Suggested beginning of propofol infusion syndrome in an adult patient without lactacidosis: a case report

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EDITOR:

Propofol infusion syndrome (PRIS) is a rare and often fatal disease associated with propofol sedation at doses of more than 5 mg kg^{-1} h^{-1} for more than 48 h. PRIS is characterized by lipaemic plasma, fatty liver enlargement, metabolic acidosis, rhabdomyolysis or myoglobinuria, cardiac arrhythmia and acute bradycardia progressing to asystole. The syndrome usually occurs in patients with central nervous system damage on catecholamine and glucocorticoid therapy [1].

Recent reports described patients with non-fatal suspected PRIS initially presenting with lactacidosis. The symptoms included rhabdomyolysis, arrhythmia, metabolic acidosis and renal failure [2]. Lactacidosis has been discussed as an early sign of PRIS [3], but we present a report of a case of suspected PRIS without lactacidosis.

Case report

A 21-yr-old previously healthy female (169 cm, 65 kg) was admitted to the ICU with cerebellar bleeding involving the fourth ventricle. She was sedated with sufentanil (0.3 μg kg^{-1} h^{-1}) and propofol (Disoprivan 2%, 5.7 mg kg^{-1} h^{-1}). Cardiovascular stability was maintained with a norepinephrine infusion (0.005–0.1 μg kg^{-1} min^{-1}) that was required from day 2 to day 10 with a maximum infusion rate on day 5 to maintain cardiovascular stability. Mean arterial pressure was maintained at 70–90 mmHg and there were no signs of hypovolaemia. Central venous pressure was 8–10 mmHg and urine output was 2–4 mL kg^{-1} h^{-1}. Intracranial pressure (ICP) was controlled by an external liquor drain. Digital subtraction angiography revealed an arteriovenous malformation of the brain stem.

At day 2 after admission, the propofol infusion rate was reduced to 4.3 mg kg^{-1} h^{-1}. The patient's condition remained stable, and ICP, cardiovascular and respiratory variables and laboratory parameter were within normal ranges. On day 3, C-reactive protein (CRP), procalcitonin (PCT) and interleukin (IL-6) increased and reached maximum values on days 5 and 6 (CRP 195.6 U L^{-1}, PCT 0.64 ng mL^{-1}, IL-6 1000 pg dL^{-1}). Hydrocortisone was infused at 200 mg day^{-1} from day 4 to day 13 with the intent to reduce catecholamine requirements. On day 4, generalized cerebral oedema developed with an acute increase of ICP up to 40 mmHg. Surgical decompression of the occipital cranium was performed. The onset of ventricular ectopic beats and ST-segment depression in leads II, III and aVF was noted on day 5. Total creatine kinase (CK) was 5194 U L^{-1} on the morning of day 6 with normal levels of isozyme MB and troponin T. Differentiation of the CK isozymes 8 h later revealed a CK-MM value of 29424 U L^{-1} while those of the other isozymes were normal. Since PRIS was suspected the propofol infusion was stopped and sedation was continued with midazolam (0.1 mg kg^{-1} h^{-1}). The cardiac arrhythmias were treated with amiodarone (6.8 mg kg^{-1} h^{-1}). CK levels returned to normal during the following 2 weeks (Fig. 1). Myoglobin was 4880 μg L^{-1} in a serum sample obtained at the time of the maximum CK-MM level. Blood gas analyses performed every 4 h showed normal lactate, sodium bicarbonate and pH throughout the ICU stay. Aspartate-transaminase (AST) and alanine-transaminase (ALT) increased to 311 U L^{-1} and 192 U L^{-1}, respectively, concomitantly with the increase of CK. Gamma-glutamyl-transaminase (GGT), amylase and lipase levels increased to peak concentrations on day 16. Bilirubin remained normal and an ultrasound liver scan showed no signs of liver damage. Serum creatinine, serum urea and urinary output were normal throughout the patient's stay.

The cardiac arrhythmia persisted for 3 days after which the amiodarone dose could be reduced. A brain magnetic resonance imaging (MRI) on day 15 showed no ischaemic damage. Brain stem acoustic evoked potentials and somatosensory evoked potentials were normal. The arteriovenous malformation was resected and a tracheotomy was performed on day 20. Sedation was withdrawn and the patient regained consciousness. There were no focal neurological deficits and she was transferred to another hospital for rehabilitation.

On follow-up after 1 yr, the patient was suffering from ataxia but cognitive function was not impaired. Genetic and metabolic tests for medium-chain acyl-CoA dehydrogenase deficiency variants (MCADD) performed at that time did not reveal any abnormalities.

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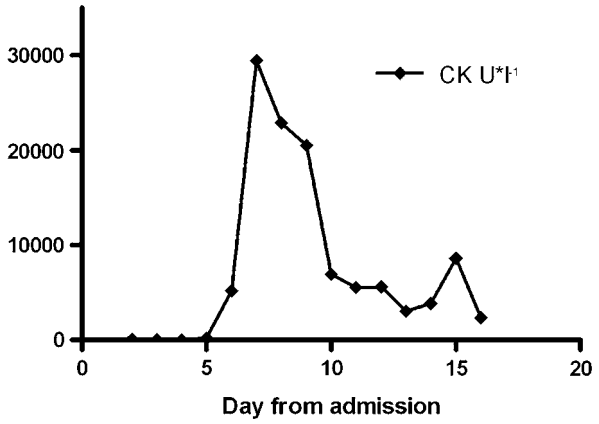

Figure 1.
Creatine kinase ($U\,L^{-1}$) from admission to day 16. Maximal serum concentration of creatine kinase was 29424 $U\,L^{-1}$.

Discussion

The presence of cardiac arrhythmia, rhabdomyolysis, cardiovascular instability and possible signs of hepatic damage together with the typical risk factors propofol infusion, cerebral lesion and catecholamine and glucocorticoid therapy suggested the diagnosis of PRIS. However, renal failure was not present and the AST and ALT pattern suggested that the enzymes were most likely of muscular and not of hepatic origin. The normal ultrasound scan made liver damage unlikely.

Metabolic acidosis and increased serum lactate concentrations were present in 13 of the 14 published adult cases of PRIS [4,5] leading to the hypothesis that lactacidosis may be an early marker of PRIS [3,6]. In contrast, our patient had normal serum lactate and normal pH.

Lactacidosis can be due to a number of causes, including hypoxia, increased glycolysis, activation of leucocytes during systemic inflammatory response syndrome (SIRS) and compromised liver function. SIRS has been identified as one factor contributing to the development of PRIS. Tumour necrosis factor, usually increased during SIRS, causes myocardial dysfunction, apoptosis of cardiomyocytes and proteolysis of peripheral muscles [5]. Together with other risk factors, this leads to the irreversible cell damage in these tissues typical for fatal PRIS. Lactacidosis in the early stage of PRIS may simply be an unspecific sign of inflammation contributing to the development of PRIS. It may be lacking if the underlying inflammation is too low grade to induce lactacidosis. Lactacidosis during PRIS can also be a consequence of mitochondrial toxicity, myocardial, liver and muscle cell damage and resulting multiple organ dysfunction.

In the present case, rhabdomyolysis was preceded by a transient increase of inflammatory markers. Apart from lactacidosis, other signs associated with SIRS occurring during sedation with propofol should be recognized as risk factors for the development of PRIS. The propofol infusion should be discontinued immediately in patients where beginning PRIS is suspected, even when the lactate concentration remains within the normal range.

It has been speculated that the absence of lactacidosis is associated with a more favourable outcome in adult patients, since surviving adult patients with PRIS-like symptoms or PRIS including our case did not have lactacidosis [5,7]. However, six of the nine reported surviving paediatric patients with PRIS did have lactacidosis [2], suggesting that the presence or absence of lactacidosis is not a suitable predictor for patient outcome.

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