

Solifenacin-induced acute urticaria and angioedema: a rare adverse effect

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ABSTRACT

Antimuscarinics are first-line medication for management of overactive bladder with solifenacin being commonly prescribed. Angioedema is the swelling of mucosa and submucosal tissue. There are no published case reports of drug-induced angioedema involving solifenacin. We report a case of a 41-year-old man with spinal cord injury who presented with oedema of face, lips, tongue and associated pruritic urticaria after taking 5 mg of solifenacin. All other possible causes including food allergy, insect bite, hereditary angioedema, use of NSAIDs, ACE inhibitors and antibiotics were ruled out. The temporal association between solifenacin and angioedema and complete resolution of symptoms after discontinuing the drug suggest that solifenacin was the most probable cause of angioedema in our patient.

BACKGROUND

Angioedema, a rare and potentially life-threatening adverse effect, is swelling in the deep layers of the skin, often seen with urticaria (hives), most commonly involved areas being the face, lips, tongue, throat and genital areas.¹ Angioedema can affect mucosal area of gastro intestinal and respiratory system. Laryngeal swelling can be life threatening. Angioedema can be associated with anaphylaxis as well. On the basis of mechanism, angioedema can be classified as histamine-mediated (allergic) and non-histamine or bradykinin-mediated (non-allergic) angioedema. Angioedema can be broadly classified as hereditary, acquired and idiopathic. Neurogenic bladder dysfunction in patients of spinal cord injury (SCI) causes significant morbidity. It leads to incontinence, urinary tract damage, urinary tract infections and calculus formation.² Successful bladder management in SCI patients include combination of pharmacological agents and clean intermittent catheterisation (CIC).³ Anticholinergic (antimuscarinic) drugs are the first-line pharmacological option.⁴ Although these drugs have shown effectiveness; however, they do have side effects (table 1).⁵ To best of our knowledge, there is no case report on angioedema due to solifenacin reported in literature.

We report a case of SCI patient who developed angioedema plus urticaria after using solifenacin.

CASE PRESENTATION

A 41-year-old man, known case of complete paraplegia secondary to traumatic fracture dislocation of thoracic vertebrae 11 and 12, SCI T10, American spinal Injury Association (AIS) A, was admitted at our unit for SCI rehabilitation. Urodynamics

studies done for his bladder management showed low compliance bladder with terminal detrusor overactivity. He was trained in managing bladder with CIC. He was prescribed tab solifenacin 5 mg/day for management of detrusor overactivity and to improve detrusor compliance and discharged with home plan. Patient reported back after 3 weeks with swelling of face, lips, tongue and pruritic urticaria over trunk, arms and thighs including groin developed overnight. Patient gave history of episodes of pruritic urticaria but of mild intensity over last 2 weeks, resolving after taking oral antiallergics at home and no medical advice was taken. There were no past episodes of any allergic reaction. He had no known food or drug allergies and had not travelled recently. There was no family history of allergic reaction or atopy and no history/evidence of insect bite. He was not on NSAIDs, ACE inhibitors or antibiotics. On examination, there was no difficulty in breathing, swallowing, stridor or hoarseness of voice. He was haemodynamically stable with 97% SaO₂ at room air on pulse oximeter. Systemic examination was unremarkable.

INVESTIGATIONS

Laboratory findings were not significant, and the eosinophilic count was normal. Patient's C4, C1 esterase inhibitors and C1q binding assay were within normal range. Allergist clinical and laboratory evaluation was not done due to non-availability of such facility in the hospital.

DIFFERENTIAL DIAGNOSIS

Patient was diagnosed as a case of angioedema with urticaria. Normal complement levels ruled out hereditary angioedema. The adverse drug reaction was scored on Naranjo Probability Scale and the patient scored 6/10 showing a probable association between solifenacin and angioedema.⁶

TREATMENT

He was administered corticosteroid and antihistamine injections. Patient's facial, lip and tongue swelling as well as pruritic urticaria resolved completely over 2 hours. He was kept under observation for 24 hours. We suspected solifenacin as the possible trigger of angioedema and discontinued it. Solifenacin was replaced by tablet mirabegron 25 mg/day.

The temporal association between solifenacin and the occurrence of angioedema and immediate resolution of symptoms after discontinuing drug suggest that solifenacin was the most probable cause of angioedema plus urticaria in



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Table 1 Adverse drug reactions of antimuscarinic drugs⁵

Adverse reactions	Common (>10 %)	Less common (1%–10%)	Rare* (<1%)
Gastrointestinal	Xerostomia Constipation	Dyspepsia Nausea Vomiting Upper abdominal pain	Abnormal hepatic functions Decreased appetite GIT obstruction
Cardiovascular		Hypertension Lower extremity oedema	Atrial fibrillation Prolonged QT interval Torsades de pointes
Central nervous system		Fatigue Depression	Confusion Delirium Hallucination
Genitourinary		Urinary tract infection Urinary retention	Renal insufficiency
Ophthalmic		Blurred vision Dry eye syndrome	Glaucoma
Respiratory		Cough	Dry nose
Miscellaneous		Influenza	Anaphylaxis Angioedema Pruritus Urticaria

*Postmarketing and/or case reports.

our patient. The incident was reported to the clinical audit committee as per hospital's adverse drug reaction policy.

OUTCOME AND FOLLOW-UP

Patient was observed for 1 week. There was no recurrent episode of angioedema or urticaria so patient was continued on mirabegron for bladder management, in combination with CIC. He was discharged home. No other events were reported on monthly follow-up visits and the patient remained stable.

DISCUSSION

Solifenacin is a competitive inhibitor of muscarinic receptor, displaying highly bladder-selective profile (M3 receptor) as compared with other antimuscarinic drugs. Clinically, it has been found effective for management of overactive bladder (OAB) by decreasing detrusor muscle contraction and pressure.⁷ Most common adverse drug reactions to solifenacin, being anticholinergic, includes dry mouth, constipation, blurred vision and nausea.⁸ In the four 12-week double-blind clinical trials, angioedema was reported in one patient taking solifenacin.⁹

Angioedema represents swelling of mucosa and submucosal tissue, presenting clinically as swollen face, lips, throat, tongue and genitalia. Involvement of respiratory airways can have serious and life-threatening outcome. Drugs are second most common cause of angioedema after food. Drugs commonly causing angioedema include angiotensin-converting enzyme inhibitors, beta-lactam antibiotics, iodinated contrast media, aspirin and other NSAIDs, and statins.¹⁰ Angioedema can be divided into allergic and non-allergic angioedema. Allergic angioedema is histamine mediated, type I hypersensitivity reaction in which allergen cross links with IgE antibody on mast cells surface leading to its degranulation and histamine release. Clinically, it presents with acute onset of swelling of mucosa/submucosa tissues and associated typical urticarial rash. Symptoms respond quickly once treated with antihistamine, epinephrine and corticosteroid. Whereas, non-allergic angioedema is bradykinin mediated, without urticarial rash and with relatively

progressive onset in contrast to allergic angioedema.^{11 12} Mirabegron is β_3 -adrenoceptor agonist and causes bladder relaxation in patients of OAB. In four 12-week phase III studies, mirabegron demonstrated superiority over placebo with respect to OAB management.¹³ Another randomised, double-blind, phase III study concluded that both mirabegron and solifenacin improved OAB symptoms and there were no statistically significant differences between the two.¹⁴

We reviewed literature in detail and could not find any published case reports of solifenacin-induced angioedema.

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Contributors UY initially identified, managed and monitored the case. He conceptualised and designed the case report. He is the guarantor of case report. OS drafted the case report in addition to extensive literature research before submission for final approval. SNM revised it critically for important intellectual content and gave final approval of version to be submitted. MTK performed detailed analysis and independent literature research to improve the manuscript in line with the kind recommendations made by the reviewers and critically revised the manuscript before resubmission for approval.

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