

Growth Hormone in the Treatment of Children with Short Stature

Therapeutic use of growth hormone (GH) in the United States generally has been restricted to GH-deficient children who, with their families, agree to participate in research. The limited supply and the considerable expense of commercially prepared GH have restricted the number of children who have received such therapy. As the medical community and public become more aware of the therapeutic potential of GH, practicing physicians are faced with mounting pressure to prescribe GH for short children who are not GH deficient. Furthermore, the promise that abundant supplies of biosynthetic GH prepared by recombinant DNA methods will soon be available adds to the fever for uncontrolled experimentation.

Twenty-five years of experience indicate that therapeutic replacement of GH is safe for GH-deficient children. Nevertheless, using GH in the treatment of children who are not deficient in GH should not be engaged in lightly, as GH is a potent metabolic agent that might have significant side effects. Because there is so little experience with the therapeutic use of GH at the pharmacologic doses that may be required to accelerate growth in non-GH-deficient children, information on side effects is limited. It is appropriate, therefore, to review (1) the accepted indications for the therapeutic use of GH (GH-deficient children), (2) the disorders in which GH has been shown to lack beneficial effect, (3) the issues to be considered in selecting for therapy patients who do not appear to have classic GH deficiency, and (4) the side effects that might occur when GH is administered as a pharmacologic agent.

TREATMENT OF GROWTH HORMONE DEFICIENT CHILDREN

Growth failure due to GH deficiency is the only universally accepted therapeutic indication for GH

treatment. For the laboratory diagnosis of GH deficiency, GH provocative testing must be completed and conditions that might result in transiently depressed GH secretion must be ruled out. The latter include chronic nonendocrine diseases, malnutrition, and psychosocial deprivation. Before testing is performed, it is imperative that the patient be euthyroid, as hypothyroidism can result in a blunted GH response. The criterion for the diagnosis of GH deficiency is failure to increase serum or plasma concentrations of GH to an acceptable level in response to provocative stimuli. Tests commonly used for this purpose include insulin-induced hypoglycemia, arginine infusion, L-dopa stimulation, and glucagon administration. Propranolol is sometimes given with the latter two stimuli.

Because none of these tests is always reliable, confirmation of the diagnosis requires that the patient fail to secrete adequate quantities of GH in response to at least two definitive stimuli. The definition of what constitutes an adequate plasma GH response to provocative stimuli remains the subject of debate. Opinions vary because of interlaboratory differences in assay techniques and variation in the potencies of purified GH standards. However, the somewhat arbitrary cutoff of 7 to 8 ng/mL has been used widely. Diagnosis is made easier when apparent GH deficiency is accompanied by evidence of deficiencies of pituitary thyroid-stimulating hormone, gonadotropins, ACTH, and/or vasopressin. It has been suggested that determination of the plasma concentration of somatomedin, a GH-dependent peptide, can be helpful in diagnosis. The value of this test is controversial, as the somatomedin concentration is influenced by a variety of factors other than GH. The measurement of somatomedin, therefore, cannot be used as a sole means for confirming the diagnosis.

The clinical criteria on which the decision to treat a child documented to have GH deficiency is based include a growth velocity that is subnormal for age and epiphyseal maturation less than 14

years in girls and 15½ years in boys. Growth hormone is ordinarily administered intramuscularly three times weekly, but subcutaneous administration appears to be equally effective. The dose of GH should be based on body weight, and initially it should be at least 0.06 to 0.1 U/kg per dose. The pretreatment growth rate of 3 to 4 cm/yr for a GH-deficient child will typically accelerate to 8 to 10 cm/yr during the first year of such a regimen. Older children may have smaller increments in growth rate. Because the effect of GH often declines after prolonged treatment, the dose may need to be increased. Data from studies in which higher doses of GH have been used suggest that the 0.06 to 0.1 U/kg dose may be suboptimal. Dose selection has been influenced to a great extent by the limited supply of GH and cost effectiveness rather than systematic study.

TREATMENT OF CHILDREN WHO ARE NOT GROWTH HORMONE DEFICIENT

For every short child who has GH deficiency, there are scores of children who are short for other reasons. Nevertheless, the medical literature contains reports of fewer than 300 non-GH-deficient children with short stature who have received GH treatment. Because so few patients have been treated, it is not possible to state with certainty that any form of dwarfism other than that caused by GH deficiency can be corrected or palliated by administering GH. Assessment of the effects of treatment in reported cases is made difficult by such variables as short duration of therapy, different doses and dose schedules, and failure to assess growth in the immediate posttreatment period when there is often a compensatory deceleration in growth. During this time the growth rate may decrease below pretreatment values and negate the gains made during therapy.

It is not surprising that GH fails to stimulate growth significantly in children with inherited limitation of the cells' capacity to divide (Down's syndrome, Silver-Russell syndrome, Seckel syndrome, progeria, Aarskog syndrome, etc), genetic abnormalities of cartilage and bone (achondroplasia, hypochondroplasia, osteogenesis imperfecta, etc), or metabolic derangements (cardiac, renal, and gastrointestinal diseases). Whereas it is not possible to state definitively that no patient with the non-GH-deficient disorders listed above will grow at a significantly better rate when treated with GH, the failure of responses in reported cases makes it clear that routine treatment of such patients is inappropriate.

One group of non-GH-deficient patients who might benefit from GH therapy is those with

Turner's syndrome. Preliminary data suggest the possibility that such patients might benefit from GH in combination with anabolic steroid therapy or even from GH alone. Studies are currently underway to test these possibilities.

More than 60 children with intrauterine growth retardation and postnatal short stature have received therapeutic regimens of GH. The heterogeneity of this group is reflected in the varied responses to treatment. Whereas it is clear that linear growth will improve in response to GH in a significant number of such patients, there are no reliable methods for determining which children will respond. Furthermore, only exceptional children from this group exhibit group responses equal to those of children with hypopituitarism. Additional carefully controlled studies of GH therapy are needed.

TREATMENT OF CHILDREN WHO DO NOT APPEAR TO HAVE CLASSIC GROWTH HORMONE DEFICIENCY

The greatest numbers of short children in whom study of the efficacy of GH seems appropriate include those with the designations of familial short stature and constitutional growth delay. The term familial short stature ordinarily refers to otherwise healthy individuals who have ancestors with adult height in the lower centiles, and whose height during childhood is appropriate for genetic background. Constitutional growth delay refers to individuals (usually boys) with delayed linear growth, in whom commensurate delays in skeletal and sexual maturation suggest that they will reach normal adult height. In many short children, familial short stature and constitutional growth delay are thought to be present simultaneously.

Despite scattered reports of both short-term success and failure, there is insufficient information on the response of such children to GH therapy to determine whether they are suitable candidates for such therapy. It seems probable, however, that injections of GH will promote growth in at least some of these children, as the excess GH in children with pituitary tumors causes rapid growth. Although large GH doses could accelerate growth of short children, GH therapy may also stimulate skeletal maturation. Therefore, there is no certainty that long-term therapy will make such children taller adults. Because these children should not have gonadotropin deficiency, their growth pattern should not resemble that of pituitary giants, whose tumors impair gonadotropin secretion and delay puberty.

There is current debate regarding whether some of these children possess subtle abnormalities of GH secretion or defects of GH action. Reports suggest that some children classified as having con-

stitutional growth delay may secrete less GH than normal children of the same age and have "partial GH deficiency." Furthermore, the concentration of GH in the circulation could be rate-limiting for the growth of some children whose plasma GH responses to provocative stimuli are greater than the arbitrarily defined lower limits of normal. It has been proposed that some children who secrete normal amounts of immunoreactive GH in response to provocative stimuli may produce a defective form of GH that is biologically inactive. The amount of receptor-reactive GH in plasma is taken as the measure of biologic activity.

Also, it has been suggested that plasma somatomedin responses to acute (four to ten days) or long-term (four months or more) administration of GH can be used to predict the long-term growth response to therapy. These observations, however, have not been corroborated in other studies, and they should not be taken as reliable methods for predicting long-term responses. Likewise, the degree of nitrogen retention that occurs during the initial phases of GH treatment is not predictive of long-term growth response. As yet, the only fool-proof method for determining how a patient will respond to GH treatment is to observe the growth response over several months. Even then the growth achieved in the first few months of treatment may not predict long-term success.

POSSIBLE SIDE EFFECTS OF GROWTH HORMONE THERAPY

Little information is available to reassure the physician or patient that GH is harmless when used as a pharmacologic agent, as nearly all past experience is limited to replacement of GH in children with hypopituitarism. In such children, formation of antibodies to GH has been common and hypothyroidism sometimes develops. As the quality of GH preparations has been improved, the prevalence of antibodies after treatment has decreased, as has the likelihood of growth attenuation due to antibodies. Nevertheless, a small percentage of patients can be expected to form antibodies. It remains to be determined whether children without GH deficiency will develop hypothyroidism while receiving GH therapy.

Our knowledge of the effects of chronic GH excess is derived almost entirely from observation of adults with acromegaly. Childhood GH excess is so rare that it is impossible to define fully the nature and frequency of associated pathophysiologic changes. Although the episodic secretion of GH makes it difficult to determine daily GH production, it has been estimated that acromegalic patients with serum GH concentrations in the range

of 5 to 30 ng/mL have production rates of 1.5 to 9 mg/d. At the commonly used GH doses (0.1 U/kg three times weekly), a 50-kg individual would receive 1 mg/d ($2 U \approx 1 \text{ mg}$). Therefore, a twofold or greater increase in dose might deliver enough GH to cause some of the biochemical or clinical changes observed in acromegaly.

Of the possible side effects of GH therapy, insulin resistance, hyperinsulinism, and impaired glucose tolerance are among the most likely. Approximately 10% to 20% of adults with acromegaly develop clinical diabetes mellitus. This in turn may contribute to the acceleration of atherosclerosis. The possibility that therapeutic GH may alter carbohydrate homeostasis is suggested by the marked increase in plasma insulin levels observed after glucose loading of children with hypopituitarism who are given continuous, chronic infusions of GH at three times the standard replacement dose.

Hypertension also is common in acromegalic patients, and although it is seldom severe, it has been associated with cardiac and cerebrovascular lesions. It therefore seems prudent to monitor blood pressure in children receiving GH, especially when using doses greater than those used in children with hypopituitarism.

Whereas there is evidence that GH and/or the somatomedins may support or accelerate the *in vitro* growth of certain leukemias and solid tumors, there is no evidence for an increased incidence of malignancy in acromegalic patients. Likewise, despite concerns, there is no evidence that GH promotes tumor recurrence in children with hypopituitarism who have had tumors.

SUMMARY

1. Replacement of GH in GH-deficient children is the only established indication for GH therapy. Treatment of all non-GH-deficient patients must be considered experimental.
2. There is a pressing need for carefully controlled clinical trials of the effect of GH in patients with constitutional growth delay, intrauterine growth retardation, and Turner's syndrome.
3. Research is needed to develop reliable methods for predicting which short, non-GH-deficient children will respond to GH therapy.
4. GH is a potent metabolic agent, and its safety when used in pharmacologic doses for treatment of short, non-GH-deficient children has not been established. Until adequate experience is gained under controlled conditions, GH should not be used indiscriminately. As the investigational use of GH is expanded, researchers and clinicians should bear in mind that handicaps resulting from short stature often have psychological origins. Therefore, even

for experimental studies, GH therapy should be restricted to children in whom it is judged that emotional status can be significantly improved. The potential for benefit should outweigh the problems of long-term parenteral therapy. In selecting patients for GH trials the wise physician might adhere to the old adage, "If it ain't broke, don't fix it."

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