Letter to the Editors

Safety of olmesartan in a patient with telmisartan-induced myotoxicity: a case report

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Introduction

Drug-induced myotoxicity ranges from asymptomatic elevation of creatinine phosphokinase (CPK) to rhabdomyolysis [1]. Various routinely prescribed medications, such as statins, corticosteroids, antiretrovirals and immunosuppressants, are known to cause myotoxicity as a common side-effect [1]. Angiotensin receptor blockers (ARBs) are another class of routinely used drugs known to cause myotoxicity. According to the prescribing information on the various ARBs, myalgia with elevated CPK has been reported as a common adverse event (≥1/100, <1/10) with telmisartan and as an uncommon (≥1/1000, <1/100) or very rare adverse event (<1/10 000) with olmesartan, losartan, candesartan and valsartan [2, 3]. Although all the ARBs are known to cause myotoxicity, with varying incidences, there are no data on the cross-reactivity of the ARBs in causing myotoxicity. Here, we report a case of telmisartan-induced myotoxicity that did not have cross-reactivity with olmesartan.

Case report

A 49-year-old man, a doctor (weight 90 kg; height 165 cm; body mass index 33.1 kg m−2), was known to have hypertension and was taking 20 mg olmesartan per os (p.o.) every 12 h, with metoprolol 50 mg p.o. and torsemide 5 mg p.o. every 24 h. During his regular follow-up visit, his blood pressure was found to be elevated. On repeated examination after a few days, his blood pressure was still elevated; therefore, his antihypertensive regimen was changed to telmisartan 80 mg p.o. plus chlorothalidone 12.5 mg p.o., with bisoprolol 5 mg p.o. plus amlodipine 5 mg p.o. every 24 h.

After about 2–3 weeks on this new regimen, the patient's blood pressure was well controlled and he continued to take this regimen of four drugs. After ∼6 weeks of continued treatment he complained of malaise, low-grade fever and muscle pain.

On preliminary investigation, his complete blood count, erythrocyte sedimentation rate, peripheral blood smear, urine test and chikungunya antigen test were found to be within clinically acceptable limits, but his serum CPK level was found to be elevated [1022 U dl−1 (normal 25–308 U dl−1)]. The patient did not have a history of statin or other medical therapy, vigorous exercise, smoking, alcohol intake or previous similar complaint. He was treated symptomatically, but his condition did not improve; instead, his muscle pain increased and he also developed muscle weakness in the following week.

As his condition deteriorated clinically, additional investigations such as serum thyroid-stimulating hormone, T3, T4, and electrolytes were performed to rule out other medical conditions, but all these were found to be within a clinically acceptable range. This time, his CPK level was further raised to 1650 U dl−1. As no pathology could be detected, the antihypertensive medicines were suspected to be the culprits. According to the statin-related myotoxicity (SRM) phenotype classification of Alfirevic et al., this myotoxic reaction belonged to category 3 [4].

His new regimen was withdrawn completely and returned to the old regimen, consisting of olmesartan, metoprolol and torsemide. After 5 days of this regimen, the patient’s symptoms started to improve and his CPK level was found to be 332 U dl−1. After 15 days, the patient had completely recovered and his CPK levels were in the normal range (blood pressure 160/90 mmHg). Being a doctor himself, the patient challenged himself by replacing olmesar t and torsemide with telmisartan 80 mg p.o. plus chlorothalidone 12.5 mg p.o. from his regimen (he continued to take metoprolol at the prescribed dosage). On the third day, he started to experience muscle pain (category 1 according to the statin-related myotoxicity classification). He immediately switched back to his original regimen of olmesartan and torsemide and became free of symptoms within 48 h.
After 2 months on a stable regimen of olmesartan, metoprolol and torsemide, the patient rechallenged himself by replacing torsemide 5 mg p.o. with chlorothalidone 12.5 mg p.o. (blood pressure 164/90 mmHg). The patient did not have any symptoms of myotoxicity and his CPK level was 199 U dl⁻¹ after taking chlorothalidone along with olmesartan and metoprolol for 2 months.

The patient was finally maintained on a four-drug regimen of olmesartan 20 mg, chlorothalidone 12.5 mg and bisoprolol 5 mg plus amlodipine 5 mg for >7 months and experienced good blood pressure control without any signs of myotoxicity. On the World Health Organization causality assessment scale, myotoxicity with telmisartan was found to be ‘certain’ [5].

**Discussion**

This is a case of a patient who developed muscle pain and weakness along with elevation of CPK approximately five times the upper normal limit. The temporal relationship between the suspected drug and occurrence of the event, exclusion of other causes, positive dechallenge and rechallenge with the combination of telmisartan plus chlorothalidone and a negative rechallenge with chlorthalidone alone confirmed telmisartan as the offending agent.

Drug-induced myotoxicity can be caused by various different on-target or off-target actions of the drugs. It has been hypothesized in previous published reports that angiotensin II can cause muscle atrophy through inhibition of protein synthesis and augmentation of proteasome activity. Myopathy has also been reported with angiotensin-converting enzyme inhibitors such as captopril, ramipril and enalapril due to their effect on angiotensin II concentrations, but the myotoxicity in our case could not be attributed to the effect on angiotensin II only, because both telmisartan and olmesartan have similar effects on the renin–angiotensin system [6, 7].

Some ARBs have an off-target action on peroxisome proliferator-activated receptor-γ (PPAR-γ) and have been found to increase insulin sensitivity in the skeletal muscles [8]. Telmisartan and irbesartan induce transcriptional activity of PPAR-γ at therapeutic levels, while losartan affects PPAR-γ at a high concentration, and other ARBs, such as eprosartan, olmesartan and valsartan, do not have any effect on PPAR-γ activity [8, 9]. The PPAR-γ-activating effect of ARBs is independent of their action on the renin–angiotensin system [8]. Increased activity of PPAR-γ has been associated with myalgia and rhabdomyolysis. Drugs that primarily modulate PPAR-γ activity, such as pioglitazone, troglitazone and rosiglitazone, are associated with similar adverse events; thus, the off-target action of telmisartan on PPAR-γ activity could be one of the reasons for myotoxicity in our case [10–12]. Lipophilicity is an important factor that enables drugs to cross cell membranes, and lipophilic drugs have greater affinity for the PPAR-γ receptor. Although all the ARBs are lipophilic to some extent, their lipophilicity varies markedly. Telmisartan is highly lipophilic, whereas olmesartan is the least lipophilic [13]. Differences in lipophilicity and activation of PPAR-γ receptor may be the reason for development of this reaction with telmisartan but not with olmesartan.

A patient who develops myotoxicity due to an ARB can be prescribed other ARBs which lack the PPAR-γ-activating property and are least lipophilic. Early identification and withdrawal of an offending agent can prevent further damage. Administration of other concomitant myotoxic drugs should be carried out with caution.

**Competing Interests**

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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