Ibuprofen-induced localized frontal and temporal forehead swellings: A rare case report

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Abstract:
Ibuprofen, nonselective nonsteroidal anti-inflammatory drugs (NSAIDs), is one of the most commonly prescribed analgesics for managing musculoskeletal, orofacial, and postoperative pain after periodontal therapy. Although considered as one of the safest analgesic agents, the onset of adverse drug reactions after ibuprofen intake has been recently observed. The present report aims to highlight the development of localized swellings in the temporal and frontal forehead following intake of 200 mg of ibuprofen after routine oral prophylaxis. This is the first case report to document the development of an adverse drug reaction with ibuprofen in a patient following a routine dental procedure. The article also aim to comprehensively describe the most appropriate and effective method to diagnose, manage, and prevent NSAIDs-induced adverse drug reactions in routine dental practice.

Key words:
Angioedema, hypersensitivity reactions, ibuprofen, nonsteroidal anti-inflammatory drugs

INTRODUCTION
Ibuprofen, organically known as (2RS)-1-(4-[2-methyl propyl] phenyl, is a commonly prescribed analgesic with good anti-inflammatory and antipyretic properties. It is a propionic acid derivative that belongs to the category of non-selective nonsteroidal anti-inflammatory drug (NSAID).[1,2] Ibuprofen is one of the most commonly prescribed analgesics for managing mild to moderate musculoskeletal pain such as migraine, osteoarthritis, rheumatoid arthritis, soft-tissue disorders, and postoperative pain following various dental and periodontal procedures. Although considered to be one of the safest analgesics with minimal side effects, few adverse drug reactions have been reported recently in the literature.[2] This case highlights the development of localized swelling and angioedema on the frontal and temporal forehead in a 57-year-old systemically healthy male on the intake of a single dose of ibuprofen following routine prophylaxis.

CASE REPORT
A 57-year-old male patient (weight: 62 kg) reported with a chief complaint of bleeding gums from the upper back tooth region for 1 month. On examination, a generalized probing depth of 6–7 mm with the moderate horizontal bone loss was observed. The oral hygiene of the patient was fair with a moderate amount of supragingival and subgingival deposits. The patient was systemically healthy with no history of any cutaneous skin lesions, drug intake, or allergic reaction to any medication or irritant. A nonsurgical phase one therapy comprising of full mouth oral prophylaxis and root surface debridement was initiated. Ibuprofen 200 mg was prescribed post-treatment in case any pain or discomfort was experienced. The patient was recalled after 2 weeks for re-evaluation and follow-up. However, the patient reported back within 1 h, with the development of a sudden, localized, soft, edematous, non-fluctuant, and nonmovable lobular swelling on the frontal and temporal part of his forehead. The swelling was tender on palpation with slight erythema on its outer surface [Figure 1]. The patient also reported the development of a mild rise in body temperature, lassitude, and malaise.

Based on the patient’s history and the timing of onset of allergic response, ibuprofen-induced hypersensitivity reaction was suspected. The patient was questioned regarding the onset of any similar incidents in the past. The patient how to cite this article: Chopra A, Pappu R, Sivaraman K. Ibuprofen-induced localized frontal and temporal forehead swellings: A rare case report. J Indian Soc Periodontol 2020;24:178-81.
then reported the onset of a similar swelling a few years back (etiology unknown). The patient was immediately referred to a physician, and blood was withdrawn to check for the total and differential blood count delete was done. The blood reports showed increases in the eosinophils (absolute eosinophil count = 9.67 × 10^3/µL (H); differential cell count = 16.5%) suggestive of an allergic reaction [Table 1]. A local prick skin test with ibuprofen was also performed to confirm the hypersensitivity reaction [Figure 2]. To exclude the cross-reactivity and tolerance to other chemically unrelated NSAIDS, an oral challenge with other COX 1 inhibitors (aspirin) was done. The patient was immediately administered 10–20 mg intravenous injection of pheniramine maleate to control the reaction. A drastic reduction in the temporal swelling was observed within 24 h. The patient was kept under observation and was prescribed 10 mg of pheniramine maleate twice a day for 3 days. The patient was instructed not to take any nonselective NSAIDs in the future. The complete resolution of the swelling and urticaria was observed within 72 h.

Since the allergic response to ibuprofen was immediately observed in the absence of any previous history of cutaneous lesion, bronchial asthma, respiratory disorders along with cross-reactivity to two or more NSAIDs, a diagnosis of NSAID-induced urticaria/angioedema (NIUA) was established based on the European Academy of Allergy and Clinical Immunology)/WAO nomenclature [Figure 3].

### Table 1: Complete blood profile of the patient immediately after the allergic reaction

| Test                        | Results          | Methods          |
|-----------------------------|------------------|------------------|
| Hemoglobin                  | 15.3 g/dL        | Photometric      |
| Hematocrit                  | 43.9%            | Calculated       |
| RBC count                   | 5.31 × 10^12/µL | Impedance        |
| Total WBC count             | 4.1 × 10^12/µL  | Impedance        |
| Neutrophil                  | 50.4%            | VSC technology/layer microscopy |
| Lymphocyte                  | 26.5%            | technology/light |
| Monocyte                    | 6.0%             | VSC technology/layer microscopy |
| Eosinophil                  | 16.5% (H)        | VSC technology/layer microscopy |
| Basophils                   | 0.6% (L)         | VSC technology/layer microscopy |
| Absolute eosinophil count   | 9.67 × 10^3/µL (H) | Calculated      |
| Absolute neutrophil count   | 0.2 × 10^12/µL  | Calculated       |
| Erythrocyte sedimentation rate | 23 mm/h       |                  |

RBC – Red blood cell; WBC – White blood cell; VSC – volume, conductivity, and light scatter

**DISCUSSION**

The localized frontal and temporal angioedema following ibuprofen intake is a rare manifestation of NSAIDs-induced adverse drug reaction. The onset of this unique response confirmed the complex and varied nature of NSAIDs-induced hypersensitivity reactions and is a fertile area for further research. NSAIDs are the most frequent cause of drug hypersensitivity with NIUA being the most common phenotypic characteristics. The main mechanisms of such non-immunological reactions are the inhibition of the cyclooxygenase enzyme of the arachidonic acid pathways and activation of lipoxygenase pathways. According to the “cyclooxygenase hypothesis,” the inhibition of COX-1 receptors by aspirin or other related NSAIDs such as ibuprofen metabolizes the arachidonic acid to inhibit the release of various proinflammatory cytokines such as prostaglandins, thromboxanes, and prostacyclin. This release of the proinflammatory mediators from the inflammatory cells deviates the arachidonic acid pathway toward the 5-lipoxygenase pathway. The activation of lipoxygenase eventually releases a large amount of cysteiny lipoxygenase (Cys-LTs 5 LTC4, LTD4, and LTE4) both locally and systemically in the systemic circulation. Cys-LTs are 100 times more potent than histamine in inducing hypersensitivity reactions. Recent studies have confirmed elevated levels of urinary LTE4 on aspirin administration in patients with chronic urticaria, NSAID intolerance, and aspirin-exacerbated respiratory disease. The severity of NSAIDs-induced hypersensitivity reaction also shows temporary fluctuations related to the nature and potency of the offending drug to inhibit the COX receptors, cross-reactivity among NSAIDs, and the presence of underlying chronic systemic and cutaneous disease. The heteroaryl acetic acid group of NSAIDs such as naproxen, diclofenac, and ibuprofen has shown a higher risk for anaphylactic or immediate hypersensitivity reactions. In patients with pyrazolone-induced drug hypersensitivity, a strong association between human leukocyte antigen (HLA)-DQ and HLA-DR gene loci and severity of allergic response has been documented. In addition, it has also been observed that NIUA patients may develop tolerance to NSAIDs over time, a process that seems to be influenced by atopy and type of clinical reaction.

Thus, it is important to promptly identify and sequentially manage such an allergic response to avoid untoward complications. A detailed clinical history highlighting the timing of onset of the allergic event along with the name, dose, brand, route of the administration of the culprit drug; pattern and chronology of the allergy response; the time interval between the last dose and onset of symptoms and the time of disappearance of symptoms after drug withdrawal should be recorded. The name and doses of the previously tolerated NSAIDs, history of underlying chronic disorders such as bronchial asthma, chronic rhinosinusitis, nasal polyps, and chronic spontaneous urticaria/angioedema should also be recorded. In vitro skin testing techniques such as intradermal patch tests, oral challenge test, and/or drug provocation test with the suspected and alternative drugs should also be done to confirm the etiology of such adverse drug reactions. It is important not to carry out any provocation testing if the adverse drug reaction has resulted in a life-threatening reaction or anaphylaxis. In case the causative drug is
aspirin, the patient can be tested with another strong COX-1 inhibitor to confirm the cross-reactive type of hypersensitivity. An inhaled route of provocation with lysine aspirin can also be used in patients with a history of bronchial asthma and related respiratory symptoms. Moreover, skin testing should be avoided for immediate hypersensitivity reactions such as type III serum sickness reactions, Stevens–Johnson syndrome, toxic epidermal necrolysis, and drug reaction/rash with severe eosinophilia and systemic symptoms.

**CONCLUSION**

NSAID, such as ibuprofen, should be considered as a potential and common etiological agent for hypersensitivity reactions.
in dental clinics. NSAIDs-induced adverse drug reactions can be a complex and intimidating situation if not managed appropriately. Therefore, a comprehensive knowledge and understanding of the complex pathogenic mechanisms that govern such an allergic response would help clinicians to arrive at a correct and timely diagnosis and provide appropriate treatment. Furthermore, additional research analyzing the pharmacokinetics and pharmacodynamics of the ibuprofen that is related to the various adverse drug reactions should be explored. Moreover, it is important to understand the mechanism by NSAIDs such as ibuprofen interact with the body to develop novel therapeutic modalities by which NSAIDs-induced adverse drug reactions can be prevented.

**Declaration of patient consent**
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**
There are no conflicts of interest.

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