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SUMMARY

Propofol is very rarely associated with seizure like phenomena (SLP), despite widespread use for anaesthesia and sedation. This case report describes a young lady with prolonged SLP lasting for more than 4 weeks after a single dose of propofol. The underlying pathophysiology of this condition is poorly understood but a psychological component should also be considered as a cause of such prolonged symptoms.
Prolonged myoclonus after a single bolus dose of propofol

Introduction

Propofol is indicated for both induction and maintenance of general anaesthesia in adult and paediatric patients. It is commonly used for Intensive Care Unit (ICU) and procedural sedation. Although it has also been employed as an anticonvulsant, there have been reports of seizure-like phenomena (SLP) associated with the administration of propofol. This neurological side effect was usually short lived but in some patients it lasted for weeks and there is still no conclusion on the safety of propofol in patients with epilepsy. This case report describes a young lady with good past health and without any pre-existing neurological illness who developed prolonged myoclonus after one single bolus dose of propofol used for general anaesthesia in a minor operation.

CASE HISTORY

This patient was a healthy 50 kg (normal body mass index), 28-year-old Chinese woman, who had undergone a left knee arthroscopy. She had been taking herbal medication which contained cassia obtusifolia, plantain seed, alisma orientale and semen pharbitidis for weight control during the 2 weeks prior to surgery, otherwise she had not consumed any other drugs. She had undergone general anaesthesia on one previous occasion and this was apparently uneventful, although her medical records were not available. This time anaesthesia was induced with 150 mg of propofol (Diprivan 1% ®) and 50 mcg of fentanyl, 5 mg of cis-atracurium was given to facilitate intubation and anaesthesia was maintained for 30 minutes with sevoflurane and 66% nitrous oxide in oxygen. Ondansetron 4 mg was given as prophylaxis against nausea and vomiting.

Anaesthesia and surgery were uneventful. No muscle relaxant reversal agent was given after the operation. Extubation was smooth and she was transferred to the recovery
room for observation. The patient was slightly drowsy and she had no nausea, vomiting or pain. Fifteen minutes later, when a nurse replaced a blood pressure cuff on her arm, the patient suddenly developed violent repetitive myoclonic-dystonic shaking of all 4 limbs. She remained conscious throughout.

The anaesthetist was called back to attend the patient and gave her 2 mg of intravenous midazolam and the twitching stopped. A provisional diagnosis of epilepsy was made and she was transferred to a general ward for observation. Computer tomography of the brain, and blood test results were all negative. As she had no further episodes, she was discharged home the following morning.

She felt tired at home and the twitching recurred without any provocation. It lasted 2 minutes and stopped spontaneously. Her family immediately took her to their local hospital Accident and Emergency department for medical attention and she was admitted to a medical ward.

The twitching attack was in the form of myoclonic jerky movements, mainly involving all 4 limbs and truncal muscles with sustained back arching. They increased in frequency and she required repeated doses of intravenous midazolam to control them. The movements usually lasted less than 1 minute, with one to two attacks every hour. The doctors in the ward gave her 2 mg midazolam whenever the attacks occurred but it did not improve the condition. The patient became more tired but was still arousable and remained conscious throughout the attacks. She had transient apnoea for 15-45 seconds after every twitching spell and the lowest oxygen saturation measured was 90% breathing room air. An electroencephalogram (EEG) was normal and a neurologist diagnosed her as having opisthotonus and myoclonus. There were 20 to 30 attacks of myoclonus and opisthotonus per day, with less frequency when the patient was asleep.
The Poison Information Centre was consulted about her herbal medication. Cassia obtusifolia is laxative; plantain seed, alisma orientale and semen pharbitidis are diuretics. There are no known neurological effects from these herbs.

As she had received repeated boluses of midazolam, she was transferred to ICU for observation. The patient was frightened and repeatedly asked why the shaking would not stop. She became less anxious after an infusion of midazolam was commenced, but the involuntary myoclonic-dystonic motor movement persisted for the next 24 hr. Since midazolam was ineffective, she was commenced on oral clonazepam with intermittent bolus injections of midazolam on patient demand but she did not improve. On one occasion, all medications were stopped, and the myoclonic spells increased the following day. This was suspected to be a withdrawal effect from benzodiazepines so clonazepam 0.5 mg twice daily was resumed with a gradual tapering dose. The myoclonus remained episodic and only moderately responded to treatment.

The myoclonus and opisthotonus gradually improved during 2 weeks of ICU care from 20 times to between 5 and 7 times per day. She was transferred back to the medical ward on day 13. She was bad tempered, frequently quarrelled with the attending medical staff and refused a psychiatric assessment.

During the first week of treatment in ICU, it was noticed that physical distraction could alleviate the severity of myoclonus. During the attack, sometimes the severity of her twitching would lessen when she was asked to pay attention to particular subjects. Around the second week of ICU care, 0.9% saline was deliberately injected instead of midazolam and produced the same pharmacodynamic effect; the myoclonus stopped and the patient requested another dose during the next attack. This placebo effect was later discovered by the patient when she read her medication record and she
became very angry as a result. She was also aware that being cold could trigger the attack so she deliberately removed all her bed covers to cool herself on the day of her EEG recording. She explained that this would induce more myoclonus for the neurologist to analyse. She felt that she could switch the myoclonus "ON and OFF".

Fortunately, the condition eventually resolved spontaneously after a period of about 1 month. The patient's myoclonic spell lasted for 27 days in total. During this period, she stayed in hospital for observation. The attacks improved to 1 to 2 times per week without trigger. During this period, she was in rehabilitation with occasional physiotherapy exercises; otherwise she chose to stay in bed most of the time. She continued with the oral clonazepam in the medical ward, under the care of neurologists. The drug dosage was tapered down gradually in view of the clinical improvement. Clinical psychologist assessment was done but no psychological problem identified. She was discharged with a long period of work disability leave and was followed up by the neurologists. The medication was stopped completely 3 months after the initial attack and, currently, she is well without any residual neurological disability.

DISCUSSION

Propofol (2,6 di-isoprophylphenol, Diprivan®) was commercially introduced in the 1980s by Zeneca Pharmaceuticals. Its rapid onset, fast recovery time and lack of accumulation have made it very popular for induction and maintenance of anaesthesia as well as sedation. Common side effects include local pain on injection, dose dependent cardiovascular and respiratory depression. Myoclonus, seizures and other movement disorders have been reported in conjunction with propofol administration but they are very rare. The package insert of Diprivan® mentions that opisthotonus and other epileptiform movements are rare complications, occurring in less than 1 in 1,000 to 10,000 patients. The manufacturer, AstraZeneca, has described these rare complications as "almost always self-limiting and short lived with no treatment needed", “although in
various patients benzodiazepines have been given”. In May 1989 the Committee on Safety of Medicines (UK) issued a warning as a result of 268 reports of adverse reactions

In 2002 a review of neurological complications associated with propofol identified 516 reports of neurological movement disorders associated with administration. The movement disorders were described as seizure-like phenomena (SLP). These SLPs can occur during induction, maintenance or emergence from anaesthesia but can occasionally have a delayed onset (more than 30 minutes after the end of anaesthesia or sedation). SLPs have at least five presentations: generalized tonic-clonic seizures (GTCS), focal motor seizures, events presenting as increased tonus with twitching and rhythmic movements not perceived as GTCS, opisthotonous and involuntary movements like myoclonus.

Propofol can induce myoclonus in mice. The precise mechanism of SLP still remains to be elucidated, although various theories have been proposed:

1. Imbalances between excitatory and inhibitory pathways in the brain. Propofol desensitizes chloride channels which prevents further action of gamma amino butyric acid (GABA). This results in disinhibited excitatory action in the thalamocortical circuits. The imbalance may occur between cortical and subcortical structures, as well as via decreased inhibitory output from the formatio reticularis.

2. Toxic metabolites: after a single bolus injection, propofol is rapidly distributed from the central compartment and, therefore, has a very short redistribution half-life of 2–7 min and, subsequently, a relatively short context sensitive half-life. The terminal elimination half-life, however, ranges from 60 min to 3 days, which depends on sex, age, pre-existing illnesses, concomitant medication and the duration of administration. Propofol slowly returns from poorly perfused peripheral compartments back into the central compartment, albeit in very low concentrations. Hence propofol persists inside the
body for quite a long time. It is metabolised in the liver, forming glucuronides and sulphates, and these inactive conjugates are excreted by the kidneys. It has been suggested that these metabolites may cause neurological complications.\textsuperscript{10}

3. Propofol also contains fat and other substances. The fat emulsion by itself has been reported to induce high fever in septic or severely neurotraumatised patients.\textsuperscript{5}

Paradoxically although propofol has been accused of causing seizures and movement disorders, it has also been used as an anticonvulsant and there is evidence that propofol can reduce seizure duration during electroconvulsive therapy.\textsuperscript{11} There are reports of its ability to successfully terminate status epilepticus.\textsuperscript{12,13} The beneficial effects of propofol on epilepsy may be related to its depressant effect on the central nervous system, involving GABA, glutamate and aspartate mechanisms.\textsuperscript{14}

The conflicting data concerning propofol in seizures raise questions on the safety of its use in patients with epilepsy. Some argue that those case reports associating propofol with epilepsy had no EEG assessment or the movement disorders were wrongly diagnosed as seizures.\textsuperscript{4} Thus the controversy persists.

In our patient, the diagnosis of SLP after propofol was made by the exclusion of other possible causes. Epilepsy was unlikely as the patient remained conscious during these episodes with a normal EEG. The stable haemodynamic status, normal physical examination and blood biochemistry results made malignant hyperthermia, serotonin syndrome, tetanus, central nervous system infection, electrolyte disturbance or oculogyric crisis very unlikely. The other anaesthetic drugs administered to the patient were checked. Nitrous oxide, fentanyl and isoflurane may cause neurological complications\textsuperscript{15-18} but seldom result in opisthotonus and myoclonus. On the other hand
propofol has frequently been reported to cause this movement disorder.\textsuperscript{3,4,7,10,14,19} SLP associated with propofol remains the likely cause after ruling out other possibilities.

The treatment of SLP is mainly conservative, as it is self-limiting, and no mortality has been reported. Benzodiazepines and anticonvulsants are usually tried in these patients. Even if drugs are not successful in controlling the condition, it usually resolves spontaneously with the range being from a few hours to 21 days.\textsuperscript{5} Our patient had this attack for 4 weeks, with a poor response to pharmacological agents. Fortunately it stopped gradually. The cause of such a prolonged attack is not clear, although we think a psychological element played a part. The SLP was triggered by cold ambient temperature and the patient would deliberately remove the bed covers to trigger more attacks. Patients have been reported to have attacks upon sensation stimulation. There is one case where a patient's myoclonus could be triggered by cold air.\textsuperscript{3} The sensory input triggered more excitatory activities and imbalances in the nervous system. Psychological elements became more prominent through the successful alleviation of SLP via distraction and the administration of a placebo. It is possible that she initially had a bone fide physical problem but then learned how to self provoke or mimic the attacks for attention.

To conclude, propofol neurological complications are very rare but they do occur. The pathophysiology of this condition is poorly understood and a psychological component should be considered when cases are prolonged.

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