PATIENT REPORT

LYMPIDEM® (A COUMARIN DERIVATIVE) INDUCED REVERSIBLE HEPATOTOXICITY IN AN ADULT SRI LANKAN

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SUMMARY

Lympidem® is a coumarin derivative which is advocated for treatment of mainly chronic lymphedema by the manufacturer. Since its introduction there had been several reports with regard to coumarin-induced hepatotoxicity from Europe. We report an adult Sri Lankan middle-aged female who presented with abnormal liver functions due to Lympidem®, which resulted in discontinuation of the drug, while no other etiology could be found. To the best of our knowledge, this is the first reported case from South East Asia. We recommend monitoring of liver functions while on coumarin therapy to prevent irreversible damage.

KEY WORDS

Lympidem®, coumarin, hepatotoxicity, lymphedema

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INTRODUCTION

Drug-induced hepatotoxicity is an important cause of hepatocellular injury /1/. Hepatic necrosis may range from asymptomatic elevations in transaminases to fulminant hepatic failure and death. Coumarin is used in the treatment of lymphedema and certain forms of metastatic malignancies. The drug is almost completely metabolized in the liver. Though it is a well known rat hepatotoxicant, only a few cases of coumarin-induced hepatotoxicity have been previously reported in humans. The predisposition for hepatotoxicity is to a certain extent genetically determined. We report this case because, to the best of our knowledge, it is the first in South Asia.

PATIENT REPORT

A 63 year-old female was admitted to Sri Jayewardenepura General Hospital, Kotte, Sri Lanka, with a one week history of jaundice, pruritus, malaise and dark colored urine. She had started on coumarin two weeks previously for chronic left lower limb lymphedema. The drug history was significant for coumarin. She was conscious, rational, icteric, and the liver was not palpable. Hematological and biochemical investigations were as follows: WBC 9,600/μl, hematocrit 33.3%, hemoglobin 11.8 mg/dl, platelets 267,000/μl, ESR 18 mm/1st hour, CRP 12 mg/dl, AST 1,096 U/l (normal 0-31), ALT 1,137 U/l (7-35), alkaline phosphatase 511 U/l (80-290), γGT 205 (5-85), total bilirubin 10.1 mg/dl (0-1.0), direct bilirubin 5.6 mg/dl, total protein 7.6 mg/dl (6.7-8.2), albumin 3.9 mg/dl (3.8-5.3), serum amylase 44 U/l (0-95), blood urea 16 mg/dl (10-52), serum creatinine 55 μmol/l (53-97). Urinalysis revealed +++ for bilirubin and ++ for urobilinogen. Viral serologic markers were as follows: anti-HAV-IgM negative, HbsAg negative, anti-HBc IgM negative, anti-HBc IgG negative, anti-HCV negative, anti-HEV IgM negative, CMV IgM negative, EBV IgM negative, HIV screening negative, ANA and AMA negative. Ultrasonography showed normal liver architecture with normal intrahepatic bile ducts and gall bladder. Two-dimensional transthoracic echocardiogram was normal. Coumarin was stopped on the day of admission. Her symptoms rapidly resolved after cessation of coumarin therapy, and 3 weeks later AST was 152

and ALT was 52. Two months later, liver enzymes were normal with complete resolution of symptoms.

DISCUSSION

In the absence of systemic disease findings, including autoimmune manifestations, tumoral infiltration of liver disease, congestive hepatic disorders and other diseases affecting the liver seemed unlikely. There was no history of other drug usage. Drug cessation was followed by complete resolution of the clinical and biochemical evidence of hepatotoxicity. The case was diagnosed as coumarin-induced hepatitis.

Coumarin (*cis-o*-coumarinic acid lactone,1,2-benzopyrone) is a natural product derived from tonka bean and lavender oil, but is now synthetically produced. It has been used since the mid-1980s to reduce lymphedema /2/ and more recently on an experimental basis on its own and in combination with other drugs to treat patients with metastatic renal cell carcinoma, prostatic cancer /3/ and malignant melanoma /4/. Coumarin is a well recognized rat hepatotoxicant in a dose dependent manner, though reports of adverse effects in humans are rare and idiosyncratic /5/.

This species differences in coumarin toxicity appear to be metabolism-mediated, and two major Phase I metabolic pathways are thought to be important to hepatotoxic outcome. In humans, coumarin is hydroxylated to 7-hydroxycoumarin (7-HC), a non-toxic metabolite /6/. This reaction is catalyzed by CYP2A enzymes /7/. However, in rats, CYP2A enzymes preferentially catalyze 7α-hydroxylation of testosterone rather than coumarin 7-hydroxylation. As a result, the formation of 7-HC is extremely low in rats, and the lack of this reaction is thought to render rats more susceptible to hepatotoxicity /8/. The formation of 7-HC is a major metabolic pathway in humans /9/. The second important pathway involved in coumarin metabolism and toxicity is epoxidation at the 3,4-double bond. This reaction is catalyzed predominantly by CYP1A and CYP2E enzymes, and yields CE, a reactive intermediate. It has been postulated that in the absence of detoxification through 7-HC, epoxidation is favored in rats, leading to dose dependent hepatotoxicity /10/.

It has been suggested that individuals who are polymorphic for CYP2A enzymes, the major metabolic pathway for coumarin metabolism in humans, may be at increased risk of hepatotoxicity following

coumarin exposure /11/. The genetic polymorphism of CYP2A6 involves more than 10 different allelic variants, with the most common being the CYP2A6*2 variant that encodes an inactive enzyme, and the CYP2A6*4A variant that represents a gene deletion. Overall, the variant alleles are reported to occur in less than 2% of the Caucasian population, whereas the CYP2A6*4 gene deletion is present in Asian populations at 15-20% frequency. More recently, Burian *et al.* /12/ determined the CYP2A6 genotype of patients who were dosed with 90 mg coumarin/day as part of the clinical evaluation of the efficacy and safety of coumarin for the treatment of chronic venous insufficiency. Out of 231 patients, 16 (7.4%) were found to be defective for the CYP2A6 genotype, and all were heterozygous for the CYP2A6*2 allele. During the course of the 16-week study, nine patients showed elevations in serum liver enzymes, with only one patient with a CYP2A6*2 variant allele showing evidence of hepatotoxicity. All other affected patients were identified as wild-type homozygotes. That study represents the most extensive analysis of the contribution of CYP2A6 polymorphism to coumarin-induced hepatotoxicity conducted to date and indicates that genetic polymorphism of CYP2A6 is not the only cause of liver dysfunction observed with therapeutic dosages of coumarin /12/.

In 1996, The Australian Drug Evaluation Committee (ADEC) received ten reports of patients who developed abnormalities in liver function tests or more serious signs of hepatotoxicity, including two fatalities, associated with the use of tablets containing 200 mg coumarin /13/. Consequently, in August 1996, the health authorities cancelled registration of coumarin in Australia.

In 1988, coumarin was launched in France for the adjuvant therapy of lymphedema of the upper limb following radiosurgical treatment of breast cancer. Since then, 34 cases corresponding to an elevation of ALT over twice normal and/or alkaline phosphatase over 1.5 normal have been reported. However, among these cases, a causal relationship was considered likely or probable for only 15 of them, including two positive rechallenges. Of all the reported cases, severe liver failure with encephalopathy justified liver transplantation once and led to encephalopathy and fatal evolution in two cases /14/. Consecutively, the drug was suspended in France in 1997. However, a study conducted in the US was unable to establish coumarin as a significant hepatotoxicant in humans /15/.

The widely held view that coumarin is an effective agent in reducing lymphedema was also disputed recently. In 1993, Casley-Smith *et al.* /16/ reported the results of a double-blind, crossover trial of coumarin in 31 women with postmastectomy lymphedema and 21 men and women with lymphedema of the leg of various causes. Coumarin was reported to be more effective than placebo in reducing the volume of edema fluid in the arm, in reducing skin temperature, and in increasing the softness of the limb tissue /16/. However, this was challenged by Loprinzi *et al.* in 1999 in a study with better statistical power, which showed that coumarin was ineffective for ameliorating lymphedema of the arm in women who had undergone local or regional therapy for breast cancer /17/.

CONCLUSIONS

From the evidence based on data available in the literature, from Europe and Australia, we would strongly caution against the use of coumarin in the treatment of conditions advocated by the manufacturer due to the recently shown lack of efficacy in clearing lymphedema and potentially fatal hepatotoxicity. The present case is the first from Southeast Asia.

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