Bispectral Index: A New Monitor In The Management of Acute Alprazolam Poisoning: Alprazolam Poisoning And BIS

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Citation

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Abstract

Alprazolam is a triazolobenzodiazepine, which has antidepressant properties. Few overdoses were described with this agent. Major clinical symptoms of these overdoses are sedation. The bispectral index (BIS), a numeric value derived from bispectral analysis of EEG, has been introduced as a monitor of the hypnotic component of anaesthesia. In this case, our aim is to demonstrate the usefulness of BIS monitoring in the management of patients who were poisoned with benzodiazepines such as alprazolam.

INTRODUCTION

Alprazolam, a triazolobenzodiazepine derivative is mainly used as an anxiolytic and antidepressant. It is also efficient in the treatment of agoraphobia, panic attacks and panic disorders. It is one of the most widely prescribed benzodiazepines in the United States ([1]). As stated by McCormick S. R. ([2]), if the frequency of overdose with tricyclic antidepressants is any indication, increased use of alprazolam for depression will probably be followed by an increased incidence of suicide attempts with this agent. Therapeutic plasma levels of alprazolam range from 5 to 50 µg/L, toxic concentrations are between 100 and 400 µg/L ([3]). In the alprazolam toxicities, the outstanding clinical symptom is drowsiness ([4]).

The Bispectral Index is a complex mathematical evaluation of relevant, descriptive electroencephalographic parameters of the frontal cortex corresponding to varying levels of sedation ([5]). For several end points and for several anaesthetic regimens, it yields the best combination of sensitivity and specificity of any commercially available depth-of-anaesthesia monitoring device ([6]).

We aimed to demonstrate the usefulness of the BIS monitoring in the management of the patients who were poisoned with alprazolam.

CASE REPORT

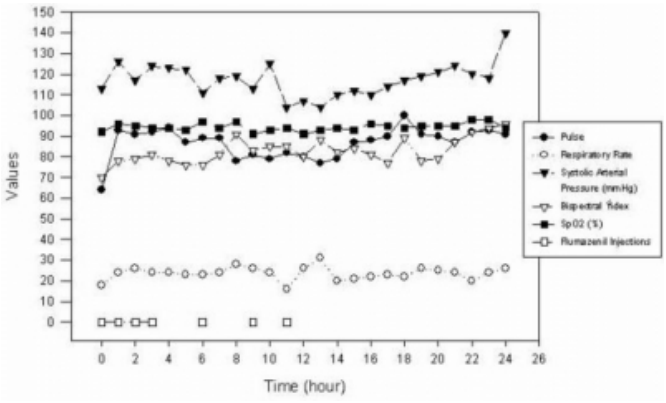
A 36 year old, 75-kg male, with history of chronic depression ingested 50 1mg tablets of alprazolam (Xanax®, Eczacibasi, Turkey) the night before admission to the intensive care unit (ICU). He slept overnight, and was brought to the emergency room 12 hours after the ingestion of alprazolam. Physical examination upon admission to the ICU demonstrated blood pressure of 113/83 mmHg, pulse 64 /min, transcutaneus oxygen saturation (SpO2) 92 %, respiratory rate 18 /min and skin temperature 36,8 °C. Neurological examination showed deep coma, bilateral constructed pupils which reacted minimally to light, bilateral extensor plantar response, diminished tendon reflexes and retention of urine. There was no response to painful stimuli. His Glasgow Coma Scale (GCS) score was 3. Bispectral index monitoring (Aspect® Medical Systems, Natick, MA, USA) was used to measure levels of sedation, and the index detected 70. An admission serum sample, which was assayed by reversed phase high performance liquid chromatography (HPLC), contained 527 µg/L of alprazolam. At the same time, serum benzodiazepine level was measured with Abbot's TDX-FLX method and the value was 271 µg/L. Analyses of serum and urine were negative for alcohol and other drugs. Routine biochemical and haematological tests were normal.

A nasogastric tube (Levin Nazogastrik Kateter®-Bicakcilar, Turkey) was placed and the patient's gastric lavage returned no pill fragments. Activated charcoal 50 g (Eucarbon®-Santa Farma, Turkey) was given through the Levin tube and the same doses repeated after 6 hours. After establishment of

intravenous access, patient received titrated doses of flumazenil (Anexate®, Roche, Turkey) to a total of 1 mg. Then, the patient rapidly became more alert and tearfully anxious. At that time, BIS increased to 98 and GCS scale was 15. The patient gradually became more obtund and returned to his pre-flumazenil state after one hour (unresponsive to painful stimuli). At that time, BIS value decreased to 70. Flumazenil was given in doses of 0.1 mg when the BIS value showed less than 75 and no clinical significant decreases were seen in pulse rate, blood pressure, SpO2, or respiratory rate (Figure 1). The patient was not intubated endotracheally. Sedation scores were measured according to Observer's assessment of alertness/sedation scale ([7]) (OAA/S); score: 5= awake/alert to 1=deeply sedated. OAA/S varied between 2 and 3 points after flumazenil injections. After overnight observation and 24 hours after admission to the ICU, the patient was well recovered.

Figure 1

Figure 1: Patient's records



DISCUSSION

The patient described in this report had serum alprazolam levels approximately ten times greater than the expected levels following usual therapeutic doses. There is no published data in the literature as high as this patient's plasma alprazolam levels. Alprazolam, an intermediate-acting benzodiazepine, is rapidly absorbed and has an elimination half-life of 6-26 hours (2). This suggests that the patient's alprazolam level of 527 µg / L; obtained 12 hours after ingestion would be considerably less than his peak alprazolam level. Alprazolam is metabolized by oxidation and conjugation. The principal metabolites are µ-hydroxyalprazolam, 4-hydroxyalprazolam, µ 4-dihydroxyalprazolam and 3-hydroxy-5-methyltriazolyl chlorobenzophenone (HMTBP). µ-hydroxyalprazolam and 4-hydroxyalprazolam are both metabolites that are pharmacologically active with approximately 66 % and 19 %, the potency of alprazolam, respectively (1). But these metabolites were not studied in the blood for this case. The clinical symptoms of acute poisoning due to benzodiazepine are drowsiness, ataxia, hypotension, respiratory depression, papillary constriction and coma. Coma and respiratory depression are rarely observed in benzodiazepine overdose, but if seen, they occur with other central nervous system depressants (4).

The present case had coma, constricted pupils, bilateral extensor plantar with diminished tendon reflexes, and retention of urine without respiratory depression. Flumazenil has been proven to be an effective benzodiazepine antagonist by clinical investigations in both anesthesia and benzodiazepine poisonings experimentally, and it may have a weak partial agonist and an inverse agonist effect ([8]). However, it has been reported that flumazenil should not be used for treatment since it may precipitate convulsions or acute withdrawal syndromes, and it has a short half-life (1-2 h), making repetitive doses and continued monitoring necessary ([9]).

In our case we observed acute withdrawal syndrome of benzodiazepine after 1 mg of flumazenil infusion. BIS monitoring was used as a guide of sedation level and to determine the time of injections and doses of flumazenil. Therefore, we avoided these withdrawal attacks after large doses of flumazenil. That is, flumazenil doses were titrated as sedation level. More recently, bispectral index monitoring is being used to objectively measure levels of sedation in several clinical settings (6, [10]). There is substantial literature that suggests that using the BIS monitor to guide the administration of a general anesthetic can reduce expenditure for anesthetic agents, reduce side effects associated with general anesthesia, and reduce the consumption of recovery room resources ([11,12,13]). It has also been reported that the BIS might be able to provide better information for sedation/analgesia in the ICU ([14]). However, there are many reports in the literature showing a lack of correlation between the BIS and the level of sedation making it difficult to predict sedation depth. It has been reported that BIS appears to have drug-specific characteristics or varies individually ([15]).

A review of Medline from 1966 to present reveals no previous report of alprazolam with the use of BIS. Sandler et al. ([16]) reported that there was a strong relationship between

the objective BIS values and subjective assessment (OAA/scale) of the depth of anesthesia with midazolam-fentanil-propofol sedation. In another study it is reported that BIS monitoring may detect the effect of oral diazepam premedication ([17]). We observed objectively that BIS monitoring reflected alprazolam sedation in this case. And BIS trends in this case help to titrate the flumazenil better than level of consciousness.

It is concluded that the BIS monitoring was quite useful in the management of the patients poisoned with benzodiazepines such as alprazolam.

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