Propofol-Induced Pancreatitis

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Propofol is a sedative hypnotic agent administered as a fat emulsion for sedation of critically ill patients in the intensive care unit (ICU). It is effective in both adults and children for inducing and maintaining general anesthesia in surgical procedures. Propofol can be easily titrated and has gained popularity for use in the ICU setting. Recently, propofol has been implicated as a cause of acute pancreatitis.[1–7] The pathogenesis of drug-induced pancreatitis is not well understood.

This article reports a case of presumed propofol-induced pancreatitis that occurred in an ICU. This episode was associated with increased levels of triglycerides. After propofol was discontinued, the pancreatitis resolved and the patient's triglyceride level returned to normal. This article demonstrates that critically ill patients with multiple coexisting medical conditions and medications may be at risk for developing acute pancreatitis as a result of propofol administration.

CASE PRESENTATION

Initial Presentation and History

A 70-year-old man with type 2 diabetes mellitus and hypertension presented to the emergency department (ED) with a 1-day history of fever, lower abdominal pain, and 1 episode of vomiting. His temperature recorded at home was 103°F (39.4°C). Prior to his arrival at the ED, his family found him to be mildly confused. He did not have diarrhea or constipation, and he had no complaints of chest pain, shortness of breath, or cough. He had no history of alcohol or recreational drug use, and he stopped smoking cigarettes 34 years ago. Past medical history was unremarkable for gallstones, hypertriglyceridemia, or pancreatitis, and he had a remote history (in the 1980s) of deep vein thrombosis. His home medications included losartan potassium, metformin, and amlodipine.

Physical Examination

The initial physical examination revealed a mildly confused man who was tachypneic. His temperature was 103.4°F (39.7°C), pulse was 72 bpm, respiratory rate was 36 breaths/min, and blood pressure was 136/42 mm Hg. His oxygen saturation was 96% on room air. His neck was supple. The lungs were clear to auscultation, and air entry was good and equal on both sides. The cardiovascular examination revealed normal heart sounds, and there was no murmur. Auscultation of the abdomen revealed normal bowel sounds, and the abdomen was soft and nontender. There was no lymph node enlargement. Results of the rectal examination were normal with no enlargement of the prostate.

Laboratory and Diagnostic Evaluations

The patient's blood chemical values on admission are presented in **Table 1**. The complete blood count showed a leukocyte count of $16.9 \times 10^3/mm^3$ with 95% neutrophils, hemoglobin level of 10.1 g/dL, and platelet count of $194 \times 10^3/mm^3$. The urinalysis revealed positivity for protein and leukocyte esterase; leukocyte count of 21–30/high power field (HPF); erythrocytes packed/HPF; and epithelial cell count of 0–2/HPF.

A computed tomographic scan (with oral contrast and without intravenous [IV] contrast) of the abdomen performed at the time of admission showed a normal pancreas, liver, spleen, and appendix. The abdominal obstructive series showed distended colon with mild mucosal thickening. An electrocardiogram was performed and showed a normal sinus rhythm.

Hospital Course

The initial clinical diagnosis in the ED for this patient was sepsis, which was presumed to be secondary to a urinary tract infection. The differential diagnosis at this

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Table 1. Serum Laboratory Values of Case Patient on Admission

Variable	Result	Normal Value
Urea nitrogen (mg/dL)	32	10–26
Creatinine (mg/dL)	2.6	0.7–1.5
Total bilirubin (mg/dL)	1.16	0.20–1.20
Calcium (mg/dL)	7.6	8.2–10.7
Magnesium (mg/dL)	1.2	1.6–2.2
Phosphate (mg/dL)	3.1	2.5–4.5
Albumin (g/dL)	3.2	3.5–5.2
Aspartate aminotransferase (IU/L)	15	0–41
Alanine aminotransferase (IU/L)	14	0–65
Alkaline phosphatase (IU/L)	63	50–136
Electrolytes (mEq/L)		
Sodium	121	135–145
Potassium	4.1	3.4–5.2
Chloride	88	96–109
Carbon dioxide	23.5	24–32

Table 2. Case Patient Lipase, Amylase, and Triglyceride Levels Over Time

Hospital Day	Lipase* (IU/L)	Amylase† (mg/dL)	Triglycerides‡ (IU/L)
1	NA	NA	NA
2	13	45	NA
3	67	112	1278
4	133	NA	NA
5	201	102	1181
7	622	210	NA
8	492	196	NA
9	217	147	NA
10	153	144	365
11	110	113	323
12	60	76	238
66§	NA	NA	53
74§	NA	NA	58

NA = not available.

*Normal = 4–24 IU/L.

†Normal = 30–150 mg/dL.

‡Normal = 25–120 IU/L.

§Obtained as an outpatient.

time included bowel ischemia and myocardial infarction. The patient was given IV antibiotics (levofloxacin and cefoxitin) in the ED, and was admitted initially to the general medical floor.

The patient's blood pressure was 86/48 mm Hg at the time of arrival to the general medical floor. Normal saline (1 L) was administered as an IV bolus, and the patient's blood pressure rose to 100/40 mm Hg in the supine position. Ten minutes following the saline bolus, the patient's blood pressure again dropped to 73/40 mm Hg, and he was immediately transferred to the ICU. Six hours later, in the ICU, he developed acute respiratory distress and was intubated and placed on mechanical ventilation.

While on the mechanical ventilator, on the first day of his hospitalization, he was agitated and was started on propofol continuous IV drip, which was titrated to achieve adequate sedation. The maximum rate of IV propofol infusion was 30 μg/kg body weight per minute. On hospital day 2, the patient's lipase and amylase levels were within normal limits (**Table 2**). On day 3, the patient's blood cultures grew *Escherichia coli*, and he was treated for *E. coli* urosepsis. The abdomen appeared distended and bowel sounds were sluggish. Triglyceride levels were measured and were elevated at 1278 mg/dL (**Figure 1**), and lipase and amylase levels were increased compared with the previous day's levels (Table 2). A diagnosis of acute pancreatitis was made. On the same day, the patient's calcium level was 6.5 mg/dL and the albumin level was 2.2 g/dL. The patient was given IV calcium gluconate for his low calcium level. The medications administered at this time included pantoprazole, heparin, propofol (infusion), dopamine (infusion), magnesium sulfate, amikacin, piperacillin-tazobactam, and insulin. An ultrasound examination of the hepatobiliary system performed on hospital day 3 showed a normal gallbladder, liver, biliary tree, and pancreas. Because the patient's clinical condition was not stable, an endoscopic retrograde cholangiopancreatography was not considered at this time. By day 5, the patient's leukocyte count had steadily increased to 31 × $10^3/mm^3$. On day 5, the propofol IV infusion was stopped because of progressively increasing lipase levels, which were thought to be secondary to hypertriglyceridemia from propofol infusion.

In the ICU, the patient was initially started on nasojejunal feeding. As the patient worsened, the nasojejunal feeding was switched to total parenteral nutrition (per the recommendation of the gastroenterologist) on day 6 of his admission. No lipids were administered in the total parenteral nutrition bag because of his elevated triglyceride level. Two days after the discontinuation of the propofol infusion (ie, hospital day 7), the lipase level peaked at 622 IU/L (**Figure 2**) and the amylase level

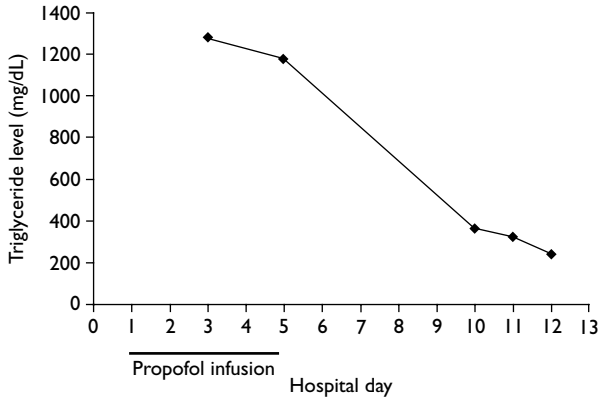

Figure 1. Trend of triglyceride levels in relation to propofol infusion in the case patient.

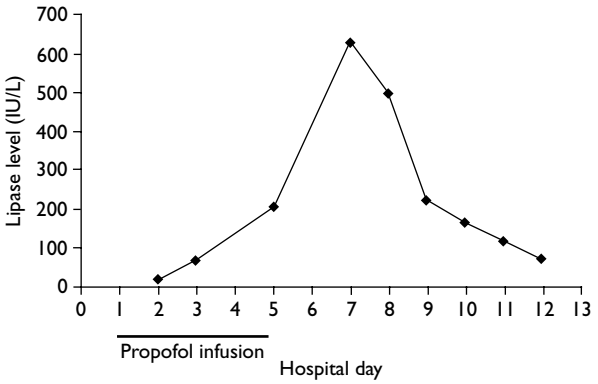

Figure 2. Trend of lipase levels in relation to propofol infusion in the case patient.

peaked at 210 IU/L (**Figure 3**). A computed tomographic scan (with oral and IV contrast) of the abdomen obtained on day 8 showed a normal liver, spleen, and pancreas. Four days after discontinuation of the propofol infusion (hospital day 10), the patient's triglyceride level had decreased to 365 mg/dL. The patient's hospital stay was remarkable for acute respiratory distress syndrome, acute renal failure (hemodialysis was necessary at some points during his treatment), acute myocardial infarction, acute hepatitis due to shocked liver, severe leucocytosis, and anemia. The patient's condition improved over several days; by day 12, his amylase level had returned to normal and his lipase level had decreased significantly. He was discharged after 3 weeks in the hospital. The patient was seen in the outpatient clinic 10 weeks after the initial event and exhibited a good recovery. The laboratory values at this time showed a triglyceride level of 58 mg/dL, a calcium level of 9.4 mg/dL, and a creatinine level of 1.3 mg/dL.

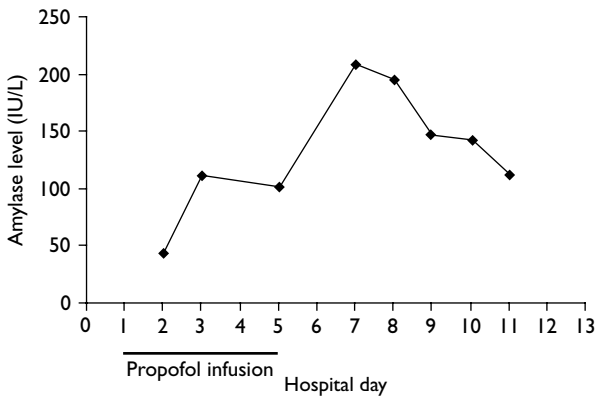

Figure 3. Trend of amylase levels in relation to propofol infusion in the case patient.

DISCUSSION

Propofol was approved by the US Food and Drug Administration in 1989 and since then has become a popular sedative/hypnotic agent. Propofol is 2,6-diisopropylphenol available in the United States as a 1% solution in an aqueous solution of 10% soybean oil, 2.25% glycerol, and 1.2% purified egg phosphatide (lecithin). In 1997, disodium edetate 0.005% was added to the drug formulation to retard microbial growth but does not provide antimicrobial activity under US Pharmacopoeia standards.

Pancreatitis is a common disease in the United States. Gallstones and alcohol are the most common causes of acute pancreatitis. Conditions associated with marked elevations of serum triglyceride levels and pancreatitis include pregnancy, estrogen therapy, and vitamin therapy. In hypertriglyceridemia, free fatty acids produced by pancreatic lipase are increased in toxic concentrations, which cause injury to various tissues and induce inflammatory changes.[8] Clinically significant acute pancreatitis does not appear to occur unless the serum triglyceride level reaches 1000 to 2000 mg/dL. Hyperlipidemia has been shown to intensify the course of acute edematous pancreatitis in rats.[9]

More than 85 drugs are reported to cause pancreatitis.[10] These drugs can be classified as those with a definite association (eg, azathioprine, mercaptopurine, estrogen), those with a probable association (eg, L-asparaginase, corticosteroids), and those with a proposed association but with inadequate evidence (eg, propofol, amphetamines, opiates, rifampin).[1]

Different mechanisms of action have been proposed for drug-induced pancreatitis. Some drugs (ie, azathioprine) appear to cause injury by a hypersensitivity phenomenon within a month of exposure.[10] Others (ie, valproic acid, pentamidine, didanosine) appear to cause

pancreatitis by toxic injury within weeks to months, and still others (ie, acetaminophen) can cause pancreatitis after a single dose.[10]

As of 1999, 25 cases of pancreatitis associated with propofol were reported in the federal drug registry.[1] An increase in the biologic markers of pancreatitis after the initiation of propofol treatment, followed by a decline of the same markers after stopping treatment, shows a possible relationship between pancreatitis and propofol infusion. The mechanism by which this occurs, however, is not clear. Wingfield et al[11] reported that 4 patients who were diagnosed with pancreatitis were diagnosed after propofol was administered as anesthesia, but the authors did not suggest that these cases were caused by any single drug or combination of drugs.

Because propofol is a fat-based emulsion and is similar to 10% intralipid fat emulsion, it has been suggested that it causes pancreatitis by increasing levels of triglycerides.[1,4] Propofol has been shown to cause hypertriglyceridemia in a study by Carrasco et al[12]; in other studies, however, infusion of propofol did not increase lipid levels.[13,14] Jawaid et al[2] reported pancreatitis in a young woman after a single dose of propofol without evidence of hyperlipidemia. Mateu and Barrachina[15] hypothesized that propofol per se somehow causes hypertriglyceridemia, and that this effect would manifest when propofol doses approach 5 to 6 mg/kg per hour and infusion lasts approximately 100 hours. Mateu and Barrachina also have suggested that some patients could have a special susceptibility to developing hypertriglyceridemia during propofol infusion. The hypertriglyceridemia could be explained by an action of propofol or by an effect of the emulsion vehicle.[16] In a study examining the effect of the emulsion, there was no difference in triglyceride levels in patients receiving propofol 2% in an emulsion consisting of both medium-chain and long-chain triglycerides, compared with those taking propofol in an emulsion consisting of long-chain triglycerides only.[17]

Kumar et al[1] reported a case of pancreatitis that occurred in a patient on propofol drip, and the episode was associated with hypertriglyceridemia. After the resolution of pancreatitis, the patient inadvertently was rechallenged with propofol and had a recurrence of pancreatitis. This time, however, the pancreatitis was not associated with hypertriglyceridemia. This leads us to infer that propofol can cause pancreatitis by more than one mechanism.

In animal studies, Donmez et al[18] noted a trend toward more cases of pancreatitis with propofol use, but this difference did not reach statistical significance. In clinical observations, Donmez and colleagues did not observe pancreatitis or elevated amylase or lipase levels in their patients on propofol.[19] An earlier review found that evidence regarding the effect of IV fat emulsions on pancreatic secretions was conflicting.[20]

CONCLUSION

Although acute pancreatitis is an infrequent adverse effect of drug therapy, it is imperative that the offending drug be discontinued when an association is suspected. Review of the literature suggests that propofol causes pancreatitis by more than one mechanism. In the patient presented here, hypertriglyceridemia appears to be the cause. Pancreatitis also can occur when triglyceride levels are normal. Based on our observations and review of prior publications, we feel that propofol should be included in the list of drugs that cause pancreatitis. Because pancreatitis is associated with serious complications and high morbidity and mortality, the medical community should be aware of this adverse effect of propofol. Every effort should be made to discontinue prolonged continuous propofol infusion in the presence of hypertriglyceridemia. **HP**

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