Abstract: Propofol is a short-acting intravenous anesthetic agent widely used for sedation in anesthesia and intensive care. However, during the last 15 years there have been quite a lot of publications reporting unexplained deaths among pediatric and adult critically ill patients. These cases shared common symptoms and signs unrelated with initial admission diagnosis and were under long-term propofol infusion at high doses. A new syndrome called ‘propofol infusion syndrome’ was defined, including cardiovascular instability, metabolic acidosis, hyperkalaemia and rhabdomyolysis, with no evidence for other known causes of myocardial failure. One common denominator in these patients was the presence of hypoxia and tissue hypoperfusion. It seems that during states of increased metabolic demand, the reduced energy production related to an inhibitory propofol action at the level of mitochondrial oxidative phosphorylation and lipid metabolism may lead to the manifestation of the syndrome. Furthermore, cases of early toxicity due to failure in cellular energy production with development of lactic acidosis have been also described during anesthesia. For the above reasons, recommendations for the limitation of propofol use have been devised by various institutions, whereas physicians need to be cautious when using prolonged propofol sedation and alert for early signs of toxicity.

Key words: Anesthesia ; catecholamines ; critical care ; propofol, rhabdomyolysis.

INTRODUCTION

Propofol was introduced into the market as an emulsion of soya oil/propofol mixture in water by AstraZeneca Pharmaceuticals (Mississauga, Canada) in 1986, with the brand name Diprivan (67). The elimination half-life of propofol ranges between 2-24 hours, however, in the clinical setting the duration of clinical effects is much shorter, due to its rapid distribution in peripheral tissues (23). This, together with its rapid effects and the moderate induced amnesia, makes it an ideal drug for short-term intravenous (IV) sedation in anesthesia and intensive care (40).

Propofol has been known to cause hypotension (through vasodilation), transient apnoea, pain on injection and rarely, myoclonia and dystonia (23). However, during the last 15 years many reports have been published in the literature relating propofol administration, particularly in the Intensive Care Unit (ICU) with unexplained deaths and the development of a new ‘syndrome’. At the same time, different Institutions have published guidelines relevant to propofol use in specific clinical settings. The purpose of this review is to discuss the current literature and the proposed pathophysiological mechanisms responsible for propofol toxicity and finally help clinicians in recognising early warning signs and taking preventive measures in order to avoid full development of ‘propofol-infusion syndrome’ that is associated with high mortality.

BACKGROUND

Many authors have reported deaths among pediatric intensive care patients under unexplained circumstances, with a distinct pattern of symptoms, where sedation with propofol was considered as the main common factor (4, 6).

History and definitions

In 1992, Parke and co-workers reported five cases of critically ill children, who under sedation with propofol, developed metabolic acidosis and
fatal myocardial failure (43). In 1996, Marinella reported a case of an unexplained anion gap metabolic acidosis and elevated serum lactate, 2 hours after propofol infusion, in a 30-year-old woman with an exacerbation of asthma and mechanical ventilatory support. After discontinuation of propofol, pH, lactate levels and anion gap subsequently normalized (38). In 1998, Bray reviewed 18 cases, including the original five of Parke, in which critically ill children suffering from sepsis due to severe respiratory disease and under sedation with propofol developed a combination of symptoms, which he thought to be a syndrome, linked to the propofol administration (9). Propofol infusion syndrome (PRIS) has been defined by Bray as the occurrence of acute bradycardia resistant to treatment and progressing to asystole, associated with propofol infusion. In order to meet the criteria of PRIS, bradycardia has to be combined with lipaemic plasma, fatty liver enlargement, metabolic acidosis with base excess >-10 mmol/l, rhabdomyolysis or myoglobinuria.

In 2001, Cremer and colleagues published a retrospective review of seven adult intensive care patients with head injuries and multiple traumas, who died after having developed clinical features similar to those described by Bray (15). He proposed diagnostic criteria for the new ‘adult propofol infusion syndrome’ after excluding patients with evidence of sepsis, multiple organ failure, and known causes of hyperkalaemia, acidosis and rhabdomyolysis. The proposed criteria include: 1. progressive myocardial failure with dysrhythmias (cardiac output dependent on tachycardia), 2. two of the following: metabolic acidosis, hyperkalaemia, evidence of muscle cell destruction, 3. absence of known causes of myocardial failure, 4. aged 18-55 years.

In general, PRIS has been associated with the use of high doses of propofol (> 4 mg/kg/hour) for prolonged periods of administration (> 48 hours). The syndrome has been described in approximately 32 critically ill children (4, 5, 8, 11, 12, 14, 27, 29, 39, 43, 45, 54, 57, 63, 64) and 29 adult intensive care patients (15, 22, 24, 34, 44, 53), whereas several risk factors have been recognized, such as airway infections, severe head injury, high-dose sedation for more than 48 hours, increased catecholamine and glucocorticoid serum levels and low energy supply (25, 41). Tables 1 and 2 summarize some of the published cases of propofol toxicity in adult and pediatric patients respectively.

A case of a syndrome similar to PRIS has been described after cerebral activity suppression with thiopental that was delivered for the treatment of epileptic state. The patient died of cardiac failure, rhabdomyolysis, renal failure, metabolic acidosis and hepatic failure and the authors hypothesized a relationship between the total suppression of cerebral activity and the development of a PRIS-like syndrome (3).

**PRIS in anesthetic practice**

Recently, three case reports have been published in the literature suggesting that continuous propofol infusion during anesthesia in adult patients may result in metabolic (lactic) acidosis (10, 49, 37). In the first report, a 31-year-old woman during radiofrequency ablation for chronic atrial fibrillation developed unexplained metabolic acidosis after receiving propofol sedation, titrated between 50 and 125 µgr/Kg/min, for approximately 395 minutes. After propofol infusion was discontinued, pH returned towards normal values. In the second case, a 64-year-old man developed significant lactic acidosis 2 hours after propofol anesthesia administration for radical prostatectomy. In the third report, a 42-year-old man who underwent elective surgery for a brainstem cavernous angioma under anesthesia with propofol (9 mg/Kg/min) for 3 hours developed a marked lactic acidosis with mild signs of renal impairment and rhabdomyolysis, without evidence of haemodynamic instability. In all three cases, other possible causes of intra-operative metabolic acidosis were excluded (severe hemorrhagic shock, hyperchloremic metabolic acidosis due to large volume of 0.9% normal saline infusion, cardiopathic hypoxia secondary to sepsis).

**The con’s and pro’s for the existence of PRIS**

In 1999, the manufacturer sponsored a systematic review of all adverse events in pediatric patients treated in intensive care units (ICUs) who developed PRIS (1). According to his point of view, all cases had relevant independent risk factors for the development of symptoms and signs included in Cremer’s description. In the study of Cremer, the reported events occurred in adults with severe head injuries, which are known to cause cardiovascular instability, arrhythmias and hyperkalaemia (18, 56). Furthermore, the initial dose was within recommended limits; however, it was progressively increased to two or three times higher, probably not only for sedation but also for intracranial hypertension control. At the same time, the infusion rate of inotropes and vasoconstrictors were increased in...
parallel, in order to maintain cerebral perfusion pressure (CPP) at or above 70 mmHg. In conclusion, Ahlen and co-workers based on their findings from their retrospective study denied completely the fact that propofol could be responsible of cellular toxicity, at least in some specific settings.

Although causality is not clearly proved by the available data and despite the rarity of PRIS in relation to the widespread use of propofol in anesthesia, different pathophysiological mechanisms seem to support the theory that propofol is the causal agent. Nevertheless, except for coherence and plausibility, the rest of Hill’s criteria for causation, especially consistency and consideration of alternate explanations, have to be taken into account in order to define a truly new ‘syndrome’ (28). Only one case report (21) has applied criteria for causality to propofol.

### PATHOPHYSIOLOGY

In all reported cases, there is evidence of failure of adequate tissue oxygen uptake or utilization. Propofol effects in mitochondria have been demonstrated 20 years ago, from Scutari and colleagues who reported the first observations of propofol induced uncoupling of oxidative phosphorylation and energy production (51). Since then, other authors have also identified an inhibition of electron flow along the mitochondrial electron transport chain (47, 50). In addition, propofol prevents long chain free fatty acids (FFA) form entering the mitochondria through an inhibition of carnitine palmitoyl transferase I whereas medium- and short-chain FFA that do not require enzyme-mediated transfer cannot be utilized due to a propofol induced complex II inhibition (Fig. 1). In general, PRIS seems to

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**Table 1**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Diagnosis</th>
<th>Dose (mg/Kg/h)</th>
<th>Duration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marinella 1996</td>
<td>Severe asthma</td>
<td>NA</td>
<td>12 h</td>
<td>Survived</td>
</tr>
<tr>
<td>Hanna and Ramundo 1998</td>
<td>Refractory epilepsy</td>
<td>8.8-17.5</td>
<td>44 h</td>
<td>Died</td>
</tr>
<tr>
<td>Steilow 2000</td>
<td>Refractory asthma</td>
<td>13.3</td>
<td>36 h</td>
<td>Died</td>
</tr>
<tr>
<td>Perrier 2000</td>
<td>Severe head trauma</td>
<td>5.8-7.6</td>
<td>98 h</td>
<td>Died</td>
</tr>
<tr>
<td>Cremer 2001</td>
<td>7 cases with severe head trauma</td>
<td>Average 5.5-6.5</td>
<td>Average 100-110 h</td>
<td>Died</td>
</tr>
<tr>
<td>Kelly 2001</td>
<td>Head trauma</td>
<td>7.5</td>
<td>55 h</td>
<td>Died</td>
</tr>
<tr>
<td>Friedmann 2002</td>
<td>Refractory epilepsy</td>
<td>12</td>
<td>106 h</td>
<td>Died</td>
</tr>
<tr>
<td>Ernest and French</td>
<td>Head trauma</td>
<td>4.1</td>
<td>65 h</td>
<td>Died</td>
</tr>
<tr>
<td>Cassery 2004</td>
<td>Cerebral sinus thrombosis</td>
<td>8.58</td>
<td>72 h</td>
<td>Died</td>
</tr>
<tr>
<td>Burrow 2004</td>
<td>Propofol anesthesia</td>
<td>75 µg/Kg/min</td>
<td>395 minutes</td>
<td>Alive</td>
</tr>
<tr>
<td>Salegnos 2004</td>
<td>Propofol anesthesia</td>
<td>Total 2500 mg</td>
<td>4.5 h</td>
<td>Alive</td>
</tr>
<tr>
<td>Liolios 2005</td>
<td>Propofol anesthesia</td>
<td>9 mg/Kg/h followed by 2.3 mg/Kg/h</td>
<td>3 h followed by a 2+ dose for 20 h</td>
<td>Alive</td>
</tr>
</tbody>
</table>

NA : not available.

**Table 2**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Diagnosis</th>
<th>Dose (mg/Kg/h)</th>
<th>Duration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parke 1992</td>
<td>Laryngotracheobronchitis</td>
<td>4.8</td>
<td>&gt; 96 h</td>
<td>Died</td>
</tr>
<tr>
<td>Barclay 1992</td>
<td>Laryngotraheobronchitis</td>
<td>7.9</td>
<td>&gt; 96 h</td>
<td>Died</td>
</tr>
<tr>
<td>Bod and Endreisen 1992</td>
<td>Acute stridor</td>
<td>10</td>
<td>&gt; 96 h</td>
<td>Died</td>
</tr>
<tr>
<td>Strickland and Murray 1995</td>
<td>Subglottic stenosis</td>
<td>7.1-10.7</td>
<td>&gt; 96 h</td>
<td>Died</td>
</tr>
<tr>
<td>Bray 1995</td>
<td>Epiglottitis</td>
<td>5-10</td>
<td>&gt; 48 h</td>
<td>Survived</td>
</tr>
<tr>
<td>Plotz 1996</td>
<td>Epiglottitis/laryngitis</td>
<td>5-9</td>
<td>&gt; 48 h</td>
<td>Died</td>
</tr>
<tr>
<td>Van Straaten 1996</td>
<td>Laryngitis</td>
<td>9.4</td>
<td>38 h</td>
<td>Died</td>
</tr>
<tr>
<td>Croy 1998</td>
<td>Respiratory track infection</td>
<td>4.5-6.2</td>
<td>72 h</td>
<td>Died</td>
</tr>
<tr>
<td>Metha 1999</td>
<td>Laryngitis</td>
<td>5-10</td>
<td>60 h</td>
<td>Died</td>
</tr>
<tr>
<td>Cannon 2001</td>
<td>Respiratory track infection</td>
<td>8.6</td>
<td>72 h</td>
<td>Survived</td>
</tr>
<tr>
<td>Wolf 2004</td>
<td>Severe head trauma</td>
<td>5</td>
<td>50 h</td>
<td>Survived</td>
</tr>
<tr>
<td>Baumeister 2004</td>
<td>Severe head trauma</td>
<td>5-5.9</td>
<td>168-196 h</td>
<td>Died</td>
</tr>
<tr>
<td>Withington 2004</td>
<td>Refractory status epilepticus</td>
<td>11.7</td>
<td>24-48 h</td>
<td>Survived</td>
</tr>
<tr>
<td>Holzki 2004</td>
<td>Aspiration pneumonia</td>
<td>4-20</td>
<td>23 h</td>
<td>Died</td>
</tr>
</tbody>
</table>

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be the final result of an imbalance between energy demand and supply within the cells where impaired mitochondrial respiratory chain function and disruption of free fatty acids β oxidation may result in widespread failure in energy production in the mitochondria and cellular necrosis.

The metabolic defects associated with PRIS occur mostly in cells with high energy demands such as the heart and muscle cells, resulting in a syndrome similar to mitochondrial cytopathies and acquired carnitine deficiency (17, 25).

**Cardiac cell toxicity**

1. **Biochemical alterations**

Propofol related cardiac cellular actions include an antagonizing effect on β-adrenoceptor binding (69) and direct inhibition of calcium-channel proteins (68), resulting in diminished contractility. Nevertheless, the extensive protein binding of plasma propofol may limit mitochondrial exposure to as little as a tenth of the investigated conditions (1). In addition, propofol decreases oxygen consumption to the same extent as midazolam (36).

Inhibition of β oxidation by propofol may lead to high levels of plasma FFA, which have been identified as a pro-arrhythmogenic risk factor (32, 58). Particularly, in myocardial cells the accumulation of acyl-carnitine inhibits outward potassium channels and up-regulates α1 adrenoceptors, leading to Ca2+ accumulation, changes in the period of repolarization and refractoriness, after-potentials generation and cell death (46). Furthermore, lipaemic plasma may prevent propofol from diffusion to its sites of action due to its high lipid solubility, leading to a progressive increase in dose requirements (35).

2. **Electrophysiological alterations**

Cardiovascular instability and cardiac death have been recently related to a specific electrocardiogram (ECG) pattern, characterized by covered-type ST-segment elevation in the right precordial leads, resembling the ECG pattern of an inherited sudden cardiac death syndrome known as the
Brugada syndrome (59). Vernooy and colleagues investigated retrospectively ECG abnormalities in 6 patients with PRIS, from a cohort of 67 head-injured patients and concluded that a Brugada-type ECG pattern is a sign of cardiac electrical instability and can predict imminent cardiac death. ST-segment elevation is thought to result from an outward shift in the balance of ionic currents at the end of phase I of the epicardial ventricular action potential (2), especially at the level of the right ventricular outflow tract, leading to the predominance of the above ECG pattern in right precordial leads (60). It is possible that high-dose propofol might have an indirect effect in the balance of inward and outward ionic currents, facilitating ST elevation and development of re-entry arrhythmias, especially in the presence of other predisposing factors, such as acidosis, fever or ischemia (20, 2). The above ECG findings could be of significant value as early diagnostic signs of PRIS and must always be interpreted with caution by attending physicians managing patients with a combination of symptoms and signs attributed to propofol toxicity.

3. Histopathological alterations

Except for electrical instability, cardiovascular failure can be related to direct myocytolytic effects of propofol and catecholamines co-administration (58). A catecholamine-propofol vicious cycle has been described, whereas an inotrope-related increase in cardiac output is linearly associated with a reduction in propofol serum levels from baseline, leading to a reversal of anesthesia (42). Such results are attributable to increased first-pass dilution and clearance of propofol, secondary to the hyperdynamic circulation. Critically ill septic and trauma patients require adequate levels of sedation. The negative inotropic effects of propofol and the augmented catecholamine requirements may create a vicious cycle where both agents are responsible for a progressive myocardial defect. The anatomic/pathological findings of the above myocardial injury have been described as myofibrillar degeneration (MD), contraction band necrosis or coagulative myocytolysis (48). This situation resembles that seen in patients with pheochromocytoma and involves histological changes different from those related to myocardial infarction (MI) (13, 48). Muscle fibers remain in a contracted state with prominent contraction bands, early monocyte activation and subsequent calcification whereas in MI, myocytes die in a relaxed state, with polymorphonuclear cell infiltrations that appear late in the progress of the disease and without calcification (13, 33). Injury to the myocardium, related to various levels of non-ischemic stress has also been demonstrated by increase in the concentration of cardiac troponin I (cTnI > 0.8 µg/L) in serum (65), which is found exclusively in cardiac muscle (7).

Peripheral muscle cell toxicity

Rhabdomyolysis, associated with acute renal failure and metabolic acidosis has been reported in many cases of head injured patients suffering from PRIS (15, 34, 44). Similar to myocardial histological findings, microscopic examination of peripheral skeletal muscles has demonstrated myopathic changes, secondary to propofol infusion. The main anatomic findings include an acute necrotic reaction in muscle fibers with swelling, loss of striation and vacuole formation, without the presence of inflammatory response or any morphological change in vessel walls (53) (Fig. 2). The lack of inflammatory infiltrates confirms the acuity of this process. Muscle damage is associated with elevated creatine phosphokinase (CPK) levels (reference intervals: 60-300 U/L for males and 40-200 U/L for females), release of toxic intracellular contents (potassium, protons, lactate), myoglobinuria and renal failure (52), because myoglobin is nephrotoxic, depletes renal adenine nucleotide pools (66) and inhibits proximal tubular cell proliferation (31). However, muscle damage, elevated CPK levels and rhabdomyolysis have multiple causes in critically ill patients. Inadequate oxygen delivery to skeletal muscles due to prolonged systemic hypoperfusion or hypoxia, with or without episodes of acute hypotension, use of vasoconstrictive agents in brain trauma patients for supporting a falling cerebral perfusion pressure (CPP = 60-70 mmHg), increased sympathetic activity, hyperosmolar states related to diabetes insipidus, hypokalaemia and extensive use of mannitol infusion can trigger damage of muscle cell membranes, leading to various levels of myopathic changes not related to propofol infusion (1, 26, 52, 61). In addition, concomitant use of steroids and/or vecuronium, particularly in patients with severe asthma or septic shock (19, 30, 62), has been implicated in the development of rhabdomyolysis with similar histological alterations in skeletal muscles (steroid myopathy).

Fat metabolism

Lipid metabolism in the liver is based on appropriate intake of carbohydrates. In their absence, energy demand is satisfied by lipolysis,
thus favouring free fatty acid accumulation and cardiac toxicity. Inadequate carbohydrate administration in critically ill patients in relation with lipid infusion (included propofol formulations) may progress to hyperlipaemia, along with liver fatty infiltration, something that has been correlated to higher propofol and lipid infusion rates (1).

Children are more prone to the development of PRIS due to lower glycogen storage in their liver and high dependence on FFA β oxidation (25). In a recent report of a pediatric patient who developed PRIS after receiving propofol with a mean dose of 4.7 mg/Kg/hour for 130 hours and low carbohydrate substitution (2 mg/Kg/min), increased levels of plasmatic malonyle- and acyl-carnitine indicated an association between high FFA plasma levels and propofol related β oxidation inhibition. In addition, carnitine levels rose above normal range at day 4 after increasing propofol dose at day 3 and subsequently, propofol infusion was stopped (64). The above findings underlie the importance of adequate carbohydrate intake in order to reduce lipid load and the significant value of monitoring carnitine plasma levels in specific clinical settings, as an early preventive measure for avoiding or reducing propofol toxicity.

In conclusion, propofol seems to result in various metabolic alterations associated with an energetic cellular crisis due to an imbalance between energy supply and demand and may lead to cardiac and peripheral muscle cell stress and necrosis. Early diagnosis and prevention is of paramount importance in order to prevent the high mortality that accompanies propofol toxicity. In every case of unexplained or worsening lactic acidosis in patients receiving high-dose and long-term propofol this drug should be stopped at once and alternative sedation should be considered.

Nevertheless, the term PRIS according to Vasile, is misleading because both a priming factor (critical illness) and a triggering factor (high dose of propofol, catecholamines and steroids) are needed for the description of the syndrome (58). In addition, there is an overlapping between those two factors. The author proposed a new description term of ‘critical illness, cardiac failure and rhabdomyolysis associated with high dose propofol, catecholamines or steroids’.

**THERAPY AND PROPHYLAXIS**

Therapy for PRIS includes general supportive measures for the support of cardiac and renal failure and immediate stop of propofol infusion. However, bradycardia may be resistant to conventional therapy, such as catecholamines and external pacing (41). Seven patients have been reported to survive after renal replacement therapy, using haemodialysis or haemofiltration and two other patients survived PRIS with the assistance of extracorporeal membrane oxygenation (ECMO) (25).

Guidelines of the Society of Critical Care Medicine and the American College of Chest Physicians have stated that propofol infusion should be limited to the dose of less than 4 mg/kg/hour in children, whereas doses of more than 5 mg/kg/hour are associated with an increased risk of cardiac arrest in adults (25). The Task Force of the American College of Critical Care Medicine and the Society of Critical Care Medicine has recommended a maximum dose of 4 mg/kg/hour of propofol, for no more than 48 hours in head injured patients, accompanied by frequent monitoring of pH, serum lactate and creatine kinase (55). In addition, carbohydrate substitution should be delivered at 6-8 mg/kg/min, for the prevention of lipaemia.

In conclusion, in critically ill patients where various combinations of propofol, catecholamines and steroids can be implemented, it is prudent to avoid prolonged infusion of high dose propofol. Lorazepam or midazolam can be considered as equally effective alternatives (55, 58). At the same time, frequent monitoring of acid-base status, CPK and lipid serum levels can lead to an early recognition of a possible propofol-related metabolic disturbance, after excluding other causes. Finally, unexplained intra-operative lactic acidosis under propofol anesthesia must prompt physicians to discontinue its use and consider it as the main causative mechanism, after excluding other causes.
GENERAL CONCLUSIONS

Propofol infusion-related combination of physical and laboratory signs cannot be considered a 'syndrome' yet, as underlying pathologic mechanisms are still not clear. Especially in the critical care setting, complexity of physiological derangements, interactions of causative stimuli with multiple physiologic and therapeutic responses and lack of a fundamental understanding of how these combine as manifestations of a common biologic process make discrimination between association and causality extremely difficult (16). However, the available data suggest that propofol infusion rate and duration of administration could be associated with increased mortality, but causality needs to be tested using rigorous methodological tools, such as the Hill’s criteria. In addition, despite the absence of randomized clinical trials (RCT’s) and despite the sometimes heterogeneous details of the cases reported in the literature, propofol can be deleterious in some patients. Since there is still a lack of a gold standard method for the early diagnosis of PRIS, physicians dealing with sedation or even anaesthesia with propofol should be aware of its detrimental effects, try to detect early signs of toxicity and avoid prolonged use of high doses.

References

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