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ENDOCRINOLOGY OF OPIOIDS

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Abstract

The use of opioids has grown substantially over the past two decades reaching the dimensions of a global epidemic. These drugs have effects on multiple levels of the endocrine system through mechanisms which are still not fully elucidated, and awareness of their endocrine sequelae is vital for all specialists prescribing or managing patients on them. Hypogonadism is the most well recognised consequence of opioid use (prevalence 21-86%) which, however, may remain undiagnosed with potential adverse outcomes for the patients. Although less frequent, cortisol deficiency can be also found. Furthermore, there is negative impact on bone health (with reduced bone mineral density and increased fracture risk) and occasionally hyperprolactinaemia, whereas the clinical significance of alterations in other hormones remains to be clarified. Discontinuation or reduction of the opioid and, in cases of chronic pain, consideration of alternative therapies for pain relief are potential management options. Hormonal replacement, especially when the above measures are not practically feasible, needs to be considered. Further studies are needed to clearly establish the prevalence of hormonal abnormalities with various regimes, doses and routes of opioids and to address reliably the long-term benefits and risks of hormonal treatment in patients on opioids. Until evidence-based, safe and cost-effective clinical guidelines become available, periodical assessment of the gonadal and adrenal function (particularly when relevant clinical manifestations are present) and evaluation of the bone health status are advised.

Introduction

Opium is acquired in the dried latex form from the seed pod of the opium poppy (Papaver somniferum), initially cultivated by the Sumerians at around 4000 BC. The naturally occurring alkaloids of opium and the drugs synthesized from it are described as 'opiates', whilst all natural or synthetic chemicals that bind to opioid receptors are included in the term 'opioids'. The main classes of opioids include natural opiates (alkaloids in the resin of the opium poppy, mainly morphine, codeine and thebaine), esters of morphine [e.g. morphine diacetate or diamorphine (heroin)], semi-synthetic opioids (produced from the natural opiates or morphine esters, e.g. hydromorphone, hydrocodone, oxycodone, oxymorphone, buprenorphine), fully synthetic opioids (e.g. fentanyl, pethidine, methadone, tramadol) and endogenous opioid peptides produced in the body (e.g. endorphins, enkephalins)[1].

Opioids exert their actions by binding to receptors which belong to the family of G-protein coupled ones, and their activation produces a range of different effects[1]. There are many types of opioid receptors with the three main being μ, κ, δ (that are naloxone sensitive), whereas the nociceptin receptor, with effects not reversed by naloxone, was discovered in 1994[2]. The opioids used in clinical practice have various indications and are mainly offered as analgesic agents (Table 1), whereas heroin is used as a recreational drug due to its euphoric effects (illicit use). The most commonly available opioids (morphine, codeine, fentanyl, and their derivatives, methadone, tramadol, pethidine) are primarily μ-receptors agonists, whilst buprenorphine and pentazocine are mixed agonists/antagonists[3]. Pentazocine acts as a partial agonist on δ- and κ-receptors and as an antagonist on the μ-receptor, whilst buprenorphine has partial agonist activity on μ- and nociceptin receptors and antagonist activity on κ-receptors[4].

The use of opioids has grown over the past two decades; between 2000 and 2014, it increased 216% in USA and 210% globally making opioid consumption a real global epidemic[5]. Notably, in 2014, USA used around 69% of the world's supply of opioids; prescribers involve a wide range of health professionals including pain physicians, family physicians, orthopaedic surgeons, anaesthesiologists, psychiatrists, physical medicine and rehabilitation specialists[5]. Data from the UK

Clinical Practice Research Datalink confirm a significant rise in strong opioid prescriptions (buprenorphine, fentanyl, morphine and oxycodone) between 2000 and 2010, with the majority administered for non-cancer patients[6]; in this report, the number of strong opioid users increased from 9479 to 53,666 during the study period. In addition, prescription of long-acting opioids in patients with chronic non-cancer pain has been associated with a significantly elevated risk of all-cause and of cardiovascular-specific mortality, compared with analgesic anticonvulsants or low dose tricyclic antidepressants[5, 7].

Exogenous opioids can have various effects on the endocrine system, which, nonetheless, may remain underdiagnosed with potential adverse sequelae for the patients. The aim of this manuscript is to provide a review of these effects and their underlying mechanisms, to discuss their clinical significance and management and to identify areas requiring further research in this field.

Hypothalamo-Pituitary-Gonadal axis

Opioids, both endogenous and exogenous, modulate gonadal function primarily by acting on opioid ε-receptors in the hypothalamus[8]. This leads to reduced release or disruption of the normal pulsatility of gonadotropin-releasing hormone (GnRH) secretion and reduction of the release of luteinising hormone (LH) and follicle-stimulating hormone (FSH - to a lesser extent) from the pituitary gland, and of testosterone or oestradiol from the gonads[9-16]. Opioids may also directly inhibit the pituitary release of gonadotropins[17]. Hyperprolactinaemia that can be occasionally caused by opioids may contribute to their suppressive effects on the HPG axis[9]. Opioids have also direct effects on the gonads: these include decreased production of sperm, testicular interstitial fluid, and intra-testicular testosterone[18].

The effects of long-term opioid use on the gonadal status have been studied extensively in the past four decades and the reported prevalence of opioid-induced hypogonadism ranges between 21% and 86%[10-16, 19]. This wide range is attributed to the heterogeneity of the studies (differences in the populations assessed, variations in the type, dose, route and duration of opioid administration,

potential impact of pain, of other comorbidities and of concurrent medications, and possibly differences in the age of the patients included).

The initial studies involved mainly heroin addicts and patients on methadone for maintenance and had demonstrated reduction of testosterone levels in males, with an associated reduction in LH and/or FSH[20-22]. The decrease in testosterone occurs within a few hours of opioid administration; in a study of 13 males on acetylmethadol for opioid dependence, there was significant reduction of testosterone four hours after the ingestion of the drug, with the levels remaining low around 24 hours after the drug administration and returning to baseline values 48 hours post-acetylmethadol use[23]. Woody *et al.* had similar results, albeit the duration of recovery was shorter[11]. In another study with male heroin addicts, recovery of testosterone to normal occurred after about one month of drug abstinence[21]. Furthermore, methadone has a dose-dependent effect on the testosterone levels of heroin addicts on methadone detoxification[22]. In female heroin addicts, amenorrhoea and galactorrhoea may be present[24]; nonetheless, series systematically assessing this group of patients are not available.

Hypogonadism is also present in both male and female patients on opioids (oral, transdermal or intrathecal) for cancerous or non-cancerous pain in cohort or cross-sectional studies; it should be noted, however, that other factors may also contribute to the hypogonadism including pain pathophysiology, pain comorbidities and patients' age and these need to be taken into account when interpreting their results[12-14, 16, 25-29]. The effects on the HPG axis begin as soon as the opioid is taken[12, 13, 16, 30] and the hormonal changes are dose-related[13, 31]. The resultant clinical manifestations include erectile dysfunction, decreased libido, infertility, fatigue, depression, hot flushes and night sweats in males[13, 16, 27-29] and reduced libido, ameno- or oligomenorrhoea with anovulation in premenopausal females[16]. In postmenopausal women, LH and FSH levels can be decreased[16]. The prevalence of hypogonadism is higher in men than in women taking oral opioids for chronic non-cancer pain[15]. In premenopausal chronic pain patients, the suppression of LH may be less profound when opioids are administered orally/transdermally compared with the intrathecal route[9]. Notably, chronic use of long-acting opioids is associated with greater odds of androgen deficiency compared to chronic use of short-acting ones[31, 32]. Furthermore, transdermal fentanyl, methadone, and oxycodone (long- and short-acting formulations combined) are associated with higher odds of androgen deficiency when

compared to hydrocodone[33]. It should be pointed out, however, that these findings reflect the observations at the doses used for different opioids in the various studies. Buprenorphine, a partial μ-receptor agonist and κ-receptor antagonist used as maintenance for opioid dependence or for the management of acute/persistent pain results in less severe hypogonadism when compared to methadone[34, 35]. Reduction in the dose or cessation of therapy reverses the hypogonadism [26, 30, 36, 37] but the time course of this has not been systematically studied.

Despite the abundance of evidence indicating that opioids lead to hypogonadotropic hypogonadism, this condition remains underdiagnosed in daily practice; this may relate with lack of symptoms reporting by the patients combined with the underappreciation of this common problem amongst the clinicians. Currently, there is no consensus or clinical guidelines for the diagnosis and management of opioid-induced hypogonadism. Manifestations of hypogonadism should be enquired before, as well as during opioid treatment and patients should be educated on this potential side effect and encouraged to report hypogonadal symptoms should they experience any. Laboratory evaluations need to be taken periodically (and also when changing dose or regime of opioid) and include measurement of blood testosterone (in a morning sample before 10 am) and gonadotropins in men and oestradiol and gonadotropins in women (combined with menstrual history)[38]. Measurement of prolactin (PRL) and taking into account the impact of other medications and co-morbidities, as well as exclusion of other causes of hypogonadotropic hypogonadism are also advised.

Management of the opioid-induced hypogonadism includes discontinuation or reduction of the dose of the opioid and consideration of alternative therapies for patients on chronic pain requiring pain relief. When the above measures are not viable, gonadal hormone replacement should be considered with a number of studies showing beneficial effects. Aloisi *et al.*, in a series of nine males (aged between 44 and 75 years) on epidural morphine for non-oncological chronic pain treated with testosterone gel for 12 months, demonstrated improvement in the sexual dimension of the Aging Males' Symptoms scale and in the Mental Index of the SF-36 questionnaire[39]. The patients also reported increase in the growth of body hair and improved appetite and their prostate-specific antigen (PSA) levels remained within normal limits. None of the Profile of Mood State subscale scores or Centre for Epidemiological Studies Depression Scale ratings showed significant changes[39]. Daniell *et*

al., in an open-label pilot study on 16 men (aged between 34 and 55 years) with opioid-induced androgen deficiency (on oral sustained release oxycodone or oral methadone for pain syndromes) offered testosterone transdermal patches for 24 weeks, found improvement in androgen deficiency symptoms, sexual function, psychological well-being and depressed mood by using validated questionnaires, as well as of the haemoglobin and haematocrit[40]. Basaria *et al.*, in a randomised, double-blind, parallel placebo-controlled trial of 65 males (aged between 18 and 64 years) with opioid-induced androgen deficiency and chronic non-cancer pain, randomised to receive transdermal testosterone or placebo for 14 weeks, found that men in the testosterone arm demonstrated greater improvement in mechanical and pressure hyperalgesia and in sexual desire, as well as reduction in fat mass[41]; elevation in PSA >4 ng/ml was seen in two patients, one in each group, and erythrocytosis occurred in neither group. Notably, Huang *et al.*, in a placebo-controlled, double-blind randomized trial from the same centre of 64 non-diabetic men (aged between 18 and 64 years) on opioid analgesics for chronic non-cancer pain and morning total testosterone <12 nmol/L (as measured by liquid chromatography-tandem mass spectrometry), randomised to 14 weeks of transdermal testosterone gel or placebo gel daily, found that changes in lipid profile, fasting glucose and insulin, homeostatic model assessment for insulin resistance and C-reactive protein were similar from baseline to the end of treatment in both groups; glucose and insulin response to 75 gr oral glucose load, inflammatory markers and adipokines also did not differ between the two groups[42]. However, the duration of this study was not long enough to evaluate cardiovascular safety of testosterone therapy in these patients. In contrast to their male counterparts, series looking at gonadal hormone replacement in opioid-induced hypogonadism in women are not available.

In summary, opioid use has an inhibitory effect on the HPG axis through action at various levels leading to hypogonadism. Discontinuation or reduction in the dose of opioid can reverse this sequela but when this is not possible, gonadal hormone treatment needs to be considered. Adequately powered well-designed studies are needed to establish the long-term benefits and risks of hormone replacement in this group of patients, as well as the potential impact of hormonal treatment on pain sensitivity and on the recovery of patients on methadone for opioid use disorder.

Hypothalamo-pituitary-adrenal axis

Opioids suppress the HPA axis mainly at the hypothalamic-pituitary level by inhibiting corticotropin-releasing hormone (CRH) and vasopressin secretion and by reducing their effect on adrenocorticotropic hormone (ACTH) and cortisol release[43-47]. The receptors involved are not entirely known but κ- are considered to be the predominant type; δ-receptors have also been implicated[8, 48, 49]. Nonetheless, the increasing evidence of secondary adrenal insufficiency in patients receiving μ-receptor agonists suggests a potential role of this subtype in the opioid-induced regulation of HPA axis (morphine, hydromorphone, methadone, tramadol, diamorphine, fentanyl and loperamide act predominantly through this receptor)[36, 37, 50-54]. This is also supported by the observation that human subjects carrying the A118G single nucleotide polymorphism of the μ-receptor encoding gene *OPRM1* (which has been shown to increase the receptor's binding affinity to β-endorphin) show blunted ACTH response to metyrapone and exaggerated cortisol release to naloxone[55, 56]. Opioids have also direct effects on the adrenal glands, independently of their effect on the hypothalamo-pituitary unit; naloxone administration in patients with hypothalamo-pituitary disconnection led to higher cortisol (but not ACTH) levels compared with saline[57] and β-endorphin suppressed ACTH-stimulated cortisol production in isolated human adrenocortical cells[58].

Acute administration of opioids in animals results in an exaggerated response of the HPA axis which may be followed by a rebound decrease of its activity[59, 60]. Data from animal studies assessing the effects of chronic administration of opioids on ACTH and glucocorticoid release are conflicting showing activation[61], suppression[59] or no effect[62].

Single administration of various opioids (morphine, heroin, buprenorphine, remifentanil) in normal subjects results in suppression of ACTH and glucocorticoid secretion, blunted pituitary-adrenal response to CRH, and diminished cortisol response to psychosocial or surgical stress[45, 46, 63-65]. Notably, gender may play a role in the effect of opioids on the HPA axis. Women demonstrate a greater sensitivity to opioid receptor antagonists (naloxone and naltrexone) on their cortisol response compared to men suggesting sex differences in the endogenous opioid system[66-68]. Menstrual cycle

may also be implicated with a study showing that women in the luteal phase of their cycle had greater naltrexone-induced increases in serum cortisol than women in the early follicular phase[69].

In addition, diamorphine has an acute suppressive effect on HPA axis in heroin dependent addicts on heroin-assisted treatment[70]. Opioid dependent patients on maintenance treatment with intravenous diacetylmorphine have reduced serum levels of vasopressin and cortisol compared to healthy controls[43]. It is of note that in heroin addicts there is a disturbed cortisol circadian rhythm with lower morning cortisol levels compared with controls[65, 71].

Several case reports documenting secondary adrenal insufficiency after oral or transdermal opioid administration of variable duration (including even of a few days) mainly for pain relief have been published[36, 37, 50-54]. The accurate prevalence of adrenal insufficiency in these patients has not been clearly defined and chronic pain can be a major confounder (chronic pain has been associated with loss of the diurnal variation of blood cortisol, lower morning blood cortisol and 24-hour urinary free cortisol levels compared with controls and hyper-reactive ACTH release to CRH stimulation)[72, 73]. Aloisi *et al.* showed that intrathecal administration of morphine (0.9 mg/day) for 15 days in patients with persistent severe pain led to reduction in the blood cortisol levels with an immediate effect from Day 1 to Day 15 in both sexes; the levels rose on Day 16, 24 hours after the opioid withdrawal[30]. In contrast, transdermal buprenorphine (35mcg/h every 72 hours) for acute/persistent pain for six months did not inhibit the HPA axis. Gibb *et al.*, in a series of 48 patients attending chronic tertiary pain clinics and treated with long-term opioid analgesia (tramadol, oxycodone, morphine sulphate, fentanyl or buprenorphine patch, dihydrocodeine – median daily opioid dose 68 mg as determined by morphine sulphate equivalent dose) for at least 6 months and no recent exposure to exogenous glucocorticoids, found 8.00 am blood cortisol <100 nmol/L in 8% of them and failure to respond to synthetic ACTH stimulation (peak cortisol <430 nmol/l) in 6%[74]. When focusing on the 33 patients on high-dose opioid analgesia (excluding tramadol and dihydrocodeine), approximately 10% of those assessed had an initial suboptimal cortisol response to synthetic ACTH. Intrathecal administration of morphine or hydromorphine in 72 patients with non-malignant pain (mean daily dose 4.8 ± 3.2 mg and mean duration of treatment 26.6 ± 16.3 months) resulted in basal cortisol levels <5 μg/dl and peak cortisol value <18 μg/dl during an insulin tolerance test (ITT) in 9% and 15% of them, respectively[16];

one of the patients in this series developed Addisonian crisis during pneumonia. Furthermore, 33% of 20 chronic pain patients receiving chronic pump intrathecal morphine infusion (0.2-10 mg/day) and 50% of 20 patients on oral morphine (60-120 mg/day) demonstrated hypoadrenalism (defined as stimulated cortisol levels during ITT <18 μg/dl)[75]. Additionally, there is reduction of the adrenal androgen dehydroepiandrosterone sulfate levels during opioid therapy in patients with chronic non-malignant pain[14, 75, 76]. Factors predicting the development of abnormal cortisol stress response are not as yet established. However, given, the widespread use of opioids, it is anticipated that a large number of patients are possibly at risk of cortisol deficiency.

The altered HPA axis function of opioid users improves or returns to normal after discontinuation or reduction in the dose of the drug[36, 37, 50, 51, 53, 54] but the time interval of this has not been systematically studied. Interestingly, Nenke *et al.*, in a pilot, randomized, double-blind, placebo-controlled crossover study with 17 patients on long-term opioid therapy for chronic non-cancer pain and mild hypocortisolism (defined by a plasma cortisol response ≤350 nmol/L at 60 min following a cold pressor test), found that hydrocortisone therapy (10 mg/m^2/day) led to improvement in vitality and pain tolerance compared to placebo[77].

In summary, opioids exert inhibitory actions on the HPA axis by acting at various levels. Although it could be argued that hypocortisolism is an adaptive response to opioids, the reported cases of improvement of clinical manifestations resembling those of cortisol deficiency after glucocorticoid administration[52, 53, 74, 77] and the description of Addisonian crises whilst on these agents[16, 54] suggest that, at least in some patients, hypocortisolism is of clinical significance. Further studies are needed to define the prevalence of hypoadrenalism with different opioids at various regimes and routes, to establish the clinical significance and potential consequences/adverse outcomes of the biochemical findings (particularly if these reflect modest changes in the HPA axis) and to provide clear guidance on the reversibility and the time course of the hormonal changes following withdrawal or reduction of opioid dose. Although the existing literature cannot provide robust evidence for safe and cost-effective clinical guidelines, patients on opioids should be considered at risk of hypoadrenalism and checking an early morning plasma cortisol (particularly in the presence of relevant clinical manifestations) is a sensible approach. Further dynamic assessment of the HPA axis will depend on

the results of the basal cortisol. The frequency of the HPA axis assessment is not known but certainly the presence of symptoms/sings of cortisol deficiency should prompt investigations towards this direction.

Somatotroph axis

In animal models, acute opioid administration stimulates growth hormone (GH) secretion[78, 79]. On the other hand, chronic administration has led to no[61, 80] or to stimulatory effect[81]. Studies on the pathways and mechanisms involved on the effects of opioids on GH release show that various types of opioid receptors (μ, κ, δ) are implicated, but their activation effects vary between reports[82-84]. A reset of the hypothalamic GH pulse generator via opioid receptor stimulation is also a possible mechanism[85]. Treatment of rats with antiserum against GHRH inhibited the GH stimulatory response to different types of opiates[86, 87]. In addition, opioids exert inhibitory effect on somatostatin release[88] and action[89]. Finally, chronic treatment with morphine decreased GH mRNA levels in rat pituitary and concomitant administration of naloxone inhibited this[90]. Notably, gender may influence the effects of these drugs on the GH secretory dynamics. Continuous morphine exposure of male rats resulted in increased basal and mean GH concentrations, as well as in a modest increase of the GH pulse frequency but not of pulse amplitude; in females, morphine, apart from a marked reduction in the pulse amplitude, had little effect on other parameters of GH secretion[91].

In human subjects, there are acute stimulatory effects of opioids on GH secretion which relate with the dose offered[92, 93]. Thus, intravenous morphine at doses of 5 mg and 10 mg did not promote GH secretion but a higher dose of 15 mg did[92, 94, 95]. Notably, administration of a Met-enkephalin analogue G-DAMME, in healthy men combined with a maximally stimulatory dose of a GHRH analogue resulted to an enhancing effect of the GHRH-induced GH release, suggesting that other mechanisms are also implicated[93]. Data on possible sex differences are contradictory. Naloxone infusion decreased the growth hormone-releasing hormone (GHRH)-induced GH release in healthy women but had no effect in normal men[96]. On the other hand, in another study, naloxone significantly blunted the GH response to GHRH in healthy male volunteers[97].

Humans treated with intrathecal opioids (morphine and hydromorphine) for non-malignant pain had significantly lower serum insulin-like growth factor 1 (IGF-1) levels compared with controls; 17% of the subjects had IGF-1 concentrations more than two standard deviations below the mean, whilst 15% of them showed peak GH <3 μg/L during ITT[16]. Abnormal GH response on ITT was also detected in 26% of methadone-treated patients and in 31% of heroin addicts[98]. In this study, a maximal level of GH >9 μg/L or an increment over the baseline >10 μg/L were defined as criteria of a normal response; using the cut-off of <3 μg/L, a compromised GH response would be found in 5% and 6% of methadone and heroin users, respectively. Finally, chronic pain patients on oral opioids had no abnormal IGF-1 levels or a difference in GH response to the glucagon stimulation test when compared to a control group receiving non-opioid analgesia[99]; a suboptimal GH response found in two cases was finally attributed to obesity.

The above data demonstrate the complexity of the effects and relevant mechanisms of opioids on the GH axis. Overall, acute administration of opioids increases GH secretion but the impact of chronic use varies considerably. Gender, opioid type, route and dose are factors that influence the action of opioids on GH release. The clinical significance of these findings in patients using long-term opioids remains to be elucidated.

Prolactin

Opioids can have a stimulatory effect on PRL secretion mediated by μ-, κ- and δ-opioid receptors in the hypothalamus[100].

Acute administration (oral or intravenous) of morphine increases PRL in healthy men[101] and postmenopausal women[94]. In women, sex steroids may alter the opioid-induced effects on PRL secretion; thus, whilst naloxone had no effect on PRL secretion in postmenopausal and hypogonadal women, as well as women in the early follicular phase of the menstrual cycle, when administered for 7 days in the luteal phase, it induced PRL release[9].

In chronic use of opioids, the effects are variable. PRL levels have been found high in opioid addicted subjects and in opium smokers[18, 102, 103]. Furthermore, oral opioids for chronic pain increase PRL[104, 105]. On the other hand, morphine offered intrathecally for chronic non-cancer pain had no effect on PRL[16]. Finally, buprenorphine or methadone maintenance therapy for opioid dependence did not lead to high PRL[34, 106].

Opioid-induced hyperprolactinaemia can lead to painful gynecomastia, galactorrhoea and hypogonadism[104].

Bromocriptine has been successfully used in cases of hyperprolactinaemia due to opioid use[107].

Overall, high PRL can be detected in patients on opioids, although the effect of pain on this finding needs to be taken into account. The frequency of hyperprolactinaemia and the impact of dose, route and type of drug have not been clearly established, but the clinician needs to be aware of this potential consequence and its clinical sequelae (particularly on the gonadotroph axis).

Hypothalamo-pituitary-thyroid axis

Based on most animal studies, opioids have inhibitory effect on thyroid-stimulating hormone (TSH) secretion and this is observed mainly with pharmacological doses[108, 109].

In humans, acute intravenous administration of morphine in normal volunteers led to a significant increase in serum TSH and enhanced the response of TSH to thyrotropin-releasing hormone stimulation[110].

In chronic use of opioids for cancer pain and in opioid addicts, there was no difference in basal levels of TSH and peripheral thyroid hormones compared with from controls[16, 104, 111, 112]. However, opium smokers had lower TSH levels compared with healthy volunteers[102].

The potential clinical significance and the implications of these data remain to be elucidated and, therefore, at this stage, clinical recommendations cannot be provided.

Arginine Vasopressin

Opioids affect arginine vasopressin (AVP) secretion through μ-[113] and possibly κ-opioid receptors[114].

Acute opioid administration can lead to a rise in AVP levels. Fentanyl offered in two continuous intravenous infusions in five healthy volunteers increased plasma AVP in a dose-dependent manner[115]. Notably, a case of a patient on fentanyl patches who developed syndrome of inappropriate antidiuretic hormone secretion has been published [116].

Boulton *et al.* showed that in patients undergoing coronary artery bypass surgery, the levels of AVP were significantly higher with fentanyl than with sufentanil during induction of anaesthesia[117]. Administration of extradural injection of morphine six hours after surgery in six patients produced increase in plasma AVP[118]. Bozkurt *et al.*, in a series of children undergoing surgery (major genito-urinary or abdominal operations), found that both a single dose of epidural morphine post-induction or morphine infusion led to increase in serum ADH levels[119].

Overall, the studies on the impact of exogenous opioids on AVP in humans are confounded by the differences in the fluid status of the subjects, as well as by the side effects of opioids, including hypotension and nausea, which can stimulate AVP release. Therefore, the interpretation of the published data and the extraction of robust conclusions for clinical practice remain challenging.

Bone Mineral Density and Fracture Risk

Exogenous opioids have a negative impact on bone health. Opioid-induced hypogonadism, as well as direct action of these drugs on bone formation are potential contributing factors. Osteoblasts express opioid receptors and opioids inhibit the growth of human osteoblast tissue cultures; this effect was prevented by opioid antagonists[120]. Furthermore, opioids inhibit osteocalcin production in osteoblast tissue cultures[120].

Male chronic heroin users have significantly lower vertebral bone mineral density (BMD) compared with healthy age- and sex-matched control subjects[121]. In a cross-sectional study of patients taking methadone maintenance therapy, BMD was lower from control values throughout the skeleton in men but not in women; notably in this series, the male patients had lower serum testosterone than

the controls[122]. In another study, 50% of men and 21% of women on chronic oral opioids had osteopenia; in this report, however, males had used opioids for a longer period and had higher prevalence of hypogonadism compared with women[15]. In addition, in a study of 14 males on intrathecal opioids for chronic non-malignant pain and hypogonadism, osteoporosis was observed in 21% and osteopenia in 50%[25]. In a cross-sectional analysis of adults aged 17 years and older from the Third National Health and Nutrition Examination Survey, opioids were associated with significantly reduced BMD besides anticonvulsants[123].

In a case control study from a nation-wide register in Denmark, there was increased fracture risk in users of morphine and other opioids[124]. Notably, the authors suggested that this increase, which was observed even on very low doses, may be related with the risk of falls owing to the acute central nervous system effects of opioids[124]. This view was further supported by a nested case-control study using the UK-based General Practice Research Database in which a clear dose-response relationship between current cumulative opioid use and risk of fracture was found[125]; thus, current light use of opioids was associated with increased the risk of fractures in adults with non-cancer pain, particularly during the initial weeks of administration, whilst current heavy cumulative opioid use was not, particularly in women[125]. Finally, the contribution of limitations in mobility (due to chronic pain) on the higher risk of fractures cannot be excluded.

There is no consensus on the monitoring of the BMD in patients on opioids but those with risk factors and particularly hypogonadism require assessment. Discontinuing the opioid, if possible, and treatment of osteoporosis or osteopenia according to the current guidelines are management approaches.

Conclusions and future perspectives

Exogenous opioids have effects on multiple levels of the endocrine system through mechanisms which are still not fully elucidated (Table 2). Hypogonadism is the most well recognised consequence of opioid use which, however, may remain undiagnosed with potential adverse sequelae for the patients. Although less frequent, cortisol deficiency can be found. The data on the impact of opioids

on GH and TSH are less clear and often complex, whereas hyperprolactinaemia can be occasionally detected. AVP levels may be increased in patients on these drugs but a number of confounding factors do not allow clear conclusions to be drawn. Of particular importance is the negative impact of opioids on bone health, which may be overlooked during the care of these patients.

Discontinuation or reduction of the opioid and, in cases of chronic pain, consideration of alternative therapies for pain relief are potential management options. Hormonal replacement, especially when the above measures are not practically feasible, needs to be considered (Table 2). Awareness of the endocrine effects of opioids by all specialists prescribing or managing patients on these drugs is vital, particularly given the expanding dimensions of this problem as a global epidemic.

Further research is needed to clearly establish the prevalence of hormonal abnormalities with various regimes, doses and routes of opioids, the impact of partial agonists (like buprenorphine) and the clinical significance of the biochemical findings from the HPA axis. Finally, well designed prospective rather than cross-sectional studies taking into account the effect of confounding factors (like other co-morbidities, drugs or pain) are needed to clarify the long-term benefits and risks of hormonal treatment and its effects on other areas, including pain sensitivity and potential reduction in opioid dose, and recovery of patients on methadone for opioid use disorder. These will finally lead to safe and cost-effective clinical guidelines, but until these become available, periodical assessment of the gonadal and adrenal function (particularly when relevant clinical manifestations are present) and evaluation of bone health status are advised.

Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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