Bupropion-Induced Delayed-Onset Anaphylaxis

To the Editor: Although bupropion-induced urticaria or angioedema are relatively rare, delayed anaphylactoid reactions to bupropion are even rarer. To our knowledge, we report the first case of bupropion-induced delayed-onset anaphylaxis.

Case report. Ms A, a 29-year-old woman with a psychiatric history significant for depression, presented to the emergency department (ED) complaining of a diffuse rash with mild difficulty swallowing and chest tightness for 1 day. She had already taken 3 doses of diphenhydramine 25 mg with no benefit. She had 1 similar episode 3 years ago while pregnant with her first child, which was determined to be caused by ondansetron. She denied any recent changes in foods, detergents, soaps, clothes, or medications or any family history of angioedema. Ms A had recently seen her psychiatrist for depression, who initiated a cross-taper by decreasing escitalopram from 20 mg daily to 10 mg daily and starting bupropion sustained-release 150 mg daily for 1 week, then increasing to 150 mg twice daily. At initial presentation to the ED, Ms A was on day 21 of bupropion therapy.

At the examination, Ms A was found to be tachycardic and nonedematous and had diffuse urticaria. There was no evidence of oropharyngeal swelling or macroglossia. She was given epinephrine, methylprednisolone, ranitidine, and diphenhydramine. During Ms A's 4-hour stay in the ED, her urticarial rash worsened, but she remained otherwise stable and was discharged on prednisone. While driving home from the ED, she became extremely pruritic, self-administered her epinephrine, and took her first dose of prednisone. She returned to the ED later that evening with shortness of breath and chills, as well as worsening of her pruritus, chest tightness, and urticarial rash. The examination was notable for hypotension, diffuse urticaria, and lower lip and anterior tongue swelling. Ms A was admitted to the intensive care unit for refractory hypotension and was maintained on intravenous fluids, methylprednisolone, diphenhydramine, ranitidine, and epinephrine as needed for throat tightness or shortness of breath. She was continued on her home regimen of escitalopram 10 mg daily and bupropion 150 mg twice daily. Laboratory workup revealed metabolic acidosis and leukocytosis. Her hypotension continued despite aggressive fluid resuscitation. The next day, Ms A's urticaria and lip swelling continued. The psychiatry department was consulted after Ms A developed some anxiety symptoms, which were eventually attributed to her frequent dosing of epinephrine.

Following completion of the initial psychiatric consultation, bupropion was discontinued (day 23 of bupropion therapy) as a possible cause of delayed anaphylactoid reaction. By the next day, her urticaria had improved significantly, and disappeared within 2 days of discontinuation of bupropion. At the same time, her leukocytosis and lactic acidosis resolved. The next day, the lip and tongue swelling had resolved, and epinephrine, diphenhydramine, and ranitidine were discontinued. She was discharged home the following day with a prednisone taper anaphylaxis kit and escitalopram. At discharge, 4 days after bupropion discontinuation, Ms A had no further symptoms and felt back to baseline.

As an effective and well-tolerated medication, bupropion has become a popular treatment for depression and smoking cessation, as well as for attention-deficit/hyperactivity disorder. As such, it is becoming increasingly important to educate patients regarding potential adverse drug reactions (ADRs), as more patients are being prescribed bupropion. According to Tripathi and Greenberger,[1] several reported ADRs associated with bupropion include agitation (32%), dry mouth (28%), headache (26%), rash (4%), pruritus (3%) and urticaria (2%). It is imperative that prescribing clinicians be aware of both common and uncommon ADRs. Even more serious ADRs, such as angioedema, delayed hypersensitivity, and anaphylactoid reactions, are documented on the bupropion product labeling.[2] These latter ADRs are rarer, and according to Tackett and Smith,[3] occur at a rate of approximately 0.1%–0.3%. Furthermore, a nationwide study performed by Hu et al[4] showed that these ADRs demonstrate a delayed onset (latency period of about 10–20 days), which was unique to bupropion when compared to other antidepressants.

To our knowledge, this is the first case report published of true bupropion-induced delayed anaphylaxis. As outlined by Tackett and Smith[3] and McCollom et al,[5] delayed anaphylactoid ADRs can include fever, arthralgia, myalgia, lymphadenopathy, pruritus, urticaria, angioedema, and dyspnea. Given that Ms A developed the latter 4 symptoms as well as refractory hypotension, we believe this case exemplifies bupropion-induced delayed anaphylaxis. Unfortunately, delayed-onset symptoms can lead to underreporting. Mintzes et al[6] estimate that about 10% of ADRs are reported. Additionally, delayed symptom onset contributes to delayed recognition, delayed discontinuation of the offending medication, and increased risk for more severe symptoms.

Had bupropion been promptly discontinued during her first visit to the ED, Ms A's return to the ED and subsequent 6-day stay in the intensive care unit and hospital could have been prevented. Her symptoms began on day 20 of bupropion therapy, consistent with the established latent period, and completely resolved on day 27, 4 days after discontinuing bupropion. Interestingly, in light of Ms A's prior history of ondansetron-induced urticaria, Hu et al[4] found that the only known independent risk factor for delayed hypersensitivity reactions is a personal history of urticaria. Furthermore, according to the Naranjo Adverse Drug Reaction Probability Scale by Naranjo et al,[7] bupropion is the "probable" cause of Ms A's symptoms.

Ms A benefited fortuitously when the psychiatry department was consulted after she developed epinephrine-induced anxiety. Prompt recognition of bupropion-induced delayed-onset anaphylactoid reactions is critical to favorable patient outcomes and would have greatly improved Ms A's hospital course. As physician awareness of this rare ADR grows, bupropion-prescribing physicians can further its recognition by becoming familiar with bupropion's common and uncommon ADRs and educate patients appropriately.

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