Hypoprothrombinemic hemorrhage due to cholestyramine therapy

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Only two cases of severe hypoprothrombinemia with bleeding due to cholestyramine therapy are reported in the literature.[1,2] The following is the first report of such a case in a child.

Case report

A 35-month-old girl was admitted to our hospital Sept. 14, 1983, because of jaundice for 2 weeks and pruritus for 6 months. She weighed 11.9 kg (10th percentile). From her serum the following levels were recorded: total bilirubin, 145 (normally 2 to 20) μmol/L; conjugated bilirubin 99 (normally less than 7) μmol/L; alkaline phosphatase, 720 (normally 70 to 260) U/L; and glutamic oxaloacetic transaminase, 90 (normally 10 to 35) U/L. Her hemoglobin level was 121 g/L, platelet count 430 × 10^9/L, prothrombin time (PT) 12.2 seconds (100% = 11.4 seconds) and activated partial thromboplastin time (APTT) 31.2 (normally less than 40) seconds. A liver and spleen scan showed these organs to be of normal size; a liver biopsy demonstrated marked cholestasis, periportal fibrosis and depletion of intrahepatic ducts.

Six days after admission, because of severe pruritus, therapy was started with cholestyramine (0.5 g four times a day), phenobarbital (30 mg twice a day), a water-soluble vitamin E tablet and a daily multiple-vitamin tablet containing vitamins A, B_1, B_2, B_6, B_{12}, C and D, niacinamide, iron and calcium, and she was discharged.

In December 1983 the child began experiencing recurrent epistaxis, and in May 1984 easy bruising was noted and epistaxis became more frequent. She was readmitted June 18 because of severe epistaxis. She was pale and had a few bruises on her extremities. Her liver was 5 cm and her spleen 2 cm below the costal margin, but she had no jaundice. Her serum bilirubin level was 18 μmol/L, serum glutamic oxaloacetic transaminase level 115 U/L, hemoglobin level 58 g/L, platelet count 333 × 10^9/L, PT more than 50 seconds and APTT more than 180 seconds. A new sample of blood showed the same PT and APTT, a thrombin time of 7.6 seconds (control time 7.8 seconds), a plasma fibrinogen level of 2.8 (normally 1.7 to 4.0) g/L, and factor II, VII, X, IX and V levels of 2%, 3%, 3%, 3% and 111% (all normally 50% to 150%) respectively.

At the time of admission the child was transfused with 200 mL of packed cells, and 4 hours later she was given a single 5-mg dose of vitamin K_1 intravenously and then 140 mL of fresh frozen plasma; 6 hours later her PT was 11.8 seconds and her APTT 39 seconds. The cholestyramine, phenobarbital and vitamin therapy was continued. A 72-hour stool collection demonstrated steatorrhea (5.4 g of fat in a 24-hour collection, or 24% of the daily fat intake). Ten days after admission her PT had increased to 17.1 seconds and her APTT to 46.1 seconds; her levels of factors II, VII, X, IX and V were 38%, 27%, 28%, 38% and 129% respectively. Cholestyramine therapy was stopped, but the other treatments were continued, and she was discharged.

Oct. 10, when the child's PT was 12.6 seconds, her APTT was 36.5 seconds and her factor II, VII, X, IX and V levels were 98%, 108%, 96%, 83% and 98% respectively, therapy with cholestyramine at the same dosage was restarted because of severe, distressing pruritus. By Oct. 23 her PT had risen to 13.6 seconds, and by Nov. 9 it was 15.7 seconds and the levels of factors II, VII, X, IX and V were 54%, 63%, 33%, 26% and 112% respectively. Epistaxis developed 3 days later. She was given another 5-mg dose of vitamin K_1 intramuscularly, and the cholestyramine therapy was stopped. The next day her PT was 11.4 seconds and her APTT 31.7 seconds. In the following 8 months her PT, PTT and levels of vitamin-K-dependent clotting factors remained normal despite the continuation of phenobarbital therapy and the persistence of her cholestasis.

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Discussion

Cholestyramine is an anion exchange resin with strong affinity for bile salts. It was originally used for relief of pruritus associated with biliary atresia and subsequently has been used to reduce the serum cholesterol level. In our patient it was used because of severe pruritus attributed to bile salt retention.

Vitamin K, being fat soluble, requires bile salts for its absorption. Cholestyramine, by preventing bile salt reabsorption and producing bile salt deficiency, is expected to reduce vitamin K absorption. However, in view of the rarity of hypoprothrombinemia in patients receiving cholestyramine, one has to consider other factors when this complication becomes severe enough to cause bleeding. Among 12 adults who had been taking 12 to 24 g of cholestyramine daily for 1 to 5 years Casdorph[3] found PTs of 100% in 6 and 60% to 93% in the remaining 6; 2 of the first group and 4 of the second had not received any supplemental vitamin K. The 1985 edition of the "Compendium of Pharmaceuticals and Specialties"[4] states that five cases of hypoprothombinemic bleeding have occurred with the long-term use of cholestyramine, but we have found only two reports of this complication in the literature,[1,2] both in adults, and in both cases the bleeding occurred within 3 weeks after the start of cholestyramine therapy.

In our patient the prompt and complete response to vitamin K therapy, the normal factor V and plasma fibrinogen levels, and the fact that her PT remained normal for 8 months after cholestyramine therapy was stopped indicate that the patient's biliary dysplasia by itself was not enough to account for her hypoprothrombinemia. However, the addition of phenobarbital therapy may have aggravated the hypoprothrombinemia produced by cholestyramine. Several cases of hemorrhagic disease of the newborn due to vitamin K deficiency have been reported in neonates born to women receiving anticonvulsants that included phenobarbital,[5-7] and recently Davies and colleagues[8] reported an increased level of decarboxylated prothrombin in adults with epilepsy who were receiving phenobarbital with or without other anticonvulsants, which indicates that anticonvulsant therapy can produce subclinical vitamin K deficiency. Despite the rarity of hypoprothrombinemic hemorrhage due to cholestyramine therapy, most authors have recommended the prophylactic use of fat-soluble vitamins in patients, especially children, receiving long-term cholestyramine therapy.[1-3,9] Our experience supports this recommendation.

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