Case Report

Bupropion-Induced Erythema Multiforme

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The high rate of dermatologic adverse effects associated with bupropion use may extend to its sustained-release preparation, currently prescribed extensively for smoking cessation as well as for treatment of depressive conditions. We report what we believe to be the first case, in a 31-year-old woman, of erythema multiforme after administration of sustained-release bupropion (Wellbutrin SR) for treatment of depression. This report emphasizes that prescribers must aggressively follow up their patients who have rashes or urticaria, discontinuing the medication as soon as erythema multiforme is suspected and watching closely for the emergence of potentially life-threatening dermatologic conditions.

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Bupropion has long been associated with dermatologic adverse effects. As early as 1983, Van Wyck Fleet et al[1] reported that dermatologic reactions in bupropion recipients—primarily urticarial or pruritic rashes—warranted surveillance. A study by Conners et al[2] in children aged 6 to 12 years described dermatologic reactions twice as frequently in the drug group as in the placebo group, with 4 reactions involving rash and urticaria serious enough to require cessation of bupropion treatment. McCollom et al[3] recently reported 3 cases of a bupropion-induced serum sickness–like reaction. The first 3 cases of bupropion-induced serum sickness were published in 1999,[4-6] and 2 suspected cases of erythema multiforme (EM) and 1 case of Stevens-Johnson syndrome were reported to the Canadian Adverse Drug Reaction Monitoring Program in the 3½ months after bupropion, under the brand name Zyban, was introduced in Canada in August 1998 for smoking cessation.[7] The Canadian cases are not described in detail but rather merely listed in a compendium of adverse effects associated with the Zyban introduction. A search of *Index Medicus* revealed no other reported cases.

Compared with other commonly prescribed antidepressants, bupropion appears to have a higher incidence of dermatologic adverse effects. In a 1995 review, Preskorn[8] reported a placebo-adjusted 3.7% incidence of rash and pruritus with bupropion compared with 2% for nefazodone and 1% or less for fluoxetine, paroxetine, sertraline, and venlafaxine. While bupropion data were collected by using an adverse events questionnaire rather than by relying on spontaneous patient reports, the incidence of dermatologic adverse effects is still markedly elevated.

REPORT OF A CASE

Sustained-release bupropion (Wellbutrin SR) was prescribed for treatment-resistant major depressive disorder in a 31-year-old woman. Her symptoms included depressed mood, decreased interest in activities of daily living, decreased appetite, psychomotor retardation, irritability, decreased energy, decreased concentration, and intermittent hopelessness without current suicidality. These symptoms severely impaired her routine daily functioning.

She had first presented 17 months earlier after nearly a year of depressive symptoms accompanied by intermittent suicidal thoughts without intent or plan. She described considerable stress associated with moving away from her support systems in Japan, her native country. When bupropion was started, treatment had failed with sertraline, secondary to nausea after 1 dose, and paroxetine, which she discontinued after several weeks of taking a 20-mg daily dose because of her perception that it interfered with her concentration. Her only other medication was a multivitamin. Her medical history was remarkable only for a positive Mantoux skin test and 6 months of subsequent isoniazid treatment 3 years earlier. She had no history of an eating disorder or seizure activity. She did not use tobacco products or recreational drugs, and she did not drink alcohol. She denied a family history of diagnosed depression but described a chronically unhappy mother.

She began to take sustained-release bupropion at a dose of 150 mg a day. In follow-up 15 days later, she related a slight improvement in her depressive symptoms but also

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noted some "shakiness" along with mild pruritus. Because of her tremulousness, one of us, her psychiatrist (T.W.L.), elected not to increase her dose of bupropion and planned a return visit 4 weeks hence.

One week later (day 22 of bupropion use), she presented to a physician assistant in her family practice clinic with the complaint of severe itching for 2 days and "rash" over her entire body. The physician assistant prescribed diphenhydramine, 25 mg every 6 to 8 hours as necessary, and told her to stop using an over-the-counter oatmeal bath product she had begun to use to relieve the itching.

She returned to the family practice clinic a day later with worsening symptoms. The physician who saw her advised stopping the bupropion and started hydroxyzine, 25 mg up to 4 times a day, with follow-up in 2 days.

The next day (day 24), progressively more symptomatic, she appeared in the emergency department. One of us, the consulting dermatologist (G.E.P.), noted targetoid erythematous papules and macules most numerous on the dorsal hands and feet but also present on the palms, soles, and proximal extremities. The patient had few truncal lesions and neither mucosal involvement nor bullous component to any lesion. She was afebrile and otherwise felt well. The dermatologist diagnosed EM, with biopsy deferred, both because of the lesions' classical presentation and morphology and because of the patient's preference to avoid a procedure. In the absence of a universally recommended treatment protocol, a tapering oral prednisone course (60 mg daily for a week, 40 mg daily for a week, 20 mg daily for a week) was prescribed, with the goal of limiting inflammation, and she was instructed to call immediately if mucosal or painful, tender, necrotic skin lesions developed.

Her skin lesions and itching resolved completely over the next few weeks, although she was left with postinflammatory hyperpigmentation, which had not fully faded after 8 months of follow-up. Rechallenge with bupropion was considered inappropriate.

DISCUSSION

According to Thomas,[9] Albert and Bazin first described cases of EM in 1822, but it was not until 1866 that von Hebra[10] categorized these polymorphous erythematous eruptions, labeling them erythema exudativum multiforme. Erythema multiforme is a hypersensitivity reaction, typically occurring 1 to 2 weeks after exposure to a drug or other antigenic stimulus.[11] The specific hypersensitivity mechanism appears to be a cell-mediated reaction (type IV or delayed-type hypersensitivity).[11,12] Occurring most frequently in young adults and more often in men,[9,13] EM is a spectrum disorder, with mucosal lesions occurring in 25% to 60% of cases. Lesions progress from initial erythema to edema and erosion, usually with pseudomembrane formation.[13]

The milder form, EM minor (von Hebra syndrome), is often associated with herpesvirus infection, especially EM that is recurrent, but it can also result from a drug reaction, as it did in our patient.[12] Mucosal lesions were not part of von Hebra's original description,[10] although they can occur in EM minor as mild and limited involvements of the mouth and lips.[13] Erythema multiforme major (Stevens-Johnson syndrome) is most often a drug reaction and usually presents with fever and mucosal lesions. Prodromal symptoms are rare in EM minor, but fever, malaise, headache, rhinorrhea, sore throat, and cough may precede EM major.[9]

The development of cutaneous lesions in EM usually begins symmetrically from the acral extremities proximally, especially favoring the palms, soles, and dorsal aspects of the hands and feet. Typical lesions are erythematous macules, progressing rapidly to targetoid papules with dusky centers and pink-to-red peripheries.[13] Blisters (bullae) also sometimes develop.

There is no consensus on whether EM minor can progress to EM major or even to toxic epidermal necrolysis. This last syndrome, consisting of extensive blistering and necrosis of skin, carries a mortality rate of 20% to 80% depending on the severity and areas of involvement and whether patients receive their care in a specialized burn unit. There is also disagreement about treating EM minor patients with systemic corticosteroids, since infectious complications can be fatal in severe cases, even though corticosteroids can limit severity if used early. Regardless, in order to limit severe complications, suspected culprit drugs must be discontinued as soon as EM is diagnosed, while watching for the possible emergence of even more severe potentially life-threatening dermatologic conditions.

Management includes both a discontinuation of suspect medications and a search for such common causative infectious agents as herpesvirus or mycoplasma. If systemic corticosteroids are used, 1 mg/kg is an appropriate starting dose with subsequent tapering. Symptoms of EM minor can last for up to 4 weeks, and EM major symptoms can persist for as long as 6 weeks.[13] Corticosteroid treatment is absolutely contraindicated in patients with compromised immune function or premorbid infectious processes in which further corticosteroid-induced immunosuppression could be dangerous. Tuberculosis is an example of one such particularly problematic infection.

Our patient's progression of symptoms was consistent with a mild case of EM minor induced by bupropion. There was no reason to suspect an infectious cause, and her only other medication was a multivitamin. She may have avoided a more florid presentation by discontinuation of the drug before she had reached the standard daily bupropion dose of 300 mg. The decision to discontinue

the bupropion as soon as drug eruption was suspected may have truncated the antigenic stimulation of her immune system and spared her the discomfort and risks associated with EM major. We know of no objective evidence that dose size matters in terms of intensity of EM presentation.

As bupropion is prescribed increasingly not only for depressive disorders but also for smoking cessation, we expect more reports of dermatologic adverse effects to enter the literature. All prescribers of sustained-release bupropion should take their patients' skin complaints seriously.

REFERENCES

1. Van Wyck Fleet J, Manberg PJ, Miller LL, et al. Overview of clinically significant adverse reactions to bupropion. *J Clin Psychiatry*. 1983;44(5, pt 2):191-196.
2. Conners CK, Casat CD, Gualtieri CT, et al. Bupropion hydrochloride in attention deficit disorder with hyperactivity. *J Am Acad Child Adolesc Psychiatry*. 1996;35:1314-1321.
3. McCollom RA, Elbe DH, Ritchie AH. Bupropion-induced serum sickness-like reaction. *Ann Pharmacother*. 2000;34:471-473.
4. Tripathi A, Greenberger PA. Bupropion hydrochloride induced serum sickness-like reaction. *Ann Allergy Asthma Immunol*. 1999;83:165-166.
5. Peloso PM, Baillie C. Serum sickness-like reaction with bupropion [letter]. *JAMA*. 1999;282:1817.
6. Yolles JC, Armenta WA, Alao AO. Serum sickness induced by bupropion. *Ann Pharmacother*. 1999;33:931-933.
7. Hebert S. Bupropion (Zyban, sustained-release tablets): reported adverse reactions. *CMAJ*. 1999;160:1050-1051, 1054-1055.
8. Preskorn SH. Comparison of the tolerability of bupropion, fluoxetine, imipramine, nefazodone, paroxetine, sertraline, and venlafaxine. *J Clin Psychiatry*. 1995;56(suppl 6):12-21.
9. Thomas BA. The so-called Stevens-Johnson syndrome. *BMJ*. 1950;1:1393-1397.
10. von Hebra F. On the polymorphous erythemata, I: erythema exudativum. In: Fagge CH, ed. *On Diseases of the Skin, Including the Exanthemata*. Vol 1. London, England: New Sydenham Society; 1866:285-289.
11. Dahl M. *Clinical Immunodermatology*. 3rd ed. St Louis, Mo: Mosby; 1996:327-329.
12. Zaim MT, Giorno RC, Golitz LE, Kunke KS, Huff JC. An immunopathological study of herpes-associated erythema multiforme. *J Cutan Pathol*. 1987;14:257-262.
13. Huff JC, Weston WL, Tonnesen MG. Erythema multiforme: a critical review of characteristics, diagnostic criteria, and causes. *J Am Acad Dermatol*. 1983;8:763-775.