Acute Medicine 2010; 9(2): 70-72

Case Report

Angioedema caused by bupropion treatment

R Bhella & J Southgate

Key Point
- Consider bupropion as a course for acute urticaria or angioedema.

Abstract

Reports of urticaria and rash with bupropion are common, with an estimated incidence of 1-4%. Serious adverse reactions, including seizures and angioedema occur less commonly, but may be dose related. Rarely patients present with fever, arthralgia and myalgia resembling a serum-sickness reaction. A case of a 30 year-old man presenting with a rash, angioedema, and arthralgia 19 days after commencing bupropion treatment to aid smoking cessation is described. Treatment with antihistamines and steroids, resulted in improvement within 3 hours, and complete resolution after 3 days. Management also included identifying and discontinuing the causative agent. Recent concerns over neuropsychiatric side effects of bupropion are highlighted. The literature is reviewed and recommendations for safer prescribing discussed.

Keywords

Angioedema, adverse reaction, allergy, bupropion,

Case History

A 30 year-old man presented to the Emergency Department with a four-day history of rash on his back and upper chest, and swelling of his lips, hands and feet. He had recently started oral bupropion sustained release for smoking cessation. He was on day 19 of therapy, having commenced 150 mg daily for six days, followed by 150 mg twice daily. He had abstained from smoking during that time. There was no history of any other drug use, either prescribed or otherwise.

The patient had no past medical history, no known drug allergies, and no history of hypersensitivity reactions or seizures. On day 15 the patient noticed an erythematous, itchy rash on his back and upper chest. On day 17 the patient developed swelling in his hands and lower lip.

He attended the Emergency Department and a diagnosis of a reaction to an insect bite was made. Treatment with chlorpheniramine 10 mg and prednisolone 40 mg resulted in a modest improvement of his symptoms and he was discharged on these medications. As he had had no advice to the contrary, he continued to take the bupropion as prescribed.

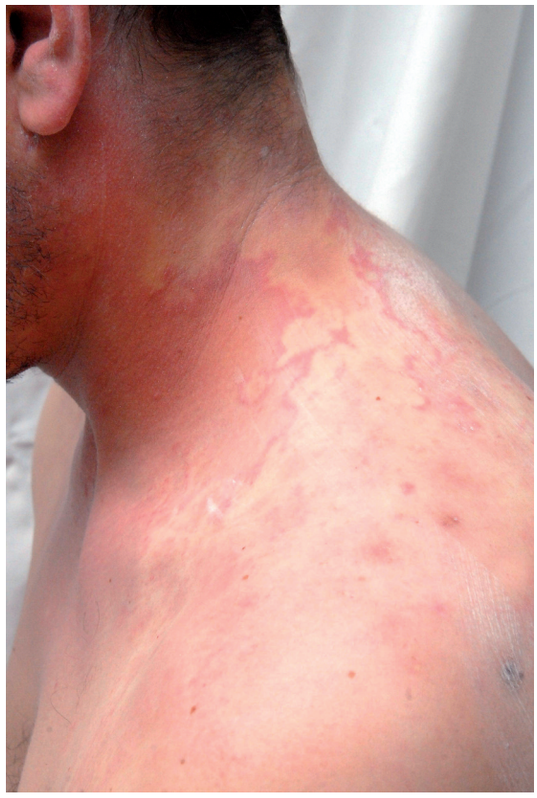
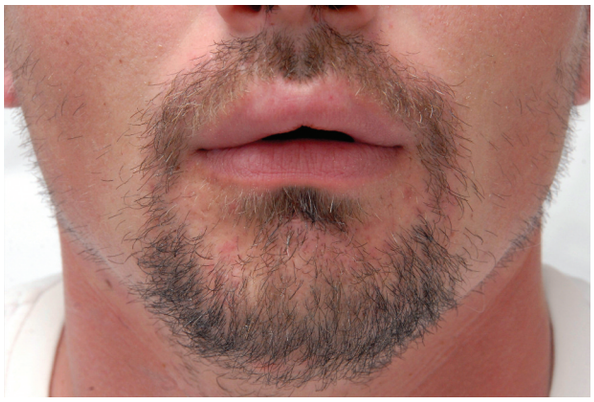


Figure 1. Patient's erythematous rash at second emergency department visit, day 19 of bupropion therapy. Day 4 of symptoms.

The patient re-attended the Emergency Department 2 days later with tongue swelling and worsening pruritis. His airway was not compromised. He was referred to the Acute Medical

Dr Randeep Bhella
FY2
Norfolk and Norwich University Foundation Trust

Dr Jo Southgate
BM BSc FRCP
(Corresponding author)
Consultant Acute Physician
Norfolk and Norwich University Foundation Trust
Colney Lane,
Norwich, NR4 7UY
Email: joanne.southgate@nnuh.nhs.uk



Figures 2. Patient's lip swelling at second emergency department visit, day 19 of bupropion therapy. Day 4 of symptoms.

Unit for further management. He had a diffuse, erythematous, maculo-papular rash covering the upper back (see Figure 1) and swelling of the upper lip (Figure 2). He also had metacarpo-phalangeal swelling, causing discomfort on forming a fist and swelling of his feet.

The possibility of allergy to bupropion was considered likely, and the patient was re-prescribed oral prednisolone and chlorpheniramine. He was advised to discontinue bupropion. The angioedema improved and the rash faded. His symptoms completely resolved within a few days.

Discussion

Bupropion (Zyban) was licensed by the Medicines Control Agency in the UK in June 2000 as a non-nicotine aid to smoking cessation. It is a selective inhibitor of the presynaptic uptake of norepinephrine and dopamine. It also inhibits uptake of serotonin and has modest anticholinergic activity.[1] It is used as an antidepressant (Wellbutrin) of the aminoketone class, chemically unrelated to other known agents. The mechanism by which bupropion enhances the ability of patients to abstain from smoking is unknown.[2]

Adverse reactions occur up to 3 weeks after initiating treatment. Younger people appear more at risk of developing cutaneous reactions and younger women are reported to be more prone to angioedema.[2] The response appears to be dose-dependant and in this case it occurred after an increase in dose.

Angioedema is swelling of the deep layers of the subcutaneous/ submucosal tissue due to capillary leak as a result of inflammation. It causes non-pitting oedema of the lips, face, tongue, hands and feet. Angioedema can be alarming to the patient and potentially compromise the airway if the larynx or the tongue is markedly swollen. In severe cases, intramuscular epinephrine (adrenaline) or emergency tracheostomy may be required.[3]

The pathogenesis of drug-induced urticaria, angioedema and anaphylaxis remains uncertain. Urticaria is mostly IgE mediated, but some drugs can induce immune complex reactions and activate a complement cascade, while others can induce direct activation of mast cells and degranulation or activation of complement by non-immune mechanisms.[1]

- In July 2009 the US Food and Drugs Administration issued new boxed-warnings on serious neuropsychiatric symptoms and suicidal thoughts and behaviour associated with treatment with bupropion. A Medicines Guide is now recommended in USA to encourage safer use.[8] Zyban and Wellbutrin SR should not be administered concurrently.
- Bupropion should not be administered to patients with a history of seizures or conditions altering the seizure threshold, including anorexia nervosa or bulimia, patients with potential benzodiazepine or alcohol withdrawal, those with head trauma or central nervous system pathology, or patients taking antipsychotic drugs, systemic steroids, quinolone antibiotics or antimalarial drugs.[9]
- To avoid prolonged QT interval and ventricular arrhythmias secondary to thioridazine toxicity, bupropion should not be administered if a monoamine oxidase inhibitor or thioridazine antipsychotic drug has been given within the past 14 days.[10]
- Bupropion is contraindicated in patients with severe hepatic impairment.[8,11]

Figure 3. Summary of recommendations for safe prescription of Buproprion.[7-11]

A serum sickness-like reaction presents as fever, rash, arthralgia and lymphadenopathy. Bupropion and its major active metabolite hydroxybupropion are highly protein-bound. The serum sickness-like reaction is believed to be an immune-complex-mediated illness precipitated by the drug acting as a hapten in a protein-hapten complex, provoking an immune response, with antibody production.[4]

Other drugs commonly implicated in these types of reactions include non-steroidal anti-inflammatory drugs, which cause cyclo-oxygenase 1 inhibition and overproduction of leukotrienes. This is responsible for cutaneous and respiratory symptoms.[2] Angiotensin converting enzyme inhibitors can cause fatal angioedema, which is partially explained by bradykinin excess and impairment of aminopeptidase P and dipeptidyl peptidase IV that are involved in the metabolism of substance P and bradykinin.[5] It may occur after many months of a stable dose of treatment.

Bupropion-induced adverse reactions typically occur 6 - 21 days after treatment starts.[6] Monitoring for adverse events should occur for up to 2 weeks after an increase in dose. Although doses of up to 300mg per day are advocated, there is a clear association between increased doses and serious adverse reactions such as seizures and angioedema.[2] The lower dose may be more appropriate in young women and patients with low or normal BMI. Patients should be warned of the risk of potential serious adverse effects and be advised to stop treatment if these develop. Angioedema responds well to steroids. A patient information sheet is now available online.[7] A variety of recommendations are available for the safe prescription of Buproprion, and these are summarized in Figure 3.

Angioedema caused by bupropion treatment

References

1. Dwoskin LP, Rauhut AS. Review of the Pharmacology and Clinical Profile of Bupropion, an Antidepressant and Tobacco Use Cessation Agent. *CNS Drug Reviews* 2006; **12(3)**: 178–207.
2. Beyens MN, Guy C, Mounier G *et al*. Serious adverse reactions of bupropion for smoking cessation: analysis of the French Pharmacovigilance Database from 2001 to 2004. *Drug Saf*. 2008; **31(11)**: 1017–26.
3. Kaplan AP, Greaves MW. Angioedema. *Journal of the American Academy of Dermatology* 2006; **53(3)**: 373–388.
4. McCollom RA, Elbe DH, Ritchie AH. Bupropion-induced serum sickness-like reaction. *Ann Pharmacother*. 2000; **34(4)**: 471–3.
5. Toncic RJ, Marinovic B. Nonallergic Hypersensitivity to Nonsteroidal Antiinflammatory Drugs, Angiotensin-Converting Enzyme Inhibitors, Radiocontrast Media, Local Anesthetics, Volume Substitutes and Medications used in General Anesthesia. *Acta Dermaovenerol Croat*. 2009; **17(1)**: 54–69.
6. Tackett AE, Smith KM Bupropion-induced angioedema. *Am J Health Syst Pharm* 2008; **65(17)**: 1627–30.
7. Bupropion (Zyban): Patient UK Leaflet. EMIS 2009; Doc ID 4544, Version 39.
8. Medication Guide: Zyban (bupropion hydrochloride) Sustained-Release Tablets. GlaxoSmithkline 2009; NDA 20-711/S-032. Approved by the U.S. Food and Drug Administration.
9. British National Formulary 55. March 2008.
10. Wooltorton E. Bupropion (Zyban, Wellbutrin SR): reports of deaths, seizures, serum sickness. *JAMC* 2002; **166(1)**: 68
11. Humayun F, Shehab TM, Tworek JA. A fatal case of bupropion (Zyban) hepatotoxicity with autoimmune features: Case report. Journal of Medical Case Reports 2007; **1**: 88.