

# Oropharyngeal Angioedema due to Nifedipine Hypersensitivity Post-hemithyroidectomy

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## Abstract

Nifedipine, a calcium channel blocker, is generally considered as safe but sublingual administration of immediate release nifedipine (IRN) formulations are sometimes associated with serious side effects. An 82-year-old male was presented with oropharyngeal angioedema, with no history of similar episodes, allergy to drug or food. The symptom began 20 minutes after IRN administration. He was admitted to ICU and a protective endotracheal intubation was performed. Over the first six days, his tongue continued to swell, starting with the right side, progressing to the left, hypopharynx, and epiglottis. Intravenous infusions of prednisolone, diphenhydramine and famotidine, were initiated; however, without improvement. The patient received nanofiltered Berinert® 2000 IU IV, but no improvement. Edema of the tongue reduced slowly after the seventh day and further improved over the next five days. Careful evaluation indicated nifedipine as the chief etiology for angioedema in the patient. IRN may triggers severe hypersensitivity and oropharyngeal angioedema, requiring immediate special care and thus should be used carefully.

Keywords: Nifedipine; angioedema; hypersensitivity; sublingual.

## INTRODUCTION

Nifedipine (Adalat) [4-(2-nitrophenyl)-2, 6-dimethyl- 3, 5-dicarbomethoxy-1, 4-dihydropyridine] is a calcium channel blocker used for treating various cardiovascular diseases. Nifedipine is used for treating hypertension, cardiac angina, and Raynaud's disease including others [1]. It is generally considered a safe drug; however, sublingual administration of immediate release nifedipine (IRN) formulations is associated with serious side effects. These side-effects are extremely rare and sporadic; however, the reported incidences of such cases have apparently increased [2]. These reported cases were described in patient severe hypotension receiving IRN in emergency and in pregnant women with severe hypertension. Cases were also reported in patients with aggravated existing myocardial infarction or induction of new events in elderly patients [3-5]. Further, there is only one reported case of IRN side effect with allergic hypersensitivity involving the larynx [6]. We describe a case of acute oropharyngeal angioedema with mostly unilateral involvement of the tongue precipitated by sublingual administration of IRN.

## Case Report

An 82-year-old Caucasian male was admitted to our hospital for elective hemithyroidectomy. For general anesthesia induction the patient received (0,1mg) Fentanyl, (140 mg) Propofol and (10 mg) Mivacurium. The operation achieved without complications. Pos-operatively, in the recovery room, the patient was administered with sublingual IRN capsule (10 mg) to control his blood pressure (140/90 mmHg) as quick and simple solution. Twenty minutes later, the right side of his tongue started to swell gradually. Therapeutically, intravenous infusions of prednisolone (250 mg) and antihistamines (H1- and H2-blockers), diphenhydramine and famotidine (mg) were initiated. However, no improvement was noticed; instead, a gradual progression in edema of the tongue was observed. The edema was mostly on the right side. As a protective measure, the patient transferred to the intensive care unit (ICU). Auscultation of the chest and abdomen was normal.

Over the next few hours, a clear progression of the edema was noticed on the right side. A protective endotracheal intubation was performed to protect the airway. To clarify the diagnosis of the upper respiratory airway condition, a diagnostic nasal

fiberoptic laryngoscopy was performed, and exhibited a glassy, edematous unilateral swelling of the tongue, hypopharynx, and epiglottis. A repeated bolus of intravenous prednisolone (250 and 500 mg) was administered to control the edema; however, showed no improvement. By this time, the tip of the tongue started to point more towards the left side. On the second day, despite the normal quantitative C1- esterase inhibitor concentration (C1-INH) (24 mg/dL) the normal value is (19-37 mg/dL), the patient did receive nanofiltered Berinert® 2000 IU IV, but no noticed improvement. Over the next six days, the patient was kept in the ICU under continuous observation. The tongue was completely swollen. We didn't have permission to publish any photo

On the seventh day, edema of the tongue showed gradual decrease with some restoration of its intraoral position. However, the laryngoscopy performed showed pale, glassy pharyngeal edema with no view of the glottis. Therefore, a planned tracheostomy was performed. On the ninth day, the epiglottis and glottis were visualizable on laryngoscopy, however, the lateral walls of the pharynx were still edematous. On the eleventh day, the patient was extubated and was able to breathe unassisted and was subsequently moved from the ICU to the outpatient department.

## Discussion

Nifedipine was initially developed in the Germany in 1970s. It is a di-hydropyridine calcium channel blocker which is generally prescribed for Prinzmetal and angina hypertension [1, 6]. Common side effects include lightheadedness, dizziness, facial flushing, peripheral edema and gastrointestinal symptoms like heartburn and nausea [7]. Even though the side effects of IRN are well documented, it is still used widely. In the present case study, we report a case of acute oropharyngeal angioedema with mostly unilateral involvement of the tongue. The angioedema progressed bilaterally, necessitating urgent respiratory intervention in the patient and thus was treated with sublingual nifedipine. The patient had no such previous history, and no history of allergy to drug or food. No family history of similar condition.

Angioedema mediated by various pathophysiological pathways, including those involving Histamine and bradykinin. Bradykinin-mediated angioedema may be caused by hereditary defects in (C1-INH) protein production, may be a side effect of ACE, or may reflect an acquired (C1-INH) protein deficiency. Our patient did not receive angiotensin converting enzyme inhibitor ACE or angiotensin II receptor antagonist. A very good treatment option was administration of nanofiltered (pnfC1-INH) protein Berinert® 2000 IU which can lead to a rapid symptomatic recovery in patient in acute attack of angioedema [8] [9], which is happened only in second day and he showed no improvement. The plasma-derived, highly purified, nanofiltered C1-inhibitor concentrate (Berinert; "pnfC1-INH") is approved in the United States for treating hereditary angioedema (HAE) attacks and in many European countries for attack treatment and short-term prophylaxis with high level of safety [10].

Our patient had a normal (C1-INH) protein level, this normality may rule out Type I hereditary angioedema (HAE) but not type two, where a nonfunctional inhibitor is transcribed and the level in serum is normal or may elevated with low C4 level, and normal C1q level.

Another treatment option, that could be useful is using Icatibant - selective B2 receptor antagonist, but due to unavailability of this medication in our center, we didn't use it. Icatibat its selective B2 receptor antagonist, that have no affinity to B1 receptors or other peptide receptors, approved to manage hereditary angioedema (HAE) type I and II. This medication showed a good reverse effect to vascular permeability in patient with Hereditary Angioedema, who have a deficiency or dysfunctional C1-esterase inhibitor, in addition to patient who developed upper airway angioedema after receiving ACE- inhibitor [11].

This was an uncommon adverse effect of the widely Nifedipine used drug. The side effects of Nifedipine (IRN) are rare and generally sporadic, but in the recent times incidences of such cases have evidently increased [2]. The rapid decline in blood pressure may compromise the myocardial and cerebral perfusion with severe consequences. Several cases are reported in the literature of such calamities after the administration of sublingual nifedipine including the cases of severe hypotension, acute myocardial infarction, cerebrovascular ischemia, fetal distress, conduction disturbances and even death [3,12]. The sublingual absorption of nifedipine is reported as weak and majority of drug is absorbed by intestinal mucosa only, it can be expected that other immediate release formulations may exhibit similar side effects [13]. (IRN) did not approved to treat sever hypertension or emergency hypertension.

Similar to our case of tongue angioedema has been reported in patients who were administrated with aspirin and angiotensin receptor II blockers [14, 15]. However, to our best knowledge, this is the first case of angioedema of the tongue associated with

sublingual nifedipine administration. This reaction was most likely triggered by the unusually high local concentration of nifedipine under the right side of the tongue, where the manually punctured IRN capsule was placed by the treating staff. This unusual high concentration may have irritated the mucosal lining of right side of the tongue, and effectively, extended the edema to the pharynx and the larynx. Also, a similar case of IRN side effect with allergic hypersensitivity involving the larynx was reported in 1995. The examination of study patient suggested that the local concentration of the drug might be unusually high, causing the laryngeal irritation. This reaction can also be a direct allergic response to drug, but no further testing was done to confirm.

According to American Geriatrics Society (AGS), 2019 updated AGS criteria for potentially inappropriate medication use in older adults, this type of formulation is associated with serious side-effects. They suggested that these drugs should be avoided in older patients, 65 years and older, due to potential risk of hypotension and myocardial ischemia as IRN may cause severe hypersensitivity and oropharyngeal angioedema, requiring immediate and specific respiratory care [16]. Therefore, we recommend that sublingual nifedipine must be use cautiously and with restrictions. Furthermore, large randomized clinical trials must be done to show the study these adverse effects of IRN use.

## Conclusions

In the present report, careful evaluation of the patient showed nifedipine as the chief etiology for angioedema. The use of IRN may cause severe hypersensitivity and oropharyngeal angioedema, requiring immediate special care and thus should be used carefully. Extra caution is thus called for such patients. We recommend that IRN must not be readily available for non-selective use. Further, all health care professionals are required to know serious dangers associated with this drug and thus they should be continuously educated and trained.

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