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
support the use of opioids in pain therapy without dele-
terious 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 anal-
gesic that binds to μ-opioid receptors (MOR, partial
agonist) and κ-opioid receptors (antagonist) with high
affinity. Buprenorphine TDS slowly dissociates from
MOR, giving this drug a slow onset but a long-last-
ing effect [13]. Many studies have described the good
analgesic effect of Buprenorphine TDS, its high safety
and the good compliance by patients in different dis-
ease 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 flexi-
bility, complete and stable analgesia for several days
and psychological advantages), thus increasing com-
pliance [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 (mix-
ing the data), consider only a few parameters and
involve short-term observations, we assessed the effi-
cacy 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 lev-
els 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 deter-
minations 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-can-
cer musculoskeletal pain (low back pain) with VAS >
60 were asked to participate in the study. The follow-
ing conditions were considered exclusion criteria: neu-
rological pathologies; severe and/or uncompensated
cardiac, respiratory, metabolic, hepatic, renal and gas-
trointestinal pathologies; tumoral pathologies; inflam-
mation 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 replace-
ment therapy; hormonal contraceptive method; preg-
nancy 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 comprehen-
sive visit. After a general personal interview includ-
ing 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. moder-
ate, 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 anti-
emetic 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 gonadotropins (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 androstadiol 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, cortisol, corticosterone, deoxycorticosterone and 11-deoxycortisol. The lower limit of quantitation of serum C measured by this assay was 0.9 μg/L. The intra- and inter-assay coefficients were 6.5% and 9.3%, respectively, at the normal adult male range: 10.0-25.1 μg/L in our laboratory.

Sex hormone-binding globulin (SHBG) was measured by RIA 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 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
Buprenorphine and chronic pain in women

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 ($r=0.19, p>0.05$).

**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.

<table>
<thead>
<tr>
<th>Pain Parameters</th>
<th>Pre-M T0</th>
<th>Pre-M T1</th>
<th>Pre-M T3</th>
<th>Pre-M T6</th>
<th>Post-M T0</th>
<th>Post-M T1</th>
<th>Post-M T3</th>
<th>Post-M T6</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS</td>
<td>83.8</td>
<td>50.6</td>
<td>42.5</td>
<td>35.6</td>
<td>81.0</td>
<td>50.0</td>
<td>41.5</td>
<td>36.5</td>
</tr>
<tr>
<td>SF-MPQ</td>
<td>25.9</td>
<td>20.0</td>
<td>18.6</td>
<td>14.1</td>
<td>24.7</td>
<td>18.7</td>
<td>17.1</td>
<td>13.0</td>
</tr>
<tr>
<td>PPI</td>
<td>4.50</td>
<td>3.25</td>
<td>2.50</td>
<td>2.13</td>
<td>4.10</td>
<td>2.70</td>
<td>2.20</td>
<td>1.80</td>
</tr>
</tbody>
</table>

$p<0.05$ 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.

<table>
<thead>
<tr>
<th>Blood Parameters</th>
<th>Pre-M T0</th>
<th>Pre-M T1</th>
<th>Pre-M T3</th>
<th>Pre-M T6</th>
<th>Post-M T0</th>
<th>Post-M T1</th>
<th>Post-M T3</th>
<th>Post-M T6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrogen mg/dL</td>
<td>34.3</td>
<td>33.6</td>
<td>30.6</td>
<td>31.8</td>
<td>53.1*</td>
<td>53.6*</td>
<td>52.3*</td>
<td>54.1*</td>
</tr>
<tr>
<td>Glucose mg/dL</td>
<td>78.0</td>
<td>82.6</td>
<td>78.1</td>
<td>82.4</td>
<td>96.3</td>
<td>106.7</td>
<td>101.4</td>
<td>96.6</td>
</tr>
<tr>
<td>Creatinine mg/dL</td>
<td>0.86</td>
<td>0.82</td>
<td>0.84</td>
<td>0.83</td>
<td>0.93</td>
<td>0.94</td>
<td>0.98</td>
<td>0.98</td>
</tr>
<tr>
<td>GOT U/L</td>
<td>21.1</td>
<td>37.9</td>
<td>23.3</td>
<td>22.6</td>
<td>17.6</td>
<td>20.1*</td>
<td>19.0</td>
<td>19.6</td>
</tr>
<tr>
<td>GPT U/L</td>
<td>21.9</td>
<td>37.4</td>
<td>23.3</td>
<td>21.1</td>
<td>16.7</td>
<td>16.5*</td>
<td>15.4</td>
<td>19.2</td>
</tr>
<tr>
<td>γ-GT U/L</td>
<td>15.7</td>
<td>28.3</td>
<td>24.3</td>
<td>17.0</td>
<td>23.1</td>
<td>21.3</td>
<td>21.4</td>
<td>21.9</td>
</tr>
<tr>
<td>Protein g/L</td>
<td>7.3</td>
<td>7.2</td>
<td>7.3</td>
<td>7.1</td>
<td>7.0</td>
<td>6.9</td>
<td>6.9</td>
<td>6.9</td>
</tr>
<tr>
<td>Red cells 10⁶/mL</td>
<td>4.3</td>
<td>4.3</td>
<td>4.4</td>
<td>4.4</td>
<td>4.6</td>
<td>4.6</td>
<td>4.8</td>
<td>4.7</td>
</tr>
<tr>
<td>White cells 10³/mL</td>
<td>5.6</td>
<td>5.4</td>
<td>5.4</td>
<td>5.9</td>
<td>6.1</td>
<td>6.1</td>
<td>5.8</td>
<td>5.7</td>
</tr>
<tr>
<td>HT %</td>
<td>36.2</td>
<td>36.6</td>
<td>36.9</td>
<td>37.0</td>
<td>39.2*</td>
<td>38.2</td>
<td>38.9</td>
<td>38.4</td>
</tr>
<tr>
<td>ESR mm/H</td>
<td>12.6</td>
<td>17.5</td>
<td>8.0</td>
<td>8.9</td>
<td>27.9*</td>
<td>16.5</td>
<td>14.3</td>
<td>14.4</td>
</tr>
</tbody>
</table>

$p<0.05$ 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.

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

$p<0.05$ 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 ($r=0.19, p>0.05$).
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 \( \mu_1 \), which acts supraspinally, and of opioid receptor \( \delta \), which acts at the spinal level, mainly has an analgesic effect, while opioid receptor \( \mu_2 \) 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.

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