

Seizures induced by recreational abuse of bupropion tablets via nasal insufflation

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ABSTRACT

Bupropion is a newer generation antidepressant that is commonly used for treatment of depression and for smoking cessation. Seizures are a frequently reported adverse effect of bupropion in therapeutic oral doses; however, there are limited data about the consequences of nasal insufflation of bupropion. We report the case of a patient who presented to the emergency department (ED) with a recent history of generalized tonic-clonic seizures whose etiology was initially a diagnostic mystery. After an initial visit to another ED, the patient presented to our ED later that day with a recurrence of the seizures after crushing and nasally insufflating oral bupropion tablets. We review important implications of this case to emergency medicine, including the potential for abuse of bupropion, the difference between intranasal and oral administration, the changing trends in the etiology of drug-related seizures and the importance of examining the nares in patients with unexplained seizure and delirium.

Keywords: bupropion, seizure, nasal insufflation, nares

RÉSUMÉ

Le bupropion est un antidépresseur de génération récente qui est utilisé couramment pour la prise en charge de la dépression et du sevrage tabagique. Les crises convulsives sont un effet indésirable fréquent du bupropion à dose thérapeutique administrée par voie orale. Par contre, il existe peu de données sur les conséquences de l'inhalation nasale de ce médicament. Nous présentons le cas d'un patient qui s'est présenté à l'urgence après avoir récemment fait des crises tonico-cloniques généralisées dont le diagnostic étiologique était initialement un mystère. Après une première visite à un autre service d'urgence, le patient s'est présenté à notre urgence plus tard dans la journée, ayant fait d'autres crises convulsives après avoir broyé et inhalé par le nez des comprimés de bupropion pour administration orale. Nous passons en revue les répercussions importantes de ce cas pour la médecine d'urgence, y compris le potentiel d'usage abusif

du bupropion, la différence entre l'administration intranasale et orale, l'évolution des tendances dans l'étiologie des crises convulsives liées à la consommation de drogues ainsi que l'importance d'examiner les fosses nasales chez les patients présentant des crises convulsives et un délire inexpliqués.

INTRODUCTION

Bupropion is a newer generation antidepressant of the aminoketone class that is currently approved by the US Food and Drug Administration (FDA) and Health Canada for treatment of depression and for smoking cessation.

Bupropion-induced seizures in therapeutic oral doses have been well described in safety surveillance data and case reports. There is limited information, however, about the consequences of nasal insufflations of bupropion, known colloquially as “snorting.” To our knowledge, this is the first report in the emergency medical literature of seizures induced by nasal insufflation of bupropion.

CASE REPORT

A 38-year-old man presented to an emergency department (ED) after having a witnessed seizure at a transition home. Upon arriving in the ED, the patient had a 20-second generalized tonic-clonic seizure witnessed by the ED medical staff. The seizure spontaneously resolved, and he was given 5 mg of intravenous diazepam and loaded with 1 g of intravenous phenytoin over 1 hour.

During the seizure in the ED, the patient bit his tongue, but experienced no incontinence. There was no history of head trauma. He had had a similar episode of seizure the previous evening and described having

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seizures approximately once per month over the previous several months. A noncontrast computed tomography scan of the head obtained 2 months before the seizure episode had been interpreted as normal. The patient had no fever, headache, nausea, vomiting or focal weakness. He denied the use of alcohol or other recreational drugs. His medical history was significant for diabetes, bipolar affective disorder and posttraumatic stress disorder. His medications included glyburide, metformin, olanzapine and bupropion.

On examination, the patient was afebrile, heart rate was 111 beats/min, blood pressure was 136/64 mm Hg, respiratory rate was 18 breaths/min and oxygen saturation was 96% on room air. His bedside glucose was 16.2 mmol/L, his Glasgow Coma Scale score was 15, his pupils were equal and reactive to light, his speech was normal and there were no focal neurologic deficits. Of note, inspection of his nasal cavity was omitted. The rest of the physical examination was unremarkable.

His serum biochemistry was normal, apart from the mildly elevated blood glucose. After 2 hours of monitoring, he was discharged back to his transition house with oral phenytoin and a follow-up appointment with the hospital epilepsy clinic.

Later that day, he presented to our ED after experiencing 2 more witnessed seizures at his transition home. The paramedics found him with a number of crushed blue pills and blue powder on his fingers and nose. He had no further seizures during this ED visit. He disclosed that he had crushed 15 bupropion SR (sustained release) 100 mg tablets and insufflated them before these 2 seizures. He also disclosed having done the same thing that morning, resulting in his earlier ED visit. He had recently been released from prison and reported that he had learned about bupropion insufflation during his incarceration, where that type of substance abuse was commonplace. He claimed that it provided him with a chemical euphoria similar to that attained from cocaine. He had last used cocaine 4 months before and denied current use of alcohol or other recreational drugs.

On examination, he was afebrile, his heart rate was 115 beats/min, his blood pressure was 120/92 mm Hg, and he had a respiratory rate of 18 breaths/min and an oxygen saturation of 96% on room air. His bedside glucose was 9.2 mmol/L, his Glasgow Coma Scale score was 15, his pupils were equal and reactive to light, his speech was normal and there were no focal neurologic deficits. The rest of the physical examination was unremarkable.

Serum biochemistry was normal, his serum toxicol-

ogy screen was negative and his serum phenytoin level was 49 $\mu\text{mol/L}$, within therapeutic range. A urine toxicology screen was not done, and bupropion levels were not available. He was given 2 mg of intravenous lorazepam, monitored in the ED for 3 hours, counseled to stop abusing bupropion and discharged back to his transition home.

DISCUSSION

Bupropion hydrochloride is structurally similar to amphetamines and is a weak catecholamine reuptake inhibitor predominantly affecting serotonin, norepinephrine and dopamine. Its exact antidepressant mechanism is unknown; however, it is presumed to be related to its dopaminergic and noradrenergic effects in the brain.¹ This case illustrates 3 important points: the potential for abuse of bupropion, the differences between intranasal versus oral administration and the importance of examining the nares, and the changing epidemiology of drug-related seizures.

Potential for abuse

Because of its structural similarities to amphetamines, the stimulant effects of bupropion have been studied. Early research demonstrated that stimulant effects in rodents manifested as increased spontaneous activity.^{2,3} Griffith and colleagues⁴ compared oral bupropion with oral amphetamine to determine its abuse potential and found that the physiologic effects of oral bupropion were not significantly different from placebo for producing stimulant effects. Others have compared oral bupropion with oral amphetamine and oral amitriptyline and found that oral bupropion did not produce any physiologic stimulant or sedative effects.⁵ In patients with a history of substance abuse, however, 400-mg oral doses produced mild, stimulant-like subjective changes.⁶ Our patient described a chemical euphoria similar to that attained from cocaine after the insufflation of bupropion.

Bupropion is not a controlled medication, and the FDA deems it to have a low risk for abuse if taken in recommended daily divided dosages. The increasing use of intranasal bupropion, gabapentin, quetiapine, trihexyphenidyl and tricyclic antidepressants (TCAs) has been reported in prison populations.⁷ The crushing of oral medications and subsequent insufflation has also been described with methylphenidate.⁸ Interestingly, our patient disclosed that he had learned this method of

bupropion administration during his incarceration. Bupropion was widely ordered as a smoking deterrent for inmates after Correctional Services of Canada attempted to ban smoking in all its security facilities in 2008 (Dr. Al McBride, Medical Director, Kingston Penitentiary Regional Hospital, Kingston, Ont.: personal communication, 2009). Physicians prescribing bupropion should consider the possibility of alternative methods of administration in groups at risk for misuse of medications.

Intranasal versus oral administration

A MEDLINE search using the keywords “bupropion” and “insufflations” identified 3 letters to the editor that reported bupropion insufflation with 2 cases that resulted in seizures.^{9–11} Bupropion-induced seizures have been well described and have been reported to occur in about 0.35% to 0.44% of all patients taking oral bupropion for depression at a dose of 450 mg/d or less.^{12,13} This risk is considered acceptable, but seizures have been documented with single doses ranging from 575 mg to 23 000 mg.^{14–16} Although bupropion’s effect of lowering the seizure threshold appears to be dose-dependent, researchers have described a group of 46 patients with a mean ingestion of 2148 mg who did not have a seizure.¹⁴ It seems that some individuals are genetically more susceptible to bupropion-related seizures.

The pharmacokinetics of bupropion have only been described with oral administration. We were unable to find any data that determined the rate of nasal absorption, but various drugs are efficacious after intranasal administration, including triptans, midazolam,¹⁷ cocaine, epinephrine and fentanyl. Furthermore, the nasopharynx offers a highly vascularized surface area for systemic drug absorption, direct entry into the brain and neuronal transport along the olfactory bulb.¹⁸

For bupropion insufflation to cause seizure, significantly elevated levels of bupropion in the cerebrospinal fluid (CSF) would be required. After oral administration, bupropion is rapidly absorbed and approximately 95% of the dose undergoes extensive first-pass hepatic metabolism, primarily by cytochrome P450 2B6, before being distributed throughout the rest of the body.¹⁹ Nasal insufflation can be expected to deliver the drug to the body and CSF before circulating through the liver, thus bypassing its first-pass metabolism and resulting in higher plasma concentrations. Consequently, ED physicians should examine the nares for powder in patients with unexplained seizure and delirium.

Drug-related seizures

Seizures are a serious complication associated with medication or drug use. Medications and drugs are an important consideration in the differential etiology of new-onset seizure, and 6.1% of new-onset seizures²⁰ and up to 9% of cases of status epilepticus²¹ are estimated to be drug-related. A retrospective analysis of data from a regional poison centre 20 years ago reported that the leading causes of drug-induced seizures at that time were TCAs, cocaine and other stimulants.²²

Because of evolving prescribing patterns and changes in patterns of drugs of abuse, the epidemiology of drug-induced seizures has also changed. A retrospective study of data from a state poison centre system in 2003 found that the leading causes of drug-induced seizures were bupropion, diphenhydramine and TCAs. The overall incidence of antidepressant-induced seizures has increased despite a decreasing trend of TCA-induced seizures. This was attributed to the large contribution of bupropion-induced seizures.²³ Other drugs like tramadol and venlafaxine have emerged as important causes as well.²³ A retrospective study of new-onset generalized seizures presenting to an ED demonstrated that, of drug-related seizures, the most common causes were cocaine, benzodiazepine withdrawal and bupropion.²⁰ These studies clearly demonstrate a shift in the etiology of drug-induced seizures of which ED physicians should be aware. Unfortunately there is no role for bupropion plasma levels, as levels have not correlated well with either therapeutic effect or incidence of seizures.^{12,24}

Phenytoin is often cited as the second-line agent in the treatment of status epilepticus, but it has not been found to be commonly useful in the management of drug-induced seizures.²⁵ Based on the timeline of seizure after bupropion insufflation in our case, phenytoin therapy should not have been given, as the seizures were likely drug-induced.

Limitations

There are several limitations to our conclusions about this case. The association between bupropion insufflation and our patient’s seizures does not prove causality. Furthermore, we have been forced to rely on the patient’s self-reported history and collateral history from the paramedics to confirm that bupropion insufflation took place. We did not perform a urine toxicology screen; if we had a urine toxicology screen positive for bupropion and its metabolites, our case presentation

would be stronger. Based on the timeline between bupropion insufflation and seizures, as well as the exclusion of other metabolic and intracranial etiologies for seizure, we believe it is reasonable to conclude that these seizures were bupropion-induced.

CONCLUSION

Bupropion is a newer generation antidepressant that is used increasingly for treatment of depression and for smoking cessation. Although it is generally believed to have a low potential for abuse, there are data to suggest it can cause mild, stimulant-like effects, especially if administered via nasal insufflation. This can bypass the drug's first-pass hepatic metabolism, resulting in higher plasma and CSF concentrations. Emergency physicians should be aware of this method of administration, especially among groups at risk for misuse of medications, and should examine the nares for powder residue. Finally emergency physicians should be aware of changing trends in the etiology of drug-related seizures, especially in the sense that bupropion and other newer drugs, like tramadol and venlafaxine, have emerged as common causes of drug-induced seizures.

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REFERENCES

1. Preskorn SH, Othmer SC. Evaluation of bupropion hydrochloride: the first of a new class of atypical antidepressants. *Pharmacotherapy* 1984;4:20-34.
2. Cooper BR, Hester TJ, Maxwell RA. Behavioral and biochemical effects of the antidepressant bupropion: evidence for selective blockade of dopamine uptake in vivo. *J Pharmacol Exp Ther* 1980;215:127-34.
3. Soroko FE, Mehta NB, Maxwell RA, et al. Bupropion hydrochloride: a novel antidepressant agent. *J Pharm Pharmacol* 1977;29:767-70.
4. Griffith JD, Carranza J, Griffith C, et al. Bupropion clinical assay for amphetamine-like abuse potential. *J Clin Psychiatry* 1983;44:206-8.
5. Peck AW, Bye CE, Clubley M, et al. A comparison of bupropion hydrochloride with dexamphetamine and amitriptyline in healthy subjects. *Br J Clin Pharmacol* 1979;7:469-78.
6. Miller L, Griffith J. A comparison of bupropion, dextroamphetamine, and placebo in mixed-substance abusers. *Psychopharmacology* 1983;80:199-205.
7. Del Paggio D. Psychotropic medication abuse in correctional facilities. *Bay Area Psychopharmacol Newsletter* 2005;8:1-6.
8. Babcock Q, Byrne T. Student perceptions of methylphenidate abuse at a public liberal arts college. *J Am Coll Health* 2000;49:143-5.
9. Hill S, Sikand H, Lee J. A case report of seizure induced by bupropion nasal insufflation. *Prim Care Companion J Clin Psychiatry* 2007;9:67-9.
10. Khurshid KA, Decker DH. Bupropion insufflation in a teenager. *J Child Adolesc Psychopharmacol* 2004;14:157-8.
11. Welsh CJ, Doyon S. Seizure induced by insufflation of bupropion. *N Engl J Med* 2002;347:951.
12. Davidson J. Seizures and bupropion: a review. *J Clin Psychiatry* 1989;50:256-61.
13. Johnston JA, Lineberry CG, Ascher JA, et al. A 102-center prospective study of seizure in association with bupropion. *J Clin Psychiatry* 1991;52:450-6.
14. Spiller HA, Ramoska EA, Krenzelok EP, et al. Bupropion overdose: a 3-year multi-center retrospective analysis. *Am J Emerg Med* 1994;12:43-5.
15. Storrow AB. Bupropion overdose and seizure. *Am J Emerg Med* 1994;12:183-4.
16. Harris CR, Gualtieri J, Stark G. Fatal bupropion overdose. *J Toxicol Clin Toxicol* 1997;35:321-4.
17. Wermeling DP, Record KA, Archer SM, et al. A pharmacokinetic and pharmacodynamic study, in healthy volunteers, of a rapidly absorbed intranasal midazolam formulation. *Epilepsy Res* 2009;83:124-32.
18. Graff CL, Pollack GM. Nasal drug administration: potential for targeted central nervous system delivery. *J Pharm Sci* 2005;94:1187-95.
19. Bryant SG, Guernsey BG, Ingram NB. Review of bupropion. *Clin Pharm* 1983;2:525-37.
20. Pesola GR, Avarsarala J. Bupropion seizure proportion among new-onset generalized seizures and drug related seizures presenting to an emergency department. *J Emerg Med* 2002;22:235-9.
21. Lowenstein DH, Alldredge BK. Status epilepticus at an urban public hospital in the 1980s. *Neurology* 1993;43:483-8.
22. Olson KR, Kearney TE, Dyer JE, et al. Seizures associated with poisoning and drug overdose. *Am J Emerg Med* 1994;12:392-5.
23. Thundiyil JG, Kearney TE, Olson KR. Evolving epidemiology of drug-induced seizures reported to a poison control center system. *J Med Toxicol* 2007;3:15-9.
24. Preskorn SH. Antidepressant response and plasma concentrations of bupropion. *J Clin Psychiatry* 1983;44:137-9.
25. Kunisaki T, Augenstein W. Seizures. In: Ford M, DeLaney K, Ling L, et al., editors. *Clinical toxicology*. 1st ed. Philadelphia (PA): WB Saunders; 2001. p. 155-67.

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