Reduction of Growth Hormone Secretion Following Clomiphene Administration

Mark Perlow, Jon Sassin, Robert Boyar, Leon Hellman, and Elliot D. Weitzman

Serial plasma growth hormone (GH) concentrations were measured every 20 min for 24 hr before and after the administration of clomiphene citrate (100 mg/day for 7 days) to four healthy young adult male subjects. The number of GH secretory episodes and the magnitude of the peak plasma concentrations during both wakefulness and sleep were decreased after the clomiphene treatment periods.

THE SPONTANEOUS 24-hr pattern of release of human growth hormone (GH) has been well studied in recent years.[1-7] Although GH is frequently released during wakefulness, a major GH release in adults is associated with the first 1-2 hr after sleep onset.[1-6,8-11] The administration of glucose, corticosteroids, propranolol, phentolamine, and chlorpromazine, agents that modify GH response to other stimuli during the waking day, have been shown to be without effect on the sleep-mediated GH release.[1,7,11-15] Pharmacologic doses of medroxyprogesterone[16] and imipramine,[1] however, are capable of suppressing the sleep-associated release of GH.

Clomiphene citrate (Clomid), 1-*p*-(diethylaminoethoxy) phenyl-1, 2-diphenyl-1-2-chloroethylene, increases the urinary excretion of estrogens,[17-22] gonadotropins,[17,18,23,24] ketosteroids,[17,18,24] and the plasma follicle stimulating hormone (FSH),[25,26] luteinizing hormone (LH),[23,26-28] and testosterone[27] in normal subjects. In women it is capable of inducing ovulation.[29,30] The site and mechanism of action of clomiphene are not well understood, although it appears to compete with androgens and estrogens for hypothalamic-pituitary receptor sites.[17,27,31-33]

Recent evidence suggests that estrogen[34,35] and testosterone[36] can increase GH release to insulin hypoglycemia and arginine infusion. In women, the GH response to arginine infusion is reduced by prior administration of clomiphene citrate.[37] This study was designed to determine if administration of clomiphene will alter the spontaneous 24-hr GH secretory pattern in normal men.

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MATERIALS AND METHODS

Subjects

Four normal men (ages 21–37) were studied. Three of these subjects (RM, ES, HS) were included in a recent study of the 24-hr pattern of luteinizing hormone secretion.[38] All subjects reported a normal sleep–waking cycle with 7–8 hr of regular nocturnal sleep. None of the subjects took any medications or drugs for at least 1 mo prior to the study. The subjects were individually hospitalized in a light-controlled and sound-attenuated room on the Clinical Research Center, Montefiore Hospital. A normal hospital routine and diet were maintained with meals at 8 a.m., 12 noon, and 5 p.m. Room lights were on from 7 a.m. to 11 p.m. and off from 11 p.m. to 7 a.m. All subjects had monitoring of continuous nocturnal EEG, submental electromyogram, and electro-oculogram. These polygraphic recordings were scored for sleep stage according to the criteria of Rechtschaffen and Kales.[39] Blood samples (5 ml) were taken every 20 min for a 24-hr period via an intravenous catheter that extended into an adjoining room. The details of obtaining and handling plasma samples have been described in previous reports from this laboratory.[40–42] The 20-min plasma samples were frozen until assayed for luteinizing hormone (LH) and GH. The above procedure was then repeated 1–2 mo later after each subject had taken clomiphene citrate (100 mg/day) for 7 days prior to and on the day of study.

Hormone Measurements

The plasma growth hormone (GH) was determined in duplicate by the radioimmunoassay method utilizing the charcoal–dextren separation of bound from free hormone.[43] The lowest detectable concentration of GH varied in individual assays between 0.5 and 1.5 ng/ml. Plasma luteinizing hormone (LH) was determined by a modification of the double antibody radioimmunoassay technique described by Midgley.[38]

RESULTS

The 24-hr catheterization procedure was well tolerated by all the subjects, and no symptoms were noted as a result of the ingestion of clomiphene. All subjects slept without difficulty; the per cent of total sleep spent in the various sleep stages was within normal limits and comparable from night-to-night in three of the four subjects (Figs. 1 and 2). The abnormal prolonged stage 2 seen early during the clomiphene study of subject MS was considered an isolated event unrelated to the drug.

Growth Hormone

GH was secreted throughout the 24-hr period in an episodic manner for the control and clomiphene study periods (Figs. 1 and 2). Secretory episodes occurred during wakefulness and sleep in three of the four subjects (ER, HS, MS). One subject (RM) secreted GH only during sleep in the control study. He did not secrete GH during wakefulness or sleep in the clomiphene study. The average number of awake secretory episodes per subject decreased from 3.7 to 0.7 after clomiphene administration (Table 1). The average peak GH concentration during wakefulness fell from 10.2 ng/ml to 3.0 ng/ml. The average number of sleep-associated GH secretory episodes per subject fell from 1.7 to 1.0 after clomiphene administration, whereas the average peak GH concentration during sleep decreased from 11.4 ng/ml to 3.9 ng/ml (Table 1). Although the number of sleep-associated GH secretory episodes was reduced in subject MS, the peak GH concentration was unchanged. Quantification by planimetry of the curves depicting GH concentration as a function of time also showed a reduction of GH secretion after clomiphene administration (Table 1).

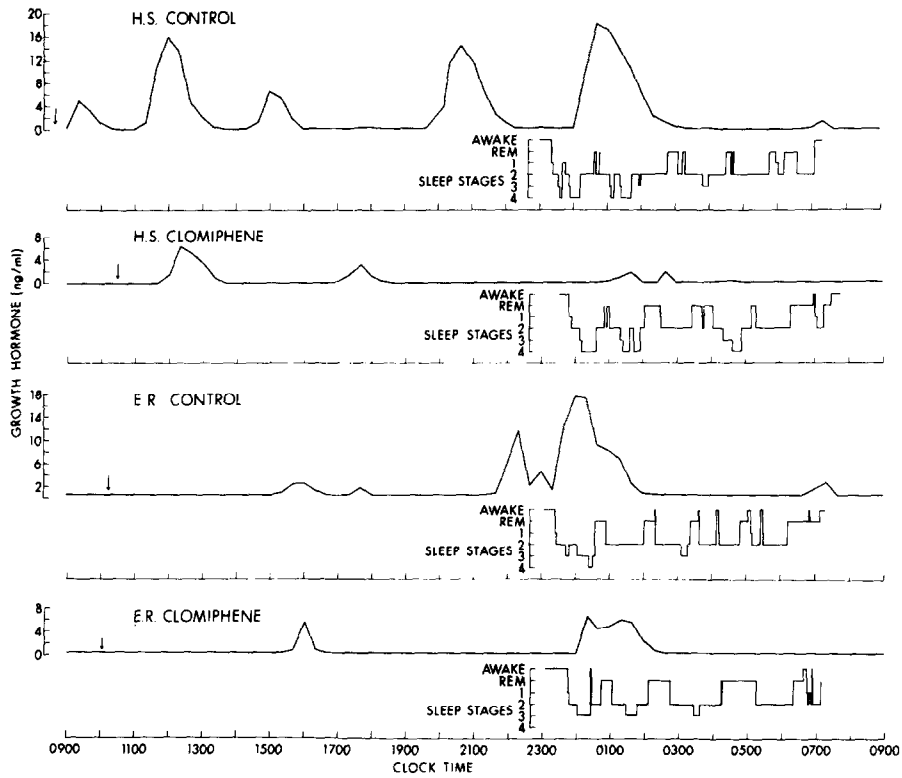

Fig. 1. Plasma GH concentration sampled every 20 min for 24 hr during control and clomiphene treatment periods. Sleep stage histogram is shown beneath the 8-hr period of nocturnal polygraphic recording. The time of insertion of the venous catheter is indicated by the arrow. Subjects HS and ER.

Luteinizing Hormone

LH was released in an episodic pattern in all studies. A description of this pattern has been reported previously.[38] During clomiphene administration, the mean 24-hr LH concentration increased 93% (range, 35%–149%) (Table 1).

DISCUSSION

The results of this study show that clomiphene citrate decreases spontaneous sleeping and waking GH secretion in normal young adult men. Although the day-to-day reproducibility of a subject's wakeful GH release has not been fully elucidated, the consistent results in this study suggest that clomiphene can reduce the frequency and magnitude of the spontaneous episodic release of GH during waking in normal men.[6,8–11,44]

Since the sleep-associated GH release has been shown to be reduced by interruption of sleep and/or stage 3–4 sleep deprivation,[1,2,45,46] it is crucial that sleep stage profiles for control and experimental nights be comparable. Since the sleep stage profiles for three of these subjects differed only slightly from night-to-night, and were within the limits of normal for this laboratory, the observed reduction of GH secretion during clomiphene administration appears to be an effect of the drug rather than due to an alteration of sleep stage characteristics.

Table 1. Effect of Clomiphene Citrate on Release of Plasma HGH and LH in Normal Men During 24-Hour Sleep-Wake Cycle

Subject	Study	Number of HGH Releases Per 24 Hr*	Area of HGH Release Per 24 Hr†	Peak HGH During Wakefulness (ng/ml)	Peak HGH During Sleep (ng/ml)	Area of HGH Releases During Sleep†	Average LH Concentration for 24 Hr (mIU/ml)
ER	Control	6 (4,2)	77	12	18	56	11.8‡
	clomiphene	2 (1,1)	26	6	7	22	18.0
HS	Control	6 (4,2)	149	16	18	61	7.4‡
	clomiphene	4 (2,2)	22	6	2	4	18.4
RM	Control	1 (0,1)	9	0	4	9	5.5‡
	clomiphene	0 (0,0)	0	0	0	0	12.9
MS	Control	5 (3,2)	40	13	7	20	3.4‡
	clomiphene	1 (0,1)	16	0	7	16	5.0

*Number of wakeful and sleep-associated HGH releases in parentheses, respectively.

† Area expressed in arbitrary units determined by planimetry of a curve depicting HGH concentration as a function of time.

‡ Mean LH concentration during clomiphene administration period was significantly different than mean concentration during control period with a $p < 0.001$ (Student's t test).

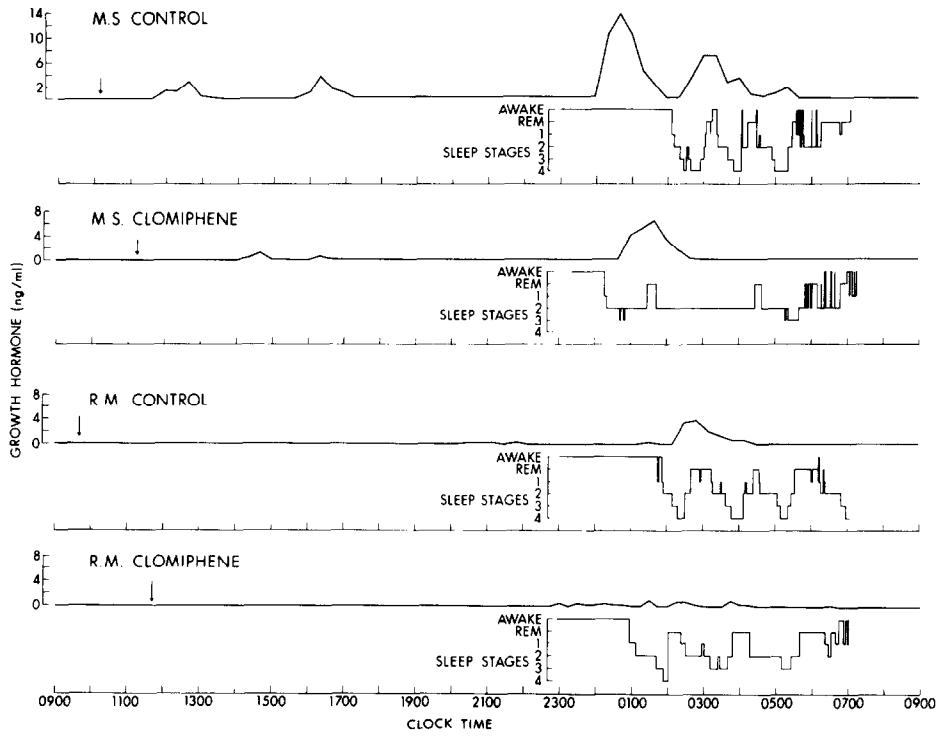

Fig. 2. Plasma GH concentration sampled every 20 min for 24 hr during control and clomiphene treatment periods. Sleep stage histogram is shown beneath 8-hr period of nocturnal polygraphic recording. The time of insertion of the venous catheter is indicated by the arrow. Subjects MS and RM.

Plasma GH concentrations are similar in men and women in the basal state, but are elevated in women after ambulation or mild exercise.[34,47] Sex differences have been shown to modify the mean 24-hr,[11] the sleep-associated,[6,44] the arginine-induced,[35] and perhaps the insulin-induced[48] GH releases. Ambulatory concentrations of GH are elevated during the periovulatory and premenstrual phases of the menstrual cycle.[34,49]

Administration of estrogens to normal men and postmenopausal women increases mean plasma GH concentration in ambulatory subjects[34] and arginine-induced GH secretion in resting subjects[35] to values observed in menstruating females. The elevation of mean plasma GH concentration in ambulatory individuals as a result of ingestion of combination oral contraceptives,[50] and the increase in the hypoglycemic-induced GH response following the ingestion of sequential oral contraceptives[51] are considered to be secondary to the estrogen content of the medications. Estrogen treatment of children increases their GH responsiveness to arginine and insulin infusions.[52] Clomiphene citrate, presumably by direct effect on pituitary GH release, or as a result of competitive inhibition with estrogen at hypothalamic receptor sites,[17,27,31–33] has been shown to reduce the magnitude of the arginine-induced GH release in females at midcycle.[37] Although no studies have been performed testing the effects of estrogens on the spontaneous wakeful and sleep-associated GH release, it is

possible that the same mechanism of action might account for the effects observed in response to clomiphene. Whether clomiphene citrate can reduce GH secretion in acromegaly remains to be determined.

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