Acute Hepatotoxicity Caused by Enalapril: a Case Report

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Abstract

A case of enalapril-induced acute hepatotoxicity with an unusual morphology is described. This morphology was characterized by macro- and microvesicular steatosis associated with neutrophil infiltration and Mallory bodies, occasionally with satellitosis. These alterations were most abundant in zone 1 of the periportal region, less common in zone 2 and rare in zone 3. There was also confluent periportal necrosis with sinusoidal fibrin deposits associated with intense ductal metaplasia and an infiltrate of inflammatory cells that included plasmocytes and a few eosinophils, as well as focal biliary damage. This morphology, that may be referred as „predominantly periportal steatohepatitis”, was distinct from that associated with non-alcohol and alcohol-induced steatohepatitis, both initiated in acinar zone 3 and subsequently extended to other zones.

Keywords

ACE inhibitors – enalapril – acute hepatotoxicity – liver steatosis.

Introduction

During the last 20 years, angiotensin-converting enzyme (ACE) inhibitors have been extensively used to treat cardiovascular disorders, including hypertension. These drugs are generally well tolerated [1, 2]. However, hepatic injuries, which are rare [3, 4], have been reported in patients treated with captopril [5-8], lisinopril [9, 10], ramipril [2] and enalapril [1,11-14,15-18]. In this report, we describe a case of acute hepatotoxicity that involved unusual morphological alterations referred to as „predominantly periportal steatohepatitis” in an individual treated with enalapril.
Although there were many potentially hepatotoxic chemicals involved in this case, the clinical signs and laboratory findings following the re-introduction of enalapril therapy, together with the total recovery in hepatic function when treatment with enalapril was interrupted, confirmed this drug to be the cause of hepatotoxicity.

An overdose of acetaminofen (paracetamol) can result in perivenular necrosis (acinar zone 3), with panacinar necrosis leaving only small portions of normal tissue in the periportal region [4, 19]. This damage profile is completely different from that seen here.

Intoxication by diazinon (Madaldrin-Pikapau®, an organophosphate) results in manifestations typical of poisoning by organophosphates, including the cholinergic syndrome [20], but was not present in our patient. Poisoning by Mirex-S-Sulphluramide® (N-ethyl-perfluoroctane sulfonamide), a fungicide with intrinsic hepatotoxicity, causes typical periportal steatosis in rats [21], similar to that seen here. However, the patient had had only minimal contact with this agent. In addition, such hepatic damage has been

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<th>Biochemical data upon admission and at subsequent intervals.</th>
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<td><strong>Total bilirubin (mg/dl)</strong></td>
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**Fig 1.** A – Periportal steatosis and associated focal parenchymal infiltrate of inflammatory (predominantly polymorphonuclear) cells (H-E, x40). B – Detail of (A) (H-E, x400). C – Confluent periportal necrosis with sinusoidal deposits of fibrin (H-E, x100). D – Portal infiltration of inflammatory cells, mainly plasmocytes, with focal damage to biliary ducts (H-E, x200).
Acute hepatotoxicity caused by enalapril

reported exclusively in rats, with no descriptions in humans. Intoxication by Tanidi® [an ectoparasiticide (Carbaril) - associated with cipermetrine] can result in transitory disturbances in carbohydrate metabolism, protein synthesis and normal detoxification functions. In addition, Carbaril causes transitory inhibition of cholinesterase activity [22]. Our patient showed none of these alterations.

The patient had been on corticoid therapy (40 mg/day) for one year, and this could have contributed to the development of steatosis. In addition, the patient had recently been in contact with organic solvents that cause direct or indirect hepatotoxicity, possibly involving auto-immune mechanisms. However, since the patient’s contact with these substances had been minimal, they were not considered to be the principal cause of the damage observed.

The histological analysis of hepatic tissue excluded chronic hepatitis caused by SLE since this is normally characterized by autoimmune responses, e.g., a portal infiltrate of lymphomononuclear inflammatory cells rich in plasmocytes, with intense parenchymal involvement, including the formation of pseudo-rosette hepatocytes.

Liver injury caused by toxins or chemicals is generally associated with acute or chronic damage. Injury by cytotoxins is characterized by necrosis, steatosis or both, whereas cholestatic lesions are characterized by bile retention and may or may not be associated with portal inflammation. Chronic injuries include chronic hepatitis, steatosis, phospholipidosis, veno-occlusive illness, cirrhosis, peliosis and neoplasia. Such damage may involve intrinsic toxicity of the compound itself, uncommon host susceptibility or a combination of both. Uncommon susceptibility may result from immunological idiosyncrasy (hypersensitivity reaction) or toxic reactions to drug metabolites (metabolic idiosyncrasy) [23]. In this regard, the mechanism by which ACE inhibitors cause liver injury remains unclear, mainly because of the lack of a suitable experimental model [23]. An immunological idiosyncrasy could be involved and would concord with the low incidence of this phenomenon, its occurrence at low doses and the range of clinical manifestations (cutaneous rash, fever, myalgia and eosinophilia) that may accompany this response [7, 10]. On the other hand, a metabolic idiosyncrasy could involve the sulphhydryl group or terminal proline ring of captopril; this ring structure also occurs for the leucotriene levels, resulting in hepatocellular and biliary damage may involve intrinsic toxicity of the compound itself, uncommon host susceptibility or a combination of both. Uncommon susceptibility may result from immunological idiosyncrasy (hypersensitivity reaction) or toxic reactions to drug metabolites (metabolic idiosyncrasy) [23]. In this regard, the mechanism by which ACE inhibitors cause liver injury remains unclear, mainly because of the lack of a suitable experimental model [23]. An immunological idiosyncrasy could be involved and would concord with the low incidence of this phenomenon, its occurrence at low doses and the range of clinical manifestations (cutaneous rash, fever, myalgia and eosinophilia) that may accompany this response [7, 10]. On the other hand, a metabolic idiosyncrasy could involve the sulphhydryl group or terminal proline ring of captopril; this ring structure also occurs for

The inhibition of bradykinin inactivation could result in enhanced arachidonic acid release and conversion into prostaglandins such as 16,16-dimethyl-prostaglandin E2 that reduces bile flow in humans. Biliary stasis would increase the leucotriene levels, resulting in hepatocellular and biliary toxicity, as seen in animals with ligated biliary ducts [2, 6]. A metabolic idiosyncrasy may also involve reactive metabolites produced by the cytochrome P450 system, with direct or immune-mediated toxicity; indeed, cytochrome P450 may be involved in the activation of enalapril and glutathione detoxification [11]. Modulation by enhanced eicosanoid formation and increased hepatic bradykinin levels has also been suggested [3, 6, 11]. In agreement with this, several of the clinical and laboratory findings of our patient (fever, cutaneous rash, myalgia and eosinophilia) must be thought of as manifestations of an immunological idiosyncrasy [7, 10]. However, the long period between the beginning of enalapril treatment and the first signs of liver damage suggests the possibility of a metabolic idiosyncrasy [4].

In the present case, an enalapril dose of 10 mg/day was apparently well-tolerated for 2.5 years. However, an increase in the dose to 20 mg/day during the previous six months coincided with the clinical alterations described here. Other literature reports of hepatotoxicity caused by enalapril have shown that the onset of clinical manifestations occurs within a few weeks [12] to four years [11] after the start of treatment. In a similar case, captopril at a dose of 25 mg/day was well-tolerated for two years, but when the dose was increased to 50 mg/day the patient presented with jaundice and mental confusion six weeks later.

There is little information on the hepatic morphological alterations caused by enalapril and other ACE inhibitors. Specifically for enalapril, the alterations reported include (a) destructive cholangitis with ductopenia and insufficient ductal proliferation evolving to chronic cholestasis [12], (b) minimal cholestasis associated with a moderate inflammatory infiltrate and fibrosis [11], (c) areas of focal necrosis, predominantly centrolobular, with a parenchymal inflammatory infiltrate and portal mixture containing eosinophils, lymphocytes, plasmocytes and histiocytes arranged in a granuloma-like formation [18], (d) sudden hepatitis with massive hepatic necrosis [13], and (e) confluent necrosis, with architectural collapse similar to the disorganization seen in halothane-induced hepatotoxicity, including an inflammatory infiltrate and moderate eosinophilia [1].

Hepatic damage associated with captopril includes massive hepatic necrosis [5], portal widening with a chronic inflammatory infiltrate and interface activity (active chronic hepatitis) [5], and cholestatic alterations with biliary plugs within canaliculari, feathery degeneration of hepatocytes and portal inflammatory infiltrate of lymphomononuclear cells with or without eosinophils [5, 8]. With regard to the use of ramipril, the principal alterations involved include cholangiodestructive injuries resulting in ductopenia, with incipient evolution to biliary cirrhosis [2] while for lisinopril the major changes involve centrolobular necrosis, cholestasis and an inflammatory infiltrate of polymorphonuclear cells with a portal and parenchymal localization [10].

None of the foregoing reports described morphological alterations similar to those seen here, including the extensive perportal necrosis. The few agents that typically produce such injury include phosphorus, ferrous sulfate (high doses), acetic acid (90%), allyl alcohol and its esters, Proteus endotoxins, and certain compounds such as halothane [23]; none of these substances was involved in this case.

The present case clearly shows that enalapril can cause significant and unusual hepatic morphological lesions, and also highlights the need for close clinical monitoring, possibly including hepatic histological analysis of patients being treated with enalapril.
References