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Is the flumazenil administration diagnosis or treatment? Two case reports

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ABSTRACT

Benzodiazepine has the central nervous system (CNS), cardiac and respiratory side effects when intaked more than therapeutic doses. Acute benzodiazepine poisoning may be manifest taken in the form of dizziness, ataxia, nystagmus, dysarthria, hypoxia, hypothermia, hypotension, bradycardia, apnea, pulmonary aspiration, respiratory depression, coma, cardiopulmonary arrest and death. Alprazolam is the most toxic form of benzodiazepines and unless combined with the other CNS depressants such as barbiturates and alcohol, death is rare. When benzodiazepine intoxication is suspected, the next step is flumazenil administration to reverse the CNS and respiratory system depression. In this case report, we aimed to point to the diagnosis and treatment of benzodiazepine intoxications by representing two intoxicated patients with coma.

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1. Introduction

Benzodiazepines commonly used against various disorders such as anxiety and insomnia, potantialise gamma-aminobütirik asit (GABA) neurotransmission in all parts of the central nervous system (CNS) (Tunçok and Kalyoncu, 2007). Most common side effects are sedation and ataxia, and the body develops tolerance against such effects in the course of time. Tolerance development against anxiolytic effects is rarely observed.Acute benzodiazepine poisoning may be manifest itself in the form of dizziness, ataxia, nystagmus, dysarthria, hypoxia, hypothermia, hypotension, bradycardia, apnea, pulmonary aspiration, respiratory depression, coma, cardiopulmonary arrest and death (Welch et al., 1977; Michaud et al., 1999). Unless combined with other CNS depressants such as barbiturates and alcohol, death is rare (Hung et al., 1992, Koski et al., 2003). Alprazolam is the most toxic form of benzodiazepines (Ramadan et al., 2006).

Alprazolam is a benzodiazepine derivative mainly used as an anxiolytic and antidepressant. It is rapidly absorbed through the gastrointestinal tract; and reaches maximum blood concentration in around one and half hour. While elimination half life is 11 hours in juveniles, it is longer in the elder (Güloglu and Söğüt, 2004).

The objective of this article is to present two intoxication patients who referred to the emergency department for loss of consciousness, and further to highlight the diagnosis and treatment of benzodiazepine poisoning.

2. Case-1

A male patient at the age of 57 was brought to our emergency department for loss of consciousness. According to the information obtained from the patient's relatives, the patient had taken 150 cc of alcohol at dinner, and then he started to rest at around 10.00 am., next day he wasn't found in his room where he stayed, and then he found unconscious in a hotel room at around 12.00 pm. The initial physical examination of the patient revealed that his Glasgow Coma Scale (GCS) was 4, his pupils were miotic, pupillary light

reflex (PLR), plantar responses were indifferent, and that he showed no lateralizing finding. Other physical examinations of the patient were normal. Finger stick testing revealed normal glucose levels. To avoid any airway obstruction and in consideration of the aspiration risk, endotracheal intubation was applied, and then the patient was taken under monitoring with respiratuar support. His vital signs, laboratory analysis results and cerebral computed tomography (CT) findings were within the normal range. Cerebral magnetic resonance imaging (MRI) was applied against any potential brain stem ischemia, however no limitation of diffusion was observed. According to the information provided by the immediate relatives of the patient that subsequently showed up to our emergency department, the patient was in a depressive mood nowadays, called them at around 10.00 pm on the day of incident, and said goodbye. Considering that the patient might be suffering intoxication, thiamine and naloxane were administered in appropriate doses. However, as the patient gave no response, total of five doses of 0.3 mg flumazenil, one per minute, were administered. Once the patient started to give response, administration regime was changed to 0.5 mg per 20 minutes. After almost 24 hours following the patient admittance to the emergency department, the patient's conscious is opened . At the end of the 3rd day in the hospital, the patient was discharged as extubated with full recovery.

Case-2

A female patient at the age of 43 was brought to our emergency department for loss of consciousness. According to the information provided by the patient's relatives, the patient was being medically followed up with the diagnosis of major depressive disorder, the patient went to his room for sleep on the day of the incident, then they could not wake him up and he had growling respiration during that time. The initial physical examination of the patient revealed that her GCS was 3, her pupils were miotic, PLR, plantar responses were, and she showed neck stiffness. The findings of the other physical examination on the patient were normal. Finger stick testing revealed normal glucose levels. Her vitality, laboratory analysis results and cerebral CT findings were within the normal range. The level of the valproic acid used by the patient due to her major depression diagnosed was observed to be normal. In view of the patient's medical history and examination, it was considered that the patient might be suffering intoxication. Nasogastric irrigation was applied to the patient and active coal was administered. Naloxane was administered to the patient but no response could be received. Then, total of six doses of 0.3 mg flumazenil, one per minute, were administered. Once the patient started to give response, administration regime was changed to 0.5 mg per 20 minutes. After 6-h flumazenil treatment, GCS of the patient enhanced to 9. Extubated after 24 hours, the patient was medically followed up for a period of one week, and then discharged with full recovery.

3. Discussion

In patients referring to the emergency department in coma, ethiology constitutes a wide range. Therefore, detailed medical history and exhaustive physical examination on these patients are of great essence. Coma is a clinical symptomatic situation revealed by an underlying disorder. In other words, the cause should be explored and discovered. However, priorities should be kept in mind. The first priority is to ensure that the patient has an unobstructed airway, intact respiration and circulation. It should be kept in mind that intoxications are more often seen in patients with depression, and that they are one of the noteworthy diagnoses involved in the coma ethology (Michaud et al., 1999).

Acute benzodiazepine poisoning may manifest itself in the form of dizziness, ataxia, nystagmus, dysarthria, hypoxia, hypothermia, hypotension, bradycardia, apnea, pulmonary aspiration, respiratory depression, coma, cardiopulmonary arrest and death (Michaud et al., 1999). It is known that benzodiazepine overdose is characterized with morbidity and mortality (Guadreault et al., 1991). Severe intoxication or mortality rather occurs in case of combination with other medication or parenteral administration (Güloglu and Söğüt, 2004). Both of our cases had a history of depression-related complaints. However, high doses of benzodiazepines such as triazolam, alprazolam and temazepam may lead to severe toxicity alone (Güloglu and Söğüt, 2004). The facts that both patients were unconscious at the time of referral, their relatives did not initially report a medical history of self-suicide for them or no finding like an empty pillbox was present beside of the patients that would cause us to doubt about primarily intoxication, we firstly strived to exclude organic causes. First, the airway safety of patients was secured, and their respiratory and circulatory functions were supported, this is what constitutes the typical practice that should be applied to all patients regardless of intoxication presence. Both cases developed change of consciousness (coma) due to high dose of alprazolam. First case reached our emergency department around 14 hours later and second case probably after four hours. Neurological examinations of both patients revealed coma situation, demonstrating the severity of toxicity.

Treatment for intoxication due to such group of drugs involves ensuring the stability of the patient followed by usual gastrointestinal system (GIS) decontamination procedures and the necessary supporting treatment. As benzodiazepines highly binded to proteins, they have a wide volume of distribution. That's why; force diuresis and hemodialysis are not helpful. In case of benzodiazepine overdose, flumazenil that is a specific competitive receptor antagonist is used (Seger, 2004).

Flumazenil is a benzodiazepine antagonist. In case of intoxications due to benzodiazepine, the CNS and respiratory depressions are prevented (Seger, 2004). In case it is doubted that the patient with coma referring to the service took more than one drug, differential diagnosis is also applied (Tunçok and Kalyoncu, 2007). Following an initial dose of 0.3 mg for adult patients, the regime may be applied with a maximum dose of 2 mg in every 1-2 minutes. As the action time of benzodiazepines may exceed that of flumazenil, additional doses may be necessary if sedation repeats after recovery. Maintenance dose is 0.1-0.4 mg. However, as it may particularly lead to benzodiazepine withdrawal and epileptic seizure, it is not routinely recommended for every patient (Tunçok and Kalyoncu, 2007).

Ritz et al. (1990) administered flumazenil to 28 patients monitored in intensive care unit due to coma, and reported that flumazenil reversed coma resulting from benzodiazepine intoxication, yet they were useless in patients with coma not

due to benzodiazepine intoxication. In a double-blind study performed by Weinbroum et al. (1996). it was reported that flumazenil may be used in both the diagnosis and treatment of benzodiazepine intoxication in patients with coma, and that it further eliminates respiratory failure and depression in CNS caused by benzodiazepine intoxication. Likewise, Güloğlu and Söğüt, (2004) presented three patients on alprazolam with change of consciousness. It was reported that all three patients were administered with flumazenil, and that they all were discharged with full recovery. While two of the patients had a history of alprazolam reception at the time of referral to the emergency department, it is observed that the drug taken by the third patient was not clear, and that flumazenil was administered across a clinical suspicion In both of our cases, medical history did not suffice to conclude benzodiazepine intoxication. After organic causes were excluded, we doubted about intoxication at first hand and administered naloxane in appropriate doses, yet could not take any response. Accompanied with physical examination, flumazenil was administered in appropriate doses to both cases upon the suspicion of benzodiazepine intoxication, and patients gave expected responses to the initial 2-mg loading dose. In our cases, flumazenil was employed not only for treatment but also for diagnosis. In both cases, both the respiratory and the CNS depression disappeared. After the regain of consciousness, both patients stated that they had taken alprazolam. After the medical follow-up was completed, both patients were discharged with full recovery.

Medical history is crucial for patients with coma brought to the emergency department. Generally, medical history and physical treatment highly lead to a proper diagnosis. When benzodiazepine is administered over therapeutic doses, the CNS symptoms, respiratory and cardiac impacts may occur. The severity of such impacts may vary based upon the dosage, time during which the drug is absorbed throughout the gastrointestinal system, whether early intervention can be applied or not, and the patient's sensitivity to the drug. Dextrose, thiamine and naloxane are of essence in the treatment of coma. If it is doubted that there is benzodiazepine intoxication, the next step is flumazenil, which reverses CNS and respiratory depression in benzodiazepine intoxication.

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