Three case reports of chronic pain with neuropathic component — the importance of individualized therapy

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ABSTRACT

Background: Pain is the most common symptom present at any stage of life. The pain can be divided into acute or chronic considering the duration of symptoms. Chronic pain approach is complex and it is a clinical challenge. Two main mechanisms are traditionally described: pain nociceptive (caused by ongoing tissue damage, somatic, or visceral) or neuropathic (damage or dysfunction in the nervous system). For the treatment of chronic moderate-severe pain, opioids are the standard treatment but the undesirable side effects cause a high discontinuation rate. Tapentadol was developed to improve the therapeutic range of opioids by adding two complementary mechanisms of action which seem to contribute to the reduction of side effects.

Case Presentation: The authors describe three cases of neuropathic chronic pain. One case describes neuropathic pain caused by degenerative changes and osteoporotic fracture, the second case was a woman with an important renal impairment, who complained of generalized arthralgia (under cancer treatment), and a third case of a man presented with diminished muscle strength in the lower right limb, most probably due to chemotherapy-induced peripheral neuropathy.

Conclusion: The management of chronic pain requires a multimodal approach, that is part of the individual as a whole, and a multidisciplinary approach is needed to relieve chronic pain with minimal side effects.

Keywords: Pain, neuropathic pain, cancer, analgesics, opioid, case report.

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Background

Pain is the most common symptom present at any stage of life. It is understood as a protective mechanism for survival, functioning as a warning signal against possible damage to the body. It is a difficult symptom to classify since it has a subjective and emotional experience base [1].

Pain can be acute or chronic considering the duration of symptoms. Chronic pain, a disease, has a duration of more than 3 months and requiring a multi-therapeutic and multidisciplinary approach. Chronic pain has a strong impact on the quality of life; restrictions on activities of daily living (ADL), social and professional life, sleep disorders, anxiety and depression, with a high number of direct and indirect costs for the individual and society. Pain is termed as nociceptive when it is caused by ongoing tissue damage (somatic or visceral) or neuropathic [1,2]. The International Association for the Study of Pain defined neuropathic pain (NP) as "pain caused by a lesion or disease of the somatosensory nervous system." NP could have various etiologies and can be peripheral (peripheral nerves' damage or dysfunction) or central (central lesion or disease). In Europe, chronic pain affects about 25%–30% of the population and 20% of which are NP [3-5].

Chronic pain approach is complex and it is a clinical challenge. European Pain Federation position on appropriate opioid use in chronic pain management stated that poorly controlled pain is a global public health issue [6,7]. Opioids have been the standard treatment for moderate-severe chronic pain and were also recommended when other therapies were unsuccessful [7,8]. The management of NP or chronic pain with neuropathic component was based on opioids, as first-line, usually requiring high doses and combination with adjuvant drugs (if incomplete response to opioid), which normally had a modest effect. [9]. Moreover, due to the undesirable side-effects, high discontinuation rates had been recorded, having gastrointestinal and central nervous system side-effects the main factors responsible for that. Some patients with refractory pain or moderate-severe adverse events with opioids can benefit from interventional therapies [10].

Tapentadol was developed in an attempt to improve the therapeutic range of opioids by adding two complementary mechanisms of action in a molecule: μ-opioid receptor agonist and inhibition of noradrenaline reuptake. The first one disrupts pre- and post-synaptic transmissions of the ascending pain pathway and centrally activates downstream inhibitory projections (effective in moderate-severe acute pain). The second one increases the concentration of noradrenaline in the synaptic cleft, increasing the inhibition of pain in the descending pathway (useful in chronic

NP). This mechanism reduces the opioid burden, which seems to contribute to the reduction of side-effects [11–13]. Several studies have shown the action of tapentadol in chronic pain [11–15].

The goal of this paper was to present three cases of NP, which represented a challenge and pretended to illustrate the difficulty in evaluation and treatment of this disturbing symptom.

Case Presentation

A 60-year-old female patient, with a medical history of depression, osteoarticular degenerative disease, and obesity, reported moderate localized lumbar pain, with no radiation; she started diclofenac (50 mg every 8 hours). As the pain worsened, became more intense, with left lower limb irradiation and *de novo* claudication, the patient sought medical advice. Paracetamol/thiocolchicoside (500 mg/2 mg; two tablets tid), associated with anti-inflammatory drugs (AIDs) were prescribed. After 5 days, after the prescribed medication, the pain worsened and she returned to the emergency department with an intense pain classified as nine on a numeric scale of 0–10, within 2 weeks of evolution and increasing intensity, associated to paresthesia and electric shock sensation on the left lower limb. Pain was aggravated by ambulation and flexion of the body and improved when lying down. The patient denied trauma. On physical examination, Lasegue test was positive in left lower limb, the patient was unable to walk on flexed feet and she had left limb claudication. No pain at spinous processes palpation. The lumbar spine X-ray revealed an L3 fracture. Lumbar spine magnetic resonance imaging revealed L3 vertebral body recent fracture, circumferential disc herniation in L4–L5 with left predominance, degenerative alterations of the posterior articular masses, and deformation of the thecal sac with the commitment of the left L5 root. There was a reduction in the amplitude of the conjugation holes with the subsequent compromise of left L4 root and probable conflict, especially on orthostatic position. The pain was classified as mixed; nociceptive somatic and neuropathic due to left lumbosciatica (compression of the left L4 and L5 roots) and concomitant L3 fracture. The patient was medicated with paracetamol/tramadol 325 mg/37.5 mg tid, naproxen 500 mg bid, diazepam 10 mg id (once a day), and a lumbar stabilization orthosis. She was advised to change her lifestyle and started a diet to reduce weight. Due to the inefficacy of tramadol/paracetamol, the dose was doubled with no therapeutic success and then she started on tramadol ascending dose (up to 300 mg/day). She spent most of the time in bed for disabling pain and needing help in ADL. As the patient was still in pain, analgesic was rotated to tapentadol 50 mg bid and AIDs. Three days after that, the patient reported improvement of pain with a decrease in worst pain of 3 (intensity 6/10), and could walk with crutches. Tapentadol dose was increased to 100 mg bid. Patient reported a progressive improvement with no side effects. On the third week of using tapentadol, the pain was classified as 2/10, with no need of AIDs, and she could perform her ADL, requiring no aid. Later, she maintained tapentadol 100 mg bid, ibandronate, and calcium/vitamin D supplementation (due to the fracture was secondary to osteoporosis).

The second case is of a 77-year-old female patient with the past medical history of gastric adenocarcinoma (total gastrectomy in 2001), arterial hypertension, and chronic hypertensive kidney disease (glomerular filtration rate of 30 ml/minute). In September 2011, invasive mucinous carcinoma of the left breast was diagnosed and she was subjected to total mastectomy followed by adjuvant endocrine therapy with an aromatase inhibitor. It metastasized 8 months later to bone and liver. She was prescribed dorsal spine radiotherapy (RT), chemotherapy (ChT) (several lines of treatment), and bisphosphonates. The patient started a complex picture of pain complaints during metastatic disease: diffuse and bilateral pains on the face, jaw, and tongue. Osteonecrosis of the mandible was discarded and after etiological investigation, these complaints were attributed to muscular tension under the clinical context of reactive depression. Psychiatric support was provided. She also complained of generalized arthralgias with an important impact on ADL as well as severe cervicalgia, moderate intensity pain in the left hemithorax with no relation to the effort—metastatic bone lesions were excluded. She tried several analgesics such as paracetamol/tramadol 325/37.5 mg, prolonged-release morphine 10 mg, and buprenorphine 12.5 mcg/hour with poor tolerance (constipation, drowsiness, and cognitive impairment). Later, a trial of tapentadol 50 mg bid was started. The patient reported progressive improvement of pain complaints, currently maintaining this daily dose with no significant side effects.

The third case is of a 60-year-old man, with a past medical history of hypertension, type 2 well-controlled diabetes, cerebellar infarction with dizziness as sequelae symptom, and L4–L5 level herniated disc. In 2011, a rectal adenocarcinoma was diagnosed, and he was subjected to neoadjuvant infusional 5-fluorouracil and RT, followed by anterior rectum resection and postoperative ChT with 5-fluorouracil, leucovorin, and oxaliplatin (cumulative dose = 789 mg/m2). He complained of a pain characterized as “ants” (sic), below the knees, symmetrical with progressive and ascending onset, “stocking” pattern, constant, with nocturnal aggravation, and intensity 7/10. Pain was triggered by prolonged immobilization and relieved by 30-minutes walks. He did not mention the limitation of ADL. He was medicated with pregabalin 75 mg bid, with no improvement; he did not tolerate an increase in dose. The patient denied exposure to neurotoxic metals such as lead or arsenic, denied smoking, and reported drinking a glass of wine at meals. On physical examination, he

presented diminished muscle strength (grade 4/5) in the lower right limb, with no evident alteration of the superficial sensitivity. The most probable diagnosis was polyneuropathy secondary to ChT, not excluding, although less likely, the possibility of polyneuropathy associated with alcohol consumption and diabetic neuropathy. The exclusion of vitamin deficits and thyroid dysfunction was done. Electromyography revealed decreased amplitude of all sensory potentials determined, normal corresponding sensory conduction velocity, and normal motor conduction studies. The results were compatible with a sensory neuropathy secondary to ChT. Therapy with tapentadol 50 mg bid was started with gradual improvement of paresthesia. The patient also reported improvement in sleep patterns. The therapeutic dose was escalated up to the current dose of 150 mg bid. There was no significant toxicity.

Discussion

Three patients were reported with different kinds of pain, different impact on the function as well as different symptom clusters.

In the first report, the pain evolved into a mixed type of pain with an important neuropathic component and functional repercussion; an appropriate etiological diagnosis was pursued. Although the patient started medication early in the pain process, and titration was done, she kept on with worsening pain. The unmet need for treating the neuropathic component was resolved after tapentadol was started. Studies have shown that many patients with NP do not receive the appropriate treatment, largely due to difficulty in diagnosis and use of ineffective drugs [2,3,10,14].

The second clinical reports a complex case of multiple locations and different types of pain in a patient with metastatic breast cancer and emotional suffering. The etiological diagnosis aimed to exclude treatable causes of pain; the final diagnosis reported a case of total pain, and the toxicity of cancer treatments was an important component of pain. The complexity of cancer pain treatment was briefly highlighted, its multiple causes, and the essential multidisciplinary approach needed for effective pain control. Comorbidities need to be considered, as chronic kidney disease, and the inefficacy of previous analgesics justified the option for tapentadol [13,14]. As the patient was evaluated for pain outcome, tapentadol was assumed to be effective in relieving pain and suffering with no associated side effects at the prescribed dose.

The third case was related to a clinical case of ChT induced neuropathy (CIPN). Neurotoxicity associated with anti-cancer drugs is usually cumulative and, therefore, a dose-limiting factor. In many cases, it is the main reason for the premature withdrawal of treatment and decreasing dose intensity may have a negative effect on treatment efficacy. The diagnosis of CIPN needs a differential diagnosis with other situations, namely polyneuropathy of metabolic, endocrine, infection, or toxic cause. In the treatment of any of these, there is a need for a multimodal approach that goes through metabolic corrections and/or toxic eviction and directed medication. The early use of effective drugs in the treatment of CIPN may allow resuming suspended medications with improved efficacy profile of anti-neoplastic treatments. Given the good treatment control, such as the one documented in this case, we propose that in situations of dose-limiting neurotoxicity, we might try the early prescription of active drugs to keep with the efficacy of antitumor treatment.

Tapentadol is a drug that associates two mechanisms in the same molecule, and there are no similar approved drugs. The literature suggests it has a wide field of prescription as it was shown to be effective in a wide variety of causes of chronic NP as it associates mu opioid inhibition with anti-neuropathic action. The two-different mechanisms of action give it a high analgesic potency in several situations; in particular cases of NP, the noradrenaline reuptake inhibition seems to predominate. In non-neuropathic settings, it appears to have the efficacy of opioids, with fewer side-effects, even in complex cases of pain [11–15].

Although NP is considered frequently in cancer patients and difficult to manage, few data are available on its prevalence and a much higher incidence is expected associated with inflammatory and degenerative osteoarticular pathology. NP, either caused by tumor infiltration or due to paraneoplastic or treatment-induced polyneuropathy, might be treated by opioids alone or in combination with adjuvant drugs. The need for various medications, elderly patients or those with renal and hepatic impairment frequently place limitations on the drugs and doses to be used [10].

The added value of this work was to alert to the underdiagnosis of NP, the need to implement NP surveys (which facilitate not only the screening of this entity but also clinical studies about it), and appropriate treatment of the etiological mechanism of pain.

Conclusion

Tapentadol may be a relevant drug in chronic NP, with proven efficacy and fewer side effects compared to other opioids. Its mechanism of action was considered innovative but it benefits over other opioids is not consensual.

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List of abbreviations

ADL	Activities of daily living
AID	Anti-inflammatory drugs
CIPN	ChT induced neuropathy
ChT	Chemotherapy
NP	Neuropathic pain
RT	radiotherapy

Consent for publication

Informed consent was taken from the patients.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

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Summary of the case

Patient (gender, age)	1	Female, 60 year old; Female, 77 year old; man, 60 year old
Final Diagnosis	2	Neurophatic pain
Symptoms	3	Lumbar pain, left lower limb irradiation and claudication; severe cervicalgias, moderate intensity pain in the left hemithorax; pain characterized as “ants” (sic), below the knees, symmetrical, with progressive and ascending onset, “stocking” pattern, constant, with nocturnal aggravation.
Medications	4	Opioids, Tapentadol 50 mg bid
Clinical Procedure	5	Pain management
Specialty	6	Oncology