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Ramipril

Updated: February 11, 2018.

OVERVIEW

Introduction

Ramipril is an angiotensin-converting enzyme (ACE) inhibitor used in the therapy of hypertension and heart failure. Ramipril is associated with a low rate of transient serum aminotransferase elevations and has been linked to rare instances of acute liver injury.

Background

Ramipril (ra' mi pril) is an ACE inhibitor widely used in the therapy of hypertension, heart failure and for reduction in risk of myocardial infarction and stroke. Like other ACE inhibitors, ramipril inhibits the conversion of angiotensin I, a relatively inactive molecule, to angiotensin II which is the major mediator of vasoconstriction and volume expansion induced by the renin-angiotensin system. Other enzymes besides that which converts angiotensin I to II may also be inhibited, which may account for some of the side effects of ramipril and other ACE inhibitors. Ramipril was approved for use in the United States in 1991 and is available in 1.25, 2.5, 5 and 10 mg capsules or tablets in generic forms and under the trade name Altace. In adults, ramipril is usually started in a dose of 2.5 mg daily and then adjusted based upon blood pressure response and tolerance to 10 to 20 mg daily. It is typically used long term. Common side effects include dizziness, fatigue, headache, cough, gastrointestinal upset and skin rash.

Hepatotoxicity

Ramipril, like other ACE inhibitors, has been associated with a low rate of serum aminotransferase elevations (<2%) that, in controlled trials, was no higher than with placebo therapy. These elevations were transient and rarely required dose modification. Rare instances of clinically apparent acute liver injury have been reported with ramipril therapy. The onset is usually within 2 to 12 weeks of starting therapy and the serum enzyme pattern is typically cholestatic (Case 1). In some instances, cholestasis has been prolonged and relapsing and associated with persistent elevations in serum alkaline phosphatase, suggestive of vanishing bile duct syndrome. Immunoallergic manifestations (rash, fever, eosinophilia) are infrequent and most patients do not develop autoantibodies. Rare instances of ramipril injury with a hepatocellular pattern and cases with a long latency (one or more years) have been described as well. Likelihood score:

Likelihood score: C (probable rare cause of clinically apparent liver injury).

Mechanism of Injury

The cause of the minor serum aminotransferase elevations associated with ramipril therapy is not known. The clinically apparent acute liver injury due to ramipril is idiosyncratic and is likely due to a reaction to a minor metabolite. Ramipril is hydrolyzed in the liver to its active carboxylic metabolite ramiprilat, but undergoes little further hepatic metabolism.

Outcome and Management

Only a few cases of ramipril associated liver injury have been reported, but the rare instances that have been published have resembled typical ACE inhibitor related hepatic injury. Most instances of acute liver injury related to ACE inhibitors have been self limited, but severe cases of cholestatic hepatitis can result in prolonged jaundice and vanishing bile duct syndrome. Patients with severe ramipril induced acute liver injury or hypersensitivity should avoid use of other ACE inhibitors, although cross sensitivity to liver injury among the members of this class of agents has not always been shown.

References to the safety and potential hepatotoxicity of ramipril are given in the Overview section on the Angiotensin-Converting Enzyme (ACE) Inhibitors.

Drug Class: Antihypertensive Agents, Angiotensin-Converting Enzyme Inhibitors

CASE REPORT

Case 1. Acute hepatitis due to ramipril.

[Modified from: Yeung E, Wong FS, Wanless IR, Shiota K, Guindi M, Joshi S, Gardiner G. Ramipril-associated hepatotoxicity. Arch Pathol Lab Med 2003; 127: 1493-7. PubMed Citation]

A 51 year old Jamaican born man was started on ramipril and atorvastatin after an acute myocardial infarction and 2 weeks later developed anorexia, jaundice and pruritus. He had a history of tuberculosis, recurrent kidney stones and parotid gland infections, and type 2 diabetes. His only other medications at the time were insulin and aspirin, and he specifically denied use of over-the-counter and herbal preparations. He had no history of liver disease, alcohol abuse or risk factors for viral hepatitis. Laboratory testing showed a total bilirubin of 8.4 mg/dL and alkaline phosphatase of 112 U/L (Table). Both atorvastatin and ramipril were discontinued, but he did not improve and subsequently developed diarrhea and weight loss. Three months after onset he was reevaluated. Tests for hepatitis A, B and C were negative as were autoantibodies. Endoscopic retrograde cholangiopancreatography showed no evidence of biliary obstruction. A liver biopsy showed marked cholestasis, bile duct injury and increased fibrosis compatible with early cirrhosis. He was treated with ursodiol but continued to have jaundice. A year after onset of injury, he was found to have ascites and esophageal varices. Two years later he was still jaundiced. He was listed for liver transplantation but returned to his country of origin and was lost to follow up.

Key Points

Medication:	Ramipril (2.5 mg daily)
Pattern:	Cholestatic
Severity:	4+ (prolonged jaundice)
Latency:	4 weeks
Recovery:	None
Other medications:	Atorvastatin, insulin, aspirin

Laboratory Values

Months After Starting	Months After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
1	0		112	8.4	Anorexia, pruritus
4	2.5	103	957	15.5	INR=1.22, liver biopsy
15	4	71	939	11.8	INR=1.3
Normal Values		**<45**	**<125**	**<1.2**	

Comment

Case 1 from a published series of 3 patients with suspected ramipril induced liver injury from an experienced group of hepatologists from Toronto. The latency period of 4 weeks and general clinical presentation as cholestatic hepatitis is typical of ACE inhibitor related drug induced liver injury. While few cases have been linked to ramipril, the lack of other explanations for the liver injury in the three cases and improvements on stopping ramipril in the other two cases were highly suggestive of its role. Patient 1 had persistence of jaundice after the initial episode and a subsequent course that was suggestive of vanishing bile duct syndrome.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Ramipril – Generic, Altace®

DRUG CLASS

Angiotensin-Converting Enzyme Inhibitors

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Ramipril	87333-19-5	C23-H32-N2-O5