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Case Report

Prolonged myotonia and dystonia after general anaesthesia in a patient taking gabapentin

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This is the report of a 55-yr-old female who developed severe myotonia and dystonia after general anaesthesia. Before starting on gabapentin therapy for a neuropathic pain condition, she had undergone numerous uneventful general anaesthetics. Since receiving treatment with gabapentin, she has experienced severe movement disorders on emergence from each subsequent general anaesthetic. The events were unrelated to the choice of anaesthetic or anti-emetic. The most recent event that required a protracted stay in hospital after a day-case surgery is presented in detail, and the possible mechanisms to explain the interaction are discussed.

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Mild transient movement disorders associated with induction and emergence from anaesthesia are a common occurrence. These are very often attributable to the use of propofol or certain anti-emetics. Severe and persistent myotonia and dystonia after emergence from anaesthesia is very rare in a patient without a prior diagnosis of movement disorder. Movement disorders are recognized side-effects of gabapentin therapy, but occur only rarely. General anaesthesia has never previously been reported to exacerbate this side-effect of gabapentin.

Case report

A 55-yr-old female (160 cm, 60 kg) underwent elective removal of metalwork from the right first metatarsal bone in the day-surgery unit. She had a past medical history of chronic right shoulder pain. This was attributed to a previous rotator cuff tear, subsequent repair, and post-operative infection requiring several washout procedures. She had been taking paracetamol 1 g as required, codeine phosphate 50 mg as required, and gabapentin 600 mg three times per day. She did not smoke or drink alcohol. The other significant history she reported was an 'allergy' to propofol. Before taking long-term analgesics (since May 2005), she had undergone at least five general anaesthetics using a variety of inhalation and i.v. techniques for minor orthopaedic procedures. All these anaesthetics had been uneventful and recovery had been swift and uncomplicated. However, since starting on the analgesics, in July 2005 she underwent a total i.v. general anaesthetic for Scarf and Akin osteotomies, and developed a severe movement disorder on emergence from anaesthesia. The anaesthetic lasted for 90 min, during which she received alfentanil 0.5 mg, fentanyl 0.1 mg, dexamethasone 8 mg in addition to propofol. This movement disorder was myoclonic in nature, involving mainly her upper limbs, she was conscious throughout the episode. The episode persisted for 3 h and was not relieved by benztropine 2 mg. She was discharged without further symptoms after an overnight stay for observation.

In June 2006, she underwent general anaesthesia for varicose vein surgery. Anaesthesia was induced with propofol 150 mg and fentanyl 50 mg, and was maintained with isoflurane 0.9–1.4%, oxygen, and air. On emergence from anaesthesia, she again developed a severe myoclonic movement disorder involving all limbs, which persisted for several hours, and was not relieved by midazolam administered in boluses of 1 mg. She remained conscious throughout the episode. A neurological opinion was obtained; however she was not symptomatic during the subsequent assessment. She was kept in overnight for observation, but was discharged symptom free the next day. Upon discharge, she was advised that the movement disorder episodes were related to propofol, a medic alert bracelet recommended, and appropriate documentation made in the medical notes to this effect.

The most recent presentation was in December 2006. At the pre-anaesthetic consultation, the notes were reviewed and a plan for gaseous induction and

maintenance of anaesthesia was agreed between the patient and anaesthetist. During the 20-min procedure, in addition to sevoflurane 1.8–2.2%, oxygen, and air, she received dexamathasone 8 mg and fentanyl 0.1 mg. Upon emergence from anaesthesia, she developed a violent dystonic movement disorder affecting her torso and limbs. This was so dramatic that she nearly fell over the cot sides of her recover trolley. The dystonia appeared to come in episodes lasting 1–5 min and would then subside for the same period. It was punctuated by a severe myoclonic jerking of her upper limbs. During these episodes she was conscious and very distressed by the symptoms. The baseline monitoring, as far as it was possible, indicated that she was normotensive, and apyrexial, with oxygen saturation between 93 and 99% while receiving oxygen 2 litre min^{-1} via nasal canula. Before each episode she would develop a sinus tachycardia 100–130 beats min^{-1}. She was initially treated with procyclidine 10 mg without any benefit, and then with midazolam 2 mg boluses, which gave symptomatic relief for 5–10 min while she slept. Each time she woke up, the movement disorders returned with the same ferocity. A consultant neurologist then treated her with longer acting benzodiazepines including diazepam and lorazepam; however, these too were time-limited in their efficacy. The movement disorders gradually diminished over a period of 5 days, and required close observation in a high-dependency environment to ensure patient safety. Electroencephalogram study of an episode did not show any epileptiform basis for the movement disorder. Given the exquisite timing of the three episodes with general anaesthesia, it was decided that magnetic resonance imaging (MRI) was not appropriate during the acute episode, as it would require further general anaesthesia. Gabapentin was withdrawn, but she continued to receive paracetamol and codeine phosphate as required.

Before her discharge, a full history was obtained. She reported no family history of movement disorders or any history of epilepsy or head injury. However, she reported a feeling of 'twitchiness' on occasions during the evening. This symptom had been present for more than a year. She did not believe there had been any physical manifestations of this symptom. She did not recall having felt this symptom before starting the treatment with gabapentin. The patient was discharged home 7 days after her elective admission for day-case surgery. At discharge she reported still feeling 'twitchy'. She was advised to discontinue gabapentin and was referred to the Pain Management Service for a review of treatment options for her shoulder condition. Her general practitioner was advised to supply a suitable medic-alert bracelet.

Discussion

In 1994, gabapentin was originally approved by the US Food and Drugs Administration as an adjuvant medicine in the treatment of partial seizures. In 2002, approval was granted for gabapentin to be used in the treatment of post-herpetic neuralgia and other neuropathic pain conditions. Gabapentin (1-aminomethyl-cyclohexaneacetic acid) is structurally similar to the neurotransmitter gamma-amino butyric acid (GABA). Its mechanism of action is not completely understood,[1] and it is not clear whether it acts upon GABA receptors. A number of binding sites have been identified for gabapentin, including the $\alpha_2\delta$ subunit of voltage-dependent calcium channels in the central nervous system (CNS).[2 3] It is via this binding site that gabapentin is thought to mediate its analgesic activity.

This is the first reported case of a movement disorder developing as a result of interaction between general anaesthesia and gabapentin. In this case, the patient had previously undergone numerous general anaesthetics before the treatment with gabapentin without any complication. However, after starting the treatment with gabapentin each subsequent general anaesthetic resulted in progressively severe movement disorders. The onset of the movement disorder appeared to be independent of anaesthetic technique. During the most recent episode, the movement disorder manifested despite avoiding the known precipitants such as anti-emetics or propofol,[4] was resistant to anticholinergic treatment and benzodiazepine therapy, and it lasted for 5 days.

Acute dystonia after general anaesthesia has been previously reported, although these cases have been attributed to the extrapyramidal effects of certain anti-emetics and to the movement disturbances associated with propofol anaesthesia.[5–7] There have also been several case reports of patients undergoing treatment with gabapentin for essential tremor[8 9] and for partial seizures[10] who have subsequently developed movement disorders. Pfizer reports in the advisory literature for gabapentin that the drug can cause dystonia infrequently (0.1–1%) and localized myoclonus rarely (<0.1%).

It is not immediately clear how gabapentin and general anaesthesia could have interacted in this case to cause the movement disorders. One possible mechanism could be that gabapentin was somehow displaced from its binding site by general anaesthesia, resulting in a sudden elevation of free drug in the plasma. Serial samples of plasma obtained on the day of the episode and subsequent days do not support this hypothesis. The initial plasma concentration was 2.2 mg $litre^{-1}$ (reference range 2–20 mg $litre^{-1}$) and the concentration rapidly decreased to undetectable over the following days.

Another possible mechanism is that of a direct interaction between the general anaesthetic and gabapentin at the cellular level. It has been established that gabapentin has multiple transmembrane binding sites within the CNS, including various ion channels such as the $\alpha_2\delta$ subunit of the voltage-gated calcium channel. It is also accepted that the final common mechanism of general anaesthesia is to somehow disrupt the normal function of ion channels within the CNS. This calcium channel is found throughout the CNS including the basal ganglia. The binding of

gabapentin to the $\alpha_2\delta$ subunit results in reduced monoamine release[11] which could reduce dopamine release at this site. A disruption in the balance of dopaminergic and cholinergic transmission at the basal ganglia could induce movement abnormalities.

Recently, there has been renewed interest in the activity of gabapentin at the $GABA_B$ receptor complex.[8] Given the fact that the GABA receptor is implicated in the mechanism of action of general anaesthetics, this might present the possibility of an alternative site for direct interaction.

An alternative explanation for these events would be that of attention-seeking behaviour. However, our patient did not show such behaviour on other occasions. Also, she was directly observed by a number of doctors over the period of her stay, including a consultant neurologist, none of whom questioned the veracity of her symptoms.

There would appear to be a risk of severe prolonged movement disorder associated with general anaesthesia in patients taking gabapentin, particularly those individuals who report a history of previous minor movement disturbances related to gabapentin use. Where possible in such cases, it may be advisable to use alternative techniques to achieve anaesthesia. It is clear that we do not fully understand the mechanism of action of numerous drugs used in routine practise. This case serves to highlight the need for continued research in this field.

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