Case Report

# Androgen Deficiency in Long-Term Intrathecal Opioid Administration

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**Background:** Intrathecal drug delivery of opioids is an efficient and effective treatment option for pain management in the chronic nonmalignant pain population. As with all treatments, in addition to the benefits, risks and side effects exist. One such risk in intrathecal opioids is opioid-induced androgen deficiency.

**Objective:** This study evaluates opioid-induced androgen deficiency in long-term intrathecal opioid administration in chronic nonmalignant pain.

**Study Design:** Case series. Sixteen consecutive patients with intrathecal drug delivery with opioids were screened for androgen deficiency.

**Setting:** Academic university-based pain management center.

**Method:** All the subjects were seen in a 2 month period, during a scheduled maintenance refill visit. Eight consecutive men and eight consecutive women receiving intrathecal drug delivery therapy for non-malignant chronic pain were ordered blood work and asked to complete a questionnaire. Patient and patient-related data were also collected.

**Results:** Ten of the 16 (62.5%) patients were found to have androgen deficiency, 4 of 8 men based on free testosterone levels and 6 of 8 women based on DHEA levels. In men, erectile dysfunction correlated with endocrine dysfunction ($P$ = 0.02) while depressive symptoms correlated in women ($P$ = .03). Overall, 2 of the 16 patients had hydromorphone as the opioid in the intrathecal system. Both patients had normal endocrine functions. Both patients with hydromorphone were men and the use of hydromorphone showed an insignificant trend ($P$ = 0.06). Three of the 4 men with normal endocrine functions had in addition to an opioid, bupivacaine, in the intrathecal system. The presence of bupivicaine in men was significant ($P$ = 0.02). No women had bupivicaine while one of the 8 women had clonidine in addition to the opioid. Presence of another substance in addition to the opioid showed an insignificant trend ($P$ = 0.08).

**Limitations:** Study limitations include the small sample size and case series nature. Additionally the symptoms data was solely based on subjective patient reports.

**Conclusions:** Androgen deficiency is common in patients treated with intrathecal opioids for chronic nonmalignant pain. Patients experience numerous and wide ranging symptoms. Erectile dysfunction may be more suggestive for androgen deficiency in men while complaints of depressed mood may be correlative in women. Additionally, combining bupivicaine with the intrathecal opioid may provide a protective role.

**Key words:** Androgen deficiency, endocrine dysfunction, chronic nonmalignant pain, intrathecal opioid, intrathecal drug delivery, side effects

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Intrathecal drug delivery (IDD) is an effective and efficient alternative in the administration of opioids (1-4). Initially used for intractable cancer pain, intrathecal opioid administration is now increasingly utilized for non-malignant chronic pain, particularly in patients who have failed conventional treatment or could not tolerate traditional therapy due to its side effects (4-5). However, the increased use is not without concern. Concerns regarding the use of a drug delivery systems range from its invasiveness to complications from the procedure to the exposure to long-term opioids, and therefore it is generally considered as a last resort for severe chronic pain control (6,7). The benefits to intrathecal administration of opioids include cost effectiveness, ability to provide low dose opioids in comparison to oral or transdermal administration, decreased systemic absorption, as well as the decreased need for supplemental opioids. Additionally, because of the ability to deliver medication into the cerebral spinal fluid with close proximity to the receptors within the spinal cord, analgesia can be obtained with sufficient comparable pain control with minimal side effects caused by systemic opioids at significant lower doses (8-13).

Currently, morphine is the only Food and Drug Administration (FDA) approved opioid for intrathecal administration. However, other opioids, independently or in combination with local anesthetics, are routinely used. In addition to being effective and inexpensive, intrathecal administration is overall well tolerated. However, side effects do exist (14). Most of the side effects are caused by the opioid presence in the cerebral spinal fluid or vasculature (15). The high hydrophilic property of morphine intrathecally produces slow onset and prolonged duration of antinociception but with higher incidence of certain side effects compared to lipophilic opioids. More common side effects consist of pruritis, urinary retention, and gastrointestinal effects such as nausea, vomiting, and constipation. Other concerns include sedation as well as respiratory depression.

With the increased application and duration of intrathecal opioid administration, more clinically relevant side effects have become evident. One such area of concern is opioid-induced androgen deficiency (16). Prolonged opioid use has been thought to interfere with the human hypothalamic-pituitary-gonadal axis (HPG) (17-19). Yet it has also been observed as early as one week following the initiation of intrathecal administration (20). The endocrine changes that occur with opioid use have been known for over a century, yet they remain underappreciated in the clinical setting (21). Opioid receptors can be found in the hypothalmus, and both endogenous and exogenous opioids affect the HPG axis. The stimulated opioid receptors disrupt and decrease the pulsatile release of gonadotropin releasing hormone (GnRH) from the hypothalmus, which leads to a decrease of lutenizing hormone (LH) and follicle stimulating hormone (FSH) from the pituitary, which can result in inadequate production of testosterone and estradiol from the testes and gonads respectively. When testosterone levels are low, a host of side effects can occur in both men and women. Low testosterone can lead to weight gain, decreased muscle mass and strength, depression and emotional disturbances, fatigue, impaired glucose tolerance, dyslipidemia, and decreased stress response. In women low testosterone can lead to amenorrhea or menstrual irregularities, decreased fertility, and osteoporosis. The most characteristic symptom in both genders is diminished libido (22). Even more important in pain management is that opioid endocrinopathy can cause hyperalgesia. Opioid induced hypogonadism is underrecognized and therefore undertreated. Patients do not routinely complain of such symptoms, or some patients may attribute their signs and symptoms to their chronic medical condition, rather than the intrathecal opioids (23).

In general, some have proposed screening in those with daily regimen equivalent to 100 mg of oral morphine or more (24,25). Testosterone is mostly found in the bound form, but free unbound testosterone is the active type. Serum-free testosterone concentration is the principal laboratory test for diagnosis of hypogonadism in men (25). There is no consensus on when the testing should be performed but should be considered in patients with symptoms of endocrine dysfunction. Some have recommended testing to include serum prolactin, gonadotropin levels (LH and FSH), and hemoglobin and hematocrit (26). In women, Dehydroepiandrosterone Sulfate (DHEAS) level is the preferred indicator (27). However, the diagnosis of opioid endocrinopathy can be challenging when one considers the patients' medical comorbidities, medication side effect profiles, and their ages.

## Methods

### Patients

All the patients were seen in a 2 month period, during a scheduled maintenance refill visit at an academic medical center in 2013. Eight consecutive men

and eight consecutive women receiving IDD therapy for non-malignant chronic pain were included. All patients were receiving intrathecal opioids, either as a sole or in-combination therapy.

### Procedure

On the scheduled encounter, patients were ordered blood work and asked to complete a questionnaire. Additionally, patient and patient-related data were collected.

### Data Collection

The questionnaire was completed and collected prior to the end of the visit. The results of the blood work were collected prior to the subsequent visit.

### Statistical Analysis

Due to relative small number of patients, the averageswere calculated and compared. T Test was used for determination of significance. *P*-values less than 0.05 was considered significant.

## Results

The average age for the 16 patients was 60.25 years. Average weight was 195.25 pounds with the average intrathecal morphine equivalent concentration dose of 18.19 mg/mL at a rate of 7.32mL/day for 68.7 months. Men were on average 60.13 years of age, 210.75 pounds, with morphine equivalent concentration dose of 25.6mg/mL, rate of 12.3mg/day for 82.75 months (Table 1). Women were on average 60.4 years old, 179.75 pounds, with intrathecal morphine concentration of 10.75mg/mL, rate of 2.35mg/day for an average of 54.6 months (Table 2). No correlation of significance was seen in regards to age, weight, concentration, rate, or duration of the intrathecal system.

Ten of the 16 (62.5%) of the patients were found to have androgen deficiency, 4 of 8 men based on free testosterone levels and 6 of 8 women based on DHEAS levels. In men, erectile dysfunction correlated with endocrine dysfunction ($P = 0.02$) while depressive symptoms correlated in women ($P = .03$). Overall, 2 of the 16 patients had hydromorphone as the opioid in the intrathecal system. Both patients had normal endocrine functions. Both patients with hydromorphone were men and the use of hydromorphone showed an insignificant trend ($P = 0.06$). Three of the 4 men with normal endocrine functions had in addition to an opioid, bupivacaine, in the intrathecal system. The presence of bupivicaine in men was significant ($P = 0.02$). No women had bupivicaine while one of the 8 women had clonidine in addition to the opioid. Presence of another substance in addition to the opioid showed an insignificant trend ($P = 0.08$).

## Discussion

The majority of the patients, 10/16 (62.5%), were found to have androgen deficiency. The prevalence was greater in women than men, 6/8 (75%) vs 4/8 (50%). Other studies have shown similar rates in intrathecal opioid population with variations seen based on diagnostic criteria (17,28,29). The rates of androgen defi-

Table 1. *Male patients*

| Patient | Age (years) | Weight (pounds) | Diagnosis | Opioid | Duration intrathecal opioid (months) | Dose (mg/mL) | Rate (mg/day) | T (ng/dL) | Free T (ng/dL) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 67 | 146 | PLLS* | M**/ B*** | 154 | 10/0.75 | 3.48/1 | 452 | 37.1 |
| 2 | 55 | 290 | PLLS | H****/ B | 96 | 10/1.5 | 7.85/1.2 | 800 | 44 |
| 3 | 54 | 182 | PLLS | H/ B | 96 | 20/1.5 | 7.75/1 | 249 | 9.8 |
| 4 | 57 | 240 | PLLS | M | 66 | 10 | 2.75 | 271 | 9.8 |
| 5 | 80 | 210 | PLLS | M | 48 | 10 | 5.123 | 41 | 0.7 |
| 6 | 57 | 214 | PLLS | M | 46 | 5 | 2.5 | 175 | 5.3 |
| 7 | 54 | 174 | PLLS | M | 84 | 10 | 2.87 | 23 | 1.1 |
| 8 | 57 | 230 | PLLS | M | 72 | 10 | 3.5 | 127 | 0.2 |

*Post lumbar laminectomy syndrome
**Morphine
***Bupivicaine
****Hydromorphone

Table 2. *Female patients*

| Patient | Age (years) | Weight (pounds) | Diagnosis | Opioid | Duration intrathecal opioid (months) | Dose (mg/mL) | Rate (mg/day) | T (ng/dL) | Free T (ng/dL) | DHEA (ng/dL) |
|---|---|---|---|---|---|---|---|---|---|---|
| 9 | 85 | 141 | PLLS* | M** | 48 | 5 | 1.75 | 4 | 0.4 | 15 |
| 10 | 43 | 127 | PLLS | M | 12 | 5 | 0.25 | 3 | 0.2 | 25 |
| 11 | 46 | 285 | PLLS | M | 21 | 5 | 0.87 | 5 | 0.4 | 20 |
| 12 | 63 | 232 | PLLS | M | 32 | 10 | 3.75 | 10 | 0.2 | 4 |
| 13 | 55 | 240 | PLLS | M/C*** | 96 | 5/500 | 1.5/135 | 10 | 0.2 | 3 |
| 14 | 59 | 105 | PLLS | M | 84 | 5 | 1 | 22 | 1.6 | 120 |
| 15 | 64 | 164 | PLLS | M | 24 | 1 | 0.18 | 15 | 0.6 | 84 |
| 16 | 68 | 144 | PLLS | M | 120 | 50 | 9.51 | 5 | 0.6 | 3 |

*Post lumbar laminectomy syndrome
**Morphine
***Clonidine

ciency in the general population have been found to be around 10% (30-32). The development of androgen deficiency is multifactorial. In the study patients, no correlation was seen with age ($P$ = 0.8) or weight ($P$ = 0.69). Some risk factors for androgen deficiency include common conditions such as hypertension, diabetes, and obesity. All of the subjects were treated for hypertension while the only diabetic was a male with normal endocrine function.

In 3 of the 4 (75%) men with normal levels, bupivicaine was combined with opioids in the intrathecal delivery. The use of bupivicaine in combination with an opioid was significant for normal endocrine function in men ($P$ = 0.02). No women were infused with bupivicaine in addition to an opioid. Though the role, if any, of the bupivicaine is unknown, it may act to dilute the opioid infusion. However, there was no correlation between opioid concentration ($P$ = 0.2), rate ($P$ = 0.73), or even duration ($P$ = 0.16) of intrathecal drug delivery. Of the 3 men with normal androgen levels, 2 had hydromorphone as the opioid in the intrathecal delivery. However, this was insignificant ($P$ = 0.13). Both also were infused with bupivicaine in combination to the hydromorphone.

The diagnosis of androgen deficiency should be dependent on history and examination in conjunction to laboratory testing. However, the clinical presentation is varied and diagnosis can be difficult. Focusing on common signs and symptoms may lead to missing deficient patients (33). Studies have shown decreased libido or erectile dysfunction in a majority of men treated with intrathecal opioids (17). In the study men's complaints of erectile dysfunction were significant for diagnosis of androgen deficiency ($P$ = 0.02) while complaints of decreased libido were not since as all 8 men noted decreased libido. Erectile dysfunction results from the anticholinergic effects of opioid therapy (34). In men, no correlation was seen in any other symptoms including depression, fatigue, weight gain, or sweating. All the men also complained of fatigue and weight gain with the intrathecal therapy. In the women, correlation was seen with depressive symptoms ($P$ = 0.03) only for androgen deficiency. Mood disorders such as depression have been clearly demonstrated to be a potential consequence of androgen deficiency (34).

Opioid induced androgen deficiency is characterized by the presence of inappropriately low levels of gonadotropins leading to inadequate production of sex hormones, particularly testosterone. The principal laboratory test used for diagnosis is serum testosterone concentration in men. The levels should be obtained in the morning as they can vary throughout the day. Subsequent measure of free testosterone is recommended for confirmation (25). There are no absolute levels for diagnosis but most recommend the use of a threshold (200 – 300 ng/dl) for androgen replacement (35,36). Though many studies have been conducted on opioid induced androgen deficiency in men, limited studies have investigated similar effects in women. DHEAS levels have been observed to be decreased in women receiving sustained-release opioids (37,38). However, no diagnostic criterion has been established. Regardless, DHEAS may be the preferred indicator (27). Interestingly, total testosterone ($P$ = 0.004) and free testosterone ($P$ = 0.03) levels correlated with DHEAS level in the women.

Due to the small sample size and nature of the case

series, the study is limited. There is no control group for comparison and there is no data available to evaluate the pre-intrathecal opioid androgen status. Additionally, LH and FSH levels were not obtained for evaluation of primary versus secondary androgen deficiency. All of the patients with androgen deficiency were referred to the endocrine service for further evaluation and treatment.

## Conclusion

Androgen deficiency is common in patients treated with intrathecal opioids for chronic nonmalignant pain. Patients experience numerous and wide ranging symptoms. Erectile dysfunction may be more suggestive for androgen deficiency in men while complaints of depressed mood may be correlative in women. Additionally, combining bupivicaine with the intrathecal opioid may provide a protective role.

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