Opioid induced hypogonadism

Hypogonadism in both sexes is a common result of ongoing treatment with opioid analgesics and can be treated with suitable hormone replacement therapy

Raghava G Reddy specialist registrar, Theingi Aung specialist registrar, Niki Karavitaki consultant, John A H Wass professor

Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Oxford OX3 7LJ

“[Opium] has kept, and does now keep down the population: the women have fewer children than those of other countries … the feeble opium-smokers of Assam … are more effeminate than women.”

Charles Alexander Bruce, 1839

Opioids (any drug which binds to the opioid receptors in the central nervous system, of which (natural) opiates are a subclass) are now increasingly prescribed worldwide in every age group, for acute and chronic, cancerous and non-cancerous, pain. They are also used in managing people who have been addicted to heroin. The NHS Prescription Services reported a 5.6% increase in prescription of analgesics in 2008 compared with 2007 (buprenorphine prescriptions rose by 41.3%, morphine sulphate by 15.3%, tramadol hydrochloride by 11.6%, and co-codamol by 5.9%). In 2008, around 14.8 million opioid prescriptions (32% codeine or dihydrocodeine, 38% tramadol, and 30% others) were dispensed in the community in England. Opioids are considered to be the main drugs of misuse worldwide. According to a survey published by the UK Home Office, in 2006-7 in England, 273 123 people aged 15-64 used opioid drugs.

The high prevalence of opioid induced hypogonadism in both sexes is not widely recognised. We report two cases of opioid induced hypogonadism and discuss the literature on the effects of opioids on the hypothalamic-pituitary-gonadal axis.

Case reports

Case 1

A 42 year old man, followed up in our department for primary hyperparathyroidism, presented with episodes of flushing and sweating. His medical history included chronic back pain secondary to a lumbar spine disc prolapse, polycythemia rubra vera, cholecystectomy, colonic polyps, and osteoarthritis of knees. As his back pain was uncontrolled by regular analgesics including tramadol and codeine, he was started on morphine sulphate by his general practitioner, titrating the doses of morphine sulphate to 120 mg per day about six months before this presentation. He had received codeine phosphate and tramadol for over 10 years for pain relief. His drugs also included aspirin, propranolol, omeprazole, fluoxetine, and loperamide. On examination, he had normal secondary sexual characteristics. Luteinising hormone was 0.4 IU/l (normal range 1.5-9.3 IU/l), follicle stimulating hormone 1.0 IU/l (2-20 IU/l), testosterone 1.1 nmol/l (8.4-18.7 nmol/l), prolactin 552 pmol/l (92-769 pmol/l), insulin-like growth factor 1 32.8 nmol/l (10.5-35 nmol/l). Full blood count; ferritin concentration; renal, thyroid, and liver function tests; and concentrations of calcium, C reactive protein, calcitonin, chromogranins A and B, plasma and urine metanephrines, and urine 5-hydroxyindoleacetic acid (5HIAA) were normal. On magnetic resonance imaging the pituitary was normal.

Case 2

A 37 year old woman, the mother of two children and a regular wheelchair user, presented with a history of lumbosacral fusion, osteopenia, and multiple fractures. She had a history of amenorrhoea since the delivery of her last child seven years ago, which coincided with starting high doses of morphine sulphate (110 mg twice a day) for musculoskeletal pain. Luteinising hormone was 0.1 IU/l (normal range 2-10 IU/l), follicle stimulating hormone 2.4 IU/l (1.5-33 IU/l), oestradiol <37 pmol/l (40-1930 pmol/l), insulin-like growth factor 1 22.2 nmol/l (14.5-47 nmol/l), and prolactin 119 pmol/l (123-1271 pmol/l). Renal, thyroid, and liver function tests and C reactive protein concentration were normal. On magnetic resonance imaging the pituitary was normal.

Outcomes

In both these cases, hypogonadotrophic hypogonadism was most likely to have been caused by the chronic use of opioids.
As opioids could not be stopped or reduced on account of ongoing severe pain, hormone replacement therapy was started to prevent long term complications like osteoporosis and also to relieve symptoms. Symptoms of flushing and sweating resolved with testosterone treatment in case 1, and regular withdrawal bleeding was achieved with oestrogen and progesterone replacement in case 2.

**Discussion**

The flushing and sweating and the amenorrhoea were secondary to opioid induced hypogonadism. Opioids, both endogenous and exogenous, modulate gonadal function primarily by acting on opioid receptors in the hypothalamus. This leads to the decreased release or disruption to the normal pulsatility of gonadotrophin releasing hormone secretion, resulting in a reduction of the release of luteinising hormone and follicle stimulating hormone from the pituitary gland, and of testosterone or oestradiol from the gonads. Opioids may also have direct effects on the pituitary gland and the testes. Opioids are occasionally reported to increase prolactin levels, thereby reducing testosterone secretion. Hyperprolactinaemia also, through opioids, tonically inhibits the secretion of gonadotrophin releasing hormone.

Low serum testosterone concentrations in male heroin and methadone users were first reported in the 1970s. Since then, several studies have been performed in animals and humans to investigate the influence of opioids on the hypothalamic-pituitary-gonadal axis. The reported prevalence of opioid induced hypogonadism ranges from 21% to 86%. Testosterone concentrations seem to drop more than 50% within a few hours of taking an opioid, usually returning to baseline within 24-48 hours after withdrawal; depending on the dose used, it may take up to a month to recover. A prospective study in 2002 found that intrathecal opioid administration resulted in a significant reduction in serum testosterone (from 7.7 (SE 1.1) nmol/l at baseline to 2.0 (0.7), 2.8 (0.5), and 4.0 (0.9) nmol/l at 1, 4, and 12 weeks; P<0.0001), and also reported a reduction in libido. Concentrations of luteinising hormone and follicle stimulating hormone remained within reference range and were not raised, indicating central hypogonadism. A small observational study examined 54 men taking oral opioids, including methadone, and found that 89% had significantly decreased concentrations of free testosterone, oestradiol, dihydrotestosterone, luteinising hormone, and follicle stimulating hormone. All the men reported normal erectile function before using opioids, but 39 (87%) reported severe erectile dysfunction or diminished libido after starting opioid treatment. In another study, men had stopped taking opioids for 12 weeks, and compared with women with chronic pain who did not use opioids, concentrations of luteinising hormone, follicle stimulating hormone, oestradiol, and adrenal androgen were considerably lower in both premenopausal and postmenopausal women.

A recent study reported hypogonadism in 75% of 12 men and 21% of 14 women, suggesting that opioid use may be associated with a higher prevalence of hypogonadism in men than in women. In a cohort of patients who received opioids intrathecally for non-malignant chronic pain for a mean of 26 months, decreased libido or impotence was found in 96% (23/24) of men and reduced libido in 69% (22/32) of women. Eighty per cent (25/29) of men had testosterone <9 nmol/l (reference range 9-26 nmol/l); 14 of 21 (67%) premenopausal women developed amenorrhoea, and the other seven developed irregularities in menstruation.

Buprenorphine, a partial opioids agonist, has been associated with significantly higher gonadotrophin concentrations and a lower incidence of sexual dysfunction than methadone. In an open label study, testosterone replacement improved the sexual function of men with opioid related hypogonadism.

Opioid induced hypogonadism is under-recognised and undertreated. The prevalence may be higher in men, and in those receiving a larger dose of opioids, especially via the intrathecal route. While there are no current standards for monitoring these patients, the available evidence suggests that we should routinely screen for relevant manifestations, and arrange laboratory investigations to assess the gonadal function (luteinising hormone, follicle stimulating hormone, and testosterone or oestradiol). Monitoring of bone density should also be considered. Management includes reducing the dose, or substituting the opioids with other appropriate analgesic treatments. For those who cannot avoid opioids, hormone replacement therapy (testosterone in men, and oestrogen with or without progesterone in women) should be offered as appropriate, to relieve symptoms and prevent the long term consequences (box).

Hypogonadism can lead to erectile dysfunction, impotence, a loss of muscle mass in men, and irregular periods or amenorrhoea in women. Symptoms of flushing, sweating, decreased libido, infertility, osteopenia, osteoporosis, and depression are also common in both sexes. If people taking opioids present with depression, a diagnosis of remediable hypogonadism may be considered.

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Consequences of hypogonadism

In men:
• Erectile dysfunction
• Impotence
• Loss of muscle mass and strength

In women:
• Irregular menstrual periods, oligomenorrhoea, amenorrhoea

In both:
• Flushing and sweating
• Loss of libido
• Infertility
• Depression and anxiety
• Low energy levels
• Osteoporosis and fractures

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