Hypertriglyceridemia, Lipemia, and Elevated Liver Enzymes Associated With Prolonged Propofol Anesthesia for Craniotomy

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Abstract: Lipemic blood was noted in the surgical field by a neurosurgeon after 12.5 hours of anesthesia consisting of infusions of propofol (total dose, 14,956 mcg) and remifentanil (total dose, 25,091 mcg). For most of that time, the rate of propofol was 120–160 mcg·kg⁻¹·min⁻¹ and never exceeded 160 mcg·kg⁻¹·min⁻¹. Lipemia was confirmed by allowing a sample of the patient’s blood to settle in a syringe. The triglyceride concentration was 15.8 mmol/L. There was no metabolic acidosis or other indications of propofol infusion syndrome. Postoperatively, liver enzymes were elevated (peak aspartate aminotransferase, 420 units/L) but returned to nearly normal within 5 days. The patient recovered from surgery uneventfully. Reports of intraoperative lipemia during propofol anesthesia are very rare but raise concerns about the safety of prolonged propofol infusion.

Key Words: propofol, lipemia, triglyceride, liver enzymes, propofol infusion syndrome

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The patient is a 39-year-old, 165-cm, 111-kg woman with a diagnosis of a giant vestibular schwannoma. Resection of this very large tumor through retrosigmoid and transpetrosal approaches was planned in 2 stages 5 days apart. This case report refers mainly to the second operation where the majority of the tumor resection was achieved by the petrosal approach. The patient had a history of hypertension that was treated with atenolol and hydrochlorothiazide but was otherwise healthy. She had undergone a delivery by cesarian section 1 month ago (the anesthetic details from an outside hospital were not available). Her medications also included dexamethasone and phenytoin that were prescribed in connection with her neurosurgical procedures.

Anesthesia was induced with fentanyl 150 mcg, propofol 150 mg, and lidocaine 100 mg. After administration of vecuronium 7 mg, the trachea was intubated by direct laryngoscopy and the lungs were mechanically ventilated to maintain normocarbia. Anesthesia was maintained with infusions of remifentanil (0.1–0.3 mcg·kg⁻¹·min⁻¹) and propofol (25–160 mcg·kg⁻¹·min⁻¹). A nicardipine infusion was used for blood pressure control. Drug infusions were based on a weight of 100 kg, although the patient’s actual weight was 111 kg. For most of the total anesthetic time of 19 hours and 22 minutes, the propofol infusion rate was between 120 and 160 mcg·kg⁻¹·min⁻¹. During the final 5 hours and 25 minutes, the propofol dose was between 50 and 100 mcg·kg⁻¹·min⁻¹. The total infusion dose of propofol was 14,956 mg and the total dose of remifentanil was 25,091 mcg. For comparison, the total infusion doses given during her first operation, 5 days earlier, were propofol 12,557 mg and remifentanil 20,250 mcg; that operation was unremarkable from an anesthetic standpoint.

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Total intravenous anesthesia with propofol and remifentanil (or some other opioid) has become increasingly popular, especially for neurosurgical anesthesia. The relative lack of interference with neuromonitoring is a key reason for the popularity of this technique. Although propofol is generally considered to be a relatively safe and nontoxic anesthetic, prolonged propofol infusion may be associated with some unusual problems.

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Three very experienced senior attending anesthesiologists were involved sequentially in providing anesthesia care. Shortly after the second anesthesiologist assumed care, after approximately 12 hours and 30 minutes of anesthesia time, the neurosurgeon noted that the blood appeared “milky.” Blood samples for blood gas tensions and other laboratory tests were obtained immediately because of concern about the possibility of propofol infusion syndrome, although there were no other manifestations beside lipemia. The results were pH 7.465, PaO₂ 461 mm Hg, PaCO₂ 36.7 mm Hg, hematocrit 0.293, sodium 144 mmol/L, potassium 3.7 mmol/L, calcium (ionized) 1.12 mmol/L, and glucose 6.77 mmol/L. Triglyceride concentration was 15.8 mmol/L (normal fasting concentration <1.69 mmol/L; triglyceride concentration can be measured in plasma or serum, with nearly identical results’). A syringe containing the patient’s blood was allowed to settle,
revealing frankly lipemic blood (Fig. 1). The third anesthesiologist then assumed care. The laboratory battery was repeated (except for triglyceride) approximately 5 hours later, with similar results. In the absence of metabolic acidosis, the propofol was continued at \( \geq 100 \text{ mcg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) until 4 hours and 30 minutes before the end of the anesthetic, at which time neuromonitoring was no longer needed. The propofol infusion was then reduced to \( 50 \text{ mcg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) and sevoflurane was added. The lipemic appearance of blood in the surgical field persisted through the end of surgery.

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Propofol is formulated in a lipid emulsion. Infusion of large doses of propofol over longer periods of time can result in lipemic blood (blood that appears milky because of high concentrations of triglyceride). Lipemia may also occur after a fatty meal. Despite the very widespread use of propofol infusions for sedation or anesthesia, the incidence and clinical implications of lipemia associated with propofol seems not to be very well studied.

We can find only 2 case reports of intraoperative lipemia associated with infusion of propofol. Vokes et al noted milky blood in the surgical field after 6 hours of infusion of propofol during a radical neck dissection. They confirmed the presence of lipemia by drawing a blood sample in a syringe that revealed lipemic blood after standing for 20 minutes. Their case report did not include a complete description of the anesthetic but stated that the propofol infusion rate was \( 350 \text{ mcg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \). They discontinued the propofol infusion 60 minutes before the conclusion of surgery and noted that the milky appearance of the blood disappeared. No clinical sequelae of lipemia were found in their patient. They also noted that a similar observation of milky appearing blood had been made in a previous patient of theirs. Roccisano et al reported a patient who underwent complex intrathoracic spine surgery with 547 minutes of propofol infusion ranging from 175 to 225 \( \text{mcg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \). The surgeon noted a white milky substance pooling at the bottom of the surgical cavity. The surgical team initially thought this might be due to a chyle leak; however, eventually a conclusion was reached that hypertriglyceridemia from propofol was responsible for the Milky appearance of the fluid in the chest cavity.

**FIGURE 1.** A syringe of arterial blood was allowed to settle, revealing lipemia in the blood layer.

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After surgery, the patient was taken to the intensive care unit intubated, and the propofol infusion was continued at 50 \( \text{mcg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \). The patient extubated herself approximately 4 hours later but did well clinically afterward. Liver function tests were obtained approximately 5.5 hours before the end of anesthesia, an hour after the end of anesthesia, and daily thereafter for 5 days. Alanine aminotransferase (ALT, also known as SGPT) and aspartate aminotransferase (AST, also known as SGOT) were substantially elevated, and alkaline phosphatase was slightly elevated during and immediately after surgery. ALT was still slightly elevated after 5 days, but AST and alkaline phosphatase were normal (Fig. 2). Triglyceride concentration was not measured postoperatively. Pancreatic enzymes were not measured, and there was no clinical evidence of pancreatitis.

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There are several studies of triglyceride concentrations during propofol infusion for sedation of patients in the intensive care unit. Some of these studies reported hypertriglyceridemia or lipemia, whereas others did not. A published guideline suggested monitoring triglyceride concentration after 2 days of propofol infusion. Coetzee et al studied 57 adult patients who were sedated with propofol (randomized to 1% or 2% propofol; 2% propofol is not available in the United States) in the intensive care unit for at least 72 hours, using propofol doses of 17–65 \( \text{mcg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \). Triglyceride concentration was measured, and the presence of lipemia was noted by visual inspection of blood samples. Blood was visibly lipemic in 5 of 57 patients. Maximum blood triglyceride concentrations ranged from 0.8 to 5.47 mmol/L.

McLeod et al studied 30 adult patients during a 50-hour infusion of 2% propofol in the intensive care unit. The mean propofol dose was 16 \( \text{mcg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) (range, 1.2–51 \( \text{mcg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \)). The blood triglyceride concentration was measured 3 times. Median triglyceride concentration increased from 1.43 mmol/L at 2 hours to 1.91 mmol/L, a change that was not statistically significant. Triglyceride concentration was weakly but significantly correlated to propofol dose. No lipemia was observed. Peak triglyceride concentrations were only mildly elevated (>3 mmol/L) in 8 patients.

Concerns about harmful effects of hypertriglyceridemia associated with propofol infusion revolve mainly around pancreatitis and propofol infusion syndrome. Hypertriglyceridemia is a risk factor for pancreatitis. Devlin et al performed a retrospective review of 159 adult patients in intensive care unit who received propofol for 24 hours or longer and had at least 1 serum triglyceride concentration. Twenty-nine of 159 patients had elevated triglyceride concentration (>4.5 mmol/L), and of those, 6 had triglyceride concentration >11 mmol/L. Pancreatitis (defined by serum amylase >125 IU/L and serum lipase >60 IU/L and a clinical picture of pancreatitis) occurred in 3 of the 29 patients with elevated triglyceride. Causes of pancreatitis...
There is some evidence that the pathologic mechanism of propofol infusion syndrome is poisoning of oxidative phosphorylation in mitochondria by propofol.\textsuperscript{16–19} There is some evidence that the pathologic mechanism of the syndrome is poisoning of oxidative phosphorylation in mitochondria by propofol.\textsuperscript{16–18} The syndrome has usually been documented in patients receiving propofol at greater than 85 mcg·kg\textsuperscript{-1}·min\textsuperscript{-1} for at least 48 hours. Whether hypertriglyceridemia is involved in the pathogenesis of propofol infusion syndrome, or whether it is simply incidental to the administration of large doses of propofol, is unknown. However, the rabbit model of propofol infusion syndrome described by Ypsilantis et al\textsuperscript{20} is interesting in this regard because they found that propofol administration resulted in severe hypertriglyceridemia (approximately 100 mmol/L), about 14 times greater than that produced by administration of Intralipid (Fresenius Kabi AB, Germany) alone (approximately 7 mmol/L), suggesting that propofol itself is involved in producing lipemia, perhaps by interfering with the metabolism of triglyceride. Propofol is not ordinarily considered to be hepatotoxic per se; a report of 13 patients undergoing propofol infusion for 10 hours (at approximately 100 mcg·kg\textsuperscript{-1}·min\textsuperscript{-1}) did find elevation of liver function tests.\textsuperscript{21}

In this case report, a patient developed lipemia during intraoperative infusion of propofol and had elevation of liver enzymes postoperatively. The patient apparently did not suffer any clinical sequelae from this, although the appearance of lipemic blood in the surgical field was notable to the neurosurgeons, and there was concern on the part of the anesthesiologists for the possibility of propofol infusion syndrome. Little is known about the appearance and significance of intraoperative hypertriglyceridemia or lipemia associated with propofol. None of the 3 very experienced senior anesthesiologists involved in the care of this patient had ever observed, or even heard, of intraoperative lipemia that produced visibly milky blood in the surgical field. Our neurosurgeons reported that they had seen lipemic blood occasionally in the past during prolonged cases, as did the surgeons in the previous case report of Vokes et al,\textsuperscript{2} suggesting that intraoperative lipemia may be underreported. It is interesting that this patient received a similar dose of propofol during the first of the 2 staged operations but lipemic blood was not noted during that operation.

The cause of elevated liver enzymes in this case is unknown; because there were no measurements of liver enzymes immediately preoperatively, we cannot be certain that the elevation of liver enzymes occurred intraoperatively. However, alkaline phosphatase, AST, and ALT had been measured 2 weeks before the second craniotomy (Fig. 2). At that time, alkaline phosphatase and ALT were slightly elevated, but AST was not. This raises the possibility that there was some underlying problem with liver function that was exacerbated during surgery. There is a possibility that the elevation of liver enzymes was related to administration of propofol. There is also a possibility that hyperlipidemia associated with propofol administration was exacerbated by underlying liver dysfunction because the liver has a central role in lipid metabolism. Liver dysfunction and elevated liver enzymes have sometimes been included in descriptions of propofol infusion syndrome, although in this case there was no metabolic acidosis, cardiac dysfunction, or other manifestations of propofol infusion syndrome. An observational study of 30 children undergoing craniotomy under propofol anesthesia found that mean blood concentrations of liver enzymes, triglycerides, and amylase were elevated after surgery compared with preoperative concentrations, although mean values remained within the normal range.\textsuperscript{22}

Interestingly, preexisting hyperlipidemia or liver function abnormalities are not generally considered to be contraindications to the administration of propofol in anesthesia practice. However, given the association of hypertriglyceridemia with pancreatitis, and the occurrence of elevated liver function tests in patients with propofol infusion syndrome, we
should pause to reconsider whether administration of propofol to certain patients is advisable. Nevertheless, there are no suitable population data by which to gauge these concerns. Further studies of intraoperative lipid metabolism and liver function during propofol infusion would seem to be warranted, and consideration given to the possibility that there may be unappreciated safety issues associated with prolonged intraoperative infusion of propofol.

REFERENCES