

PRopofol Infusion Syndrome (PRIS) - 2009

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After long-term, high-dose propofol (>48 hours/ higher than 4 or 5 mg/kg per h,) may cause a rare, but frequently fatal complication known as PRopofol Infusion Syndrome (PRIS) an 'all or none' syndrome with sudden onset and probable death. The entity is characterized by:

- 1) Metabolic acidosis: Propofol may impair mitochondrial free fatty acid metabolism, resulting in an imbalance between energy demand and utilization and thus compromising cardiac and peripheral muscle cell function leading to lactate acidosis and muscular necrosis.
- 2) Lipemia
- 3) Rhabdomyolysis of both skeletal and cardiac muscle myocardial failure and renal failure and cardiovascular collapse
- 4) Arrhythmias (bradycardia, AF, VT and SVT, BBB and asystole whit Sudden cardiac death or
- 5) Brugada-like ECG pattern: The development of an acquired Brugada-like ECG pattern.
- 6) Hepatomegaly,
- 7) Renal failure: Rhabdomyolysis of skeletal and myoglobinuria is the cause. Hyperkalemia is observed.

The safe dosage of propofol may need re-evaluation, and new studies are needed because fatal case of PRIS at a low infusion rate (1.9-2.6 mg/kg/h) has been reported. Probably similar to your case dear Adriansinho It has been described only with acute neurologic injury or acute inflammatory diseases complicated by severe infections or sepsis or patient exposed to high catecholamine and cortisol levels have been identified as trigger substrates.

PROPOFOL INFUSION SYNDROME REFERENCES

Fodale V, La Monaca E. Propofol infusion syndrome : an overview of a perplexing disease. Drug Saf. 2008; 31(4):293-303.

Department of Neurosciences, Psychiatric and Anaesthesiological Sciences, University of Messina, Messina, Italy.

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.

PMID: 18366240 [PubMed - in process]

Corbett SM, Montoya ID, Moore FA. Propofol-related infusion syndrome in intensive care patients. *Pharmacotherapy*. 2008 Feb;28(2):250-288.

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The Institute of Medicine has identified adverse drug events as factors that significantly contribute to increased patient morbidity and mortality. As critically ill patients receive numerous drugs to treat a multitude of complicated health problems, they are at high risk for adverse drug events. Sedation is often a key requirement for the optimal management of critical illness, and propofol, a common sedative, has many desirable characteristics that make it the ideal agent in numerous circumstances. However, over the last decade, increasing numbers of reports have described a potentially fatal adverse effect called propofol-related infusion syndrome. Whether this adverse drug event is preventable is unclear, but recommendations have been proposed to minimize the potential for development of this syndrome. Research is under way to collect data on the use of propofol in intensive care units and on its prevalence.

PMID: 18225970 [PubMed - indexed for MEDLINE]

Kam PC, Cardone D. Propofol infusion syndrome. Anaesthesia. 2007 Jul; 62(7):690-701.

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The clinical features of propofol infusion syndrome (PRIS) are acute refractory bradycardia leading to asystole, in the presence of one or more of the following: metabolic acidosis (base deficit > 10 mmol.l(-1)), rhabdomyolysis, hyperlipidaemia, and enlarged or fatty liver. There is an association between PRIS and propofol infusions at doses higher than 4 mg.kg(-1).h(-1) for greater than 48 h duration. Sixty-one patients with PRIS have been recorded in the literature, with deaths in 20 paediatric and 18 adult patients. Seven of these patients (four paediatric and three adult patients) developed PRIS during anaesthesia. It is proposed that the syndrome may be caused by either a direct mitochondrial respiratory chain inhibition or impaired mitochondrial fatty acid metabolism mediated by propofol. 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 praecordial leads (V1 to V3) of the electrocardiogram. Predisposing factors include young age, severe critical illness of central nervous system or respiratory origin, exogenous catecholamine or glucocorticoid administration, inadequate carbohydrate intake and subclinical mitochondrial disease. Treatment options are limited. Haemodialysis or haemoperfusion with cardiorespiratory support has been the most successful treatment.

PMID: 17567345 [PubMed - indexed for MEDLINE]

Sabsovich I, Rehman Z, Yunen J, Coritsidis G. Propofol infusion syndrome: a case of increasing morbidity with traumatic brain injury. Am J Crit Care. 2007 Jan;16(1):82-85.

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A previously healthy 16-year-old boy with a closed, severe traumatic brain injury was admitted to a surgical and trauma intensive care unit. He was given a continuous infusion of propofol for sedation and to control intracranial pressure. About 3 days after the propofol infusion was started, metabolic acidosis and rhabdomyolysis developed. Acute renal failure ensued as a result of the rhabdomyolysis. Tachycardia with wide QRS complexes developed without hyperkalemia. The patient died of refractory cardiac dysrhythmia and circulatory collapse approximately 36 hours after the first signs of propofol infusion syndrome appeared. Propofol infusion syndrome is a rare but frequently fatal complication in critically ill children who are given prolonged high-dose infusions of the drug. The syndrome is characterized by severe metabolic acidosis, rhabdomyolysis, acute renal failure, refractory myocardial failure, and hyperlipidemia. Despite several publications on the subject in the past decade, most cases still seem to remain undetectable.

PMID: 17192529 [PubMed - indexed for MEDLINE]

Chukwuemeka A, Ko R, Ralph-Edwards A. Short-term low-dose propofol anaesthesia associated with severe metabolic acidosis. *Anaesth Intensive Care*. 2006 Oct;34(5):651-655.

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Propofol-induced metabolic acidosis is well recognised in the paediatric literature, but the existence of such a syndrome in adults remains contentious. In most reported cases, metabolic acidosis complicated prolonged administration of propofol in critically ill patients. We present a case of severe non-fatal reversible metabolic acidosis, without ventilatory depression or hypoxia, related to short-term propofol infusion in an adult during and after coronary artery bypass grafting. We suggest that lactic acidosis occurred in a genetically susceptible patient with an abnormality of mitochondrial function. This report discusses an unusual adverse effect of propofol anaesthesia and sedation and highlights the need for further investigation to define propofol toxicity.

PMID: 17061643 [PubMed - indexed for MEDLINE]

Vernooy K, Delhaas T, Cremer OL, Di Diego JM, Oliva A, Timmermans C, Volders PG, Prinzen FW, Crijns HJ, Antzelevitch C, Kalkman CJ, Rodriguez LM, Brugada R. Electrocardiographic changes predicting sudden death in propofol-related infusion syndrome. *Heart Rhythm*. 2006 Feb;3(2):131-137.

Comment in:

***Heart Rhythm*. 2006 Feb;3(2):138-139.**

Cardiovascular Research Institute Maastricht, Maastricht, The Netherlands.

BACKGROUND: The occurrence of metabolic acidosis, rhabdomyolysis, hyperkalemia, and sudden cardiac death after long-term, high-dose propofol infusion has been referred to as propofol infusion syndrome (PRIS).

OBJECTIVES: The purpose of this study was to explore the ECG abnormalities observed in a patient with PRIS in order to identify possible pathophysiologic mechanisms of the syndrome. **METHODS:** ECG changes in the index case were characterized by down-sloping ST-segment elevation in precordial leads V1 to V3 (Brugada-like ECG pattern). We subsequently assessed the relationship between this ECG pattern and the propofol infusion rate, the development of arrhythmias, and the occurrence of sudden death in a previously described cohort of 67 head-injured patients, seven of whom had been identified as having PRIS. **RESULTS:** Six of the PRIS patients developed the ECG pattern of ST-segment elevation in leads V1 to V3 and died within hours of irrecoverable electrical storm. This ECG pattern was the first aberration recorded hours before the death of these patients. ECGs that were available for 30 of 60 unaffected patients exhibited a normal pattern. None of the 60 patients developed ventricular arrhythmias.

CONCLUSION: Our findings indicate that development of an acquired Brugada-

like ECG pattern in severely head-injured patients is a sign of cardiac electrical instability that predicts imminent cardiac death. Future studies will determine whether such an ECG pattern also predicts imminent cardiac arrhythmia in other patient populations.

PMID: 16443524 [PubMed - indexed for MEDLINE]

Eriksen J, Povey HM. A case of suspected non-neurosurgical adult fatal propofol infusion syndrome. *Acta Anaesthesiol Scand*. 2006 Jan;50(1):117-119.

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A previously healthy woman (20 years old) was admitted to our hospital with several fractures after a car accident. She was sedated with propofol, etc. in doses ranging from 1.4 to 5.1 mg/kg/h for 88 h. She developed multiple organ failure with rhabdomyolysis and died. This case fulfils (except acidosis) the criteria of propofol-infusion syndrome (PRIS) in a young adult.

PMID: 16451160 [PubMed - indexed for MEDLINE]

Kumar MA, Urrutia VC, Thomas CE, Abou-Khaled KJ, Schwartzman RJ. The syndrome of irreversible acidosis after prolonged propofol infusion. *Neurocrit Care*. 2005; 3(3): 257-259.

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INTRODUCTION: Propofol infusion syndrome is described in the pediatric literature as metabolic acidosis, rhabdomyolysis, and bradycardia that results in death. The pathogenesis of this syndrome is thought to be activation of the systemic inflammatory response, which culminates in acidosis and muscle necrosis. **MATERIALS AND METHODS:** Retrospective chart review of three patients in the Neurological Critical Care Units at Hahnemann and Massachusetts General Hospitals between October 2001 and September 2004. **RESULTS:** Patient 1: A 27-year-old woman had seizures secondary to hemorrhage from an arteriovenous malformation. Propofol coma was induced for sedation. After initiation of propofol, she developed a metabolic acidosis, hypotension, and bradycardia and expired. Patient 2: A 64-year-old man presented in status epilepticus. After prolonged propofol administration, he developed metabolic acidosis, hypotension, and rhabdomyolysis and expired. Patient 3: A 24-year-old woman presented in status epilepticus secondary to encephalitis. Propofol was added for seizure control. She developed hypotension, metabolic acidosis, and bradyarrhythmias. Despite transvenous pacing, she expired. **CONCLUSION:** These data show an association between extended propofol use and metabolic acidosis, rhabdomyolysis, and death in adults, as well as children. Risk factors for propofol infusion syndrome in adults include lean body mass index, high dose, and administration of more than 24-hour duration. Creatine phosphokinase, lactic acid levels, electrolytes, and arterial blood gases should be monitored frequently. Both bacterial and fungal cultures should be obtained. If this syndrome is suspected, hemodialysis should be considered. In fatal cases, autopsy should include electron microscopy of cardiac and skeletal muscle to look for mitochondrial dysfunction. Further study is warranted.

PMID: 16377841 [PubMed - indexed for MEDLINE]

Casserly B, O'Mahony E, Timm EG, Haqqie S, Eisele G, Urizar R. Propofol infusion syndrome: an unusual cause of renal failure. *Am J Kidney Dis.* 2004 Dec;44(6):e98-101.

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Propofol infusion syndrome has been increasingly recognized as a syndrome of unexplained myocardial failure, metabolic acidosis, and rhabdomyolysis with renal failure. It has been described only with acute neurologic injury or acute inflammatory diseases complicated by severe infections or sepsis. It appears to develop in the context of high-dose, prolonged propofol (100 microg/kg/min) treatment in combination with catecholamines and/or steroids. This was first noted in children but is increasingly recognized in adults. This is a case report of 2 patients (a 42-year-old man and a 17-year-old girl) who had acute renal failure associated with use of propofol in the appropriate clinical setting. It examines the pathophysiology and the possible mechanisms of this condition and illustrates the need to consider it as the cause of rhabdomyolysis and acute renal failure in critically ill patients.

PMID: 15558515 [PubMed - indexed for MEDLINE]

Cannon ML, Glazier SS, Bauman LA. Metabolic acidosis, rhabdomyolysis, and cardiovascular collapse after prolonged propofol infusion. *J Neurosurg.* 2001 Dec;95(6):1053-1956.

Comment in:

[J Neurosurg. 2001 Dec;95\(6\):925-6.](#)

[J Neurosurg. 2002 Jun;96\(6\):1160-1; author reply 1161.](#)

[J Neurosurg. 2002 Jun;96\(6\):1161-2; author reply 1162.](#)

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The authors present the hospital course of a 13-year-old girl with a closed head injury who received a prolonged infusion of propofol for sedation and, subsequently, died as a result of severe metabolic acidosis, rhabdomyolysis, and cardiovascular collapse. The patient had been treated for 4 days at a referring hospital for a severe closed head injury sustained in a fall from a bicycle. During treatment for elevations of intracranial pressure, she received a continuous propofol infusion (100 microg/kg/min). The patient began to exhibit severe high anion gap/low lactate metabolic acidosis, and was transferred to the pediatric intensive care unit at the authors' institution. On arrival there, the patient's Glasgow Coma Scale score was 3 and this remained unchanged during her brief stay. The severe metabolic acidosis was unresponsive to maximum therapy. Acute renal failure ensued as a result of rhabdomyolysis, and myocardial dysfunction with bizarre, wide QRS complexes developed without hyperkalemia. The patient died of myocardial collapse with severe metabolic acidosis and

multisystem organ failure (involving renal, hepatic, and cardiac systems) approximately 15 hours after admission to the authors' institution. This patient represents another case of severe metabolic acidosis, rhabdomyolysis, and cardiovascular collapse observed after a prolonged propofol infusion in a pediatric patient. The authors suggest selection of other pharmacological agents for long-term sedation in pediatric patients.

PMID: 11765823 [PubMed - indexed for MEDLINE]

Hanna JP, Ramundo ML. Rhabdomyolysis and hypoxia associated with prolonged propofol infusion in children. Neurology. 1998 Jan;50(1):301-303.

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Propofol, a new anesthetic, is now used more commonly to sedate patients in the intensive care unit. Propofol's rapid elimination has popularized its use to induce and maintain hypnosis in patients with refractory status epilepticus. It is also associated with occasional severe metabolic acidosis and hypoxia of indeterminate cause in children. We report a child and an adolescent who developed severe metabolic acidosis, progressive hypoxia, and rhabdomyolysis during maintenance infusion of propofol for the treatment of refractory status epilepticus. We suggest that propofol should not be used for prolonged sedation in children until its safety can be ensured.

PMID: 9443502 [PubMed - indexed for MEDLINE]

van Straaten EA, Hendriks JJ, Ramsey G, Vos GD. Rhabdomyolysis and pulmonary hypertension in a child, possibly due to long-term high-dose propofol infusion. Intensive Care Med. 1996 Sep;22(9):997.

PMID: 8905442 [PubMed - indexed for MEDLINE]