TRATAMIENTO DEL NIÑO CON TALLA BAJA EN PUBERTAD: ROL DE LOS INHIBIDORES DE LA AROMATASA

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HIGH DOSE GH

A number of strategies have evolved in the last few years that attempt to increase height potential in growth retarded children who are in puberty. Since growth hormone (GH) production rates more than double during adolescence, the use of high-dose GH therapy has been studied in this period. In a randomized trial of conventional vs. high dose GH therapy for 36mo in GH deficient pubertal children we observed a significant increase in the adult height potential of the subjects in the high-dose group (net predicted height gain +4.9cm) as compared to conventional doses. This led to the US Food and Drug Administration approval of the use of higher GH doses in puberty in those kids most growth retarded during this period, or in those whose height potential is still quite limited and they are in puberty.

GNRH ANALOGUES

In addition, abundant data show that suppressing the production of sex steroidal hormones with gonadotropin hormone releasing hormone analogues (GnRHa) delays epiphyseal fusion and can ultimately render youngsters with precocious puberty taller than they would be otherwise. This strategy has now been tried not only in children with sexual precocity but in those with GHD that are in physiological puberty and even those with short stature not due to GHD with mixed results.

In the patients treated with both GH and GnRHa, improvements in height predictions (as determined by bone ages) have ranged from 7.9 cm to 14 cm when the children are treated for 2 to 4 years. More recently, Lin-su et al, reported data on 14 children with adrenal hyperplasia treated with GH/GnRH analogue for about 4years and compared the data with those of historic controls treated only with glucocorticosteroids. In the treated group, the final height of -0.4 ± 0.8 SD was much greater than at baseline (-1.5 ± 0.9, p=0.0001) and than the control group (-1.4 ± 1.1, p=0.01), suggestive that the GnRHa and GH combination is effective increasing adult height when administered for a long enough period. GhRHa therapy alone has been less successful in augmenting final height when used in children with normal variant short stature and cannot be recommended. The consequence of gonadal suppression,this approach as it pertains to bone accretion/bone density, and the psychological impact of suppressing physiological puberty in an already short child have not been fully studied to date. Even 10 weeks of GnRHa therapy in healthy young adult males is associated with substantial changes in body composition and intermediate metabolism with increased adiposity, decreased rates of protein synthesis, decreased lipid oxidation, decreased energy expenditure and decreased muscle strength. Using stable tracers of calcium, our studies in GnRHa-treated males show a marked increase in urinary calcium losse and in bone calcium resorption rates, indicating the crucial role of sex steroidal hormones in bone mineralization, even in the male.

ESTROGEN BLOCKERS

Estrogen, in both females and males, is the principal regulator of epiphyseal fusion as evidenced by detailed studies of male patients with point mutations either in the estrogen receptor gene or in the aromatase enzyme gene. When an estrogen receptor blocker was given to estrogen-treated mice, the acceleration in bone maturation caused by estrogen was blocked, supporting further the effect of estrogen on bone maturation. Hence, a third strategy has evolved which involves the more selective suppression of estrogen production or action in puberty in those children that are very short.

The estrogen synthetase or aromatase enzyme, is a product of the CYP 19 gene and catalizes the conversion of androgens to estrogens. It is expressed in ovary, liver, adipocite, bone, sincitiotrophoblast and breast tumors. The availability of selective aromatase blockers and sensitive estrogen assays now allow for the careful study of this issue in children. Three commercially available aromatase inhibitors include: Anatrozole (ArimidexÆ), Femara (LetrozoleÆ) and Exemestane (AromasinÆ). Anatrozole is a reversible blocker of the enzyme, with a peak concentration about 2hrs after administration and a predominantly hepatic metabolism. Femara also reversibly blocks aromatase, with steady state concentrations in 2hrs and a mostly renal clearance. Exemestane is different from the others in that this is an irreversible

blocker of the enzyme, it is an analogue of androstenedione that competes for binding sites, it peaks 3hr post administration and is eliminated in urine and feces. Exemestane needs to be taken with food. Data in a group of boys with a history of constitutional delay of puberty treated with Testosterone and either placebo or Letrozole for 12 months showed a 5cm increase in predicted adult height in the Letrozole-treated group. We also conducted detailed studies in adolescent and young adult males to investigate the metabolic effects of selective estrogen suppression using Anastrozole. We observed no negative effects of estrogen suppression on rates of whole body protein synthesis and degradation, bone calcium accretion and deposition, as well as plasma lipids and growth factor concentrations after 10w of Anastrozole treatment, despite a 50% reduction in circulating estradiol concentrations. This is in sharp contrast to the deleterious effects of GnRH analogue therapy described above.

We hence designed an open label study to gather pilot data on the safety, tolerability and efficacy of Anastrozole in suppressing estradiol concentrations and delaying epiphyseal bone fusion in 10 pubertal boys with GHD treated for one year and compared their data with those of 10 age-matched, GH-only controls. We observed that 12mo treatment with the combination of the aromatase blocker and GH in adolescent boys, results in a significant and sustained suppression of circulating estrogen concentrations and reciprocal increases in testosterone concentrations as compared to controls. Levels of plasma IGF-I, IGFBP-3, bone markers, insulin, glucose and lipids remained normal as well. Anastrozole treatment did not have any detrimental effects on body composition, the tempo of puberty or bone mineralization and was well tolerated and safe. Although there were no demonstrable changes in adult height predictions after only 12mo of treatment, it is clear that changes in predicted adult height take longer to be observed.

Interestingly, plasma IGF-I concentrations remained unchanged during one year of Anastrozole treatment in GH deficient boys whereas they increased by 45% in the GH-only treated control group. This is similar to what we observed in 10w experiments in young males reported previously. The mechanism for these findings is not fully understood as GH is "clampedó by fixed exogenous administration. A similar lack of increase in IGF-I concentrations with Anastrozole has not been accompanied by changes in pulsatile GH concentrations previously and IGFBP-3 concentrations, which are entirely GH dependent, did were not change in the present experiments in either group. Collectively, these data suggest that endogenous estrogens affect IGF-I production through a GH-independent mechanism, possibly through a modulation of hepatic transcription for IGF-I. Sperm analysis of the adolescents who participated in the study were comparable in motility and counts among those GH deficient young men who took the aromatase inhibitor and those that did not and healthy controls. We are in the midst of a 3 year, double blind, placebo-controlled trial looking at the effects of long term aromatase blockade and GH in boys with GH deficiency who are in puberty. Data will soon be available to answer the question as to whether this class of compounds plays a role in the treatment of poor growth in the pubertal male.

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