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

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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. Upto now it is estimated that over 200 million people worldwide suffer from osteoporosis (1). Loss of bone mass is one of the most feared complication 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-
receptors on osteoblasts (26) and similarly mu, delta, and kappa cern female but also male undergoing chronic treatment with opioid diminished libido (19, 20). The risk of osteoporosis and fractures con- lead to osteoporosis, infertility, and increased cardiovascular risk, osteoporotic pain, osteoporosis is itself a symptom of hypogonadism term and/or high-dose treatment (18). While opioids relieve the CNS effects can persist over time (22). Although opioids can be drugs, 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 hypotalamic-pituitary-adrenal axis, but these effects are not as well characterized as that of the hypotalamic-pituitary-gonadal axis. Main contributor of hypoadrenalinism 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 billion 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, fen-tanyl, 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 noradre-nalin reuptake (NRI, noradrenalin reuptake inhibitor). MOR and NRI activities are performed directly by the mother molecule without metabolization 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 (ERI) (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 adminis-tration of tapentadol IR or placebo. In four-period, dose-esca-lation 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 tapen-tadol were within the normal reference range. In the forced-titra-tion study in male and female patients with chronic osteoarthri-tis knee pain (study 3), mean concentrations of testosterone, FSH and LH were comparable at 29 days after treatment with tapen-tadol ER and placebo. On the contrary, the patient population trea-ted with oxycodone CR shows a greater reduction in the testo-sterone concentration, which remains below the normal referen-ce range on days 15 and 29 in a greates number of patients. Specifi-cally focusing on different opioids emerges as buprenorphine and tapentadol are promising analgesics, having lowest endo-crinopathic effects.

Conclusions and clinical implications

Opioids represent one of the first choice drug for relieving moderate to severe pain precipitated by osteoporosis. Despite published gui-delines 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-pharmacologi-cal interventions, such as psychological therapies (e.g. cognitive behavourial therapy) or physisiatic 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 prac-tice, 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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All other Authors declare that they have no conflicts of interest.

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