Case Report
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A Case of Codeine Induced Anaphylaxis via Oral Route

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Codeine is widely prescribed in clinical settings for the relief of pain and non-productive coughs. Common adverse drug reactions to codeine include constipation, euphoria, nausea, and drowsiness. However, there have been few reports of serious adverse reactions after codeine ingestion in adults. Here, we present a case of severe anaphylaxis after oral ingestion of a therapeutic dose of codeine. A 30-year-old Korean woman complained of the sudden onset of dyspnea, urticaria, chest tightness, and dizziness 10 minutes after taking a 10-mg dose of codeine to treat a chronic cough following a viral infection. She had previously experienced episodes of asthma exacerbation following upper respiratory infections, and had non-atopic rhinitis and a food allergy to seafood. A skin prick test showed a positive response to 1-10 mg/mL of codeine extract, with a mean wheal size of 3.5 mm, while negative results were obtained in 3 healthy adult controls. A basophil histamine release test showed a notable dose-dependent increase in histamine following serial incubations with codeine phosphate, while there were minimal changes in the healthy controls. Following a CYP2D6 genotype analysis, the patient was found to have the CYP2D6*1/*10 allele, indicating she was an intermediate metabolizer. An open label oral challenge test was positive. To the best of our knowledge, this is the first report of a patient presenting with severe anaphylaxis after the ingestion of a therapeutic dose of codeine, which may be mediated by the direct release of histamine by basophils following exposure to codeine.

Key Words: Anaphylaxis; basophil degranulation test; codeine

INTRODUCTION

Codeine is a methylated morphine derivative that is found naturally in poppy seeds.[1] Codeine has analgesic and antitussive activities, and has been widely prescribed in clinical settings. Common adverse drug reactions include constipation, euphoria, nausea, and drowsiness. Immediate allergic reactions such as pruritus and urticarial skin rashes can develop, but severe anaphylactic reactions are very rare.[2-4]

CASE REPORT

A 30-year-old woman experienced dyspnea, urticaria, chest discomfort, and sweating within 10 minutes after taking codeine orally to treat a chronic cough. She had suffered from bronchial asthma since 2010, and her asthma was frequently exacerbated following multiple attacks of upper respiratory infection. Since her severe cough did not improve after the viral infection, codeine phosphate at a dose of 10 mg a day was prescribed to suppress her symptoms for 1 week. She did not experience any adverse drug reactions during the first week of codeine treatment; however, after 1 week, approximately 10 minutes after taking the codeine, she began to develop dyspnea, urticaria, sweating, and chest discomfort. In response to these symptoms, she stopped taking the medication. The patient had perennial rhinitis and a food allergy to shellfish, which presented as hives; however, she had no previous history of any drug allergies. She was referred to our clinic for the evaluation of her codeine allergy and the uncontrolled asthma. On the first visit, eosinophilia was not detected in peripheral blood, sputum, or nasal smears. Serum total and specific IgE levels to shrimp and crab were within the normal ranges. A skin prick test (SPT) to all of the common inhalant allergens (Bencard, Bradford, UK) showed negative responses. A forced expiratory volume at 1 second (FEV1), as measured by spirometry, was 62.5% predictive.

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After stabilizing her asthma, we planned to perform *in vivo* and *in vitro* tests to confirm whether her systemic reactions were caused by codeine and to evaluate the mechanism of the codeine-induced anaphylaxis. A SPT, a basophil histamine release test, and an open-label oral challenge test (OPT) were performed with codeine phosphate after obtaining informed consent. Furthermore, CYP2D6 genetic polymorphisms, which are often responsible for differences in responses to codeine between individuals, were evaluated. The SPT was performed with codeine (0.1-10 mg/mL) and morphine (0.1-10 mg/mL) extracts. Histamine and saline were tested as positive and negative controls, respectively. The SPT was positive to 1-10 mg/mL codeine with a mean wheal size of 3.5 mm, while negative results were obtained in 3 healthy adult controls. (No response to saline, 6×4 mm to histamine, 2×2 mm to morphine 0.1 mg/mL, 5×4 mm to morphine 1-10 mg/mL.) The OPT revealed a positive response. There was no response to initial intake of 5 mg codeine phosphate. When 10 mg codeine phosphate was administered after 2 hours, she immediately developed a systemic reaction, including dyspnea, wheeze, chest tightness, dizziness, and vomiting. Her blood pressure was 140/80 mmHg, pulse rate 95/minute, and body temperature was 36.8°C. The basophil histamine release test, which was performed according to previously described methods,[5] showed a dose-dependent increase with serial additions of codeine phosphate, while minimal changes were noted in the 2 controls (Figure). The CYP2D6 genotyping results revealed that the patient had the CYP2D6*1/*10 allele, which indicated that she was an intermediate metabolizer according to the expected enzyme activities reported on the CYP2D6 allele web site (http://www.imm.ki.se/CYPalleles/cyp2d6.htm). Based on these findings, the expert definition of her final diagnosis was codeine-induced anaphylaxis.[6] We recommended her to avoid taking any codeine-based products.

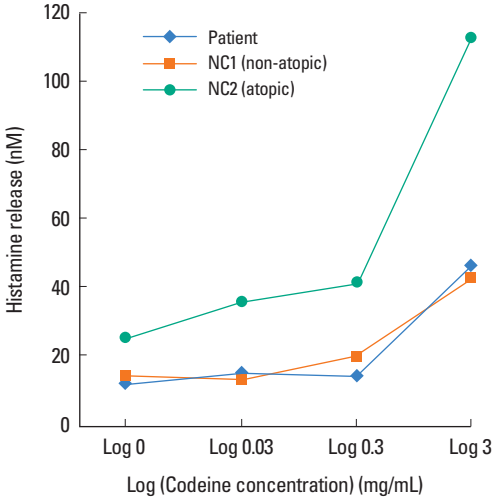

Figure. Comparison of histamine concentrations released from basophils after serial additions of codeine phosphate in the patient and the 2 healthy normal controls (NC1 and NC2).

Her asthma and rhinitis were controlled using a medium dose of inhaled corticosteroids with a long-acting beta2-agonist inhaler, a leukotriene receptor antagonist, and an intranasal steroid. After 1 year, her FEV1% had improved to 87.3% predictive (2.23 L) compared to her initial FEV1 level (62.5% predictive, 1.58 L).

DISCUSSION

To the best of our knowledge, this is the first report of a patient who presented with codeine-induced anaphylaxis after taking an oral therapeutic dose. Codeine is commonly prescribed for the symptomatic relief of non-productive coughs, alongside other antitussives or expectorants. It suppresses the cough reflex by acting directly on the central medulla of the brain. In this study, the patient took codeine due to severe cough symptoms of asthma. Immediately after codeine ingestion, she developed anaphylaxis. Previous studies have suggested that cutaneous allergic reactions to codeine can be induced by the non-immunological induction of histamine release.[3,7,8] There have been even rarer hypersensitivity reactions to codeine, including generalized maculopapular eruptions, bullous eruptions, fixed drug eruptions, drug-induced hypersensitivity syndrome, or even toxic epidermal necrolysis.[2,9-13] In this study, we confirmed anaphylaxis by OPT. To clarify the pathogenic mechanism, we performed SPT and found positive reactions to codeine extracts.[14] We performed an *in vitro* basophil histamine releasing test, which showed a significant increase in codeine-induced effects, compared to the results in 2 controls. At least 1 patient demonstrated the presence of serum-specific IgE antibodies to morphine and codeine and a life-threatening anaphylactic reaction developed after intravenous administration of a mixture of morphine and codeine hydrochloride.[15] Previous research has shown that opiate codeine can cause direct mast cell degranulation without the presence of a specific IgE antibody. As a result, it has been used as a positive control in SPTs.[16-18] To exclude the possibility that our patient was an ultra-rapid metabolizer carrying 2 alleles of active CYP2D6,[19] we performed a CYP2D6 genotype analysis and found that she was an intermediate metabolizer carrying the CYP2D6*1/*10 allele.[20] This indicates a low possibility that her anaphylaxis is derived from the rapid metabolism of codeine followed by a morphine overproduction. As we could not confirm the presence of serum-specific IgE to codeine, we cannot completely exclude any possibility of IgE-mediated anaphylaxis. However, based on the above results, we suggest that the anaphylaxis in the present study could be caused by a codeine-induced direct histamine releasing effect on basophils.

We conclude that oral administration of codeine can induce anaphylaxis via a non-immunologic mechanism, such as a direct basophil histamine releasing effect in susceptible subjects. Further studies will be needed to investigate predisposing fac-

tors to screen susceptible subjects.

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REFERENCES

1. Armstrong SC, Cozza KL. Pharmacokinetic drug interactions of morphine, codeine, and their derivatives: theory and clinical reality, Part II. Psychosomatics 2003;44:515-20.
2. de Groot AC, Conemans J. Allergic urticarial rash from oral codeine. Contact Dermatitis 1986;14:209-14.
3. Sung JM, Shin YS, Kim MJ, Lee YS, Choi GS, Park HJ, Hur GY, Ye YM, Park HS. A case of codeine induced urticaria/angioedema. Korean J Asthma Allergy Clin Immunol 2008;28:234-7.
4. Schoenfeld MR. Acute allergic reactions to morphine, codeine, meperidine hydrochloride, and opium alkaloids. N Y State J Med 1960;60:2591-3.
5. Hur GY, Sheen SS, Kang YM, Koh DH, Park HJ, Ye YM, Yim HE, Kim KS, Park HS. Histamine release and inflammatory cell infiltration in airway Mucosa in methylene diphenyl diisocyanate (MDI)-induced occupational asthma. J Clin Immunol 2008;28:571-80.
6. Ben-Shoshan M, Clarke AE. Anaphylaxis: past, present and future. Allergy 2011;66:1-14.
7. Nasser SM, Ewan PW. Opiate-sensitivity: clinical characteristics and the role of skin prick testing. Clin Exp Allergy 2001;31:1014-20.
8. Arndt KA, Jick H. Rates of cutaneous reactions to drugs. A report from the Boston Collaborative Drug Surveillance Program. JAMA 1976;235:918-23.
9. Rodríguez A, Barranco R, Latasa M, de Urbina JJ, Estrada JL. Generalized dermatitis due to codeine. Cross-sensitization among opium alkaloids. Contact Dermatitis 2005;53:240.
10. Golembiewski JA. Allergic reactions to drugs: implications for perioperative care. J Perianesth Nurs 2002;17:393-8.
11. Choi Y, Lim WS, Jin SY, Lee JH, Lee SH, Lee AY. Nonpigmenting fixed drug eruption due to codeine. Korean J Dermatol 2011;49:822-5.
12. Enomoto M, Ochi M, Teramae K, Kamo R, Taguchi S, Yamane T. Codeine phosphate-induced hypersensitivity syndrome. Ann Pharmacother 2004;38:799-802.
13. Iriarte Sotés P, López Abad R, Gracia Bara MT, Castro Murga M, Sesma Sánchez P. Codeine-induced generalized dermatitis and tolerance to other opioids. J Investig Allergol Clin Immunol 2010;20:89-90.
14. Gómez E, Torres MJ, Mayorga C, Blanca M. Immunologic evaluation of drug allergy. Allergy Asthma Immunol Res 2012;4:251-63.
15. Harle DG, Baldo BA, Coroneos NJ, Fisher MM. Anaphylaxis following administration of papaveretum. Case report: implication of IgE antibodies that react with morphine and codeine, and identification of an allergenic determinant. Anesthesiology 1989;71:489-94.
16. Casale TB, Bowman S, Kaliner M. Induction of human cutaneous mast cell degranulation by opiates and endogenous opioid peptides: evidence for opiate and nonopiate receptor participation. J Allergy Clin Immunol 1984;73:775-81.
17. Lin RY, Erlich ER, Don PC. Skin prick test responses to codeine, histamine, and ragweed utilizing the multitest device. Ann Allergy 1990;65:222-6.
18. Sheen CH, Schleimer RP, Kulka M. Codeine induces human mast cell chemokine and cytokine production: involvement of G-protein activation. Allergy 2007;62:532-8.
19. Leppert W. CYP2D6 in the metabolism of opioids for mild to moderate pain. Pharmacology 2011;87:274-85.
20. Lee SY, Sohn KM, Ryu JY, Yoon YR, Shin JG, Kim JW. Sequence-based CYP2D6 genotyping in the Korean population. Ther Drug Monit 2006;28:382-7.