Growth hormone responsiveness in children

Results of Swedish multicenter clinical trials of growth hormone treatment

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av medicine doktorsexamen framläggs till offentligt förvar i Sal D, unod T9, byggnad 1D, plan 9, Norrlands Universitetssjukhus fredagen den 2 juni, kl. 13:00.
Avhandlingen kommer att förvaras på engelska.

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**Abstract**

The general aims of the thesis were to study GH responsiveness by estimation of pharmacokinetics and bioavailability of injected recombinant human GH (rhGH), of growth response as gain in heightSDS during childhood and puberty, and IGF-I response as change in circulating IGF-I SDS and IGFBP3 SDS. **Methods** Short children were recruited during 1988–1999 into two national randomized multicentre clinical trials on growth until adult height. A group of 117 GHD patients who had been treated from prepuberty with a single GH dose of 33 µg/kg/day for at least 1 year were randomized at onset of puberty either to remain on this dose regimen or to an increased dose, GH67 µg/kg/day, administered once daily or divided into two doses, GH33 and GH67 µg/kg/day. Data on IGF-I SDS and IGF binding protein 3 (IGFBP3) SDS were available from 111 patients and analysed as stated below. The 151 short prepubertal non-GHD patients were randomized into three groups: untreated controls, GH33 or GH67 µg/kg/day. A subpopulation from both trials, 128 patients examined annually in Gothenburg, formed the study sample on GH uptake. They received sc GH injections to obtain 16–24 hour GH curves and the GH pharmacokinetics and bioavailability was calculated. **Results:** A dose-dependent effect on Cmax was found with great intra- and inter-individual variability. Of the Cmax variability, 43% was explained by the rhGH dose and proxies for injection depth. Median bioavailability of the injected dose was 71%, with great variation, mainly dependent on injection depth. In the IGHD group a dose-dependent difference in pubertal gain in heightSDS was found, with mean of 0.8 for the GH67 group and 0.4 for GH33, p<0.01. The mean total gain in heightSDS during treatment was 1.9 for GH67 and 1.4 for GH33, p<0.01. A dose-dependent pubertal ΔIGF-I SDS was 0.5 vs −0.1, p=0.007, correlating to pubertal gain in heightSDS, p=0.003; and was the most important variable to explain the variation in pubertal gain in heightSDS. In the non-GHD group the ΔIGF-I SDS from baseline to mean study level was dose-dependent 2.07 vs 1.20, p=0.001; and correlated negatively with baseline values of IGF-I SDS, ρ=−0.56 for GH67, p=0.001, vs ρ=−0.82 for GH33, p=0.0001, and correlated positively with gain in heightSDS in both GH-treated groups, ρ= 0.42, p<0.001. In multivariable regression analyses, ΔIGF-I SDS was always an important explanatory variable for long-term growth response from the prepubertal period until adult height, while the IGF-I SDS study level per se was not. **Conclusion:** Growth response to GH treatment was dose dependent with great variability between patients. More pubertal growth was attained by an increased rhGH dose, mimicking the physiology of healthy children, in whom GH secretion rate increases during puberty. This resulted in a gain in IGF-I SDS closely correlating to pubertal gain in heightSDS in both IGHD and non-GHD patients. A broad range in GH responsiveness was found for both growth and IGF response in both diagnostic groups, but lower in the non-GHD group. Higher uptake of a given GH dose was observed after a deep injection and a higher GH concentration. These results are clinically applicable for individuals who remain short close to onset of puberty; by identifying and deeply injecting a rhGH dose that accounts for individual responsiveness, we can stimulate an increment in IGF-I SDS that correlates to gain in heightSDS during puberty.

**Keywords:** gain in height, puberty, IGHD, non-GHD, IGF-I, bioavailability