Pharmacologic Leg Pain: An Unrecognized Cause of Claudication

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Case Study

A 63 year-old male patient with a 10-year of chronic hypertension was well controlled on Olmetec (olmesartan medoxomil, Merck Canada Inc., Kirkland, PQ). In 2018, when Olmetec came off patent, generic versions became available. For two months while on generic olmesartan medoxomil (JAMP Pharma Group, Boucherville, PQ), the patient noted unusual episodic, fleeting pain localized in the lateral thigh or calf either proximal or distal but always highly variable with its location and intensity. The pain was aching, like a vise. It could occur at rest but was dramatically worsened with exercise, primarily walking. When it occurred with walking, the patient needed to stop. After resting, the patient could walk again for the same variable distance. Physical examination of the lower extremities showed that his pedal pulses and Doppler examination (including the ankle-brachial index) was normal. CPK and LDH were normal. X-Rays of the hips and back showed normal changes related to age. An MRI of the head and spine was also normal. When the pain caused progressive shortening of the walking distance and rest pain that woke the patient from sleep, generic olmesartan was voluntarily stopped. Within 5 days, the pain had significantly reduced and the patient was able to walk any distance without stopping. However, the patient’s blood pressure had increased, so the patient resumed the medication (Figure 1). Again, within 5 days, the same left lower extremity symptoms returned (the right lower extremity was always asymptomatic) as before. When this occurred a second time, the patient stopped the generic medication completely and informed his family physician. Olmetec was restarted. This incident was reported to Health Canada.

Discussion

Claudication was first described by Charcot in 1858 as “weakness, numbing, cramming and stiffness of the legs with walking” [1]. It is classified as either arteriogenic (from intraluminal or extraluminal causes) or neurogenic. Arteriogenic claudication is a symptom of peripheral arterial disease with patient complaints of pain is the muscle beds of the buttock, thigh, calf, or foot with ambulation. Uncommonly, arteriogenic claudication may present due to vascular conditions such as popliteal artery entrapment, adventitial cystic disease, and venous compartment syndrome [2]. Poor arterial flow results in hypoperfusion of affected muscles during exercise but is quickly relieved with rest. These symptoms are presumably due to the accumulation of lactic acid in the exercising muscle.

Neurogenic conditions such as nerve root compression from herniated disks, spinal stenosis [3], and tumors of the spinal cord may also produce symptoms that mimic arteriogenic claudication [4]. However, these symptoms typically occur with changes in posture, are not quickly relieved with rest, and produce different qualities of pain often described as sharp or lancinating and radiating down the leg [2]. Nonetheless, both conditions tend to occur in the elderly and can be difficult to distinguish [1]. The etiology of how nerve root irritation causes these symptoms is not understood.

In this case report we describe another condition that can mimic arteriogenic claudication, viz. drug side effect. The patient described had no clinical signs of peripheral arterial disease (normal pulses and Doppler examination) and no evidence of degenerative disk disease based on the MRI results. Although he was not taking statins, a class of medications known to produce thigh pain, his CPK was normal. The patient had noted that there had been a change to a generic form of Olmetec in the months preceding the onset of pain. By withdrawing the generic drug and noting resolution of pain followed by reintroducing the drug (when his blood pressure became elevated) with resumption of the pain confirmed the diagnosis as the other more common possibilities had been excluded.

The drug in question, olmesartan, is a member of the "sartan" family of Angiotension Receptor...
Blockers (ARB). Since 2018 more than two dozen ARB products have been recalled in the United States due to the presence of potentially carcinogenic nitrosamine impurities in some lots of these drugs. The concern has been that nitrosamine impurities can form during active pharmaceutical ingredient processing [5]. In Canada, five sartan drugs (valsartan, candesartan, irbesartan, losartan, and olmesartan) have been reviewed with several valsartan products being recalled. All five compounds share a tetrazole ring in their structures [6]. At present, Health Canada has requested companies recall products found to contain excessive nitrosamine levels. In addition, the import of active pharmaceutical ingredients from the Zhejiang Huahai Pharmaceuticals in China has been stopped due to concerns with their manufacturing process. For patients, however, there have been no recommendations to stop using these medications as there is no immediate risk [6].

Muscle cramps, pain, spasm, or stiffness are rare reported side effects of olmesartan [7]. The cause of this is unknown. In this case, why these symptoms occurred only with the generic version raises the question of how different are generic versions of brand-name drugs. In a meta-analysis of 47 articles covering cardiovascular medications including ARBs, Kesselheim et al. showed no evidence of the superiority of brand-name drugs compared with generics although many editorials recommended against the interchangeability of brand-name drugs with generics [8]. More recently, Leclerc et al. reported on the adverse outcomes of three generic ARBs (losartan, valsartan and candesartan) in the province of Quebec, Canada, following commercialization of their generic versions. Among generic users, there was a significant immediate or delayed increase in adverse event rates right after generic commercialization for all three ARBs [9]. This sobering finding suggests that the increase in adverse events following the release of generic medications may lead to additional emergency room visits, hospitalizations and cost. Nonetheless, this was an observational study and systemic biases such as the preferential use of generics based on socioeconomic class may exist [10].

In conclusion, pharmacologic claudication should be considered if arteriogenic and neurogenic causes of claudication have been excluded. Especially, this should be considered if a patient develops unusual symptoms following changing from a well-tolerated name brand drug to its generic version.

References