NOTE

A Patient with Hypogonadotropic Hypogonadism Successfully Treated by Long-Term Pulsatile Administration of Luteinizing Hormone-Releasing Hormone

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Abstract

A male patient with hypogonadotropic hypogonadism has been treated by pulsatile administration of luteinizing hormone-releasing hormone (LHRH) (20–25 μg, every 2 hours, sc) for 4 years 6 months. His plasma testosterone (T) concentration began to increase after 4 weeks of treatment and reached the normal range in week 5. He showed complete secondary sexual development after 1 year of treatment. His sperm count was normalized after 1 year of treatment. He was married after 29 months of therapy, and has a healthy male child. Blood type tests showed his paternity of the child. During the long duration of pulsatile LHRH therapy, his gonadotropin secretion has been stimulated by LHRH and his T level has been maintained with no observable side effects. There are no other reports of patients treated by pulsatile LHRH injection for such a long duration, but finding in this patient indicated that long-term pulsatile LHRH therapy is a useful and safe method for treatment of hypothalamic hypogonadotropic hypogonadism.

The necessity of hypothalamic pulsatile release of luteinizing hormone-releasing hormone (LHRH) for adequate secretion of gonadotropins is well established (Clark and Cummins, 1982; Santen and Bardin, 1973). Pulsatile administration of LHRH has been shown to be an effective method for treating patients with hypothalamic hypogonadotropic hypogonadism (Hoffman and Crowley, 1982). However, we do not have enough information about long-term treatment with LHRH, because LHRH therapy has only recently been developed. In this paper, we report a male patient with hypogonadotropic hypogonadism who has received pulsatile LHRH injections for more than 4 years with successful results.

Case Report

A 25-year-old man visited our hospital
because of lack of secondary sexual development. He had experienced asphyxia when he was born in vertex presentation. His growth was normal except for lack of secondary sexual characteristics. His sense of smell was normal. There was no family history of hypogonadism or anosmia. His height was 166 cm, his arm span was 167 cm and his body weight was 65 kg. His external genitalia were childish: his testicular volume was 2 ml and his penile length was 2.5 cm and no pubic hair was observed.

The plasma concentration of testosterone (T) was 0.6 ng/ml, and increased to 1.7 ng/ml after the administration of human chorionic gonadotropin (hCG) at a dose of 4,000 U/day for 3 days (Fig. 1). His serum level of luteinizing hormone (LH) was 5.4 mIU/ml and that of follicle stimulating hormone (FSH) was 5.5 mIU/ml. His serum levels of LH and FSH increased after the administration of 100 μg of LHRH (Fig. 2). The secretions of growth hormone, adrenocorticotropic hormone, thyrotropin and prolactin were normal. Brain CT scanning revealed no abnormality of the hypothalamic-pituitary region. From these findings, a diagnosis of idiopathic hypothalamic hypogonadotropic hypogonadism was made.

Methods

One mg of LHRH (Tanabe Seiyaku Co. Ltd, Osaka) dissolved in 100 μl of saline was administered to the patient intranasally 3 times a day at intervals of 8 hours for 6 months. After therapy by nasal insufflation, he received 20-25 μg of LHRH subcutaneously every 2 hours by means of infusion pump (SP-13, Nipro, Osaka). This pulsatile LHRH therapy has been continued for 4 years and 6 months.

Blood specimens were taken repeatedly for measurement of LH, FSH and T. Serum LH, FSH and T were measured by radioimmunoassays using commercially available kits (LH and FSH: Daiichi RI Laboratory, T: Eiken Immunochemical Laboratory).

Pubertal development was measured according to the criteria of Tanner. The testis size was measured with a Prader orchidometer.

Results

The serum levels of LH and FSH during LHRH therapy by nasal insufflation (1 mg,
Fig. 3. Serum LH and FSH responses to LHRH given by nasal insufflation (1 mg×3/day).

Fig. 4. Plasma testosterone concentration during LHRH therapy by nasal insufflation (1 mg every 8 h). The normal range is shown by a hatched bar.

Fig. 5. Clinical course of this patient during pulsatile LHRH therapy. Normal ranges are shown by hatched bars.
every 8 hours) are shown in Fig. 3. LH and FSH secretions were stimulated by nasal administration of LHRH. However, his plasma T did not increase to normal levels during the 6 month period of treatment (Fig. 4). On the other hand, pulsatile administration of LHRH resulted in an increase in the plasma T concentration, which reached the normal range after 5 weeks of treatment (Fig. 5).

His testicular volume increased from 2 ml before pulsatile LHRH therapy to 6 ml after therapy for three months. After three months of treatment, his penile length increased from 2.5 cm to 5.0 cm and pubic hair appeared. He showed complete secondary sexual development after 1 year of treatment.

No seminal fluid was obtained before pulsatile LHRH therapy. After 4 weeks of therapy, ejaculation for sperm analysis became possible, though no sperm were detected in the seminal fluid. The sperm count was 0/ml after therapy for 2 months, $4.35 \times 10^6$/ml after 6 months, $10 \times 10^6$/ml after 8 months, $100 \times 10^6$/ml after 12 months, $100 \times 10^6$/ml after 24 months and $85 \times 10^6$/ml after 48 months. Thus, his sperm count was normalized after 12 months of treatment.

After 29 months, he got married. He had no problems in his sexual life, and after 6 months his wife became pregnant and had a healthy male baby. Blood type tests (ABO, MNSs, Rh and Lewis) showed his paternity of the child.

Discussion

The patient described here showed increases in concentrations of serum LH and FSH after administration of LHRH intranasally. However, his plasma T levels did not increase during nasal insufflation of LHRH for 6 months. Mortimer et al. (1974) observed a rise in the T level in hypogonadal males on subcutaneous administration of 500 µg of LHRH at 8-hour intervals. They also observed improvements in pubertal rating in some patients. However, the results of Mortimer et al. could not be confirmed by others. Hashimoto et al. (1975) gave 200 µg of LHRH daily to 4 patients with hypothalamic hypogonadotropic hypogonadism for 32–62 days and observed an increased response of their serum LH to LHRH, but no increase in plasma T during LHRH treatment. High-dose LHRH treatment with subcutaneous injection of 200 µg of LHRH three times daily for 4 weeks (Krabbe and Skakkebaek, 1977), 500 µg twice daily for 1 year (Brook and Dombey, 1979), 500 µg three times daily (Happ et al., 1975) or 1 mg twice daily for 6 months (Rabin and McNeil, 1981), did not result in a good gonadal response.

Many LHRH agonistic analogues have been synthesized. Daily administration of 5 µg of D-Ser (TBU)6-LHRH-EA10, one of the most potent LHRH analogues, for one week produced a significant decrease in the plasma T concentration in normal subjects, but no change in plasma T in hypogonadal males (Smith et al., 1979). Administration of D-Trp6-Pro9-N-ethylamide-LHRH, another potent LHRH agonist for 6 to 10 weeks decreased the plasma T in normal subjects. Their serum gonadotropin concentration also fell during the treatment (Linde et al., 1981). These results indicate that LHRH agonists are not useful for treating patients with hypogonadotropic hypogonadism.

Continuous administration of LHRH to normal postmenopausal women initially stimulated gonadotropin secretion, but later the gonadotropin concentration decreased toward or below the preinfusion levels without any change in plasma estradiol (Dorsa et al., 1981). Continuous LHRH infusion is thought to decrease gonadotropin secretion by down-regulation of pituitary gonadotropin secretion. Vierhapper and Waldhäusl (1983) reported that FSH secretion
was not increased by subcutaneous administration of LHRH but was increased by pulsatile LHRH treatment. These results indicate that continuous administration of LHRH may not be effective in treating patients with hypothalamic hypogonadotropic hypogonadism.

Pulsatile LH secretion has been observed in normal men and women, and individuals with gonadal failure (Boyar et al., 1972; Santen and Bardin, 1973). Santen and Bardin (1973) reported that in normal men the secretory spike occurred 3.7 times/6 h and in normal women it occurred 3.2 times/6 h in the luteal phase. Clarke and Cummins (1982) collected hypothalamo-hypophyseal portal blood from conscious ovariectomized ewes, and measured the LHRH concentration in portal plasma and the LH concentration in the peripheral plasma. Their results showed exact synchrony of LHRH and LH secretions at 90-120 min intervals. This result indicates that the pulsatile LH secretory episode results from pulsatile discharge of LHRH from the hypothalamus via the portal network. Pulsatile LHRH administration was first tried by Jacobson et al. (1979). They administered 40 µg of LHRH subcutaneously in hourly pulses for consecutive nights to immature males with Kallmann's syndrome with a portable battery-operated infusion pump adapted for home use. Pulsatile LHRH produced a progressive increase in urinary gonadotropin excretion, a significant increase in mean basal plasma FSH, and pulsatile LH release. One subject showed a striking increase in plasma T in response to LHRH pulses. Valk et al. (1980) observed increases in plasma LH, FSH and T concentrations on day 5 of pulsatile LHRH administration (0.025 µg/kg, every 2 h) in five males with hypogonadotropic hypogonadism. Schoemaker et al. (1981) induced ovulation in a patient with clomiphene-resistant secondary amenorrhea by self administration of LHRH (20 µg/kg, every 2 h, iv) from 700 h–2300 h continuously for 90 days. This patient conceived during the third cycle. Hoffman and Crowley (1982) treated 6 patients with idiopathic hypogonadotropic hypogonadism with LHRH (0.025 µg/kg, every 2 h, sc). During the treatment of these patients, the gonadotropin concentration rose to the normal adult range within one week and to the supraphysiologic level by day 14. The testis size increased in four patients, and spermatogenesis was achieved in three patients by week 43 of therapy. Several other successful treatments of hypogonadotropic hypogonadism were reported later (Morris et al., 1984; Skarin et al. 1983; Donald et al., 1983). Various treatment schedules with LHRH treatments at intervals of 1 to 2 hours were used. As LH peaks occur with a frequency of 1 pulse per 90–120 min in normal adult human subjects (Santen and Bardin, 1973), LHRH stimulation every 90–120 min may be most physiological. The dose of LHRH per pulse ranged from 1.5 µg to 40 µg. Skarin et al. (1983) reported that infusion of 1 µg of LHRH every 90 min for 90 days did not normalize the T concentration, but when the dose was increased to 5 µg during the following 130 days, the serum T concentration increased to the normal range and was maintained at a normal level during further treatment. In the successful treatments reported, the T level began to increase within 4 weeks. Therefore, if a small pulsatile dose of LHRH for one month does not increase the T concentration in patients with hypogonadotropic hypogonadism, the dose should be increased.

The patient reported here has been given 20–25 µg of LHRH every 2 h. His T level began to increase after 4 weeks of treatment and was normalized in week 5. After 1 year of therapy, his sperm count was normalized. The purpose of LHRH therapy is to have children, and he was able to realize his dream. As he wants to have another baby, pulsatile LHRH therapy is
being continued. After he has the second child, LHRH is going to be replaced by a depot form of testosterone injection.

The side effects of LHRH reported are an inflammatory reaction at the infusion site and skin flush. Nakai et al. (1987) reported that 2 of 31 patients who developed a mild skin flush did not need any therapy. It is possible that an antibody to exogenous LHRH is produced and causes a diminished response to LHRH. This patient who has been treated with LHRH for 4 years and 6 months still shows a good response of gonadotropins. As LHRH is a small peptide that is produced by humans themselves, exogenous LHRH is not likely to act as an antigen in patients with LHRH deficiency.

Human chorionic gonadotropin (hCG) and human menopausal gonadotropin (hMG) have been used in treating patients with hypogonadotropic hypogonadism (Finkel et al., 1985). Klingmüller et al. (1983) compared the effects of long-term treatment with pulsatile LHRH substitution and chronic human hCG administration in patients with Kallmann’s syndrome. They demonstrated that the clinical and endocrine changes associated with puberty could be initiated in patients with Kallman’s syndrome by either long-term pulsatile LHRH or hCG treatment, but that LHRH treatment appeared to initiate endocrine changes associated with puberty more rapidly than conventional hCG treatment. hCG in addition to hMG usually increases the sperm count to normal in men with hypogonadotropic hypogonadism of pubertal onset, though in some patients, especially those with cryptorchidism, hCG-hMG therapy failed to normalize spermatogenesis (Finkel et al., 1985). Further studies are necessary to compare the effects of hCG-hMG and pulsatile LHRH in treatment of hypothalamic hypogonadotropic hypogonadism. A serious problem for patients with hypogonadotropic hypogonadism is that they have little opportunity to marry, and even if they get married, they are unlikely to have children. We expect that pulsatile LHRH therapy, a reasonable and useful tool for treatment of patients with hypothalamic hypogonadotropic hypogonadism, will help to overcome this problem.

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