Delayed postoperative neurological deterioration from prolonged sodium nitroprusside administration

Case report

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Sodium nitroprusside is commonly used for the induction of hypotension during neurosurgical procedures. Although rare, the main toxicity of sodium nitroprusside is related to its breakdown to cyanide, with deaths reported from cyanide poisoning in several patients treated with this hypotensive agent. Thiocyanate poisoning may also result with low doses of sodium nitroprusside administered over several days. In such cases, symptoms ranged from dizziness to psychosis, coma, and death. Autopsy reports of patients with nitroprusside toxicity describe the characteristic lesions of cyanide encephalopathy following therapy with sodium nitroprusside.

A patient is described in whom delayed neurological deterioration occurred during prolonged administration of sodium nitroprusside for severe postcraniotomy hypertension. Cyanide poisoning was probably the cause of his condition, as specific antidotal therapy resulted in complete reversal of his symptoms within hours.

Case Report

This 53-year-old hypertensive man was admitted to the emergency room complaining of right-sided weakness and speech disturbance which appeared 1 hour prior to admission. The patient soon became comatose.

Neurological examination disclosed dense hemiplegia on the right side, a dilated nonreactive left pupil, and a bilateral Babinski sign. Computed tomography (CT) showed a large intracerebral hematoma in the left temporoparietal region. A temporoparietal craniotomy was performed and the hematoma was removed.

Postoperatively, severe hypertension (250/140 torr) developed which did not respond to hydralazine or intravenous nitroglycerin administration. Sodium nitroprusside (Nipride) was initiated as an intravenous drip at maximum doses of 2.5 µg/kg body weight/min and titrated continuously according to blood pressure measurements. Propranolol was reinstituted at a dose of 160 mg/day. Blood pressure stabilized at 150/90 torr, but attempts to reduce the rate of sodium nitroprusside infusion caused prompt elevation of blood pressure. On the 3rd postoperative day, the patient started to obey commands and during the following days he was able to communicate with his family. Neurological examination revealed flaccid hemiparesis on the right. Routine laboratory studies were normal. A CT scan on the 4th postoperative day showed some blood in the right occipital horn but no intracerebral blood. There was minimal edema and midline shift.

Seven days postoperatively the patient became drowsy.
and less responsive to vocal and painful stimuli. His respiratory rate increased from 18 beats/min to 26 to 30 beats/min. Arterial blood gas determination showed good oxygenation (98 torr) with mild metabolic acidosis (pH 7.32, base excess of −7.4). Shortly thereafter, he became deeply comatose with dense hemiplegia on the right. A CT scan showed severe edema in the left hemisphere, obliteration of the ventricular system (especially on the left), and hypodense areas in the left parieto-occipital regions. No intracerebral blood was present.

The timing and clinical course during nitroprusside administration as well as the CT findings led us to suspect that cyanide poisoning caused the deterioration. Blood was drawn for future assays of cyanide, and an intravenous bolus of 250 mg of 4-dimethylamino phenol (4-DMAP) was administered to induce methemoglobinemia. This was followed by infusion of sodium thiosulfate (12.5 gm in 50 ml of a 5% dextrose solution). Sodium nitroprusside was discontinued and blood pressure was successfully maintained at acceptable levels by increasing the dose of propranolol to 320 mg/day. Ventilation with 100% oxygen was begun. Hemodialysis was then performed for possible concomitant accumulation of thiocyanates. Four hours later, the patient became conscious again, his respiratory rate returned to normal, and the metabolic acidosis was corrected. A CT scan obtained 24 hours later showed a significant decrease in the amount of edema, ventricular compression, and midline shift. However, neurological examination revealed dense hemiplegia on the right and severe expressive aphasia which were still present on follow-up neurological examination 1 month later. Cyanide and thiocyanate plasma levels were not measured since no laboratory with reliable assays for cyanide and thiocyanates could be found.

Discussion

Sodium nitroprusside has become the drug of choice for the induction of hypotension during various neurosurgical procedures. It gained popularity as some data suggested that cerebral blood flow and cardiac output remain near normal limits when mean arterial pressure is decreased to values allowing intact cerebral autoregulation.1,2 At lower mean arterial pressures, in the presence of diffuse brain pathology and in some patients with brain tumors, sodium nitroprusside may in fact bring about an elevation of intracranial pressure by decreasing cerebrovascular resistance and increasing cerebral blood volume.1,2,5,6

The main toxicity of sodium nitroprusside is related to its breakdown to cyanide. Sodium nitroprusside contains five cyanide groups (Na2Fe(CN)6NO). One heme group on the hemoglobin molecule is oxidized to ferric form (Fe+++), and, by trapping one of five cyanide groups, forms cyanomethemoglobin. The other four cyanide molecules diffuse into red blood cells and bind to the heme molecule on the cytochrome oxidase, a phenomenon that leads to cellular hypoxia.4

Signs and symptoms of cyanide toxicity are related to cellular hypoxia and are nonspecific. The severity of symptoms depends on the dose, route, and rate of exposure. The central nervous system is the organ most sensitive to cyanide poisoning. Early symptoms include lightheadedness, tachypnea, nausea, vomiting, confusion, and anxiety; in severe poisoning, these progress to stupor, coma, convulsions, and death. Higher doses of cyanide will produce cardiovascular depression with bradycardia and hypotension.4

Pathological findings in patients who died from cyanide poisoning following the administration of sodium nitroprusside included bilateral necrosis of the globus pallidum and the putamen.7 More diffuse lesions of both gray and white matter were described in laboratory animals exposed to hydrogen cyanide.8

The maximum safe dose and infusion rates of sodium nitroprusside vary among different investigators.14 The initial dose given to our patient was 2.5 μg/kg/min. This was reduced to an average maintenance dose of 1 μg/kg/min. These dosages fall within the values considered safe by most investigators.14

Even under these circumstances, the possibility of cyanide intoxication cannot be precluded. Many factors may interact in the biodegradation of nitroprusside and cyanide, and conditions such as renal and hepatic disease may greatly enhance the toxicity.7,14 The diagnosis of cyanide toxicity is difficult because of the absence of pathognomonic signs. However, in a patient who receives sodium nitroprusside, the presence of neurological deterioration, tachypnea, bright red venous blood, and metabolic acidosis should alert physicians to the possibility of cyanide poisoning.

In our patient, neurological deterioration after a period of initial improvement suggested the possibility of cyanide toxicity as the cause of his condition. The severe edema in the left hemisphere developed probably because the regions in the vicinity of the intracerebral hematoma, which had a marginal blood supply, were further compromised by cellular hypoxia induced by cyanide poisoning. This in turn aggravated the ischemic edema. The successful effect of the specific antidotal treatment of 4-DMAP and sodium thiosulfate which reversed his symptoms supported that assumption even in the absence of plasma cyanide levels. Hemodialysis was performed as the only way to eliminate the possible concomitant thiocyanate toxicity. The contribution of thiocyanates to the toxicity in our patient remains unclear, however.

Treatment of cyanide toxicity includes supportive as well as specific antidotal therapy. Most antidotes induce methemoglobinemia, which is thought to attract cyanide off the hema group of cytochrome oxidase, allowing thiosulfate to detoxify the cyanide. A detailed review of the treatment of cyanide poisoning is given in the textbooks.

The prolonged administration of sodium nitroprusside carries the risk of cyanide toxicity. This risk can be prevented or reduced by the concomitant infusion of

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hydroxycobalamin. This compound combines with cyanide to form cyanocobalamin (vitamin B₁₂), which is excreted by the kidney. Unfortunately, this was not done in our patient. Plasma cyanide and thiocyanate levels should be monitored and treatment given if toxic levels are reached.

References


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