LOSARTAN-INDUCED SUB-FULMINANT HEPATITIS: A CASE REPORT AND LITERATURE REVIEW
HEPATITE SUB-FULMINANTE INDUITE PAR LE LOSARTAN : CAS CLINIQUE ET REVUE DE LA LITTERATURE

H. AFFES[1,3,*]; L. CHTOUROU[2,3] ; S. HAMMAMI[1,3]; Z. SAHNOUN[1,3]; N. TAHRI[2,3]; K. M. ZEGHAL[1,3] ET K. KSOUDA[1,3]

1: Laboratory of Pharmacology - Sfax- Tunisia
2: Departement of Gastroenterology, Hedi Chaker University Hospital – Sfax - Tunisia
3: Faculty of Medicine - University of Sfax - Tunisia

***E-mail de l'auteur correspondant :** affeshanen13@yahoo.fr

Abstract

Losartan, an angiotensin II receptor antagonist (ARBs), is widely used for treatment of hypertension and heart failure. It was rarely responsible of severe adverse drug reaction. Losartan-induced hepatic toxicity was rare. The causality assessment of losartan- induced liver injury was evaluated according to conclusions of the international consensus meeting. We report a case of severe liver injury induced by losartan. We review the mechanism and risk factors of this adverse effect. The clinician should be aware of this toxicity, especially during the initial phase of treatment to avoid serious consequences.

Key - words: Losartan; Hepatic injury; Severe hepatitis; Adverse effect.

Résumé

Le losartan, un antagoniste des récepteurs de l'angiotensine II (ARA), est largement utilisé pour le traitement de l'hypertension et de l'insuffisance cardiaque. Il a rarement été responsable d'un effet indésirable grave. La toxicité hépatique induite par le losartan est rare. L'évaluation de l'imputabilité des lésions hépatiques au losartan a été évaluée conformément aux conclusions de la réunion de consensus internationale. Nous rapportons un cas d'atteinte hépatique sévère induite par le losartan. Nous passons en revue le mécanisme et les facteurs de risque de cet effet indésirable. Le clinicien doit être averti de cette toxicité, en particulier pendant la phase initiale du traitement pour éviter des conséquences graves.

Mots - clés: Losartan ; Lésion hépatique ; Hépatite grave ; Effet indésirable.

ملخص

يستخدم اللوسارتان ، وهو أحد مضادات مستقبلات الأنجيوتنسين 2 (ARBS) ، على نطاق واسع في علاج ارتفاع ضغط الدم وفشل القلب. نادرا ما كان مسؤولا عن رد فعل دوائي ضار شديد. كانت السمية الكبدية التي يسببها اللوسارتان نادرة للغاية. تم تقييم العلاقة السببية لإصابة الكبد التي يسببها اللوسارتان وفقًا لاستنتاجات اجتماع الإجماع الدولي. أبلغنا عن حالة إصابة الكبد الحادة الناجمة عن اللوسارتان. نقوم بمراجعة الآلية وعامل الخطر المتسببين في هذا التأثير الضار.
يجب أن يكون الطبيب على دراية بهذه السمية ، خاصة خلال المرحلة الأولى من العلاج لتجنب العواقب الوخيمة.

الكلمات المفاتيح : اللوسارتان ; إصابة الكبد ; الآثار السلبية.

INTRODUCTION

Losartan, a-benzylimidazole-5 acetic acid derivative, was the first angiotensin II antagonist to be marketed. It was prescribed for control of essential hypertension and heart failure. This class of drugs selectively blocks angiotensin II subtype 1 receptor, which responsible for pressure-related effects of angiotensin. Losartan was a very well tolerated drug. It was rarely implicated in severe life threatening adverse effect [1, 2]. We report a losartan- induced fatal liver injury.

CASE REPORT

A 76-year-old woman, with no history of liver disease, illness involving the biliary tract, blood transfusion or alcohol abuse, treated for more than 3 years with alendronate for osteoporosis. For hypertension, she started taking losartan 50 mg daily. Thirty days after, she developed tea-colored urine and jaundice. This symptomatology worsened progressively and she became obnubilated and sedated. So, she was hospitalized and losartan with alendronate were stopped. Physical examination revealed icterus and mild abdominal tenderness under the right costal arch, without fever, ascites, hepatomegaly or other signs of heart and lung abnormality on auscultation. Liver biochemical tests were listed in table I. Blood cell counts showed a normal eosinophil counts. Abdominal ultrasound examination completed with biliary magnetic resonance imaging showed a peri portal edema with thickening of the gallbladder wall suggestive of hepatitis with no bile duct dilatation. Tests for hepatitis B virus, A virus, C virus and cytomegalovirus were all negative. Anti mitochondrial, antinuclear, anti-smooth muscle and liver kidney microsomal antibodies were absent in the serum. An echocardiogram and a doppler ultrasound exam wasn't reveal signs of right heart failure. Hepatic veins and inferior vena cava were not dilated. A liver biopsy was done revealing drug-induced hepatitis with isolated cytolysis, inflammatory foci and moderate or minimal cholestasis intra hepatocyte or intra canalicular. The tumor markers (carbohydrate antigen 19-9, alpha-fetoprotein, carcinoembryonic antigen) were negative. Ten days after his hospitalization, hepatic disorders were deteriorated with a prothrombin time evaluated as 35%. She developed encephalopathy degree IV and died few days after.

DISCUSSION

According to conclusions of the International Consensus Meeting [3], the type of liver damage in this case was hepatocellular. The causality assessment of losartan- induced liver injury (applying the CIOMS score: council for international organizations of medical sciences) was probable for the following reasons: (a) no history of disease of the liver or biliary tract; (b) no other cause of acute hepatitis based on negative diagnostic work-up; (c) losartan was the drug recently given to this patient; (d) liver injury worsened as long as this drug was administered; (e) other drugs were administered for more than 3 years, without any adverse reaction. Other etiologies excluded in our case by detailed investigations, and a liver biopsy was performed, which revealed findings of drug induced hepatitis.

Drug-induced liver injury was often reversible. Stopping earlier the responsible-drug, could avoid serious and sometimes irreversible damages. In our patient, liver injury was severe (prothrombin level at 35% and encephalopathy) and probably irreversible unlike cases published in the literature.

Losartan could rarely induce life-threatening adverse effect. A first severe hepatic encephalopathy induced by losartan associated with angiotensin-converting enzyme inhibitor (ACEIs) in patient with liver cirrhosis, has been reported by Oertelt-Prigione S *and al* [1]. In our case, liver damage may be potentiated by association with alendronate which also could induce hepatitis in predisposed patient [2]. Raised liver enzyme values have occurred rarely in patients receiving losartan. In the literature, severe acute hepatotoxicity developed in a patient 1 month after losartan initiation. The patient recovered when losartan was withdrawn but symptoms and raised liver enzyme concentrations recurred following rechallenge [4]. Losartan had induced other reversible cases of hepatic injury [5]: one occurred in a patient who had been taking losartan 150 mg daily for 6 weeks and the second occurred in a patient five months after taking 50 mg daily of losartan [6].

Few cases of cholestatic jaundice associated with irbesartan [7, 8], candesartan [9] and with valsartan therapy had also been reported [10, 11]. The jaundice resolved slowly once irbesartan was withdrawn. Cytolysis hepatitis has also been reported with irbesartan [12].

As previously described in animal models [13], angiotensin II (ATII) is essential to the control of

ammonia production and excretion by the proximal tubule. Although the effects on serum ammonia levels of a pharmacological block by renin-angiotensin system in humans was still undefined. We speculate that this adverse reaction may be directly related to the effect of angiotensin II on the excretion of blood ammonia. Therefore, we suggest that patients with liver cirrhosis and portal hypertension were at risk of developing clinically relevant encephalopathy when angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker combination therapy was administered, thus indicating the need for a careful clinical follow-up.

Elderly patients and female sex were reported to be more likely to have hepatic toxic reactions induced by ARBs [8, 14]. Cholestasis was the most of hepatic reaction described with ARBs. The mechanism of losartan-associated liver injury is unclear. It was presumed to be idiosyncratic injury that is not accompanied by clinical hallmarks of hypersensitivity, and that may appear after widely varying periods of exposure of this drug, was assumed to result from metabolic idiosyncrasy. The mechanism of ARBs-induced hepatotoxicity was most likely mediated metabolically. Immune mechanism is operating in some cases. Annicchiarico BE and Siciliano M reported an irbesartan-induced autoimmune hepatitis [15]. Other authors report that genetic variations in ARBs metabolism could predispose patients to drug hepatotoxicity by generating reactive metabolites through cytochrome P450 metabolism in the liver [8,16].

CONCLUSION

Although rare, drug-induced hepatic toxicity may be seen in patients taking losartan. Because it causes hepatic injury during the initial phase of treatment period, the clinician should be aware of this side effect when prescribing this drug. We suggest a careful clinical follow-up and, possibly, monitoring of prothrombin levels when ACEI and ARB combination therapy was administered in patients with liver cirrhosis or portal hypertension.

TABLE I : Evolution of Liver biochemical tests of the patient after Losartan intake

Day after Losartan intake	Day 30	Day 40
Total bilirubin (<23 µmol/L)	553 (24N)	531 (23N)
ALT (<45 U/L)	544 (12N)	451 (10N)
AST (<40 U/L)	515 (12.8N)	623 (15.5N)
GGT (<64 U/L)	183 (2.8N)	205 (3.2N)
ALP (<121 U/L)	575 (4.7N)	196 (1.6N)
Prothrombine time	60 %	35 %

(x N): upper limit of normal range.
ALT: Alanine aminotransferase
AST: Aspartate aminotransferase
GGT: Gama-Glutamyl-transferase
ALP: Alcaline phosphatase

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