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# Long Term Use of Benzodiazepines and Delayed Awakeness from General Anesthesia: A Case Report

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**Abstract** **Case Report**

We present two delayed awaken cases that underwent general anesthesia and showed altered mentality with unresponsiveness in the postanesthesia care unit (PACU) after successful extubation in the operating room. Both patients had been taking benzodiazepines chronically before surgery. In case 1, extubation was carried out without any problems and arrived at the PACU. After 15 minutes, she suddenly developed hyperventilation, shivering, and a state of consciousness that does not respond to verbal command. Eyes were kept closed and she showed decreased pain withdrawal response in all extremities. After 90 minutes at PACU, she was able to obey simple verbal instructions. All symptoms showed gradual improvement within 5-6 hours. In case 2, 20 minutes after transferal to PACU, the patient showed drowsy mentality with no response to verbal or pain stimuli. Altered mental state lasted 3 days and motor weakness of extremities lasted 5 days. Brain MRI and other examinations showed no abnormalities. They were discharged without any neurological complications.

**Keywords:** Benzodiazepins, Delayed awakeness, General anesthesia.



## INTRODUCTION

Delayed awakening from general anesthesia is one of the biggest concern for an anesthesiologist and is not an uncommon complication. Moreover, although this condition is benign in most cases, rarely it may be due to more serious causes such as stroke or anoxic-ischemic brain injury or other neurologic or no-neurologic diseases [1]. We present two cases that underwent general anesthesia and showed altered mentality with unresponsiveness in the postanesthesia care unit (PACU) after successful extubation in the operating room.

## CASE 1

A 66-year-old woman was admitted for ureteroscopic lithotripsy. She had a medical history of dementia, anxiety disorder and depression. she has been daily medicated etizolam 0.5 mg, tianeptine sodium 12.5 mg, zolpidem tartrate 10 mg until a week before surgery, and alprazolam 0.25 mg until the day before surgery. Laboratory tests on admission revealed mild hypokalemia with potassium levels of 3.1 mEq/L. Her condition was otherwise evaluated as normal. Induction of general anesthesia was done with propofol and rocuronium. Anesthesia was maintained by desflurane (with 40% of $FiO_2$ by oxygen and air) for 30 minutes. No opioids were administered during surgery. After operation, neuromuscular blockade was reversed by 100 mg of sugammadex and subsequently the train-of-four ratio showed 98%. The tracheal tube was removed when the patient responded to verbal commands such as opening her eyes and spontaneous breathing recovered.

On arrival in the PACU, the patient received oxygen (5 L/min) via face mask and her breathing was stable. After 15 minutes, she suddenly developed hyperventilation of respiratory rate 40~50/min, shivering, and a state of consciousness that does not respond to verbal command. Eyes were kept closed and she showed decreased pain withdrawal response in all extremities. She was normothermic and blood sugar test showed glucose level of 90 mg/dL. 45 minutes after the onset of event, a neurologist arrived and conducted a neurological examination then advised to rule out motor aphasia due to transient ischemic attack or somatoform disorder. After 90 minutes at PACU, she was able to obey simple verbal instructions, such as opening her eyes or raising her arms, though still unable to make her

voice. All symptoms showed gradual improvement within 5-6 hours. The day after the operation, brain magnetic resonance imaging (MRI) and electroencephalography were conducted, and their results were normal. The patient was discharged without any neurological complications.

## CASE 2

A 39-year-old woman was admitted to neurology department under diagnosis of medication overuse headache and insomnia. On hospital day 19, she received entropion & trichiasis repair surgery under general anesthesia. The surgery was previously scheduled under local anesthesia but converted to general anesthesia due to her anxiety. Laboratory tests showed no abnormality. She has been daily medicated clonazepam 0.5 mg, diazepam 3 mg, mirtazapine 30 mg until the day before surgery. Induction of general anesthesia was done with propofol and rocuronium. Anesthesia was maintained by sevoflurane (with 50% of $FiO_2$ by oxygen and air) for 90 minutes. During operation, alfentanil was administered twice in 0.25 mg each for a total of 0.5 mg. After operation, neuromuscular blockade was reversed by 15 mg of pyridostigmine with 0.4 mg of glycopyrrolate.

20 minutes after transferal to PACU, the patient showed drowsy mentality with no response to verbal or pain stimuli. She had adequate spontaneous ventilation and was hemodynamically stable. Arterial blood gas analysis (ABGA) performed in the PACU showed that her blood pH level was 7.429, $PaCO_2$ level was 35 mmHg, $PaO_2$ level was 238 mmHg, bicarbonate level was 24 mmol/L and glucose level was 91 mg/dL. Oxygen saturation was 99% with oxygen mask 5L/min. Serum electrolytes and other serum chemistries were within normal limits.

A neurological consultation was obtained and pupil reflex showed normal. She was subsequently transferred to the intensive care unit for further evaluation including diffusion MRI which showed no significant interval change. Also there was no definite electrophysiologic evidence of peripheral neuropathy or radiculopathy based on nerve conduction study and electromyography. Altered mental state lasted 3 days and motor weakness of extremities lasted 5 days. Among the drugs administered to the patient, clonazepam 0.5mg was replaced to alprazolam 0.5mg from the day after entropion repair.

On hospital day 25, the patient complained of abdominal pain and received laparoscopic appendectomy under general anesthesia. Agents used for general anesthesia was identical, except desflurane was used instead of sevoflurane. There were no specific complications after the operation unlike the prior case.

## DISCUSSION

Pharmacological, metabolic, psychogenic and neurological can cause, delayed regain of consciousness after general anesthesia. Occasionally, residual anesthetic drugs may delay emergence from anesthesia as a result of overdosing or recurarization [2-4]. In these cases, the patients were chronically medicated with benzodiazepines (BDZs) and atypical antidepressants due to anxiety disorder and insomnia, respectively. Although it took an unexpectedly long time, the patients spontaneously regained consciousness without any neurological complications. Both cases and several other studies suggest that long-term use of BDZs and/or atypical antidepressants enhances the clinical pharmacological effect of anesthetics, resulting in delayed emergence after general anesthesia.

In the second case, after the event of delayed awakeness after anesthesia, alprazolam was prescribed instead of clonazepam. Both are short acting drugs, but clonazepam stays in the body for longer than alprazolam. The half-life of alprazolam is 6–25 hours, while for clonazepam, it is 22–54 hours. Changing drug to a shorter half-life BDZ might have prevented delayed awakeness after the second operation – laparoscopic appendectomy.

Central nervous system depressing effect of BDZ is often underestimated. The effect of propofol is considered to be enhanced by BDZs because its mechanism is mainly mediated via activation of gamma-aminobutyric acid (GABA), which is the same mechanism as BDZs [1]. So, during a preanesthetic visit, it is necessary to determine whether to stop or continue drug use by figuring out the patient's drug intake history, and to be aware of the possibility of delayed awakeness.

In our case, anesthesia depth monitoring was not performed, which may also have affected delay awakeness. The dose of anesthetic used without monitoring may have been overdose in these patients. Psychogenic coma was also considered as a cause of delayed awakeness, but since psychogenic coma can be diagnosed after excluding all other causes, we determined that the cause was taking chronic BDZs [5].

Of course, in all cases, other risk factors such as hypothermia, hypothyroidism, opioid overdose, remained muscle relaxation, electrolyte imbalance should not be ruled out. Measuring the patient's body temperature, carrying out neuromuscular transmission test, administration of flumazenil, naloxone, sugammadex and obtaining ABGA can be useful to find out the reason of delayed awakeness.

## CONCLUSION

Delayed awakeness is a rare complication but can be serious. We should take patient's past medical

history with a variety of medications before anesthesia and to be aware of the possibility of delayed awakeness.

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