Shedding Light on Propofol Infusion Syndrome: Questions Abound

You can download the audio version and take the post test at: www.apexanesthesia.com

PROPOFOL'S HIGHLY CONTROLLABLE AND predictable pharmacodynamics and speedy reversibility make it a foundation of modern anesthetic care. Even the World Health Organization includes propofol in its list of essential drugs that should be on hand. When used carefully and titrated to effect, it is relatively free of untoward or unexpected adverse events. One issue that we should all be aware of is known as propofol infusion syndrome (PfIS). The following example serves as an illustration.

You cared for a healthy, 76 kg, 51-year-old female undergoing elective surgery for a brainstem cavernous angioma. High-dose propofol (8 mg/kg/hr) was given for approximately 3 hours during surgery as the surgeon requested somatosensory evoked potentials and no more than 0.5 MAC of sevoflurane be used. Due to surgical concerns of inadvertent spinal cord trauma, the patient remained intubated, transferred to the ICU for continued monitoring and care, and a lower dose of propofol continued at 2.5 mg/kg/hr. Marked lactic acidosis with laboratory signs of renal impairment and elevated potassium concentration ensued. Rhabdomyolysis developed, and a tentative diagnosis of PfIS was made. Propofol was stopped 27 hours after ICU admission, with serum creatinine returning to preoperative values within 24 hours. The arterial lactate completely normalized after 48 hours, and the patient recovered uneventfully from her surgery.

Unraveling the clinical aspects of propofol infusion syndrome (PfIS)

PfIS was first reported as a potentially fatal concern in children in 1990, with subsequent reports in adults surfacing when used for longer than 48 hours in high doses (usually > 5 mg/kg/hr).[1, 2] The initial reports of death in children noted severe metabolic acidosis and bradycardia progressing to asystole. These features and those reported in adults with PfIS led to it being described as a syndrome of cardiac failure, rhabdomyolysis, severe metabolic acidosis, and renal injury or failure.

Since those initial observations, several more exacting clinical features have been described that help clarify the diagnosis of PfIS. These include

- a spectrum of aberrant cardiac issues:
  - heart failure with pulmonary edema.
  - widening QRS complex.
  - bradycardia.
  - ventricular tachycardia/fibrillation.
  - cardiac arrest.
- hypotension.
- acute kidney injury/change in urine color (often green).
- rhabdomyolysis.
- metabolic acidosis.
- hyperkalemia.
- liver injury with elevated transaminases.

Despite the case reports and published forums about PfIS, there is still no consensus on the syndrome's absolute definition. Some suggest that the many reported cases are as likely to be manifestations of an underlying critical illness rather than a distinct entity caused by propofol. Given that there are at least 200 instances of PfIS in the form of case reports and reviews, it seems quite clear that propofol, under certain circumstance in select patients, can cause a syndrome that can prove severe and even fatal.

An informative British report by Hemphill *et al*. reviewed the literature of published cases of PfIS, noting that no one clinical characteristic was found in all the cases involving both children and adults.[3] The most common manifestation was metabolic acidosis occurring in nearly 8 out of 10 cases, with ECG changes from baseline as the second commonest manifestation. Rhabdomyolysis and acute kidney injury followed respectively as presenting signs.

For obvious reasons, there are no studies that deliberately exposed patients to large doses of propofol in an attempt to trigger PfIS. This leaves us with an extensive literature that provides a strong association of propofol to the condition.

What are the most appreciated risk factors for PfIS?

In published reports to date (at least in adults) it is the cumulative, total dose of propofol that is the primary risk factor. There is also a strong and seemingly predictive relationship between the dose of propofol and the number and severity of presenting signs of PfIS, as well as the extent of organ systems affected. That said, there are reports where PfIS developed even at relatively low total doses of the drug, suggesting that there are underlying factors (comorbidities, genetics, etc.) yet to be identified.

Body type may be a factor though reported cases are often missing key information rendering any firm conclusions concerning this attribute unreliable. Based on well-conducted pharmacokinetic studies, it is widely agreed that the dose of propofol for sedation be calculated based on lean, rather than actual, body weight.[4] It is unclear in many of the published reports how the infusion dose was calculated.

Some have suggested that there may be a "priming" effect for the development of PfIS secondary to administration of steroids in the operative or ICU phase of care. This line of thought emerged based on the putative role of steroids in the genesis of ICU-related myopathy, thus linking rhabdomyolysis in those with PfIS and concomitant steroid administration. Bench research in animals reveals that propofol can impair mitochondria, thus concerns that it should be avoided in certain mitochondrial diseases. Some believe steroid use may be implicated in the development of ICU myopathy by triggering what is known as the ubiquitin proteasome pathway. This results in rhabdomyolysis secondary to myofilament derangement.[5] The ubiquitin proteasome pathway is the principal mechanism for protein catabolism in our cells. This pathway may also be a factor in the development of PfIS. Much of this is conjecture given that to date, there are only associations, as a controlled study in humans is ethically impossible. However, the influence of steroids on the genesis of PfIS continues to receive considerable attention.

Deciphering the mechanism of propofol infusion syndrome

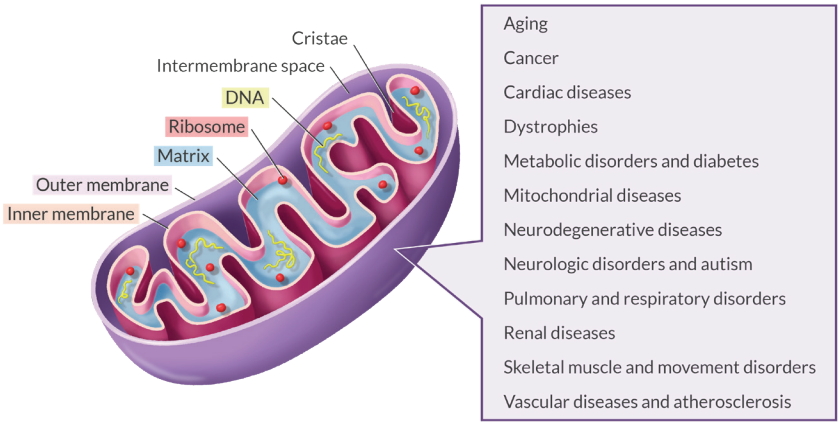
With those first reports of PfIS in children emerging in the early 1990s, followed rapidly by reports in adults, the FDA investigated the role of propofol administration and deaths. Eventually, the FDA recommended that propofol not be used for long-term sedation in children; the first adult death attributed to PfIS occurred in 1998.[6]

Despite abundant concern and clinical research interest, the exact mechanism accounting for PfIS remains uncertain. The following are examples of theories implicating propofol as a direct cause of the syndrome:

- Accumulation of metabolites
- Lipid microembolization
- Impaired liver lactate metabolism
- Deficiency in coenzyme A dehydrogenase deficiency
- Inhibition of coenzyme Q
- Several mitochondrial pathway impairments
- Altered genetics, especially at the intracellular level
- A defect in the production of ATP

The most compelling hypotheses seem to involve our intracellular powerhouses, the mitochondria, and in particular at the level of the respiratory chain. This isn't an easy domain of research to access, and more definitive work may eventually better clarify the precise mechanism.

The sentinel paper of Rutter *et al.* published in the *European journal, Anaesthesia*, first described the use of propofol as an anesthetic induction agent, generating worldwide enthusiasm. Once it became widely available, it rapidly displaced other IV induction agents.[7]. It did not take long to find uses both as a surgical anesthetic infusion and in settings outside the OR.



The mitochondria are indeed our cellular powerhouses! Their dysfunction is involved in the pathogenesis of many human afflictions and our aging process

Calculating an incidence of a rare syndrome is always challenging and made all the more so when a condition may be misdiagnosed or simply mired in a given patient's unique critical care illness. The best current estimate of PfIS in the ICU is about 1.1%. In a busy ICU, this averages three to four patients affected each year.[8]. Preventing PfIS thus amounts to not using propofol. This seems unlikely given the syndrome's rarity, the absence of an economically feasible alternative, and no real competitor that is both safe and effective (some might suggest dexmedetomidine but it is currently pricey and has a complication profile of its own). Remaining vigilant with a high index of suspicion and using the lowest effective dose for the shortest time are the mantras to be followed when using propofol as a long-term infusion.

What is the of the art regarding the management of propofol infusion syndrome?

In a nutshell, there is nothing firm and evidence-based. What we do know is that its early recognition is essential so the infusion can be terminated. Once the administration is stopped, sedation can be maintained using an alternative hypnotic agent such as dexmedetomidine or midazolam. While a specific antidote isn't available, this will allow the body to eliminate propofol and permit monitoring and treating the manifesting symptoms.

The literature is clear that the initial treatment should be directed at manifestations that are most clearly associated with very poor outcomes, including death. These include ECG changes, rising serum potassium levels, low blood pressure, fever, and of course, any evidence of metabolic acidosis. Case reports with treatment suggestions include

- increasing minute ventilation as a compensatory mechanism.
- bicarbonate infusions.
- fluid infusions.
- vasopressors.
- dextrose infusions in response to mitochondrial concerns.
- hemofiltration.
- extracorporeal membrane oxygenation.

All of these have revealed some benefit in selected cases depending on whether or not basic measures did not correct or abort the cardiac, cardiovascular, and febrile manifestations.[9]

Revisiting the pharmacokinetics of propofol: achieving a good understanding of its onset and offset

Given that propofol is the offending agent, it is prudent to eliminate it from the patient as soon as possible by discontinuing its administration and understanding the drug's pharmacokinetics. We know propofol as a highly lipophilic agent with a fast onset and a short, predictable duration of action. It has a rapid infiltration across the blood-brain barrier distributing itself into the CNS. This is followed by redistribution to inactive tissue depots such as muscle and fat.

The blood concentration curve of propofol is ideally fitted to a three-compartment model. The first phase half-life of 2 to 3 minutes mirrors its rapid onset of action. The second phase (about one-half to a full minute) is one of high metabolic clearance. With a half-life of about 200 to 500 minutes, the long third phase describes the slow elimination of a small percentage of the drug remaining in very poorly perfused tissues. After both a single IV injection and a continuous intravenous infusion, the blood concentrations rapidly decrease below those necessary to maintain sleep, based on the rapid distribution, redistribution, and metabolism during the first and second phases. Over 70% of the drug is eliminated during these first two phases. During long-term intravenous infusions, the accumulation of the drug and its effects might be expected, but the recovery times do not appear to be much delayed even then.

The liver is the main eliminating organ, and renal clearance appears to play a minor role in the total clearance of propofol. However, because total body clearance may exceed liver blood flow, an extrahepatic metabolism or extrarenal elimination (e.g., via the lungs) may be in play. Approximately 60% of a radiolabeled dose of propofol is excreted in the urine as 1- and 4-glucuronide and 4-sulphate conjugates of 2,6-diisopropyl 1,4-quinol, and the remainder consists of conjugated propofol.

Hepatic and renal disease, the surgical procedure, gender, and obesity appear to have little clinically significant changes in propofol's pharmacokinetic profile. However, a decrease in the clearance value in elderly patients might produce somewhat higher concentrations during a long-term infusion. In addition, lower induction doses observed with regards to older age might be partly explained by a smaller central volume of distribution.

At the onset of unconsciousness, a mean blood concentration of around 6 to 10 mg/L is needed. But during maintenance of anesthesia, lower levels are effective, especially if other CNS depressing agents are administered.

Propofol is a very unique drug, unlike anything available to us previously. Knowledge of its unique and predictable properties empowers us to make well-informed decisions about its onset and offset. Of particular relevance to PfIS is that despite a very long terminal half-life related to a high volume of distribution, the recovery from propofol is short and predictable. However, the drug's slow residual presentation due to that third phase may have relevance in those recovering from PfIS. Although the intervention can't eliminate the highly lipophilic parent drug, continuous hemofiltration may eliminate the water-soluble, propofol metabolites.[(10)]

A case of death due to PfIS?

The following is a slight modification (to protect the identity of those involved) of a published case of a fatality from PfIS. A 41-year-old man was admitted to the hospital by ambulance after a motor vehicle accident where he sustained a closed head injury and an open fracture of his tibia. He was agitated, his vital signs were stable, and further assessment did not reveal any injuries other than his closed head injury. He was intubated and sedated as part of his initial management. A CT scan of his brain was reported as normal, and he was subsequently transferred to the ICU for further management. The initial ECG demonstrated an incomplete right bundle branch block and a QT interval within normal limits. A CT scan repeated on day 2 was reported as without abnormality, but a lumbar puncture revealed an increased CSF pressure (25 cm H_2O) and an increased protein level.

Over the next 5 days, the creatine level rose and the ECG showed the addition of T-wave abnormalities and prolongation of the QT interval. On day 6, the cardiologist suggested a propofol drip due to agitation.

Propofol was administered as the primary sedative agent, combined on a number of days with occasional boluses of both IV midazolam and morphine. The propofol was administered as both a high-dose background IV infusion supplemented by intravenous boluses over most of the patient's 8-day stay in the ICU. The following illustrates his 8-day treatment regimen that includes both his continuous infusion and incremental, 50mg IV boluses (usually given due to a bout of agitation or abrupt awakening):

Day in the ICU	Total 24 hour dose (mg)
1	1,000
2	3,000
3	7,000
4	8,000
5	6,000
6	9,000
7	12,000
8	2,000

On postoperative day 3 he was taken to the OR for open reduction and internal fixation of the fractured tibia. The anesthetic management consisted essentially of continuing the ICU rate of propofol, adding 0.5 MAC of sevoflurane, and 15 mg of morphine.

It was not until day 6 of his ICU stay that disturbing symptoms arose. On that day, a third head CT scan was performed, demonstrating signs consistent with sinusitis. He was tachycardic, and his renal function had deteriorated, a finding attributed to contrast nephropathy. His ECG revealed ST-T wave segment elevation, which later that same day developed into inferolateral ST segment elevation. A TEE demonstrated normal left ventricular size associated with moderate hypertrophy and preserved left ventricular function. His urine developed a green color, which was particularly disturbing to the staff members. On day 8, the patient's clinical condition had deteriorated further, and he was noted to have developed a metabolic acidosis (base excess –4.9 mmol/L, serum lactate 0.6 mmol/L). His plasma was strongly lipid in nature on laboratory examination, and the propofol infusion was abruptly decreased. The ECG had progressively become more abnormal with bizarre ST-T wave changes and broadening of the QRS complex that degenerated into a polymorphic ventricular tachycardia and subsequent ventricular fibrillation for which resuscitation was unsuccessful. An autopsy failed to reveal any specific pathology to explain the circulatory collapse, the extensive rhabdomyolysis, or the metabolic acidosis.

The patient's death resulted in litigation against the providers. It was argued that an excessively high dosage of propofol over a prolonged period caused the fatal outcome. The outcome of the case aside, we should be aware that PfIS may occur, and thoughtful care and vigilance to symptoms suggestive of its development are essential. One wonders if the anesthesia providers on day 4 had any suspicion of its potential occurrence. There was no information to that effect in the published report.

Clinical contemplations

- Have you ever encountered a patient with a history of PfIS. If so, how did that modify the course of care that you provided?
- Have you ever altered your intraoperative clinical management out of concern for PfIS? What did you change?
- Given what we know about PfIS, what would you advise those providers new to the field, and even experienced colleagues, to be on alert for in a patient who might be experiencing PfIS?
- Given the fatal case report of the 41-year-old, would you have altered your anesthetic plan in any way?

Summary and conclusions

Given our growing experience and knowledge regarding PfIS, and the need for more formal guidelines regarding its diagnosis and management, some suggest that it is time to update its description. One such suggestion follows: PfIS occurs most frequently in critically ill patients receiving propofol infusions, typically either high dose (exceeding 5 mg/kg/hour) or for a duration greater than 48 hours. It is associated with one or more otherwise unexplained manifestations: metabolic acidosis, rhabdomyolysis, ECG changes, hyperkalemia, lipidemia, cardiac failure, fever, elevated liver enzymes, or raised lactate.[3]

While that definition is long and laborious, it speaks to the complexity in its diagnosis and the importance of recognizing it early so that the drug can be discontinued and supportive measures instituted. It is clear that many questions remain unanswered and await elucidation.

PfIS can present in many ways: cardiovascular collapse, a metabolic response, rhabdomyolysis, and/or high fever. It is a syndrome affecting many organ systems. There is currently no diagnostic test; thus, a high degree of clinical suspicion is essential in all patients receiving high-dose short-term infusions and patients receiving long-duration infusions with a variable dose range.

It is advised that all members involved in the care of those receiving longer-term infusions maintain a high index of suspicion. Regardless of whether the infusion was started preoperatively, or if it was started intraoperatively and continued into the postoperative period. Treatment is currently supportive, and clinicians should consider the syndrome in cases of unexplained metabolic acidosis, ECG changes, and rhabdomyolysis. Early termination of the infusion is the best single intervention that is currently advised.

References

1. Hatch DJ. “Propofol-infusion syndrome in children.” *Lancet* 1999; **353**:1117–1118.
2. Diedrich DA, Brown DR. “Analytic reviews: propofol infusion syndrome in the ICU.” *J Intensive Care Med.* 2011; **26**:59–72.
3. Hemphill S *et al*. “Propofol infusion syndrome: a structured literature review and analysis of published case reports.” *Brit J Anaesth*. 2019; **122**:448–459.
4. Servin F *et al*. “Propofol infusion for maintenance of anesthesia in morbidly obese patients receiving nitrous oxide. A clinical and pharmacokinetic study.” *Anesthesiology.* 1993; **78**:657–665.
5. Mitch W *et al*. “Mechanisms of muscle wasting. The role of the ubiquitin-proteasome pathway.” *N Engl J Med*. 1996; **335**:1897–1905.
6. Hanna J *et al*. “Rhabdomyolysis and hypoxia associated with prolonged propofol infusion in children.” *Neurology.* 1998; **50**:301–303.
7. Rutter D *et al*. “ICI 35868 (Diprivan): a new intravenous induction agent. A comparison with methohexitone.” *Anaesthesia*. 1980; **35**:1188–1192.
8. Roberts R *et al*. “Incidence of Propofol-related infusion syndrome in critically ill adults: a prospective, multicenter study.” *Crit Care.* 2009; **13**:R169
9. Culp K *et al*. “Clinical management of cardiogenic shock associated with prolonged propofol infusion.” *Anesth Analg.* 2004; **99**:221–226.
10. Honore P *et al*. “Propofol infusion syndrome: early blood purification to the rescue?” *Crit Care.* 2016; **20**:197.