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Propofol Infusion Syndrome
An Overview of a Perplexing Disease

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Contents

Abstract

Propofol (2, 6-diisopropylphenol) is a potent intravenous hypnotic agent that is widely used in adults and children for sedation and the induction and maintenance of anaesthesia. Propofol has gained popularity for its rapid onset and rapid recovery even after prolonged use, and for the neuroprotection conferred. However, a review of the literature reveals multiple instances in which prolonged propofol administration (>48 hours) at high doses (>4 mg/kg/h) may cause a rare, but frequently fatal complication known as propofol infusion syndrome (PRIS). PRIS is characterized by metabolic acidosis, rhabdomyolysis of both skeletal and cardiac muscle, arrhythmias (bradycardia, atrial fibrillation, ventricular and supraventricular tachycardia, bundle branch block and asystole), myocardial failure, renal failure, hepatomegaly and death. PRIS has been described as an 'all or none' syndrome with sudden onset and probable death. The literature does not provide evidence of degrees of symptoms, nor of mildness or severity of signs in the clinical course of the syndrome. Recently, a fatal case of PRIS at a low infusion rate (1.9–2.6 mg/kg/h) has been reported.

Common laboratory and instrumental findings in PRIS are myoglobinuria, downsloping ST-segment elevation, an increase in plasma creatine kinase, troponin I, potassium, creatinine, azotaemia, malonylcarnitine and C5-acylcarnitine, whereas in the mitochondrial respiratory electron transport chain, the activity of complex IV and cytochrome oxidase ratio is reduced. Propofol should be used with caution for sedation in critically ill children and adults, as well as for long-term anesthesia in otherwise healthy patients, and doses exceeding 4–5 mg/kg/h for long periods (>48 h) should be avoided. If PRIS is suspected, propofol must be stopped immediately and cardiocirculatory stabilization and correction of metabolic acidosis initiated. So, PRIS must be kept in mind as a rare, but highly lethal, complication of propofol use, not necessarily confined to its prolonged use.

Furthermore, the safe dosage of propofol may need re-evaluation, and new studies are needed.

Propofol (2,6-diisopropylphenol) is a potent, intravenous hypnotic agent that is widely used for the induction and maintenance of anaesthesia in adults and children aged ≥3 years, and for the sedation of patients in intensive care units. It has gained popularity for its rapid onset and recovery time,[1] with patients recovering rapidly even after prolonged use. In addition, it confers neuroprotection by the inactivation of GABA receptors and blockade of excitatory neurotransmitters, which play a role in neuronal death induced by brain ischaemia.[2,3] Propofol decreases cerebral oxygen consumption and reduces intracranial pressure. It is a potent antioxidant, has anti-inflammatory properties and is a bronchodilator. As a consequence, propofol has also been increasingly used in the management of epilepsy, alcohol withdrawal delirium, asthma and in patients critically ill with sepsis.[4] In patients with refractory status epilepticus (RSE), barbiturates such as pentobarbital or thiopental sodium have been used, inducing coma and electroencephalogram suppression,[5] but their effectiveness has not been studied systematically. Superior pharmacokinetics and a favourable adverse effect profile could make propofol the drug of choice in the treatment of patients with RSE. The two main advantages of propofol are its rapid onset and short duration of action.

Propofol has been shown to be as safe and efficacious as midazolam, alone or in combination with midazolam, in the prolonged sedation of a homogeneous group of severe trauma patients, particularly in mechanically ventilated adults with head trauma. Patients treated with propofol have been shown to have shorter wake-up times than those receiving midazolam,[6,7] and have been reported to have a better quality of sedation,[8] and a shorter withdrawal time after prolonged administration, resulting in a favourable economic profile.[9,10]

Despite these encouraging findings, a review of the literature reveals multiple instances in which prolonged propofol administration (>48 hours) at high doses (>4 mg/kg/h)[1,11] may cause the rare, but frequently fatal complication, propofol infusion syndrome (PRIS). The syndrome was first described in critically ill children[12,13] and later in adults[14-16] and is characterized by metabolic acidosis, lipaemic plasma and myocardial failure.[17] Rhabdomyolysis of both skeletal and cardiac muscle,[18] hyperkalaemia, renal failure and death[5] have also been associated with this syndrome.[19-21] PRIS can be caused by popofol alone, and when propofol is used in combination with catecholamines and/or corticosteroids.[22] Theories as to causality include mitochondrial toxicity, mitochondrial defects, impaired tissue oxygenation and carbohydrate deficiency. A review of published and confidential safety data concluded that the major risk factors for the development of PRIS appear to be poor oxygen delivery, sepsis, serious cerebral injury and high propofol dosage.[23]

PRIS has been described as an 'all or none' syndrome with sudden onset and probable death. The literature does not provide evidence of degrees of symptoms, nor of mild or severe signs in the clinical course of the syndrome.

Development of PRIS has been reported not only in patients undergoing long-term sedation with propofol but also during propofol anaesthesia of 5 hours' duration.[24] In another report, a high dose of propofol was given for only 3 hours during surgery, followed by a low-dose infusion for 20 hours postoperatively, co-administered with methylprednisolone.[25] Recently, fatal cases of PRIS at low infusion rates (1.9–2.6 mg/kg/h and 1.4–5.1 mg/kg/h) have been reported.[15,26]

Therefore, with regard to its use in the perioperative setting, physicians should be aware of the risk of toxicity associated with propofol and stop infusion in the presence of acute metabolic acidosis after accurate differential diagnosis.[27,28]

This review provides an update on recent findings and describes case reports of PRIS.

1. Epidemiology

Data on the incidence of PRIS are not yet available. Patients affected are mainly described in case reports in anaesthesiology and intensive care publi-

cations, and in general scientific journals. This syndrome occurs in critically ill children and adults undergoing long-term propofol infusion. Table I and table II summarize the published cases regarding children and adults, respectively. Table III presents cases occurring during the perioperative period (during anaesthesia). Many case reports include children in paediatric intensive care units (PICUs) with upper or lower respiratory infections who were receiving several different drugs and who were seriously ill.

It is reasonable to suppose that such a group would have a significant mortality rate, but it is unusual to see deaths of this type in children experiencing respiratory tract infections.[17] Nevertheless, some factor other than propofol may have been responsible – for example, the drug was selected for the most severely ill children – but no evidence of this could be found.[17]

The syndrome does not appear to be age-related.[34] It has been reported mostly in patients with acute neurological illnesses or acute inflammatory diseases complicated by severe infections or sepsis who are receiving catecholamines or corticosteroids in addition to propofol.[1] A relationship between the total suppression of cerebral activity by any sedative drug and the development of a PRIS-like syndrome has been hypothesized.[18]

A genetic susceptibility, in terms of an inborn error of mitochondrial fatty acid oxidation, has also been suggested.[13,35] To identify genetic markers for patients at risk, screening of a large variety of genetic variants of mitochondrial defects in patients surviving PRIS would be necessary. Genetic markers could then be used to identify individuals with a risk of developing of PRIS.[43,44] Unfortunately, we do not currently have any clues as to which patients may be susceptible to developing the syndrome.

2. Pathophysiology

At the intracellular level, propofol impairs oxygen utilization and inhibits electron flow along the mitochondrial electron transport chain in cardiomyocytes. Propofol also significantly decreases ventricular performance in the isolated, perfused heart,[11,46] impairs oxidation of fatty acid chains and inhibits oxidative phosphorylation in the mitochondria, resulting in an imbalance between energy demand and utilization, thus compromising cardiac and peripheral muscle cell function.[47]

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.[13] Free fatty acids are the most important fuel for myocardial and skeletal muscle under fasting or in critical conditions (i.e. critically ill patients). 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 impairment of free fatty acid utilization leads to various grades of myocytolysis.[11]

Another mechanism by which propofol exerts its effects is by uncoupling β-oxidation (the complex pathway to create energy for the organism) and the respiratory electron transport chain at complex II,[11,13] meaning that neither medium- nor short-chain free fatty acids, which freely cross the mitochondria membranes, can be utilized. Low energy production can lead to cardiac and peripheral muscle necrosis if energy demand is high. Furthermore, accumulation of unutilized free fatty acids could predispose the patient to arrhythmias,[11] probably related to Ca^{2+} overload in myocardial cells.[48,49]

The responsiveness of cardiac β-adrenergic receptors is reduced by propofol, and it also acts on calcium channel proteins, contributing to diminished cardiac contractility.[50] This might explain the lack of response to catecholamines and the need for increasing inotropic support in critically ill patients.

3. Risk Factors

There are a number of genetic factors which are thought to predispose individuals to PRIS. A typical genetic disorder impairing fatty acid metabolism is medium-chain acyl Co A dehydrogenase (MCAD) deficiency, which causes impaired fat metabolism with acute metabolic decompensation during catabolic episodes.[51] MCAD deficiency may be caused by a combination of 18 different MCAD gene variations,[52] and other genetic defects in mitochondrial metabolism may have similar complexity to the recently differentiated MCAD variants. Some of

Table I. Case reports of propofol infusion syndrome in paediatric intensive care units

Case reports	Patients (sex, age [y], diagnosis)	Propofol dosage (mg/kg/h)	Infusion duration (h)	Biochemical data	Use of corticosteroids and/or catecholamine	Clinical features	Outcome
Parke et al.[29]	5 M and F, 4 wk–6 y, 4 laryngotracheo-bronchitis bacterial, 1 bronchiolitis	7.4–10	66–115	Lipaemia, ↑ K^+, ↓ Ca^{2+}	Yes/yes	Metabolic acidosis, brady-arrhythmia, right bundle branch block, myocardial failure pyrexia, hepatomegaly, renal failure, hypotension	Died
Barclay et al.[30]	M, NA, epiglottitis	7.4	56	Lipaemia, ↓ Ca^{2+}, ↑ AST, CK and lactate, myoglobinuria	NA	Metabolic acidosis, bradycardia, hypotension, oliguria, coma, focal muscle necrosis	Survived
Bodd and Endresen[31]	NA, NA, laryngitis	5–9	3–5	↑ Liver enzymes	NA	Hepatomegaly, metabolic acidosis	Died
	NA, NA, epiglottitis	NA	4 d	↑ Liver enzymes	NA	Hepatomegaly, metabolic acidosis	Died
Strickland and Murray[32]	M, 11, astrocytoma	6–12	72	Lipaemia, ↑ K^+	NA	Metabolic acidosis hypotension, oliguria, junctional rhythm, ventricular fibrillation, renal failure	Died
Bray[17]	NA, NA, laryngotracheal bronchitis	4.5	72	pH normal, no lipaemia	NA	Bradycardia, heart block, hepatomegaly	Died
Plotz et al.[33]	M, NA, laryngitis	5–10	60	↑ CK and lactate, myoglobinuria	Yes/yes	Metabolic acidosis, hypotension, pyrexia, bradycardia with right bundle branch block, ventricular tachycardia	Died
Cray et al.[34]	M,10 mo, oesophageal foreign body	10	50.5	↑ Amylase, AST, CK, lactate, triglycerides, creatinine, ↓ Ca^{2+}, pyruvate	No/yes	Metabolic acidosis, bradycardia with right bundle branch block, myoglobinuria, hepatomegaly, encephalopathy, muscle necrosis	Survived
Hanna and Ramundo[12]	M, 7, refractory status epilepticus	10–27	63	↑ CK and lactate	Yes/yes	Tachycardia, bradycardia, asystole, tea-coloured urine, oliguria, hypotension, severe metabolic acidosis, hypoxia, rhabdomyolysis	Died
Wolf et al.[13]	M, 2, head trauma	4–5.2	72	↑ K^+, urea, CK creatinine, malonylcarnitine, C5-acylcarnitine, myoglobinaemia	No/yes	Nodal bradycardia, severe metabolic acidosis, hypoxia, rhabdomyolysis, green urine	Survived
Cannon et al.[20]	F, 13, severe head trauma	100 μ/kg/min	96	↑ AST, ALT, CKMB, CK, cTnI	No/yes	Fever, green urine, metabolic acidosis, right bundle branch block, bizarre wide QRS, hypotension	Died
Withington et al.[35]	M, 5 mo, cleft lip repair	NA	>48	↑ mulonylcarnitine, C5 acylcarnitine AST, ALT, CK	NA	Metabolic acidosis, multiple cardiac arrhythmias, hepatic and renal failure	Survived
Holzki et al.[36]	M, 3, NA	20	15	NA	Yes/no	Metabolic and respiratory acidosis, bradycardia, cardiac failure	Died

CK = creatine kinase; **CKMB** = myocardial fraction of CK; **F** = female; **h** = hours; **M** = male; **NA** = data not available; ↑ indicates increase; ↓ indicates decrease.

Table II. Case reports of propofol infusion syndrome in adults occurring in intensive care units

Case report	Patients (sex, age [y], diagnosis)	Propofol dosage (mg/kg/h)	Infusion duration (h)	Biochemical data	Use of corticosteroids and/or catecholamine	Clinical features	Outcome
Marinella[37]	F, 30, asthma	NA	12	↑ Lactate	Yes/no	Metabolic acidosis	Survived
Hanna and Ramundo[12]	M, 17, epilepsy	8.8–17.5	44	↑ CK, lipaemia, myoglobinuria	No/yes	Metabolic acidosis, hypoxia bradycardia, hypotension, rhabdomyolysis, anuria	Died
Perrier et al.[38]	F, 18, polytrauma	5.8–7.6	98	↑ CK, K^+, methaemoglobin lipaemia, myoglobinuria	No/yes	Atrial fibrillation, left bundle branch block, metabolic acidosis, cardiac failure, hypotension, pulseless electrical activity	Died
Stelow et al.[21]	F, 47, asthma	12	36	↑ CK, K^+, cTnI, ↓ Ca^{2+}	Yes/yes	Hypotension, anuria, dark urine, metabolic acidosis, hyperthermia, ventricular tachycardia and cardiac arrest	Died
Stelow et al.[21]	M, 41, asthma	13.3	144	↑CK and cTnI, myoglobinuria	No/yes	Oliguria, dark urine, cardiac failure	Survived
Cremer et al.[14]	5 M and F, head injury	5.5–7.4	65–106	Myoglobinuria, ↑ CK, K^+, lipaemia	No/yes	Metabolic acidosis, rhabdomyolysis, supraventricular tachycardia	Died
Kelly[6]	NA, NA, head trauma	7.5	55	↑ Azotaemia, creatinine	NA	Metabolic acidosis, cardiac and renal failure	Died
Friedman et al.[39]	M, 23, epilepsy	12	106	↑ K^+	No/yes	Metabolic acidosis, cardiac failure, ventricular and supraventricular tachycardia	Died

Continued next page

Table II. Contd

Case report	Patients (sex, age [y], diagnosis)	Propofol dosage (mg/kg/h)	Infusion duration (h)	Biochemical data	Use of corticosteroids and/or catecholamine	Clinical features	Outcome
Ernest and French[40]	M, NA, head injury	NA	NA	NA	No/yes	Cardiocirculatory collapse, metabolic acidosis, mild rhabdomyolysis, renal failure	Died
Casserly et al.[22]	M, 42, NA; F, 17, NA	6	>48	Myoglobinuria, ↑ CK, K^+, lipaemia, azotaemia, creatinine	Yes/yes	Renal failure, rhabdomyolysis, metabolic acidosis	Both survived
Kumar et al.[41]	F, 27, seizures secondary to haemorrhage from an arteriovenous malformation; M, 64, status epilepticus; F, 24, status epilepticus	NA	NA	↑ CK, lactate myoglobinuria,	No/yes	Metabolic acidosis, hypotension, bradycardia, rhabdomyolysis	Died
Liolios et al.[25]	M, NA, neurosurgery	9 (intraoperative)	3	NA	Yes/no	Metabolic acidosis, rhabdomyolysis, renal failure	Survived
		2.3 (postoperative)	20				
Eriksen and Povey[15]	F, 20, trauma	1.4–5.1	88	↑ Azotaemia, creatinine	Yes/yes	Multiple organ failure, rhabdomyolysis	Died
Corbett et al.[42]	M, 21, head trauma	NA		↑ Lactate	No/yes	Metabolic acidosis, severe left ventricular dysfunction and cardiomyopathy	Survived

CK = creatine kinase; **CKMB** = myocardial fraction of CK; **CTn1** = cardiac troponin; **F** = female; **h** = hours; **M** = male; **NA** = data not available; ↑ indicates increase; ↓ indicates decrease.

Table III. Case reports of propofol infusion syndrome in paediatric and adult anaesthesia

Case report	Patients (sex, age [y], diagnosis)	Propofol dose (mg/kg/h)	Infusion duration (h)	Biochemical data	Use of corticosteroids and/or catecholamine	Clinical features	Outcome
Paediatric patients							
Mehta et al.[45]	F, 18 mo, underwent elective surgery for bilateral talipes correction	6	5	↑ CK and lactate	No/yes	Acidosis metabolic, multiple cardiac arrhythmias, oligoanuria	Survived
Adult patients							
Liolios et al.[25]	M, NA, neurosurgical procedure	9 (intra-operative)	3	NA	Yes/no	Metabolic acidosis, rhabdomyolysis, renal failure	Survived
		2.3 (post-operative)	20				

CK = creatine kinase; **F** = female; **h** = hours; **M** = male; **NA** = data not available; ↑ indicates increase.

these may also result in susceptibility to the development of PRIS.[27,53]

Low carbohydrate supply is another risk factor for PRIS, because energy demand is met by lipolysis if carbohydrate supply is low, thus leading to an accumulation of free fatty acids. Consequently, children could be more prone to the development of PRIS as a result of low glycogen storage and a high dependence on fat metabolism.[54] In such instances, a carbohydrate intake of 6–8 mg/kg per minute is required to suppress fat metabolism.[34]

It has been postulated that propofol might act as a trigger for PRIS in the presence of priming factors. The priming factors may be severe diseases to which the patient has been exposed, whereas propofol, hydrocortisone and catecholamines serve as possible triggers.[24] This is in accordance with the hypothesis that the pathogenesis is thought to involve activation of the systemic inflammatory response, which culminates in acidosis and muscle necrosis.[41] The stress response usually has an anti-inflammatory and immunosuppressive effect. If this is inadequate, susceptibility to inflammatory disease is enhanced. A persistent pro-inflammatory state with hyper catabolism causes progressive organ dysfunction, including cardiac and skeletal muscle dysfunction. Thus, high doses of drugs such as propofol, glucocorticoids and catecholamines may trigger the syndrome of cardiac failure and rhabdomyolysis, followed by metabolic acidosis and acute renal failure.[11]

It is of interest that catecholamines are associated with direct myocytolytic effect and increased cardiac output. As a consequence, propofol concentration is reduced to the lowest levels with a reversal of anaesthesia,[55] meaning clinicians are led to increase the propofol infusion rates further. The negative inotropic effect of propofol, resulting in increased catecholamine requirements, could create a vicious circle, whereby propofol and catecholamines are causes of myocardial derangement.[11]

4. Clinical Features and Outcomes

Common clinical features of PRIS may include: metabolic acidosis, rhabdomyolysis, arrhythmias, myocardial and renal failure, hepatomegaly, hyperkalaemia and lipaemia (table IV).[16,19,30] Rhabdomyolysis is a clinical entity that evolves after skeletal muscle injury. The symptoms and signs are secondary to muscle injury and the effects of the release of toxic intracellular contents. They include muscle weakness, myoglobinuria and renal failure.[21] Death related to PRIS may occur in adults as well as in paediatric patients.[35]

5. Laboratory and Instrumental Findings

The main laboratory findings associated with PRIS are summarized in table V. It should be emphasized however, that laboratory findings listed in the case reports of PRIS are not definitive.[13,35,56] Arterial blood analysis showing lactic acidosis is a clear diagnostic marker for PRIS.[35] Even if a differential diagnosis of lactic acidosis can be difficult to make in the acute care setting, frequent evaluation of lactic acidosis is very important. It is easy to do at

Table IV. Main clinical features of propofol infusion syndrome

Metabolic acidosis
Rhabdomyolysis of both skeletal and cardiac muscle
Arrhythmias (bradycardia, atrial fibrillation, ventricular and supraventricular tachycardia, bundle branch block and asystole)
Myocardial failure
Renal failure
Hepatomegaly

the bedside and monitoring should be carried out frequently during long infusions of propofol as it is a useful possible early marker of drug toxicity.

Laboratory findings including hepatic dysfunction, coagulophathy and acute renal failure with hyperkalaemia, hyperphosphataemia and rhabdomyolysis,[35] myoglobinuria and large increases in plasma troponin I and creatine kinase levels have been documented in children and adults during propofol infusion. Myoglobinuria, troponin I and CK are indicators of a direct necrotizing effect on the peripheral and cardiac muscles.[22] Evidence of this necrosis has been supported by histological studies showing signs of severe myocytolysis in the skeletal muscle and myocardium of affected patients.[11]

In patients with PRIS returning to normal after recovery, biochemical analyses have shown large increases in plasma concentrations of malonylcarnitine and C5-acylcarnitine. [13,35] Propofol can impair the mitochondrial electron transport chain and affect fatty-acid oxidation inducing an increase in malonylcarnitine. This inhibits the transport of long-chain fatty acids by carnitine palmitoyl transferase 1. Medium-chain and short-chain fatty acids will continue to penetrate into the mitochondria by diffusion. However, a secondary inhibition of the respiratory chain at complex II also occurs with increase in C5-acylcarnitine.

Arrhythmias such as bradycardia, atrial fibrillation, ventricular and supraventricular tachycardia and bundle branch block are frequently documented in electrocardiographic analysis. A relationship between down sloping ST-segment elevation in precordial leads V_1 to V_3, and the propofol infusion rate has recently been identified.[57]

In muscle biopsies of subjects with the clinical features of PRIS, decreased mitochondrial complex IV activity and a low complex IV/cytochrome oxidase ratio of 0.004 (normal range 0.014–0.034) suggested a mitochondrial respiratory electron transport chain enzyme deficiency that may be a result of propofol infusion.[11,58]

6. Prevention

Arrhythmia, metabolic acidosis, cardiac failure and death related to propofol use can occur in adults as well as in children. Because of its possible fatal adverse effects, propofol should be used with caution for sedation in critically ill children and adults, as well as for long-term anaesthesia in otherwise healthy patients. It is recommended that long-term administration of propofol (>48 hours) should never exceed the dosage of 4–5 mg/kg/h.[16,47]

Nevertheless, as stated previously, reports of PRIS at low doses have recently been published.[15,26] Carbohydrate substitution at 6–8 mg/kg per minute is also recommended, which might prevent PRIS.[13,44]

Better prevention is possible if physicians are aware of PRIS, thereby reducing the death rate, and it is recommend that clinicians inducing propofol sedation and anaesthesia keep their patients under close observation and discontinue the agent if arrhythmias or metabolic acidosis develop.[24,38] Arterial blood gases and lactic acid levels should be monitored frequently,[41] and the monitoring of levels of creatine kinase, troponin I, myoglobin and electrolytes can also be useful.

7. Therapy

Once the development of PRIS is suspected, propofol infusion, as a specific therapeutic measure, must be stopped immediately and cardiocirculatory

Table V. Laboratory and instrumental findings in propofol infusion syndrome

Myoglobinuria
↑ Plasma creatine kinase
↑ Plasma troponin I
↑ Plasma K^+
↑ Lipaemia
↑ Creatinine and azotaemia
↑ Plasma malonylcarnitine and C5-acylcarnitine
Downsloping ST-segment elevation in precordial leads V_1 to V_3
↓ Complex intravenous activity and complex IV cytochrome oxidase ratio of 0.004 (normal range 0.014–0.034)

↑ indicates increase; ↓ indicates decrease.

stabilization and correction of metabolic acidosis initiated as therapeutic supportive measures.

To increase the elimination of propofol and its potential toxic metabolites, haemodialysis or haemofiltration are recommended.[24] Unfortunately, patients in whom the syndrome is accompanied by arrhythmias may not usually be resuscitated and are minimally responsive to the use of multiple inotropic agents or cardiac pacing.[34]

8. Differential Diagnosis

When faced with possible PRIS, it is important to exclude other pathological conditions. Acute differential diagnosis of metabolic acidosis is very important, even if very difficult in critically ill patients, as it could save lives if recognized and corrected early. For example, intraoperative metabolic acidosis results from an obvious cause, such as lower body perfusion after release of an aortic clamp or severe haemorrhagic shock. More recently, the infusion of relatively large volumes of 0.9% saline has been associated with hyperchloraemic metabolic acidosis.[59] Also, metabolic acidosis is associated with excessive generation of organic acids (lactate and ketones). In critically ill patients, sepsis, low cardiac output with hypoperfusion ketoacidosis, diabetes mellitus and renal failure could be the cause.

There are many possible aetiologies of rhabdomyolysis, the most common being trauma, seizure and alcohol use. Infection, drugs and toxins have also been implicated.[21,60] Systemic infection, an inborn error of metabolism, acute pancreatitis and Reye's syndrome (cerebral oedema and hyperammonaemia) must also be excluded as causes of rhabdomyolysis.

Echocardiography should not show a structural lesion, nor demonstrate poor contractility suggestive of myocarditis or cardiomyopathy.[34]

9. Discussion and Conclusion

PRIS is an iatrogenic disease that must be added to the list of other iatrogenic diseases generated by intensive medical treatments, such as prolonged paralysis after discontinuation of neuromuscular blocking drugs or during therapy with very high doses of corticosteroids. In this sense, PRIS and critical illness myopathy and polyneuropathy share several features, including the facilitating role of corticosteroids, and present mostly in patients with acute inflammatory diseases, severe infections or sepsis.

For a long time, PRIS has been unrecognized and its significance underestimated. Some authors have previously contested the existence of the syndrome, as the data available were insufficient to determine, beyond reasonable doubt, whether this rarely occurring event was caused by the administration of propofol.[61] The controversy was added to by the occurrence of a case of metabolic acidosis, cardiac failure, rhabdomyolysis, renal failure, hepatic failure and death in a patient who had received thiopental for treatment in an epileptic state.[62] But the absence of reports in the early years following the marketing of propofol is probably be related to the fact that the clinical signs were correlated to patient diseases or to the critically ill status of the patient.

As previously stated, in light of the possibility of fatal adverse effects, the use of propofol for long-term sedation in critically ill patients should be reconsidered.[24] Recently, recommendations for the limitation of propofol use have been devised by various institutions.[44]

Making changes to the way propofol is used will not be easy, considering that the drug has been enthusiastically adopted by anaesthesiologists and intensive care physicians over the last two decades and is suggested for prolonged anaesthesia and intensive care sedation. More than 330 million people have been exposed to propofol since its launch in 1986.[63] Nevertheless, it is now suggested the selection of other pharmacological agents as an alternative to propofol for long-term sedation, especially in paediatric patients, is now suggested.[20]

A review of data from randomized, controlled clinical trials evaluated the safety and effectiveness of propofol versus standard sedative agents in paediatric ICU patients and showed an increase in deaths in patients treated with propofol.[64] Based on this, the US FDA has not approved this drug for sedation in paediatric patients and has stated that the drug should not be used for this purpose.[63]

There is much clinical experience with the use of midazolam in the PICU population, and it remains the most commonly used benzodiazepine. There are limited reports regarding the use of pentobarbital in

the PICU setting, with one study raising concerns of a high incidence of adverse effects associated with its use.[65] As experience of the long-term use of sedatives in paediatric patients increases, it appears that there will be a role for newer agents such as dexmedetomidine. Dexmedetomidine has α_2-adrenergic receptor activity and is capable of inducing a dose-dependent decrease in the release and turnover of noradrenaline, dopamine and serotonin in the CNS.[65] Dexmedetomidine may evolve into an agent with qualities comparable to midazolam and propofol, and it may even become a drug of choice in selected patients; however, further study is required.[66]

Because of their adverse effects on haemodynamics and the immune response, barbiturates are no longer used as long-term sedative agents. However, they are still recommended in cases of refractory intracranial hypertension[67] and in patients with status epilepticus.[66]

Therefore, the risks related to the use of the available alternative sedatives to propofol make the choice very difficult and not free from concern. We recommend that lactic acidosis of unknown origin could be an early warning marker of the syndrome, prompting physicians to stop propofol infusion in susceptible patients.

Propofol remains the optimal sedative agent owing to the properties discussed here. PRIS must be kept in mind as a rare, but highly lethal complication of propofol use, not necessarily confined to its prolonged use.[44] Furthermore, the safe dosage of propofol may need re-evaluation, and new studies are needed.[15]

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