Crit Care Shock (2022) 25:123-128

Assessment of the frequency of propofol-associated hypertriglyceridemia and pancreatitis in adult intensive care patients

Nathan Kellock[1,2], *Jerrold Perrott*[1,2]

Abstract

***Objective*: Infusions of propofol have been associated with hypertriglyceridemia and acute pancreatitis; however, the incidence of these adverse events is not well characterized in the literature. Therefore, we aimed to characterize the incidence and management of hypertriglyceridemia (>4.5 mmol/l) as well as hypertriglyceridemia-associated pancreatitis in adult intensive care unit (ICU) patients.**

***Design*: Retrospective cohort study.**

***Setting*: Adult tertiary medical/surgical/trauma/neurosciences ICU.**

***Patients and participants*: Adult patients who received a propofol infusion for at least 24 hours between April 15, 2015 and November 25, 2015 to reach a convenience sample of 150 patients.**

***Interventions*: Observational design only.**

***Measurements and results*: Fourteen (9.3%) of 150 patients developed hypertriglyceridemia, but none of these patients went on to develop acute pancreatitis. The median time to discontinuation of propofol in patients who developed hypertriglyceridemia was 7.4 h and propofol was discontinued within 24 h of detection in 86% of these patients.**

***Conclusions*: A clinically important proportion of patients receiving propofol infusions developed hypertriglyceridemia. Although the vast majority of these patients were managed appropriately with prompt discontinuation of propofol, there was a need for regular triglyceride monitoring in these patients in order to ensure that hypertriglyceridemia can be identified for appropriate management.**

Key words: Propofol, hypertriglyceridemia, pancreatitis, intensive care, sedation.

Introduction

Propofol is a short-acting anesthetic that is often used in critically ill patients for sedation and facilitation of mechanical ventilation. (1) Propofol use in intensive care unit (ICU) patients has been shown to shorten ICU stays relative to benzodiazepines and decrease the duration of mechanical ventilation. (2) Administered by continuous intravenous infusion in this setting, propofol acts by stimulating γ-aminobutyric acid type A (GABAA) receptors, inhibiting N-methyl-D-aspartate (NMDA) receptors, and modulating calcium channel activity to achieve sedation. (3) With a largely non-polar chemical structure, propofol is highly lipophilic and is formulated as an oil-in-water emulsion for administration. (3)

The most common adverse effects of propofol infusion include a decrease in heart rate and blood pressure; however, its use is also associated with a number of other adverse events, including propofol infusion syndrome (PRIS), hypertriglyceridemia, and pancreatitis. (3,4) PRIS is a rare but severe complication of propofol administration and is characterized by a constellation of non-specific clinical findings: metabolic acidosis, rhabdomyolysis, elevated serum potassium and liver enzymes, cardiac dysfunction, and acute kidney dysfunction. (4) Al-

[1.] Vancouver General Hospital, Vancouver, BC, Canada
[2.] Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada

Address for correspondence:
Dr. Jerrold Perrott
Pharmacy Department, Vancouver General Hospital
855 West 12th Ave, Vancouver, BC V5Z 1M9, Canada
Tel: +1 604-875-4111 ext. 63459
Email: jerrold.perrott@vch.ca

though PRIS is rare, it is more frequently observed in patients receiving a propofol infusion of greater than 67 μg/kg/min (4 mg/kg/h) and in patients on propofol for more than 48 h. (4) Propofol has also been associated with an increase in triglycerides and rare cases of acute pancreatitis; however, researchers are uncertain whether these effects occur as part of PRIS, or if they are independent risks related to propofol administration. (4)

It is unclear whether propofol-associated hypertriglyceridemia is primarily a consequence of the drug itself, the lipid emulsion in which the drug is infused, or a combination of both. (5,6) The triglyceride measurements used to define the stages of severity differ depending on the reference. According to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), normal triglyceride levels are defined as <1.7 mmol/l (<150 mg/dl), borderline high levels as 1.7-2.2 mmol/l (150-199 mg/dl), high levels as 2.3-5.6 mmol/l (200-499 mg/dl), and very high levels as ≥5.7 mmol/l (≥500 mg/dl). (7)

Acute pancreatitis is a life-threatening condition involving inflammation of the pancreas and it is typically characterized by abdominal pain as well as elevated serum lipase and amylase. (8,9) In order to be diagnosed with acute pancreatitis, patients must have at least two of the following: abdominal pain, serum lipase or amylase greater than 3 times the upper limit of normal, and radiologic imaging consistent with acute pancreatitis. (8,9) The most common causes of acute pancreatitis are gallstones and alcohol abuse, but hypertriglyceridemia is estimated to be responsible for between 1% and 4% of cases. (8) A serum triglyceride level of greater than 11.3 mmol/l (1000 mg/dl) is generally observed in patients with hypertriglyceridemia-associated acute pancreatitis. (8) Though there is limited published literature on the topic, there are case reports of acute pancreatitis in patients on propofol infusions. (5)

Literature on the incidence of propofol-associated hypertriglyceridemia and pancreatitis in the ICU is sparse, consisting of case reports and small retrospective studies. (10) In the 2005 study by Devlin et al, the incidence of hypertriglyceridemia (defined as ≥4.5 mmol/l) was 18% in ICU patients on propofol. (5) Despite nearly 1 in 5 patients developing hypertriglyceridemia, triglyceride levels were monitored in only 31% of patients on propofol. (5) In the same study, 10% of patients with hypertriglyceridemia developed acute pancreatitis. (5) By determining the incidence and management of hypertriglyceridemia and pancreatitis in ICU patients on propofol at our centre, we hope to provide more insight into the magnitude of this problem.

Materials and methods

This was a single centre, retrospective, observational study of adult ICU patients who received propofol infusions at Royal Columbian Hospital, a tertiary hospital providing medical, surgical, neurosciences, and trauma services. In order to be included in the study, patients had to be at least 18 years of age, admitted to the ICU during or prior to December 2015, on a propofol infusion for at least 24 consecutive hours, and have had at least one triglyceride measurement during the infusion. Patients were excluded if they had a documented baseline triglyceride concentration of ≥2.3 mmol/l (≥200 mg/dl), received other lipid-containing preparations (eg. total parenteral nutrition) during the propofol infusion, or had a documented history of acute pancreatitis prior to starting the infusion.

Data collection began with the most recently admitted patients and continued backward until a convenience sample of 150 patients had been reached. This sample size was selected based on the results of Devlin et al (5) whereby we expected similar rates of occurrence of outcomes. Hospital electronic pharmacy records were searched to generate a list of patients admitted to the ICU for whom propofol was ordered. This list of patients was cross-referenced with computerized laboratory databases to determine which patients had triglyceride levels measured. Electronic charts were reviewed for patients who had triglyceride levels measured and data were collected for patients who met the inclusion criteria. An ICU clinical database was used to obtain Acute Physiology and Chronic Health Evaluation (APACHE) II scores for included patients.

Our primary objective for the study was to determine the incidence of patients who developed hypertriglyceridemia and acute pancreatitis. Our secondary objective was to characterize the management of patients who developed hypertriglyceridemia. Hypertriglyceridemia was defined as a measured triglyceride concentration greater than or equal to 4.5 mmol/l (400 mg/dl). This value is consistent with the definition used in the Devlin et al (5) study in order to facilitate a comparison of findings and is based on the NCEP ATP II criteria for high triglycerides. In patients who developed hypertriglyceridemia, acute pancreatitis was defined as the presence of at least two of the following: a serum lipase of greater than 3 times the upper limit of normal, clinical exam findings characteristic of pancreatitis, and radiographic findings indicative of pancreatitis. (11) Management of incident hypertriglyceridemia was characterized by the time to propofol discontinuation, dose reduction, or change to an alternative sedative agent. In addition to the data re-

quired for our primary outcomes, baseline patient characteristics (gender, age, weight, body mass index [BMI], ICU admission type, and admitting diagnosis), as well as triglyceride and infusion parameters, were documented to help better describe our study population.

By comparing the number of patients who developed hypertriglyceridemia and acute pancreatitis to the total number of patients included in the study, the incidence of these two outcomes was determined. Microsoft Excel 2010 was used to calculate descriptive statistics, including medians and interquartile ranges.

Our study received Fraser Health Research Ethics Board approval in September 2015 and the need for informed consent was waived based on its low-risk, retrospective design.

Results

To meet our convenience sample of 150, sequential patient data were reviewed for 163 patients meeting our inclusion criteria admitted from November 25, 2015 back to April 14, 2015. Thirteen of these patients were excluded: eight patients had elevated triglycerides at baseline, four had a history of acute pancreatitis, and one received total parenteral nutrition (TPN) during the propofol infusion.

Baseline patient characteristics are presented in **Table 1**. Of the 150 patients included in the study, 14 patients developed hypertriglyceridemia, giving an incidence of 9.3%. None of these patients went on to develop acute pancreatitis.

Table 2 presents hypertriglyceridemia detection and propofol infusion and exposure characteristics, while **Table 3** provides an overview of how the 14 patients who developed hypertriglyceridemia were managed.

Discussion

Our study stands as one of only a few publications that attempt to characterize the risk of propofol infusion associated with hypertriglyceridemia and pancreatitis in the ICU. Our findings of a clinically meaningful risk of hypertriglyceridemia (9.3%) reinforce the importance of careful clinical monitoring for all patients on continuous propofol infusions for greater than 24 hours. The absence of cases of pancreatitis in our population was potentially due to chance alone or could be the result of the prompt and effective clinical management of the patients who did develop hypertriglyceridemia.

Our findings present some notable differences compared to what was observed in a similar study by Devlin et al conducted in 2005. (5) A lower median age was observed in our patients who developed hypertriglyceridemia compared to those who did not develop hypertriglyceridemia, while the patients with hypertriglyceridemia had a higher mean age than the patients without hypertriglyceridemia in the Devlin study. Patients who developed hypertriglyceridemia were more likely to be a surgical/trauma admission (64%), whereas the vast majority of patients (90%) who developed hypertriglyceridemia in Devlin et al were medical admissions, despite having a higher overall proportion of surgical admission patients (72%) in that study. In our study, the median duration of propofol infusion prior to the development of hypertriglyceridemia was 2.1 days versus 3.7 days in the Devlin study. With these differences, the frequency of hypertriglyceridemia in our study was approximately half the frequency observed by Devlin et al, with an incidence of 9.3% and 18%, respectively. In addition, while 10% of patients with hypertriglyceridemia were noted to develop acute pancreatitis in the Devlin study, no cases of acute pancreatitis were identified in our study.

A number of limitations should be considered when interpreting the results of this study. Our study was retrospective in design and thus dependent on the quality of recorded data; however, as we accessed standardized electronic records the risk of missing data or data errors was low. Our findings did not capture patients who received an infusion of propofol for less than 24 hours and patients who developed hypertriglyceridemia within the first 24 hours of starting propofol were observed, but these patients were excluded from the trial because they did not meet our inclusion criteria. Clinically, though, it may not be as critical to identify cases of hypertriglyceridemia in these patients with shorter infusions, since it would likely have minimal impact on management. In addition, because so few patients had documented baseline triglyceride levels (prior to starting propofol), it is possible that some patients in which hypertriglyceridemia was observed had elevated triglycerides at baseline. Many patients were excluded as a result of the low frequency of triglyceride monitoring in the ICU, which may have contributed to selection bias.

Conclusions

Propofol infusion associated with hypertriglyceridemia occurs with a frequency that is clinically meaningful and there likely exists a small risk of development of subsequent pancreatitis despite our negative results. This risk can likely be mitigated through a practice of careful clinical monitoring of serum triglycerides for all patients receiving propofol infusions for more than 24 hours and

prompt management of propofol infusions, with an aim to reduce or stop continued propofol administration for those that develop hypertriglyceridemia. We would suggest that for patients on prolonged propofol infusions, their serum triglyceride levels (as well as creatinine kinase and lactate levels, to assess for other manifestations of PRIS) be checked every 48 hours. In those patients who remain on propofol with elevated triglycerides, close (we suggest daily) monitoring for biochemical and physical exam findings of pancreatitis should be undertaken to ensure early detection of cases to allow appropriate definitive diagnosis and clinical management.

Competing interests
None for either author.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions
Both authors contributed substantially to the conceptualization, methodology development, data curation, analysis, and writing of this manuscript and approve it for publication.

Ethics
This study was completed under approval by the Fraser Health Research Ethics Board and in accordance with the standards laid down in the 1964 Declaration of Helsinki. Given the retrospective nature of the study, the need for written informed consent was waived by the Research Ethics Board.

Table 1. Summary of baseline patient characteristics

Parameter	Patients with hypertriglyceridemia (n=14)	Patients without hypertriglyceridemia (n=136)	Overall (n=150)
Age (years)	53 (42-62)	60 (49-69)	58 (47-69)
Male, n (%)	10 (71)	93 (68)	103 (69)
Weight (kg)	93 (81-100)	81 (70-92)	82 (70-95)
BMI (kg/m^2)	31 (28-32)	27 (23-30)	27 (23-30)
APACHE II[#]	21 (21-31)	22 (15-25)	22 (15-25)
Length of ICU stay (days)	15.1 (7.6-18.8)	6.4 (4.1-12.0)	7.3 (4.2-15.0)
Total duration of infusion (hours)	50.0 (33.3-73.1)	48.0 (34.2-63.4)	48.0 (34.1-64.3)
Service, n (%) - Medical - Surgical/trauma	 5 (36) 9 (64)	 64 (47) 72 (53)	 69 (46) 81 (54)

Legend: BMI=body mass index; APACHE=Acute Physiology and Chronic Health Evaluation; ICU=intensive care unit. Values are presented as median (interquartile range) unless otherwise specified. [#]Scores (12) were only available for 116 patients overall and 7 of the 14 patients with hypertriglyceridemia.

Table 2. Triglyceride and infusion characteristics in patients who developed hypertriglyceridemia

Parameter	Value
Frequency of triglyceride monitoring (tests/day)	0.9 (0.66-1.08)
Time to detection of hypertriglyceridemia from the start of propofol infusion (hours)	36.4 (28.2-62.1)
Infusion rate at time of detection of hypertriglyceridemia (mcg/kg/min)	58 (41-79)
Total propofol exposure (mg/kg)	119 (87-213)
Highest detected triglyceride level (mmol/l)	5.9 (5.5-7.6)

Legend: Values are presented as median (interquartile range) unless otherwise specified.

Table 3. Management of patients who developed hypertriglyceridemia

Parameter	Value
Time to discontinuation (hours)	7.4 (5.5-12.4)
Discontinuation within 24 hours of detection of hypertriglyceridemia, n (%)*	12 (86)
Dose reduction, n (%)*	6 (43)
Time to dose reduction (hours)	0.7 (0.3-1.8)
Change to the alternative sedative, n (%)	1 (7.1)
Time to change to the alternative sedative (hours)	6.8

Legend: Values are presented as median (interquartile range) unless otherwise specified. *Four patients were initially managed with a dose reduction prior to discontinuation.

References

1. Reade MC, Finfer S. Sedation and Delirium in the Intensive Care Unit. N Engl J Med 2014; 370:444-54.
2. Ho KM, Ng JY. The use of propofol for medium and long-term sedation in critically ill adult patients: a meta-analysis. Intensive Care Med 2008;34:1969-79.
3. Kotani Y, Shimazawa M, Yoshimura S, Iwama T, Hara H. The Experimental and Clinical Pharmacology of Propofol, an Anesthetic Agent with Neuroprotective Properties. CNS Neurosci Ther 2008;14:95-106.
4. Mirrakhimov AE, Voore P, Halytskyy O, Khan M, Ali AM. Propofol Infusion Syndrome in Adults: A Clinical Update. Crit Care Res Pract 2015;2015:1-10.
5. Devlin JW, Lau AK, Tanios MA. Propofol-Associated Hypertriglyceridemia and Pancreatitis in the Intensive Care Unit: An Analysis of Frequency and Risk Factors. Pharmacotherapy 2005;25:1348-52.
6. Devaud J-C, Berger MM, Pannatier A, Marques-Vidal P, Tappy L, Rodondi N, et al. Hypertriglyceridemia: a potential side effect of propofol sedation in critical illness. Intensive Care Med 2012;38:1990-8.
7. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143-421.
8. Tsuang W, Navaneethan U, Ruiz L, Palascak JB, Gelrud A. Hypertriglyceridemic pancreatitis: presentation and management. Am J Gastroenterol 2009;104:984-91.
9. Lankisch PG, Apte M, Banks PA. Acute pancreatitis. Lancet 2015;386:85-96.
10. Haffar S, Kaur RJ, Garg SK, Hyder JA, Murad MH, Abu Dayyeh BK, et al. Acute pancreatitis associated with intravenous administration of propofol: evaluation of causality in a systematic review of the literature. Gastroenterol Rep (Oxf) 2019;7:13-23.
11. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis - 2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62:102-11.
12. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818-29.