# Unilateral Eyelid Angioedema With Congestion of the Right Bulbar Conjunctiva Due to Loxoprofen Sodium

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*Angioedema is a variant of urticaria that causes deep dermal and subcutaneous swelling. It frequently is a unilateral reaction and usually lasts for several hours but may persist for several days. We report 2 cases of angioedema that involved the right upper and lower eyelids and was associated with congestion of the right bulbar conjunctiva; the symptoms started approximately 1 to 2 hours after taking loxoprofen sodium. All of the symptoms subsided after oral corticosteroid therapy. In both cases, an oral challenge test with 60 mg of loxoprofen sodium (contained in a tablet) caused swelling of the right upper eyelid within several hours, followed by swelling of the right bulbar conjunctiva. We believe the drug reaction in both patients is angioedema.*

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Angioedema is a variant of urticaria that causes deep dermal and subcutaneous swelling.[1] It occurs as a clinical manifestation of immunologic, inflammatory, or idiopathic reactions. Angioedema frequently is a unilateral reaction and usually lasts for several hours but may persist for several days.[1] When angioedema is associated with drug use, it usually is an IgE-mediated immediate hypersensitivity reaction to the drug(s).[2] We report 2 cases of angioedema that involved the same sites in both patients—the right upper and lower eyelids as well as the right bulbar conjunctiva—starting 1 to 2 hours after taking loxoprofen sodium.

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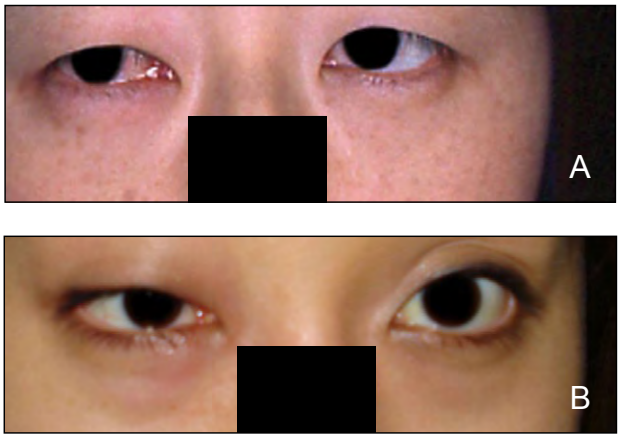
## Case Reports

*Patient 1*—A 35-year-old woman presented to our hospital with pruritic swelling of 10 months' duration that always occurred at the same site, the right upper and lower eyelids. Associated congestion of the right bulbar conjunctiva started approximately 1 hour after taking oral loxoprofen sodium for menorrhalgia. The patient experienced these symptoms every time she took loxoprofen sodium (a total of 5 times). Clinical examination revealed erythematous swelling of the right upper and lower eyelids and congestion of the right bulbar conjunctiva. She did not have nausea, vomiting, dyspnea, or hypotension. All of the symptoms subsided within several hours following oral corticosteroid therapy.

Laboratory blood examination revealed no abnormalities, except for slight elevation of the total serum IgE level (320 U/mL; reference range, 12–310 U/mL). The results of prick, scratch, and intradermal tests of loxoprofen sodium 0.1%, 1%, and 5% in distilled water were negative. With informed patient consent, an oral challenge test with 60 mg of loxoprofen sodium was conducted. Ingestion of the loxoprofen sodium tablet caused swelling of the right upper eyelid within 45 minutes, followed by swelling of the right bulbar conjunctiva (Figure, A). The reactions subsided after administration of intravenous hydrocortisone sodium succinate (total of 500 mg) over an hour. The results of oral challenges with diclofenac sodium, indomethacin, and tiaramide hydrochloride were negative. Based on the clinical course and the results of the oral challenge, we diagnosed her with a drug reaction caused by loxoprofen sodium.

*Patient 2*—A 30-year-old woman presented to our hospital with pruritic unilateral swelling of the right upper and lower eyelids after taking an unknown nonsteroidal anti-inflammatory drug (NSAID), possibly aspirin orally for headache. She noticed these symptoms twice and therefore had not been able to subsequently take any analgesic drugs. She was referred to our hospital for drug allergy testing. There were no abnormal laboratory findings. We initially tried prick and scratch tests using a variety of NSAIDS (ie, diclofenac sodium, tiaramide hydrochloride, loxoprofen sodium, meloxicam, acetaminophen, mefenamic acid, aspirin), but the reactions were all negative. Next, we initiated a challenge test using loxoprofen sodium because it is a commonly used drug in Japan (the market leader) and has a favorable side-effect profile. With informed consent obtained from the patient, we conducted an oral challenge test with 0.6, 6, 20, and 60 mg of loxoprofen sodium. There were no initial symptoms after 0.6, 6, or 20 mg of loxoprofen sodium challenge; however, within 90 minutes, she noticed swelling of the right bulbar conjunctiva as well as swelling of the right upper and lower eyelid with the 60-mg dose (Figure, B). The reaction subsided 3 hours after administration of a 5-mg prednisolone tablet. Based on the clinical course we have described, we diagnosed a drug reaction caused by loxoprofen sodium. A subsequent challenge test with another NSAID, tiaramide hydrochloride, caused no symptoms. The patient refused to be challenged with other NSAIDs.




Erythematous swelling of the right upper and lower eyelids and congestion of the right bulbar conjunctiva after a challenge test with loxoprofen sodium in patient 1 (A) and patient 2 (B).

## Comment

Loxoprofen sodium is an NSAID, which relieves inflammatory conditions.[3] It is an acid NSAID that belongs to the phenylpropionic acid group of drugs.[4] It is a prodrug that is converted from an inactive form to its *trans*-type active form after absorption. Its excretion into urine is rapid,[4] so it rarely causes side effects. It was reported that only 0.21% of 13,486 patients who were prescribed loxoprofen sodium showed skin-related side effects. Of 13,486 patients, 0.17% reported eczema, 0.08% itch, 0.04% urticaria, and 0.01% other skin-related side effects.[5] As this drug is mainly used in Japan, reports of side effects associated with loxoprofen sodium have been published mainly in Japan; thus far, multiple fixed drug eruptions,[6] urticarial drug eruptions,[4,7,8] overlap Stevens-Johnson syndrome and toxic epidermal necrolysis,[9] erythema nodosum,[5,10] erythroderma,[11] anaphylaxis,[12] vasculitis,[13] drug hypersensitivity syndrome,[14,15] acute generalized exanthematous pustulosis,[16] erythema of the lip and auricle,[17] and a psoriatic drug eruption[18] have been reported.

We believe that the drug reaction in both of our patients is angioedema because of the typical clinical appearance, the onset of symptoms within 1 to 2 hours, the unilateral nature of the reaction, the main symptoms being related to vascular dilatation, and the presence of pruritus. Phenylpropionic acid itself rarely causes urticarial drug eruptions, but 3 prior cases of urticarial drug eruption[4,7,8] and 1 case of anaphylaxis[12] have been reported to be induced by loxoprofen sodium. Because it is well-known that patients who are intolerant of aspirin also react to a variety of NSAIDs,[19] we conducted oral challenge tests in our patients; results with diclofenac sodium and indomethacin were negative in patient 1 and results were negative with tiaramide hydrochloride in both patients. Based on our findings, patient 1 is not aspirin intolerant, but because the second patient refused further challenge with NSAIDs, aspirin intolerance is a possibility. Thus far, we do not know why the symptoms always occur at the same sites (ie, right upper and lower eyelids, bulbar conjunctiva).

Unfortunately, results of the scratch test for loxoprofen sodium were negative in both patients. We believe it is likely that this discrepancy was caused by failure of the inactive loxoprofen sodium to be converted to the *trans*-type active form in the testing method that we used.

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