Long-Acting Growth Hormone

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Human growth hormone (GH) is a 22 kDa protein synthesized and secreted in the anterior pituitary gland. GH synthesis and release is induced by hypothalamic GH-releasing hormone (GHRH) and ghrelin and attenuated by somatostatin and negative feedback by insulin-like growth factor (IGF)-I [1]. The secretion of GH is episodic with several secretory peaks. The majority of spontaneous peaks occur during sleep, but it is also influenced by age, gender, intercurrent and chronic illnesses, and by nutritional status [1, 2].

GH is required for linear growth during childhood and adolescence. GH regulates the production of IGF-I, which is mostly produced in the liver, and, together, GH and IGF-I stimulate skeletal growth [1]. GH also has profound metabolic effects throughout life [2]. Through its anabolic, lipolytic, and antinatriuretic effects, it increases muscle mass and bone formation, reduces fat mass, and increases total body water. GH augments metabolic activity, resulting in a rapid and large increase in resting energy expenditure and fat oxidation, and protein synthesis increases [3]. Additionally, the peripheral conversions of thyroxine (T4) to triiodothyronine (T3) and of cortisol to the inactive cortisone rise. Furthermore, GH increases insulin resistance and causes hyperinsulinaemia. The lipolytic effect, and hence the impact upon body composition, is of course most readily appreciated during the initial years of replacement therapy, since a new steady state will be reached [4].

The diagnosis of GH deficiency (GHD) requires demonstration of a blunted response to stimulation tests according to specific diagnostic criteria [5, 6]. Insulin-induced hypoglycaemia (insulin tolerance test [ITT]) is the reference golden standard for diagnosing GHD, but the GHRH–arginine test and glucagon test are commonly used, with different cut-offs applied for the different tests. IGF-I is correlated with GH secretion, but because of overlap in IGF-I levels in healthy individuals and patients with GHD, IGF-I is not useful for diagnosing GHD [7]. However, IGF-I expressed as age- and gender-adjusted standard deviation score (IGF-I-SDS) is routinely used for monitoring GH dosing.

GHD during childhood results in growth retardation, as well as an abnormal body composition, with more body fat than lean body mass, and decreased physical capacity and quality of life. Treatment with GH in children with GHD has been well established for some 20–30 years and has, in several studies, been verified to promote linear growth and improve metabolism [6]. In fact, replacement of GH today extends long into adult life and even into senescence.

Nowadays, indications include GHD in both children and adults, children with Prader–Willi Syndrome, Turner Syndrome, and Noonan Syndrome, as well as idiopathic short stature (ISS), children born small for gestational age (SGA), and children with chronic renal insufficiency (CRI).

Treatment with GH became possible in the late 1950s following the isolation and purification of GH from human cadaver pituitary glands by Raben [8]. Since only extracts from the human pituitary gland were effective in humans, the availability of GH for clinical use was very limited. Following the introduction of the biosynthetically derived natural sequence (22 kDa GH) in the mid 1980s, there has been no shortage of GH for clinical use.

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Initially, GH was administered to GHD children as an intramuscular injection three times a week. This regimen was obviously far from the physiological secretion pattern, and the administration route was rather inconvenient. In 1983, daily subcutaneous injections were introduced, and it was demonstrated to be both more efficacious in terms of growth as well as less inconvenient to children [9]. Today, daily subcutaneous injection is the standard regimen.

In animal models, pulsatile administration of GH has proven to be superior to continuous administration, as judged from effects on growth and of IGF-I generation [10, 11]. By contrast, studies in GHD humans have not revealed any significant differences when results from daily subcutaneous injections of GH were compared with those of several injections per day using the same daily total doses [12, 13]. Likewise, continuous GH administration to adults with GHD by means of a subcutaneous infusion pump has not demonstrated any clinically meaningful differences in the metabolic response when compared with daily injections over 6 months [14].

It has for many years been a wish, particularly among paediatric endocrinologists, that a long-acting formulation would become available in order to reduce the inconvenience for patients of daily injections, and thereby potentially increase adherence to therapy [15–18]. Over the last 2 decades, several attempts to produce a long-acting GH preparation have been undertaken within the pharmaceutical industry, utilizing a number of different techniques [19–24], details of which are not included in this editorial. Some years ago, one long-acting GH preparation made it to the market but was subsequently withdrawn because of inferior efficacy revealed during post-marketing follow-up [19]. The inferior efficacy during clinical use was most likely because the preparation was more painful when injected than the usual GH preparations. Although only one injection per week was necessary, this obviously did not translate into a clinical benefit, presumably because the children skipped some of the painful injections. From this experience, it can be concluded that in the development of future long-acting GH preparations, convenience in relation to the injection procedure should not be underestimated.

Concerns have been voiced by some regulatory authorities that the constantly elevated GH levels induced by the long-acting GH preparations might imply a risk for supra-physiological IGF-I levels. Such a rise has even been suggested to increase the risk of developing neoplasia. These speculations have been raised in the absence of any direct or indirect evidence. In fact, experimental evidence from administering equivalent GH doses, either continuously or by daily injections has not revealed any tendency towards an increase in circulating IGF-I levels [10, 11, 14].

Furthermore, no major difference in the impact upon glucose metabolism could be demonstrated.

In our opinion, the present way of administering GH in daily clinical use is already non-physiological compared with the very fine-tuned and complicated regulation of GH secretion seen in healthy individuals. Hence, the development and use of long-acting preparations will not further compromise an already very un-physiological therapy.

It is therefore likely that long-acting GH preparations—if developed to meet the criteria of non-inferiority in efficacy and convenience—will prove to be a successful addition to the present armamentarium for the treatment of various conditions in childhood and beyond. The studies on the sustained-acting formulations published recently support this view, reporting comparable efficacy and side effects [20–24].

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