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A Case of Bupropion Overdose in Intensive Care Unit

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Abstract: Cigarette smoking is one of the most common causes of preventable mortality. Bupropion is a new-generation monocyclic antidepressant used orally in the treatment of depression, seasonal affective disorder and smoking cessation. It is known to function by inhibiting dopamine and norepinephrin uptake. Its potential effect in reducing nicotine dependence was discovered by chance. Bupropion is the first non-nicotine agent approved by the FDA in smoking cessation. The clinical effects following overdosing occur primarily in the neurological, cardiovascular and gastrointestinal systems. In addition to these systems, it can cause potentially life-threatening psychiatric side-effects such as suicidal ideation, agitation, psychosis and mania. The purpose of this report is to describe the psychiatric side-effects in therapeutic doses and excessive doses of bupropion.
Keywords: Bupropion, hallucination, overdose, cigarette cessation.

INTRODUCTION

Approximately 4.5 million people a year die from smoking-related diseases [1]. Cigarette smoking is one of the most common causes of preventable mortality. Smoking cessation treatments are supported by such different methods as psychotherapy techniques, patient education, group therapies and pharmacological therapies [2, 3].

Bupropion is a new-generation monocyclic antidepressant used orally in the treatment of depression and seasonal affective disorder and in smoking cessation. The potential effect of this drug, which is being increasingly used for the purpose of smoking cessation, in reducing nicotine dependency was discovered by chance **[**4,5**]**. First-stage non-nicotine treatments approved for use in nicotine dependency are bupropion and varencicline **[**6**]**. While the mechanism involved in the pharmacological effects of bupropion are unclear, it is known to function by inhibiting dopamine and norepinephrin uptake. It has no effect on serotonin reuptake **[**7**]**. Bupropion significantly extends intervals between cigarettes and has been licensed for that purpose **[**8**]**. Since the drug has begun being widely used across the world, its psychiatric and other undesirable side-effects have begun attracting attention and being taken seriously by physicians prescribing it **[**4**]**. The immediate release (IR), sustained release (SR) and extended release (XL) forms of bupropion are available as the brands Wellbutrin® and Zyban®. The purpose of this report is to describe the psychiatric side-effects in therapeutic doses and excessive doses of bupropion.

CASE REPORT

A 21-year-old woman was brought to the emergency department due to loss of consciousness. We learned that four days previously she had been prescribed 30 tablets of 150 mg bupropion (Wellbutrin XL®) for the purpose of quitting smoking, and that as advised by her physician she had taken 150 mg for the first 3 days and 300 mg bupropion on the 4th day. The patient had no psychiatric disease in her own or family histories. On the 4th day of drug use, depressive behavior, sleep disorder, gastric burning and acidity, weakness, clumsiness, tremor, sweating, dizziness, feelings of faintness and auditory hallucinations developed. Auditory hallucinations suggesting that she needed to take the entire drug and would feel better if she did so developed. In that state, the patient accidentally and not fully consciously took the entire content of the drug in the box. She was subsequently found unconscious at home and brought to the emergency department. Active charcoal therapy was initiated in the emergency department, but the patient was transferred to intensive care due to the risk of respiratory depression and potential mechanical ventilator requirement.

On admission to intensive care her vital findings were stable and Glasgow Coma Score (GCS) was 9. Serum electrolytes and other biochemical parameters were normal. No rhythm disturbance or conduction defects were encountered at electrocardiography. Temporary memory loss involving a 24-h period after drug intake was determined at

subsequent evaluation. We learned that approximately 2-3 h had passed between drug ingestion and admission to the emergency department. During monitoring, her general condition improved and no complications involving the neurological, cardiac or other systems were observed. Following consultation with the psychiatry department the patient was discharged on the 36th hour of hospitalization.

DISCUSSION

Bupropion, an antidepressant drug, was approved by the Food and Drug Administration (FDA) in 1997 for the purpose of helping adult smokers quit. Bupropion is the first non-nicotine agent approved by the FDA for smoking cessation [9].

The chemical structure of bupropion differs from those of selective serotonin reuptake inhibitors (SSRI), cyclic antidepressants and other agents typically used in the treatment of depression. In contrast to other antidepressants on the market, bupropion has a monocyclic aminoketone structure. Its chemical structure resembles that of diethylpropion, a sympathomimetic amine and appetite inhibitor. Bupropion has been determined to cause less weight gain in patients quitting smoking compared to other antidepressants. It also causes less sexual dysfunction [4].

Bupropion has been shown to have 3 active metabolites, hydroxybuprion, trihydrobupropion and erythrohydrobupropion. Bupropion and its active metabolites enter into an advanced biotransformation and conjugation process for the production of meta-chloro hippuric acid, a major urine metabolite [10]. The use of various non-nicotine drugs other than bupropion (doxepin, fluoxetine, dexfenfluramine, buspirone, mecamylamine, clonidine, naloxone, naltrexone, moclobemide and nortriptyline) in smoking cessation has been investigated. However, the data obtained regarding the effects of these agents in smoking cessation are insufficient and their use has not been officially approved [9, 11].

The effectiveness of bupropion increases in line with the dosage used [12]. No significant difference has been determined in responses to bupropion between males and females [11]. The use of bupropion in smoking cessation involves an initial dose of 150 mg/day for the first 3-5 days followed by a maintenance dose of 300 mg/day. The daily dosage must not exceed 300 mg [10, 11]. Our patient used 150 mg/day for the first 3 days, and symptoms began on the 4th day, when she ingested 300 mg/day.

The peak effect of bupropion is 1-3 hours, and its half-life is 12 hours. Absorption by the gastrointestinal system is good, and it is metabolized in the liver [4, 5]. Our patient was brought to the emergency department within 2-3 hours after ingesting an excessive dose. Predicting that the effect of the drug with its 12-hour half-life would continue, she was transferred to intensive care due to the risk of respiratory depression and to prevent other potential complications.

Side-effects of the drug, reported to be significantly higher compared to placebos in studies, include sleeplessness, headache and xerostomia [12]. Other side-effects include nausea, vomiting, weight and appetite changes, sensitivity to light, hyperglycemia, hypoglycemia, syndrome of inappropriate antidiuretic hormone secretion syndrome (SIADH) and tremor. In addition to severe psychiatric side-effects such as suicidal ideation, agitation, psychosis and mania, epileptic seizures that may occur at therapeutic or excessive doses may be life-threatening [5]. It has been suggested that a drug with a sympathomimetic amine structure may release catecholamine in the central nervous system and cause hypothalamic stimulation. This mechanism may be partly responsible for the seizures seen in cases of bupropion overdose. Convulsion is one of the described risks in bupropion use and may be seen at both therapeutic doses and in cases of overdose [13]. No convulsion occurred in our case, but depressive behaviors sleep disturbance, gastric burning and acidity, weakness, clumsiness, tremor, sweating, dizziness, stupor and feelings of faintness beginning on the 4th day of drug use are compatible with the side-effects of the drug. Auditory hallucinations to the effect that she would recover if she took the entire drug, rather than suicidal ideation, also occurred.

Very few data are available concerning the combined use of bupropion and other drugs. In addition, there is a possibility of interaction between bupropion and drugs that affect the CYP2B6 isoenzyme. Additionally, bupropion inhibits the activity of the CYP2D6 isoenzyme that metabolizes some antidepressants (tricyclic and SSRI), ß-blockers, antiarrhythmics and antipsychotics. Care is required over the use of such drugs together with bupropion, and the dose interval should be kept at the lowest level when such drugs are used in combination [10]. There was no known additional disease in our case, and she was using no additional drugs.

Clinical effects following bupropion overdose develop primarily in the neurological, cardiovascular and gastrointestinal systems. Neurological effects may include tremor, agitation, hallucination, epileptic convulsion, confusion and coma. Tachycardia and conduction disorders may be seen in the cardiovascular system. Nausea and vomiting may be seen in the gastrointestinal system [13, 14]. In clinical studies

involving smoking cessation, three patients used excessive doses (3000 mg, 3600 mg and 'a handful'), a small number patients have experienced epileptic seizures, while other symptoms including blurred vision, confusion, numbness, nausea and visual hallucinations have been observed. All patients recovered without sequelae **[**10**]**. A standard approach depending on type of drug and time of intake is applied in the emergency department in cases of overdose. Supportive therapy is also employed. Active charcoal may be given to patients who present soon after consumption. Our patient arrived within 2-3 after drug consumption and received active charcoal therapy in the emergency department. Since no laboratory test permitting the measurement of serum bupropion levels is available in our hospital, serum drug levels could not be determined. Our patient ingested 4050 mg bupropion, and stupor, auditory hallucinations and confusion were observed. The patient was admitted in an unconscious state, but her clinical condition resolved entirely following active charcoal and supportive therapy in the emergency department.

CONCLUSION

Bupropion is a drug widely used for pharmacological support in the treatment of depression and smoking cessation. In addition to neurological and cardiac side-effects, psychiatric side-effects that may develop at therapeutic doses in individuals with no underlying psychiatric disease may be life-threatening. Greater care and awareness are essential on the subject of psychiatric and other undesirable side-effects of a drug that is being increasingly used in clinical practice.

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