Implications of analgesics use in osteoporotic-related pain treatment: focus on opioids

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Summary

Bone loss is asymptomatic and will progress without pain and other symptoms until the occurrence of a fracture. The occurrence of a breaking bone induce acute pain determined and supported by a mechanical, inflammatory and neuropathic component. Very often the acute component evolves in a chronic musculoskeletal component. Overall objectives of the analgesic therapy can be summarized in pain relief, improving sleep, improve mobility, reduce anxiety, emotional component and depression. Osteoporosis is predominantly a condition of the elderly, more likely to have coexisting cardiovascular disease and age-related decline in renal function, receiving treatment for one or more comorbid conditions, taking multiple medications. Analgesic treatment with NSAIDs has negative effects on skeletal health and healing of the injured skeleton and increase risk of adverse events especially in older patients. Despite all opioids therapy represents a mainstay in the treatment of patients with moderate to severe pain, it can induce an endocrinopathy, which may affect bone metabolism. The negative effects of opioids on hormonal axis are not the same for all molecule and the choice of drug can be crucial in the treatment of patients with chronic pain.

KEY WORDS: pain; chronic pain; osteoporosis; osteoporotic pain; osteoporosis fractures; opioids; pain treatment.

Introduction

Pain is not a symptom of osteoporosis, bone loss is asymptomatic and will progress without pain and other symptoms until the occurrence of a fracture. Up to now it is estimated that over 200 million people worldwide suffer from osteoporosis (1). Pain is one of the most feared complications of osteoporosis, which affects about 85% of the patients (2,3). Sensory nerve fibers do not appear to decline aging, whereas density of bone mass decrease (4). The occurrence of a fracture induces acute pain determined and supported by a mechanical, inflammatory and neuropathic component. Very often the acute component evolves in a chronic musculoskeletal component (4). Over time, chronic pain can be surrounded by different mechanism, for example continuous contraction of the paraspinal musculature may evolve in fatigued and painful muscles (5). It is a fact that vertebral fractures can induce a series of pathophysiological changes that evolves also in a chronic back pain having great personal and socioeconomic impact.

Objectives of pain management in osteoporosis

Treatment of osteoporosis is essential to reduce the further evolution of the disease and the perpetuation of the determinants of pain. Chronic pain caused by osteoporosis, may induce the development of significant changes in functional ability, personality and lifestyle. The simple pain treatment may be insufficient, remaining necessary break free from the vicious circle of immobility, muscle atrophy and deterioration of osteoporosis condition. Basic requirements of efficacious therapy are a multimodal approach, a continuous administration of drugs and an aggressive approach. Reduce pain is much more than treat only “an unpleasant sensory sensation”, and represents a key response in the framework of biopsychosocial model of chronic pain (6). The overall objectives of the analgesic therapy can be summarized in pain relief, improving sleep, improve mobility, reduce anxiety, emotional component and depression (6).

Pain relief in chronic osteoporotic pain

As proposed by the World Health Organization (WHO), analgesic choice is determined by the intensity of pain (7) and by the type of pain also. The analgesic treatment of osteoporotic fracture should prevent the onset of pain with drugs administered at scheduled intervals throughout the day, according to half-life and duration of action of different formulations. Moreover, the analgesics could be easy to administer, preferably by mouth, customizable to the needs of patient. The first-line approach for the treatment of mild to moderate musculo-skeletal pain is represented by acetaminophen (42, 43), however its role in the treatment of chronic pain is often limited. Acetaminophen is a low-level analgesic with a weak anti-inflammatory power, useful only as a short-term analgesic (41). Like acetaminophen NSAIDs including COX-2 inhibitors may be suitable for short time treatment of patients with bone pain. Osteo-

porosis is predominantly a condition of the elderly, more likely to have coexisting cardiovascular disease and age-related decline in renal function, receiving treatment for one or more comorbid conditions, taking multiple medications. Recently, a meta-analysis underlines that COX-2 selective drugs increase the risk of major vascular events about a third, inducing a rise of about 3/4 of the risk of major coronary events (8). All NSAIDs doubled the risk of heart failure, requiring hospital admission and increase the risk of upper gastrointestinal complications by around 2-4 times (8). In USA every year number of death NSAIDs related are similar to the number of deaths from the acquired immunodeficiency syndrome (38) and in UK higher than those for asthma or cervical cancer (9, 39). All these reasons suggest caution in the use of NSAIDs, and oblige us to reconsider the use of these molecules, as much as possible by limiting the dosage and duration of treatment. A further issue of the treatment of bone pain with NSAIDs is the negative effects on skeletal health and healing of the injured skeleton. The mechanism of these side effects is not completely clear, but prostaglandins do appear to result in a relevant role in Wnt signaling pathway required for bone formation in both the normal and fractured bone (44). In animal model, ibuprofen or COX-2 inhibitors have demonstrated to slow down fracture healing of bone fracture (45). Thus inhibition of prostaglandin synthesis might be expected to inhibit bone formation. The extent of the reduction of normal bone formation and fracture healing determined in humans by NSAIDs and COX-2 inhibitors remains to be defined (46). Although the data regarding long-term opioids therapy are far from exhaustive, these medications represent a mainstay in the treatment of patients with moderate to severe pain (7), especially for those elderly patients with gastrointestinal and cardiovascular comorbidities, when other therapies with NSAIDs and COX-2 inhibitors medications are to be avoided (10).

Risks of opioids treatment

All the active drugs on the central nervous system (CNS) administered to osteoporotic elderly patients can determine fall-related injuries (11). Often falls have many different causes resulting from the interactions between intrinsic or extrinsic risk factors (12-14). The intrinsic risks as functional impairment or balance disorders represent the common features of the frail elderly osteoporotic patient. The extrinsic risks are often linked to treatment as the adverse drug reaction. Several studies have documented that there is a relation between falling and the number of drugs used (15, 16). Drugs with central nervous system (CNS) side effects, such as benzodiazepines, antidepressants, neuroleptics, anticonvulsants (15, 16) and opioids (17) are known to increase the risk of fractures and fall-related injuries. Frequently the CNS effects of opioids happen starting opioid therapy or during substantial dose escalation. Almost always after a few days of treatment, opioids tolerance relives CNS symptoms. In people with comorbidities such as dementia or in those who receive other sedating medications, CNS effects can persist over time (22). Although opioids can be essential in the treatment of moderately severe chronic pain, is even to account the endocrinological consequences during long-term and/or high-dose treatment (18). While opioids relieve the osteoporotic pain, osteoporosis is itself a symptom of hypogonadism (18). The chronic opioid treatment in premenopausal women can lead to osteoporosis, infertility, and increased cardiovascular risk, in postmenopausal, may contribute to depressed mood and diminished libido (19, 20). The risk of osteoporosis and fractures concern female but also male undergoing chronic treatment with opioid medications (21). In animal model is detected the presence of opioid receptors on osteoblasts (26) and similarly mu, delta, and kappa receptor are expressed in human osteoblast-like cells MG-63 (27). Osteocalcin synthesis (OS) is a marker of osteoblast activity, morphine significantly reduces OS and this effect is abolished by concomitant administration of naloxone (27). Decreased serum osteocalcin levels was detected in heroin and cocaine abusing pregnant women (30). Similar low concentration was detected in the umbilical arteries of their newborns, demonstrating the effects of drugs on osteoblasts. Endogenous and exogenous opioid agonists influence gonadal function primarily by modulate the secretion of gonadotropin releasing hormone (GnRH), which regulates the release of luteinizing hormone (LH), and follicle-stimulating hormone (FSH) from the pituitary gland. Extensive preclinical and clinical data show that opioids inhibit the functioning of the entire hypothalamic-pituitary-gonadal axis. A reduction of GnRH decrease progesterone and estradiol in female, and in male testicular testosterone. In woman chronically treated with sustained-release opioids for chronic non-cancer pain LH and FSH are less than 30% in pre-menopausal and less than 70% in post-menopausal subjects, 39% of which also shows a reduction of free testosterone level (19). The opioid therapy hormonal consequences can be sexual dysfunction, menstrual anomalies, infertility, decrease muscle mass, osteoporosis with symptoms like fatigue, weakness, depression, hot flashes and night sweats (23); this syndrome is called opioid-induced androgen deficiency (OPIAD) (29). The prevalence of opioid-induced hypogonadism in patients taking chronic opioid therapy is around 90% (23, 31). Many factors as marijuana, chemotherapy, alcohol, glucocorticoids, cimetidine, ketoconazole, spironolactone and illnesses, including liver and kidney diseases may induce a reduction of sex hormone levels (23). Between the consequences of opioid-induced hypogonadism, the perception of pain and analgesia of therapy are among the least investigated. The testosterone seems to play a role in the perception of pain, indeed on animal model castration would cause increased sensitivity to pain (23) and have an impact on the effect of analgesic opioid therapy (24, 25). These effects are confirmed by restoring the normal pain sensitivity with a testosterone supplementation. Chronic opioid treatment can relapse the hypothalamic-pituitary-adrenal axis, but these effects are not as well characterized as that of the hypothalamic-pituitary-gonadal axis. Main contributor of hypoadrenalism are reduced levels of corticotropin-releasing hormone (CRH), strongly inhibited by opioids (33-35), which can lead to reduced secretion of ACTH from the pituitary (19, 32). Opioids affect, in a dose-related pattern, the capacity of the pituitary gland to respond to CRH, which interfere with adrenal gland production of cortisol and dehydroepiandrosterone (DHEA), even independently of CNS downregulation (19). Up to now low cortisol levels was demonstrated in patients given opioids for acute or chronic pain (36, 37). The risk of bone fracture remains unclear in the population of patient affected by opioid induced endocrinopathy (40).

The crucial choice of opioid

The negative effects of opioids on gonadal function are not the same for all molecule and the choice of drug can be crucial in the treatment of patients with chronic pain (28). First of all, men and women have different mechanisms of hormonal disturbance caused by opioids. OPIAD is thought to affect 230,000 to 5 million men who are taking long-term opioid therapy for chronic non-cancer pain in the United States (50). Women are not immune to OPIAD, which is only more frequent in man (21). Specifically methadone has significant endocrinopathic effects in patients there was a dose dependent decrease on testosterone levels, but only in men (47). Similarly, morphine has one of the worst depressant effect on te-

stosterone and cortisol: these effects are quickly reversible in a matter of hours or days. The data shows that after a few hours following administration of single dose has been reached castration levels of testosterone (18). In contrast to the previous opioids, in animal model buprenorphine does not reduce the testosterone levels compared to saline injection, on the contrary morphine, fentanyl, or tramadol administration significantly decrease hematic hormone levels (48). These data were corroborated by a clinical trial with transdermal buprenorphine, where in females all hormones showed slight changes during the observation period of 6 months. The only exception, in males, was the free testosterone, which appeared to have decreased after 3 months, but was encouraging the absence of significant differences for any other hormones. In both sexes the hypothalamic-pituitary-adrenal axis was not inhibited, since cortisol progressively increased during treatment. The most recent synthesized centrally acting analgesic is tapentadol with a dual mode of action mediated by the agonist effect on mu opioid receptor (MOR), and an action which enhances noradrenergic transmission due to the inhibition of noradrenalin reuptake (NRI, noradrenalin reuptake inhibitor). MOR and NRI activities are performed directly by the mother molecule without metabolizitation and are simultaneous and synergic. Even though the desired effect analgesia is enhanced by synergy, the same does not apply to the adverse effects, which are lesser than with traditional opiates thanks to the moderate MOR agonist effect (μ-sparing effect). A recent study collects data from three randomized, double-blind studies of tapentadol immediate release (IR) or tapentadol extended release (ER) (49). In four-way crossover study in healthy male subjects (study 1), tapentadol IR have the same effects of placebo on testosterone and LH concentration, while morphine IR decrease these hormones. Mean testosterone concentrations were within the normal range at 6 hours after administration of tapentadol IR or placebo. In four-period, dose-escalation study in healthy subjects (study 2), mean testosterone concentrations at 24 hours was similar and within the normal range after the first doses of tapentadol and placebo. In the same manner LH concentrations at 24 hours after the first doses of tapentadol were within the normal reference range. In the forced-titration study in male and female patients with chronic osteoarthritis knee pain (study 3), mean concentrations of testosterone, FSH and LH were comparable at 29 days after treatment with tapentadol ER and placebo. On the contrary, the patient population treated with oxycodone CR shows a greater reduction in the testosterone concentration, which remains below the normal reference range on days 15 and 29 in a greates number of patients. Specifically focusing on different opioids emerges as buprenorphine and tapentadol are promising analgesics, having lowest endocrinopathic effects.

Conclusions and clinical implications

Opioids represent one of the first choice drug for relieving moderate to severe pain precipitated by osteoporosis. Despite published guidelines and WHO's pain ladder the treatment of chronic pain from osteoporosis put specialist in front of a lot of tough choices, which often follow multidisciplinary perspective. Non-pharmacological interventions, such as psychological therapies (e.g. cognitive behavioural therapy) or physiatric approach, can also be particularly useful in the treatment of chronic pain. Surely today there is no single ideal drug to treat elderly population with pain caused by osteoporosis, while it is necessary to develop a clinical strategy able to answer adequately to pain and suffering. In clinical practice, a specialized and multidisciplinary approach, which includes the careful selection of individual and meticulous monitoring make it possible to provide opioids to almost all osteoporotic patients who can benefit. For the future will need to develop research to better define the role of opioid drugs in that context, molecules with a lower osteoporotic effect than others and strategy to define and antagonize the gonadal effects of therapy.

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