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CASE REPORT

Propofol induced neuroexcitation: an underrecognised complication

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Abstract

Neuroexcitatory symptoms are rare after general anaesthesia. A previously healthy, 39-year-old woman underwent surgery for an elective laparoscopic tubal ligation under general anaesthesia. She developed myoclonus, tonic spasms, muscle hypertonia, and hyperreflexia during recovery from anaesthesia. Her symptoms were controlled using benzodiazepines; initially intravenous, followed by oral. Serum biochemistry was unremarkable except for a high serum creatine phosphokinase. Neuroimaging, electroencephalogram, and cerebrospinal fluid studies were unremarkable. Eventually her neuroexcitatory symptoms gradually subsided and were attributed to propofol. Clinicians who use propofol should be aware about this rare complication to facilitate prompt diagnosis and management.

KEYWORDS
Neuroexcitatory symptoms, myoclonus, propofol, anaesthesia

INTRODUCTION

Common post-anaesthesia complications are related to the cardiovascular system (tachycardia, hypotension) or the respiratory system (upper airway problems and respiratory depression).[1] Pain, shivering, nausea and vomiting are also other commonly encountered problems in the recovery room.[1] Common neurological complications observed in the recovery room are delirium, agitation and postoperative cognitive disorders.[1] Neuroexcitatory symptoms are rare but well reported.[1,2] We discuss a patient who underwent surgery with propofol induced general anaesthesia, and developed myoclonus, tonic spasms, hyperreflexia and hypertonia during recovery from anaesthesia.

CASE PRESENTATION

A 39-year-old, average built, previously healthy woman (63 kg weight and BMI 23.2 kg/m^2) was anaesthetized for laparoscopic tubal ligation surgery. She received a routine induction with intravenous (IV) propofol 150mg, IV fentanyl 100µg and IV suxamethonium 100mg, followed by IV atracurium 10mg and IV morphine 4.5mg. General anaesthesia was maintained with 1% isoflurane (flow rates were adjusted to maintain the minimum alveolar concentration). She was also given IV cefuroxime 1.5g and IV ondansetron 4mg during her uncomplicated intraoperative period. Surgery lasted 30 minutes. She was extubated uneventfully and was sent for routine postoperative observation. While in the recovery room, she developed brisk intermittent synchronous jerky movements of all four limbs with flexion of the neck and trunk and each movement lasted 1-2 seconds. The phenomenology of the movements was suggestive of limb myoclonus and tonic spasms of the trunk. These abnormal movements were predominantly noted to occur upon arousal rather than spontaneously. Jerky limb movements were also noted during voluntary action, therefore were suggestive of an action myoclonus. She did not have

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stimulus-sensitive myoclonus. She was drowsy but responded when awakened. She had quadri-hyperreflexia and hypertonia without clonus or an extensor plantar reflex. The rest of her neurological examination was normal. Her body temperature was 37°C and autonomic functions including light reaction of pupils, heart rate, blood pressure, and sphincter functions were unremarkable.

The patient was further sedated with IV midazolam 5mg and transferred back to the ward, where her movements were noted to be less frequent by the following day. Complete blood count, serum sodium, potassium, calcium, magnesium, creatinine, and transaminase levels were normal. Her creatine phosphokinase level was 980U/l (26-192U/). This was attributed to excessive muscle contractions. C-reactive protein was 12mg/l. Her Magnetic Resonance Imaging scan of the brain was normal, and electroencephalography did not capture any epileptiform discharges. The cerebrospinal fluid opening pressure was 12 cmH_2O and the full report revealed protein of 35mg/dl, no cells, and sugar of 75mg/dl. They were all within normal ranges. Clonazepam, via oral route, at a dose of 0.25mg in the morning and 0.5mg in the night was administered to control her abnormal movements. She made a marked improvement by the third day following surgery and was discharged home with a nocturnal dose of oral clonazepam. The abnormal movements resolved within one week and the oral clonazepam was shortly discontinued.

DISCUSSION

Neuroexcitatory symptoms are not common postoperatively. However, there are case reports of neuroexcitatory symptoms being noted at induction and maintenance of anaesthesia, postoperatively in the recovery room, as a delayed presentation in the ward or even after being discharged.[3]

This case describes the development of myoclonus, tonic spasms, hypertonia and hyperreflexia following general anaesthesia with propofol. Propofol is commonly used in general anaesthesia due to its rapid onset of action, and shorter recovery time.[1] Common side effects of propofol are hypotension, respiratory depression, site of injection pain, hypertriglyceridaemia, and rarely but significantly, propofol infusion syndrome.[1] Although rare, propofol induced myoclonic movements and other neuroexcitatory symptoms have been reported.[1,2] In a case series of 44 patients, the described neuroexcitatory symptoms included increased muscle tone, opisthotonos, extensor movements, rhythmical involuntary movements, myoclonus, muscle twitches, focal or generalized dystonic reactions and seizures.[2] In this case series, symptom onset varied from a few minutes to 44 hours from induction and the persistance of symptoms ranged from minutes to months.[2] Apart from the abnormal movements, severe forms of propofol induced neuroexcitatory symptoms include disorders of consciousness ranging from intermittent loss of consciousness to marked agitation and even delirium, sometimes referred to as “propofol frenzy”.[4]

The pathophysiology of these symptoms is largely unknown, but several possible mechanisms have been described. The sedative action of propofol which is centrally mediated is related to the action on the gamma aminobutyric acid (GABA) pathway.[1,2] The mechanism of neuroexcitation could be that propofol causes an imbalance between the activity of excitatory and inhibitory pathways in the brain.[2] The neuroexcitation has also been postulated to be due to an imbalance between cortical and subcortical structures and a reduction of inhibitory output from the reticular formation.[2] Other mechanisms described are direct activation of sodium channels, potentialization of the inhibitory effect of glycine receptors, inhibition of N-methyl-D-aspartate (NMDA) glutamate receptors, and possible activity via the endocannabinoid system.[4]

Since propofol is a drug used in status epilepticus and it can also induce seizures as a neuroexcitatory effect, there is an ongoing debate about the safety of using propofol in epileptic patients due to these pro- and anticonvulsant effects. The precise underlying mechanisms of the effects of propofol on seizures have not been clearly described. The anticonvulsant effects of propofol may be secondary to its central nervous system depressant action, GABA-mediated pre- and postsynaptic inhibition by enhancing inward $GABA_A$ Cl^- currents, and by decreasing the release of the excitatory transmitters glutamate and aspartate.[5] The proconvulsant effects are probably due to intrinsic subcortical glycine antagonism as suggested by animal data.[5] These pro- and anticonvulsant effects are reported to be dose dependant and proconvulsant effects are seen when propofol is given in low or subanaesthetic doses and disappears when the dose is increased.[5]

Apart from propofol, several other drugs used in general anaesthesia such as fentanyl, ramonsetron, nefopam, enflurane, etomidate and opioids are also known to cause neuroexcitatory symptoms.[2,6,7] We also looked into the neuroexcitatory properties of other drugs given to our patient. Ondansetron a $5\text{-}HT_3$ receptor antagonist, is also known to cause serotonin toxicity when interacting with other serotonergic drugs. There are reported cases of ondansetron induced myoclonus in patients treated with drug combinations.[8] Although opioids are also known to induce myoclonus, it is rare that opioid withdrawal causes myoclonus.[6] Patients reported with opioid withdrawal myoclonus, were on relatively higher doses of opioids.[9] It is less likely that a small dose of fentanyl could cause withdrawal myoclonus in our patient. Isoflurane is also known to induce seizures.[2] There are many mechanisms of action suggested for isoflurane

induced seizures and one main mechanism is modulation of the serotonergic system.[10] Our patient had myoclonic jerks but no clinical seizures and electroencephalography during the event was unremarkable. This made her symptoms less likely to be due to isoflurane.

Since postanaesthetic neuroexcitatory symptoms are rare, there is no consensus on specific therapeutic options and in most reported cases, the management involved benzodiazepines.

CONCLUSION

Neuroexcitatory symptoms rarely occur following general anaesthesia. They are often self-limiting and treatable with appropriate symptomatic therapies. Clinicians who use propofol should be aware about this rare manifestation to facilitate prompt diagnosis and treatment.

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