

Timing *isn't* everything: A case of recurrent angio-oedema



To the Editor,

Angiotensin-converting enzyme (ACE) inhibitors are a popular set of the most frequently prescribed medications with usage estimates of approximately 40 million patients. These agents are routinely prescribed for conditions including hypertension, myocardial infarction, heart failure with systolic dysfunction, chronic kidney disease, and diabetic nephropathy. Angio-oedema is one of the rare but potentially fatal side effects occurring in 0.1–0.7% of patients.¹ Incidence varies among different subgroups and increased to 1.62% in the black population in one study.² Despite the relatively low incidence, ACE inhibitors account for 20–30% of all angio-oedema cases presenting to emergency departments and in a five-year retrospective study of 182 patients presenting to a tertiary care hospital with angio-oedema, 63% were attributed to ACE inhibitor.^{3,4} While ACE inhibitors are usually quickly identified as the culprit medication, this is a case report of a patient in whom the diagnosis was more challenging.

A 67-year-old Caucasian male presented to our clinic with recurrent episodes of angio-oedema spanning several months. In February 2012, the patient underwent dental extraction and received amoxicillin for endocarditis prophylaxis. The patient took amoxicillin and the following day developed moderate tongue angio-oedema with no associated urticaria or pruritus. He went to his local emergency room and received intravenous diphenhydramine and possibly intravenous corticosteroids. About a month later, by March 2012, he went to the emergency room with a similar episode of tongue angio-oedema, again without any associated urticaria or pruritus. He was no longer on amoxicillin, and the reaction was attributed to lisinopril, which he had been taking for several years. His lisinopril was stopped, and he was observed in the intensive care unit overnight by which point his symptoms had resolved. At discharge, he was instructed to discontinue lisinopril permanently. Two months later in May 2012, the patient had a similar but less severe occurrence of tongue swelling, again without urticaria or pruritus. He took two diphenhydramine tablets, with resolution of symptoms after several hours. It was noted that the patient had been recently started on Niaspan two days prior. His Niaspan was discontinued, and the patient was subsequently referred to an allergy clinic for evaluation.

His past medical history was significant for type II diabetes, hypertension, hyperlipidaemia, and obesity. His daily medications included aspirin 81 mg daily, amlodipine 10 mg daily, metoprolol 100 mg bid, metformin 1000 mg bid, glipizide 10 mg bid, insulin glargine 35 units qHS, cholecalciferol/Vit D 1000 IU daily, omega 3 900 mg qid, multivitamins daily along with the previously discontinued lisinopril and niacin. He denied any prior urticaria, pruritus, drug allergies, food allergies, asthma, allergic rhinitis, or eczema. The patient was uncertain if he had ever received penicillin prior to the dental procedure in February 2012 but did not recall any adverse reactions to any medications in the past. Family history was non-contributory for any of

the aforementioned conditions including no family history of angio-oedema.

Laboratory data showed C1 inhibitor quantitative 36, C1 esterase inhibitor functional >90%, C3 188, C4 30.7, and C1Q complement 19 (all values within normal limits).

The patient returned at a later date to undergo penicillin skin testing and oral graded challenge to niacin. His metoprolol was held the day prior to the procedures. Penicillin skin testing was negative. The patient subsequently underwent graded challenge to niacin and developed flushing, a well-known side effect of this drug, but otherwise experienced no other adverse reactions. On the basis of clinical and laboratory findings, the patient was diagnosed with ACE inhibitor-induced angio-oedema.

The patient was informed he could safely continue his niacin, which he continues to take. The patient has done well since without any further episodes of angio-oedema.

Workup for angio-oedema includes a careful review of the patient's medications with particular attention to any new ones. In our patient's case, one of the three angio-oedema episodes occurred with the introduction of amoxicillin while another incident arose with initiation of niacin, obscuring the eventual diagnosis of ACE inhibitor-induced angio-oedema. Making this diagnosis required two modalities of allergy testing: skin testing to rule out penicillin allergy and graded oral challenge to exclude niacin allergy. Niacin allergy is relatively rare and a literature search yielded no previously published protocols. Our case proposes a suggested graded challenge protocol for niacin (Table 1).

Had the patient not undergone graded challenge for niacin, the third angio-oedema episode may have been erroneously attributed to the newly begun medication, thus depriving the patient of a medication for which he has a medical need.

The other causes of angio-oedema other than ACE inhibitor-induced can generally be divided into two categories: mast cell-mediated and bradykinin-mediated. Mast cell-mediated angio-oedema is typically associated with urticaria and/or pruritus. Angio-oedema without urticaria and/or pruritus is bradykinin-mediated and points to hereditary or acquired angio-oedema, idiopathic angio-oedema, or ACE inhibitor-induced angio-oedema. Hereditary angio-oedema (HAE) and acquired angio-oedema (AAE) are both characterised by C1 esterase inhibitor deficiency or dysfunction with the former due to an autosomal dominant condition and the latter associated with lymphoproliferative disease.⁵ Attacks in hereditary angio-oedema and ACE inhibitor-induced angio-oedema have been reported to be precipitated by trauma including dental work or surgical trauma.^{6,7} Acute attacks of angio-oedema due to HAE or ACE inhibitor can be treated with bradykinin B2 receptor antagonist and/or complement C1-inhibitor.^{8,9}

Finally, our case highlights that ACE inhibitor-induced angio-oedema can recur even months after discontinuing the medication. In a long-term observational study in which 111 patients with ACE inhibitor-induced angio-oedema were followed for at least one year and up to 14 years, 51 patients (46%) had further recurrences after discontinuation. The majority of those patients (88%) relapsed within one month of stopping the medication while another patient had an episode three months after discontinuation.¹⁰ Even after

Table 1 Niacin graded challenge protocol administration record.

Time (h)	Dose (mg)	Therapeutic dose (%)	Cumulative dose (mg)	Symptoms
0.0	25	5	25	None
0.5	50	10	75	None
1.0	100	20	175	None
1.5	250	50	425	Flushing

Flushing, a well-known side effect, was mild and resolved completely within 5 min. After the final dose, the patient was observed for an hour and 15 min without incident.

cessation, ACE inhibitors should always be considered in the differential for angio-oedema, particularly if recently stopped.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this investigation.

Patients' data protection. The authors declare that they have followed the protocols of their work centre on the publication of patient data and that all the patients included in the study have received sufficient information and have given their informed consent in writing to participate in that study.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects mentioned in the article. The author for correspondence is in possession of this document.

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Contact urticaria to *Cannabis sativa* due to a lipid transfer protein (LTP)



Cannabis sativa, which belongs to the Cannabaceae family, contains about sixty compounds named cannabinoids which are involved in its psychoactive effects, as well as antiemetic and anti-inflammatory properties. Hypersensitivity reactions to *C. sativa* are uncommon (or not recorded) probably because its consumption is illegal in most countries and patients do not address the physician for this reason. The possible involvement of LTP in *C. sativa* allergy has been pointed out¹ and recently several new putative *C. sativa* allergens have been described.^{2,3}

A 30-year-old man without atopy history began to work in *C. sativa* harvesting for therapeutic use. After two months he developed several episodes of wheals and pruritus immediately after the contact of the skin with the leaves while collecting the plant. The symptoms disappeared spontaneously in less than an hour.

He previously consumed *C. sativa* recreationally (smoked) with good tolerance. He never experienced other allergies.

After obtaining informed consent and approval from the Hospital Ethics Committee, prick-by-prick test was carried out with dried and fresh *C. sativa* leaf obtaining positive results (mean wheal diameter of 6 mm and mean flare 10 mm). Positive (histamine dihydrochloride 10 mg/mL; Alk-Abelló, Madrid, Spain) and negative controls (saline) were