

Successful management of bupropion poisoning: Possible benefit of acidosis treatment

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ABSTRACT

Bupropion is used as an antidepressant and smoking cessation aid. It has been described in the literature as a norepinephrine-dopamine reuptake inhibitor and is also a nicotinic antagonist. Bupropion itself is not a common cause of intoxication cases seen in Emergency Department (ED). The most important side effect is an increase in risk for epileptic seizures. We aimed to present the management of a 29-year-old female patient in ED with epileptic seizures and acidosis due to bupropion intoxication, who had taken 30 bupropion 150 mg tablets and 16 fluoxetine 20 mg tablets for suicidal purpose. According to her blood gas counts sodium bicarbonate therapy was begun in ED and after having response to the treatment was continued in intensive care unit. She was discharged three days later without any other seizures and complications. Although bupropion intoxication is rare it can cause severe metabolic acidosis and epileptic seizures. There is no specific antidote therapy to bupropion so symptomatic therapy still have benefit.

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Introduction

Bupropion is a unicyclic aminoketone antidepressant, which is lipophilic at a high rate. Bupropion is a selective reuptake inhibitor of noradrenaline, dopamine and serotonin [1, 2]. Bupropion is currently used in the treatment of major depression and smoking cessation [3]. In addition to being effective in depression treatment. Bupropion was approved by the Food and Drug Administration (FDA) in 1997 for smoking cessation treatment, and was the first non-nicotine pharmacological agent [3]. Bupropion lowers the seizure threshold [1, 4]. Therefore, bupropion can cause seizures at therapeutic doses. Seizures are thought to be the most likely side

effects in bupropion overdose [5]. In cases of overdose of bupropion, acidosis treatment may be effective [6]. The main recommendation in most reported cases is that early recognition and treatment of shock and metabolic acidosis together with the intensive care therapy of the neurological effects are essential. Our recent experience of a 29-year-old female who had ingested 4500 mg of bupropion and expected to have a fatal outcome, showed that early gastric lavage with serum physiologic solution, oral activated charcoal and intravenous sodium bicarbonate treatment contributed to survival.

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Case Presentation

A 29-year-old female was found unconscious at home by her husband. While being brought to hospital, she experienced a generalized tonic clonic seizure in the ambulance. 10 mg midazolam was given in ambulance Intravenously. The history revealed that 2.5 months previously, the patient had consulted a psychiatrist because of complaints of introversion, insomnia and lack of enjoyment of life and treatment was started of slow-release bupropion 150 mg/day and fluoxetine 20 mg/day. It was reported that 2 hours before the patient was found unconscious at home by her husband, she had been normal. From the history supported by the empty medicine packages brought by her husband, it was determined that approximately 3 hours previously, the patient had taken 30 bupropion tablets plus 16 fluoxetine (20 mg) and 10 tablets containing alverine citrate and simethicone. On presentation, the blood pressure measurement was 100/60 mmHg, pulse was 143/min, temperature was 36.6°C and SO₂: 99%. ECG was consistent with sinus tachycardia. Gastric lavage and active charcoal were applied. The patient arrived in the Emergency Department (ED) at 05:02 and the first blood gas was taken at 05:11. Meanwhile, the patient experienced a generalized tonic clonic seizure. Diazepam IV 10 mg was applied at the dose of 0.15 mg/min/kg in bolus form and 18 mg/kg phenytoin. Blood gas results were determined as pH: 7.00 and HCO₃: 10.6. As the patient had metabolic acidosis, firstly 100 meq

NaHCO₃ (2 meq/kg) was administered IV and a maintenance dose of 120 meq NaHCO₃ IV infusion was administered in 6 hours. A total of 2000 cc 0.9% NaCl was administered to the patient.

During the treatment, the patient experienced a second seizure at 07:15 and a second 10 mg IV diazepam bolus was administered. Under observation in the ED, a third seizure occurred at 11:30. A total of five seizures had the patient experienced, three of those were in ED. Detailed seizure intervals are on Table 1. The patient was observed neurologically normal after seizures and any kind of respiratory distress did not occur. Blood gas values taken at 18:03 and subsequently were seen to be within the normal range (Figure 1). No other seizure occurred during follow-up of the patient.

No pathology was observed on computed brain tomography. No abnormality was determined in the full blood count or biochemical parameters. It was thought that the generalized tonic clonic seizures of the patients could be associated with the slow-release Bupropion and fluoxetine. The patient responded to the NaHCO₃ treatment given in the ED and was admitted to the Internal Medicine Intensive Care Unit. On the 3rd day, the patient was discharged. During a 3-month follow-up period, the patient experienced no further seizures. On the magnetic resonance imaging (MRI) and electroencephalography (EEG) follow-up examinations, the results were normal. We obtained written informed consent from the patient.

Table 1. Seizure, location, happening time and blood gases results.

Seizure	Location	Time	Time to take Blood gases	pH
1 st	Home	04:30 AM Patient was found fainted. According to her husband she has a tonic clonic seizure.	-	Unknown
2 nd	Ambulance	04:48 AM According to ambulance health worker, she has a tonic clonic seizure.	-	Unknown
3 rd	ED	05:11 AM Generalized tonic clonic seizure	07:11 AM	7.02
4 th	ED	07:15 AM Generalized tonic clonic seizure	07:24 AM	7.17
5 th	ED	11:30 AM Generalized tonic clonic seizure	11:43 AM	7.18

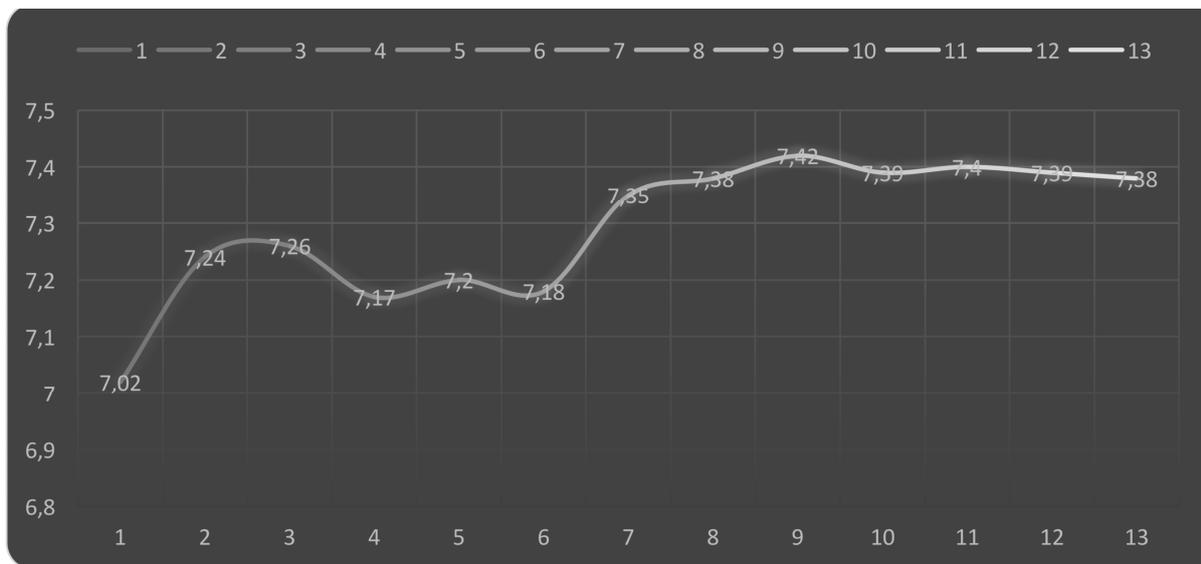


Figure 1. The pH (power of hydrogen) curve of the blood gases taken during the follow-up of the patient. The figure was formed from the results of 13 blood gases taken during follow-up.

Discussion

The transformation of bupropion to the active metabolite hydroxy bupropion has been shown to be related to cytochrome CYP2B6 [3]. There is a potential interaction between bupropion and drugs affecting CYP2B6 isoenzyme (carbamazepine, rifampicin) [3]. Bupropion also inhibits the anti-arrhythmic and anti-psychotic metabolizing CYP2D6 isoenzyme activity of some antidepressants (tricyclic

and SSRI) [3, 7]. Care must be taken with the use of these drugs and bupropion together, and when they are used together the dose should be kept in the possible lowest dose. The current case had taken these two drugs together with the aim of committing suicide. As a result of a seizure, the patient was taken to the ED. Patients presenting at the ED because of seizure must be questioned in respect of medications used and overdose. In these types of cases, blood gas measurements are extremely helpful.

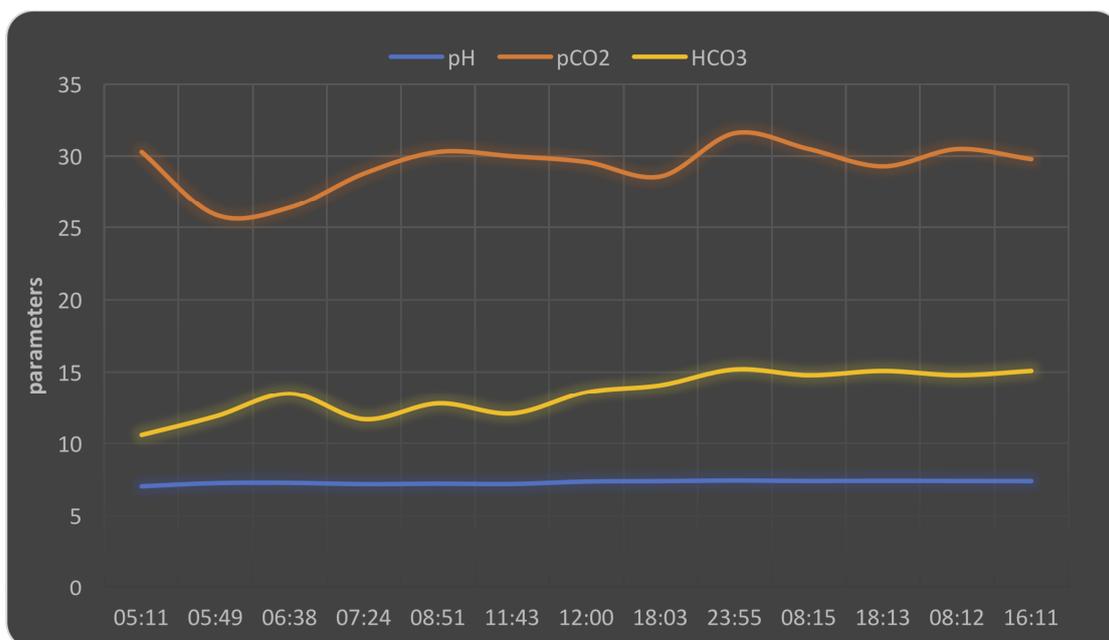


Figure 2. The times at which blood gas measurements were taken and the changes during the follow-up of the patient. The figure was formed from the results of 13 blood gas taken during follow-up. (pH: Power of hydrogen, pCO₂: partial pressure of carbon dioxide, HCO₃⁻: bicarbonate.). Time at blood gases were measured; (First day; 05:11, 05:49, 06:38, 07:24, 08:51, 11:43, 12:00, 18:03, 23:55), (Second day; 08:15, 18:13), (Third day; 08:12, 16:11).

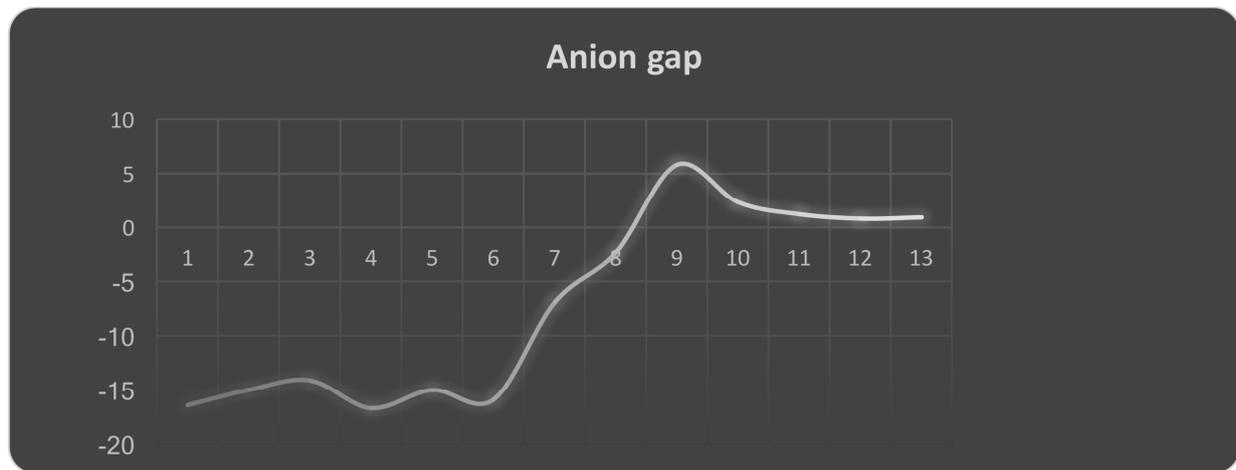


Figure 3. The base deficit curve in the blood gases taken during the follow-up of the patient. The figure was formed from the 13 blood gas results taken during follow-up.

The etiology of spontaneous seizures is not known completely. GABAergic mechanisms primarily have been invoked for the generalized inhibition [8]. Endogenous adenosine release and actions on purinergic receptors have been implicated as well [9]. One intriguing line of speculation involves modulation of ion channels by protons a notion supported by long-standing historical observations that neuronal activity and seizures can reduce brain pH [10].

Bicarbonate should be given at an arterial blood pH of ≤ 7.0 . The amount given should be what is calculated to bring the pH up to 7.2. The urge to give bicarbonate to a patient with severe acidemia is apt to be all but irresistible. Metabolic acidosis is an acid-base disorder characterized by a primary consumption of body buffers including a fall in blood bicarbonate concentration. The optimum extracellular pH for all physiologic mechanisms and organ functions is 7.4. By contrast, intracellular pH is approximately 7.1 in virtually every tissue studied. Many diverse mechanisms are in place to maintain both extracellular and intracellular pH within this very narrow range. Deviations from normal pH will obviously decrease the efficiency of all reactions, although the degree will vary depending on the specific event. For example, whereas acidemia protects the central nervous system against seizures, it sensitizes the myocardium to arrhythmias. Because we do not measure intracellular pH, we have to use extracellular pH (arterial or venous) as a surrogate. Most authorities in acid-base physiology would give bicarbonate to a patient with an arterial pH < 7.1 . In some patients, only a small amount of bicarbonate may be required [11].

In the current case, it was determined that all the seizures occurred when the pH value was < 7.2 (Figures 1 and 2). In cases of deep acidosis, the

necessary treatments should be given without any loss of time. It is extremely important that repeated blood gas measurements are taken during follow-up. Not only the pH value, but also the pCO₂, base deficit and HCO₃ levels are helpful in the follow-up of treatment [3]. In cases of Bupropion overdose, acidosis treatment can be useful [6]. It was also seen in the current case that with an improvement in the base deficit, no further seizures occurred (Figure 3).

At approximately 3 hours after ingestion, bupropion reaches an effective plasma concentration and the elimination half-life is approximately 21 hours [1, 12]. Bupropion maximum plasma concentration of around 140 g/L is reached approximately 3 hours after oral ingestion of 150 mg. In a study by Spiller et al. [13] of 4 autopsy cases, the bupropion level was found to be 3.1-20 mg/L.

In terms of the patient prognosis, the time from taking the drug to arrival at the ED is extremely important. The current case presented at the ED after 3 hours. Bupropion is dependent on plasma proteins at the rate of 85% [3, 14]. The therapeutic treatment margin of bupropion is very narrow. In 21% of patients who have taken a high dose, seizure activity is observed [12]. As this side-effect is related to the pharmaceutical form of the drug and the dose, the slow-release form was produced in 2003 to be able to reduce this side-effect [7, 14]. It has been reported in literature that seizures are very rarely seen with this form. When necessary, follow-up should be made in intensive care units until stabilization of seizures is achieved. In the current case, follow-up was applied for 2 days in intensive care and for one day in the clinic. Intensive care stays preferred due to observe possible aspiration risk during metabolic acidosis. The patient at last was removed to clinic and then was

discharged the next day.

The most frequently seen side-effects of bupropion are insomnia (34%-42%), headache (26%) and mouth dryness (10%) [1, 14]. Rashes, nausea, excessive sweating, tinnitus and hypertension (especially in patients with underlying hypertension) are also seen [15]. The use of bupropion is contraindicated in those using monoamine oxidase inhibitor (MAOI) and in those with anorexia or bulimia, head trauma or a family history of epileptic seizures [14]. In our case, we used to benzodiazepines for treatment seizures. Because; benzodiazepines are the first medications to be used and are the seizure of treatment. They function by stimulating GABA receptor subunits. This leads to the inhibition of chloride through the channel with neurotransmission induced hyperpolarization of resting membrane [16]. At high levels, benzodiazepines function in similar to phenytoin [16].

Due to the rapid and continuous release form of bupropion, there is a high rate of correlation between the dose and risk of seizure. In study of mice by Silverstone et al. [17], seizures occurred in 40 of 120 mice. There is the potential to reduce the seizure threshold associated with the dose by combined use with tricyclic antidepressants (TCA) and MAOI [17]. When prescribing these drugs, other drugs with which there can be an interaction must not be prescribed. In patients with the potential for suicide, care must be taken in the use for smoking cessation.

Conclusion

Although bupropion intoxication is a rarely encountered event, it can lead to severe metabolic acidosis and seizures. As there is no specific antidote treatment, a symptomatic approach provides benefit to these patients. It is important to monitor the patient's blood gases. Bicarbonate treatment is effective for patients who have experienced a seizure. In literature, benefit has been shown from lipid treatment in bupropion intoxication. With this case report, by showing that bicarbonate treatment could be useful in bupropion intoxication, it was aimed to make a contribution to literature. There is a need for further research to be able to fully explain the effects on the brain.

Informed consent

Written informed consent was obtained from the patient for the publication of this case report.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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