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Effects of Opium Dependency on Hypothalamic Pituitary Gonadal Axis

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The aim of this study was to determine the effect of opium on hypothalamic pituitary gonad function. Fifty-six opium dependent (28 men and 28 women; mean age, 25±5 year) were enrolled for hypothalamic pituitary gonadal axis. The control group considered of 56 non-opium dependent subject (28 men and 28 women; mean age 25±5 year). Decreased libido or impotency was present in 26 of 28 opium dependent men. The serum testosterone level was below 9 nmol L^{-1} in 24 of 28 men and was significantly lower than that in the control group ($p<0.001$). The free androgen index was below normal in 16 of 28 men and was significantly lower than that in the control group ($p<0.001$). The serum LH level was less than 2 U L^{-1} in 17 of 28 men significantly lower than that in the control group ($p<0.001$). Serum FSH was normal in both groups. Decreased libido was present in 16 of 28 women opium dependent. Serum LH, estradiol and progesterone levels were lower in opium group. In conclusion, of all opium addicts the large majority of men and all of women developed hypogonadotropic hypogonadism. The results reveal that opium can extract deleterious actions upon male and female hypothalamic pituitary gonadal axis and these findings suggested that further investigations are required to determine the need for endocrine work-up in opium dependent and the important substitutive therapy.

Key words: Opium, LH, FSH, testosterone, gonadal function

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INTRODUCTION

Opium, smoked for centuries in the repursuit of pleasure, was quickly recognized as providing relief of subjective discomfort. Opium contains more than 20 distinct alkaloids, the first of which (morphine) isolated in 1806. Many semi synthetic derivatives are made by relatively simple modifications of major opium alkaloids, morphine or thebaine. Thebaine has little analgesic action but is a precursor of several important compounds, such as oxycodone. In addition to morphine, codeine and the semi synthetic derivatives of the natural opium alkaloids, a number of other structurally distinct chemical classes of drugs have pharmacological actions similar to those of morphine (Susan and Thomas, 1999). Opioid peptides are found throughout the central nervous system. Both acute and chronic neuroendocrine effects of opiates and different opioid peptides have been studied extensively in animals and humans. In humans the acute administration of opioids decreases LH release (Morley, 1981; Grossman, 1983; Abs and Verhelst, 2000). The restraint on LH release is predominantly mediated through central inhibition of hypothalamic GnRH secretion (Rasusmussen and Liu, 1983). It is possible that βEND may be an indirect modifier (via Sertoli cells) of Leydig cell steroidogenic activity. In accordance with this hypothesis the observation that βEND significantly inhibits FSH in rats (Morris *et al*., 1987). It must be noted that exogenous opioids are direct stimulant of βEND receptors in adult rat testis (Adams and Cicero, 1991; Adams *et al*., 1991) and it has been suggested that opioids may act through testicular βEND to suppress the synthesis and release of testosterone (Adams *et al*., 1991). Exposure to opioids for 3 days caused a significant increase in [3H] etorphine specifically bound to the Sertoli cells (Fabbri and Morris, 1985). Taking in to account the receptor subtypes, TSH is preferentially activated by receptors and the inhibitory control of LH involves receptors (Delitala and Grossman, 1983; Grossman and Moult, 1986). Despite the fact that opioids are known to control or influence several endocrine pathways (Morley, 1981), no studies have looked systemically for possible hypothalamic pituitary gonadal axis changes induced by opium dependency. Therefore, we thoroughly studied the hypothalamic pituitary gonadal axis of large group opium addict and compared these results to the data obtained from a control group of non-opium dependent subjects.

MATERIALS AND METHODS

Patients: Total 56 opium dependent with a mean age of 25±5 year was enrolled in this case-control study they consisted of 28 males and 28 females. They all suffered opium dependency that they referred to Rahaee addiction up clinic of Zabol of Iran in 2004. No subject had been given corticosteroids during the previous 6 months. The mean duration of opium dependency at the time of analysis was 5±2 year. adverse events related to opium dependency were actively sought, in particular the sexual history.

Control population: The control group considered of 28 male with mean age 25±5 year and 28 female with the same age.

For all patients and controls the following variables were recorded: gender, age, body mass index, blood pressure.

The gonadal axis was evaluated by determining serum estradiol and progesterone in females and by determining serum testosterone and sex hormone binding globulin (SHBG) and calculating the free androgen index (FAI = Testosterone/SHBG) in males.

LH and FSH were measured twice with a 15-min interval between measurements and the lowest value was chosen to avoid a peak due to pulsatile secretion (Abs and Verhelst, 2000).

Differences between groups were tested for significance using Student t test $p<0.001$ was considered statistically significant.

RESULTS AND DISCUSSION

No differences were found between the opium dependant group and the control group for following parameters: gender, age, body mass index, blood pressure (Table 1).

Twenty six of 28 males from the opium dependent group, retrospectively considered libido as normal before opium dependency, whereas 25 of 28 control group had no sexual complaints. Twenty of 26 males 76.9% reported a rather sudden decrease and even disappearance of libido and potency shortly after initiating opium abuse.

Serum testosterone ($p<0.001$) and FAI ($p<0.001$) were significantly lower in the opium dependent group compared to the control group.

The serum LH concentration was significantly lower in opium dependent group ($p<0.001$). Seventeen of the

Table 1: Clinical characteristics of groups

Parameters	Opium group	Control group	p-value
No.	56	56	NS
Gender	23M/23F	23M/23F	NS
Age (year)	25±5	25±5	NS
Systolic pressure (mmHg)	125.3±11.3	110±12.5	NS
Diastolic pressure (mmHg)	80±5.5	75.0±8	NS

Table 2: Pituitary gonadal axis in groups

	Normal Values	Opium group	Control group	p-value
Males	-	28	28	
Testosterone (nmol L^{-1})	9-26	5.5±4.9	16±4	<0.001
Free androgen Index	20-80	22.5±19.6	50±18.7	<0.001
LH(U L^{-1})	2-9	1.3±0.9	5.3±3.3	<0.001
FSH(U L^{-1})	2-7	4.3±2	6.0±3.9	NS
Females		28	28	
Pre menopausal Females	-	16	10	NS
LH(U L^{-1})	2-8	2.1±186	14±13.2	NS
FSH(U L^{-1})	2-8	6.0±5.0	8.9±8.5	NS
Estradiol (pmol)	110-800	130±118	356±390.3	NS
Progesterone (pmol)	3-60	2±2.3	8.6±11.0	NS
Post menopausal Females	-	12	18	NS
LH(U L^{-1})	>13	4.1±3.6	27.0±13.8	<0.001
FSH(U L^{-1})	>38	15.0±16.4	37±21.3	0.015
Estradiol (pmol)	<110	105±116.7	55.9±37.4	NS
Progesterone (pmol)	<3	1.3±0.7	1.6±0.4	NS

28 male opium dependent (60.7%) and one control subject had a LH level less than 2.0 U L^{-1}. There were no differences in serum FSH between the groups. Four of the 28 (14.2%) male opium dependents and no control patients had a FSH level less than 2.0 U L^{-1}. Sixteen of 28 women opium libido as normal before opium dependency the start of opium use. Libido decreased or disappeared shortly after initiating opium dependency in 10 of 16 women (62.5%).

Serum LH, FSH, estradiol and progesterone were clearly lower in the opium group than in the control group. Seven of the 16 pre menopausal opium dependents (43.7%) and no control subject showed a LH level less than 2 U L^{-1}. Four of the 16 pre menopausal opium group (25%) and no control women showed a FSH level less than 2 U L^{-1}.

In the 12 post menopausal women, serum LH ($p<0.001$) and FSH concentrations were significantly lower than those in the 5 post menopausal control women. All 12 post menopausal opium dependents (100%) and no control individuals showed a LH level less than 13 U L^{-1}. Ten of the 12 post menopausal opium group (83.3%) and one control individuals showed a FSH level less than 38 U L^{-1} (Table 2).

Opium, smoked for centuries in the repursuit of pleasure, was quickly recognized as providing relief of subjective discomfort (Susan and Thomas, 1999). Opium dependence is an important health problem and opium is traditional drug for abuse and addiction in Iran. In this case-control study we were able clearly demonstrate that opium dependency my have profound effects on hypothalamic pituitary gonad function. The present results showed a clear and significant suppression of LH and testosterone in virtually all males and a similar decrease in LH secretion with a disrupted menstrual cycle in females. Despite the significant difference in LH, estradiol and progesterone levels in premenopausal women, was significant. Opioid peptides are found throughout the central nervous system. Endogenous opiates play a major role in the regulation of gonadotropines, especially LH, through a tonic inhibitory control and probably a minor acute neuromodulatiory role in the stimulatory regulation of TSH. This is in contradistinction with the rate in which endogenous opiates appear to have a much more significant effect on TSH (Morley, 1981). Both acute and chronic neuroendocrine effects of opiates and different opioid peptides have been studied decreases LH release (Morley, 1981; Grossman, 1983; Abs and Verhelst, 2000). The restraint on LH release is predominantly mediated through central inhibition of hypothalamic GnRH secretion (Rasusmussen and Liu, 1983). Reduced libido is a well-known phenomenon for those using heroin or in methadone maintenance program. Animal studies confirm that opioids lower testosterone levels and suppress sexual function in males (Celani *et al*., 1984). Early case studies of persons using heroine or methadone described diminished libido, sexual dysfunction, reduced testosterone levels men and amenorrhea in women (Lafisca *et al*., 1981; Mendelson *et al*., 1975). Two mechanisms are thought to be responsible for the reported reduction in libido associated with opioid use. Opioids inhibit the production of gonadotropin releasing hormone, subsequently decreasing the release of Luteinizing Hormone (LH), thus and decreasing the production of testosterone. Opioids also produce hyperprolactinemia, which causes negative feedback on the release of LH and decreases the production of testosterone (Ragni *et al*., 1985). Opioids are known to alter the normal function of hypothalamic pituitary gonadal axis (Wang *et al*., 1978). More recent case reports of patients receiving opioids for relief of chronic pain suggest these same findings (Abs and Verhelst, 2000). Although the limited research that has examined the

relationships among sexual functioning, chronic pain, opioid therapy and testosterone levels has been predominantly evaluated in men, anecdotal clinical experience supports similar relationship in women. Recent empirical support has been documented for women in a study that examined the endocrine consequences of long-term intrathecal administration of opioids. Reduced libido was reported in 95 percent of men and 68 percent of women, with significant reduction in serum LH for both groups and serum testosterone for the men all of the premenopausal women (n=21) developed either amenorrhea or an irregular menstrual cycle with ovulation in only one women (Abs and Verhelst, 2000). All above studies and data are paralleled with this study. Thus we argue that these findings should be taken in to account in all opium dependent subjects and endocrine check up is necessary.

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