Clinical Reports

Delayed seizures following sedation with propofol

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Seizures occurred in two adolescents approximately six hours after sedation with propofol for bone marrow biopsy. Case #1 was a patient with chronic renal failure, hypertension, and anaemia. Case #2 had just been diagnosed with acute lymphocytic leukaemia. Neither child had experienced seizures before, and both recovered without neurological sequelae. Although other factors may have caused the seizures, the episodes have raised concerns about the safety of propofol for patients travelling home after out-patient surgery. Further study is required to explain the cause of this complication or, at least, to identify risk factors.

Des convulsions surviennent approximativement six heures après sédation au propofol pour biopsie osseuse chez deux adolescents. Dans le premier cas, il s'agit d'un insuffisant rénal chronique, hypertendu et anémique. Dans le deuxième, on vient tout juste de diagnostiquer une leucémie lymphoïde aiguë. Aucun des enfants n'avait auparavant présenté de convulsions et n'ont subi de séquelles neurologiques par la suite. Bien que d'autres facteurs puissent expliquer ces convulsions, on doit se questionner sur la sécurité du propofol chez les patients qui doivent retourner à domicile après une chirurgie ambulatoire. Par des études ultérieures, il faut trouver une cause à cette complication ou tout au moins identifier les facteurs de risque.

Key words
ANAESTHESIA: paediatric;
ANAESTHETICS, INTRAVENOUS: propofol;
COMPLICATIONS: seizures.

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Propofol has been received with enthusiasm by anaesthetists and patients since becoming available for clinical use. Rapid recovery and lack of postoperative nausea have made it particularly valuable in emergency and out-patient surgery.[1-3] However, unusual muscular movements have been reported during propofol induction, especially in children.[4,5] Withdrawal symptoms, including seizures, have followed prolonged sedation of children with propofol in intensive care units,[6] and the drug is no longer recommended for this use.[7] We report two cases of seizures that developed hours after propofol sedation for brief procedures.

Case #1

A 13-yr-old girl with chronic renal failure due to rapidly progressive glomerulonephritis required a bone marrow aspiration and biopsy. She had undergone haemodialysis three days before and was quite stable, except for episodes of hypertension as high as 170/110 mmHg, which were treated with sub-lingual nifedipine. She had no history of seizures. Her chronic medications included lisinopril (an angiotensin converting enzyme inhibitor), prednisone, nifedipine, and erythropoietin. Treatment of her glomerulonephritis with cyclophosphamide had been stopped five weeks earlier due to anaemia and thrombocytopenia. The patient was sedated for bone marrow biopsy with fentanyl 2 $\mu g \cdot kg^{-1}$ *iv*, followed by freshly opened propofol 1 $mg \cdot kg^{-1}$ *iv* and lidocaine 1 $mg \cdot kg^{-1}$ (without epinephrine) by infiltration at the biopsy site. The procedure was completed quickly, and the patient was comfortable, pain-free, and responsive to verbal commands throughout. She was alert within minutes and fully awake with normal head control and ambulation two hours later.

Approximately 6.5 hr after the procedure, she was given nifedipine sub-lingually twice for blood pressures of 165/102 mmHg which decreased to 140/86 mmHg. Ten minutes later she became dizzy and sweaty, which had never occurred before after nifedipine, and then had a generalized tonic-clonic seizure which lasted for 90 sec. Her blood pressure was 149/72 mmHg following the sei-

zure. The paediatric resident arrived and witnessed two more one-minute seizures which the patient was able to predict. Three hours later she was treated with diazoxide *iv* to reduce her blood pressure from 160/100 to 158/84 mmHg. She had two further seizures in spite of treatment with sub-lingual lorazepam 15 min before the last. These started focally in the left arm and then became generalized. All the seizures were of less than two minutes in duration and self-limited. A left fronto-temporal headache was noted between episodes, and she appeared to have post-ictal drowsiness, although she was not incontinent. Metabolic and electrolyte screen at the time of the seizures showed no evidence for a metabolic cause, and her blood pressure following the last episode was 134/82 mmHg. CT scan was normal. She made a complete neurological recovery with no subsequent seizures.

Case #2

An 11-yr-old, previously well, boy presented with a three-week history of sore throat, anorexia, weight loss, and fever. He had been treated for ten days with penicillin at the onset of his illness, but had taken no other medication except acetaminophen. Past medical history was positive only for several "faints" that he had experienced while ill more than one year previously. He had no history of seizures, head injuries, or neurocutaneous illness. Neurological examination prior to his seizure was normal with no neck stiffness. he had mild splenomegaly and mild anterior cervical adenopathy.

He received propofol 5.2 $mg \cdot kg^{-1}$ *iv* in small bolus doses for sedation, and lidocaine 15 mg (as 1%) without epinephrine for local anaesthesia for bone marrow biopsy and aspiration and diagnostic lumbar puncture. The procedure lasted 20 min and the patient recovered uneventfully and was fully awake within 25 min. He had no headache or other neurological symptoms. Four hours following recovery from the sedation, during which time he had been ambulatory and awaiting results, he suffered a 20-sec generalized tonic seizure with urinary incontinence while moving from a sitting to a standing position. Post-ictally he was mildly confused for about one hour. He reported no antecedent dysgeusia or dysosmia but stated that he felt as if he was "in a balloon" just before the onset of the seizure. His physical examination was unchanged. No treatment was given and he had no further seizures.

Laboratory tests before sedation showed a haemoglobin of 108 $g \cdot L^{-1}$, white cell count $37 \cdot 10^9 \cdot L^{-1}$, and platelets $108 \cdot 10^9 \cdot L^{-1}$. PT, PTT, and serum electrolytes, magnesium, BUN, creatinine, and glucose were all within normal limits. Serum phosphate concentration was low at 0.90 $mmol \cdot L^{-1}$ (normal range 1.3–1.8). Cerebrospinal fluid taken at the time of the sedation showed WBC 1, RBC 0, blasts 0, and normal protein and glucose, and a second sample 18 hr later was unchanged. No intravenous or intrathecal chemotherapy had been given before the seizure. His bone marrow findings were consistent with acute lymphocytic leukaemia.

Discussion

Many of the reported complications of propofol involve seizures, opisthotonus, or unusual muscle activity at induction, or emergence from anaesthesia, or in the recovery room (i.e., very shortly after anaesthesia). Saunders and Harris described four adult cases of opisthotonus, tonic-clonic movement, and delayed emergence from propofol anaesthesia.[8] All occurred in the recovery room in patients who had no known predisposition to seizures. Three of the patients had electroencephalograms (EEG) during the episodes, and no epileptiform activity could be shown. All of the patients recovered without sequelae.

Two similar cases were reported by DeFriez and Wong with an onset in the recovery room and no important sequelae.[9] Seizure activation in patients with known epilepsy has also been reported,[10-12] although other evidence suggests that propofol has anti-convulsant activity.[13-15]

Our experience mirrors that of Collier and Kelly's third case, a 16-yr-old boy who had propofol induction for anaesthesia of brief duration (15 min) and seemed perfectly well until he developed a grand mal convulsion six hours after anaesthesia.[12] The seizure lasted only one minute and he recovered completely, but he had another grand mal seizure 21 hr after induction. Collier also reported two other cases of delayed seizure activity in adults occurring 3.5 hr and 9 hr, respectively, after uneventful general anaesthesia which included propofol.[16]

No clear explanation for the excitatory effects of propofol has been suggested. Seizure activity has rarely been identified on surface EEG recording, although this is, of course, usually done after the episode.[17] Some authors feel that the "seizure" activity is sub-cortical in origin,[5,9] and drug-induced decerebrate rigidity[8] or glycine antagonism[18] have been considered as possible mechanisms. Mackenzie suggests that there may be dose-related effects on both inhibitory and excitatory neurons.[14]

Propofol has become an extremely popular anaesthetic agent for out-patient and emergency surgery, and is developing a role in sedation for brief diagnostic or therapeutic procedures. Rare episodes of prolonged emergence or myoclonic activity occurring in the recovery room with no serious sequelae may be considered an acceptable risk. However, the possibility of delayed seizure-like activity (whether true epileptic seizures or not) is much more disturbing. Many of our out-patient surgery and clinic patients travel hundreds of kilometres home by private car or bus on the day of surgery. An

episode such as the ones described would be frightening to the child's parents and other witnesses and potentially dangerous to the patient.

Both of the cases we described may have had other contributing factors. Both patients received other drugs (fentanyl in Case #1, and lidocaine in both). The first patient was haemodialysis-dependent and could have had a metabolic or hypertensive cause for her seizures, although the laboratory results and the changes in blood pressure were not unusual for her. She was given a very small dose of propofol, but the excretion of propofol or its metabolites may have been delayed. The second patient had a history of syncope and had just had his diagnosis of leukaemia confirmed prior to his seizure – a vasovagal attack may have precipitated the seizure. However, the apparent association with propofol sedation, and the similarity to at least one other reported case, has raised concerns among both anaesthetic staff and our paediatric colleagues. We are reporting these cases in the hope that either the association can be disproved, a mechanism for the episodes can be suggested, or at least that risk factors for this complication can be determined.

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