Propofol-related infusion syndrome (PRIS) – a review

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Abstract

Propofol related infusion syndrome (PRIS) is a rare and controversial clinical entity that was described in patients who got this sedative drug for long periods of time, mainly in the critical care environment, and very often in doses larger than those recommended by literature. Initially it was described in children, but soon some cases of adult patients in critical condition were published. Acute neurological conditions such as head trauma or status epilepticus are among those clinical situations that predispose to PRIS development. PRIS is characterized by severe clinical and laboratory signs, such as bradycardia, cardiac failure, hypotension not responding to vasopressors, lactic acidosis, and signs of rhabdomyolysis.

It seems that administration of propofol in large doses and for long duration has a pathological influence on mitochondrial activity, but disturbances in lipid metabolism and free fatty utilization have also been incriminated as being part of the pathophysiological explanation of the syndrome.

The article presents the main prophylactic measures to be taken when propofol is administered in large doses and for long periods of time, as well as proposals for management of PRIS. Since a good part of the literature questions even the existence of the syndrome, the article presents some data regarding this controversy and proposes a very careful approach to every case in which PRIS is suspected.

Keywords: propofol, side effects, propofol related infusion syndrome

Introduction

Propofol became part of the anesthesia drug arsenal in the second part of the 1980s and its place was well established in the operating room as a new and valuable induction agent [1]. It proved to be a reliable agent, possessing a very quick onset and, in usual dosage, it was not accompanied by important side effects. Used alone for induction no significant hypotension was reported [2].

Very soon its indications were enlarged and propofol was included in the list of hypnotic agents that could be used in continuous infusion for maintenance of general anesthesia [3]. This new indication could be easily explained by propofol’s rapid clearance from the body (by a conjugation process in the liver) and by the fact that its metabolic pathway does not produce active metabolites.

These advantages created the base for starting the use of propofol in continuous infusion outside the operating room, for sedation purposes, mainly for the critical care patient. One of the first reports on the use of propofol in the intensive care units (ICU) included ten patients, under mechanical ventilation, who received a continuous eight-hour infusion of the undiluted drug for sedation, with almost no untoward effects (except a statistically insignificant decrease in blood pressure) and rapid recovery after discontinuation of the drug [4].

Soon propofol became the drug of choice for sedation in ICUs. In 2001 Bertolini et al. [5] published the results of a survey among 128 Italian ICUs, including
Propofol's advantages over other sedative drugs for use in the ICU are evident: there is no need for a loading dose (and this could prevent a hypotensive effect), its clearance is 3-5 times more rapid than that of midazolam, and it has rapid elimination from the central compartment. Like any other drug, its elimination is slower in elderly patients.

Its influence on the cardiovascular system can be minimized by a correct adjustment of the dosage. We reported in 1996 a study regarding the use of propofol in the ICU with the aid of an EEG parameter, spectral edge frequency (SEF), in order to establish the proper dosage. We reported a cardiovascular stability much more evident when the dosage was adjusted in accordance to SEF values [6].

Some data from the literature mentioned the ease of managing the propofol infusion in comparison to midazolam, a classical drug for sedation in ICU. Chomorro et al. [7] reported that propofol use was very easy and/or easy in 96% of cases, while in the case of midazolam this percentage reached only 69%.

Finally, nowadays the cost of propofol does not seem to be an obstacle, since in recent years its price dropped dramatically.

So, there is a clear reason for using propofol in continuous infusion for sedation of a critically ill patient.

Propofol-related infusion syndrome – a clinical entity

Unfortunately, propofol infusion for a longer period of time proved to be accompanied by secondary effects, the most evident and dangerous being the so-called PRIS (propofol-related infusion syndrome), described for the first time in 1992 in children who received the drug in continuous infusion for a prolonged period of time [8]. Some years later a first connection between propofol infusion and lactic acidosis was published [9]. Bray, in 1998, proposed for the first time the term “propofol infusion syndrome” [10].

The syndrome soon became an impediment to recommending propofol as a drug of choice for continuous infusion in ICUs, but in recent years some measures to be taken have been proposed in order to prevent or minimize the negative effects.

A case report

A 28-year-old patient was admitted to an ICU after a motor vehicle accident that produced a severe head trauma and open fractures of left femur and tibia. A right craniotomy and evacuation of hematoma was performed as well as external fixation of both fractures prior to the patient’s transfer to ICU.

Once arrived in the ICU, a continuous infusion of propofol was begun and its dose was adjusted in accordance to the level of sedation (Ramsay scale 3). The patient was kept intubated and ventilated and the dose of propofol was gradually increased to 6.5 mg/kg/hour because of signs of restlessness and opposition to the ventilator.

Methylprednisolone 125 mg and mannitol 100 ml 10% twice a day were added in order to reduce the intracranial pressure.

On the 7th day after the accident, signs of sepsis developed (leukocytosis, fever, and a purulent secretion from the metal insertion point in the left leg). The patient became hemodynamically unstable and the rate of noradrenaline infusion was gradually increased.

The next day the patient became oliguric (15 ml/hour), adrenaline was added to the infusion, bicarbonate decreased to 15.6 mEq/l, creatinine kinase was 2450 u/l, and serum potassium level was 6.1 mEq/l. A supraventricular tachycardia appeared, accompanied by right bundle branch block (RBBB) simulating Brugada syndrome.

Hemodialysis was immediately started and transesophageal echocardiography showed evident signs of cardiac failure, with ejection fraction of 28%.
The patient died on the 11th day with combined signs of cardiogenic shock unresponsive to catecholamine infusion, severe metabolic acidosis, and rhabdomyolysis.

**Incidence of PRIS**

PRIS is a rare and often fatal syndrome, usually presenting as acute bradycardia progressing to asystole, combined with lipemic plasma, fatty liver enlargement, metabolic acidosis with negative base excess, rhabdomyolysis and/or myoglobinuria associated with prolonged infusion of propofol [12].

In a recent study, the percentage of PRIS among 1017 critically ill adult patients receiving propofol i.v. infusion for more than 24 hours was 1.1% [13].

It seems that the syndrome is more frequent when prolonged propofol infusion is administered in the presence of airway infections, severe head injury, poor oxygen delivery, sepsis, renal failure, and prolonged hypotension necessitating vasopressor therapy. Table 3 presents the main risk factors implicated in the appearance of PRIS.

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<th>Table 3. Risk factors related to development of PRIS</th>
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<tr>
<td>Young age</td>
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<td>Neurological damage</td>
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<td>Administration of catecholamines</td>
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<td>Administration of steroids</td>
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<td>Renal failure</td>
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Vasile et al. [14] tried to find the common denominator of PRIS in patients with head injury and status epilepticus published in the literature. They found that the usual propofol dose was 5.8-13.3 mg/kg/h for more than 48 hours, with a need for catecholamine dosage increase in 12 cases, metabolic acidosis in 11 cases, and hyperkalemia in 8 cases. Only two out of 38 patients survived.

Cremer et al. [15] reported that PRIS incidence was 17% in patients receiving 5-6 mg/kg/h and 31% in patients receiving a larger dose.

**Pathophysiology of PRIS**

Some hypotheses have been published with the aim of explaining the phenomenon.

The first linked the effect of propofol continuous infusion on uncoupling the respiratory chain in heart and muscle cells, liberating free fatty acids, and leading to cardiac arrhythmias.

The other related PRIS to the effect of propofol on cardiac output. It seems that large doses of propofol produce a decrease in the cardiac output, a situation that demands the use of catecholamines, which in turn increase the cardiac output and thus increase the rate of propofol metabolism, which leads to the need to augment the propofol dosage in order to keep the patient sedated.

Early theories also included impaired hepatic lactate metabolism caused by intralipid present in propofol. The soybean in propofol produces a rise in the serum level of free fatty acids (FFA), which are metabolized and produce toxic compounds that might be responsible for aggravating acidosis.

The connection of PRIS with neurological diseases (head trauma, status epilepticus, subarachnoid hemorrhage) seems to be evident. The explanation could be that so many neurological conditions are accompanied by sympathetic stimulation and release of large amounts of noradrenaline into the myocardium, and at the same time propofol, by its hypotensive effects, demands more exogenous catecholamines for preserving the cardiac output.

In addition, many neurological conditions are treated by steroids [14]. A combination of catecholamines and steroids exerts a profound effect on immunity and inflammation, such as impaired lymphocyte traffic and proliferation, and decrease in the activity of lymphoid cells. The result would be a net immunosuppressive effect in the presence of major injury and stress.

Propofol was directly accused of having an inhibitory effect on cardiac beta-adrenoceptor binding and calcium channel protein function [16, 17].

Finally, at the subcellular level, propofol impairs FFA utilization and mitochondrial activity, creating an imbalance between energy demand and utilization, which may lead to cardiac and peripheral muscle necrosis [14, 16]. Since propofol uncouples oxidative phosphorylation and energy production in the mitochondria, it impairs the FFA utilization, an effect that leads to muscle necrosis and rhabdomyolysis.

An increase in the serum level of FFA could be one of the explanations for the cardiac rhythm disturbances, since FFAs are known to have pro-arrhythmogenic activity [18]. If so, one can easily conclude that PRIS is produced by a dreadful pharmacological triangle: propofol-catecholamines-steroids.

**Treatment of PRIS**

It is obvious that the propofol infusion must be immediately stopped once the first signs of PRIS show up: cardiac arrhythmias or unexplained hyperkalemia, metabolic acidosis, or early signs of rhabdomyolysis.
In most cases PRIS is accompanied by cardiovascular instability and thus vasopressors and fluids are to be added to the treatment in order to bring blood pressure to the normal range. It seems that bradycardia is very often resistant to catecholamines and external pacing [12]. Hemodialysis, hemofiltration, and extracorporeal membrane oxygenation (ECMO) have been tried, with success in some cases. Da Silva [19] reported the successful use of partial-exchange blood transfusion in a child with PRIS and malignant refractory status epilepticus.

Diedrich and Brown [20] proposed some therapeutic measures that might reduce PRIS mortality, among them: improving oxygenation, glucagon (and not catecholamines) for increasing blood pressure, cardiac pacing, ECMO, and early renal replacement. Carbohydrate administration could help the lipid metabolism, by maintaining an adequate hepatic function [21].

Thus, it seems that there is no specific treatment for patients who develop PRIS, but rather several measures supporting the vital organs’ functionality.

**Prophylaxis of PRIS**

The first logical supposition regarding PRIS prophylaxis implies the interdiction of using propofol in large doses and for prolonged duration, especially in children and in patients with head injury, acute respiratory infections, or any acute neurological lesion. As far as we know today, it would be impossible to define what “not too much and not too long” means [22], but the propofol infusion has to be kept in low doses and stopped as soon as possible and replaced by other sedation regimens.

A dose limit of 4 mg/kg/h is recommended for sedation of adult patients and a period of seven days in a row should not be exceeded [12].

Based on clinical experience, it seems that propofol should be used as a sole sedation drug and any combination with other hypnotic drugs should be avoided.

Laboratory monitoring is compulsory when the patient is under propofol sedation in the critical care area. It includes blood gas analysis and serum levels of lactate, creatinine kinase, potassium, and bilirubin.

**A final but important question: Does PRIS really exist as a clinical entity?**

In 2006, Ahlen et al. published a comprehensive paper that represented the drug manufacturer’s answer to the fact that propofol could be responsible for the appearance of a clinical syndrome, albeit in a very small percentage of patients, but with a high rate of fatality [21].

Here are the main points raised by the above paper, which tries to question the connection between continuous propofol infusion and the development of a clinical picture compatible with the definition of PRIS:

1. **PRIS was described in cases of acute neurological conditions.** But severe head trauma, for instance, is known to be accompanied by cardiovascular instability, arrhythmias, ischemia, and hyperkalemia.

2. **The management of head trauma or subarachnoid hemorrhage includes fluid restriction with hypovolemia and the use of inotropes and vasoconstrictors to maintain a cerebral perfusion pressure above 70 mmHg.**

3. **In most cases labeled as PRIS the propofol dose used for sedation exceeded the recommended dose by at least 25%, mainly for controlling the intracranial pressure.**

4. **In some cases of status epilepticus, there were reports of using unlicensed propofol, and in very high dosage, 30-40 mg/kg/h.**

5. **Sepsis (which was described as part of the clinical features of PRIS) is very often accompanied by hypotension, acidosis, and vital multi-organ failure, a clinical picture that frequently leads to death, even in the absence of propofol administration.**

6. **The concomitant use of steroids in ICU patients could be a risk factor for rhabdomyolysis, independent of propofol administration.**

7. **Since the carbohydrate reserves are very limited in ICU patients, administration of lipids (including propofol formulations) could lead to impairment of lipid metabolism and accumulation up to pathological levels. Lipemia itself can impair mitochondrial oxygen uptake, promoting the development of some clinical aspects included in the definition of PRIS.**

**Back to our patient**

It is obvious that our patient illustrated the syndrome well. He had head trauma resulting from a car collision, and there was a need to use increasing doses of propofol in continuous infusion in order to keep him well sedated and avoid an increase in intracranial pressure. He became septic, and then developed metabolic acidosis, hypokalemia, Brugada syndrome – an electrocardiographic change usually seen during PRIS, and also laboratory signs of muscular necrosis. He died because of irreversible cardiac failure that was unresponsive to vasopressors. According to this clinical evolution, he had a chance of dying of some 30%, and this in spite of the fact that his vital multi-organ failure was managed specifically.
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ECMO and cardiac pacing are missing from the list of the therapeutic methods used in this case, but one could have doubts if these would have changed the patient outcome.

Conclusions

Propofol is still the most used sedation drug in ICUs. Imam [23] estimated that some 5 million patients are annually admitted to an ICU in the USA, and propofol is used by 80% of clinicians.

In spite of some controversial points of view in the literature, one cannot deny propofol’s contribution to the development of this clinical syndrome in very severely ill patients who received large doses of the drug and for long periods of time.

PRIS is accompanied by a high rate of mortality. In one of the biggest adult patient groups studied, by Roberts et al. [13], the death rate was 18%. Fong et al. [24] presented an analysis by the Food and Drug Administration, which reported 30% mortality in cases of PRIS.

It seems that PRIS is strongly connected to young age (especially children) and a prolonged infusion of propofol in large doses. Nevertheless, PRIS cases have been described after short-term infusion for maintenance of general anesthesia [21] and also after a low-infusion rate (1.9-2.6 mg/kg/h) [25].

The literature is almost unanimously in agreement that propofol continuous infusion should be carefully used in children, the dose must be lower than 4-5 mg/kg/h, and, if possible, for not more than 48 hours [26]. But one cannot forget that signs of PRIS have been reported to appear even after a short duration of propofol infusion. Koch et al. [27] described a case of a 5-year-old girl who developed lactic acidosis only six hours after initiating a 15 mg/kg/h propofol infusion.

Also, its use for patients with acute neurological conditions should be restricted and alternative methods of sedation should be used.

From the therapeutic point of view, the most important measure to be taken is interruption of the propofol infusion immediately after the appearance of the first sign compatible with PRIS.

Beyond any doubt PRIS develops in the critical care milieu, in patients with very serious conditions. Roberts et al. [13], in their large series of studied cases (1017 patients, 35% medical and 25% neurosurgical), found that the APACHE score in PRIS patients was significantly higher than in those who did not develop the syndrome, but the duration of propofol use was similar in both subgroups.

Last but not least, Crozer’s statement from 2006 [22] should be taken into consideration when a correct conclusion about PRIS is to be drawn: “The available data is still insufficient to determine beyond reasonable doubt if this rarely occurring event is caused by administration of propofol, and some authors contest the very existence of the syndrome.”

The practical approach to this controversy implies that the clinician should be alerted by the multiple question marks raised by the existence of PRIS. It means that PRIS is to be an ultimate diagnostic, after all the other clinical possibilities have been ruled out. But at the same time, there is an obligation to stop the propofol infusion at the first suspicion of appearance of PRIS.

Clinical judgment is a crucial tool in dealing with this rather cumbersome clinical situation.

Conflict of interest

Nothing to declare

References

Sindromul perfuziei cu propofol – o actualizare

Rezumat

Sindromul perfuziei cu propofol (PRIS) constituie o entitate clinică rară și controversată, care a fost descrisă în cazul unor pacienți care au primit propofol în perfuzie continuă, în scop sedativ, pentru perioade îndelungate de timp, în special în terapie intensivă, și foarte adesea în doze mai ridicate decât cele recomandate în literatură. Inițial a fost descris la copii, dar curând după aceea au fost publicate cazurile unor adulți aflați în stare critică. Afecțiuni neurologice acute ca: traumatismele cranio-cerebrale sau statusul epileptic sunt dintre acele situații clinice particulare care predispun la dezvoltarea PRIS. PRIS este caracterizat printr-o simptomatologie clinică severă și importante modificări de laborator: bradicardie, insuficiență cardiacă, hipotensiune arterială care nu răspunde la vasopresoare, acidoză lactică și semne de rabdomioliză. Se pare că administrarea de propofol în doze ridicate și pentru o perioadă lungă de timp are o influență patologică asupra activității mitocondriale, dar tulburările metabolismului lipidic și în utilizarea acizilor grași liberi au fost de asemenea incriminate ca parte a mecanismului fiziopatologic al acestui sindrom. Articolul prezintă principalele măsuri profilactice care trebuie luate atunci când se administrează propofol în doze ridicate pentru perioade mai lungi de timp, precum și propunerile de management al PRIS. Atât timp cât o mare parte a literaturii pune sub semnul întrebării însăși existența acestui sindrom, articolul prezintă câteva date despre această controversă și propune o atenție sporită în abordarea fiecărui caz cu suspiciune de PRIS.

Cuvinte cheie: propofol, efecte secundare, sindromul perfuziei cu propofol