Plasma Testosterone and Sexual Function in Men Receiving Buprenorphine Maintenance for Opioid Dependence

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High-dose methadone is well known to cause testosterone deficiency and sexual dysfunction in opioid-dependent men. Buprenorphine is a new drug for the pharmacotherapy of opioid dependence. Its influence on the gonadal axis has not been investigated to date. We therefore assayed testosterone, free testosterone, estradiol, SHBG, LH, FSH, and prolactin in 17 men treated with buprenorphine. Thirty-seven men treated with high-dose methadone and 51 healthy blood donors served as controls. Sexual function and depression were assessed using a self-rating sexual function questionnaire and the Beck Depression Inventory. Patients treated with buprenorphine had a significantly higher testosterone level (5.1 ± 1.2 ng/ml (17.7 ± 4.2 nmol/liter) vs. 2.8 ± 1.2 ng/ml (9.7 ± 4.2 nmol/liter); P < 0.0001) and a significantly lower frequency of sexual dysfunction (P < 0.0001) compared with patients treated with methadone. The testosterone level of buprenorphine-treated patients did not differ from that of healthy controls. In conclusion, we demonstrated for the first time that buprenorphine, in contrast with high-dose methadone, seems not to suppress plasma testosterone in heroin-addicted men. To this effect, buprenorphine was less frequently related to sexual side effects. Buprenorphine might therefore be favored in the treatment of opioid dependence to prevent patients from the clinical consequences of methadone-induced hypogonadism. (J Clin Endocrinol Metab 90: 203–206, 2005)

In the 1970s, high-dose methadone was shown to depress plasma testosterone levels (1–3), and clinical studies have reported decreased sexual drive and performance in male heroin addicts (4). The methadone-induced suppression of testosterone levels is mediated by the inhibition of hypothalamic GnRH production (5) as well as direct reduction of testicular testosterone secretion (6). Buprenorphine, a partial opioid agonist, is a new drug for the pharmacotherapy of opioid dependence (7). To the best of our knowledge, the influence of buprenorphine on plasma testosterone levels and sexual function has not been investigated to date. Therefore, the aim of our study was to investigate the frequency of hypogonadism and sexual dysfunction in men receiving buprenorphine maintenance compared with that in methadone-treated men.

Subjects and Methods

Subjects and ethical approval

We investigated 54 male narcotic addicts maintained on buprenorphine or methadone for at least 3 months. All patients provided written consent. The human subjects review committee of the University of Bonn approved all forms and procedures. Seventeen patients, aged 34.7 ± 7.4 yr (mean ± sd), were maintained on sublingual buprenorphine (11.2 ± 4.3 mg/d; range, 8–20 mg/d). Thirty-seven patients, aged 37.5 ± 6.9 yr, were maintained on oral high-dose methadone (88.4 ± 16 mg/d; range, 60–120 mg/d; Table 1). Of the patients treated with methadone, 72% were hepatitis C virus seropositive, 19% were hepatitis B virus seropositive, and none was human immunodeficiency virus seropositive. Of the patients treated with buprenorphine, 65% were hepatitis C virus seropositive, 12% were hepatitis B virus seropositive, and none was human immunodeficiency virus seropositive. The mean level of the liver enzymes γ-glutamyltransferase, aspartate aminotransferase, and alanine aminotransferase did not differ significantly in the methadone and buprenorphine group (Table 1). Patients taking neuroleptics were excluded from the study, because neuroleptic-induced hyperprolactinemia might impact the testosterone level. Tricyclic antidepressants were used by 65% of the patients treated with methadone and by 76% of the patients treated with buprenorphine.

Fifty-one healthy male blood donors, aged 35.2 ± 4.5 yr, served as controls for the hormone analysis. They were in good physical health, had normal medical and laboratory screening examinations, and did not use any concurrent medication.

Hormone assays

Blood samples of all patients and all healthy controls were obtained directly before the daily morning dose of methadone or buprenorphine between 0900–1100 h. Testosterone, LH, FSH, estradiol, and prolactin were assayed using an automated chemiluminescence assay system (Immulite, Diagnostic Products Corp., Los Angeles, CA). Free testosterone and SHBG were assayed using an immunoradiometric assay (Immulite, Diagnostic Products Corp.). The sensitivities for testosterone, free testosterone, SHBG, estradiol, LH, FSH, and prolactin were 0.2 ng/ml (0.7 nmol/liter), 0.15 pg/liter (0.5 pmol/liter), 0.04 nmol/liter, 12 pg/ml (44 pmol/liter), 0.05 U/liter, 0.1 U/liter, and 0.16 ng/ml (3.4 nmol/liter), respectively. The interassay coefficients of variation were 11.8%, 8.5%, 7.9%, 7.0%, 6.7%, 5.5%, and 6.9%, respectively. The normal ranges of testosterone, free testosterone, SHBG, estradiol, LH, FSH, and prolactin were determined to be 3.1–10 ng/ml (10.8–35 nmol/liter), 8.8–27 pg/ml (31–94 pmol/liter), 10–73 nmol/liter, 12–56 pg/ml (44–206 pmol/liter), 0.8–7.6 U/liter, 0.7–11.3 U/liter, and 2.5–17 ng/ml (53–360 nmol/liter). All samples were assayed for concentrations of

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Abbreviation: BDI, Beck Depression Inventory.

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Assessment of illicit opioid use

Urine specimens were randomly collected under observation once weekly and analyzed for opioids by the CEDIA opiate enzyme immunoassay system (Microgenics, Fremont, CA). Findings of opioid metabolites at a level of 300 ng/ml or more were considered positive results. We analyzed the results of the last 4 months and calculated the percentage of positive urine specimens.

Assessment of sexual activity and depression

Sexual function was assessed using a self-rating scale. The sexual parameters assessed included changes in libido and potency. The impairment of libido and potency was quantified using a rating scale from 0 (not at all) to 6 (extremely). Suggested cut-off values of the sexual function questionnaire are: 0–10 no impairment of libido or potency; 1–2 = mild impairment; 3–4 = moderate impairment; and 5–6 = severe impairment of libido or potency. Depression was assessed using the Beck Depression Inventory (BDI). Suggested cut-off values of the BDI are: 0–10 = no depression; 11–17 = mild depression; 18–23 = moderate depression; and 24 or higher = severe depression (8).

Statistical analysis

Statistical analysis was performed using SPSS version 11 (SPSS, Inc., Chicago, IL). To compare the frequency of sexual dysfunction among the different groups, the χ² test was applied. The association between opioid use, and sexual dysfunction and testosterone values was also tested with a χ² test statistic. The differences in the extent of impairment of sexual function between the opioid treatment groups was calculated using the Mann-Whitney test for unpaired data. The differences in hormone levels among the groups were compared using the t test for independent samples. To analyze the interrelation of testosterone level and BDI score of the patients treated with methadone, we calculated the Pearson product-moment coefficient. The confirmatory statistical comparisons of all data were carried out at a significance level set at P = 0.05 (two-tailed).

Results

Hormone analysis in patients taking buprenorphine compared with patients receiving high-dose methadone maintenance

The patients maintained on buprenorphine had significantly higher mean total and mean free testosterone levels compared with the patients maintained on methadone [51 ± 1.2 ng/ml (17.7 ± 4.2 nmol/liter) vs. 28.2 ± 1.2 ng/ml (9.7 ± 4.2 nmol/liter); t(52) = 6.7; P < 0.0001; 17.1 ± 4.8 pg/ml (59.5 ± 16.7 pmol/liter) vs. 7.8 ± 2.9 pg/ml (27.0 ± 10.2 pmol/liter); t(52) = 7.8; P < 0.0001, respectively]. Their testosterone levels did not differ significantly from the mean testosterone level of the controls [5.1 ± 1.2 ng/ml (17.7 ± 4.2 nmol/liter) vs. 4.9 ± 1.3 ng/ml (17.0 ± 4.5 nmol/liter); t(66) = 0.45; P = 0.66; Fig. 1]. In all of these patients, testosterone values were within the normal range. The mean testosterone level in methadone-treated patients was significantly lower than that in healthy controls [28.2 ± 1.2 ng/ml (9.7 ± 4.2 nmol/liter) vs. 4.9 ± 1.3 ng/ml (17.0 ± 4.5 nmol/liter); t(86) = −8.2; P < 0.0001; Fig. 1]. In both opioid therapy groups, the mean SHBG and estradiol levels were in the normal range and did not differ significantly from each other. Controls and opioid therapy groups had normal LH, FSH, and prolactin levels (Table 1). With respect to the low mean testosterone value of the methadone group, LH was considerably low in this group, indicating central hypogonadism.

Sexual function in patients receiving buprenorphine or high-dose methadone maintenance

In patients treated with buprenorphine, libido was reduced in 23%, and potency was reduced in 12% of the subjects. The frequency of sexual dysfunction was significantly lower than that in methadone-treated men [χ² libido (I) = 15.8; P < 0.0001; χ² potency (I) = 12.6; P < 0.0001; Fig. 2]. Patients taking methadone had a very high frequency of sexual dysfunction; libido was reduced in 83%, and potency was reduced in 72%. The degree of impairment of libido and
potency was higher in the methadone group than in the buprenorphine group (by Mann-Whitney test, \( P < 0.0001 \); Table 2). One sexual function questionnaire from a patient in the methadone group was not evaluable because the patient marked several numbers on the scales.

**BDI scores in patients receiving buprenorphine or high-dose methadone maintenance**

The mean BDI score in the methadone group was 21.5 ± 9.7. It did not differ significantly from the mean BDI score in the buprenorphine group (16.4 ± 13.0). In the methadone group, 15% had no depression, 21% had mild depression, 18% had moderate depression, and 47% had severe depression. In the buprenorphine group, 36% had no depression, 21% had mild depression, 14% had moderate depression, and 29% had severe depression. The BDI score did not correlate with the testosterone values in the methadone group (\( r = -0.016 \); \( P = 0.93 \)).

**Illicit opioid use**

According to the frequency of urine specimens positive for opioid metabolites, 26% of our patients treated with methadone had no illicit opioid use, 56% had infrequent use, and 18% had frequent illicit opioid use. In the buprenorphine group, 35% had no illicit opioid use, 45% had infrequent use, and 20% had frequent opioid use. The frequency of sexual dysfunction and subnormal testosterone values in the methadone group did not differ between those patients with and without illicit opioid use [\( \chi^2 \) libido (1) = 0.39; \( P = 0.6 \); \( \chi^2 \) potency (1) = 0.1; \( P = 1.0 \); \( \chi^2 \) testosterone (1) = 0.75; \( P = 0.46 \)].

**Discussion**

For 3 decades, high-dose methadone has been well known to cause hypogonadism and sexual dysfunction in men (2–4). Our findings of a high frequency of reduced sexual function and hypogonadism in a sample of methadone-treated men add to these foregoing studies and clearly demonstrate the clinical importance of methadone-induced hypogonadism. Because high-dose methadone is frequently used in maintenance therapy (9), and the number of addicts maintained on methadone has increased over the last few decades, it can be assumed that many addicts are suffering from untreated hypogonadism. Apart from sexual dysfunction, postpubertal testosterone deficiency is associated with several physical symptoms, such as osteoporosis, infertility, impairment of testicular volume, decrease in strength and muscle mass, and decreased amount of axillary and pubic hair (10).

Buprenorphine is a new drug for maintenance therapy of opioid dependence. Unlike methadone, a pure agonist at the \( \mu \)-opioid receptor, it is a mixed agonist-antagonist opioid with low intrinsic activity and high affinity at the \( \mu \)-opioid receptor and with no intrinsic activity, but high affinity, at the \( \kappa \)-opioid receptor (11). Buprenorphine has a good safety profile and a decreased abuse potential, and it suppresses opioid withdrawal, all of which make it very suitable for the maintenance therapy of heroin addicts. Additionally, it blocks the effects of concurrently administered opioids and thereby reduces the risk of relapse in buprenorphine-maintained patients (7). The efficacy of buprenorphine in comparison with methadone in the therapy of opioid dependence has been firmly established (12).

Despite the increasing application of buprenorphine in the therapy of opioid dependence, we are not aware of any report about its effects on the gonadal axis. Surprisingly, our investigation demonstrated that buprenorphine at a dose of 8–20 mg/d did not suppress plasma testosterone in our patients. To that effect, the frequency of sexual dysfunction was significantly lower compared with that in the group treated with high-dose methadone. The opioid therapy groups did not show any significant differences with respect to age, medical status, length of addiction, concurrent medications, frequency of illicit opioid use, or degree of depression rated by the BDI. Therefore, we are not aware of any other variables that might have contributed to the observed group differences in testosterone levels.

The mean buprenorphine and methadone doses used in our study were previously shown to be equivalent with respect to retaining patients in treatment and reducing illicit opioid use (9, 13). Thus, we deduce that buprenorphine can effectively be applied in the therapy of chronic opioid dependence without inducing hypogonadism.

However, the observation that buprenorphine does not
suppress testosterone levels in heroin-addicted men at a dose of 8–20 mg/d is somewhat puzzling, because Cicero (14) clearly demonstrated that narcotic-induced serum testosterone depletion in the male rat correlates very well with the narcotic’s analgetic potency. Why, then, should it not correlate with the potency to treat opioid dependence? Buprenorphine is different from methadone insofar as it is a partial µ-opioid receptor agonist and a pure antagonist at the κ-opioid receptor. These differing effects at µ- and κ-opioid receptors are used to explain the unusual pharmacological effects of buprenorphine (7). The stimulation of κ-opioid receptors causes a suppression of the gonadal axis (15). The antagonism of buprenorphine at the κ-opioid receptor may possibly counteract the µ-opioid receptor-mediated depression of the gonadal axis. Preclinical studies with adult male rats will be conducted to assess the dose response of buprenorphine on testosterone levels. Thus, we speculate that the doses of buprenorphine needed to cause clinically relevant testosterone depletion will be higher than the doses needed to treat chronic heroin addiction and possibly also higher than the doses needed to treat unbearable chronic pain. Because these findings impact clinical practice, a study with a larger number of patients should be conducted to confirm these results.

In conclusion, we have demonstrated for the first time that buprenorphine, in contrast with high-dose methadone, seems not to suppress plasma testosterone in heroin-addicted men. To this effect, buprenorphine was less frequently related to sexual side effects. Buprenorphine might, therefore, be favored in the treatment of opioid dependence to prevent patients from the clinical consequences of methadone-induced hypogonadism.

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