Vitamin K deficiency and bleeding after long-term use of cholestyramine

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ABSTRACT

Although it has been long known that in theory the use of cholestyramine can cause coagulopathy due to reduced absorption of vitamin K, only a few cases have been reported. In those cases the coagulopathy occurred within a few weeks to months after the start of therapy. We report a patient with severe pruritus due to intrahepatic cholestasis, who was on cholestyramine therapy for over 25 years before haemorrhage occurred. This case demonstrates that one should be aware of the possibility of depletion of fat-soluble vitamins during the long-term use of cholestyramine.

INTRODUCTION

Pruritus is a distressing manifestation of intrahepatic cholestasis. Severe pruritus, causing unrest and sleep deprivation, needs to be treated. The exact pathogenesis of pruritus in patients with cholestasis remains unknown. One of the possible explanations is bile acid deposition on nerve endings in the skin.1,4 It is possible that besides bile salts also endogenous opioids play a role in pruritus.3,4 The pruritus of intrahepatic cholestasis can be relieved by cholestyramine, an anion exchange resin that binds bile acids. This effective binding leads to the lowering of the free bile salt concentration in the jejunum and reduced enterohepatic circulation of bile salts. As a response, the liver will increase bile salt synthesis. If the compensatory capacity of the liver is reached during cholestyramine therapy, the bile salt concentration will fall, leading to steatorrhoea and malabsorption of fat-soluble vitamins.5 Until now, four cases of coagulopathy due to cholestyramine therapy have been reported (table 1). Recently we saw a patient with a coagulopathy after the use of cholestyramine for more than 25 years.
CASE REPORT

Sixteen months after birth (October 1974), our patient suffered from his first period of jaundice; the level of bile acids in his blood was 219 mmol/l (normal <10 mmol/l). Cholestyramine therapy was initiated to relieve his pruritus. In the following years recurrent periods of jaundice occurred.

The patient was first diagnosed as having benign recurrent intrahepatic cholestasis (BRIC). Later on, he appeared to have multiple episodes of hepatic inflammation, which is uncommon in BRIC. A liver biopsy showed bile duct paucity, consistent with the diagnosis of Byler’s disease (progressive familial intrahepatic cholestasis, PFIC). Patients with Byler’s disease type 1 and 2 typically show a low serum gamma-glutamyl transpeptidase (GGT), which is discordant with the severe cholestasis.9 This was also observed in our patient.

The patient was first admitted in 1990, because of severe pruritus. Ursodeoxycholic acid was tried instead of cholestyramine, but the pruritus worsened and cholestyramine was started again. During the following years he took doses of cholestyramine varying from 8 to 24 g daily. In addition, ursodeoxycholic acid and rifampicin were used intermittently and several other drugs were tried to relieve the pruritus, namely simvastatin, naltrexone and clomipramine.

On 24 August 2000 the patient was admitted to hospital. His ankle had become swollen a week before admission, without any known trauma. He had also noted that a few days after the ankle, his thumb had started to swell too. Physical examination showed a moderately ill man. His ankle was red, swollen, shiny and painful. The bleeding concentration is a controversial subject,18,19 but rifampicin might have contributed to the development of the coagulopathy. However, the patient had been on the combined treatment of cholestyramine and rifampicin for two years. It remains unclear if it is necessary to add fat-soluble vitamins to the therapy with cholestyramine. The prevalence of these deficiencies is not known and there are no cost-benefit studies available.

the apparent malabsorption of fat-soluble vitamins, the patient was discharged with the additional medication of vitamins A, E and K. The patient has had no complaints since, except for pruritus, which is still difficult to control with medication.

DISCUSSION

In all four known case reports concerning coagulopathy due to the use of cholestyramine, bleeding occurred soon after the start of therapy, varying from two weeks to eight months. In the present case, the bleeding only occurred after using cholestyramine for more than 25 years. This shows that caution should be taken when treating a patient with long-term cholestyramine, even if no sign of coagulopathy is present at the beginning of therapy. There is no known aggravating circumstance for this coagulopathy to suddenly develop in this patient and the patient had no history of bleedings. PT, APTT and TT values from previous years showed normal results.

The malabsorption of the different fat-soluble vitamins during treatment with cholestyramine has been the subject of many studies. Although some show no influence of cholestyramine on the absorption of fat-soluble vitamins,10 others have found malabsorption.5-9,13-17 It can therefore be concluded that malabsorption of fat-soluble vitamins when using cholestyramine is an existing phenomenon. Besides cholestyramine, the patient was also taking rifampicin. The influence of rifampicin on vitamin K concentration is a controversial subject,18,19 but rifampicin might have contributed to the development of the coagulopathy. However, the patient had been on the combined treatment of cholestyramine and rifampicin for two years. It remains unclear if it is necessary to add fat-soluble vitamins to the therapy with cholestyramine. The prevalence of these deficiencies is not known and there are no cost-benefit studies available.

Due to the short half-life and low body storage of vitamin K, it is believed not to be useful to monitor haemostasis on a three to six month basis. Vitamin K deficiency-related coagulopathy can probably develop within a few days. The best option seems to keep in mind that malabsorption can occur and to warn patients that bleeding may happen. In case of vitamin K deficiency, spontaneous cutaneous purpura, epistaxis and gastrointestinal, genitourinary or gingival bleeding often occur. Other types of bleeding can

also develop.20 The patients should alert their doctor immediately if they notice bleeding without trauma. Then, fat-soluble vitamins should be added to the therapy. Since no severe haemorrhage has been reported thus far, such a wait-and-see attitude seems justified.

REFERENCES