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Propofol and Postoperative Pancreatitis

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This case report is accompanied by correspondence. Please see: Wingfield TW: Pancreatitis after propofol administration: Is There a relationship? ANESTHESIOLOGY 1996; 84:236, and Goodale DB, Suljaga-Petchel K: Reply. ANESTHESIOLOGY 1996; 84:236–7.

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SINCE its approval by the Food and Drug Administration (FDA) in 1989, propofol has become popular as an induction and maintenance hypnotic agent. It is often the drug of choice for induction of anesthesia in outpatients undergoing ambulatory surgical procedures.[1] Its clinical uses have expanded to include long-term infusions to provide sedation in intensive care units. We report a possible association between the use of propofol and the development of postoperative pancreatitis.

Case Report

An otherwise healthy 34-yr-old, 100-kg man was scheduled to undergo aspiration of the seminal vesicles as part of his workup for infertility. He was receiving no medications and had no known drug allergies. He was a nonsmoker and denied the use of alcohol. Previously, he had orthopedic surgery on his left shoulder and a testicular biopsy, both performed under general anesthesia without complications. On preoperative physical examination, he was noted to have a I/VI systolic murmur heard at the left sternal border without radiation. His lungs were clear to auscultation. His abdomen was soft, nontender, and without masses or organomegaly.

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He received 2 g intravenous mezlocillin preoperatively. Induction of anesthesia was accomplished with 3 mg d-tubocurare, 100 μg fentanyl, 200 mg propofol, and 100 mg lidocaine. Tracheal intubation was facilitated by the administration of 120 mg succinylcholine. Neuromuscular blockade was not maintained during the procedure. Anesthesia was maintained with 70% N_2O/30% O_2 and isoflurane. The patient's intraoperative course was unremarkable, and the duration of the anesthetic was 65 min. He received 80 mg intravenous gentamicin at the end of the procedure. The trachea was extubated uneventfully in the operating room. In the recovery room, he had one episode of emesis (approximately 150 ml) and received no medications. No signs of arterial hypotension or hypoxemia were detected. He was discharged to home feeling well.

The following day, the patient presented to his local emergency room complaining of severe abdominal pain and a low-grade fever. On admission, he had a leukocyte count of 12,800/mm³, hemoglobin of 14.6 g/dl, hematocrit of 42.1%, and serum electrolytes, blood urea nitrogen, and creatinine within normal limits. Serum amylase on admission was 2,270 IU/l (normal 25–130). Blood cultures were negative. Chest x-ray revealed a small left pleural effusion, but the results were otherwise normal. Abdominal ultrasound showed no evidence of gallstones or biliary dilatation and minimal inflammation of the pancreas consistent with mild pancreatitis. He was fasted and received only intravenous fluids for 4 days. His serum amylase decreased to 722 IU/l on the 2nd hospital day and then to 183 IU/l on the 4th hospital day. His abdominal pain and fever resolved, and he was discharged to home.

Discussion

Propofol, 2,6-diisopropylphenol, is available as a 1% solution in an aqueous solution of 10% soybean oil, 2.25% glycerol, and 1.2% purified egg phosphatide (lecithin). Since its introduction, the nonhypnotic therapeutic applications of propofol have become widely appreciated and include antiemetic, antipruritic, and anxiolytic effects. However, as drugs are found to possess new and unexpected properties, new adverse effects become apparent.

A possible association between propofol use and pancreatitis has not previously been published. The temporal relationship between our patient's anesthetic and subsequent development of pancreatitis suggests a link between these two events. His medical evaluation and history provided no other cause for his episode of acute pancreatitis. The type of surgical procedure he underwent is not associated with the disease nor has there been reported a link between the development of acute pancreatitis and the use of fentanyl, succinylcholine, nitrous oxide, isoflurane, mezlocillin, or gentamicin. However, between 1991 and 1994, seven cases of postoperative acute pancreatitis in association with propofol use have been collected by the FDA's

spontaneous data reporting system. Review of these cases shows that one patient had undergone coronary artery bypass graft surgery, one patient had an increased lipid concentration before administration of propofol, and one patient was septic on admission. These three patients had complicating processes that might account for the development of pancreatitis. However, the remaining four cases are similar in presentation to our case of a previously healthy patient undergoing nonabdominal surgery (table 1). Of note, two of those four died because of the severity of the pancreatitis.

Pancreatitis is a common disease in the United States. It has a number of causes, an obscure pathogenesis, few truly effective treatments, and an unpredictable outcome. Some cases are mild; others are fatal. Gallstones are the most common cause of acute pancreatitis, accounting for about 45% of cases. Alcohol is the second most common cause, accounting for 35% of cases. Miscellaneous causes such as trauma, ischemia, toxins and drugs, infection, metabolic abnormalities, and penetrating peptic ulcers account for about 10% of cases. The remaining 10% of cases are idiopathic.

The pathogenesis of acute pancreatitis remains obscure. A number of factors have been identified that can initiate the process, including exposure to ethanol and other toxins, obstruction and overdistension of the pancreatic duct, hyperstimulation of the gland, hypercalcemia, and hypertriglyceridemia. Through an unknown mechanism, these factors ultimately initiate a massive cellular metabolic disturbance, presumably when zymogens undergo inappropriate activation. Once these zymogens become activated, the pancreas can undergo a spectrum of changes from mild, localized, self-limited inflammation to severe necrosis with the systemic release of toxic substances, leading to multiorgan failure and possibly death.[2]

A possible pathogenesis of pancreatitis secondary to propofol can only be speculated. Because hypertriglyceridemia is a known cause of pancreatitis, the possibility that pancreatitis could occur due to hypertriglyceridemia induced by propofol must be addressed.[2] The effects of propofol on serum lipid concentrations remain controversial. Gottardis et al. studied the changes in serum lipid concentrations in ten patients receiving a 3-day continuous propofol infusion in an intensive care unit. They found that serum lipid concentrations were not significantly influenced by propofol.[3] In contrast, a study by Carrasco et al. demonstrated a significant increase in triglyceride concentrations in 10 of 20 patients sedated with propofol after

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Table 1. Cases of Postoperative Pancreatitis after Use of Propofol in Previously Healthy Patients Undergoing Nonabdominal Surgery

Patient No.	Age (yr)	Sex	Propofol Dose	Diagnosis	Laboratory Results	Comedications	Comments
1	43	M	1–1.5 mg/kg	Acute pancreatitis	Amylase 1,130 U/L, pancreatic CT: inflammation	Isoflurane, nitrous oxide, alfentanil	Previously healthy, acute pancreatitis developed a few days after removal of wrist plates, patient recovered
2	58	M	150 mg	Acute pancreatitis	Amylase 740 U/L (nl 53–123 U/L), ECG, lung scan, gallbladder ultrasound, chest x-ray, hepatobiliary scan all nl, pancreatic CT: inflammation	Isoflurane, home medications: Darvocet, Parafon, Maxzide, Calan, Elavil	Patient had an uneventful left subcutaneous mastectomy, was kept overnight for observance, experienced severe abdominal pain and some chest pain postoperative day 1; workup was unremarkable except for an amylase level and CT scan; patient recovered but was readmitted 1 month later for a relapse of pancreatitis, and again recovered
3	77	F	100 mg	Acute pancreatitis	Lipase 8,110 U/L, amylase 2,364 U/L, pancreatic CT: inflammation	Fentanyl, succinylcholine, midazolam, desflurane, home medications: Cardizem, synthroid	Patient had a breast lumpectomy and axillary dissection, after surgery she became hemodynamically unstable and developed acute pancreatitis, amylase and lipase concentrations decreased to normal by postoperative day 8; she eventually developed ARDS thought to be secondary to pancreatitis and died
4	58	F	150 mg	Acute pancreatitis	Lipase 969 U/L, amylase 1,326 U/L, pancreatic CT: inflammation	Succinylcholine, alfentanil, fentanyl, xylocaine, rocuronium, Cefazolin, desflurane	Patient had hip surgery and developed pancreatitis postoperatively; lipase and amylase concentrations returned to normal by postoperative day 7; oliguric renal failure 2° to pancreatitis ensued, requiring dialysis; she developed metabolic acidosis and thrombosis, requiring above right knee right leg amputation; patient died due to severe metabolic acidosis and renal failure

M = male; F = female; CT = computed tomography; ECG = electrocardiogram; ARDS = acute respiratory distress syndrome.

3 days.[4] Cook and Palma reported an increase in lipid concentrations in patients sedated with propofol for 2 to 3 days.[5] Boyle *et al.* reported 22 patients receiving propofol infusions for sedation. Propofol maintenance infusion rates ranged from 10 to 230 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Propofol did not affect lipid concentrations in patients receiving low infusion rates. However, serum triglyceride concentrations were markedly increased in the two patients who received infusion rates exceeding 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (6 $mg \cdot kg^{-1} \cdot h^{-1}$) over 12 days.#

Although long-term infusions of propofol at high doses may increase serum lipids, there is no evidence that a single dose of propofol can cause hypertriglyceridemia. Interestingly, none of the patients above with hypertriglyceridemia experienced pancreatitis. The administration of intravenous fat emulsion has been reported to cause acute pancreatitis, especially in patients with Crohn's disease.[6] However, it remains unclear whether hypertriglyceridemia secondary to the intravenous fat emulsion is a prerequisite for the development of acute pancreatitis.

Postoperative pancreatitis is a well described complication and usually follows surgery involving the abdomen or use of cardiopulmonary bypass.[7,8] It also has been described in association with transurethral resection of the prostate.[9] The incidence of pancreatitis after other types of surgery is rare and unknown. To date, no association has been found between aspiration of the seminal vesicles and development of pancreatitis. Consequently, we do not believe that any statistical analysis can be applied comparing the incidence of pancreatitis in patients who received propofol with those not receiving the drug. It remains possible that

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pancreatitis may result from another drug or anesthetic used.

Although the association of pancreatitis related to propofol use remains unproved, clinicians should be aware of this possible association because of the expanding use of this drug and the potentially devastating consequences of acute pancreatitis. A thorough evaluation of abdominal pain after an otherwise uncomplicated anesthetic for a nonabdominal procedure is indicated. Careful analysis will be required to determine whether these reported cases of pancreatitis are associated with *a priori* administration of propofol or whether they simply reflect a certain spontaneous rate of pancreatitis among the surgical population undergoing such uncomplicated procedures.

Any serious adverse events suspected to be associated with drug use should be reported to the FDA's MedWatch system (telephone 1-800-FDA-1088).

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