Effects of Various Doses of Growth Hormone on Serum Total Cholesterol, Phospholipid, and Bile Acid in a Patient with Cholestasis

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Abstract

To determine whether growth hormone (GH) has any impact on the hyperlipidemia seen in cholestatic patients, graded doses of GH in the sequence of 0.1, 0.2, 0.4, and 0.6 u/kg every other day were administered sc to a patient with Alagille syndrome.

Serum total cholesterol, phospholipid, and bile acid were measured. The serum levels of all three decreased markedly after GH administration and the lowest levels were observed on the second day after the GH dose of 0.4 u/kg. However, they increased thereafter despite the administration of an increased dose of GH; especially the serum bile acid level returned to the initial value by day 8.

Serum levels of SM-C and fT3 were not correlated with the changes in total cholesterol, phospholipid, and bile acid after GH administration.

We suggest that the administration of GH may affect the state of hyperlipidemia seen in cholestatic patients.

Physiologic and clinical studies suggest that GH has many effects on carbohydrate, protein and lipid metabolism (Konobil, 1966; Raiti and Blizzard, 1970; Merimee and Rabin 1973). The reports dealing with the effect of GH on serum lipids are controversial (Friedman *et al.*, 1970; Friedman *et al.*, 1974; Aloia *et al.*, 1975; Winter *et al.*, 1979; Merimee and Pytkinen, 1980; Blackett *et al.*, 1982; Asayama *et al.*, 1984). Most of the above reports were limited to the subject of GH deficiency with only mild hypercholesterolemia, except for the study of Friedman *et al.* (1974) in which they found

that daily administration of a very high pharmacologic dose of GH (25 u) to even normocholesterolemic and moderately hypercholesterolemic adults who had no reported GH deficiency caused a decrease in their serum cholesterol concentrations in one week. The effect of GH on the hyperlipidemia of cholestatic patients has not been studied, although such a study may help to find the exact effect of GH on serum lipid.

This report describes the effect of GH on hyperlipidemia in a boy with Alagille syndrome.

Materials and Methods

Subject

An 8-year-old boy with Alagille syndrome was studied. His height was 109.2 cm (-2.86 SD, height age $5\frac{6}{12}$ yr) and his weight was 20.5 kg. Bone age determined by the standards of Greulich and Pyle was 5 yr. Peak serum GH levels during an insulin-arginine tolerance test when he was 7 years old were 16 and 6.2 ng/ml, respectively. Serum SM-C was 0.38 IU/ml. He has had chronic cholestasis since his neonatal period. His liver function was disturbed after his birth but improved and remained stable after he was 6 years old. Although hyperbilirubinemia disappeared after infancy, serum total cholesterol and bile acid levels remained high. The yearly laboratory data since his birth are summarized in Figure 1. His face is characteristic of the syndrome, with prominent forehead, moderate hypertelorism, deepset eyes, small chin, and

saddle nose. He also has peripheral pulmonary stenosis.

Study protocol

The patient was asked not to modify his diet until after all the blood specimens were obtained. In considering the half life of human growth hormone (hGH) and SM-C, and to determine whether the effect of GH on hyperlipidemia is dose dependent or not, graded doses of hGH in the sequence of 0.1, 0.2, 0.4, and 0.6 u/kg every other day were administered sc to this patient at 15:00. Blood samples were drawn at the same time and samples were drawn on the day of hGH injection before the injection. The plasma was separated immediately and stored frozen at -20°C until the assay. A total of nine samples were collected for the determination of total cholesterol, phospholipid, bile acid, SM-C, and FT3 levels. All determinations were made in a single run to avoid interassay variations.

Analytic methods

Serum total cholesterol (Richmond, 1973), bile acid (Mashige *et al.*, 1981), and phospholipid (Takayama *et al.*, 1977) were all measured with commercial kits. SM-C was assayed with a double antibody RIA Kit (Eiken Immunochemical Laboratory, Tokyo, Japan). FT3 was assayed with an Amerlex RIA Kit (Amersham International of PLC, Buckinghamshire, England).

Results

Laboratory data before, during and after the administration of various doses of hGH are summarized in Figure 2. Total cholesterol, phospholipid, and bile acid decreased from 362 mg/dl, 520 mg/dl, and $72\text{ }\mu\text{mol/L}$ to 268 mg/dl, 381 mg/dl, and $10.6\text{ }\mu\text{mol/L}$ respectively, two days after the injection of a low dose (0.1 u/kg) of hGH. Their lowest levels (214 mg/dl, 274 mg/dl, and $3.5\text{ }\mu\text{mol/L}$, respectively) were observed simultaneously one day after the third injection (0.4 u/kg). But thereafter rebounding increases were found with maximal levels of 256 mg/dl, 392 mg/dl, and $300\text{ }\mu\text{mol/L}$, respectively, two days after the fourth injection

Fig. 1. The yearly laboratory data after birth.

(0.6 μ /kg). Four weeks after the course of hGH administration, total cholesterol, phospholipid, and bile acid had returned to high levels (384 mg/dl, 548 mg/dl, and 97.4 μ mol/L, respectively) (Table 1).

SM-C increased after each dose of hGH. Although the magnitude of the increase in SM-C was small, it was dose dependent. FT3 showed no obvious changes after hGH

injection. Neither SM-C nor fT3 showed any changes correlated with total cholesterol, phospholipid, or bile acid.

Discussion

Previous studies dealing with the effect of GH on serum lipids are controversial (Friedman *et al.*, 1970; Friedman *et al.*, 1974; Aloia *et al.*, 1975; Winter *et al.*, 1979; Merimee and Pulkkinen *et al.*, 1980; Blackett *et al.*, 1982; Asayama *et al.*, 1984). Treatment with GH lowered cholesterol concentrations in hypox rats (Friedman *et al.*, 1970) and GH-deficient individuals in two studies (Blackett *et al.*, 1982; Asayama *et al.*, 1984) but had no effect in GH-deficient patients in two others (Winter *et al.*,

Table 1. hGH treatment

	Before	During	After (4 wks)
Bile acid (μ mol/L)	71.2	3.5	97.4
T. cholesterol (mg/dl)	365	214	387
phospholipid (mg/dl)	520	274	548

Concentration of bile acid, total cholesterol and phospholipid before, during (the lowest levels) and 4 weeks after hGH administration.

Fig. 2. Laboratory data before, during and after various doses of hGH administration. GH dose: $\downarrow$ 0.1, $\downarrow$ 0.2, $\downarrow$ 0.4, $\blacksquare$ 0.6 u/kg.

1979; Merimee and Fulkkinen, 1980). In normal individuals, GH caused a decrease in cholesterol after 1 week's administration of very large doses (Friedman *et al.*, 1974) but not after 6 months' administration of lesser amounts (Aloia *et al.* 1975). The effect of GH on the hyperlipidemia seen in cholestatic patients has not been studied. Our results indicate that GH at a proper dose may lower not only the high level cholesterol but also the high levels of phospholipid and bile acid in cholestatic patients.

The basic defect leading to cholestasis in Alagille syndrome is not well known. In spite of the absence or paucity of intrahepatic bile ducts, variable amounts of bile secreted into the intestinal lumen can be demonstrated in the majority of patients with Alagille syndrome; extrahepatic biliary ducts are usually patent, although they can be hypoplastic (Watson and Miller, 1973; Henriksen *et al.* 1977; Grosse, 1979; Gorelick *et al.*, 1982; Kahn *et al.*, 1983; Markowitz *et al.*, 1983). The intralobular bile is probably drained through a network of functional canaliculi to an area where bile ducts are patent. Patients with this syndrome have high levels of serum bilirubin and bile acid during infancy, but after that period bilirubin decreases to the normal level and the bile acid remains high (Riely *et al.*, 1979). The dissociation between bile acid and bilirubin may indicate that a disturbance in bile acid secretion is involved in this syndrome. The precise mechanism of the dramatic decrease in serum bile acid after hGH administrations as found in this patient, although not clear, may be due to the enhancing effect of GH on bile acid secretion from canaliculi. Since the changes in serum levels of total cholesterol and phospholipid were almost concomitant with the change in the serum bile acid level, the decreases in both may be due to the excretion of both from bile acid (Grundy and Metzger, 1972). But to confirm this, a study of the influence of GH on gallbladder

bile composition, bile (concentration of cholesterol, bile acids, and phospholipids) would be necessary. The rebounding increases in total cholesterol, phospholipid, and especially bile acids after large doses of hGH (0.4 and 0.6 u/kg) may be explained by the feed-back secretion of somatostatin, since somatostatin has a cholestatic effect on bile secretion by enhancing ductal or canalicular bile reabsorption (Holm *et al.* 1978; Meyer *et al.*, 1979; Ricci and Fevery, 1981; Rene *et al.*, 1983).

Subclinical hypothyroidism developing during GH therapy may be related to the mild hypercholesterolemia seen in some GH-deficient subjects (Goodman *et al.*, 1968; Porter *et al.*, 1973) suggesting that thyroid hormone may have an effect on cholesterol metabolism. The administration of hGH did not change the concentration of fT3 in this patient, indicating that the reduction in serum cholesterol that was observed could not have been due to thyroid hormone. Changes in serum SM-C were not correlated with the changes in total cholesterol, phospholipid, and bile acid, suggesting that the three may not be related to SM-C.

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