The role of drugs in bone pain

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Summary

Painful symptomatology in the skeletal system can be found in various pathological conditions and can be either localised or diffused. Bone tenderness is common in those who are of an elderly age.
Treatment strategy. **Patients should be informed of the possible causes of their pain and the different therapies that could alleviate it; furthermore they should be encouraged to have an active role in their therapy. It is necessary to prevent the onset of the pain (by the clock) by considering the biological half-life, the bioavailability and the duration of action of the therapy.**
According to the World Health Organization (WHO), pain treatment is based on a three-step ladder.
Adjuvant therapies. **Adjuvant therapies are often associated with the drugs in the WHO three step ladder. This heterogeneous group of non-analgesic drugs is used in the treatment of bone pain by bettering the analgesia or reducing the side effects brought on by analgesics.**
Conclusion. **In the daily struggle that doctors face to treat their patients, pain management should not be disregarded. Among the various types of pain, bone pain, must not be underestimated but be fought against by using all means available. Patients need to be treated depending on the severity of their pain, NSAIDs should be the preferred choice of treatment for acute pain but not for that of chronic pain. In the case of chronic pain opioids should be used in their most recent fomulations as they can guarantee fewer side effects. Patients should also be prescribed adjuvant drugs as well as being given psychological support in order to ensure successful treatment.**

KEY WORDS: bone pain; drug therapy.

Introduction

Pain is an unpleasant sensory and emotional experience, associated with actual or potential tissue damage, or described in terms of such damage (IASP). Depending on its duration pain can be classified as acute or chronic, though according to aetiology it is classified as nociceptive, neuropathic and idiopathic. Painful symptomatology in the skeletal system can be found in various pathological conditions and can be either localised or diffused. Bone tenderness is common in those who are of an elderly age. In fact, as a person ages muscular mass and bone density tend to decline while nociceptors which innervate the bone remain mostly intact. This predisposes to lesions caused by wear and tear and fractures. Common bone pain can be triggered by temperature differences, excessive sedentary behaviour, hormonal changes (e.g. menopause) and bad posture habits. Sensations of numbness or heaviness can be caused by infective diseases, such as seasonal flu. Bone pain is a symptom of arthritis, a degenerative process of the cartilage which covers the bone ends of joints. The painful symptoms of this chronic disease are usually worsened by damp-cold, strain and poor posture. At times, bone pain is associated with disease that compromises the structure and regular functioning of bones. Osteoporosis, hyperparathyroidism, osteomalacia, rickets, *osteogenesis imperfecta* and Paget's disease of the bone are a few of these. Bone pain can also be caused by multiple myeloma, leukemia, primary bone cancer and metastatic cancer. The difference between bone pain and muscular and joint pain can be attributed to the fact that bone pain may occur during physical activity and rest. Causes of bone tissue pain can be:

- fractures
- alteration in bone mineralization density
- neoplasm bone metastasis and bone cancer
- blood disorders
- infections
- leukemias.

Treatment strategy

Patients should be informed of the possible causes of their pain and the different therapies that could alleviate it; furthermore they should be encouraged to have an active role in their therapy. It is necessary to prevent the onset of the pain (by the clock) by considering the biological half-life, the bioavailability and the duration of action of the therapy. It is best to prescribe a therapy which is simple to be administered and easy for both the patient and their family to manage. Oral administration should be the first choice. Where opioids are prescribed then it is important to talk to the patient and their family about any fears they may have over taking this type of medication. Correct information and patient involvement in symptom management improves communication and has a beneficial effect on the pain experience. It is important to consider an alternative route for administration when oral administration is not possible (e.g. due to vomiting, bowel obstruction, severe dysphagia, and poor pain control that requires rapid dose escalation). Preventing and treating possible side-effects is also necessary. Therapies should be personalised: the dosage, type and method of administration ought to be chosen based on the needs of each

individual patient. The stage of the illness, the overall condition of the patient, other pathologies, characteristics of the pain and the psychological state and culture of the patient are all factors which must be taken into consideration for personalised pain management. The standard treatment mainly consists of two substance groups:
"Non-opioid analgesics": where the peripheral effect is greater than the central effect;
"Opioids": where the central effect is greater than the peripheral effect, without the ceiling effect;
Ceiling effect: when a drug reaches a maximum effect and increasing the drug dosage does not increase its effectiveness, the side effects of the drug, however, may worsen. Adjuvant drugs, drugs that are not typically used for pain but may be helpful for its management, are also taken into consideration. According to the World Health Organization (WHO), pain treatment is based on a three-step ladder:

Step I: MILD PAIN – NON-OPIOIDS (associated or not with adjuvants): acetylsalicylic acid, paracetamol, NSAIDs.
Step II: MILD TO MODERATE PAIN – MILD OPIOIDS: codeine, dihydrocodeine, tramadol, dextropropoxyphene.
Step III: MODERATE TO SEVERE PAIN – STRONG OPIOIDS: morphine, methadone, hydromorphone, oxycodone, fentanyl transdermal, transmucosal fentanyl.
Transition from Step I to Step II and from Step II to Step III occurs as pain increases.

Non-opioid therapies

Non-opioids (WHO Step I), including NSAIDs (non-steroidal anti-inflammatory drugs) and paracetamol are recommended for treating mild pain. Each patient can respond differently to treatment with these drugs, and so the choice of therapy should be based on a previous positive response from the patient regarding a specific analgesic. Usually, the administration of only NSAIDs as an analgesic is indicated for a period of 3-5 weeks because of the lack of effectiveness of this drug over a long period and the side effects which can occur from long-term use at high doses. Increased pain intensity and ineffective pain management indicate a need to introduce opioids.

Mild opioid therapies

Weak opioids most frequently used are codeine, dihydrocodeine, tramadol and dextropropoxyphene (WHO Step II). Unlike strong opioids, which are universally recognised as a treatment of moderate-severe pain, there is no general consensus concerning the efficacy of mild opiods as a treatment of mild-moderate pain. The controversal aspects are: the absence of data which proves the efficacy of mild opioids there are few available studies which demonstrate any real advantages of weak opioids rather than opioids drugs in Step II are often given in lower doses in combination with non-opioids such as paracetamol or NSAIDs. The cost of the drug outweights the benefits it guarantees. One of the most talked about questions is the difference, in terms of analgesic efficacy and tolerability, between "weak" opioids and low doses of strong opioids in treatment for mild-moderate pain. Some studies have shown that switching directly from non-opioids to strong opioids reduces the number of days on which pain intensity is medium-high (values of 5 to 7 on a 0 to 10 point scale), a reduction however that is associated with an increase in complications like anorexia and constipation.

Strong opioid therapies

For moderate-severe pain treatment the opioid of first choice is oral morphine. Aside from the oral route it can also be administered subcutaneously or intravenously in cases where the subcutaneous route is counterindicated or the patient has a central venous catheter. For patients in need of regular doses of morphine then continuous subcutaneous administration is the best route. There are, however, valid alternatives to morphine: methadone, in patients who do not respond to morphine or other opioids or as a substitute for these when they cause side effects such as myoclonus, sedation, confusion, nausea and vomiting. More caution must be taken when administering methadone than with morphine. High doses or frequent doses over a long period of time can cause problems with toxicity which can have side effects including respitory distress and changes in cardiac rhythm. Hydromorphone, in patients who require high dose of morphine (the analgesic potency of hydromorphone is roughly 5 times that of morphine), whose pain is difficult to treat, who suffer from side effects or cannot have a therapy which involves more than one administration per day of opioids. Oxycodone, available in slow-release or immediate-release formulations, the latter in combination with paracetamol. The actual role and added benefits this combination has as opposed to oxycodone alone are still be clarified. Transdermal opioids (administered via a patch containing the required opioid) offer an interesting alternative to oral morphine for cancer patients with chronic pain. Compared to morphine, fentanyl transdermal (TDS) seems to have less side effects on the gastrointestinal tract and in particular constipation. This formulation is counterindicated in the management of breakthrough pain as the drug is released slowly and continuously from the patch. Buprenorphine is a suitable solution for transdermal patch administration. Transmucosal fentanyl (OTFC) is a formulation in which the fentanyl is embedded in a sweetened matrix that is dissolved in the mouth (also known as the fentanyl lollipop). It is immediate release with the analgesic effect being obtained within 5-10 minutes. Its use is limited to breakthrough pain management in patients already undergoing a strong opioid therapy for chronic pain.

Adjuvant therapies

Adjuvant therapies are often associated with the drugs in the WHO three step ladder. This heterogeneous group of non-analgesic drugs is used in the treatment of bone pain by bettering the analgesia or reducing the side effects brought on by analgesics. Adjuvant therapies are usually administered for neuropathic pain, that is, for acute or chronic pain caused by a primary lesion or dysfunction of the nervous system. Neuropathic pain in cancer patients can result as a consequence of therapy (chemotherapy or radiotherapy) or due to progression of the disease. Even though a large number of adjuvant drugs have been shown to have analgesic properties, to date this evidence has not been universally confirmed on cancer patients. Tricyclic antidepressants (amitriptiline, imipramine, desipramine) have demonstrated analgesic efficacy in various neuropathic syndromes such as postherpetic neuralgia or diabetic neuropathy, their efficacy, however, upon malignant neuropathic pain is less clear. Corticosteroids are often prescribed to cancer patients even though their efficacy on pain management has only been demonstrated in few clinical trials. Some of these trials, however, have shown that dexamethasone is effective in managing pain from metastatic spinal cord compression and in treating headaches due to increased intercranical pressure. Antiepileptic drugs (carbamazepine, fenitoina, sodium valproate, clonazepam, gabapentin) are used to treat neuropathic pain which is defined as "stabbing" or "shooting",

however, also in this case there is not enough clear evidence on their efficacy of neuropathic cancer pain. Gabapentin would seem to increase the analgesic efficacy of opioids used to treat cancer patients suffering from neuropathic pain. Concerning local anesthetics, lidocaine and other oral local anesthetics are safe drugs for neuropathic pain management, they are more effective than the placebo and have analgesic properties similar to those of other analgesics. Future clinical trials should enlist patients tumoral pathologies in order to demonstrate if they are indicated in cancer patients. Different studies have shown the effectiveness of bisphosphonates in the prevention of skeletal related complications, the reduction in the need for orthopedic surgery following fractures and radiotherapy and in cases of bone metastases where pain was not effectively managed by analgesic treatment or radiotherapy. The scarce number of studies with relevant data means which bisphosphonates are the most effective and what their efficacy concerning primary tumours is cannot be determined. In patients with diffuse bone metastases and pain that is difficult to manage with radiotherapy then treatment with beta emitting radiopharmaceuticals such as stronzio-89, samario-153 and renio-188 should be taken into consideration. Although the mechanism of action of these radiopharmaceuticals in relieving bone pain is not completely known, a possible explanation is that the perception of pain is reduced due to a decrease in the number of cells involved in inflammatory reactions.

Corticosteroids

Corticosteroids have a moderate analgesic effect in cancer patients. However, given the exiguity of reported studies, the evidence is low grade. The clinical guidelines that recommend the use of steroids in cancer pain are based on expert opinion rather than evidence. A moderate dose of dexamethasone (8 mg/day) appears to be well tolerated for about 7 days, but higher doses for several weeks can lead to the onset of significant side effects and increase mortality. This is because the toxicity increases with dose and duration of therapy. Literature data show that the analgesic effect on pain occurs within 5-7 days. If not observed any benefit, therapy should be suspend. The decision to introduce a steroid therapy should be individualized for each patient and should take into account his clinical status, comorbidities and concomitant therapies, assessing the possible benefits and risks to which steroid therapy could bring. The most used steroid is the dexamethasone.

Anticonvulsants and antidepressants

The use of these drugs (gabapentin, pregabalin or amitriptyline) could be considered in cancer patients with pain of a neuropathic component, although evidence is scarce (see Neuropathic pain).

Muscle relaxant

Muscle relaxants are used especially for pain due to muscle hypertonia, for which morphine has no effect. Benzodiazepine, but in particular diazepam is used (Valium®), otherwise muscle relaxants like baclofene (Lioresal®) or tizanidine (Sirdalud®) are used.

Bisphosphonates

Bisphosphonates act as bone resorption inhibitors and they increase bone mineral density; they should be considered as a part of the therapeutic regimen for the treatment of patients with/without pain due to metastatic bone disease. The most widely used bisphosphonate in oncology is zoledronic acid (Zometa®), followed by ibandronate sodium and pamidronate. Zoledronic acid not only reduces the risk of pathological fractures, but also significantly reduces bone pain from metastases. Recent studies have confirmed that clodronate is also very useful in reducing pain caused by vertebral fractures, algodystrophy, bone metastases, rheumatoid arthritis, transient osteoporosis and in shoulder pain. Preventitive dental measures are necessary before starting bisphosphonate administration. The main counterindications are periodontal infections due to the risk of osteonecrosis, kidney failure and hypocalcemia. After the first intravenous administration, pain may appear or existing pain may intensify; patients should be informed of this and the necessary prescriptions made. A new therapy being used is denosumab, a targeted RANK-L inhibitor which could be considered as a valid alternative to bisphosphonates for the treatment of patients with/without pain due to metastatic bone disease. This type of therapeutic approach merits further study. Also the prescriptions of denosumab should be started after preventitive dental measures.

Conclusion

In the daily struggle that doctors face to treat their patients, pain management should not be disregarded. Among the various types of pain, bone pain, must not be underestimated but be fought against by using all means available. Patients need to be treated depending on the severity of their pain, NSAIDs should be the preferred choice of treatment for acute pain but not for that of chronic pain. In the case of chronic pain opioids should be used in their most recent fomulations as they can guarantee fewer side effects. Patients should also be prescribed adjuvant drugs as well as being given psychological support in order to ensure successful treatment.

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