

# Angioedema due to fixed dose combination of telmisartan plus ramipril

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## ABSTRACT

The risk for angioedema has been suggested lower with angiotensin receptor blockers (ARBs) than with angiotensin-converting enzyme inhibitors (ACEIs) or aliskiren. Many isolated reports do exist, reporting angioedema with ARBs such as olmesartan, valsartan, losartan and telmisartan. To the best of our knowledge this is the first case report of telmisartan plus ramipril fixed dose combination leading to angioedema from India questioning the rationality of ARBs plus ACEIs combination in the treatment of hypertension.

**Key words:** Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, fixed dose combination, Telmisartan, Ramipril

## INTRODUCTION

Anti-hypertensive drug combinations are very commonly prescribed in Indian population. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are among the first line anti-hypertensive drugs. However, the rationality of fixed dose combination of ACEIs and ARBs is a matter of ongoing debate. Some studies have reported beneficial effect of combination therapy on overt proteinuria in a patient with type 1 diabetic nephropathy<sup>[1]</sup> and reduction in left ventricular hypertrophy in hypertensive patients.<sup>[2]</sup>

However, recently a meta-analysis suggested that such combinations fail to reduce mortality and is associated with an excessive risk of adverse events such as hyperkalemia, hypotension and renal failure compared with monotherapy.<sup>[3]</sup>

Moreover, telmisartan has been shown equivalent to ramipril in patients with vascular disease or high-risk diabetes and less likely to cause angioedema. The combination of the two drugs however in the same study has been shown to be associated with more adverse events without an increase in benefit.<sup>[4]</sup> In spite of the non-availability of clear evidence of superiority of combination of ACEIs and ARBs, these combinations are still marketed and being prescribed. The risk for angioedema has been suggested lower with ARBs than with ACEIs or aliskiren.<sup>[5]</sup> However, many isolated reports do exist, reporting angioedema with ARBs such as olmesartan medoxomil, valsartan, losartan and telmisartan.<sup>[6-9]</sup>

Such an adverse drug reactions (ADR) may be potentially serious if not picked up and managed timely as it is usually associated with airway obstruction and respiratory distress

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which may lead to death in some cases. Although few isolated case reports with various ARBs exist<sup>[6-9]</sup> presenting with angioedema but to best of our knowledge this is the first case report of telmisartan plus ramipril fixed dose combination leading to angioedema from India questioning the rationality of this combination in management of isolated hypertension (HT).

## CASE REPORT

We hereby report a rare case of a telmisartan plus ramipril ( $40 \pm 5$  mg once daily) fixed dose combination induced angioedema in a 52 year old postmenopausal woman with 72 kg weight, prescribed for recently diagnosed stage-2 hypertension, as per Joint National Committee 7 (JNC-7) classification. She presented with diffuse swelling of her face, neck, lips and tongue 10 days after initiation of the fixed dose combination [Figure 1]. The patient presented in the emergency with complaints of low grade fever, dyspnea, breathlessness, restlessness, discomfort and chest pain. There was no associated urticaria or rash. On examination there was no pallor, cyanosis, pedal edema or signs of ischemic heart disease, chronic obstructive pulmonary disease and bronchial asthma. Pulse rate was 100/min and blood pressure measured in both limbs were 100/60 mm Hg. On auscultation, there was chest bilateral wheeze and stridor. There was no sign of any respiratory distress at the time of admission. Heart sounds were normal. Laboratory investigations are shown in table 1. Ultrasonography abdomen, electrocardiogram and troponin *t*-test were normal.

There was no family history or any such history in the past. There was no history of any ACEI or ARBs in past. The patient was advised to stop the drug, when the cause of the angioedema could not be ascertained thinking on the line that this ADR might be due to fixed dose combination (FDC) itself. The patient was given, intravenous (i.v) fluids; injection adrenaline

subcutaneous 0.2 ml of 1:10,000; injection hydrocortisone 100 mg i.v bd; inj chlorpheniramine i.v stat, intermittent oxygenation and nebulization with salbutamol followed by oral corticosteroids and anti-histaminic after 1 day of brief hospitalization. Tracheostomy was not required. Angioedema disappeared completely on the 8<sup>th</sup> day after stopping the drug and with medical intervention. No antihypertensive treatment was required for these 8 days. Later the patient was prescribed amlodipine 5 mg o.d. for the tight control of HT. Further re-challenge was not done in the interest of the patient fearing reappearance of ADR and ethical constraints. Thus, the appearance of angioedema in a patient taking FDC of telmisartan plus ramipril could not be explained by a concurrent disease, drug or chemicals and dechallenge along with medical intervention improved the condition. On literature search, there is no such report. However, numerous reports with ACEI and few reports of ARBs exist in the literature. The current case was reported to ADR Monitoring Center GMC/Jammu, vide no. 2933/090713/ADRM/Pharma/GMC/JMU.

## DISCUSSION

This ADR can be labeled “probable” as per causality assessment with Naranjo’s algorithm with a score of six<sup>[10]</sup> and possible as per World Health Organization-Uppsala monitoring center. The present ADR was not studied for dose dependent response and was unpredictable/unusual, thus it is difficult to label it as Type-A or B class of ADR.<sup>[11]</sup>

The mechanism of the current case report is not clear. However, angioedema is often associated with the use of ACEI and is related to their well-known mechanism due to accumulation of bradykinin, decreased aminopeptidase *P* activity and dipeptidyl peptidase *P* in the substance *P* degradation pathways. ARBs are rarely known to produce angioedema as they do not interfere with the level of bradykinin.

Angioedema has been reported with the use of ARBs in some reports.<sup>[6-9]</sup> In such cases it has been suggested that alternative pathways might be responsible for such an ADR. One of the hypotheses is that it may be due to overstimulation of angiotensin II AT2 receptors producing increase levels of bradykinin. However, it remains the matter of future research.

Angioedema related to ARBs is reported to be less severe and occurs earlier compared with angioedema that develops during ACEI therapy.<sup>[12]</sup>

The risk for angioedema has been recorded lower with ARBs than with ACEIs or aliskiren. A total of 4511 angioedema events (3301 for ACEIs, 288 for ARBs, 7 for aliskiren) has been observed with adjusted hazard ratios to be 3.04 (95% confidence interval [CI], 2.81-3.27) for ACEIs, 1.16 (95% CI, 1.00-1.34)



**Figure 1:** Angioedema due to fixed dose combination of telmisartan plus ramipril showing diffuse swelling on the face and lips

**Table 1: Laboratory investigations****Biochemical Parameters**

Hemoglobin 11 g%
Total leukocyte count 8400/cmm
Platelet count 2.4 lacs/cmm
Blood urea 26 mg
Serum creatinine 0.7 mg
Hemoglobin A1c 6.0%
Serum cholesterol 170 mg%
Serum triglyceride 165 mg%
High density lipoprotein 35 mg%
Blood sugar fasting 90 mg%
High-sensitivity C-reactive protein-0.7 mg/L
Erythrocyte sedimentation rate-8 mm/h
T3, T4 and thyroid stimulating hormone-95 ng/dl, 5.1 mg/dl, 2.20 µIU/ml
Liver function test-serum bilirubin (0.7 mg%), serum glutamic oxaloacetic transaminase (28 IU/L), serum glutamic pyruvic transaminase (30 IU/L)
Serum uric acid-5.4 mg%
Serum electrolyte levels-Sodium (139 mEq/L), potassium (4.1 mEq/L)
Routine urine examination-normal

for ARBs and 2.85 (95% CI, 1.34-6.04) for aliskiren in one of the study.<sup>[5]</sup>

In a study by Mancina and Schumacher, 2012<sup>[13]</sup> incidence rates of adverse events for the ACEI treatments and for telmisartan has been recorded similar (42.8% vs. 43.9%, respectively) and of the angioedema (0.2%) receiving ACEI versus none with telmisartan ( $P = 0.043$ ).

Furthermore, an estimate of a 10% or less incidence of cross reactivity of angioedema in patients who receive an ARB after experiencing ACEI-associated angioedema has been reported.<sup>[12]</sup>

Thus, it is very difficult to point out that which component of the fixed dose combination has caused angioedema in our case. As no sequential rechallenge was tried in this case to come to the final conclusion, it is beyond us to prove that angioedema was contributed by ARB use and whether there was any variation in severity and pattern of angioedema from reported cases of the angioedema presenting with ACEI or ARBs monotherapy.

The current case report is in accordance to the findings of Makani *et al.*,<sup>[3]</sup> and ONTARGET Investigators *et al.*,<sup>[4]</sup> as it clearly questions the rationality of FDC of telmisartan plus ramipril. Such combination has been shown not to provide any clear cut beneficial effect rather it may add on adverse effects due to both the components. The current case report contradict the findings of Kuriyama *et al.*,<sup>[1]</sup> and Avanza Jr *et al.*,<sup>[2]</sup> who support the hypothesis of combining ARBs with ACEI for treatment of HT.

The current case cautions to all the practitioners not to prescribe such fixed dose combination to stage 2 HT. Such combination has not being recommended also to be prescribed under JNC-7 guidelines for stage-2 HT. Moreover, such untoward effect may be potentially serious and life threatening if not picked up and managed timely warranting legal implications also to the prescriber.

## CONCLUSION

The current case report calls for greater vigilance to be adopted by practitioners while making a choice for the treatment of uncomplicated HT and to avoid using fixed dose combination of ACEI and ARBs till some conclusive evidence emerge in its favor as it can present with some cumulative serious life-threatening ADRs like angioedema.

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