

Effects of Chronic Sulpiride-Induced Hyperprolactinemia on Plasma Testosterone and Its Responses to hCG in Normal Men

FUMIMARO OSEKO, NOBUYUKI OKA, HIROSHI FURUYA, AND KEIKO MORIKAWA

To elucidate the effects of sulpiride-induced (300 mg daily) long-term (64 days) hyperprolactinemia on basal and hCG-stimulated plasma testosterone (T), hCG was given to five normal men five times at 2-week intervals (before sulpiride administration and at 2, 4, 6 and 8 weeks). Mean integrated hCG responses of plasma T did not change significantly as compared with baseline. However, mean (\pm SEM) basal plasma levels of T decreased significantly ($P < 0.05$) from 1011 ± 148 ng/dl to 852 ± 13 at 2 weeks, 520 ± 53 at 4 weeks, 572 ± 137 at 6 weeks and 554 ± 140 at 8 weeks. These results suggest that sulpiride-induced hyperprolactinemia (73.8 ng/ml, the average of mean values obtained at 2, 4, 6 and 8 weeks) for 64 days does not suppress secretion of T in response to hCG in spite of a decrease in basal plasma T concentrations. It is unlikely that the low concentrations of plasma T are due to direct effects of hyperprolactinemia on the testis.

Key words: hyperprolactinemia, drug-induced, testosterone, testis.

J Androl 1988;9:231-233.

Short-term hyperprolactinemia induced by a dopamine-blocking agent such as haloperidol increases the plasma concentration of testosterone (T) (Rubin et al., 1976; 1978). However, male patients with spontaneous hyperprolactinemia of long duration have clinical symptoms and signs of loss of libido, infertility, lack of erection and small testicles (Thorner and Besser, 1977). These patients often show low concentrations of plasma T (Nagulesparen et al, 1978; Franks et al, 1978).

Reprint requests: Fumimaro Oseko, MD, First Division of Internal Medicine, Shimane Medical University, Izumo, Shimane 693, Japan.

Submitted for publication August 22, 1986; first revised version received April 16, 1987; second revised version received November 5, 1987; third revised version received December 11, 1987; accepted for publication December 16, 1987.

From the First Division of Department of Internal Medicine, Shimane Medical University, Izumo, Shimane, Japan

It has been reported that levels of plasma T following hCG administration in men increase during short-term, drug-induced hyperprolactinemia (Ambrosi et al, 1976; Martikainen and Vihko, 1982). The present study was undertaken to determine the response of plasma T to hCG administration in normal men during long-term hyperprolactinemia induced by the dopamine-blocking agent sulpiride.

Materials and Methods

Five healthy eugonadal men between 28 and 48 years of age volunteered for this study. Informed consent was obtained from each of the subjects. Hyperprolactinemia was induced and maintained by daily oral administration of 300 mg of sulpiride for 64 days. HCG stimulation tests were carried out on each of the subjects five times, before (control period) and at 2, 4, 6 and 8 weeks of sulpiride administration. 4000 IU of hCG were given intramuscularly for 3 consecutive days and blood samples for plasma T were withdrawn from an antecubital vein with a heparinized syringe between 8:30 and 9:00 a.m. for 4 days beginning on the first day of hCG injection. Basal levels of plasma prolactin (PRL), LH and FSH were also determined in the same samples that were used as baseline in each test. The plasma was immediately separated by centrifugation and frozen at -20 C until the time of assay. Plasma T levels were determined by a commercial RIA kit (Eiken Chemical Company, Hiroshima, Japan) following N-hexane:ethyl ether (3:2) extraction. The antiserum was raised in rabbit against T-3-(O-carboxymethyl) oxime-BSA. This antiserum has a cross-reactivity of 36.5% with 5α -dihydrotestosterone, 4% with 5α -androstenediol and less than 1% with other steroids tested. Normal levels of plasma T in men aged 22 to 68 years ($n = 10$) were 874 ± 152 ng/dl

TABLE 1. Basal Levels of Plasma Testosterone in hCG Stimulation Tests in Five Normal Men Before and During Sulpiride Administration

Subjects	Testosterone (ng/dl)				
	Before Sulpiride Administration	Weeks of Sulpiride Administration			
		2	4	6	8
1	1040	706	468	360	329
2	769	779	378	317	269
3	641	520	469	433	509
4	1113	953	638	702	604
5	1492	1298	648	1050	1058
Mean (\bar{X})	1011	852	520	572	554
SEM	148	132	53	137	140
Compared with: control*		*	*	†	†
2-week values		*	*	*	*
4-week values				NS	NS
6-week values					NS

* $P < 0.05$.† $P < 0.01$; NS = not significant.

(SEM) (range = 392 to 1500). The sensitivity of the assay was 21.6 ng/dl and intraassay and interassay coefficients of variation were 4.2% and 6.6%, respectively. Plasma PRL, LH and FSH were assayed by RIA as previously described (Kawamura et al, 1978). The intraassay and interassay coefficients of variation for PRL, LH and FSH were 8.8, 9.0 and 13.3% and 20.5, 13.0 and 14.3%, respectively. For each hormone assay, all samples from each subject were measured with the same kit.

The responses of T to hCG were integrated in each test. The integrated value obtained at the control period for each of the subjects was designated 100 and the integrated values after sulpiride administration were expressed as the percent of control.

Multivariate analysis of variance was used for analysis of the data. Values are expressed as mean \pm standard error.

Results

Mean (\pm SEM) levels of PRL in the five normal men increased from 14.0 ± 0.7 ng/ml to 70.0 ± 5.6 , 67.6 ± 6.4 , 82.3 ± 8.4 and 75.3 ± 11.3 at 2, 4, 6 and 8 weeks, respectively.

Mean plasma T levels of the five subjects decreased significantly from 1011 ± 148 ng/dl during baseline to 852 ± 132 ng/dl at 2 weeks ($P < 0.05$), 520 ± 53 ng/dl at 4 weeks ($P < 0.05$), 572 ± 137 at 6 weeks ($P < 0.01$) and 554 ± 140 at 8 weeks ($P < 0.01$) (Table 1). After 4 weeks of sulpiride administration, mean plasma T levels did not differ significantly (Table 1). Mean basal plasma LH and FSH levels did not change significantly throughout the entire study.

Mean integrated T levels as percent of control were 92.2 ± 4.9 at 2 weeks, 90.0 ± 4.6 at 4 weeks, 84.3 ± 7.0 at 6 weeks and 86.7 ± 5.9 at 8 weeks. These

values were not significantly different from their respective controls. All men participating in the study complained of a slight decrease in libido after approximately 4 weeks of sulpiride administration.

Discussion

We have shown (Oseko et al, 1985) that plasma levels of PRL in the range of 75.6 to 95.3 ng/ml are sufficient to partially suppress hypothalamic function in men. Since the mean plasma levels of PRL in the present study were 73.8 ng/ml, they were considered high enough to exert hormonal effects on the hypothalamo-pituitary-testicular axis.

No difference was observed in the response of plasma T to hCG stimulation during sulpiride-induced hyperprolactinemia compared with baseline. This finding suggests that in men, sulpiride-induced hyperprolactinemia for up to 8 weeks does not suppress an hCG-induced T response from the testis. Padrón et al (1980) indicated that 96 to 144 hours after a single injection of 1500 to 6000 IU hCG in normal men, the levels of plasma T were equivalent to those found in tests of Leydig cell function employing daily injections of 3000 to 6000 IU for 4 days (de Kretser et al, 1975). Our dose of 4000 IU daily for 3 days probably attained this maximal response plateau, although we did not study dose-response relationships between hCG stimulation and T.

Responses of plasma T to hCG administration have been reported to be both "normal" (Carter et al, 1978; Franks et al, 1978) and "impaired" (Thorner et al, 1974b; Besser and Thorner, 1976; Faglia et al, 1977) in male spontaneous hyperprolactinemia. The

impairment was suggested to be due to the direct suppressive effect of hyperprolactinemia on the testis.

On the other hand, the responses of plasma T in sulpiride-induced hyperprolactinemia of short duration (5 to 10 days) have been both "normal" (Magrini et al, 1976) and "increased" (Ambrosi et al, 1976; Martikainen and Vihko, 1982). The difference between our results and those of Ambrosi et al (1976) may be due to the difference in the duration of the hyperprolactinemia.

With regard to plasma gonadotropins, other investigators have reported either "normal" (Thorner et al, 1974a; 1977; Rocco et al, 1983; Oseko et al, 1985) or "low" (Carter et al, 1978 and Nagulesparen et al, 1978) concentrations of LH and FSH in hyperprolactinemic patients. We measured LH and FSH in single samples at two weekly intervals. Small differences in mean LH and FSH are obscured by this method, whereas multiple samples obtained in short (10-minute) periods may demonstrate differences. Furthermore, subtle alterations in pulse amplitude and frequency of gonadotropins during hyperprolactinemia could decrease gonadal steroid secretion (Moult et al, 1982).

The significant reduction in the mean basal levels of plasma T in the five subjects starting 2 weeks after sulpiride administration (Table 1) was in accord with the findings of Nagulesparen et al (1978) and Franks et al (1978), who reported plasma T levels below the lower limit of the normal range in most of their hyperprolactinemic male patients. Lowered T in our five subjects may be due to chronic understimulation secondary to small changes in gonadotropin secretion that result from the sulpiride-induced hyperprolactinemia.

Although these five men complained of a slight decrease in libido, it remains unclear whether the loss of libido or impotence associated with hyperprolactinemia is solely due to the low levels of T (Franks, 1983).

Acknowledgments

We thank Ms. Ayuko Kitagawa for her excellent technical assistance, Ms. Akiko Kawakami for her secretarial skill and Mochida Pharmaceutical Company in Japan for supplying the human chorionic gonadotropins used in this study.

References

Ambrosi B, Travaglini P, Beck-Peccoz P, Bara R, Elli R, Paracchi A, Faglia G. Effects of sulpiride-induced hyperprolactinemia on serum testosterone response to hCG in normal men. *J Clin Endocrinol Metab* 1976; 43:700-703.

Besser GM, Thorner MO. Bromocriptine in the treatment of the

hyperprolactinemia-hypogonadism syndromes. *Postgrad Med J* 1976; suppl 1 52:64-70.

Carter JN, Tyson JE, Tolis G, Vliet SV, Faiman C, Friesen HG. Prolactin-secreting tumors and hypogonadism in 22 men. *N Engl J Med* 1978; 299:847-852.

de Kretser DM, Burger HG, Hudson B, Keogh EJ. The hCG stimulation test in men with testicular disorders. *Clin Endocrinol* 1975; 4:591-596.

Faglia G, Beck-Peccoz P, Travaglini P, Ambrosi B, Rondena M, Paracchi A, Spada A, Weber G, Bara R, Bouzin A. Functional studies in hyperprolactinemic states. In: Crosignani PG, Robyn C, eds. *Prolactin and human reproduction*. London: Academic Press, 1977; 225-238.

Franks S, Jacobs HS, Martin N, Nabarro JDN. Hyperprolactinaemia and impotence. *Clin Endocrinol* 1978; 8:277-287.

Franks S. Hyperprolactinemia and male reproductive function. In: Tolis G, Steganis C, Mountokalakis T, Labrie F, eds. *Prolactin and prolactinomas*. New York: Raven Press, 1983; 163-171.

Kawamura J, Daijo K, Hosokawa K, Sawanishi K, Yoshida O, Oseko F. Hypothalamo-pituitary-testicular axis in men undergoing chronic intermittent hemodialysis. *Int J Artif Organs* 1978; 1:224-230.

Magrini G, Ebner JR, Burckhardt P, Felber JP. Study on the relationship between plasma prolactin levels and androgen metabolism in man. *J Clin Endocrinol Metab* 1976; 43:944-947.

Martikainen H, Vihko R. hCG-stimulation of testicular steroidogenesis during induced hyper- and hypoprolactinaemia in man. *Clin Endocrinol* 1982; 16:227-234.

Moult PJA, Rees LH, Besser GM. Pulsatile gonadotrophin secretion in hyperprolactinemic amenorrhea and the response to bromocriptine therapy. *Clin Endocrinol* 1982; 16:153-162.

Nagulesparen M, Ang V, Jenkins JS. Bromocriptine treatment of males with pituitary tumours, hyperprolactinaemia and hypogonadism. *Clin Endocrinol* 1978; 9:73-79.

Oseko F, Note S, Morikawa K, Endo J, Taniguchi A, Imura H. Influence of chronic hyperprolactinemia induced by sulpiride on the hypothalamo-pituitary-testicular axis in normal men. *Fertil Steril* 1985; 44:106-111.

Padrón RS, Wischusen J, Hudson B, Burger HG, de Kretser DM. Prolonged biphasic response of plasma testosterone to single intramuscular injections of human chronic gonadotropin. *J Clin Endocrinol Metab* 1980; 50:1100-1104.

Rocco A, Falaschi P, Pompei P, D'urso R, Frajese G. Reproductive parameters in prolactinemic men. *Arch Androl* 1983; 10:179-183.

Rubin RT, Poland RE, Tower BB. Prolactin-related testosterone secretion in normal adult men. *J Clin Endocrinol Metab* 1976; 42:112-116.

Rubin RT, Poland RE, Sobel I, Tower BB, Odell WD. Effects of prolactin and prolactin plus luteinizing hormone on plasma testosterone levels in normal adult men. *J Clin Endocrinol Metab* 1978; 47:447-452.

Thorner MO, McNeilly AS, Hagan C, Besser GM. Long-term treatment of galactorrhea and hypogonadism with bromocriptine. *Br Med J* 1974a; 2:419-422.

Thorner MO, Besser GM, Hagan C, McNeilly AS. The relationship between prolactin and gonadotropins: effect of clomiphene administration in normal men. *J Endocrinol* 1974b; 63:43p-44p.

Thorner MO, Besser GM. Hyperprolactinemia and gonadal function: results of bromocriptine treatment. In: Crosignani PG, Robyn C, eds. *Prolactin and human reproduction*. London: Academic Press, 1977; 285-301.

Thorner MO, Edwards CRW, Hanker JP, Abraham G, Besser GM. Prolactin and gonadotropin interaction in the male. In: Troen P, Nankin HR, eds. *The testis in normal and infertile men*. New York: Raven Press, 1977; 351-366.