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Review article

Status of long-acting-growth hormone preparations — 2015

Charlotte Høybye [a,b,*], Pinchas Cohen [c], Andrew R. Hoffman [d], Richard Ross [e], Beverly M.K. Biller [f], Jens Sandahl Christiansen [g], for The Growth Hormone Research Society

[a] Department of endocrinology, metabolism and diabetology, Karolinska University Hospital, Stockholm, Sweden
[b] Department of molecular medicine and surgery, Karolinska Institute, Stockholm, Sweden
[c] Leonard Davis School of Gerontology, University of Southern California, CA, USA
[d] Department of Medicine, VA Palo Alto Health Care System and Stanford University, Palo Alto, CA, USA
[e] Department of Human Metabolism, University of Sheffield, UK
[f] Neuroendocrine Unit, Massachusetts General Hospital, Boston, MA, USA
[g] Department of Endocrinology, MEA, Aarhus University Hospital, NBG, Aarhus, Denmark

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ABSTRACT

Growth hormone (GH) treatment has been an established therapy for GH deficiency (GHD) in children and adults for more than three decades. Numerous studies have shown that GH treatment improves height, body composition, bone density, cardiovascular risk factors, physical fitness and quality of life and that the treatment has few side effects. Initially GH was given as intramuscular injections three times per week, but daily subcutaneous injections were shown to be more effective and less inconvenient and the daily administration has been used since its introduction in the 1980s. However, despite ongoing improvements in injection device design, daily subcutaneous injections remain inconvenient, painful and distressing for many patients, leading to noncompliance, reduced efficacy and increased health care costs. To address these issues a variety of long-acting formulations of GH have been developed. In this review we present the current status of long-acting GH preparations and discuss the specific issues related to their development.

1. Introduction

Only human growth hormone (GH) exerts metabolic activity in man, and it was not until its isolation from human cadaveric pituitary glands by Raben and its subsequent purification in the late fifties that clinical use of the hormone became possible [1]. Since 1960, treatment of short stature in hypopituitary children has been an accepted therapy, although its use for many years was restricted to three-times weekly dosing and to the shortest children because of the limited availability of the hormone. Since the 1980s, the availability of recombinant GH has enabled larger scale use of GH therapy on a daily basis in children and has extended its use to adults with GH deficiency (GHD).

Intramuscular injections three times per week were un-physiological and inconvenient. Careful pharmacological studies showed that daily subcutaneous injections were more effective and less inconvenient for the children, and this daily format was introduced as a routine treatment regimen during the 1980s [2].

GH has a plasma half-life of 3.4 h after subcutaneous injection and ~20 min after intravenous injection [3]. The pulsatile and very irregular secretion of GH seen in normal people are impossible to replicate clinically, even when the GH is administered several times each day. In animal models, pulsatile administration of GH results in better growth and greater IGF-I generation than does continuous GH infusion [4,5]. In contrast, studies in GH deficient (GHD) humans have not revealed any biochemical or physiological differences when comparing treatment with daily subcutaneous GH injections to therapy comprised of several injections per day using the same daily total doses [6,7]. Likewise, continuous infusion of GH in adults with GHD has not demonstrated any clinically meaningful differences in metabolic response in circulating markers of glucose-, lipid- and amino acid-metabolism during six months of therapy when compared to daily injections [8]. Thus, a perfect physiological regimen for GH therapy has not been identified and daily subcutaneous GH injections have been preferred as the most practical mode of administration. It is recommended to administer the daily injections in the evening, since this to some extent mimics the normal pattern for GH secretion and also normalizes the excursions of lipid and amino acid metabolites [2]. The clinical significance, however, of this recommendation has never been documented.

Despite ongoing improvements in injection device design, daily subcutaneous administration of GH remains inconvenient, painful and distressing for many patients [9], leading to noncompliance, reduced efficacy and increased health care costs. Compliance is a problem in up to 75% of teenagers, and growth velocity is reduced in the children

* Corresponding author at: Department of endocrinology, metabolism and diabetology, Karolinska University Hospital, 171 76 Stockholm, Sweden.
E-mail address: charlotte.hoybye@karolinska.se (C. Høybye).

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with poor compliance [9–11]. To address this problem, a variety of long-acting formulations of GH have been developed with the hope of achieving comparable efficacy and safety using fewer total injections [12,13] (Table 1). Long-acting formulations of several hormone drugs, including, GnRH, testosterone, medroxyprogesterone and others are commonly used clinically. The aim of this review is to update the current state of long-acting GH formulations.

2. Growth hormone

Human growth hormone (GH) is a 191 amino acid protein consisting of several isoforms. The most abundant pituitary form has a molecular weight of 22 kDa. GH is stored and secreted by the somatotrophs in the anterior pituitary gland; secretion is stimulated by ghrelin and hypothalamic GHRH (Growth Hormone Releasing Hormone) and inhibited by somatostatin in addition to negative feedback by insulin-like growth factor I (IGF-I) [14]. GH is secreted in pulses, most of which occur during sleep; however, the size and the numbers of pulses are influenced by several factors, including age, gender, acute and chronic illnesses, stress, and nutrition [14,15]. The highest levels of GH are reached in puberty. After puberty, GH levels gradually decline with age, but GH pulses are present throughout life. Women have a higher level of baseline GH and more pulses than do men [14].

GH regulates the production of insulin-like growth factor-I (IGF-I), and together, GH and IGF-I promote longitudinal growth and have important metabolic actions throughout life [14–16]. GH induces a rapid and large increase in resting energy expenditure and fat oxidation resulting in increased protein and glucose synthesis [16]. Through its protein anabolic, lipolytic and antinatriuric effects, GH increases muscle mass and bone formation, reduces fat mass and increases total body water [17,18]. GH increases the peripheral conversion of T4 to T3 and cortisol to inactive cortisone [14] and it may increase insulin resistance and lead to hyperinsulinaemia [15,16]. Intracellular GH signaling is mediated by the GH receptor, a type 1 cytokine receptor [14], a single transmembrane receptor found on most cells in the body. The extracellular GH binding domain of the receptor is also found in the circulation where it serves as a GH binding protein (GHBP) [14]. The GH molecule has two receptor binding sites that bind a preformed receptor dimer, creating a conformation change in the receptor and triggering intracellular signaling and receptor internalization [19].

The majority of circulating IGF-I is produced by the liver. While IGF-I can be bound to 6 different binding proteins, IGFBP 1 to 6, which modulate the effects of IGF-I [20], it is primarily bound to IGFBP-3 and to acid labile subunit [6] in a heterotrimeric complex. This large complex does not leave the circulation and can be regarded as a reservoir of IGF-I. The receptor for IGF-I is found in all tissues, and like the insulin receptor, it is a tyrosine kinase receptor [20]. It consists of two ligand-binding units and has a double trans-membrane and a cytoplasmic portion. Hybrid insulin/IGF-I receptors are abundant in the liver.

The circulating IGF-I level is commonly used as a biomarker for GH activity in humans. While other factors, including hormones, nutrition and state of health can also modulate IGF-I levels, serum total IGF-I is currently the best available biomarker for GH activity. Free IGF-I and bioactive IGF-I are not routinely measured and their clinical utilities still need to be defined. Calculation of the ratio between IGF-I and IGFBP 3 has been used as an indirect measurement of the free fraction of IGF-I.

Table 1
Long-acting growth hormone formulations.

	Product	Current status
Depot formulations	Nutropin Depot	No longer available
	LB03002	Approved in Europe
Pegylated formulations	PEG-GH PHA-794428	No longer in development
	NNC126-0083	No longer in development
	ARX201	No longer in development
	Jintrolong	Marketed in China for childhood GHD
	BBT-031	Preclinical studies only
	CP-016	Preclinical studies only
Prodrug formulations	ACP-001/TransCon	Phase 2 in children, Phase 2 in adults
	NNC0195-0092	Phase 2 in children, Phase 3 in adults
GH fusion protein technology	TV-1106	Phase 2 and 3 in adults
	MOD-4023	Phase 2 in children, phase 3 in adults
	LAPSrhGH/HM 10560A	Phase 2 in adults
	VRS-317	Phase 2 in children, Phase 3 in adults
	GX-H9	Phase 2 in adults
	ALTU-238	No longer in development
	Profuse GH	Preclinical studies only

3. Growth hormone deficiency (GHD)

The incidence of adults with childhood and adulthood onset GHD (defined as profound deficiency) has been reported to affect 1 per 100,000 people per year, with an estimated prevalence of 350/million [21], while the incidence in children has been estimated to be about 1 in 4000 [22].

The most common etiology for childhood onset GHD is idiopathic GHD [22], while the most common causes of adult-onset GHD are pituitary adenomas or other sellar or hypothalamic masses [23]. Short stature is a cardinal symptom in children with GHD [22]. GHD in adults is characterized by a number of clinical features including impaired quality of life, reduced physical activity, increased body fat, decreased lean body mass, decreased bone mineral density and an adverse metabolic profile [17,23]. None of these signs and symptoms is specific but in combination with impaired GH release they constitute a well-defined clinical entity [22,23].

The diagnosis of GHD is established according to specific criteria for the maximal GH response to various different stimulation tests, genetic tests, multiple pituitary hormone deficiencies with low IGF-I levels [22,23]. 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 except in patients with multiple other pituitary hormone deficiencies and a low IGF-I for age and sex [22,23]. However, IGF-I expressed as age-adjusted standard deviation score (IGF-I-SDS) is routinely used for monitoring GH dosing.

3.1. Treatment with daily GH

Indications for GH treatment include GHD in both children and adults, and in children: Prader Willi, Turner's, and Noonan's Syndromes, idiopathic short stature, children born small for gestational age and children with chronic renal insufficiency. In the US, GH is also approved for the use in short-bowel syndrome and AIDS wasting syndrome. The indication for GH replacement in adults is an established diagnosis of profound GHD according to consensus guidelines [18,23]. The primary objective of GH replacement therapy in children with GHD is to normalize linear growth [22]. The aims of GH treatment are to improve body composition, bone density, quality of life and the patient's metabolic profile and thereby presumably reducing the risk of cardiovascular disease. Major contraindications to GH treatment are active cancer and proliferative diabetic retinopathy [22,23]. In children, treatment is dosed by body surface area, while in adults, treatment with GH is usually initiated with a fixed low dose, and gradually titrated to an IGF-I level within the mid to upper part of the normal range for age-matched healthy controls [22,23]. Most side effects are mild and transient and are attenuated by gradual dose increments. Numerous studies have shown that GH replacement improves height, body composition, bone density, cardiovascular risk factors, physical fitness and quality of life, but there are relatively few studies beyond 5 years of treatment.