Use of opioids for treatment of osteoporotic pain

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Summary

The prevalence of osteoporosis increases markedly with age: currently it is estimated that over 200 million people suffer from osteoporosis worldwide. One of the most feared and more frequent complications of osteoporosis is pain, which affects 85% of patients. Commonly in the treatment of chronic pain the therapeutic strategy is based on a three-ladder approach, involving opioids for moderate and severe pain. As proposed by the World Health Organization (WHO), according to the intensity of chronic pain, analgesic treatment can be established. Despite the debate and updates to the analgesic ladder for pain published in 1986 by the WHO, the benefits resulting from its worldwide use are uncontested. In case the pain was not responsive to drugs of pain ladder, is necessary to resort to specialized practices (e.g. subarachnoid infusion of drugs). The oral route for administering analgesics should be preferred, provided that the patients are able to use it. About 50% of all opioid users experience at least one side effect, and more than 20% discontinued treatment due to a serious adverse event. Despite published guidelines and WHO's pain ladder for the management of chronic pain, the treatment of this condition remains suboptimal. Given the physiopsychopathology and complexity of the problems of chronic osteoporotic pain, a multimodal and multidisciplinary approach is still considered the best way to diagnose and treat this disease.

KEY WORDS: chronic pain; bone pain; opioids; osteoporosis.

Introduction

The prevalence of osteoporosis increases markedly with age, from 2% at 50 years to more than 25% at 80 years in women. Currently it is estimated that over 200 million people worldwide suffer from osteoporosis (1). In the United States, more than 40 million people either already have osteoporosis or are at high risk due to low bone mass (2). The National Institute for Health and Clinical Excellence (NICE) estimates there are 2 million women with osteoporosis in England and Wales (3). Approximately 30% of all postmenopausal women have osteoporosis in Europe and at least 40% of these women (4) and 15-30% of men (5) will sustain one or more fragility fractures in their remaining lifetime. One of the most feared complications of osteoporosis is pain. Approximately 85% of the patients with osteoporosis is affected by bone pain (6), in particular low back pain is considered the prevalent musculoskeletal pain, particularly in elderly populations (7).

Approach to pain relief

The most common used therapeutic strategy in the treatment of chronic pain is based on a three-ladder approach, involving the use of opioids for moderate and severe pain. As proposed by the World Health Organization (WHO), according to the intensity of chronic pain, analgesic treatment can be established. For mild pain (NRS ≤3) is recommend the use of NSAIDs or acetaminophen with the possibility of adding the adjuvants; for moderate pain (NRS comprised equal to 4-6), is suggested a treatment with weak opioids integrated with or without NSAIDs or acetaminophen, and with the possibility of adding adjuvants. In case of severe pain (NRS >6), the WHO plans to undertake a more integrated opioid treatment with NSAIDs or paracetamol, with the possibility of adding adjuvants. Adjuvant drugs are a class of molecules which can contribute to the reduction of pain, enhancing the effect of analgesics. Among adjuvants we can include bisphosphonates, antiepileptics, corticosteroids, antidepressants, benzodiazepines, and other classes of drugs. These drugs from time to time, according to the determinants of pain, may become the first line of treatment (e.g. bisphosphonates in osteoporotic fractures or antiepileptic drugs in neuropathic pain). This strategy has proved as effective to treat chronic pain, suggesting that the treatment should prevent the onset of pain with drugs administered at fixed times according to half-life and duration of action of different formulations. Moreover this medicament could be easy to administer (preferably by mouth), customizable to the needs of patient. Despite the debate and updates to the analgesic ladder for pain published in 1986 by the WHO, the benefits resulting from its worldwide use are uncontested (8, 9). In case the pain was not responsive to drugs of pain ladder, is necessary to resort to specialized practices (e.g. subarachnoid infusion of drugs).

The role of anti-inflammatory drugs (NSAIDs)

Among the most commonly prescribed drugs in the world (10), the non-steroidal anti-inflammatory drugs (NSAIDs) are usable to

all steps of the pain ladder. Seventy percent of the elderly patients and nearly 20% of hospitalized patients are treated with NSAIDs (10, 11). A recent meta-analysis suggests some relevant data, cox selective drugs increase the risk of major vascular events about a third, inducing a rise of about three-quarters of the risk of major coronary events (12). High dose of diclofenac has similar vascular risks to the average coxibs regimen studied (12). All NSAIDs doubled the risk of heart failure, causing hospital admission and increase the risk of upper gastrointestinal complications by around 2-4 times (12). NSAIDs may trigger different gastrointestinal lesions with or without clinical manifestations, causing 16.500 deaths every year in the USA, comparable to the number of deaths from acquired immunodeficiency syndrome (AIDS). All these reasons suggest caution in the use of NSAIDs, and oblige to reconsider the use of these molecules, as much as possible by limiting the dosage and duration of treatment.

The role of second step of the analgesic ladder

In the treatment of moderate pain the WHO recommends the application of the second step characterized by weak opioids. Codeine and tramadol are representative of weak opioids. These drugs, to carry out their analgesic action, must be transformed through an oxidative process mediated by cytochrome P2D6 into an active intermediate, respectively O-desmethyltramadol for tramadol and morphine for the codeine. The analgesic efficacy of tramadol and codeine is not always predictable for at least three reasons:

1. The CYP2D6 is deficient in approximately 10% of Caucasians (13)
2. Many drugs may play an inhibitory effect on CYP2D6 (e.g. amiodarone, fluoxetine, paroxetine, sertraline, promethazine) (14)
3. A number of individuals are ultra rapid metabolizers for the presence of multiple copies allelic functional or promoter mutated (13).

These reasons (along with the consideration that the O-desmethyltramadol and morphine are major opioids) can make us consider the possibility to skip the second step by treating the patients with small doses of opioids of the third step of the ladder.

Opioids of third step of analgesic ladder

Today the third step of pain ladder opioids are marketed in reduced doses, even in modified release formulation, so on several occasions it can be taken in place of codeine and tramadol. In chronic pain the oral route is to be preferred route of analgesic administration when a patient is physically able to take oral medication. Transdermal patch of opioids is appropriate in the setting of continuous pain in patients who cannot use the oral route of administration. In opioid-naive patients, opioids should be started at a low dose and titrated slowly, to minimize risk of opioid related adverse effects. Long-acting opioids with around-the-clock dosing could provide more consistent control of pain, lower risk of addiction or abuse and improved adherence (15).

Oral morphine

Oral morphine is considered the gold standard “step 3” opioid (8) and has been placed by WHO on its Essential Drug List. Morphine is one of 20 alkaloids isolated from opium 200 years ago, It has poor oral bioavailability of 20 to 30% and is metabolized in the liver generating three metabolites, morphine-6-glucuronide (M6G), a potent analgesic, morphine-3-glucuronide (M3G), which is not analgesic but is neuroexcitotoxic and can actually cause hyperalgesia and allodynia and normorphine, which is also analgesic. Morphine metabolites are excreted in urine and bile, M6G is a more potent analgesic than morphine and accumulates to a higher serum concentration with chronic administration. Elimination half-life is normally 2 to 4 hours. However the real difficulty in the use of oral morphine is due to the hepatic first pass metabolism, which could cause an unpredictable analgesic or toxic effect. Morphine could induce histamine release triggering itching and vasodilatation with hypotension in hypovolemic patients and problems in patients with asthma and atopy. In general, duration of analgesia or risk of adverse events increases with aging, and plasma levels were 15% higher in those older than 65 years.

Tapentadol

Tapentadol is an innovative centrally acting analgesic that combines two distinct mechanisms of action, μ-opioid receptor agonism (MOR) and noradrenaline reuptake inhibition (NRI). The synergistic interaction of the two combined effects (MOR-NRI) offers particular advantages in terms of efficacy and tolerability. Analgesia is obtained at different levels through modulation of the opioid system and the descending inhibitory noradrenergic systems. The two mechanisms of action result in different modulation of acute and chronic pain. The μ-opioid agonism is, in fact, primarily effective in controlling acute pain, whereas noradrenaline reuptake inhibition is mainly implicated in modulating chronic and neuropathic pain. The MOR-NRI mechanism of action can give advantages in terms of tolerability. Tapentadol’s noradrenergic components have an opioid-sparing effect, thus reducing GI adverse effects compared to traditional opioids (constipation, nausea and vomiting). The safety profile is improved by the fact that no relevant interactions with enzymes of the P450 cytochrome system have been registered. The drug binding to plasma protein is low, reducing pharmacokinetic interaction with other medications. Clinical trials have consistently demonstrated the efficacy and tolerability of tapentadol-prolonged release (PR) (100-250 mg bid) in the management of moderate to severe chronic pain caused by osteoarthritis, low back pain, diabetic neuropathy and cancer pain.

Oxycodone

Oxycodone is about two times more potent than morphine. It is a semisynthetic opioid. Oxycodone have high oral bioavailability between 60 and 87%, which is caused by reduced first pass hepatic clearance and is not due to increased absorption. Oxycodone predominantly binds to albumin for 45%, in a non-dose dependent manner. Oxycodone is excreted through the kidneys and his elimination is significantly influenced by the hepatic blood flow Two slow and one immediate-release formulation are available, the latter combined with paracetamol. The modified release oxycodone is sold with or without naloxone, relying on the same principle of release. Oxycodone naloxone combination

(OXN) is a new oral formulation that combines prolonged-release oxycodone and prolonged-release naloxone in a ratio of 2:1. This innovative formulation has born to counteract opioid-induced constipation development. Naloxone has a minor bioavailability than 2% after oral administration, due to the extensive first pass metabolism. This metabolism accounts the absence of withdrawal symptoms and the full analgesic effect. The oral naloxone action depends on normal liver function, any hepatic impairment should be of concern. Several clinical trials demonstrated that OXN offer the same analgesic efficacy of oxycodone, reversed the constipation effect in comparison to this last.

Buprenorphine

Buprenorphine is highly lipophilic, semi-synthetic opioid derived from thebaine. It is a partial agonist, but at the doses used for analgesia behaves as an agonist with very high affinity for the mu opiate receptors (MOP). It is 30 to 40 times more potent than morphine, because of its high affinity for MOP, may block the effect of other opioids. For this reason, during the phase of opioids rotation will provided more attentions. A transdermal patch produces 72/96 hours of systemic drug delivery through the skin and should be reserved for those patients who cannot swallow or are unable to tolerate other oral opioids. Buprenorphine is metabolized in the liver and its pharmacokinetic is not altered in the course of renal failure.

Hydromorphone

Hydromorphone is a semisynthetic opioid, its average bioavailability is 50%, in the oral route of administration. Hydromorphone potency is about five-fold higher than that of morphine, its metabolism doesn't produce active metabolites. The principal hydromorphone metabolite is inactivated in the liver and then excreted by the urinary system. Hydromorphone represents an effective alternative to oral Morphine, but different studies have not shown any advantages of hydromorphone, over others opioids.

Fentanyl

Fentanyl is 100 times as potent as morphine and is a highly lipophilic, short-acting opioid derivative of meperidine. The hepatic metabolism does not produce active metabolites, excreted in the urine. A transdermal patch produces 72 hours of systemic drug delivery through the skin, but occasionally the duration of analgesia may not exceed 48 hours. Fentanyl patches should be reserved for those patients who cannot swallow or are unable to tolerate other oral opioids. After the first application could be necessary wait 24 hours to get analgesic effect. The elimination half-life after removing the patch is at least 17 hours because of drug sequestration in adipose tissue. Initial dose calculation for switching from another opioid should be based on the calculated 24-hour morphine equivalent dose. Concomitant use of CYP3A4 inhibitors (nelfinavir, ritonavir, diltiazem, itraconazole, ketoconazole, troleandomycin, nefazadone and clarithromycin) may result in high plasma fentanyl concentrations and increased adverse drug effects.

Methadone

Methadone is a synthetic opioid, used primarily as a maintenance treatment for heroin addiction. Methadone is characterized by a large inter-individual variation in pharmacokinetics and by a rapid and extensive distribution phases (half-life of 2–3 h) followed by a slow elimination phase. This pharmacokinetic profile may cause accumulation problems if doses are too large or the dosing intervals are too short over a long period of time. Methadone provides the potential to control pain that does not respond to other opioids because methadone shows incomplete cross-tolerance with other opioid receptor agonist analgesics. Methadone represents an effective alternative to other opioids, but more caution is needed in its administration and in many ways its use is reserved for specialists.

Opioid complications and side effects

About 50% of all opioid users experience at least one side effect, and more than 20% discontinue treatment due to a serious adverse event (16). Common side effects of opioids include constipation, nausea, vomiting, pruritus, delayed gastric emptying, dizziness and sedation. Opioid-induced constipation mostly does not improve with time, as tolerance to this side effect generally does not develop. Less common side effects include sweating, urinary retention and hypogonadism (reduced testosterone, oestrogens, luteinizing hormone and gonadotropin releasing hormone) (17). Tolerance is one of the common adaptive phenomenon to opioid treatment. This complication should not be seen in a negative perspective only, because induce a reduction and disappearance of the side effects that often plague the early stages of treatment. In a negative sense opioid tolerance induces the development of reduced effect of the same dose of opioids when used over time. If during treatment a tolerance problem appears, the first approach is to increase the dosage of the opioid, ensuring the maintenance of other therapeutic procedures capable of relieving pain (18). Whereas it could present a real dose escalate, a switch in opioid can be tried, because clinical experience suggests that cross-tolerance among the various opioids can be incomplete (18). On the contrary of tolerance, physical dependence is the development of an altered physiological state that is revealed by an opioid withdrawal syndrome, which should be expected in case of abrupt discontinuation of therapy. Patients may report feeling "sick" with abdominal cramps, diarrhoea, piloerection, sweating, nausea, vomiting, muscle pain, lacrimation, agitation and anxiety or tremor (19). The use of opioids always presupposes the suspension through a gradual reduction of the dose, otherwise the appearance of a withdrawal syndrome. Addiction, or psychological dependence, is a complex neurobiological process, denoted by loss of control over drug use, characterized by the compulsive use, craving, and continued use despite harm suffered (20, 21). On the contrary some specialists use the term "pseudoaddiction" to describe a reversible condition in which patients is undertreated for chronic pain. This erratic behaviour resolves once the pain is controlled (22).

Toward individualized analgesic therapy

Prerequisite is that chronic pain should obtain the same level of importance and care as the disease that caused it (23). To

overwhelm the difficulties associated with the management of chronic pain, the physician must efficiently adapt treatment, through a personalization of the pain treatment after evaluating each individual's pain history and assessing the consequences of pain to the patient. This would involve a review of drug history, physical examination, previous diagnostic studies, and assessment for co-existing diseases or conditions. In addition to pharmacological treatment strategies should be considered non-pharmacological treatment options. These embrace physical rehabilitation programmes and behavioural management in a biopsychosocial approach to pain management that dynamically involves the patient in the plan of care (24).

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 for the management of chronic pain, the treatment of this condition remains suboptimal (23). Factors contributing to poor pain management include problems related to healthcare systems, healthcare professionals and patients (24, 25). Healthcare professionals may have insufficient knowledge of pain assessment and management, as well as concerns regarding the regulation of uncontrolled drugs, patient vulnerability to addiction or tolerance to treatment, and adverse effects of analgesia (constipation, nausea, vomiting, dizziness etc.). Monitoring of opioid therapy employed is the main strategy to reduce and avoid the risk of diversion (23). The risks of causing dependence or tolerance problems should not be considered obstacles to use of these drugs. Even though opioids are attractive as analgesic agents, their use should be carefully monitored and should be considered temporary. Since the physiopsychopathology and complexity of the problems of chronic osteoporotic pain, a multimodal and multidisciplinary approach is still considered the best way to diagnose and treat this problem.

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