The propofol infusion syndrome

Introduction

The propofol infusion syndrome (PRIS) is a rare, often fatal condition associated with high-dose propofol infusions[1] that occurs in both paediatric[2-18] and adult patients.[8;19-29] The syndrome is characterized by severe metabolic acidosis, often accompanied by rhabdomyolysis, cardiac failure, and renal failure.[30] Severe cases progress to refractory bradydysrhythmias, biventricular failure and death in spite of desperate efforts to support the circulation with inotropic drugs, vasopressors and ventricular pacing. Table 1 delineates the clinical criteria by which the diagnosis is made.

Table 1: Clinical features of the propofol infusion syndrome

1. Sudden onset of a marked bradycardia, resistant to treatment, progressing to complete heart block.
2. Lipaemic plasma.
3. Clinically enlarged liver.
4. Metabolic acidosis with a base deficit of >10 mmol.L^{-1} on at least one occasion.
5. Occasionally rhabdomyolysis or myoglobinuria.

The diagnosis is considered to be established when item #1 occurs together with any one of items #2 - 5.

Most reported cases have originated from intensive care units (ICU's). It has been suggested that the pathogenesis is multifactorial, whereby priming factors include the presence of acute neurological conditions or inflammatory disease. The triggering factors include the administration of high-dose propofol, catecholamines and/or glucocorticoids.[30] There are however, several recent reports documenting the occurrence of lactic acidosis for which there was no other explanation, after infusions of short duration[12;31;32], and even during anaesthesia in basically healthy patients.[23;26;33;34]

Pathogenesis

Laboratory investigations indicate that propofol impairs mitochondrial oxygen utilization or inhibits electron flow along the mitochondrial electron transport chain.[6;12;35-38] Several clinical reports provide evidence of impaired mitochondrial fatty acid ß-oxidation during the syndrome[17;18], leading to reduced ATP production[39] and accumulation of long- and short-chain acyl-carnitine intermediates.[17;18] The result is cellular hypoxia. The accumulated fatty acids are arrhythmogenic.[40] The syndrome is in many aspects similar to inherited defects in ß-oxidation of fatty acids, whereby patients are asymptomatic until they are stressed by starvation or infection, resulting in increased fat metabolism to produce energy. These patients subsequently develop life-threatening rhabdomyolysis, as well as cardiac, renal and hepatic failure. A problem with the propofol infusion syndrome is that there does not appear to be an underlying disorder in the survivors[17;18;41], so that there is no bedside test to indicate which patients may be susceptible.

It appears that propofol may affect mitochondrial metabolism of fatty acid in two ways.[30] Firstly, propofol may impair the carnitine transport mechanism whereby long-chain fatty acids are attached to carnitine for transport into the mitochondria.[18] Furthermore, it has been suggested that acquired carnitine deficiency may occur in critically ill patients[42], thereby predisposing to inefficient utilization of long-chain fatty acids. Secondly, there may be inhibition at some point of the ß-oxidation spiral.[6;12;17;17;18] The result is that long-chain free fatty acids (FFA) as well as medium- and short-chain FFA♣ cannot be utilized. The precise mechanism whereby propofol affects mitochondrial function is unknown. Reports of patients who survived after haemodialysis or plasmapheresis[3;6;12;16-18;43] suggest the possibility that the syndrome may be caused by a propofol metabolite. It is unlikely that the main metabolites, the glucuronide and sulfate conjugates are toxic. However, there is evidence to suggest that one of the intermediate metabolites, propofol quinone (2,6-diisopropyl-1,4-benzoquinone) generates hydroxyl free radicals.[44] Propofol itself inhibits the production of free radicals.[45]

Clinical aspects

Propofol has been used for sedation in adults in ICU's for almost 20 years[46;47] and in children for more than a decade.[48] It was approved for adult ICU sedation by the USA Food and Drug Administration (FDA) in 1993. After the early reports concerning the possible association between prolonged propofol infusions and the syndrome, both the FDA and the drug manufacturer issued warnings that propofol is not indicated for use in paediatric ICU's. The Canadian Medical Association and Health Canada also issued warnings about the off-label use of propofol for sedation in children.[49;50] Early case reports were met with scepticism concerning propofol's causative role with arguments that the evidence was circumstantial and was limited to case reports or small series of patients in whom the clinical picture could have been caused by sepsis alone.[51;52] Two relatively large case series where propofol was used for sedation, have reported no incidences of metabolic acidosis, dysrhythmias or death.[53;54] Nevertheless, it must be recognized that sufficient clinical and laboratory evidence has accumulated to conclude that the PRIS does occur in children and in adults, and that it need not necessarily arise only in ICU settings. It remains a rare event of which the true incidence is at present unknown. Therefore it behoves the prudent clinician to be aware that the syndrome exists and to be alert to the circumstances that predispose to its development. These include an excessive lipid load and a carbohydrate intake that is inadequate to suppress fat metabolism.

It is therefore recommended that should a decision be made to infuse propofol for sedation, the infusion rate be limited to less than 4 mg.kg^{-1}.h^{-1} for not more than 48 hours.[30]

♣ Medium- and short-chain FFA do not require enzyme-mediated transport across mitochondrial membranes.

Supplementing propofol sedation with opioids[55] and/or benzodiazepines helps to limit the propofol dose-rate. Patients should not receive a heavy lipid load and in addition, should receive an adequate carbohydrate intake (6 $mg.kg^{-1}.min^{-1}$) in order to suppress lipid β-oxidation. In this regard it should be noted that patients who develop PRIS often exhibit hyperlipidaemia and a "creamy" appearance of the plasma. This may occur during total parenteral nutrition (TPN) in ICU patients receiving fat emulsions. An appropriate daily fat emulsion dosage to children receiving TPN is 2-3 $g.kg^{-1}.day^{-1}$ and this is easily achieved by an infusion of 4 $mg.kg^{-1}.h^{-1}$ of 1% propofol.[41] Most reported cases of PRIS have received dose rates much greater than 4 $mg.kg^{-1}.h^{-1}$ and have therefore received an excessive lipid load due to the propofol infusion alone. Wolf[41] has pointed out that inadequate provision of carbohydrate has been noted in several cases of PRIS. Carbohydrate stores are quickly used up in children. An inadequate carbohydrate intake promotes mobilization of fat stores and increased fat metabolism, thereby exacerbating the effects of propofol on β-oxidation. A recent case report[41] suggests that propofol may have an effect on fat metabolism before any of the features of PRIS develop: An 11 year old received propofol for 6 days at a mean infusion rate of 4.7 $mg.kg^{-1}.h^{-1}$ accompanied by a carbohydrate intake of only 2 $mg.kg^{-1}.min^{-1}$. C4-acyl-carnitine increased progressively to twice the normal limit by day 5 without the development of metabolic acidosis, or cardiac or renal impairment.

Patients receiving propofol infusions for more than a few hours should be closely monitored for development of lactic acidosis, as this may occur at an early stage before irreversible cell damage has occurred.[31;32] In addition increased levels of creatine kinase, myoglobin and troponin I should alert clinicians to the development of early signs of PRIS. Propofol administration should not be re-instituted after apparent recovery, because it appears that the damage to the mitochondria persists for an unknown period, as illustrated by a reported death of a child from PRIS who was re-exposed to propofol shortly after recovering from a metabolic acidosis that occurred during a propofol infusion.[11] Patients who exhibit increasing demand for inotropic and vasopressor support in the intensive care setting should also arouse suspicions of the development of PRIS.[56] In the future it may be possible to detect impending trouble by monitoring acyl-carnitine levels. However, at present this is an assay that is beyond the capabilities of most laboratories.

Should there be no clinical improvement after stopping the propofol infusion, haemodialysis or plasmapheresis should be instituted.[17] Without dialysis mortality is nearly 100%. Severe, refractory cardiac failure has been successfully treated with extracorporeal circulation with membrane oxygenation (ECMO)7.

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This lecture will be presented at SASA Congress 2006

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