Endocrine Journal 2011, **58** (12), 1071-1078

ORIGINAL

Endocrine and behavioural effects of transdermal buprenorphine in pain-suffering women of different reproductive ages

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Abstract. Chronic pain is a common problem in clinical practice and women are affected more often than men. Morphine is often used for long-term pain relief, but it induces side effects including endocrine alterations. The aim of the present study was to assess the behavioural and hormonal effects of transdermal buprenorphine in women suffering from persistent non-malignant pain. Hormones (LH, FSH, total and free testosterone, estradiol, cortisol) and pain measures (visual analogue scale, McGill Pain questionnaire, present pain intensity test) were evaluated at baseline and after 1, 3 and 6 months. Subjects were recruited in the Second University of Naples Pain Research Centre. Eighteen chronic pain women were included in the study, divided into pre- and post-menopausal groups. A transdermal buprenorphine patch (Buprenorphine TDS, 35 μg/h) was administered every 72 h. As expected, buprenorphine administration led to a decrease in pain intensity and no side effects suggestive of hypogonadism were recorded. Pain measures decreased at the first control visit (T1) in both groups. Total and free testosterone were not reduced by treatment (they tended to increase in both groups) while cortisol progressively recovered from the quite low levels detected at the beginning of treatment. These data confirm that buprenorphine is a safe and effective drug for pain relief in women. It is free from the adverse effects on gonadal hormones frequently associated with other opioid treatments. The lack of opioid-induced effects on gonadal hormones (i.e. hypogonadism) is important to guarantee safe long-term pain treatment.

Key words: Pain, Transdermal buprenorphine patch, Gonadal hormones, Cortisol, Age

CHRONIC non-cancer pain affects one-fourth of the European population, the majority of sufferers being women [1]. In most of them, the need to treat pain compels physicians to use opioids for long periods, even though opioids can affect the hypothalamo-pituitary axis [2-4]. Indeed both endogenous (β-endorphin) and exogenous opioids are known to modulate the secretion of pituitary hormones and to change peripheral metabolism of gonadal hormones [5]. In men, morphine administration was found to induce persistent, long-lasting hypogonadism [6], a clinical syndrome associated with many physical and cognitive complaints [7]. Indeed there is substantial evidence that gonadal hormones can influence the structure and functions of neurones not only during puberty but also in adulthood, including alterations of their dendrites and synaptic connections. For instance, it was shown that synaptic connectivity in the hippocampus and prefrontal cortex of male rats normally depends on androgens. It has also been suggested that androgens might be an effective therapy for certain neurological dysfunctions such as Alzheimer's disease and schizophrenia [8-9] and that they can modulate pain [10-11]. The effects on androgens have mostly been described in men, although opioid-induced hypogonadism with clinically relevant features has also been shown in women [6, 12].

It is necessary, therefore, to find solutions able to

Submitted Jun. 27, 2011; Accepted Sep. 5, 2011 as EJ11-0095
Released online in J-STAGE as advance publication Sep. 22, 2011

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The authors declare no conflict of interest.

support the use of opioids in pain therapy without deleterious side effects like hypogonadism. As regards the efficacy/side effects ratio, 'new' opioids such as buprenorphine are indicated as one of the best/first choices, also in view of the possibility to administer the drug *via* a patch (transdermal delivery system – TDS). Buprenorphine TDS is a centrally acting analgesic that binds to μ-opioid receptors (MOR, partial agonist) and k-opioid receptors (antagonist) with high affinity. Buprenorphine TDS slowly dissociates from MOR, giving this drug a slow onset but a long-lasting effect [13]. Many studies have described the good analgesic effect of Buprenorphine TDS, its high safety and the good compliance by patients in different disease patterns as well as in non-cancer pain [14-17]. Buprenorphine TDS offers clear advantages compared with other opioids, especially in terms of doses and daily management (ease of application, dosage flexibility, complete and stable analgesia for several days and psychological advantages), thus increasing compliance [18]. Moreover, Ceccarelli *et al*. [19] reported that buprenorphine does not affect testosterone levels in the brain of male rats.

Since clinical trials usually include both sexes (mixing the data), consider only a few parameters and involve short-term observations, we assessed the efficacy and effects of Buprenorphine TDS for 6 months in women in reproductive age and in menopause. The effects of Buprenorphine TDS on pain and hormone levels were determined to provide a broader picture of the treatment-induced effects, with particular reference to the hypothalamo-pituitary-gonadal and -adrenal axes.

Material and Methods

Subjects

Subjects were recruited in the Second University of Naples Pain Research Centre, while hormonal determinations were carried out in the Pain and Stress Neurophysiology laboratory of the University of Siena. The protocol, developed in accordance with the ethical standards of the Declaration of Helsinki, was approved by the Institutional Ethics Committee. Patients signed an informed consent form before participation.

Inclusion Criteria. Female outpatients at least 18 years of age suffering from acute/persistent non-cancer musculoskeletal pain (low back pain) with VAS > 60 were asked to participate in the study. The following conditions were considered exclusion criteria: neurological pathologies; severe and/or uncompensated cardiac, respiratory, metabolic, hepatic, renal and gastrointestinal pathologies; tumoral pathologies; inflammation due to HIV; endocrine alterations; psychiatric disorders; skin diseases so widespread as to prevent correct application of the patch; positive anamnesis for alcoholism and drug abuse; verified hypersensitivity to opioids; allergic reaction to patches; hormone replacement therapy; hormonal contraceptive method; pregnancy or lactation.

Pre-menopausal women practised an effective non-hormonal contraceptive method (e.g. intrauterine device, double barrier method) before enrolment and throughout the trial. Women of childbearing potential had a negative pregnancy test at screening.

Study design

This was an open prospective study for evaluation of the analgesic efficacy and endocrine effects of long-term therapy with Buprenorphine TDS 35 μg/h to be changed every 72 h. Once included in the study, the subjects were asked to undergo a first comprehensive visit. After a general personal interview including a pathological anamnesis and objective exam, each patient underwent an evaluation of pain features *via*:

- the visual analogue scale (VAS). It consists of a straight line with one end meaning no pain and the other end meaning the worst pain imaginable (0-100). The patient marks a point on the line that matches the amount of pain he or she felt in the last 24 h.
- the short form of the McGill Pain Questionnaire (SF-MPQ). It consists of 11 questions referring to the sensory dimension of the pain experience and four questions related to the affective dimension. Each descriptor is ranked on a four point intensity scale (0=none, 1=mild, 2=moderate, 3=severe).
- the present pain intensity (PPI). It is a 5-point scale to evaluate present pain features: 1. slight, 2. moderate, 3. strong, 4. very strong, 5. unbearable.

During the visit, a blood sample was collected to determine blood and hormone parameters, and a Buprenorphine TDS (delivery rate 35 μg/h) patch was applied. In case of incidental pain episodes, the patients were instructed to use sublingual 0.2 mg hydrochloride buprenorphine tablets as rescue medication. As antiemetic prophylaxis, they could take metoclopramide. Each patient was given a diary for the daily recording of VAS, the appearance of adverse effects and the use of

rescue medication. After 15 days, the patients underwent a control visit during which the following were evaluated: pain severity with VAS and SF-MPQ, the onset of adverse effects and changes in concomitant therapies, antiemetic treatment, rescue medication, diary records (written out by the patient) and the buprenorphine dose assumed. The same procedure as during the first visit, the survey and controls, and the blood sampling were replicated after 1, 3 and 6 months.

Blood determinations

Blood collection was carried out at 0, 1, 3 and 6 months. For patients still in reproductive age, blood collection was carried out in the same menstrual phase when possible. Serum aliquots were prepared and frozen at -80°C until hormonal assay.

Hormonal determinations were carried out in the Pain and Stress Neurophysiology laboratory of the Department of Physiology, University of Siena as previously described; centralized laboratory tests (blood and clinical chemistry) and gonodotropins (FSH, LH) were carried out in the Department of Anaesthesiological, Surgical and Emergency Sciences of the Second University of Naples.

The following parameters were determined: blood nitrogen, glucose, creatinine, GOT, GPT, γ-GT, protein, erythrocytes, leucocytes, haematocrit, erythrocyte sedimentation rate (ESR), luteinizing (LH) and follicle-stimulating (FSH) hormones, total testosterone (TT), free testosterone (fT), dihydrotestosterone (DHT), estradiol (E2), sex hormone-binding globulin (SHBG), cortisol (C).

The following methods were used for steroid hormone determinations:

Total testosterone (TT) was measured by RIA using a kit from RADIM (Pomezia, Italy). The cross reactivity of the antiserum coated in the tubes was 5.6% for DHT, 1.6% for androstenedione and lower than 0.1% for androstenediol, SHBG, estrone, DHEAS, estradiol. The lower limit of quantitation of TT measured by this assay was 0.017 ng/mL. The intra- and inter-assay coefficients were 1.5% and 7.8%, respectively, at the normal adult male range: 3.5-8.5 ng/mL in our laboratory.

Free testosterone (fT) was measured by RIA using a kit from Diagnostic Systems Laboratories (Webster, Texas, USA). The cross reactivity of the antiserum coated in the tubes was 0.35% for 19-nor testosterone, 0.21% for 17 alpha-methyltestosterone, 0.13% for 11-oxo-testosterone and non-detectable reactivity for DHT, DHEA, DHEA-S, progesterone, estradiol, corticosterone and other androgens. The lower limit of quantitation of fT measured by this assay was 0.18 pg/mL. The intra- and inter-assay coefficients were 4.5% and 7.9%, respectively, at the normal adult male range: 14.7-32.7 pg/mL in our laboratory.

Dihydrotestosterone (DHT) was measured by RIA using a kit from Diagnostic Systems Laboratories (Webster, Texas, USA). The cross reactivity of the antiserum coated in the tubes was 3.3% for androstandiol glucuronide, 0.6% for testosterone, 0.03% for androstandiol and no reactivity for androstenedione, estradiol, androsterone glucuronide, dehydroepiandrosterone, cortisol, deoxycortisol, 17 alpha-OH progesterone, progesterone. The lower limit of quantitation of DHT measured by this assay was 4 pg/mL. The intra- and inter-assay coefficients were 5.5% and 9.5%, respectively, at the normal adult male range: 250-750 pg/mL in our laboratory.

Estradiol (E2) was measured by RIA using an ultrasensitive kit from Diagnostic Systems Laboratories (Webster, Texas, USA). The cross reactivity of the antiserum coated in the tubes was 2.4% for estrone, 0.21% for 17 alpha-estradiol and 16 keto-estradiol, 0.64% for estriol. The lower limit of quantitation of E2 measured by this assay was 2.2 pg/mL. The intra- and inter-assay coefficients were 6.5% and 9.3%, respectively, at the normal adult male range: 10.0-25.1 pg/mL in our laboratory.

Cortisol (C) was measured by RIA using a kit from RADIM (Pomezia, Italy). The present method has not shown cross reaction with the following steroids: estradiol, testosterone, prednisone, cortisone, corticosterone, deoxycorticosterone and 11-deoxycortisol. The lower limit of quantitation of serum C measured by this assay was 0.9 μ/L. The intra- and inter-assay coefficients were 4.9% and 7.9%, respectively, at the normal adult male range: 50-250 μ/L in our laboratory.

Sex hormone-binding globulin (SHBG) was measured by IRMA using a kit from Diagnostic Systems Laboratories (DSL, Webster, Texas, USA). Concerning the specificity, no human serum protein is known to cross react with the antibodies employed in the DSL SHBG IRMA system. The lower limit of quantitation of SHBG measured by this assay was 3 nmol/L. The intra- and inter-assay coefficients were 2.7% and 10.2%, respectively, at the normal adult male range:

28-94 nmol/L in our laboratory.

Statistical analysis

ANOVA with repeated measures (4 Time levels: basal, 1 month, 3 months and 6 months) and Menopause as grouping factor (2 levels: pre-M and post-M) was applied to all parameters. Multiple comparisons were carried with the Least Significant Difference (LSD) test when needed. A multivariate analysis was performed on plasma levels of total testosterone, estradiol and cortisol. The significance of the linear correlation coefficient (r) in the pre- and post-M groups was tested using the Steel and Torrie procedure [20].

Results

Forty-one patients were initially screened to enrol the 26 patients who met the inclusion criteria. Eighteen patients concluded the 6-month study, while the other 8 patients discontinued the therapy for various reasons after a few days of treatment. The 18 patients were divided into pre-menopausal (n=8; mean age 39.5 years, range 26-50) and post-menopausal groups (n=10; mean age 66.1 years, range 54-76).

The patients did not exhibit any significant side effects and none resorted to metoclopramide; pre-M women did not refer any changes in menstrual cycle the improvement in pain symptomatology from the beginning of treatment made the use of buprenorphine tablets as rescue medication unnecessary. No Buprenorphine TDS adjustments were required during the observation period.

Pain parameters (Table 1)

All patients recorded an improvement in their pain symptomatology, as demonstrated by VAS, SF-MPQ and PPI; this improvement was present from the first month of treatment and persisted for the whole study (see details in Table 1). Indeed, ANOVA revealed a significant effect of Time for the three parameters in both age groups (pre- and post-M), due to the progressive decrease of their scores from baseline (T0) to the end of the observation period.

Blood parameters (Table 2)

There were no significant differences in blood glucose, creatinine, protein or red and white cells between the two groups, nor any variations over time.

For blood nitrogen, GOT, GPT, γ-GT, haematocrit and blood sedimentation rate, ANOVA applied to the values of both groups determined at the four time points revealed significant differences reported in detail in Table 2. In particular:

Blood nitrogen. There was a difference between the two groups at all determinations. Throughout the observation period, the nitrogen levels were higher in post-M patients than in pre-M patients. The within-group variations were not significant.

GOT, GPT and γ-GT. These parameters increased significantly after 1 month of treatment only in the pre-M group, while in the post-M group there were no differences among time points. Thus, at T1, GOT and GTP were lower in the post-M group than in the pre-M one.

Haematocrit. At T0, the post-M patients had a significantly higher mean haematocrit level than the pre-M patients.

Blood sedimentation rate (1 h). At T0, the post-M patients had a significantly higher value than the pre-M patients. Despite a progressive decrease of this parameter, there were no significant changes over time in either group during treatment.

Hormones

Luteinizing (LH) and follicle-stimulating (FSH) hormones. LH and FSH were higher in the post-M than the pre-M women ($p<0.01$ and $p<0.03$ respectively). No differences were observed during the 6-month period in either group (Table 3).

Total testosterone (TT) and free testosterone (fT). In contrast to findings obtained with other opioids [6], in which testosterone was drastically decreased, neither TT nor fT changed significantly due to Buprenorphine TDS treatment in either group of women throughout the 6-month period (Table 3); in fact, there was a slight tendency to an *increase* in both groups. The TT and fT levels were slightly higher in the post-M women at all determinations.

Estradiol (E2). E2 levels showed strong variation from one session to another in the younger women still in the reproductive period due to the difficulty in collecting blood on exactly the same days of the menstrual cycle (Table 3). Nevertheless, as expected, E2 was higher in younger women than in older ones.

Cortisol (C). Like testosterone, the C levels were not decreased by buprenorphine treatment. Indeed, ANOVA revealed a progressive increase from baseline to the end of the observation period. In the post-M women, the increase was not significant, while in

Table 1 Pain parameters. Questionnaires were administered to pre-menopausal (Pre-M, n=8) and post-menopausal (Post-M, n=10) women during the periodic visits carried out at baseline (T0) and after 1 (T1), 3 (T3) and 6 (T6) months of treatment with Buprenorphine TDS.

Pain	Pre-M				Post-M			
Parameters	T0	T1	T3	T6	T0	T1	T3	T6
VAS	83.8	50.6#	42.5#	35.6#	81.0	50.0#	41.5#	36.5#
SF-MPQ	25.9	20.0#	18.6#	14.1#	24.7	18.7#	17.1#	13.0#
PPI	4.50	3.25#	2.50#	2.13#	4.10	2.70#	2.20#	1.80#

# $p<0.05$ *vs* T0 same group. VAS: visual analogue scale; SF-MPQ: short form-McGill Questionnaire; PPI: present pain intensity

Table 2 Blood parameters in pre-menopausal (Pre-M, n=8) and post-menopausal (Post-M, n=10) women at baseline (T0) and after 1 (T1), 3 (T3) and 6 (T6) months of therapy.

Blood	Pre-M				Post-M			
Parameters	T0	T1	T3	T6	T0	T1	T3	T6
Nitrogen mg/dL	34.3	33.6	30.6	31.8	53.1*	53.6*	52.3*	54.1*
Glucose mg/dL	78.0	82.6	78.1	82.4	96.3	106.7	101.4	96.6
Creatinine mg/dL	0.86	0.82	0.84	0.83	0.93	0.94	0.98	0.98
GOT U/L	21.1	37.9#	23.3	22.6	17.6	20.1*	19.0	19.6
GPT U/L	21.9	37.4#	23.3	21.1	16.7	16.5*	15.4	19.2
γ-GT U/L	15.7	28.3#	24.3	17.0	23.1	21.3	21.4	21.9
Protein g/L	7.3	7.2	7.3	7.1	7.0	6.9	6.9	6.9
Red cells 10^6/mL	4.3	4.3	4.4	4.4	4.6	4.6	4.8	4.7
White cells 10^3/mL	5.6	5.4	5.4	5.9	6.1	6.1	5.8	5.7
HT %	36.2	36.6	36.9	37.0	39.2*	38.2	38.9	38.4
ESR mm/H	12.6	17.5	8.0	8.9	27.9*	16.5	14.3	14.4

#$p<0.05$ *vs* T0 same group; * $p<0.05$ *vs* Pre-M group, same period

Table 3 Hormone concentrations determined in pre-menopausal (Pre-M, n=8) and post-menopausal (Post-M, n=10) women at baseline (T0) and after 1 (T1), 3 (T3) and 6 (T6) months of buprenorphine treatment.

Hormones	Pre-M				Post-M			
	T0	T1	T3	T6	T0	T1	T3	T6
Total T ng/mL	0.12	0.16	0.20	0.20	0.20	0.20	0.21	0.21
Free T pg/dL	0.77	0.72	0.77	0.69	1.26	1.13	1.51	1.04
Estradiol pg/mL	83.5	38.9	24.4	22.1	7.2*	7.3	7.3	8.8*
Cortisol µg/dL	85.5	149.3#	140.1#	170.6#	124.9	132.4	166.3	172.4
SHBG°	46.0	61.6	114.8	44.1	88.0	113.2	96.6	76.4
DHT°	26.1	29.11	32.0	42.4	23.1	21.4	16.4	10.7

# $p<0.05$ *vs* T0 same group; * $p<0.05$ *vs* Pre-M group, same period. ° (n=4 per group), in these cases no statistical evaluation was performed.

pre-M women it was significant after 1 month of treatment (Table 3).

Multivariate analysis (Fig. 1)

The changes in the three main hormones (TT, E2 and C) during the 6-month period were defined by a multivariate analysis applied to the scores generated by the factor analysis. This analysis showed a significant effect over time ($p<0.01$), although multiple comparisons between basal and visit scores showed significant changes ($p<0.01$) only in the pre-M group. As shown in Fig. 1, the correlation between VAS and the TT, E2 and C levels (using the scores generated by the factor analysis) was significant in the pre-M group ($r=0.59$, $p<0.01$) but not significant in the post-M one ($r=0.19$, $p>0.05$).

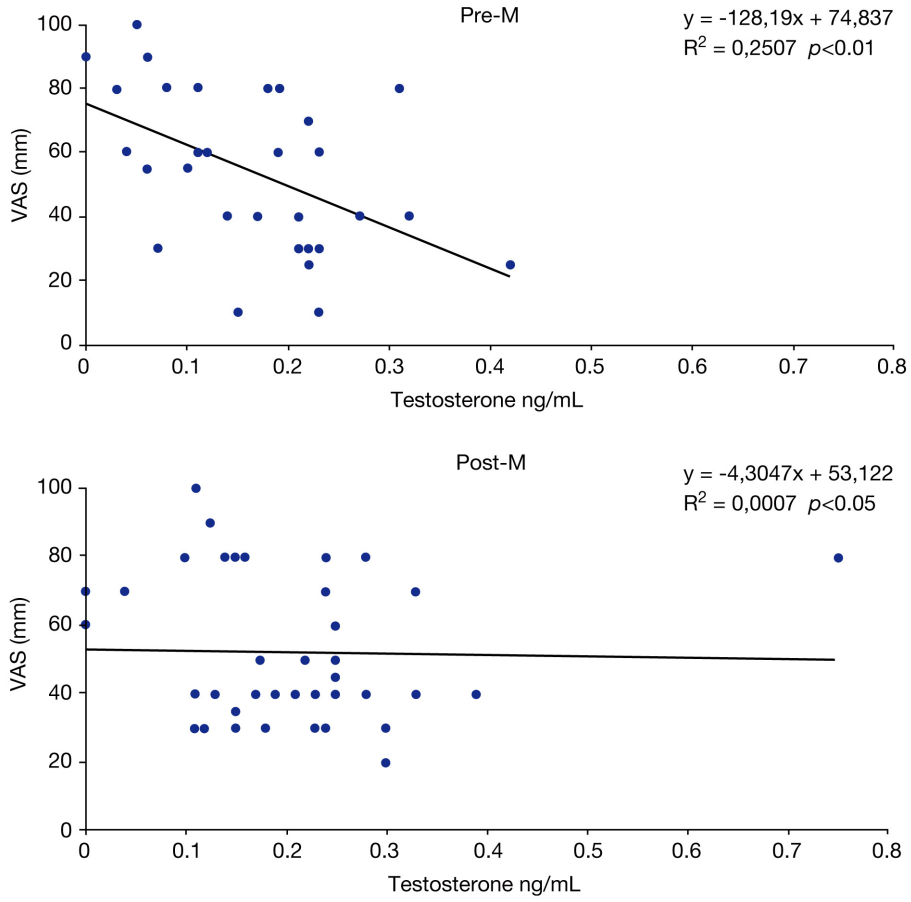

Fig. 1 Correlations between VAS values and testosterone serum levels. Statistical significance was reached only in the Pre-M group (upper).

Discussion

The present study is the first long-term assessment of Buprenorphine TDS for non-cancer pain. The main result of the study is that women treated for 6 months with Buprenorphine TDS did not show the strong endocrine impairment observed with other opioid substances [12].

Chronic non-cancer pain is a very great problem in our society, as it affects about 20% of the adult population and is severe in 13% of cases. Correct patient management and the appropriate choice of drugs are of fundamental importance for good therapeutic results [1]. Moreover, chronic pain mainly affects women, but there has been little pharmacological experimentation on them because of neuro-hormonal interference. For this reason, we investigated the effects of opioid analgesics on gonadal hormones and other blood parameters, evaluating the results of the analgesic efficacy of the therapy in both reproductive-age and menopausal patients.

The therapeutic effects of opioids depend on their interaction with specific receptors in the central and peripheral nervous systems. Each molecule has an intrinsic variability that depends not only on the substance but also on its ability to bind to the receptor and on the multiplicity of the receptors themselves. In fact, it is known that activation of opioid receptor μ1, which acts supraspinally, and of opioid receptor δ, which acts at the spinal level, mainly has an analgesic effect, while opioid receptor μ2 is responsible for the main opioid side effects; opioid receptor k is involved in both actions [21]. The high analgesic power of these drugs makes them particularly efficient in the treatment of high-intensity pain, but the risk of various side effects and of addiction and tolerance phenomena often hinders their clinical use in prolonged treatments [22].

OPIAD, i.e. opioid-induced androgen deficiency,

mainly occurs in men treated with opioids, but it has also been found in women [6, 12]. Its symptoms are fatigue, anaemia, changes in skin features, absence of libido, bad mood and depression. Therefore, it is necessary to treat pain but also to avoid other important dysfunctions that can increase the negative effects of pain, particularly when treatment is long-lasting. In this regard, buprenorphine has repeatedly been shown to have some features different from the other commonly used opioids [15]. It was found to cause a low level of addiction in experimental animals and in patients, and it does not show a "roof effect" if taken at therapeutic doses. Recent studies have demonstrated that buprenorphine, unlike other opioids, has an antihyperalgesic effect, probably due to its antagonistic properties on κ-opioid receptors [13].

For these reasons, we decided to use buprenorphine and we chose the transdermal delivery system because patients and doctors are amenable to it: it is non-invasive, has a long duration and allows a constant release of the proximate principle with high therapeutic efficacy and reduced side effects linked to plasma peaks [15].

These characteristics can also be seen in the results of our study, which showed a significant reduction of pain symptomatology in the women from the first patch application, which then persisted throughout the treatment without significant variations in relation to the menstrual cycle or menopause. This early and constant positive trend made recourse to "rescue medication" unnecessary. VAS and the other pain parameters clearly decreased already after one month of treatment and remained low till the end of treatment.

The results of our study are also encouraging in regard to side effects, particularly the nausea and vomiting that often follow opioid administration. In agreement with the international literature, which reports a reduction of side effects with the use of Buprenorphine TDS, none of our patients reported any significant side effects that required treatment. This underlines the key role of the administration technique in the genesis and severity of side effects from opioids. We must, of course, consider the different responses to the therapy, often related to the patient's condition, which also explains why four patients were excluded from the study after a short time. In fact, we believe it is very important to modulate the therapy according to individual needs.

The blood parameters never showed significant alterations that would have justified the interruption of treatment, even though we noticed significantly higher blood nitrogen and haematocrit levels in the menopausal women. This is an interesting result since it reflects the absence of detrimental effects of Buprenorphine TDS on body homeostasis but also shows that pain itself does not induce any changes and that its intensity variation is followed by immediate adjustment of all these parameters.

In previous studies on humans and experimental animals, gonadal hormones were found to be strongly affected by opioid intake. These effects were present in both sexes, although with some differences [5]. In the present study, the steroid hormones taken into consideration (testosterone, DHT, cortisol) did not show any signs of decrease; in fact, they tended to increase. Testosterone is considered a prohormone due to its continuous transformation into its metabolites DHT and estradiol. The enzymes needed to carry out the transformation into these two hormones are respectively 5α-reductase and aromatase. They are present in many tissues including the CNS. In the present study, testosterone was inversely related to VAS but only in the pre-menopausal women. This was also true when all three hormones (testosterone, cortisol, estradiol) were considered together. It is not easy to explain why the correlation was found only in the younger subjects because all recorded changes were apparently present in both groups, not only in the pre-menopausal one. However, this strong correlation suggests that the presence of the menstrual cycle was significant. Indeed, it was recently found in experimental females that, in addition to hormone replacement, the cycle plays a strong role in worsening the behavioural response to painful stimulation [23].

The need to treat pain for long periods obliges clinicians to find treatments able to ease pain without inducing side effects. Opioids induce analgesia but also long-term side effects such as hypogonadism, a condition with many bad consequences for the central nervous system and body. Therefore, it is mandatory to choose a treatment able to avoid this effect.

Acknowledgments

The authors thank Dr. Paolo Fiorenzani and Dr. Melinda Maddalena for their valuable technical support and Grunenthal Italia for its unrestricted financial support. The study was supported by an unrestricted grant from Grunenthal-Formenti, Milan, Italy.

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