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Sublingual Desensitization for Buprenorphine Hypersensitivity

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To the Editor

Buprenorphine (Subutex), a semi-synthetic opiate alkaloid derivative with partial μ -opioid receptor agonist and κ -opioid receptor antagonist activity, is used for treatment of opioid dependence or as a long-acting analgesic (1). It is available in several forms including sublingual tablets and has a mean plasma elimination half-life of 37 hours (2). Like other opioids, it can cause hypersensitivity reactions by directly activating mast cells or basophils in an IgE-independent manner (3). Reactions to buprenorphine have been reported in clinical trials and post-marketing experience: the most common reactions include rashes, hives, and pruritus. Less common reactions include bronchospasm, angioedema, and anaphylactic shock (2). Such systemic reactions to buprenorphine, however, are rare (4,5). We now report on a 21-year-old woman with a six-year history of opioid dependence, who had hypersensitivity reactions to many opioid medications, including buprenorphine, heroin, oxycodone, hydrocodone, and methadone, and who was successfully desensitized to buprenorphine.

In our patient, heroin caused severe hives, vomiting, coughing, and sensation of throat closing; oxycodone resulted in hives and vomiting; hydrocodone and methadone resulted in severe nausea and vomiting. After multiple unsuccessful attempts to quit using drugs on her own, she entered a substance abuse treatment program and achieved remission for eight months, treated with sublingual buprenorphine twice daily along with cetirizine daily to minimize adverse reactions. She initially tolerated buprenorphine with cetirizine without reactions, but six months into her treatment, after missing a dose of cetirizine, she developed hives, dizziness, and a sensation of throat closing. Although these symptoms improved with cetirizine, further buprenorphine doses were accompanied by skin tingling, flushing, hives, and sometimes also with facial edema, nausea, or respiratory symptoms (sensation of throat closing associated with coughing and difficulty breathing). Over the next two months, respiratory symptoms became more frequent and severe. Symptoms occurred several times per week, typically lasting 10

minutes, and improving with cetirizine. Because of these reactions, buprenorphine was discontinued and these symptoms abated. However, she then relapsed into heroin use, which caused severe reactions with hives, vomiting, diarrhea, and a sensation of throat closing, despite remaining on daily cetirizine. She was referred for further evaluation of buprenorphine allergy.

Physical examination was notable for mild dermatographia. Laboratory evaluation was notable for baseline total tryptase that was initially mildly elevated at 18 ng/mL (reference range, 1–15 ng/mL); repeat 13 ng/mL. CBC showed 5% eosinophils, but was otherwise normal, as were LFTs and TSH. Because she required a minimum of several months of sublingual buprenorphine to treat her substance dependence, desensitization to buprenorphine was recommended. She was advised of the risks and benefits of desensitization, agreed to proceed with the procedure, and was admitted to the intensive care unit for buprenorphine desensitization.

Commercially available buprenorphine sublingual tablets (2mg) were ground and suspended in sterile water. Since there are no data on the stability of buprenorphine in solution (2), dilutions were prepared close to the time of administration to minimize any possible loss of potency. Because our patient's symptoms to buprenorphine included severe anaphylactoid reactions with respiratory symptoms, we chose to perform a full, rather than abbreviated, desensitization protocol. After premedication with cetirizine (10 mg), the patient received eight incremental doses of sublingual buprenorphine, administered every 30 minutes (Table I). The target dose was 2 mg twice daily, a dose that was previously used in this patient with good control of her opioid withdrawal symptoms. No reactions were observed during desensitization. The patient was maintained on sublingual buprenorphine 2 mg twice daily and cetirizine 10 mg daily and remained free of adverse symptoms.

Unfortunately, three-and-a-half months after desensitization to buprenorphine, the patient relapsed into heroin use. But, whereas previous heroin injection resulted in severe anaphylactoid symptoms, while on buprenorphine, she experienced no allergic symptoms. Because of this relapse, her buprenorphine dose was increased to 3 mg twice daily, which has been maintained with cetirizine 10 mg daily. Desensitization to buprenorphine therefore has been continuous now for over four months and has not been associated with adverse effects.

We thus report the first successful sublingual desensitization for buprenorphine sensitivity. To our knowledge, desensitization for any opioid sensitivity has not been previously described, and therefore our observations are quite noteworthy. Furthermore, desensitization to buprenorphine is remarkable because opioid sensitivity is thought to be mediated by opiate receptor induced mast cell degranulation, independent of IgE and FcεR1. While morphine allergy associated with morphine-specific IgE has been described (6), the development of severe reactions to a diverse group of opioid medications in our patient suggests that her reactions were IgE-independent, as is the case in most patients with opioid sensitivity. As such, neither skin prick testing nor opioid-specific-IgE measurement has been validated as useful for diagnosing opioid sensitivity (7). While the precise mechanisms of desensitization are poorly understood, the successful desensitization to buprenorphine in our patient suggests that desensitization to mast cell-mediated disease does not necessarily require FcεR1 cross-linking, and might occur via down-regulation of the opiate receptor. Down-regulation of the opiate receptor might allow patients desensitized to one opiate to tolerate other opiates, and may explain why our patient, following desensitization to buprenorphine, became tolerant to heroin.

Our report is also remarkable because it suggests that opioid desensitization might be an appropriate alternative for patients with severe opioid sensitivity. Patients with severe opioid sensitivity have been described, but in those settings alternative treatment with other opioids or non-opioid analgesics, rather than desensitization, is recommended (8). In our patient,

alternative treatments were not possible, as she reacted to multiple different opioids, and treatment for her substance dependence required prolonged therapy with a long-acting opioid, such as buprenorphine. Therefore, treatment for substance dependence in our patient required desensitization to buprenorphine, which was induced successfully.

For desensitization, we chose to use the sublingual route of administration, which would reproduce the conditions under which buprenorphine is normally absorbed, and which is an efficacious and well-tolerated method for aeroallergen desensitization. Mast cells have been identified throughout the oral mucosa, in low levels comparable to that of the skin (9). However, in our patient, the desensitization process did not induce oral symptoms. While desensitization via the sublingual route was successful in our patient, it is possible that other routes of desensitization might also be effective.

In summary, this is first report of sublingual desensitization for severe buprenorphine sensitivity, and the first report, to our knowledge, of desensitization to any opioid. Importantly, this case suggests that mechanisms of rapid allergen desensitization include direct effects on mast cells, which can occur independently of IgE. As buprenorphine is widely prescribed for the pharmacologic treatment of opioid dependence, desensitization permits continuation of a critically important therapy in patients with opioid hypersensitivity. Finally, our report suggests that buprenorphine hypersensitivity, and potentially any opioid hypersensitivity, can be treated with sublingual desensitization.

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Abbreviations

CBC	complete blood count
LFTs	liver function tests
TSH	thyroid stimulating hormone

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Table I

Buprenorphine desensitization protocol.

Buprenorphine Solutions		
Dilution	Concentration	Preparation
Solution A	4 mg/mL	5 × 2mg crushed sublingual tablets + 2.5 mL sterile water
Solution B	2 mg/mL	1 mL Solution A + 1 mL sterile water
Solution C	0.2 mg/mL	1 mL Solution B + 9 mL sterile water
Solution D	0.02 mg/mL	1 mL Solution C + 9 mL sterile water
Solution E	0.002 mg/mL	1 mL Solution D + 9 mL sterile water
Solution F	0.2 µg/mL	1 mL Solution E + 9 mL sterile water
Solution G	0.02 µg/mL	1 mL Solution F + 9 mL sterile water

For Buprenorphine Desensitization		
Dose number	Dose administered	Preparation
1	0.002 µg	0.1 mL Solution G
2	0.02 µg	0.1 mL Solution F
3	0.2 µg	0.1 mL Solution E
4	0.002 mg	0.1 mL Solution D
5	0.02 mg	0.1 mL Solution C
6	0.2 mg	0.1 mL Solution B
7	0.6 mg	0.15 mL Solution A
8	1.2 mg	0.3 mL Solution A

Premedication: Cetirizine 10mg po 30 minutes before the desensitization

Buprenorphine was administered via the sublingual route

Successive doses were administered 30 minutes apart