Dosing Growth Hormones to IGF-1 Levels More Effective

**BY BETSY KATES**

S A N D I E G O — Short children grow taller when their growth hormone doses are adjusted according to their insulin-like growth factor 1 levels rather than to their weight, according to a randomized study results.

IGF-1 levels do matter,” said Pinchas Cohen, M.D., professor and director of research and training in the division of endocrinology at the University of California, Los Angeles, School of Medicine.

The notion of targeting dosing in order to maximize height in children of short stature is somewhat new and had been thought clinically impractical, Dr. Cohen said at a clinical symposium during the annual meeting of the Endocrine Society.

However, it was “possible and doable” to adjust doses according to a simple IGF-1–based algorithm. This approach resulted in “significant, quite dramatic improvement in height” for some children enrolled in the 2-year, multicenter trial.

In all, 172 children diagnosed with growth hormone deficiency or idiopathic short stature were enrolled in the trial sponsored by Novo Nordisk Inc., a manufacturer of human growth hormone, and the Lucile Packard Foundation for Children’s Health.

The children were aged 3-15 years and significantly below normal height for their age, with a mean standard deviation score of -2.63. They also had low levels of IGF-1, the core mediator of growth hormone action on linear growth.

The complex study design featured a comparison of three groups of children who received a conventional 40 mcg/kg per day dose of growth hormone. Two other groups received targeted, adjustable doses of growth hormone based on IGF-1 levels at 3 month check-ups.

One group received growth hormone in amounts necessary to achieve normal IGF-1 levels (a standard deviation score above the norm). The three groups achieved mean IGF-1 levels of +0.4, +0.4, and +2.0 standard deviation scores in the first 9 months of the study, and doses of 41 mcg/kg per day, 33 mcg/kg, and 110 mcg/kg per day were required to sustain these levels, said Dr. Cohen.

Only a small, nonsignificant difference was seen in children receiving standard growth hormone doses according to weight and those receiving doses targeted at a normal IGF-1.

The big difference in height was seen in children who received growth hormone at a dose aimed at raising their IGF-1 levels to two standard deviations above the norm. In this group, children with growth hormone deficiency grew 45% more, and children with idiopathic short stature grew 58% more than children in the other two groups.

Side effects and adverse events were similar in all three groups. Interestingly, a large variability was seen in the amount of growth hormone required to maintain targeted IGF-1 levels among individual patients: 9-114 mcg/kg per day in the first targeted group and 20-346 mcg/kg per day in the second targeted group.

Dr. Cohen serves as a consultant or advisory board member or receives research support from a number of companies that manufacture human growth hormone, including Genentech Inc., Pfizer Inc., Eli Lilly & Co., Novo Nordisk Inc., and Serono Inc.

ICMA Gonadotropin Test Called The Best Lab Evidence of Puberty

**BY DOUG BRUNK**

S A N D I E G O — The best laboratory test of pubertal development is a test for luteinizing hormone and follicle-stimulating hormone done by immunoenzymatic assay.

Stephen M. Rosenthal, M.D., said at a pediatric conference sponsored by Symposia Medicus.

Two labs that run the tests are Esoterix Inc. and Quest Diagnostics Inc., said Dr. Rosenthal, professor of pediatrics at the University of California, San Francisco.

“If you ever order tests for LH and FSH, it’s very important that you order them by immunochemiluminometric assays (ICMA), because [the tests] are able to distinguish between someone who’s prepubertal and the different Tanner stages,” he said.

If you get results that are difficult to interpret, Dr. Rosenthal recommended doing a GnRH stimulation test, which is also called a luteinizing hormone releasing factor (LRF) stimulation test. This involves giving a synthetic bolus of GnRH and then measuring the patient’s levels of LH, FSH, and either estradiol or testosterone.

Dr. Rosenthal noted that there have been availability problems with GnRH. If GnRH is not available, a similar test can be done with leuprolide acetate, a GnRH agonist. Guidelines for carrying out the latter test are described in the following reference. J Clin Endocrinol Metab. 1994;78:30-5.

“If you give an injection of synthetic GnRH (or agonist) to someone who’s in puberty, their own pituitary gland has been primed by their own GnRH, so when you give it, you’re going to see a surge of LH,” he explained.

The differential diagnosis of delayed puberty is defined clinically as a girl who has no evidence of breast development by age 13 years or a boy who has no evidence of testicular enlargement by age 14 years. The following are general possibilities in this differential diagnosis:

- Constitutional delay in growth. Most children seen for concerns about delayed puberty will fit this category.

- Some ‘people not only grow more slowly and reach puberty more slowly ... [they] age more slowly...’

DR. ROSENTHAL

“Is there something to be learned here to give us some insight? We don’t know the answer to that yet because there are so many variables as we get older that affect longevity.”

- Hypogonadotropic hypogonadism. In this condition, the defect is located in the hypothalamic or the pituitary gland. The cause could be Kallmann syndrome or could be associated with other conditions including cleft palate; congenital deafness; the X-linked form of congenital adrenal hypoplasia; Prader-Willi syndrome; Laurence-Moon-Biedl syndrome; central nervous system disease; and a variety of other conditions such as hypothryroidism, poorly controlled diabetes, and anorexia nervosa.

- Hypergonadotropic hypogonadism. In this condition, the defect is in the testes or ovaries. Potential causes include Klinefelter’s syndrome; phenylketonuria; congenital adrenal hypoplasia; cryp- toorchidism; XY gonadal dysgenesis; Noonan’s syndrome; Turner’s syndrome and its variants; and XX gonadal dysgenesis.