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CLINICAL STUDY

The naloxone test in Klinefelter syndrome

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Abstract

AIM OF THE STUDY: The investigation of the influence of anti-opioid drug on hypophyseal and gonadal hormones secretion in case of Klinefelter syndrome.
MATERIAL AND METHODS: The naloxone test (0,4 mg iv) was performed in 14 patients with Klinefelter syndrome aged from 19 to 32 and in 12 age matched control subjects with azoospermia and normal spermatogenesis in testicular histology. The plasma levels of FSH, LH, prolactin, testosterone and estradiol were established before and after 30, 60, 90 and 120 minutes respectively, following the drug administration.
RESULTS: Basal FSH, prolactin and estradiol levels were significantly higher whereas basal testosterone was significantly lower in patients with Klinefelter syndrome than in the control group.After the naloxone administration the mean plasma prolactin level decreased significantly ($p=0.01$) in Klinefelter subjects. The respective diminution in control group was not significant. The levels of FSH and LH as well as testosterone and estradiol did not change during the naloxone test in both Klinefelter and control subjects.
CONCLUSIONS: The naloxone administration in Klinefelter syndrome caused the decrease in plasma prolactin levels but did not affect the plasma levels of another hypophyseal and gonadal hormones. The opioid controlled gonadotropin secretion is altered in case of Klinefelter syndrome

Introduction

The true Klinefelter syndrome is a genetic disorder caused by extra X chromosome. The most often observed karyotype is 47/XXY. This pathology is a form of hypergonadotropic hypogonadism. The frequency of Klinefelter syndrome is estimated as 1 in 500 men [1,19]. Testicular atrophy and different degrees of androgen insufficiency manifest the clinical features of this syndrome. Hyalinization of the seminiferous tubules and hyperplasia of Leydig cells cause the testicular atrophy. These men are sterile. The semen analysis reveals the absence of spermatozoa – azoospermia [6,27]. Although the infertility caused by azoospermia in that syndrome seems to be not reversible, there are some literature data informing about severe oligozoospermia and pregnancies in men with non-mosaic Klinefelter syndrome [21,23,25]. The genetic disorders however, mainly the Klinefelter syndrome, according to WHO data, are still the common cause of male sterility.

There are some data concerning hormones concentrations in Klinefelter syndrome. The plasma levels of FSH, LH and estradiol are increased whereas testosterone plasma levels are diminished. The prolactin plasma levels in Klinefelter syndrome are increased [13,14,22] or normal [5,7,28].

Tomasi et al. found that one of possible causes of high level of FHS in Klinefelter subjects may be decreased concentration of inhibin-B [29].

The hypothalamo-hypophyseal-gonadal axis is influenced by endogenous opioids. The administration of antiopioid drugs such as naloxone or naltrexone, in fertile young men caused the increase of plasma LH levels as well as the increase of the frequency and amplitude of LH pulses [10,20,30,34]. The opioids cause the increase in plasma prolactin levels [15,34]. The administration of naloxone prevents the increase of plasma prolactin levels during surgical stress [26].

In previous studies performed in our Department Bablok et al. observed that intravenous administration of naloxone in patients with azoospermia and normal spermatogenesis revealed by histological examination of testicular biopsy specimen had caused the decrease of plasma prolactin levels but did not change the levels of FSH, LH, testosterone and estradiol [4].

The aim of the present study is the investigation of the influence of antiopioid drug – naloxone – on plasma levels of hypophyseal and gonadal hormones in men with Klinefelter syndrome. This way we want to elucidate the fact of increased estradiol and decreased testosterone levels in these subjects.

Material and Methods

The naloxone test was performed in 14 patients with Klinefelter syndrome with confirmed karyotype of 47/XXY. The age of them varied between 19 and 32 years (mean 25.92, SD 4.44). There were no signs of gynecomastia and galactorrhoea in any of the observed patients. The control group consisted of matched 12 men with azoospermia and normal spermatogenesis in testicular histology.

0.4 mg of antiopioid drug (Naloxone, Sanofi-Winthrop) was given intravenously to each patient. The plasma levels of FSH, LH, prolactin, testosterone and estradiol were determined before and after 30, 60, 90 as well as 120 minutes respectively, following the drug administration.

The FSH, LH, prolactin and estradiol levels were evaluated by immunoenzymatic methods (Abbott kits – USA).

Testosterone plasma levels were determined using radioimmunologic method (Farmos kits – Finland).

The plasma levels of examined hormones were presented as a mean values and standard deviations in the 30 minutes intervals after the drug administration. The percentage changes of hormone levels compared to basal levels during the test were presented as mean and standard deviations. The statistical analysis was performed using the Wilcoxon matched pair rank test and program Statistica 6.0 for Windows. As a border value of statistical significance $p<0.05$ was established.

Results

The basal FSH levels were significantly higher in men with Klinefelter syndrome when compare with the control group (42.08 11.99 vs. 6.56 ± 2.58 mIU/ml; $p<0.001$). The similar results were observed in case of both LH (27.61 ± 11.90 vs. 4.32 ± 1.76 mIU/ml; $p<0.001$) and estradiol (58.24 ± 12.10 vs. 47.62 ± 9.98 pg/ml; $p<0.05$) levels. On the contrary to these observations basal testosterone levels were significantly lower in case of Klinefelter syndrome then in the control group (3.97 ± 2.18 vs. 5.64 ± 1.69 ng/ml; $p<0.05$). Whereas the prolactin levels were statistically higher than in the control group, all the values appeared to be in the normal range (11.22 ± 5.64 vs. 6.66 ± 3.01 ng/ml; $p=0.01$) (Table I).

The plasma prolactin levels decreased after 120 minutes to 6.88 ± 3.95 ng/ml (67.2 ± 39.4%) in Klinefelter syndrome and to 5.45 ± 3.02 ng/ml (84.7 ± 27.7%) in the control group. The diminution in men affected by Klinefelter syndrome was statistically significant ($p=0.01$) after 120 minutes. However, the differences revealed in other time intervals were insignificant. The statistically significant percentage decrease in prolactin levels was not observed either in Klinefelter syndrome, or in the control group (Table I; Figure 1).

The FSH, LH, testosterone and estradiol levels in men with Klinefelter syndrome and in the control group did not change significantly during the naloxone test (Table I).

Discussion

The basal plasma values of FSH, LH and estradiol were statistically higher whereas basal plasma testosterone levels were statistically lower in Klinefelter syndrome than in the control group. These data are in accordance with observed hormone levels in Klinefelter

Table I. The hormone plasma levels during naloxone test in Klinefelter syndrome and in normal spermatogenesis.

Time (min.)	FSH(mIU/ml)x ± SD			LH(mIU/ml)x ± SD			PrI(ng/ml)x ± SD			T(ng/ml)x ± SD			E2(pg/ml) x ± SD		
	KS	CG	p	KS	CG	p	KS	CG	p	KS	CG	p	KS	CG	p
0	42.08 ±11.99	6.56±2.58	<0.001	27.61±11.90	4.32±1.76	<0.001	11.22±5.64	6.66±3.01	0.01	3.97±2.18	5.64±1.69	0.04	58.24±12.10	47.62±9.98	0.02
30	41.24±11.50	6.52±2.72	<0.001	30.50±16.98	4.63±2.69	<0.001	10.37±5.26	6.45±3.22	0.03	4.16±2.28	5.23±1.37	ns	57.64±17.05	51.78±15.06	ns
60	41.78±11.77	6.66±2.34	<0.001	26.40±11.31	4.25±2.39	<0.001	8.93±4.24	6.13±3.00	ns	3.80 ±2.02	5.34±1.56	0.04	57.16±14.61	49.31±13.89	ns
90	41.76±11.46	6.67±2.84	<0.001	26.80±10.84	4.82±3.16	<0.001	7.47±4.00	5.77±2.96	ns	3.79±1.77	5.15±1.78	ns	53.80±10.22	51.65±13.92	ns
120	41.63±10.93	6.40±2.70	<0.001	26.97±10.36	4.56±3.43	<0.001	6.88±3.95	5.45±3.02	ns	3.61±1.66	5.17±1.57	0.02	53.74±11.59	51.33±11.48	ns
P0-120'	ns	ns	-	ns	ns	-	0.01	ns	-	ns	ns	-	ns	ns	-

Time = time following the naloxone administration
KS = Klinefelter syndrome (n=14)
CG = control group - normal spermatogenesis (n=12)
ns = not significant

Table II. The percentage changes in plasma hormonal levels during naloxone test in Klinefelter syndrome and normal spermatogenesis.

Time (min.)	FSH			LH			PrI			T			E2		
	KS	CG	p	KS	CG	p	KS	CG	p	KS	CG	p	KS	CG	p
30	98.0±4.7	99.1±6.8	ns	114.2±44.5	102.7±30.4	ns	93.3±14.0	96.9±17.4	ns	108.4±25.4	94.2±7.1	ns	98.7±28.8	108.1±16.8	ns
60	99.3±7.3	102.2±15.2	ns	99.0±21.7	95.5±36.2	ns	83.5±28.2	96.6±27.0	ns	99.7±18.5	96.0±10.9	ns	98.5±22.0	103.3±18.4	ns
90	99.4±6.1	101.8±19.7	ns	100.8±21.7	105.7±52.6	ns	72.2±36.3	91.3±29.6	ns	102.1±18.9	92.7±20.9	ns	93.2±9.3	110.7±28.8	ns
120	99.5±5.2	97.1±9.1	ns	101.9±18.4	100.2±42.9	ns	67.2±39.4	84.7±27.7	ns	96.7±24.0	92.9±14.0	ns	94.5±19.4	111.5±32.4	ns
P0-120'	ns	ns	-	ns	ns	-	ns	ns	-	ns	ns	-	ns	ns	-

Time = time following the naloxone administration
KS = Klinefelter syndrome (n=14)
CG = control group - normal spermatogenesis (n=12)
ns = not significant

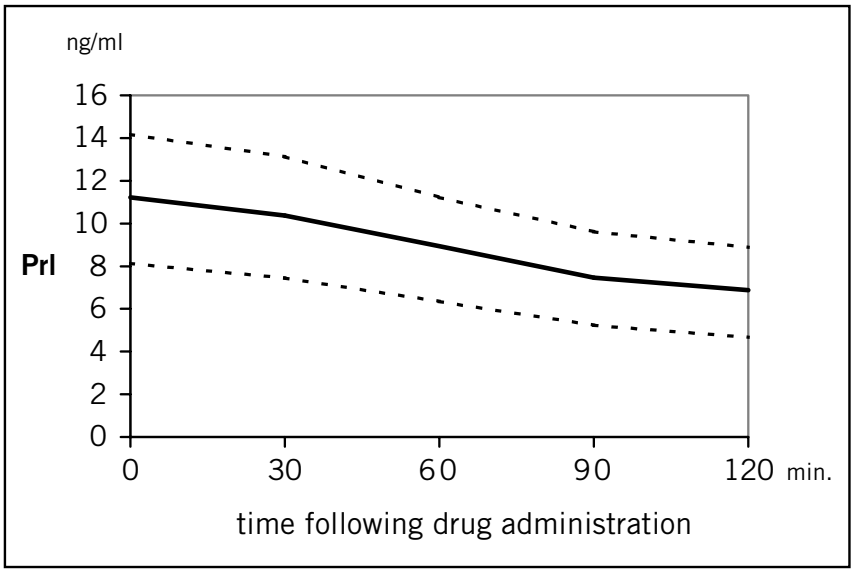

Figure 1. Prolactin levels during the naloxone test in Klinefelter subjects.

syndrome [2,12,16,17,32]. In our material the plasma prolactin levels in Klinefelter syndrome were statistically higher than in the control group. These observations are similar to data published by Gautier et al. [13], Giusti et al. [14] and Kumanov [22], who also observed the increase in plasma prolactin level in case of that syndrome. This fact may be possibly due to increased mass of adipose tissue in Klinefelter subjects and subsequently enhanced peripheral aromatisation of sex steroids. Elevated estrogen levels probably account the increased basal prolactin levels.

The intravenous naloxone administration in Klinefelter syndrome caused the statistically significant decrease in plasma prolactin levels but did not change the plasma FSH, LH, testosterone and estradiol levels. Also Foresta et al. reported the lack of changes of FSH levels after naloxone administration in Klinefelter subjects [11]. They observed however the naloxone induced LH increase in case of Klinefelter syndrome, but it was 33.4 ± 30,4% significantly lower than in controls ($p<0,001$). The comparison of our results is not fully efficient due to the different naloxone dose (20 mg vs. 0,4 mg). Furthermore those authors did not examine the influence of naloxone administration on prolactin levels.

The similar decrease in prolactin plasma levels and the absence of the changes in plasma levels of FSH, LH, testosterone and estradiol after the naloxone administration was observed in the patients with azoospermia and normal spermatogenesis [4]. The opioids are responsible for the increase of prolactin secretion. The administration of antiopioid drugs caused the diminution of plasma prolactin levels similar to these observed in our material [10,15,26,34].

In men with azoospermia and normal spermatogenesis the prolactin plasma levels were in normal range but they were statistically higher than in fertile men [3]. These men are in the permanent stress and they have the consciousness of their sterility, so it would be the possible explanation of these findings. The similar suggestion can be applied to patients with Klinefelter syndrome but we can not exclude other disturbances in neuroendocrine regulation of prolactin secretion.

In young healthy men the administration of the antiopioid drugs such as naloxone or naltrexone caused the increase in plasma LH levels [10,15,18,20,30]. Such increase was not observed in aging men and in hypogonadal men [15,24,31]. The androgen supplementation caused the increase of LH plasma levels after naloxone administration [24]. The lack of such increase of LH levels after naloxone administration in Klinefelter syndrome may be due to low plasma testosterone levels but we have to underline that the observed plasma LH levels in this syndrome are still very high. The absence of the increase of plasma LH levels in the control group may be caused by the lower dose of administered naloxone than in other studies [18]. The observations of Foresta et al. are opposite to the theory that the alteration of opioid control on gonadotropin secretion is due to androgen deficiency [11]. In their results the LH increases after naloxone infusion were not significantly different before and after testosterone treatment. They suggest that this alteration may be caused by genetic abnormalities. In our opinion also the vascular factors should be considered in this pathomechanism. The description of vascular changes in testes of Klinefelter subjects was given by De la Balze et al. [8]. Additionally our previous observations (Wielgos et al., 1999) revealed the increased values of qualitative indices of testicular artery blood flow in case of Klinefelter syndrome [33]. Those results were independent on testis volume, suggesting the increased vascular resistance in testicular artery of Klinefelter subjects. Similar results obtained Eckerhovd and Westlander [9]. Thus, in terms of worse blood supply of testes the hormonal regulation may also be altered.

Based on our results we conclude that the naloxone administration in Klinefelter syndrome cause the decrease in plasma prolactin levels but does not change the plasma levels of another hypophyseal and gonadal hormones. It means that naloxone in case of Klinefelter syndrome does not influence on normalization of LH and elevation of testosterone, observed in other individuals. This suggests that also prolactin plasma level plays no role in regulation of LH and testosterone concentration in Klinefelter subjects.

According to these observations it seems that the opioid controlled gonadotropin secretion is altered in case of Klinefelter syndrome and the only way of increase of androgen level is hormonal substitution by testosterone.

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