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REVIEW ARTICLE

The Efficacy of Aminophylline on Raising Consciousness in Benzodiazepines-Intoxicated Patients

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Abstract

Background: Loss of consciousness and respiratory failure are the most important medical problems in acute benzodiazepines (BZDs) toxicity. The possibility of respiratory apnea increases in intentional cases and also in the presence of underlying cardiopulmonary diseases. The inhibitory effect of aminophylline on adenosine receptor may be the cause of recovery of consciousness in patients intoxicated by BZDs. The effect of aminophylline as an agonist of cAMP (cyclic adenosine monophosphate), on reversal of inhibitory effects of BZDs (benzodiazepines) on the brain and increasing the level of consciousness is the main question.
Method: we reviewed literature sources on topic of aminophylline and consciousness. 29 articles were compiled from prestigious scientific databases such as PubMed, Scopus and Elsevier, from 1983 to 2017.
Results: This review showed that intravenous aminophylline can lead to clinical improvement of both consciousness and respiration via antagonizing sedation that induced by BZDs. Although administration of flumazenil is still the first choice for apnea related to BZDs overdose and it is also more potent than aminophylline on reversing sedation, aminophylline can be substituted when flumazenil is not available or when it has contraindication such as in epileptic patients and in overdoses with drugs capable of causing convulsion. Also, aminophylline is useful in those BZD-intoxicated patients with coincident underlying COPD and asthma.
Conclusion: intravenous aminophylline could decrease the sedative effects of BZDs and also speed up the recovery of consciousness in patients under sedative effects of BZDs.

Keywords: Aminophylline; Benzodiazepine; Consciousness; Toxicity

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INTRODUCTION

Adenosine is a modulator with a pervasive and generally inhibitory effect on neuronal activity. Tonic activation of adenosine A1 and A2a receptors by adenosine leads to inhibitory effects. Adenosine has a role in regulation of sleep and level of arousal (1). The inhibitory effect of aminophylline on adenosine receptor may be the cause of recovery of consciousness in patients intoxicated by benzodiazepines which is the basic theory behind the current study.

Effects of BZDs on the brain

Benzodiazepines (BZDs) are agonist of inhibitory GABA(gamma-Aminobutyric acid)-A receptors and also inhibit adenosine metabolism and reuptake. They facilitate accumulation of adenosine in the extracellular space by inhibiting adenosine uptake which in turn results in sedation (2). In 1999, Narimatsu showed that the effect of BZDs on GABA-A receptors was completely antagonized by aminophylline, an adenosine receptor antagonist (3).

Effects of aminophylline on BZDs intoxication

Aminophylline is a phosphodiesterase enzyme inhibitor and selective alpha-2 adrenergic agonist that are currently used to treat asthma and chronic obstructive pulmonary diseases. Aminophylline can cause tachycardia and tachypnea by stimulating central nervous system (CNS) respiratory center and is also used to treat neonatal apnea and bradycardia syndrome (4-8). Phosphodiesterase is responsible for degradation of intracellular cAMP (cyclic adenosine monophosphate), and cAMP is the postsynaptic second messenger in alpha adrenergic stimulation system whose clinical effects are similar to adrenergic stimulation.

Listos et al showed that adenosine receptor antagonists such as aminophylline intensified the BZDs withdrawal syndrome (9). Turan et al, in a double-blind crossover study, confirmed the hypothesis that aminophylline delayed loss of consciousness (LOC) with BZDs anesthesia (10). They showed that intravenous aminophylline with the dose 6mg/kg, followed by 1.5 mg/kg/h could decrease the sedative effects of BZDs and also speed up the recovery of consciousness (ROC) in patients under sedative effects of BZDs.

Hoegholm, in a double-blind randomized study, showed that aminophylline could reverse the sedative effects of BZDs and also shorten the sedation time in patients under BZDs sedation (11). They showed that patients who received

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aminophylline had a more rapid reversal of BZDs sedation compared to those who did not. However, thirty minutes after infusion of aminophylline and normal saline, there was no difference between these two groups. Thus, they concluded that aminophylline would not shorten the necessary observation period after BZDs sedation. Study of Aghabiklooei and Sangsefidi confirmed this idea (12). They found that sooner recovery from sedation and increasing the level of consciousness by aminophylline could alleviate the need for endotracheal intubation in severely deep comatose BZD-poisoned patients. Niemand et al in a double-blind study estimated the effects of aminophylline on deep diazepam sedation after surgery (13). They showed that low-dose aminophylline (1.5–5 mg /kg) could reverse diazepam sedation. They believed that aminophylline antagonized diazepam sedation by blocking adenosine receptors.

In a double-blind randomized study, 32 patients who had received diazepam for deep sedation before surgery were divided into two groups: one received single dose of aminophylline (60 to 120 mg) and the other received normal saline after finishing surgery (14). The aminophylline group showed a rapid reversal of sedation which persisted for 2 hours. They concluded that aminophylline was a potent antagonist of BZDs and could reverse the sedative effects of BZDs. Some other studies also confirmed that aminophylline could antagonize diazepam sedation by adenosine blockade of GABA receptors in the brain (15-17).

In a study by Foster et al in 1987, efficacy of 1.5 mg/kg of intravenous aminophylline in accelerating recovery from premedication with diazepam was assessed against placebo in 110 patients who had received intravenous diazepam before upper gastrointestinal endoscopy in a randomized, double-blind trial (18). Those patients who received aminophylline on completion of the endoscopy had faster recovery from BZDs sedation compared to the placebo group. This study showed that patients who receive aminophylline become fully alert much sooner than the placebo group. They had regained their alertness almost 30 to 60 minutes after finishing endoscopy.

A randomized blinded study by Bonfiglio et al in 1996 compared the efficacy of aminophylline and flumazenil on reversal of BZDs sedation (19). It was shown that flumazenil completely reversed BZDs sedation but only partial reversal of sedation was achieved by an aminophylline dose of 1-2 mg/kg. Other interesting finding in this study was that aminophylline prolonged the flumazenil half-life ($P < 0.05$). It can be concluded that if flumazenil and aminophylline are both administered to a BZD-intoxicated patient, aminophylline will probably decrease the dose of needed flumazenil for reversing BZDs sedative effect.

Sibai et al, in their randomized double-blind study, compared the efficacy of flumazenil with aminophylline in antagonizing the effects of midazolam in 60 patients (20). Flumazenil caused complete and rapid reversal of sedation but aminophylline caused a 42-percent reversal in the patients. In another study, patients who had been sedated with 60 mg intravenous diazepam received 60 mg intravenous aminophylline and showed immediate recovery of consciousness (21). Some other studies showed rapid awakening after injection of aminophylline in patients under sedation of propofol (22, 23). Lee et al believed that aminophylline antagonized the sedative effects of several BZDs (24). They reported that there were no side effects or delayed re-sedation after the administration of aminophylline. This study suggests that aminophylline can be a clinically useful propofol antagonist. Stirt and colleagues, Meyer and associates, and Wangler and coworkers introduced aminophylline as an antagonist of BZDs, as well (23, 25, 26).

Effects of aminophylline on respiration

Although the main problem in severe BZDs toxicity is loss of consciousness, in some patients including suicidal toxicity cases or those with underlying heart or lung diseases respiratory failure and hypoventilation may complicate the patients. Aubier showed positive effects of aminophylline on improvement of ventilation in these patients as well as increasing their consciousness (27). Aminophylline increases intracellular calcium content and improves contractility of diaphragm and respiratory muscles. It has also been demonstrated that adenosine antagonists such as theophylline and aminophylline can decrease diaphragmatic and muscle fatigue, prevent fatigue of diaphragm, and increase respiratory muscle strength. In usual therapeutic dosage, aminophylline will increase ventilation and its level is depressed in BZDs intoxication (28). Administration of aminophylline can significantly increase ventilation, tidal volume, and respiratory rate (29).

Recent research by Aghabiklooei and Sangsefidi showed the positive effects of aminophylline on increasing the level of consciousness in patients with significant BZDs toxicity after suicidal attempt (12). In this study, 5 mg/kg intravenous aminophylline could reverse the sedative effects of BZDs and the recovery of consciousness was faster compared to those who did not receive aminophylline.

Prolonged hospital stays due to BZDs poisoning may also cause complications including nosocomial pneumonia or exacerbation of underlying diseases, especially in older patients. It seems that trying to increase consciousness can reduce these complications and their morbidities. Awaking time after admission of aminophylline was 72.6 minutes versus 885 minutes in those who had not received it. Aminophylline could raise the level of consciousness and would subsequently reduce complications of BZDs toxicity like aspiration pneumonia, and decreased the rate of morbidity and mortality.

CONCLUSION

The possibility of respiratory apnea increases in intentional poisoning cases with BZDs especially in old patients with underlying cardiopulmonary diseases. Administration of flumazenil is still the first choice in special cases including those with the risk of respiratory depression and apnea following BZDs overdose. Although flumazenil is more potent than aminophylline on reversing sedative effect of BZDs, aminophylline can be substituted when flumazenil is not available or when it has contraindication such as in epileptic patients and in overdoses with drugs capable of causing convulsion or dysrhythmias. Also, we believe that aminophylline is useful in those BZD-intoxicated patients

with coincident respiratory depression or underlying COPD and asthma.

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