CASE REPORT

T-wave inversion on ECG and slightly elevated cardiac enzymes as an early sign of propofol infusion syndrome

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Abstract

Propofol infusion syndrome (PRIS) is a well-known, frequently lethal, complication of prolonged sedation with propofol. PRIS seems to be associated with infusion of high cumulative doses of propofol, prolonged infusion periods, traumatic brain injury (TBI), critical illness, concomitant use of catecholamines and glucocorticoids, and with carbohydrate depletion. Possibly, subclinical mitochondrial disease also plays a role. Manifestations of PRIS include cardiac failure with progressive arrhythmias and changes on the ECG, metabolic acidosis, renal failure, rhabdomyolysis and fever. Propofol-induced mitochondrial dysfunction and interference with fatty-acid oxidation may be underlying pathophysiological mechanisms.

We describe the case of a patient with severe TBI who received continuous propofol sedation because of high intracranial pressure. After six days of propofol treatment, T-wave inversion was observed on the ECG. There were no other manifestations of cardiac dysfunction. The ECG normalised after discontinuation of the propofol infusion. T-wave inversion may therefore represent an early warning signal for the development of PRIS.

Introduction

Propofol infusion syndrome (PRIS) is an uncommon complication of prolonged sedation with propofol, with a high mortality. A fatal outcome is reported in 35% of the patients presenting with PRIS.[1,2] It was first described in the early 1990s in a series of paediatric cases.[3,4] followed by reports in adult patients.[5] Patients showed manifestations of cardiac failure with progressive heart rhythm disturbances in conjunction with metabolic acidosis, renal failure, hepatomegaly, dyslipidaemia, fever and signs of rhabdomyolysis.[1,2,6] Patients often deteriorate acutely and rapidly.

Abnormalities on electrocardiographic examination are a frequently observed symptom in PRIS.[1,2,6-9] In a recent review of 153 cases, ECG changes were described in 67% of the patients. T-wave inversion was observed in 12%, whereas 13% of the cases displayed a Brugada-like pattern consisting of ST elevations in the precordial leads V1 toV3.[2] Other observed electrocardiographic changes are combinations of bradyarrhythmias, tachyarrhythmias, ST-segment elevation and widening of the QRS complex. These arrhythmias tend to occur late in the disease process, often followed by cardiac failure.[1,2,7-9]

Proposed risk factors for PRIS include prolonged infusion with high doses of propofol, traumatic brain injury (TBI), critical illness, concomitant use of catecholamines and glucocorticoids, carbohydrate depletion, carnitine deficiency and subclinical mitochondrial disease.[1,2,10-13] TBI is associated with PRIS, which might be related to the need for high-dose long-term sedation combined with catecholamine usage to maintain cerebral perfusion pressure (CPP).[12]

In a retrospective cohort analysis of 67 patients with head injuries, Cremer et al. described a significantly increased risk for developing PRIS when higher doses of propofol were administered, in particular with dosages of more than 5 mg/kg/h.[6] In the Brain Trauma Foundation guidelines for the management of patients with severe traumatic brain injury, propofol is recommended for control of intracranial pressure (ICP). The guideline states that extreme caution must be taken when using doses higher than 5 mg/kg/h, or when administration exceeds 48 hours.[14] Based on recent data from case series, a maximum dose of 4 mg/kg/h can be recommended for prolonged sedation (>48 hours).[1,2]

The incidence of PRIS is difficult to determine because most of the clinical data originate from case reports and different criteria are used for the diagnosis. Also, there may be a substantial underreporting of the syndrome because of unawareness or misdiagnosis of the syndrome.

Case report

A 20-year-old man was involved in a bar fight, where he received a blow to the head and fell to the floor, hitting his head. Directly after this incident, he lost consciousness for about 5 minutes. On examination by the emergency medical service, there were no signs of external trauma or neurological deficit. The patient was therefore not sent to hospital but was taken home by his friends. In the following hours, he experienced increasing headache, accompanied by nausea and vomiting, followed by a decreased level of consciousness. He was admitted to hospital after referral by the general medical practitioner service.

On examination the patient showed a decreased level of consciousness with a Glasgow Coma Scale (GCS) of 13 to 14. CT scanning of the brain showed signs of haemorrhagic contusion in the left frontal lobe and to a lesser extent in the right frontal lobe. There were also signs of either a small subdural or an epidural haemorrhage on the left frontal side, the origin of which could not be differentiated based on the images. There were no signs of traumatic abnormalities of the cervical spine. The patient was admitted to the neurological ward for observation, where he remained neurologically stable with a GCS varying between 13 and 14.

Two days after the incident, the patient developed a tonic clonic seizure, for which midazolam and phenytoin were administered. Afterwards the patient was unresponsive (GCS 3), his right pupil was dilated and not reactive to light and the patient showed tetanic contractions. Because of the low GCS and tetanic contractions, he was intubated. A CT scan of the brain was performed, which showed an increase in haemorrhagic contusion, expansion of oedema and signs of uncal herniation. An external ventricular drain was placed in the right lateral ventricle, with an intracranial pressure (ICP) monitoring device. An opening ICP of 11 mmHg was recorded.

On arrival at the intensive care unit, the ICP was 15 mmHg and the cerebral perfusion pressure (CPP) was 60 mmHg. The pupils were symmetric, small, and responsive to light, and the patient was haemodynamically stable. The treatment of the elevated ICP was performed according to international standards. [14] The patient was kept normothermic and continuous drainage of CSF was allowed through the ventricular drain. Initially the patient was sedated with propofol (7.14 mg/kg/h), midazolam (0.06 mg/kg/h) and morphine (0.06 mg/kg/h). After two hours the propofol infusion was decreased to 5.14 mg/kg/h. The next day, the propofol infusion was maintained at 4.3 mg/kg/h. In the following days the patient remained haemodynamically and respiratorily stable and noradrenaline infusion (0.1-1.4 mg/h) was titrated to maintain CPP at 60 mmHg. The ICP initially decreased.

On day 6 after the trauma, negative T waves in leads V2-V6 were observed on the ECG *(figure 1)*. Creatine kinase (CK) levels increased but remained below the normal upper limit (normal upper limit 200 U/l), whereas the high-sensitive (hs)-troponin
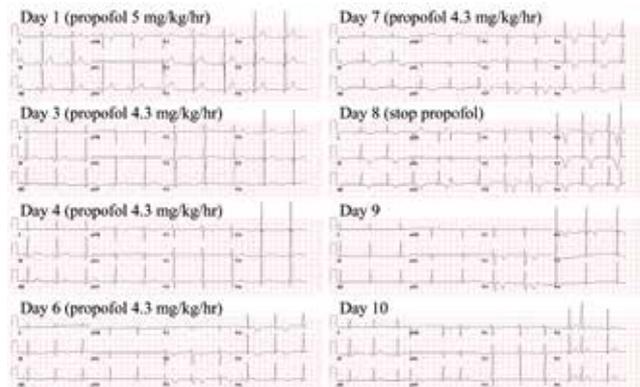

Figure 1. Course of ECGs and dosage of propofol infusion

T value was 75 ng/l (normal upper limit 14 ng/l). At that time, the ICP was 15 mmHg and the CPP was 60 mmHg. On day 7, the negative T waves on the ECG were more pronounced. The ECG abnormalities progressed and under the suspicion of a developing PRIS, the propofol infusion was stopped on day 8. The next day the ECG changes normalised *(figure 1)*. Screening bedside echocardiography was performed, which showed no signs of cardiomyopathy or akinesia, and normal ventricular function.

CK and hs-troponin T changes developed two days after the development of the T-wave inversions. The CK levels continued to increase for several days after discontinuation of the propofol infusion, reaching a maximum concentration of 400 U/l on day 10. Hs-troponin T showed a temporary increase from day 6 with a peak at day 7 and showed a decline thereafter *(figure 2)*. The serum triglyceride level was 1.73 mml/l (normal value <2 mmol/l).

The midazolam and morphine infusions were stopped two days later. On examination, the patient was alert and responsive and was subsequently extubated on day 10. Follow-up CT scanning of the brain performed on day 12 revealed regression of the cerebral oedema and uncal herniation.

The subsequent hospital stay was uneventful. The patient was discharged home 23 days after the initial trauma with no neurological sequela. Preventive antiepileptic treatment with valproic acid and phenytoin was continued.
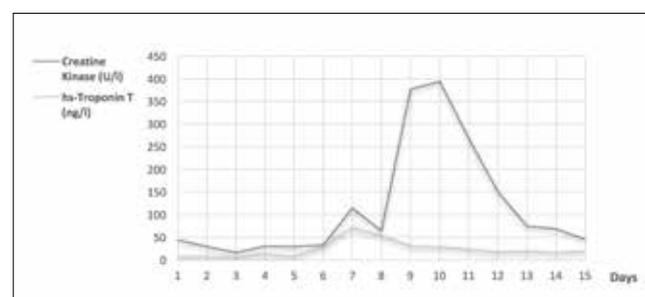

Figure 2. Course of creatine kinase and hs-troponin T during ICU admission

Discussion

Propofol infusion syndrome is a rare but extremely dangerous complication of propofol administration. The pathophysiology of PRIS is complex and not entirely understood. An important underlying mechanism is propofol-induced impairment of β-oxidation of free fatty acids (FFAs) in mitochondria, causing inhibition of intracellular energy production. Propofol inhibits the transfer of electrons in the electron transport chain, which decreases transmembrane potential and affects transportation of FFAs into the mitochondria. As a result, production of adenosine triphosphate (ATP) is decreased, which leads to widespread cell death, hepatic dysfunction, multi-organ failure and metabolic acidosis, creating an arrhythmogenic environment.[1,2,8,15-17] Also, skeletal muscle necrosis leads to rhabdomyolysis. The subsequently released myoglobin induces renal failure and hyperkalaemia. Another proposed mechanism is propofol-mediated inhibition of fatty acid oxidation with an effect on fatty acyl carnitine transferases leading to elevated levels of acylcarnitines that participate in the citric acid cycle, ketone body production and the electron transport chain. The FFAs accumulate in various tissues such as the liver and have shown to promote cardiac arrhythmogenicity, possibly explaining the observed electrocardiographic changes. Another contributing mechanism may be carbohydrate depletion, which leads to a reduction in citric acid levels, slowing lipid metabolism. Also stress-induced elevation of endogenous catecholamines, administration of exogenous catecholamines and use of glucocorticoids may play a role.[1,2,15-17] It has been shown that propofol can decrease cardiac beta-adrenoceptor responsiveness, contributing to cardiovascular depression.[18] Hypertriglyceridaemia and hyperlipaemia, frequently seen in patients with PRIS, results from the lipid emulsion used as solvent and from the accumulating FFAs and showed no effect on the outcome of PRIS.[2] In our patient, the serum triglyceride levels remained normal.

Recent data suggest that supplementation with coenzyme Q (which shares a structural similarity to propofol) may play a role in the treatment of PRIS through interference in the electron transport chain and fatty acid oxidation.[19,20]

Cardiac dysfunction is an important manifestation of PRIS. Cardiovascular symptoms include arrhythmias, widening of the QRS complex, T-wave and ST-segment changes, Brugada syndrome-like patterns, cardiogenic shock and asystole. Potential underlying pathophysiological mechanisms include a combination of a relative deficit of energy availability, destruction of cardiomyocytes, the arrhythmogenic effect of elevated FFAs and increased catecholamine levels in a state of metabolic acidosis.[1,2,15-17]

In patients with traumatic brain injury, ECG changes and elevated cardiac troponin may also be related to stress-induced cardiomyopathy, also termed Takotsubo cardiomyopathy. These ECG changes may mimic a cardiac event. A possible role in the pathogenesis is the result of excessive adrenergic activity with abnormalities in heart rate, blood pressure, thermoregulation and elevation of circulating catecholamine levels, which may lead to cardiac dysfunction by affecting the cardiac microvasculature or by directly inducing toxicity. These manifestations are frequently seen in the acute phase (<48 hours) after a neurological event.[21-23] A recently published study of 49 patients (median age 34 years) with moderate or severe TBI showed no clinically significant myocardial dysfunction on echocardiographic examination. The authors suggest that the young age of TBI patients and the absence of cardiovascular risk factors may be protective against significant myocardial injury resulting from catecholamine excess.[24]

Our patient only showed T-wave inversion on the ECG and mildly elevated levels of cardiac enzymes, without cardiovascular compromise or manifestations of other organ dysfunction. The CK level continued to increase two days after the propofol had been discontinued.

Despite a maximum recommended dose of 5 mg/kg/h in the guidelines for treatment of patients with TBI, recent data suggest to avoid dosages above 4 mg/kg/h for prolonged sedation, with careful observation of possible side effects.[1,2,14]

Our case illustrates that PRIS may develop with subtle, nonspecific symptoms, such as inverted T waves and slightly elevated cardiac enzymes. It shows that careful clinical, biochemical and electrocardiographic monitoring is strongly recommended for early detection of signs of developing PRIS.

If prolonged sedation is anticipated and persistent high dosages of propofol are needed for the treatment of elevated ICP, an early switch to another sedation regiment may be considered.

Conclusion

Propofol infusion syndrome is a rare but often catastrophic complication of propofol infusion. T-wave inversion on ECG, moderate elevation of CK and hs-troponin T in the absence of other cardiac dysfunction may be an early sign of its development. In our patient, ECG abnormalities preceded any increases in CK and hs-troponin T levels. Long-term high-dose propofol sedation is not recommended and frequent electrocardiographic and biochemical monitoring should be performed. After suspicion of PRIS, propofol infusion should be discontinued immediately.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from the patient presented in this article.

Disclosures

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