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Hormone excretion
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human growth hormone
hypo-pituitary dwarf
plasma concentration
plasma growth hormone

Plasma Growth Hormone Concentration after a Single Intramuscular Injection of Human Growth Hormone

S. Douglas Frasier[22], Gertrude Costin, Shun M. Ling, and Solomon A. Kaplan

Department of Pediatrics, University of Southern California School of Medicine, Los Angeles County-University of Southern California Medical Center, and the Children's Hospital of Los Angeles, Los Angeles, California, USA

Extract

We have investigated the concentration levels of growth hormone in plasma from six growth hormone-deficient patients who received human growth hormone (HGH) by intramuscular injection. The dose varied from 25 to 60 μg/kg body weight (38–92 mIU/kg body weight). An attempt also was made following intramuscular injection in two patients to determine the amount of hormone excreted in the urine.

Growth hormone was detected in plasma 15 min after HGH was administered and reached peak levels (65–154 ng/ml [mean 107.2 ± 16.4 ng/ml SEM]) in the 2- or 4-h samples. In three patients, the concentration of growth hormone had fallen to basal levels at 12 h; in all patients, 24 h after administration of HGH the levels of growth hormone were essentially undetectable. No growth hormone was detected in any urine samples.

The concentration of growth hormone in plasma observed after a single intramuscular injection differed markedly from the reported normal diurnal pattern.

Speculation

These studies suggest that the continued presence of growth hormone in plasma is not necessary for the promotion of growth in hypopituitary patients. Intermittent administration of growth hormone at weekly, biweekly or triweekly intervals may be associated with effects on the intracellular protein synthetic mechanisms that persist beyond the time of disappearance of growth hormone from the circulation.

Introduction

Data on the serum or plasma concentrations of human growth hormone (HGH) following an intramuscular injection are limited, and blood levels following a therapeutic dose of HGH have not been studied systematically. Parker *et al.* [13], using a radioimmunoassay method, have shown that peak concentrations of growth hormone in plasma are found between 2 and 6 h following intramuscular injection of 10 mg HGH in normal adults. Concentrations in plasma returned to basal levels between 12 and 24 h after injection. This dosage is greater than the usual therapeutic range, and the observed levels may have been influenced by endogenous growth hormone secretion during the period of observation.

The present study investigated the levels of growth hormone in plasma following an intramuscular injection of HGH at a therapeutic dose in six patients deficient in growth hormone. A preliminary report of this study has been published [5].

Material and Methods

Concentrations of growth hormone in plasma, following the initial intramuscular injection of HGH, were determined in six patients with growth hormone deficiency. The clinical diagnosis was based in each patient by evident failure to increase the plasma concentration of growth hormone in response to insulin-induced hypoglycemia, as previously described [4]. Additionally, each patient had subsequently shown a significant response to the long-term administration of HGH. Patients were clinically and chemically euthyroid at the time of HGH administration.

Each patient was fasted overnight prior to challenge. At the time of testing, a needle was inserted into an antecubital vein and was left in place for the next 48 h; a dilute heparin solution maintained patency. Immediately after obtaining a zero-time blood sample, 1 or 2 mg HGH were injected into the gluteal muscle. The growth hormone preparation used in these studies was National Pituitary Lot no. S-4 [19], which has a biological potency of 1.54 IU/mg (95% confidence limits 1.03–2.31 IU/mg). The dose of HGH administered to study patients varied from 25 to 60 μg/kg body weight (38–92 mIU/kg body weight) (table I). Patients were subsequently allowed to have a regular hospital diet and normal activity. Blood was obtained at 15 and 30 min and 1, 2, 4, 6, 8, 10, 12, 24, 36 and 48 h after HGH administration. Plasma was separated by centrifugation and stored at −20° until assayed. The concentration of growth hormone was measured by a radioimmunoassay method [4, 7], using a highly purified Wilhelmi HGH preparation (no. HS 840 FA) [20] as the standard.

Table I. Dosage of human growth hormone

Patient	Dose of growth hormone			
	mg	μg/kg	IU	mIU/kg
RS	1	25	1.5	38
MW	2	60	3	92
ML	2	55	3	85
JM	2	48	3	74
JY	2	45	3	69
JG	2	54	3	83

An attempt was also made to determine the quantity of growth hormone excreted in the urine by two patients following an intramuscular injection of HGH. Urine was collected at hourly intervals for the first 2 h, at 2-h intervals for the next 10 h, and at 6-h intervals thereafter for 24 h. An aliquot from each collection was stored at −20° until assayed. The radioimmunoassay method was applied to unextracted urine. In three preliminary experiments HGH [20], at a concentration of 50 ng/ml, was added to urine obtained from a hypophysectomized patient. Serial dilutions of this urine were assayed in duplicate. The resulting curves paralleled the assay standard curves in each experiment. Mean recovery of added growth hormone was 81%. The sensitivity of the radioimmunoassay as applied to urine was 0.2 ng growth hormone/ml; this assay will detect 1 ng growth hormone/ml in urine assayed at a dilution of 1:5. Unknown urine samples were assayed in duplicate at three dilutions (1:5, 1:10, and 1:20). Nonspecific inhibition of antibody binding of HGH-^{131}I, which could be interpreted erroneously as a result of the presence of growth hormone, was not observed in the assay of urine from a hypophysectomized patient or in 19 unknown urine samples.

Results

The plasma concentrations of growth hormone following a single intramuscular injection are shown in table II and fig. 1. Plasma growth hormone was undetected after an overnight fast in the five patients from whom a sample was available; however, 15 min after the administration of HGH, plasma growth hormone concentrations ranged between 5.2 and 29 ng/ml. Growth hormone levels in plasma rose rapidly to peak concentrations of between 65 and 154 ng/ml (mean 107.2

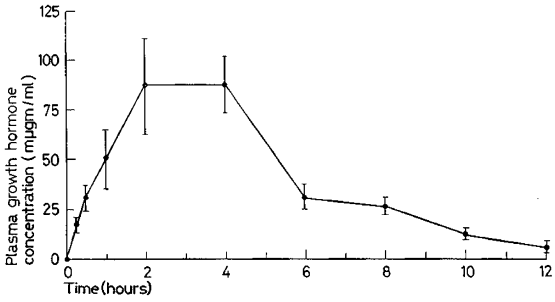

Fig. 1. Plasma concentration of growth hormone for the 12-h period following a single intramuscular injection of HGH in six patients deficient in growth hormone. The mean concentration is shown by closed circles, and ±1 SEM is enclosed in brackets.

±16.4 ng/ml SEM). At 12 h, the levels had fallen to basal values in three patients, and at 24 and 48 h growth hormone was not detected. The maximum plasma concentration observed during this time was 2.7 ng/ml (table II).

Growth hormone was not detected in any urine samples obtained following HGH administration. Since the assay will detect 1 ng growth hormone/ml of urine when assayed at a dilution of 1:5, the maximum possible concentration of growth hormone in each sample can be calculated from the volume of urine obtained over the period of sampling. The 24-h excretion of growth hormone in urine was less than 3.75 μg in patient RS, and the 12-h excretion was less than 7.5 μg in patient JG. Thus, following injection in these patients, excretion of growth hormone in the urine was less than 0.42% of the injected dose over 24 h and less than 0.36% over 12 h, respectively.

Table II. Plasma growth hormone after a single intramuscular injection

Patient	Time, h												
	0	0.25	0.5	1	2	4	6	8	10	12	24	36	48
RS	–	5.2[1]	8.5	9.5	19	*86*[2]	22	25	15	<1	<1	1.6	1.5
MW	<2	22	27	84	*154*	120	–	44	–	12	<2	–	<2
ML	<2	29	46	98	114	*128*	53	29	8.2	<4	<2	<4	<2
JM	<2	22	51	62	*145*	93	38	22	18	9.4	<2	<2	2.7
JY	<2	5.6	18	17	25	*65*	22	12	–	13	2.6	<2	<2
JG	<1	18	34	33	*65*	33	19	29	7.8	1.8	3	<2	<2
Mean±SEM	<2	17.0±3.9	30.8±6.6	50.6±14.9	87.0±24.2	87.5±14.4	30.8±6.5	26.8±4.3	12.3±2.5	6.0±2.5	<2	<?	<2

[1] Plasma growth hormone concentration (ng/ml).
[2] The maximum plasma concentration of growth hormone that was detected is *in italics*.

Discussion

HUNTER and RIGAL [11] have investigated the normal diurnal variation in plasma concentration of growth hormone in children and adolescents. In these studies, the plasma concentration showed a pattern of postprandial peaks during the day and spontaneous peaks during the night. The concentration in plasma was generally lower than 20 ng/ml, and in only one subject reached the level of 50 ng/ml during a 24-h period. The pattern of plasma concentrations observed after a single intramuscular injection was markedly different from the reported normal diurnal pattern. For six hours after HGH was injected (1 or 2 mg), the plasma concentrations were in the range usually found in acromegaly [1, 8, 9].

The applicability of the radioimmunoassay technique to the measurement of growth hormone in urine is controversial. Using this method, normal values reported for the amount of growth hormone excreted in urine varied considerably among laboratories [2, 12, 16]. A recent paper [6] suggests that substances that inhibit binding of tracer growth hormone and antibody are present in normal urine. Nonspecific inhibition of the radioimmunoassay system, not demonstrated in the present study, would give erroneously high values for urinary growth hormone.

The absence of detectable growth hormone in urine following an intramuscular injection of HGH confirms the findings of NAJJAR and BLIZZARD [12]. They administered 5 or 10 mg HGH to hypopituitary patients and detected 0.1–0.3% of the injected dose in subsequent 24-h urine collections. The rapid disappearance of growth hormone from plasma following a single injection, and the absence of the injected dose in the

urine, suggest rapid intracellular distribution of hormone. Another possible explanation for this disappearance is an alteration of administered growth hormone by proteolytic enzymes in plasma, which would alter the immunoreactivity of HGH and produce substances that, while active in promoting linear growth, are not detected by radioimmunoassay.

Human growth hormone injected at biweekly or triweekly intervals promoted linear growth in hypopituitary patients [10, 14, 17], and one report [15] suggested that weekly injections are also effective. Our observations indicated that HGH was detectable at significant concentrations in the plasma of hypopituitary patients for a maximum of 24 h following a single intramuscular injection. This finding and the results of investigative HGH therapy suggest that growth hormone has an effect on the intracellular protein synthesis that persists after the disappearance of growth hormone from the circulation. The observation of FLORINI and BREUER [3] that increased RNA polymerase activity in the rat reaches a peak in skeletal muscle 18 h after the injection of growth hormone supports this hypothesis. Increased protein synthetic activity of muscle ribosomes persists for 48 h after the injection.

Summary

Plasma concentrations of growth hormone following a single intramuscular injection of HGH were measured in six patients deficient in growth hormone. Growth hormone was detected in plasma 15 min after injection, and levels usually found in acromegaly were observed for 6–8 h after injection. Plasma levels returned to control values 24 h after HGH administration, but the pattern is markedly different from the normal diurnal variation of growth hormone concentration in plasma. Growth hormone was not detected in urine after an intramuscular injection of HGH.

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22. Requests for reprints should be addressed to: S. DOUGLAS FRASIER, M.D., Children's Division (4E8), Los Angeles County-University of Southern California Medical Center, 1200 North State Street, Los Angeles, Cal. 90033 (USA).