oddi), leading to obstruction of pancreatic enzyme flow via the pancreatic duct, resulting in acute pancreatitis. Furthermore, alpha-2 adrenergic agonists like tizanidine slow gastrointestinal motility by inhibiting gastrointestinal smooth muscle contraction, leading to ileus, which occurred in this patient. Consequently, backing up the pressure in the biliary tract likely exacerbated this episode of acute pancreatitis. Although hypertriglyceridemia was likely the major contributor to acute pancreatitis in this case because the serum values were more than twice normal, the concomitant use of tizanidine likely precipitated this attack.

Previously, one case of tizanidine causing pancreatitis was reported in the literature [6]. The United States Food and Drug Administration Adverse Events Reporting System (FAERS) lists nineteen cases of reported pancreatitis since 2003 in patients taking tizanidine [7]. It is possible that tizanidine's effects on GI tract motility lead to the development of pancreatitis in these patients. Further cases of pancreatitis may occur without reporting to the FAERS due to unknown pathophysiology.

In summary, patients with severe hypertriglyceridemia, or other potential risk factors for pancreatitis should not be prescribed tizanidine. In addition, tizanidine may need to be stopped in patients presenting with severe hypertriglyceridemia.

CONFLICT OF INTEREST STATEMENT

None to report for any author.

FUNDING

UMKC School of Medicine Sarah Morrison Research Award (YKB, VCG).

CONSENT

Written patient consent was obtained.

REFERENCES

1. Coward DM. Tizanidine: neuropharmacology and mechanism of action. *Neurology* 1994;**44**:S6–10; discussion S10–11.
2. Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J. *Harrison's Principles of Internal Medicine 19/E (Vol.1 & Vol.2) (ebook)*. New York: McGraw-hill, 2015.
3. Martins IJ, Mortimer BC, Miller J, Redgrave TG. Effects of particle size and number on the plasma clearance of chylomicrons and remnants. *J Lipid Res* 1996;**37**:2696–705.
4. Sagrada A, Fargeas MJ, Bueno L. Involvement of alpha-1 and alpha-2 adrenoceptors in the postlaparotomy intestinal motor disturbances in the rat. *Gut* 1987;**28**:955–9.
5. Coelho JC, Gouma DJ, Moody FG, Li YF, Weisbrodt NW. Influence of autonomic drugs on the motility of the sphincter of Oddi in the opossum. *Surg Gynecol Obstet* 1986;**163**:209–14.
6. Newman PM, Nogues M, Newman PK, Weightman D, Hudgson P. Tizanidine in the treatment of spasticity. *Eur J Clin Pharmacol* 1982;**23**:31–5. doi:10.1007/BF01061374.
7. US Food and Drug Administration. *FDA Adverse Events Reporting System (FAERS)*. https://fis.fda.gov/sense/app/d10be6bb-494e-4cd2-82e4–0135608ddc13/sheet/7a47a261-d58b-4203-a8aa-6d3021737452/state/analysis. Updated June 30, 2018. (24 July 2018, date last accessed).