

Propofol infusion syndrome

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Key points

Common presenting features of PRIS are new onset metabolic acidosis, cardiac dysfunction, rhabdomyolysis, renal failure, and hypertriglyceridaemia.

Risk factors for developing PRIS include severe head injuries, sepsis, high exogenous or endogenous catecholamine and glucocorticoid levels, low carbohydrate to high lipid intake, or inborn errors of fatty acid oxidation.

Propofol infusions for sedation should not exceed 4 mg kg⁻¹ h⁻¹ and routine monitoring of CK and triglycerides should be performed for the at-risk population.

The term PRIS—propofol infusion syndrome—was originally coined by Bray in 1998 to describe the adverse effects associated with the use of propofol in the paediatric population. PRIS was defined as acute refractory bradycardia leading to asystole in the presence of one or more of the following: metabolic acidosis (base excess of -10 mmol litre⁻¹), rhabdomyolysis or myoglobinuria, lipaemic plasma, or enlarged liver or fatty liver.¹

Although first described in the paediatric population, it has been increasingly reported in adult intensive care patients, particularly in neurointensive care. The safe dose of propofol infusion for sedation in intensive care is considered to be 1–4 mg kg⁻¹ h⁻¹, but fatal cases of PRIS have been reported after infusion doses as low as 1.9–2.6 mg kg⁻¹ h⁻¹ as well, promoting the idea that genetic factors may have a role to play.

Incidence

The first death associated with PRIS was reported in 1990, a Danish medical committee issued a warning about the use of propofol in the paediatric population.² In 1992, a case series published in the *BMJ* highlighted the dangers of high doses of propofol infusions in children and urged caution in adults.³ Adult case reports of PRIS started to appear in publications by 1996. An American prospective mixed adult intensive care unit (ICU) multicentre study examining the incidence of PRIS showed it to be 1.1% and to occur at a median of 3 days (range of 1–6 days) after the start of propofol.⁴ This was based on a conservative definition of PRIS, defined as metabolic acidosis with cardiac dysfunction and one or more of the following: rhabdomyolysis, hypertriglyceridaemia, or renal failure. With the incidence of 1.1% a year, an average general ICU with admission rates of 300–400 a year should see three to four cases of PRIS. An unexplained metabolic acidosis and rapid patient demise may lead to misdiagnosis of the condition. Mortality rates were shown to be 18% in patients who developed PRIS, but in the

context of a heightened awareness of PRIS, this might be lower.

An unpublished industry study involving 327 paediatric ICU patients showed a concentration-dependent increase in 28 day mortality in propofol-treated patients with a trend towards significance. The group receiving standard non-propofol sedation had 4% mortality, those treated with 1% propofol had 8% mortality, and those treated with 2% propofol had 11% mortality.²

Clinical presentation

Over the last 14 years, since the term was coined by Bray, multiple case reports have been published about PRIS. It has been established that the common presenting features of PRIS are new-onset metabolic acidosis (86%) and cardiac dysfunction (88%). Other features include rhabdomyolysis (cardiac and skeletal muscle) (45%), renal failure (37%), and hypertriglyceridaemia (15%).⁴ Other significant features include hepatomegaly, hyperkalemia, and lipaemia.

The metabolic acidosis in PRIS appears to be due to a combination of renal failure and lactic acidosis. Lactate production is emerging as an early common feature;^{2,5} however, in many early case reports, lactate was not measured and hence, not reported. Cardiac dysfunction manifesting itself as ECG changes is the first sign of impending cardiac instability. Brugada-like ECG changes (Coved type ST elevations in V1–V3) are characteristic in PRIS.² Other arrhythmias include atrial fibrillation, ventricular or supraventricular tachycardias, bundle branch blocks, bradycardias, and eventually asystole. Serum samples are often lipaemic when analysed in the lab in PRIS patients. This lipaemia may be due to increased sympathetic stimulation, high circulating cortisol and growth hormone levels, and blockade of mitochondrial fatty acid oxidation impairing lipid metabolism.¹ This leads to high circulating levels of non-esterified fatty acids and is clinically manifested as raised serum triglyceride.

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Direct muscle necrosis causes rhabdomyolysis of both skeletal and cardiac myocytes and the release of creatinine kinase (CK) and myoglobin. In most case reports, the CK at the diagnosis of PRIS is often $>10\,000$ units litre⁻¹. In our experience, increasing CK levels after 24–48 h of propofol infusion should raise the suspicion of PRIS in the absence of any other muscular pathologies. Renal failure often occurs and it is thought to be related to myoglobinuria.

Risk factors for developing PRIS include severe head injuries, sepsis, high exogenous or endogenous catecholamine and glucocorticoid levels, low carbohydrate to high lipid intake, or inborn errors of fatty acid oxidation.

Aetiology and pathophysiology

PRIS is thought to be secondary to an imbalance between energy demand and utilization caused by impairment of mitochondrial oxidative phosphorylation and free fatty acid utilization, ultimately leading to lactic acidosis and myocyte necrosis. In addition, propofol antagonizes β -adrenergic receptor and calcium channel binding thus further depressing cardiac function.

Histopathological results in PRIS show that the basic mechanism is the destruction and breakdown of skeletal and cardiac myocytes.⁶ In animal and human models, propofol uncouples intracellular oxidative phosphorylation and energy production in the mitochondria and inhibits electron flow through the electron transport chain in myocytes. This unfortunately leads to an imbalance between energy demand and utilization, thus compromising cardiac and peripheral muscle cell function.

Muscle biopsies and fat metabolism analysis of patients with PRIS resemble those found in mitochondrial cytopathies and acquired acyl-carnitine metabolism deficiencies. A hereditary mitochondrial fatty acid metabolism impairment resembling medium-chain acyl-CoA dehydrogenase deficiency has been postulated as being responsible for the susceptibility to PRIS, but research into this has been inconclusive.⁷ Propofol increases the activity of malonyl CoA, which in turn inhibits carnitine palmitoyl transferase I, responsible for the transport of long-chain free fatty acids into the mitochondria. Another mechanism by which propofol exerts its effects is by uncoupling β -oxidation and the respiratory electron transport chain at complex I, meaning that neither medium- nor short chain free fatty acids, which freely cross the mitochondria membranes, can be utilized.⁶ Free fatty acids are an essential fuel for myocardial and skeletal muscle under fasting or 'stress' conditions. Under such conditions, oxidation of fatty acids in the mitochondria is the principal process for producing electrons, which are transferred to the respiratory chain. Any prolonged impairment of free fatty acid utilization leads to muscle necrosis.⁵

Lipid overload associated with propofol or parenteral nutrition infusions may also contribute to increased plasma fatty acids. Accumulation of unutilized fatty acids has been identified as a pro-arrhythmogenic risk factor, and therefore an adequate carbohydrate intake is highly recommended to suppress lipolysis.⁶ A simple glucose infusion is usually sufficient to reduce endogenous

lipolysis. Children are more prone to the development of PRIS due to low glycogen storage and high dependence on fat metabolism.⁶

Increased endogenous catecholamine levels caused by intracerebral lesions and hyperdynamic circulations caused by systemic inflammatory response syndrome decrease propofol plasma levels by increased hepatic and extrahepatic clearance. This may lead to insufficient sedation and increased propofol infusion rates. Propofol inhibits cardiac β -adrenoceptor binding and cardiac calcium channel function. It also suppresses the activity of sympathetic nerves and the baroreceptor reflex, thus worsening the cardiac failure in PRIS and the resistance to inotropes.²

Management

The management of PRIS requires a high index of suspicion in the at-risk population and rapid recognition of the clinical signs. We monitor CK and triglyceride levels daily, after 48 h of propofol infusion. Increasing levels of CK in the absence of other muscular pathologies triggers the suspicion of PRIS and propofol is immediately stopped and alternative drugs (midazolam and alfentanil) are used for sedation. PRIS is difficult to treat once it occurs. The triggering factor is stopped and alternative sedative agents commenced. Cardiovascular support is provided as necessary and renal replacement therapy may be required to treat the ensuing lactic acidosis, clear propofol, and its metabolites from the patient rapidly.

Many published papers have reported a catecholamine-resistant shock with escalating doses of inotropes. Electrical pacing (either via temporary wire or transcutaneously) has been met with limited success for the bradycardia.² Extracorporeal membrane oxygenation has been reported as successful in the cardiovascular support of PRIS.

Prevention

Propofol should be used with caution for long-term sedation in critically ill patients. Cremer and colleagues⁸ showed a proportional risk of PRIS (odds ratio of 1.93) for every milligram per kilogram per hour increase in the mean propofol dose above 4 mg kg⁻¹ h⁻¹. It is recommended that for long-term sedation, propofol dose should not exceed 4 mg kg⁻¹ h⁻¹. Arterial blood gases, serum lactate, and CK should be monitored frequently, especially if propofol sedation is required for more than 48 h. However, Fodale and La Monaca⁵ have reviewed rare reports of the development of PRIS after 3–5 h of high-dose propofol anaesthesia and also cases where propofol infusion rates as low as 1.4 mg kg⁻¹ h⁻¹ were used.

Low carbohydrate supply can be a risk factor for PRIS due to the increased lipolysis in periods of starvation brought on by high energy demands.⁶ Providing adequate carbohydrate intake with glucose infusions and minimizing lipid loads (e.g. from lipid-based parenteral nutrition) might prevent PRIS.²

Risk factors for developing PRIS include severe head injuries, sepsis, high exogenous or endogenous catecholamine and glucocorticoid levels, low carbohydrate to high lipid intake, and inborn errors of fatty acid oxidation. A high index of clinical suspicion and routine monitoring of CK and triglyceride in high-risk groups helps to prevent most cases of PRIS from progressing.

Conclusion

Most UK general ICUs would have encountered several cases of PRIS per year, based on the incidence quoted by Roberts and colleagues.⁴ Patients of all ages with severe critical illness such as neurological injuries, severe burns, trauma, severe sepsis, and pancreatitis are at risk of PRIS. High-dose propofol for prolonged periods (>4 mg kg⁻¹ h⁻¹ for >48 h) should be avoided, or if used, should only be with regular CK, lactate, and triglyceride monitoring.

Declaration of interest

None declared.

References

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Please see multiple choice questions 9–12.