

Case Report

Severe neuroexcitatory symptoms after anaesthesia – with focus on propofol anaesthesia

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Delayed neuroexcitatory symptoms after an uneventful anaesthesia are uncommon, although described in many reports. We want to report on two cases. The first patient developed muscle hypertonicity, jerky movements and unconsciousness after an uneventful anaesthesia with propofol, and later the same thing happened after anaesthesia with thiopentone. The second patient developed similar symptoms after an uneventful anaesthesia with propofol, but she never recovered completely after this and is now severely disabled. A search of the literature and the Swedish adverse drug reactions register revealed many similar cases.

In both our patients the causal relationship between propofol and the neuroexcitatory symptoms remains uncertain, but we want to alert readers about this possible adverse reaction.

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THE UNUSUAL phenomena of hypertonic muscles and/or jerky movements, sometimes combined with unconsciousness, developing after an initially normal recovery from anaesthesia, are reported in the literature (1, 2). Many of the patients concerned have been anaesthetised with propofol, and others with enflurane, isoflurane or etomidate (2, 3).

Propofol has gained wide-spread popularity, especially in day care surgery, since it is short acting and has few side effects. However, a number of symptoms from the central nervous system, including twitching, myoclonic movements, opisthotonus, and seizures have been reported as side effects at an incidence of less than 1% (4).

We want to focus on the extremely rare phenomenon of delayed neuroexcitatory symptoms after recovery from anaesthesia. We present two case reports, and a brief review of the literature.

Case reports

These two patients were referred to the Malignant Hyperthermia (MH) unit at our hospital for evaluation of whether the incident could have been a MH reaction.

Patient A

The first patient was a healthy and fit 21-year-old woman who underwent minor orthopaedic surgery. She was without any medication. She had undergone anaesthesia with thiopentone on two previous occasions without any complications. On this occasion she received glycopyrronium 0.2 g as premedication. Anaesthesia was induced with 140 mg propofol and 100 µg fentanyl and maintained during 30 min with isoflurane, 40 mg propofol, and 0.5 mg alfentanil, and 66% nitrous oxide in oxygen. Anaesthesia and surgery were uneventful. The patient was a bit drowsy in the recovery room, and she did not receive any drugs. After two hours she became unresponsive and developed masseter spasm. She was considered unconscious. Her body temperature was 38.2°C. She had no signs of hypermetabolism, such as hyperventilation or hypercapnia. Intubation was done with thiopentone and vecuronium. The patient was put on the ventilator. An acute CT scan of the brain was normal. She woke up after six hours without any specific treatment and was extubated. She could afterwards tell that she had been aware when considered unconscious. It had been impossible for her to respond, although she had tried hard. She could relate what the

staff had been talking about and by this verify her story. Two control CT scans of the brain were completely normal. No EEG was taken. After this incident the patient suffered from headache and difficulties concentrating when studying and reading.

Three years later she was again anaesthetised and this time with thiopentone, suxamethonium, vecuronium, isoflurane and N₂O. She also received 10 mg of ephedrine. The anaesthesia was uneventful and so was the recovery, without any signs of remaining muscle relaxation. One hour later she became unconscious and developed "fits" which were described as increased muscle tone and strange movements. She was intubated and ventilated for six hours. A CT scan of the brain was normal. Also this time, she was conscious while considered unconscious.

Between the two anaesthesias the patient was tested for MH with normal results. Histopathological and histochemical investigations of muscle tissue were normal.

Patient B

This was a girl with a cerebral palsy, with cataract and porencephaly. She was only disabled by a slight left hemiplegia. She had a known abnormal neuroanatomy. Her brother had the same symptoms and signs, indicating the possibility of an inherited disorder. This girl had reacted at the age of 6 years with stiffness of the masseter and increased levels of creatine phosphokinase (CPK) and transaminases, without any other signs of MH, at an anaesthesia with halothane and suxamethonium. Due to her low age, she was not yet investigated for MH. After this event she had been anaesthetised with propofol and N₂O/O₂ without any adverse effects.

At the age of 9, she was subjected to a tonsillectomy and premedicated with diazepam 5 mg and 0.05 mg glycopyrronium i.v. Anaesthesia was induced with propofol 80 mg and fentanyl 50 µg. Intubation was facilitated with 15 mg atracurium. Anaesthesia was maintained during 25 min with 150 mg propofol and 66% N₂O/O₂. Anaesthesia, surgery and initial recovery were completely normal without any signs of hypoxia, hypotension or hypermetabolism. She was discharged to the ward after two hours of uneventful monitoring. Six hours after anaesthesia, she became unconscious. At the same time she developed strong extensor movements over the whole body and a generalised increase in muscle tone, almost like opisthotonus. This was combined with the development of intense jerky movements. Blood gas analyses and electrolytes were normal. Temperature was 37.9°C, later increasing to 38.7°C. CT scan the same day re-

vealed the same status as before the anaesthesia, but CT and MR scans some days later revealed signs of small bleedings in central parts of the brain. EEG-recordings were performed on four different occasions after the event. The background activity showed a slight asymmetry with a predominance of theta-activity in the right hemisphere, consistent with left-sided hemiplegia. No signs of epileptiform activity were recorded in any of the investigations.

Chemical investigations revealed increased levels of CPK up to 39 µkat/l (normal value <2.5) and ASAT 1.7 µkat/l (normal value <0.6) and ALAT 2.0 µkat/l (normal value <0.6). Haemoglobin, white blood cells and electrolytes were all normal. Bacteriological cultivations from cerebrospinal fluid (CSF), blood and urine were negative. No herpes virus type 1 or 2 was detected in CSF.

She was unconscious for five days. The following months she slowly regained complete consciousness. However, after 3 years she suffers from a spastic tetraplegia with dystonia and she has severe difficulties talking. Still later, it turned out that when she was 4 years old, she had had two or three episodes of epileptiform convulsions. Assessment of EEG recordings made at that time in connection with these events was essentially similar to the assessments after the postoperative event.

Review of the literature

There are reports in the literature about neuroexcitatory symptoms during induction, as well as during and after anaesthesia (7). We want to focus on symptoms occurring in the postoperative period. Many of the patients with late neuroexcitatory symptoms were anaesthetised with propofol but there are reports about other drugs as well, e.g. enflurane and etomidate (2, 3). Case reports from the literature concerning propofol and cases reported to the Swedish Adverse Drug Reaction Advisory Committee (SADRAC) are presented in Table 1. The male:female ratio is 1:2 and the median age is 27 years. The symptoms have been described as:

1. *Increased tonus in extensor muscles* described as
 - a. opisthotonus
 - b. extensor movements, increased muscle tone
 - c. hypertonic muscles
 and/or
2. *Rhythmical involuntary movements* described as
 - a. myoclonus
 - b. muscle twitches
 - c. jerky movements
 and/or

Table 1

Reports about patients who developed neuroexcitatory symptoms after anaesthesia.

Patient number	Sex	Age	Symptoms						Duration of symptoms	Reference number
			Delay in symptoms	Hyper-tonicity	Rythmic movements	"Epileptic seizures"	"Conscious while unconscious"	History of epilepsy		
1	F	6	44 h			X			5 days	6
2	F	13	6.5 h			X			?	7
3	M	16	6 h	X		X			21 h	8
4	M	11	4 h			X			1 h	7
5	F	26	85 min			X		X	min	8
6	F	26	45 min			X			30 min	9
7	M	18	35 min			X			1 week	10
8	M	31	30 min			X			?	11
9	F	28	30 min			X			3 h	12
10	F	43	30 min	X		X			1 week	13
11	F	23	20 min			X		X	21 days	14
12	F	29	20 min	X	X	X			7 weeks	15
13	F	32	15 min		X	X		X	minutes	8
14	M	23	10 min	X		X			minutes	16
15	F	38	5–10 min	X	X	X			4 days	17
16	F	29	≈5 min	X				X	75 min	18
17	F	21	5 min	X	X				<1 h	1
18	M	25	5 min			X			4 h	19
19	M	34	2 min	X		X			?	20
20	M	21	minutes	X	X		X		hours	21
21	F	44	minutes	X	X	X		X	6 h	22
22	M	15	minutes		X				1 week	23
23	M	25	minutes			X			10 min	24
24	M	24	minutes	X		X			hours	25
25	F	23	minutes			X			24 h	26
26	F	49	minutes	X	X				24 h	27
27	F	29	minutes			X			days	28
28	F	24	at recovery	X	X		X		3 h	1
29	F	27	at recovery			X		X	1.5 h	29
30	?	2 weeks	at recovery			X			10 min	30
31	F	18	(60 min)	X	X				24 h	20
32	F	55	(20 min)	X	X				48 h	31
33	F	44	(15 min)	X	X				3 days	1
34	F	26	(minutes)	X					<1 h (?)	1
35	M	33	60 min		X				4.5 h	SADRAC
36	F	36	after anaesthesia		X				?	SADRAC
37	F	63	at recovery			X			minutes	SADRAC
38	F	50	at recovery		X				5 h	SADRAC
39	M	57	at recovery	X					minutes	SADRAC
40	F	21	at recovery		X			X	short time	SADRAC
41	F	48	at recovery	X	X				5 h	SADRAC
42	F	30	at recovery			X			minutes	SADRAC
43	F	32	at recovery			X			minutes	SADRAC
44	F	5	?		X				months	SADRAC

Case reports. Patient numbers 34–44 are not published but reported to the Swedish Adverse Drug Reaction Advisory Committee (SADRAC). Delay in symptoms, denoted within parenthesis, indicates that the patient never fully regained consciousness before neuroexcitatory symptoms developed.

3. *Epileptiform seizures* described as

- a. tonic clonic seizures
- b. convulsions

In most cases the symptoms occurred after the patient had regained consciousness. There are also, as in our case A, descriptions of patients who were considered unconscious but were fully aware during the

event (Table 1: patients number 16, 20, 28). In most cases the symptoms lasted only for a short time, although in almost one-third of the cases the symptoms persisted for 24 h or more.

Two national committees of adverse drug effects have published surveys of symptoms after propofol anaesthesia. In 1989 the British Committee on Safety

of Medicine (CSM) reported 37 cases of seizures and 16 cases of involuntary movements. Another 8 patients had either a delay in regaining consciousness after anaesthesia, or woke up and then relapsed into unconsciousness again (32). The Australian Adverse Drug Reaction Advisory Committee (ADRAC) conducted a two-year intense monitoring ending in 1993. It revealed 105 adverse events after propofol anaesthesia. Forty-five of these patients had neurological events such as seizures, opisthotonus or twitches. In 17 cases the symptoms occurred 0.5–6 h after the administration of propofol. Five had a history of epilepsy, and another three had previously experienced convulsions under drug therapy or anaesthesia. Five patients developed opisthotonus. In most cases the symptoms lasted only a few minutes, but in some cases they persisted for up to 48 h. One patient was reported to have possible neurological sequelae, but all others had fully recovered (33). We also found 10 reports about late neuroexcitatory symptoms after propofol anaesthesia in the SADRAC register, not including the two cases described above (see Table 1).

Discussion

These two patients developed severe neurological symptoms with unconsciousness, increased muscle tone, intermittent movements and a slight temperature increase after propofol anaesthesia. Later one of them developed the same symptoms after anaesthesia with thiopentone.

In case A the symptoms are in agreement with those described in many other case reports concerning propofol, see Table 1. The patient was clinically “unconscious” but conscious and unable to communicate, an uncommon symptom also reported by others (1, 18, 21). Interestingly, she later developed similar symptoms after anaesthesia with thiopentone. The other drugs involved seem less likely to have produced these symptoms.

Case B is more complicated. Her initial symptoms are in agreement with case A and the other case reports. However, this patient had a pre-existing neurological disease – cerebral palsy – and known changes in the cerebral anatomy. There is a possibility of an as yet unknown inherited recessive disease in the family, since her brother has a slight hemiplegia, cataract and the same signs in CT scan of the brain. Some days postoperatively, there were signs of small bleedings centrally in the brain on the CT and MR scans. It was discussed whether the extension of the head during a tonsillectomy could have caused an impaired cerebral

circulation, resulting in cerebral damage, but this explanation of her symptoms seems less likely. Due to her cerebral abnormality, her brain could have been more sensitive to noxious factors. Although the clinical signs were similar in these two cases, it is possible or maybe probable that the aetiology in patient B is different from that in patient A.

Neuroexcitatory symptoms have also been described as withdrawal symptoms after sedation with propofol in intensive care (34–37). Other rare side effects of propofol used for sedation are metabolic acidosis and bradyarrhythmias leading to intractable asystole in small children with infectious diseases (38, 39). Some of these children had very high fever. It can be noticed that both our patients as well as patients number 25, 27, 35 and 44 in Table 1 had increased temperature some hours after anaesthesia. This might be a coincidence but there is a possibility that the fever was caused by propofol (4). In no other case reports is there any statement about the body temperature. Another explanation for the slightly elevated temperature in these patients could be the anticholinergic drug glycopyrronium. It is not listed as a side effect at recommended doses, but can appear after overdosage (4).

Many anaesthetic drugs have been reported to induce seizures clinically, or epileptiform activity in the EEG (2, 3, 40), but most of these drugs have also anticonvulsant properties (2, 3). Small changes in the structure of an intravenous anaesthetic can greatly modify the anticonvulsant and excitatory effects of the drug (41). Etomidate is known to induce myoclonias (3), and methohexital can induce epileptiform activity (3). Enflurane can induce epileptiform activity in the EEG as well as seizures (2). Isoflurane (2) and sevoflurane (42) have also been reported to induce seizures. In addition, neuroexcitatory symptoms, such as myoclonias and seizures, have been associated with some opioids and/or their metabolites (2).

Some reported patients (Table 1: patients number 5, 11, 13, 21, 29, 40) had a history of epilepsy, while others had close relatives with epilepsy (Table 1: patients number 10, 12). Our patient B had a known cerebral abnormality, as judged from CT and EEG. It was later discovered that she had had convulsions when she was 4 years old, but epileptiform activity had never been recorded in the EEG. These data indicate that patients with epilepsy or other pathological processes in the brain could be more sensitive to this type of noxious stimuli.

The pathophysiological mechanisms behind the neuroexcitatory symptoms associated with propofol are unknown but several have been proposed.

“Neurological imbalance”

One possible explanation could be that propofol induces an imbalance between excitatory and inhibitory pathways in the brain. It has been suggested that neuroexcitatory symptoms can be caused by an imbalance between cortical and subcortical structures (43), as well as decreased inhibitory output from the formatio reticularis (1, 18, 41). In this context, it is notable that when patient A developed late neuroexcitatory symptoms after anaesthesia with thiopentone, she had also received ephedrine.

The symptoms of opisthotonus can be a manifestation of reversible decerebrate rigidity (1). It is known that this could be accompanied by the preservation of consciousness (44). Neurological symptoms and “clinical” unconsciousness but preserved consciousness was seen in our case A and in other case reports (Table 1: patients number 16, 20, 28).

“Strychnine-like effects”

A contributory cause could be that propofol has strychnine-like effects (18). This is supported by the fact that strychnine potentiates both the excitatory clinical symptoms and EEG effects of propofol in mice (45). However, the results from rat brain might not be applicable to the human brain. It seems likely that the frequency of clinical neuroexcitatory phenomena after propofol anaesthesia is higher in animals. It is reported in 85% of mice (45) and 30% of dogs (46).

Induced epilepsy

Propofol has not been found to induce EEG paroxysmal discharges (47) and the drug is used for treatment of status epilepticus (48). There is no available information about electrical activity in more central parts of the brain in humans, during and after propofol anaesthesia. In none of the case reports, except in our patient B and patient number 11 in Table 1 (14), are there any EEG investigations revealing rhythmic activity.

Propofol pharmacokinetics – toxic metabolites

An altered metabolism of propofol, with formation of toxic metabolites, seems less likely to have caused the neuroexcitatory symptoms. One of our patients as well as others (26) have previously been anaesthetised uneventfully with propofol. Moreover, patient A developed the same symptoms after anaesthesia with thiopentone. However, patient number 35 in Table 1 was reported to have developed similar symptoms on a previous exposure to propofol.

“Something else”

Naturally, most of the described patients have been concomitantly exposed to other drugs and anaesthetics, but we could not find any systematic occurrence of any other particular drugs. In one report the patient received only propofol (12). An alternative explanation could be that the fat emulsion itself, or bacterial contamination of the emulsion, caused the symptoms. Fat has been reported to induce high fever in septic or severely neurotraumatised patients, but with other doses and completely other symptoms than in the patients in this report (49). Bacterial contamination of the fat emulsion has been reported (50), but the clinical course in both case A and case B argues against an infectious manifestation. Patients number 25 and 34 in Table 1 were given the diagnosis hysteria. This diagnosis is now considered outdated. We cannot entirely rule out a psychogenic diagnosis in patient A, but it seems far fetched in view of the great number of reports supporting neuroexcitatory effects of propofol in animals and humans.

Since day care surgery has gained a great popularity and in the future probably will be even more common, we want to stress the importance of an adequate recovery time and a high vigilance also to rare side effects in the postoperative period.

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