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CASE REPORT

Zoledronic acid to treat complex regional pain syndrome type I in adult. Case report*

Ácido zoledrônico como tratamento para síndrome dolorosa complexa regional tipo I em adulto. Relato de caso

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SUMMARY

BACKGROUND AND OBJECTIVES: Complex regional pain syndrome (CRPS) is a difficult to treat disabling disease. Positive results with bisphosphonates in CRPS type I patients refractory to multimode therapy have been described. This study aimed at reporting the use of zoledronic acid in CRPS type I patient refractory to traditional therapy.
CASE REPORT: Female patient, 31 years old, with CRPS for 16 years, refractory to multiprofessional and multimode treatment. Due to persistence of symptoms, zoledronic acid administration was proposed with effective control of symptoms and without adverse effects.
CONCLUSION: Zoledronic acid was effective to treat CRPS type I refractory to conventional treatment.
Keywords: Bisphosphonate, Complex regional pain syndrome, Pain.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A síndrome dolorosa complexa regional (SDCR) é incapacitante e de difícil tratamento. Resultados positivos com a utilização de bifosfonatos em pacientes com SDCR tipo I refratária a terapêutica multimodal tem sido descritos. O objetivo deste estudo foi relatar a utilização do ácido zoledrônico em paciente portador de SDCR tipo I refratária à terapêutica tradicional.

RELATO DO CASO: Paciente do sexo feminino, 31 anos, com história de SDCR há 16 anos, refratária ao tratamento multiprofissional e multimodal. Diante da persistência dos sintomas foi proposta a administração de ácido zoledrônico, com controle efetivo dos sintomas e sem a presença de efeitos adversos.
CONCLUSÃO: O ácido zoledrônico foi efetivo no tratamento da SDCR tipo I refrataria ao tratamento convencional.
Descritores: Bifosfonato, Dor, Síndrome dolorosa complexa regional.

INTRODUCTION

Complex regional pain syndrome (CRPS) is a regional pain condition associated to sensory changes caused by a noxious event, be it fracture, surgery or other type of injury. CRPS diagnosis is clinical, based on the presence of specific signs and symptoms; the presence of initial injury may be disregarded; signs and symptoms should be divided in different groups; patients should have at least two of the following symptoms: sensory (hyperesthesia), vasomotor (change in temperature, skin color or both), sudomotor / water balance (edema, sweating or both), and motor (decreased mobility, weakness, shivering, functional limb amputation) or all of them; and patients should present at least two of the following signs: vasomotor, sudomotor / water balance and motor[1]. So, CRPS is a neuropathic and disabling pain syndrome made up of motor, autonomic and sensory changes[1].
According to the Consensus of the International Association for the Study of Pain, CRPS may be classified in types I and II. Type II pain is different from type I due to the presence of nervous injury, where pain is not limited to the innervation site of the injured nerve. Regardless of CRPS type, it is known that it significantly interferes

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with patient's quality of life, impairing their daily activities. Pain intensity and functional incapacity are disproportional to the baseline injury implying the need for a multiprofessional and multimode therapeutic approach. Although several studies are carried out with therapeutic proposals[2], few have shown a really effective analgesic regimen. So, the search for a really effective treatment has become mandatory.

Positive results with bisphosphonates in patients with CRPS refractory to multimode therapy have been described. Bisphosphonates relieve bone pain in patients with osteoporosis, Paget's disease and malignant bone pain and their specific action varies according to their chemical structure[3,4]. Zoledronic acid acts specifically on the bone and inhibits osteoclasts-mediated bone reabsorption, having as major target the farnesyl pyrophosphate synthase enzyme. Exact bisphosphonates analgesic mechanism in CRPS patients is not clear, although these patients manifest some level of regional osteoporosis in the involved extremity[5,6]. Several bisphosphonates have been used to treat CRPS in adults.

This study aimed at reporting the use of zoledronic acid in CRPS type I patient refractory to traditional therapy.

CASE REPORT

Female patient, 31 years old, with history of neuropathic pain for 16 years. She reported that pain was spontaneous, very severe with intensity 10 in the worst moments, according to verbal numerical scale. Worsening factors were: physical contact, change in temperature and emotional stress. Improvement factors were: rest and analgesic drugs. Associated symptoms: mechanical allodynia, primary and secondary hyperalgesia and decreased function of left upper and lower limbs. Patient was investigated to rule out oncologic and rheumathological disease, with negative results. Lab tests and electroneuromyography were normal, however conventional X-Rays of affected limbs has shown decreased bone calcification. She had already used normal analgesics, steroids and non-steroid anti-inflammatory drugs, with mild improvement of symptoms after the use of steroids. Medical history: thrombophilia in regular follow-up with angiologist and indication of total anticoagulation. At physical exam she presented signs of autonomic dysfunction, upper and lower limbs edema and pain when moving them. Other findings: triggering point in scapular waist. Diagnostic suspicion: CRPS type I associated to myofascial pain syndrome.

Adopted approach: amitriptyline and carbamazepine in increasing regimen until the dose of 75 mg and 1200 mg of these drugs, respectively, sympathetic venous block with 2% lidocaine without vasoconstrictor and triggering point infiltration with 0.125% bupivacaine.

There has been good initial response, however with frequent recurrence of symptoms. Analgesic regimen was modified replacing amitriptyline by other antidepressants and carbamazepine by other anticonvulsants. Opioids, neuromuscular blockers, dexmedetomidine, magnesium sulfate and chlorpromazine were introduced. After several failures, patient changed behavior, becoming depressive and anxious. Multiprofessional follow-up was started with the help of the psychology and psychiatry teams.

After two years of treatment, due to persistence of symptoms, parenteral zoledronic acid (5 mg) was introduced. Patient was hospitalized due to CRPS type I decompensation and was submitted to lab tests for five days, including calcium serum dosage and monitoring of vital signs when the drug was administered and every 6 hours in subsequent days. During treatment patient received calcium supplementation to minimize the development of hypocalcaemia.

No zoledronic acid adverse effect was identified and patient was discharged after total regression of edema and pain. There has been no CRPS type I recurrence in the six months following the administration of zoledronic acid.

DISCUSSION

CRPS type I is a progressive disease with increasing pain and inactivity, generating anguish and anxiety for patients and health teams following them[1]. However, when CRPS affects children and adolescents, its clinical characteristics are different from those of adults. Children are predominantly affected in lower limbs and have better prognosis as compared to adults.

Pain persistence is a concern because it implies more distress to patients and the presence of peripheral and central sensitization caused by cytokines production and by the action of nitric oxide, oxygen free radicals and excitatory aminoacids[7]. So, early diagnosis and treatment are fundamental for adequate patient's recovery. This clinical case reports CRPS in a young patient, however with disease starting in the adolescence. Adequate therapy was instituted lately, 13 years after the appearance of the first symptoms, which may justify initial unfavorable evolution.

Therapy adopted for this patient was multiprofessional, involving a health team composed by physicians, nurs-

es, psychotherapists and physical therapists, aiming at pain relief, functional recovery and less psychological distress[8,9]. Although some studies are favorable to multidisciplinary treatment of CRPS type I patients, the literature shows major variation in implemented treatments, reflecting the complexity of this disease.

Drugs such as antidepressants, anticonvulsants and other adjuvants have been proposed to treat neuropathic pain; however there is no standard protocol for CRPS type I. This patient was submitted to different therapeutic regimens without adequate response, which has motivated the administration of zoledronic acid, which is a biphosphonate which is a class being proposed as alternative to treat patients with refractory CPRS[10].

Bisphosphonates mechanism for CRPS is not well established, however it is believed that they antagonize osteoclastogenesis, in addition to inhibiting prostaglandis E2, proteolytic enzymes and lactic acid, elements which are involved with the inflammatory process and with the generation and perpetuation of pain[11], which could justify the positive result obtained with their administration.

CONCLUSION

The use of the biphosphonate zoledronic acid was effective to treat CRPS type I.

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