## REVIEW ARTICLE

# Propofol infusion syndrome: update of clinical manifestation and pathophysiology

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#### ABSTRACT

Propofol infusion syndrome (PRIS) is defined as acute bradycardia progressing to asystole combined with lipemic plasma, fatty liver enlargement, metabolic acidosis with negative base excess >10 mmol · l-l, rhabdomyolysis or myoglobinuria associated with propofol infusion. The purpose of this review was to provide a new update of reported case reports and to describe recent retrospective studies and animal research relevant for the pathophysiology and clinical presentation of PRIS. New case reports of PRIS have confirmed previously identified risk factors, and have also further revealed the incidence of PRIS in patients previously not estimated to be at risk for this syndrome. Retrospective studies contributed new evidence to the incidence of PRIS and development of PRIS even at propofol doses commonly used for surgical anesthesia. An animal study confirmed potential pathophysiological pathways and showed new organ manifestations possibly associated with propofol infusion. Further clinical and experimental evidence has confirmed the existence of PRIS as a rare but highly lethal complication of propofol use not limited to prolonged use of propofol. PRIS has to be kept in mind if propofol is used for anesthesia or sedation. Recommendations for the limitation of propofol use have to be adhered to. Early warning signs must prompt immediate cessation of propofol infusion and adequate treatment.

Key words: Propofol - Anesthetics - Bradycardia - Acidosis, lactic...

## Clinical presentation

Propofol infusion syndrome (PRIS) has been defined as the occurrence of acute bradycardia resistant to treatment and progressing to asystole associated with propofol infusion. Bradycardia has to be combined with lipemic plasma, fatty liver enlargement, metabolic acidosis with negative base excess >10 mmol·l-¹, rhabdomyolysis or myoglobinuria.¹ PRIS usually leads to fatal cardiac and renal failure. Symptoms and signs are lactacidosis, arrhythmia, hypotension, renal, cardiac and circulatory failure, oliguria, rhabdomyolysis, elevated serum creatine kinase, serum urea and serum potassium, lipemic plasma, liver enlargement,

ketonuria, increased liver enzymes and green or red coloured urine. Risk factors identified from case reports are airway infection, severe head injury, high-dose long-term propofol sedation for more than 48 h at more than 5 mg·kg<sup>-1</sup>·h<sup>-1</sup>, increased catecholamine and glucocorticoid serum levels and low energy supply.<sup>2</sup>

Recently a retrospective database analysis was performed to identify predictors of mortality in patients with suspected PRIS. Reports from 1989 to 2005 where propofol infusion was associated with at least 1 of 24 symptoms of PRIS were included in the analysis. Three-hundred and forty-two out of 1 139 patients died in this study. Death

was more likely if the patients were younger than 19 yearsof age, males or received a vasopressor. Other identified risk factors for death were cardiac manifestations, metabolic acidosis, renal failure, hypotension, rhabdomyolysis or dyslipidemia.<sup>3</sup>

An early sign of cardiac instability associated with the syndrome is the development of right bundle branch block with convex-curved ("coved type") ST-elevation in the right precordial leads (V1 to V3) of the electrocardiogram (Brugada-like ECG pattern). The relationship between this ECG pattern and propofol infusion rate, cardiac arrhythmias, and death has been assessed in 67 head-injured patients, seven of whom had PRIS. Six of the patients with PRIS developed the described ECG pattern and died from cardiac arrhythmia. ECGs of 30 out of 60 unaffected patients were normal. The authors concluded that development of an acquired Brugada-like ECG pattern in severely head-injured patients is a sign of cardiac electrical instability predicting imminent cardiac death.5

## Incidence

PRIS has been described both in children (24 cases) and in adults (14 cases) in 2006.6,7 These cases have been summarized and the literature covering the syndrome has been reviewed comprehensively at that time.8 Since then, five pediatric and 12 adult cases of PRIS or putative early PRIS have been reported.9-25 Four patients received propofol for heart surgery, one patient was sedated after myocardial infarction, suggesting an interaction of myocardial disease and myocardial toxicity of propofol.<sup>11, 14, 19, 25</sup> Five patients suffered from the syndrome after brain injury, status epilepticus or neurosurgery, thus emphasizing the now wellknown relationship between neurological disease and the development of PRIS.8, 13, 17, 22, 23 Three cases occurred after low propofol doses compared to those typical for PRIS.<sup>20, 22, 23</sup> A patient with sepsis supports the role of infectious disease as a risk factor for PRIS.9 The other cases include conditions not commonly observed in patients with PRIS. Patients suffered from trauma without brain injury, angiography, scoliosis and lung biopsy. 10, 12, 18, 24

No prospective study on the incidence of PRIS is available so far. Due to the very low incidence of PRIS, studies have to focus on the incidence of

symptoms regarded as precursors of PRIS or on retrospective analyses of cohorts of patients at risk for undiagnosed PRIS.

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In a retrospective study charts of patients undergoing radiofrequency catheter ablation for atrial flutter or fibrillation, who received propofol were reviewed for metabolic acidosis defined as negative base excess ≥2. Carotid endarterectomy patients, who did not receive propofol were used as controls. Thirteen out of 55 (24%) of patients receiving propofol had negative base excesses ≥2, *vs* 22 out of 267 (8.2%) controls. The authors concluded that metabolic acidosis during propofol infusion is not rare. However, the study was hampered by its retrospective nature and by the lack of baseline arterial blood gas data.<sup>26</sup>

Another study was designed to evaluate the incidence of PRIS in patients with head trauma and its relation to the use of vasopressors. Patients with severe head trauma admitted to an Intensive Care Unit (ICU) were screened for use of propofol and vasopressors. Patients who had unexplained acidosis, creatine kinase elevation and electrocardiographic changes were considered having PRIS. Concomitant use of vasopressors was investigated and odds ratio for developing PRIS were determined. Three out of 50 admitted patients with severe head trauma developed PRIS. Two of them survived and one died. Concomitant use of vasopressors was associated with development of PRIS in these patients, thus emphasizing the role of sympathoadrenergic drugs in the pathophysiology of PRIS.<sup>27</sup>

Though not all patients in these studies fulfill the strict criteria for the diagnosis of PRIS, these may be valuable with respect to the occurrence of potential precursors of PRIS like acidosis, creatine kinase elevation and electrocardiographic changes. Prospective studies are required to confirm these data and are currently performed at our institution.

## **Etiology**

PRIS is usually associated with the use of high doses of propofol for prolonged periods of time. Nevertheless, it has been discussed if propofol is responsible for PRIS or if there may be a pure coincidence of propofol infusion with other causes of fatal rhabdomyolysis and cardiac failure.<sup>28</sup>

<sup>29</sup> It was argued that if a causal relationship exists, more evidence should be available taking into account the large number of world-wide propofol applications.<sup>30</sup>

AstraZeneca recently emphasized in a review the role of the most important risk factors for the development of PRIS, focussing on poor oxygen delivery, sepsis, serious cerebral injury and high propofol dosage. In addition to this, lipemia, likely due to a failure of hepatic lipid regulation, possibly related to poor oxygenation or low glucose plasma levels, could lead to sequestration of propofol into the lipid phase, thus leading to lowered free propofol levels and apparent insensitivity to propofol. The manufacturer recommends good hemodynamic and oxygen delivery management, adequate glucose control, adherence to recommended propofol dosing regimes to prevent and treat the "so-called propofol infusion syndrome".<sup>31</sup>

However, it has been emphasized that the consistency of reports of different institutions, the dose dependence and the specific temporal association to propofol infusion render a causal relationship very likely.<sup>32, 33</sup> Pathophysiological mechanisms are plausible and similarities between cases with different concomitant diseases support the theory that propofol is the causal agent.

## Pathophysiology

Pathological findings in PRIS are cytolysis of skeletal and cardiac muscle cells.<sup>34</sup> Clinical and experimental findings show that propofol uncouples the respiratory chain in heart and muscle cells.<sup>35-37</sup> Free fatty acids have been identified as a pro-arrhythmogenic risk factor,<sup>38</sup> Muscle biopsies and fat metabolism analyses of patients with PRIS resemble these found in mitochondrial cytopathias and acquired acyl-carnitine metabolism deficiencies by inhibition of beta oxidation.<sup>39-41</sup> Possibly, a hereditary mitochondrial fatty acid metabolism impairment resembling medium-chain acyl-CoA dehydrogenase deficiency is responsible for the susceptibility to the development of PRIS, but screening of patients was normal so far.<sup>8, 15, 41, 42</sup>

Low carbohydrate supply is a risk factor for PRIS, because energy demand is satisfied by lipolysis if carbohydrate supply is low. Children are more prone to the development of PRIS due to

low glycogen storage and high dependence on fat metabolism.<sup>43</sup> Fat overload associated with propofol infusion may also contribute to increased plasma fatty acids.<sup>44</sup>

Increased endogenic catecholamine levels caused by intracerebral lesions and hyperdynamic circulation caused by SIRS decrease propofol plasma levels due to increased propofol clearance.<sup>7</sup> This may lead to insufficient sedation and increased propofol infusion rates. In addition, PRIS may be aggravated by concomitant diseases like cardiomyopathy.<sup>7, 45</sup>

Propofol inhibits cardiac beta-adrenoceptor binding and calcium channel protein function.<sup>46</sup> It suppresses the activity of sympathetic nerves and the baroreceptor reflex,<sup>2</sup> thus deteriorating cardiac failure in PRIS.

#### Animal studies

The clinical syndrome of PRIS has prompted research in animal models. Eighteen healthy male rabbits were sedated with propofol 2% or sevoflurane and endotracheally intubated in a recently published study. The initial propofol infusion rate was 20 mg·kg-1·h-1 and was adjusted to maintain a standard level of sedation up to 65.7±4.6 mg·kg<sup>-1</sup>·h<sup>-1</sup>. All animals sedated with propofol but no animal sedated with sevoflurane died. Blood biochemical analysis was performed in serial blood samples and histologic examination at autopsy. Serum liver function indices, lipids, lactate and creatine kinase were significantly increased in the propofol group. Histologic examination revealed myocarditis, pulmonary edema with interstitial pneumonia, hepatitis, steatosis, and focal liver necrosis, cholangitis, gallbladder necrosis, acute tubular necrosis of the kidneys, focal loss of the urinary bladder epithelium, and rhabdomyolysis of skeletal muscles in the rabbits anesthetized with propofol. The authors concluded that propofol was able to induce a fatal syndrome similar to PRIS in rabbits.<sup>47</sup> However, the animal model is limited by high doses of propofol compared to human doses.

## Therapy

Propofol infusion must be stopped immediately. Hemodynamic stabilization has to be achieved

by routine intensive care procedures. Unfortunately, bradycardia is often resistant to catecholamines and external pacing. Carbohydrate substitution is recommended at 6-8 mg·kg<sup>-1</sup>·min<sup>-1</sup>. Extracorporeal membrane oxygenation has been used with success in two cases. Hemodialysis or hemofiltration is recommended for elimination of propofol and its potentially toxic metabolites.<sup>8</sup>

## **Prophylaxis**

The occurrence of PRIS has lead to restrictions to the use of propofol. Propofol is not approved for sedation in pediatric ICU patients. Nevertheless, off-label use at high doses is still often clinical practice, due to pharmacodynamic properties and high dose requirements of propofol in children. Monitoring of pH, serum lactate and creatinine kinase was recommended when high doses or long infusion periods cannot be avoided. The Drug Commission of the German Medical Association (Arzneimittelkommission der deutschen Ärzteschaft) recommended to avoid propofol in children younger than 16 years for intensive care sedation. A dose limit of 4 mg·kg<sup>-1</sup>·h<sup>-1</sup> is recommended for sedation of adult patients and a period of seven days should not be exceeded. Acidbase-metabolism and creatinine kinase should be monitored frequently. Propofol should not be used as the only sedative but in combination with others to avoid dose escalation.2 In our own institution the use of propofol in ICU is limited to a maximum of 4 mg·kg-1·h-1 for a maximum of 48 h.<sup>7</sup> In addition to this, long fasting times should be avoided in children and are unnecessary for most surgical procedures.

## **Putative early PRIS**

Some patients receiving propofol presented with symptoms typical for PRIS but without cardiac involvement and the reporting authors argued that these symptoms may have been precursors of PRIS. Four pediatric and six adult patients with suggested early PRIS were reported until 2006. <sup>48-53</sup> Three adults and three children developed the symptoms after infusion periods typical for surgical procedures. <sup>8</sup> Since then, another three patients had PRIS or putative early PRIS after low doses of propo-

fol compared to those estimated as risk factors for PRIS.  $^{20,\,22,\,23}$ 

However, currently total intravenous anesthesia (TIVA) with propofol is regarded as a safe procedure with few side effects in paediatric anesthesia and is considered as a standard procedure. Although PRIS was reported in patients with epilepsy, propofol is still recommended in patients with epileptic seizures due to lack of epileptic potential and postoperative agitation and delirium as compared to sevoflurane.2 Moreover, the use of propofol for anaesthesia of refractory status epilepticus was justified in a recent review, although dose limitation was emphasized.<sup>54</sup> Infusion rates of up to 9 mg·kg<sup>-1</sup>·h<sup>-1</sup> over 2-4 h are recommended for TIVA in children.<sup>55</sup> A review of standard sedation procedures in intensive care concluded that PRIS should not lead to limitation of propofol use for anesthesia.56

A recent survey concerning the use of propofol infusions by pediatric anesthetists showed that 26% of anaesthetists used propofol infusions. The maximum rate used was 30 mg·kg<sup>-1</sup>·h<sup>-1</sup> and the longest time considered for an infusion was 72 h with a wide variety in the use of propofol infusions.<sup>57</sup>

## Conclusions

In conclusion, case reports and retrospective data of potential or diagnosed PRIS suggest that PRIS may not be limited to prolonged use of propofol. The syndrome has still to be kept in mind as a differential diagnosis if typical symptoms occur during or after infusion of propofol for surgical anesthesia and sedation for non-surgical procedures.

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Conflicts of interest.—None.

Received on April 20, 2009 - Accepted for publication on April 20, 2009.

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