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Opioid-induced hypogonadism in palliative care. Does it matter? Report on four patients treated with hormone substitution

Abstract

Many patients treated for a long time with opioids develop hypogonadotropic hypogonadism with deficiencies in dehydroepiandrosterone sulphate (DHEA-S) and testosterone. It is thought that hypogonadism results in the symptoms of fatigue, depressed mood, slower cognition, increased pain sensitivity, amenorrhoea and loss of libido. It is debatable but quite possible that hypogonadism may also be one of the reasons of opioid tolerance. Substitution of the hormones; testosterone and/or DHEA may potentially break this vicious cycle, restore pain sensitivity to opioids and improve other symptoms improving patient's quality of life. In this article we describe four patients with intractable pain treated compassionately with either DHEA or testosterone. From the observations done by us, it is clear that substitution of those hormones has potentially a profound effect on opioid activity, both aimed and adverse effects. Suggestions for future studies are made.

Key words: opioid induced hypogonadism, testosterone, DHEA, pain sensitivity, opioid tolerance

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Introduction

Opioids are the mainstay of pain control in cancer [1] and are increasingly used among non-cancer patients with chronic pain [2]. One of the dreaded effects of is loss of pain sensitivity to opioids which is defined as opioid tolerance and opioid induced hyperalgesia [3, 4]. As the patients treated for their pain are nowadays living longer, these phenomena is gaining more importance in pain medicine. One, but certainly not the sole component of opioid tolerance is development of hypogonadism which decreases pain sensitivity to opioids [5–8]. Among

opioids only buprenorphine has probably less inhibitory effects on synthesis of sex hormones [9].

Opioid-induced hypogonadism is a clinical condition characterized by a low serum testosterone and DHEA-S with clinical signs, including decreased sexual desire, amenorrhoea, decreased pain threshold, decreased energy, fatigue, depressed mood, slowed cognition, impaired muscle mass and strength, and diminished bone density [10].

Opioid-induced hypogonadism was first noticed in the 1970's in patients on high dose methadone for treatment of opioid dependence [11–13]. Studies among these patients showed depressed plas-

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ma testosterone, decreased sexual drive and decreased libido. It is possible that opioid induced hypogonadism may affect many people worldwide but until now remains unrecognized and untreated. The epidemiology of this phenomenon remains unknown.

Clinical evidence

Abs et al. [8] showed that 25 out of 29 men on long term intrathecal opioids had a serum testosterone level < 9 nmol/L and a decreased libido. In the same study all pre-menopausal women developed amenorrhoea or dysmenorrhoea, and had a low serum LH, estradiol and progesterone. Eighteen out of 23 postmenopausal women were found to have a decreased serum LH and FSH. Opioids caused also central hypocorticism (in 15%), and GH deficiency (in 15%). However, the DHEA-S was not measured in this study.

A study of 54 men consuming oral opioids for non malignant pain showed that 48 (89%) men had subnormal levels of either testosterone or estrogen. This decrease in hormone level, was also related to the quality of opioid consumed, dosage and dosage form. Thirty nine men out of 45 (87%) on opioids, reported normal erectile function before opioid use, then complained of erectile dysfunction or diminished libido once commenced on opioids [14]. In the same study 47 women aged between 30 to 75 years, who were receiving oral or transdermal opioids (fentanyl) for the management of nonmalignant pain were assessed. These were compared to a control group of 68 women, not receiving opioid analgesia. It was found that the testosterone, oestradiol, and DHEA-S levels were 48% to 57% lower in the opioid using women. Also LH and FSH levels were around 30% lower in premenopausal and 70% lower in postmenopausal opioid users. These women also reported a change in menstruation cycle and often its cessation. Oophorectomised women had a decrease of testosterone by 39%. These women were not taking estrogen supplements, indicating that there is an impairment of adrenal androgen production [14].

Mechanism of hypogonadism

The mechanism by which opioids depress testosterone levels, is primarily thought to be through depression of pituitary function; decrease of gonadotrophins and decrease of hormone synthesis by the adrenals and gonads [15]. This condition is

called hypogonadotrophic hypogonadism. Additionally to a decrease in gonadotrophins there is also a decrease of ACTH [16] and increase of prolactin [17–19].

In chronic opioid use, there is inhibition of beta endorphins which may be responsible for an increased sensitivity to pain. Increased need of (exogenous) opioids may be another mechanism of opioid tolerance.

LH is normally secreted from the anterior pituitary gland in response to gonadotrophic releasing hormone (GnRH) from the hypothalamus. The LH acts on Leydig cells in the testes to increase testosterone synthesis and secretion. Along with other androgens, including DHEA-S and androstenedione. It is thought that LH secretion is also regulated by endogenous opioids, therefore in chronic opioid use, there is a tonic inhibitory effect causing suppression of androgen production [20].

Testosterone comes in the form of transdermal patches, oral tablets, gel and intramuscular injections. DHEA is available over the counter as a weak androgen and it comes in tablets of 10, 25 and 50 mg. Each method of administration has its own risks. In general the side effects of testosterone and DHEA are related to the male hormone activity. In women it can cause greasiness of the skin, unwanted hair growth and acne, these are usually avoidable in low doses. In men it can cause testicular atrophy, infertility and gynaecomastia, which are usually reversible with cessation of treatment. There are controversial views on whether testosterone substitution may cause prostate cancer (for review see: [10]) Substitution of testosterone and DHEA may have their effects in younger man but may be ineffective or even toxic in older patients [21, 22].

Polycythaemia is a risk apparent with any method of administration as testosterone stimulates erythropoiesis [22, 23]. Often this has a beneficial effect due to raising the haemoglobin level, however it can precipitate cardiac or cerebrovascular events if there is underlying disease. Lastly hepatotoxicity may occur when using the oral tablets of testosterone [24].

It appears that administration of exogenous DHEA and/or testosterone seems to correct the symptoms of hypogonadism. However, it is unknown whether abolishing hypogonadism also increases pain sensitivity to opioids. Sex steroid synthesis is very much increased in the spinal cord in some pain conditions [25, 26].

Many studies have shown that men and women differ in their pain response, both in animals and

humans. Women have a lower pain threshold than men [27–29] and this is thought to be due to the levels of testosterone.

Recently we have measured sex steroids in several patients with intractable malignant pain treated with opioids. In some patients with obvious symptoms of hypogonadism we decided to compassionately administer either testosterone (in man) or DHEA (in women). Here we describe responses of several patients to androgens.

Case 1

A 66-year-old male was diagnosed eight years ago with an ependymoma of the spinal cord. The neurosurgical procedure resulted in a permanent spinal cord lesion and paraplegia. His main problem is a constant pain in the rectum and legs, which is not well controlled by medication. He was treated with increasing doses of fentanyl (up to 350 $\mu\text{g}/\text{hour}$), oral morphine up for breakthrough pain (up to 1000 mg per day), ketamine, and gabapentin. However, this medication was at times insufficient.

His testosterone level measured 4.6 nmol/L (normal 7–25). He was prescribed testosterone tablets 40 mg tds. This dose was later reduced to 40 mg bd.

His pain response was remarkable. From alternating “good and bad days” he has now “all average days with some pain but certainly of lower intensity”. The need of the oral morphine breakthrough doses have decreased to occasional 120 mg a day. He also feels brighter in himself, and more cheerful. Due to his concerns about potential hepatotoxicity of testosterone tablets he was swapped to the testosterone patches 5 mg/24 hr after one month. He felt that the effect of the patches was less strong but when the dose of patches was doubled he felt dizzy and nauseated. He also had a skin reaction to the patch and the patches were discontinued. He then tried testosterone gel 5 g per day on the skin. He got certainly a benefit from the gel, as “if he forgets to apply it, he gets pain later in the day”. As the control testosterone level remained low (3.5 nmol/L) the dose was increased to 10 g testosterone gel a day. Three weeks after this dose escalation he became unarousable and his breathing was slow. He was admitted to the hospital where the dose of fentanyl was reduced to 300 $\mu\text{g}/\text{hour}$ and the testosterone was discontinued. He apparently has much less pain now.

Case 2

A 50-year-old man, diagnosed with non-small cell carcinoma of the lung was subjected to lobectomy and chemotherapy. On thoracotomy the tumour appeared to infiltrate the pleura. Immediately after the operation he suffered of severe post-thoracotomy pain and this pain remained intractable for 8 months. Oral morphine combined with transdermal fentanyl with multiple co-analgesics appeared to be ineffective. He also tried for a short time diamorphine 20 mg/24 hours in a continuous sc infusion, which put him asleep but relieved his pain only partially. After 8 months he was diagnosed with the tumour recurrence and started on erlotinib (Tarceva). As the pain continued to be a problem plasma testosterone was determined and was 1.2 nmol/L (normal 7–25 nmol/L). Prior to starting with testosterone supplements his medication was as follows: buprenorphine patch 55 $\mu\text{g}/\text{hr}$, pregabalin 100 mg bd, MST 60 mg bd, paracetamol 1500 mg, sevredol 50 mg PRN and dexamethasone 1 mg od. He was started on testosterone patches 5 mg/24 hours and his pain decreased rapidly within one day. He remained pain free despite CT scan showing no changes to the tumour volume as the result of treatment. Gradually the testosterone serum level has increased over 4 months to 4.8 nmol/L, 5.9 nmol/L and most recently 6.6 nmol/L.

As he continued to be pain free, he gradually reduced his medications. At that moment his medication was as follows: buprenorphine patch 10 $\mu\text{g}/\text{hr}$, pregabalin 50 mg bd, paracetamol 1 g prn, dexamethasone 1 mg od and erlotinib (Tarceva) 150 mg od. He did not experience any significant adverse effects to testosterone. Now four months later he reports still to be pain free and to have increased sense of well being, more energy and being less depressed but he has not observed any increase in libido yet. After maximal reduction of the analgesic dose we plan to discontinue testosterone.

Case 3

A 54-year-old man with multiple myeloma was suffering severe pain in his bones, muscles and joints. The history of pain preceded the diagnosis by several months. The pain was never well controlled with oral analgesics and the only period of time he can recall of being pain free was after the autologous bone marrow transplantation. However, this pain-free period lasted only for several months. The joints and bone pain reoccurred in the absence of a my-

eloma recurrence in the bone marrow. The pain was severe, generalized, worse on movement and with deep inhalation. The pain was partially relieved with combination of methadone 40 mg bd, amitriptyline 100 mg bd and prednisolone 40 mg. He could not tolerate higher doses of methadone as he was complaining of increased breathlessness. He reported that his nipples were swollen and sensitive to touch, but there was no discharge. The plasma testosterone was 3.9 nmol/L (normal 7–25 nmol/L), FSH 1.5 U/L (normal 2–9 U/L) and LH 3.9 U/L (normal 2–7 U/L). He was prescribed by the haematologist, an intramuscular depo testosterone injection of 250 mg, with the aim to repeat in 4 weeks. Within several days after injection he described his feeling as “terrible” and “getting worse each day”. The pain intensity increased, he was achy everywhere and short of breath. He was admitted to ICU eight days after injection, due to breathlessness, haemoptysis and worsening renal function (his basic plasma creatinine was 163 μ mol/L but increased after testosterone injection to 265 μ mol/L). The methadone dose was reduced to 5 mg bd and he was discharged home several days later. Eight weeks after the injection of depo-testosterone his plasma testosterone was still 9 nmol/L. He had substantially less pain than before and moved with more ease despite continuing on methadone 5 mg bd.

Case 4

A 29-year-old woman was diagnosed with an adenocarcinoma of the uterus and bony metastasis, for which she had a radical hysterectomy with left salpingo-oophorectomy and 12 cycles of chemotherapy and radiotherapy.

Her symptoms were fairly well controlled until she presented with right sided pain, which was unresponsive to fentanyl patches up to 200 mcg/hr and unresponsive to increasing doses of oral morphine up to 1400 mg per day. The pain localised in the right lumbar area and radiated down the back and side of her leg to her knee, made worse by movement. This pain was found to be due to impingement/irritation of the superior cluneal nerve, lateral cutaneous branch of the iliohypogastric nerve and lateral cutaneous branch of the XII subcostal nerve. She was treated with bupivacaine and DepoMedrone injections, which eased the pain within 20 minutes. She was then able to decrease her daily use of oral morphine to 240 mg, which at this time was enough to control all her other pain. After a while the pain in the left hip emerged and could

not be controlled by the increased doses of the opioids. Bone metastases and femoral fracture which caused this pain were treated with intra medullary nail and radiotherapy. Despite this treatment her oral opioid doses were increased again to 1200 mg per day, with only minor effect. She was admitted to the Hospice for pain control, her medications for pain at this time were fentanyl 250 μ g/hr, oral morphine sulphate up to 1000 mg a day, dexamethasone 6 mg od, amitriptyline 25 mg od, naproxen 500 mg bd and hyoscine butylbromide 60 mg a day. It was noticed that even with such a high dose of opioids she was never constipated. She was swapped gradually from fentanyl to buprenorphine 70 μ g/hour but she was still wearing a small fentanyl patch of 25 μ g/hour. With this medication she was much better pain controlled for two months and was able occasionally to go home to see her children. She then began suffering with severe left hip pain again so the buprenorphine dose was increased to 140 μ g/hr. At that moment her DHEA-S levels were below detection limit of 0.4 μ mol/L (normal 1.8–10.3 μ mol/L) and testosterone 0.76 nmol/L (normal 0–4.1 nmol/L). She was commenced on oral DHEA 50 mg od. Over night she experienced a benefit of being free from pain and therefore felt more rested in the morning. Also for the first time, she became constipated and needed laxatives. Over the next couple of days she continued to be pain free and in better spirits. However she deteriorated rapidly and passed away after being two days in coma.

Discussion

Determination of sex steroids in patients with intractable cancer pain may reveal hypogonadism. This confirms previous observations in patients with cancers and non-malignant conditions treated with high dose of opioids [5, 8, 30].

Administration of testosterone or DHEA resulted in all patients in a rapid decrease of pain intensity. However in several patients, treated with high doses of opioids administration of testosterone greatly increased their toxicity necessitating two patients to be admitted to the intensive care. In both these patients the dose of opioids was reduced and testosterone was discontinued. This resulted in long standing improvement of pain suggesting that high dose of opioids was the reason for opioid induced hyperalgesia and concomitant depression of plasma testosterone and/or DHEA-S levels.

In one patient testosterone treatment resulted in rapid and complete disappearance of longstanding intractable pain symptoms of post thoracotomy pain. This happened despite unchanged computed tomography findings which makes improbable that the observed effect was due to immunotherapy. It could be possible that long standing effects on the sex hormone levels was also due to the swap to transdermal buprenorphine. Buprenorphine had been reported not to compromise testosterone levels [9, 31].

Administration of DHEA to a young woman on high dose of opioids was not associated with increased toxicity and resulted in better pain control.

A lot needs to be investigated in adequately designed and powered clinical studies. It seems that there is a strong relationship between the high dose of opioids and hypogonadism. Sex hormones administered to patients with intractable pain may potentially be helpful. However, testosterone may also greatly increase the opioid toxicity.

Therefore it is advisable, similarly to the treatment advocated in opioid induced hyperalgesia [32] first to reduce the opioid dose. Reduction of the opioid dose by itself may relieve the hormonal suppression and result in higher sex hormones levels. So, substitution of testosterone and/or DHEA can potentially be used only for a period of several weeks or months, making the discussion of potential induction of hormone-related cancers less relevant.

The preparations used for the purpose as described above should be titrated from the low dose and should be short acting so their effect can be reversed when needed. The therapy should be monitored by the frequent measurements of testosterone and DHEA-S blood levels.

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