
Propofol infusion syndrome: what do we know, why does it happen, and when should I worry?

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Soon after the introduction of propofol into clinical anesthesia practice, it began to be used as a sedative agent in the intensive care unit. Its use became widespread because it had unique pharmacological and pharmacokinetic properties that previously used agents lacked, and it rapidly became an important drug in the ICU armamentarium.¹ Unlike previous agents used for sedation in the ICU, propofol is rapid in both onset and offset; when used as a continuous infusion it is possible to awaken a sedated patient within minutes for evaluation and return them to sleep in seconds. (Dexmedetomidine is currently perhaps the only agent that has similar characteristics, although offset may be slower after prolonged infusions, and its usefulness as an anticonvulsant is not as clear.) For patients with head injuries, for example, this allowed interval assessment of neurological status. Patients who were difficult to sedate with opioid and benzodiazepine combinations could be easily sedated with quick titration of drug level, yet still be awakened rapidly for extubation or for neurological evaluation. Although hemodynamic compromise may be seen in volume depleted patients or those with myocardial compromise, the use of this drug became common, first in pediatric critical care and then in adult ICU's. Propofol was also shown to be a potent anticonvulsant that sometimes was effective in status epilepticus refractory to other agents.

In 1992, however, a disturbing case series appeared in the British Medical Journal reporting five children who developed intractable metabolic acidosis and fatal myocardial failure while receiving prolonged infusions of propofol for sedation in the ICU.² These children all followed a similar clinical course, beginning with unexplained metabolic acidosis and lactic acidemia which was unresponsive to the administration of sodium bicarbonate, myoglobinuria and elevated serum CPK, renal failure, and hepatomegaly. They rapidly regressed to developing bradydysrhythmias and hypotension, soon followed by cardiovascular collapse and asystole or pulseless electrical activity (PEA). On laboratory and postmortem investigation, the victims exhibited lipemic serum, hepatomegaly and fatty infiltration of the liver and myopathic changes of cardiac and skeletal muscle. The complex of findings was soon termed propofol infusion syndrome (now commonly abbreviated PRIS, as "PIS" is apparently too risqué or vulgar for the medical literature!).

Following this initial report, other intensivists reported similar cases, and by 1999 there were at least 27 pediatric cases reported, as well as 14 adults.³⁻⁷ The mortality in these reports reached 85%; the only survivors had prompt institution of hemodialysis or hemofiltration. The primary risk factor for development of the syndrome was identified as a propofol infusion rate greater than 65mcg/kg/min for greater than 48 hours (the ICU literature usually describes infusion rates in mg/kg/hr-

I have converted them here to the units more familiar to anesthesiologists). A prospective randomized study of 327 pediatric intensive care patients that was sponsored by Astra-Zenica, the manufacturer of propofol, found that the mortality rate of patients receiving an infusion of the 1% propofol preparation was twice that of children receiving other drugs for sedation; those receiving a 2% preparation had a threefold increased mortality. Unfortunately, these data have never been published, and were distributed to US physicians in a letter from Astra-Zenica warning not to use propofol for prolonged sedation in the intensive care unit.

The initial reaction to these reports in the critical care community was highly contentious- editorials even appeared in the literature denying the existence of a problem.⁸ However, biochemical evidence for a putative mechanism of the syndrome has now been identified, and few now deny the existence of the “propofol infusion syndrome”.⁹ A prolonged infusion of propofol impairs free fatty acid utilization and mitochondrial activity, and an imbalance between energy demand and utilization may be a key pathogenic mechanism.⁹⁻¹⁴ One investigator likens the syndrome to the deterioration of a child with an inherited defect in β -oxidation, who is asymptomatic until starvation or infection creates conditions where fat metabolism is required for energy production.¹²

A specific disruption in fatty acid oxidation leading to impaired entry of long chain acylcarnitine esters into the mitochondria with failure of complex II of the respiratory chain has been shown in muscle biopsy of patients with the syndrome.¹⁴ This was concomitant with a rise in malonylcarnitine and C5 acylcarnitine levels in the blood. These levels can be normalized with the prompt institution of hemofiltration or hemodialysis. Impaired mitochondrial respiration has also been produced during propofol infusion in an isolated perfused guinea pig heart model.

It would seem to be a relatively simple matter to close the door on all of this by simply not using propofol for prolonged infusions in the ICU (and indeed, the package insert does list prolonged use as a relative contraindication). However, numerous case reports have now documented the propofol infusion syndrome during short-term infusions during anesthesia.¹⁵⁻²³ It is unknown if these cases represent the unmasking of a sub-clinical mitochondrial disorder, the exacerbation of mitochondrial oxidative dysfunction mediated by the stress of surgery or injury, or the revelation of sub-clinical propofol infusion syndrome in susceptible individuals. In Burow's case (reference 19), the patient was asymptomatic, and the lactic acidosis was discovered only because of delayed emergence and the incidental measurement of arterial blood gases. One patient received an infusion for only 4 hours, yet developed acidosis, dysrhythmias and signs of myocardial dysfunction that lasted several days despite an apparently otherwise uneventful procedure and anesthetic.²³ The possibility of pharmacogenomic differences in individuals, particularly the existence of polymorphisms in mitochondrial respiration and electron transport, are important variables that may likely play a role in whether a patient is at risk.²⁴ Several authors have postulated that the development of lactic acidosis may be an early warning sign for propofol infusion syndrome.^{20,25}

As of 2007 there were 61 recorded cases of PRIS in the literature; of these, 20 children and 18 adults have died.²⁶ Investigators have now begun to look beyond the overt full-blown PRIS cases with hopes of identifying early warning signs or risk factors that can identify subclinical cases. A paper by Wolf, who reported the case of a child with status epilepticus unresponsive to conventional anticonvulsants who was treated with propofol, is instructive.⁹ The authors recognized the risks and measured carbohydrate intake and C4 acylcarnitine levels daily. Although the child developed no signs or symptoms of propofol infusion syndrome, the C4 acylcarnitine levels rose steadily beginning on day 2 of the infusion despite increased carbohydrate intake, and by day 5 had reached 10x their baseline levels. This returned to normal when measured at a 6-month follow-up visit. These data suggest that even without the development of either overt biochemical or physiologic signs of propofol infusion syndrome, the perturbations of mitochondrial respiration are present during some prolonged infusions. The infusion rates used for this patient ranged from 75mcg/kg/hr (day one) to a maximum of 110mcg/kg/hr on day 4. These rates are considerably lower than used intraoperatively for anesthesia (average 150-250mcg/kg/min), so it would not be surprising that at anesthetic doses such findings might be seen over shorter time periods.

Since laboratory and animal data suggest that propofol does have a deleterious effect on mitochondrial electron transport and fatty acid oxidation, subclinical perturbation of cellular energetics might be far more common than previously thought.²⁷ In a retrospective study of adults at Mayo who received prolonged TIVA with propofol for radiofrequency ablations 24% had unexplained acidosis, as compared with 8% of matched controls receiving general anesthesia with other agents for carotid endarterectomy.²⁸ Although there are numerous methodologic problems with this study, subtle biochemical evidence of PRIS may be common if one looks carefully for it. On the other hand, it is possible that only some patients will be at risk. One can logically hypothesize that there may be a pharmacogenomic marker in those patients.²⁹ Are there specific polymorphisms of mitochondrial respiration enzymes in patients who develop evidence of electron transport dysfunction during propofol anesthesia? Or are there are some patients who have polymorphisms in propofol's metabolic pathways that are different from those who do not develop the syndrome? These are unknown at this time, but we are now enrolling patients in a prospective study to try to answer these questions.

What should one do at this time? First, as with any rare drug complication, an index of suspicion is always helpful in making an early diagnosis. For cases under 2 hours, even with high rates of infusion, the incidence is apparently rare. For longer cases, especially using high infusion rates, it may be prudent to measure pH and lactate. The development of a lactic acidosis that cannot be explained by other causes should raise the question of early PRIS. More ominous warning signs include dysrhythmias, hypotension, and dark urine suggestive of myoglobinuria or other signs of rhabdomyolysis. Blood levels of C4 or C5 acylcarnitine may be helpful in

confirming the diagnosis but this test is not commonly performed in a timely enough manner to aid in clinical decision-making.

Patients with long fasting times may be at increased risk. One should consider the addition of adequate carbohydrate substrate to intravenous fluids (4-8mg/kg/hr of glucose) if a long propofol anesthetic is considered. Additional lipid (intravenous fat emulsions for parenteral nutrition) should not be administered without adequate carbohydrate. Infusion rates should be minimized, perhaps with the addition of other drugs that reduce the propofol requirement (opioids, benzodiazepines, etc.).

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