Early propofol infusion syndrome following cerebral angiographic embolization for giant aneurysm repair

Case report

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✓ The authors report a case of short-term high-dose propofol-related metabolic acidosis in a 3-year-old girl. The patient initially presented at another institution with left fourth cranial nerve palsy, and examination revealed a large, wide-necked 19 × 22 × 17-mm aneurysm in the left internal carotid artery. She had undergone three previous unsuccessful attempts at endovascular coil embolization, which were complicated by repeated coil protrusions into the parent vessel.

During angiography and a balloon occlusion test (BOT) 80 mg propofol was given for 3 hours followed by 200 μg/kg/min for another 4 hours. The 20-minute BOT was well tolerated, and the aneurysm was occluded with stent-assisted coil embolization.

Following the procedure the patient developed severe acidosis, hypotension, tachycardia, and signs of cardiac failure. On postoperative Day 3 her metabolic acidosis resolved, and she was weaned off sedatives. She continued to improve and was discharged from the hospital on postoperative Day 7. The metabolic acidosis and hypotension were thought to be due to propofol-related infusion syndrome.

KEY WORDS  •  intracranial aneurysm  •  therapeutic embolization  •  balloon occlusion test  •  propofol  •  pediatric neurosurgery

PROPOFOL-RELATED infusion syndrome has more commonly been recognized and reported to occur in the setting of long-term sedation of patients in the ICU. It is characterized by metabolic acidosis, unexplained cardiac failure, rhabdomyolysis, and renal failure.16 Authors of recent reports have discussed the occurrence of this syndrome in the short term, usually high-dose administrations of propofol, particularly during long procedures that require sedation.7 Authors of most reported cases describe the syndrome as rare,1,6,16 although the true incidence is not known. Hence the syndrome may be more prevalent than previously thought. We present the case of a child who underwent a difficult angiographic embolization in which sedation was primarily achieved with propofol, after which she developed early signs of this syndrome.

Case Report

History and Examination. This 3-year-old, 19-kg girl was referred to our institution for consultation concerning a giant intracranial aneurysm. She had initially presented in the summer of 2004 with diplopia and strabismus. A magnetic resonance image of the brain at that time had revealed unremarkable findings. Approximately 1 year later she was seen by a neuroophthalmologist, and repeated magnetic resonance imaging of the brain revealed an intracranial aneurysm. Interventional radiologists at another institution had previously made three attempts at embolization, which were complicated by coil prolapse into the parent vessel.

During angiography and a balloon occlusion test (BOT) 80 mg propofol was given for 3 hours followed by 200 μg/kg/min for another 4 hours. The 20-minute BOT was well tolerated, and the aneurysm was occluded with stent-assisted coil embolization.

Following the procedure the patient developed severe acidosis, hypotension, tachycardia, and signs of cardiac failure. On postoperative Day 3 her metabolic acidosis resolved, and she was weaned off sedatives. She continued to improve and was discharged from the hospital on postoperative Day 7. The metabolic acidosis and hypotension were thought to be due to propofol-related infusion syndrome.

Operation. The patient was pretreated with aspirin and clopidogrel for 5 days before the procedure. The plan first entailed a 20-minute BOT of the left ICA and, if the procedure was successfully tolerated, subsequent stent-assisted embolization was to be performed after the induction of propofol anesthesia. Anesthesia was induced with boluses of 50 mg propofol/25 μg fentanyl and 30 mg propofol/50 μg fentanyl over the 1st hour. Anesthesia was maintained with 200 μg/kg/min of propofol infusion and 1 μg/kg/hr of fentanyl.

A 19 × 22 × 17-mm aneurysm was identified on the initial left ICA angiogram (Fig. 1A). The patient tolerated a 20-minute left ICA BOT well; excellent collateral flow was
and it is rou-

19.2 and 19.9 mmol/L, and base excess

Au-

3

5 ng/ml)

20–mm

During the procedure,

51 and 50 mm Hg, PaO

2.5)—a strong

This condition is more frequently re-

41

was maintained at 32 mm Hg and her


indication of myocardial injury. Her systolic blood pressure

was maintained in the range of 100 to 120 mm Hg, and her

condition stabilized to the point that vasopressor support

was removed on postoperative Day 4.

Postoperative Course. Pharmacological sedation in the

PICU was maintained, first with midazolam 50 mg/50 ml and

tentanyl 1000 μg/50 ml, and then continued with fentany1 1000 μg/50 ml, which was weaned on Day 4. The pa-
tient subsequently underwent extubation, and she experi-

enced progressive improvement. She was discharged from

the hospital on Day 7 on a regimen of aspirin and clopido-
grel.

Discussion

Propofol infusion syndrome has been reported as a com-
bination of metabolic acidosis (usually lactic acidosis), hy-
potension, bradycardia or bradycardic dysrhythmia, myo-
globinuria, and renal failure. Electrocardiography changes,
reported to occur in precordial leads V1 to V3 (downsloping
ST segment elevation), can predict sudden death in propofol
infusion syndrome.15 This condition is more frequently re-
ported to occur after prolonged administration of propofol in

critically ill patients in the ICU who require sedation.16 Au-

thors of more recent reports have described propofol syn-
drome occurring after short-term high-dose administration

of propofol during long procedures requiring sedation, par-

ticularly in adults.5 The metabolic acidosis in our case

represents an early sign of propofol infusion syndrome.6 Dur-
ing the procedure, the patient’s pCO

2 was maintained at 32 mm Hg and her

respiratory rate at 11 breaths/minute. To our knowledge no

cases of systemic metabolic acidosis have been reported
during cerebral angiography with or without a BOT, with

or without embolization. This patient did not have juvenile
diabetes, was no less active than her peers, and was in oth-

erwise good health.

Propofol is considered a safe drug for long-term infusion

in patients who have suffered brain trauma,5 and it is rou-
tinely used in pediatric and adult patients for intraoperative

sedation. The distribution and clearance of propofol in 53

children between the ages of 3 and 12 years who received

noted by direct evaluation through somatosensory evoked

potential, motor evoked potential, and electroencephalo-

graphic monitoring. Stent-assisted embolization of the an-

eurysm was undertaken (Fig. 1B), and three bioactive coils

were placed. The procedure was complicated by a stretched

coil that had dislodged into the lumen of the ICA. This coil

was snared successfully, but the maneuver substantially in-

increased the procedure time. Deployment of 22 progressively

smaller coils accomplished adequate occlusion of the an-

eurysm (Fig. 1C).

Near the 5-hour mark, the patient developed anion gap

(> 12 mmol/L) metabolic acidosis (pH 7.28, PaCO

2, 41

mm Hg, HCO

3, 18 mmol/L), which persisted until the end of

the procedure. The arterial blood gas measurements ob-
tained 30 minutes before and after completion of the pro-
cedure were the following, respectively: pH 7.18 and 7.21,

PaCO

2, 51 and 50 mm Hg, PaO

2, 125 and 156 mm Hg (FiO

2, 40%), HCO

3, 19.2 and 19.9 mmol/L, and base excess −8.7 and −7.6 mmol/L. One bolus of 8.4% (20 mEq) NaHCO

3 was added, and HCO

3 was added to the normal saline drip. Following the procedure, the patient was treat-

ed with a regimen of 81 mg aspirin and 37.5 mg clopido-
grel daily, along with an abciximab intravenous drip 4 ml/
hour for 12 hours.

Postoperatively the creatine phosphokinase, lactate dehy-
drogenase, and lactate values were 263 U/L (normal range

22–269 U/L), 179 U/L (normal range 91–180 U/L), and 1.1

mmol/L (normal range 0.7–2.1 U/L), respectively; the

blood urea nitrogen and creatinine levels were 11 and 0.6

mg/dl, respectively. In the PICU, the patient’s blood pres-

sure dropped to 60/30 mm Hg and her heart rate increased

to 150 bpm. She remained tachycardic and underwent ag-

gressive fluid resuscitation with 5% albumin, vasopressors,

and 5 mg dexamethasone every 8 hours for 5 days.

On Day 3 her salicylate (< 4.0 mg/dl) and ammonia (28

mmol/L) levels were within normal limits, and the acidosis

significantly improved. Her creatine phosphokinase level

increased to 473 to 591 U/L, with a creatine phosphokinase

2-myoglobin level of 20.7 ng/ml (normal level < 5 ng/ml)

and a relative index of 3.5 (normal index < 2.5)—a strong

indication of myocardial injury. Her systolic blood pressure

was maintained in the range of 100 to 120 mm Hg, and her

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Early propofol infusion syndrome following cerebral angiography

Propofol injectable emulsion for periods of approximately 1 to 2 hours were similar to that in adults.[12] As such, adults and children alike can be at risk for propofol infusion syndrome. However, this syndrome does not occur with every long-term or high-dose administration of propofol.

The patient in our case underwent a procedure for which a total of 80 mg propofol was administered during a 20-minute BOT. Motor and somatosensory evoked potentials were monitored and electroencephalography was performed for cerebrovascular accident prediction. In addition, the high-dose administration of 200 μg/kg/min of propofol for the remaining 4 hours of the procedure may have played a significant role in triggering an early propofol infusion syndrome. The total dosage of propofol was 992 mg over 8 hours, which is a significant amount for a 3-year-old child. The median induction dose of propofol for a surgical procedure in a child her size and age is 2.5 mg/kg (range 1–3.6 mg/kg) with a median maintenance dose of 188 μg/kg/min (range 12–1041 μg/kg/min) for 69 minutes (range 23–374 minutes).[12] However, to avoid development of propofol infusion syndrome a maintenance dose of no more than 75 μg/kg/min is suggested.[14] In 2001 the Food and Drug Administration issued a safety alert that there may be important concerns when propofol injectable emulsion is used for sedation in patients in the PICU.[3] They also reminded healthcare professionals that propofol is not approved in the US for sedation in the PICU.[3] To prevent propofol infusion syndrome, Baker and Naguib[1] suggested that the infusion amount be less than 75 μg/kg/min for sedation of critically ill children and that the duration of infusion be limited to 24 hours.

Koch et al.[9] described the case of a 5-year-old patient who had undergone endovascular embolization for an arteriovenous malformation and was required to remain sedated for at least 24 hours with propofol at a rate of 15 mg/kg/hr. This patient experienced reversal of lactic acidosis following tapering to 6 mg/kg/hr and termination of propofol. Holzki et al.[7] reported the case of a 3-year-old patient who received 20 mg/kg/hr of propofol over a 15-hour period, after which the patient developed combined respiratory and metabolic acidosis. This resolved after cessation of propofol; however, the infusion was restarted at 4 mg/kg/hr, and the patient developed intractable bradycardia and later died.[7] Recent reports of propofol infusion syndrome with short-term high-dose propofol infusion underscore the importance of extreme caution with a drug that had previously been considered safe.[8]

Metabolism of propofol may be the underlying cause of propofol infusion syndrome; high-dose infusion is associated with hypertriglyceridaemia and cardiac failure.[2] Wolff et al.[20] proposed impaired fatty acid oxidation as the probable cause of this syndrome. The authors ascribed the condition to the disruption of fatty acid oxidation caused by impaired entry of long-chain acylcarnitine esters into the mitochondria and failure of the mitochondrial respiratory chain at complex 11, resulting in uncoupling of the respiratory chain.[20]

It may be that certain individuals are more sensitive to propofol, possibly by inhibition of cytochrome c-oxidase, or poor metabolism such as that seen in slow acetylators of isoniazid and hydralazine.[13] Propofol is cleared predominantly via direct glucuronidation, although a substantial amount is metabolized through the microsomal cytochrome P450 (2B6) system.[3] Propofol inhibits cytochrome P450 1A2, 2C9, 2D6, and 3A4,[11] particularly affecting testosterone[11] and ropivacaine[13] metabolism. This degree of inhibition is relatively low, and the clinical significance has yet to be established.[11] There are few reports of possible drug–drug interactions between propofol and alfentanil[18] or warfarin,[26] and in vivo studies in individuals with possible defective enzymes have yet to be reported.

Conclusions

This is the case of a 3-year-old child developing early signs of propofol-related infusion syndrome characterized by metabolic acidosis and hypotension. The patient received more than the suggested dose of 75 μg/kg/min,[14] and the case illustrates that this syndrome can occur during long procedures requiring high-dose propofol sedation. Inhibition of fatty acid metabolism has been proposed as the likely cause. Physicians and caregivers should be cognizant of unknown differences of propofol metabolism in patients. The developments of metabolic acidosis, bradycardia, or hypertension during propofol infusion are early signs of propofol-related infusion syndrome and should be heeded as such.

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