Long-term intrathecal morphine influence on major compounds of the endocrine system in elderly population

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A B S T R A C T

Background: The influence of long-term opioid administration on hormonal levels is not well characterized in the literature. We previously showed that intrathecal opioid therapy significantly influences the homeostasis of immune and endocrine systems. Other authors confirmed that exogenous and endogenous opioids induce this effect. They have a cytokine-like behavior and may function as neurotransmitters, neuromodulators or hormones, as concerning their synthesis, storage and release.

Aims: To assess the effects of morphine long-term intrathecal administration on serum levels of Gonadal, Thyroidal and Adrenal axis hormones in an elderly population affected by chronic pain; to assess the correlation between hormone levels and morphine dosage.

Methods: Patients suffering from chronic non-cancer pain with or without intrathecal drug delivery system were studied and hormonal levels were monitored, using an immunoradiometric assay kit.

Results: The long-term administration of intrathecal morphine influenced part of the endocrine system, in particular, there was a reduction of FSH and LH and an increment of GH serum levels; this effect was morphine dose dependent.

Conclusion: Long-term intrathecal opioid administration influenced FSH, LH and GH serum levels. Data on this issue are inadequately described in the literature. The finding of endocrine effects of opioid therapy, nonetheless, cannot be ignored, as it may have clinical relevance in both elderly and young population. We believe that during long intrathecal pain treatments with morphine, clinicians should be aware of both immediate and later opioids side effects, and in particular, they should monitor immune and endocrine changes.

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1. Introduction

Intrathecal (IT) administration of opioid induces a strong analgesia through the activation of their spinal receptors (Yaksh, 1981). Their long-term IT administration is a spreading technique for the treatment of cancer and non-cancer pain, and morphine is the gold standard of IT opioids (Hassenbusch and Portenoy, 2000). We have previously reported that IT therapy is a good approach for pain treatment for elderly populations, because they can benefit from opioids use without interference on their autonomy (Raffaeli et al., 2008).

Exogenous opioids can interact with their receptors outside the classical nociceptive system, and can modulate the activity of other biological systems, such as the immune and the endocrine pathways (Vallejo et al., 2004; Raffaeli et al., 1995; Beilin et al., 1992). Little is known on intrathecal opioid effects on systems that are not related to nociception.

We showed evidence about the biological effects of exogenous opioids on the immune–endocrine–opioids system in our first studies about opioid interaction with prolactin, beta-endorphin, and pituitary hormones secretion in addicts (Raffaeli, 1984). We proved that systemic and oral chronic opioids abuse resulted in increased PRL plasmatic levels, and interfered with beta-endorphine release, which was impaired also one year after the detoxification. This interference was not due to the stress, but it was an intrinsic effect of exogenous opioid therapy (Raffaeli, 1990). Other authors reported that exogenous and endogenous opioids influence both the endocrine and the immune systems and share many properties.
with cytokines (Mellon and Bayer, 1998; Abs et al., 2000; Drolet et al., 2001; Raffaei, 2003). Endogenous opioids, moreover, may function as neurotransmitters, neuromodulators or hormones, as concerning of their synthesis, storage and release (Morley, 1981). The hypothalamus and the pituitary gland activity are thought to be a target of such function (Grossman, 1983; Wang et al., 2008).

We later showed that also intrathecal opioid administration significantly influenced the homeostasis of biological systems (Raffaei, 1999; Raffaei and Salmosky-Dekel, 2005). We proved, in particular, that an acute intrathecal morphine administration had a relevant immunosuppression effect with a little impact on hormone release (Provinciali et al., 1991, 1996). The influence of the intrathecal long-term morphine administration on the endocrine system, however, is still unclear in humans. Hence a careful insight in this system is needed to understand the biological and the clinical impacts of opioid utilization in IT long-term pain treatments. For this reason we started our study. The aims of the study were: (i) to assess the serum levels of the major endocrine compounds of Gonadal, Thyroidal and Adrenal axis in patients with long-term intrathecal administration of morphine and (ii) to verify if there is any correlation between these levels and morphine dosage.

2. Materials and methods

2.1. Study design

This is a prospective study, which was performed at the Pain and Palliative Care Unit of the Infermi Hospital of Rimini, Italy. The hospital central laboratory performed the blood sample analysis. The investigators who carried out the blood collection and analysis were blinded to the pain conditions of the subjects.

2.2. The sample

We studied 41 patients, (15 males, 26 females, mean age 72.3 ± 5.6 years) (Table 1). Patients were divided into the following study groups: (i) naive to opioids patients, suffering from chronic non-cancer pain, with indication for spinal test to establish their responsiveness to IT opioids (group CP, n = 14); and (ii) patients with chronic non-cancer pain already in treatment with IT morphine (group ITM, n = 27). We choose these two samples in order to establish if hormonal alterations were correlated to pain or to IT morphine treatment.

All enrolled patients were followed by the Pain Management Unit. Patients of group ITM were permanently implanted with an intrathecal pump from 1999 to 2007. These pumps were regularly refilled at 20–40 days intervals. The average morphine dose administered to patients was 1.03 ± 0.9 mg/day. The Intrathecal Drug Delivery System (IDDS) of ITM patients were 4 Tricumed (Anschütz); 16 Isomed (Medtronic Inc., Minneapolis, MN, USA) and 7 Synchramed (Medtronic Inc.).

Inclusion criteria: ≥18 years old, informed consent signed, chronic non-cancer pain (VAS ≥ 6), opioid naive, indication for spinal opioid responsiveness test for CP group; in therapy with intrathecal morphine for at least 12 months and VAS < 3 over the past 3 months for ITM group.

Exclusion criteria were: opioid addiction, opioid (for CP group) or steroid use (for both groups) in the 3 months prior to the study, pregnancy, diagnosis or treatment of any endocrine impairment prior to the study and the presence of infectious disease or fever (>37 °C) since the last pump refill.

2.3. Procedures

During the visit of the spinal testing (CP group) or of the pump refill (ITM group), all eligible patients were thoroughly informed by the investigators about the study aims and procedures involved. Data on general health conditions, pain scores (VAS), pain therapy, type and concentrations of IT drugs were registered. Blood samples were collected at the enrollment before the administration of the test drugs for CP group and before the pump refill for ITM group.

ACTH, cortisol, FSH, GH, LH, PRL, TSH, FT 3 and FT 4 levels were monitored (see Table 3 for abbreviations and for the expected normal values, as defined by the hospital laboratory standards). All laboratory determinations were performed using commercial RIA and immunoradiometric assay kit routinely used by the hospital analysis laboratory.

2.4. Ethics

The study was approved by the Hospital Ethics Committee and conducted according to the Helsinki declaration principles on human clinical studies. All the patients, after a through explanation of the procedure and the aims of the study, gave a written consent.

2.5. Data presentation and statistical analysis

All statistical analyses were conducted using StatView for Windows (SAS Institute Inc. Cary, NC). Continuous data are reported as the mean and (standard deviation). Proportions were expressed in percent. Correlation between morphine daily dose and hormone serum concentration was assessed using the Spearman Rank Correlation Coefficient (SRCC) method. Scattergrams and regression lines were plotted to obtain qualitative information on this relationship. T student test was used to compare continuous data. Statistical significance was defined as P < 0.05.

3. Results

3.1. The sample

ITM group included 27 patients, 63% of these (n = 17) were females. Mean age of this group was 73.2 ± 7.3 years (range 61–85 years). Mean age of the females, in particular, was 71 ± 7.5 (range 61–81 years), whereas mean age of males was 76.8 ± 5.8 (range 68–85 years). CP group (n = 14), showed similar composition: 67% (n = 9) of patients were females with overall mean age of 72.5 ± 7.1 years. Causes of pain were: peripheral arteriopathy (CP, n = 3; ITM, n = 2), failed back surgery syndrome (FBSS: CP, n = 6; ITM, n = 12), osteogenic spinal stenosis (CP, n = 2; ITM, n = 10); and neuropathic pain (complex regional syndrome type I: n = 3 in both CP and ITM groups).

Among patients of ITM group, mean duration of intrathecal morphine treatment, at the time of the study, was 38.8 ± 26.8 months (from 12 to 65.6 months). Mean morphine daily dose was 1.3 ± 0.9 mg/day (from 0.1 to 4.0 mg/day). Marcaine 0.5% was added to the IT solution in 9 patients. Mean marcaine daily dose was 0.5 ± 0.2 mg/day (from 0.2 to 0.9 mg/day).

Table 1

<table>
<thead>
<tr>
<th>Characteristics of the sample.</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>41</td>
</tr>
<tr>
<td>Average age (±SD)</td>
<td>72.3 ± 5.6</td>
</tr>
<tr>
<td>Males</td>
<td>15 (37)</td>
</tr>
<tr>
<td>Females</td>
<td>26 (63)</td>
</tr>
<tr>
<td>CP group</td>
<td>14 (36)</td>
</tr>
<tr>
<td>ITM group</td>
<td>27 (64)</td>
</tr>
</tbody>
</table>
CP group showed normal (for age and gender) serum values of the studied hormones (data not shown); whereas ITM group showed altered levels of some hormones. Mean, standard deviation and upper and lower limits of the serum concentration of the studied hormones in ITM group were reported in Table 2. Major findings in ITM group were as follows.

3.2. Gonadal axis: FSH and LH

CP group showed normal (for age and gender) LH and FSH serum levels. Mean age of the women in the ITM sample was congruent with postmenopausal condition, however, only one ITM patient had FSH concentration suitable for postmenopausal condition: 55.4 mU/mL. The other ITM women had FSH concentration far below normal values mean FSH concentration = 3.6 ± 4.3 mIU/mL, range 0.5–10.8 mU/mL (mean and range excluding the women with 55.4 mU/mL). These values were congruent with those of pre-puberty children, as shown in Table 3.

FSH concentration in 67% of the males was within normal values (range 3.8–10.9 mU/mL) whereas in 2 subjects it was above normal values (30 mU/mL).

The majority of the ITM women had extremely low LH concentration. In 80% of them it was < 6 mU/mL (slightly higher than that of pre-puberty children); whereas only one female had normal values (12.3 mU/mL). In ITM males LH concentration was normal (range 5.2–11.1 mU/mL), only two of them had low levels (2.0 mU/mL).

3.3. Thyroid function: TSH, FT 3, FT 4

CP group showed normal TSH, FT 3, FT 4 serum levels. Serum concentrations of TSH, FT 3 and FT 4 were within normal values also in ITM group, except for two females, whose TSH mean concentration was above normal values: 6.5 ± 1.5 mU/mL (Table 2).

3.4. Adrenal axis: ACTH and cortisol

Mean serum cortisol concentration was within expected values for the time of the day at which blood samples were taken in both CP and ITM groups. Only four ITM patients had serum cortisol values slightly higher, ranging from 26.8 to 28.6 ug/dL. All patients showed normal basal plasma ACTH concentration values.

3.5. Other hormonal findings: GH and PRL

Mean GH and PRL concentrations were within normal values in all CP and ITM patients. Gender differences, however, were detected in ITM group: 50% of the women had high PRL values (46.8 ± 18.1 ng/mL), on the contrary, two ITM women, had extremely low levels (0.5 ng/mL).

3.6. Morphine daily dose and endocrine profile

In order to verify the relationship between morphine dose and endocrine response, ITM subjects were subdivided into four groups

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### Table 2

Hormone levels. Mean serum levels (standard deviation) of each endocrine compound are reported in the first line of each group (the entire sample, males and females group). The rage of serum levels of each endocrine compound is reported in the second line of each group. See Table 3 for abbreviations.

<table>
<thead>
<tr>
<th>Morphine (mg/24 h)</th>
<th>ACTH (pg/mL)</th>
<th>Cortisol (ug/dL)</th>
<th>FSH (mIU/mL)</th>
<th>GH (ng/mL)</th>
<th>LH (mIU/mL)</th>
<th>PRL (ng/mL)</th>
<th>FT (3 pg/dL)</th>
<th>FT 4 (ug/dL)</th>
<th>TSH (uU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample (n = 27)</td>
<td>1.3 (0.9)</td>
<td>20.2 (8.3)</td>
<td>18.3 (7.3)</td>
<td>12.3 (15.9)</td>
<td>2.1 (1.9)</td>
<td>3.4 (4.4)</td>
<td>18.3 (21.2)</td>
<td>2.4 (0.4)</td>
<td>1.3 (0.2)</td>
</tr>
<tr>
<td>Males (n = 10)</td>
<td>0.1–4.0</td>
<td>5.3–31.2</td>
<td>6.9–28.6</td>
<td>0.5–55</td>
<td>0.1–5.5</td>
<td>0.1–12.3</td>
<td>0.5–73.8</td>
<td>1.8–3.0</td>
<td>0.9–1.7</td>
</tr>
<tr>
<td>Females (n = 17)</td>
<td>1.5 (1.0)</td>
<td>12.1–31.1</td>
<td>6.0–27.9</td>
<td>3.8–30.4</td>
<td>0.1–2.8</td>
<td>2.0–11.1</td>
<td>7.3–14.7</td>
<td>2.0–2.6</td>
<td>1.1–1.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Morphine (mg/24 h)</th>
<th>ACTH (pg/mL)</th>
<th>Cortisol (ug/dL)</th>
<th>FSH (mIU/mL)</th>
<th>GH (ng/mL)</th>
<th>LH (mIU/mL)</th>
<th>PRL (ng/mL)</th>
<th>FT (3 pg/dL)</th>
<th>FT 4 (ug/dL)</th>
<th>TSH (uU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (n = 10)</td>
<td>1.3 (0.9)</td>
<td>23.2 (7.5)</td>
<td>19.9 (8.6)</td>
<td>18.2 (13.3)</td>
<td>1.3 (1.2)</td>
<td>6.2 (4.1)</td>
<td>9.9 (3.1)</td>
<td>2.4 (0.2)</td>
<td>1.3 (0.1)</td>
</tr>
<tr>
<td>Females (n = 17)</td>
<td>1.5 (1.0)</td>
<td>18.4 (8.6)</td>
<td>17.4 (6.8)</td>
<td>8.8 (16.9)</td>
<td>2.5 (2.1)</td>
<td>1.7 (3.9)</td>
<td>23.3 (25.9)</td>
<td>2.4 (0.4)</td>
<td>1.2 (0.3)</td>
</tr>
</tbody>
</table>

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### Table 3

Description of the hormones studied.

<table>
<thead>
<tr>
<th>Endocrine compound</th>
<th>Abbreviation</th>
<th>Range unit</th>
<th>Expected values adults range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenocorticotropic hormone</td>
<td>ACTH</td>
<td>pg/mL</td>
<td>8:00 a.m.: 10.0–60.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4:00 p.m.: 5.0–37.0</td>
</tr>
<tr>
<td>Cortisol</td>
<td></td>
<td>ug/dL</td>
<td>8:00 a.m.: 8.0–19.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4:00 p.m.: 4.0–11.0</td>
</tr>
<tr>
<td>Follicle stimulating hormone</td>
<td>FSH</td>
<td>mIU/mL</td>
<td>1.0–4.2&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.8–11.2&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6.0–35.0&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30.0–120.0&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>GH</td>
<td>ng/mL</td>
<td>0.0–6.0</td>
</tr>
<tr>
<td>Luteinizing hormone</td>
<td>LH</td>
<td>mIU/mL</td>
<td>0.02–0.3&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.0–9.0&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18.0–49.0&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.0–11.0&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20.0–70.0&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Prolactin</td>
<td>PRL</td>
<td>ng/mL</td>
<td>0.5–4.8</td>
</tr>
<tr>
<td>Thyroid stimulating hormone</td>
<td>TSH</td>
<td>uI/mL</td>
<td>0.8–2.3</td>
</tr>
<tr>
<td>Thyroxine, free</td>
<td>FT 4</td>
<td>ug/dL</td>
<td>2.3–4.2</td>
</tr>
<tr>
<td>Triiodothyronine, free</td>
<td>FT 3</td>
<td>pg/dL</td>
<td>3.0–24.0</td>
</tr>
</tbody>
</table>

<sup>a</sup> Prepubertal children (12 months–8 years).
<sup>b</sup> Female menstrual cycle periods: follicular.
<sup>c</sup> Female menstrual cycle periods: mid-cycle.
<sup>d</sup> Female menstrual cycle periods: luteal.
<sup>e</sup> Female menstrual cycle periods: postmenopausal.

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on the basis of their morphine dosage in the 24 h. Group A \((n = 6)\) included subjects whose daily morphine dose was up to 0.5 mg/24 h, group B \((n = 4)\) from 0.6 to 1.0 mg/24 h, group C \((n = 7)\) from 1.1 to 1.5 mg/24 h and group D \((n = 10)\) from 1.6 to 4.0 mg/24 h.

Qualitative information about the predictability of hormonal changes as a function of morphine dose was obtained analyzing the scattergraphs of these two variables. The correlation between the morphine daily dose groups and each hormone concentration trend was reported in Fig. 1. Regression lines (with their relative \(R^2\) values) were plotted in each diagram for the entire ITM sample, for ITM female and for ITM male clusters. As morphine dose increased (groups A–D), FSH and LH concentrations decreased in ITM women; whereas GH, ACTH and Cortisol concentrations increased. Such trends were less evident in ITM male cluster. In this cluster, indeed, only Cortisol concentrations decreased as morphine daily dose increased.

Correlation between the daily dose groups and each set of individual hormone concentrations was hence calculated using the SRCC method. Hormone concentrations resulted to be independent from morphine daily dose, as none of the tested correlations was statistically significant \((P > 0.05)\).

4. Discussion

The cornerstones for pain relief by intrathecal administration of opioids are the reports of epidural (Behar et al., 1979) and intrathecal (Wang et al., 1979) administration of opioids in humans. The
capability to deliver via these routes small amounts of opioids (and local anesthetics) directly to their spinal targets has important clinical advantages, avoiding systemic exposure and, as a consequence, reducing systemic complications and side effects (Raffaeli et al., 2006a,b).

The use of intrathecal opioids for the treatment of cancer and non-cancer pain has been considerably increased in the last years and many studies have been made to assess efficacy, and safety (relative to the drugs injected and to the devices used) of this approach (Winkelmuller and Winkelmuller, 1996; Kumar et al., 2001). Nonetheless, little attention has been given to its long-term clinical consequences, other than pain reduction or pure drug side effects.

The majority of opioid short-time side effects (such as nausea, vomiting, and pruritus) are predictable and can be easily managed. Interference on the endocrine system is a later opioid-related side effect. Human and animal studies have investigated neuroendocrine consequences of both acute and chronic systemic opioid administration, showing that endocrine response to chronic administration of opioids differs from that of acute administration.

Acute administration of opioids, for example, increases PRL, GH, TSH and ACTH release in humans, and inhibits LH secretion (Raffaeli, 1984, 1990; PedronNuevo, 1997; An et al., 2008). Chronic opioid administration, on the contrary, suppresses this effect on PRL, GH, and TSH; inhibits ACTH and does not affect LH secretion (Raffaeli, 1984). Exogenous opioids are known to exert an inhibitory effect on the release of β-endorphin, ACTH, and nociceptin (Pfeiffer and Herz, 1984; Zhang et al., 1986; Raffaeli et al., 2006a.b). Long-term intrathecal opioid therapy, moreover, induces hypogonadism (Raffaeli et al., 2008; Rajagopal et al., 2004) and altered sexual function (Paice et al., 1996; Roberts et al., 2002). The endocrine response to morphine may also be administration route dependent (An et al., 2008; Foradori et al., 2007; Provinciali et al., 1991, 1996).

Our results showed that postmenopausal females and elderly males had low levels of FSH and LH. This was not found in CP group, who had normal FSH and LH levels, suggesting that this effect is not pain correlated but is IT morphine-dependent. These data are congruent with previous studies that showed significant reduction of LH and FSH both in males, pre- and postmenopausal females (Roberts et al., 2002).

Like other reports (Pedron Nuevo, 1997) also in our sample GH serum levels raised as morphine dosage was increasing. This phenomenon was particularly evident among females with morphine daily dose higher than 1.5 mg but not among males.

Pituitary hormone serum concentration (e.g. PRL, ACTH, TSH) was not altered even at high morphine daily dose. Thus it can be argued that some of the endocrine response are not influenced at all by IT morphine, as it has already been reported for acute administration.

A limitation of our study is the lack of data on the hormones serum levels in the ITM group before that intrathecal morphine therapy was started. This limitation can be overcome for two reasons. Firstly, on clinical examination before the pump implantation, no patient reported an endocrine impairment. Secondly, the study’s main objective was to investigate whether the endocrine serum profile of the ITM patients differed from that of opioid naïve subjects of peer age and pain conditions. We verified that hormonal changes were present on a randomly chosen sample of patients with intrathecal morphine therapy. These changes were not present in opioid naïve subjects (CP group), suggesting that they are morphine correlated. For this reason we suggest to perform a routinely assessment of hormonal serum levels in every patient with intrathecal devices for morphine infusion therapy.

The findings of these endocrine serum profile differences were of clinical importance, further studies are recommended, especially to assess if the interference on immune system and hormonal serum levels are IT drug type-dependent. The study of hormonal levels in patients that are in treatment with ziconotide should be of particular interest, to investigate if this drug, which actually is indicated for difficult pain treatment, can also be indicated for patients with hormonal impairment due to opioid use. We are also planning to make the analysis of the hormonal levels variation in patients with prolonged intrathecal morphine infusion, monitoring the hormonal concentration in different time points.

5. Conclusion

Long-term IT opioid administration influences multiple endocrine functions, resulting in altered FSH, LH and GH serum levels, for this reason we strongly recommend to monitor morphine effects on immune and endocrine systems in patients undergoing long-term intrathecal opioid therapies.

Conflict of Interest

None declared.

References


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