Efficacy and safety of neridronate in paediatric type I complex regional pain syndrome: a multicentre experience

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Abstract

Objective

Evidence regarding the efficacy of neridronate in the treatment of complex regional pain syndrome type I (CRPS I) is increasing, however, very little data are available in paediatric age. Our aim was to analyse the safety and the efficacy of neridronate in a case series of children with CRPS I, according to the Budapest criteria, who did not respond to previous pharmacological and physical therapy.

Methods

We collected data of children affected by CRPS I from three paediatric rheumatology centres who received neridronate. Efficacy was evaluated by changes in pain intensity, vasomotor changes, physical function, need for pain medications and MRI findings. Adverse effects were also documented.

Results

Five children (3 females and 2 males, mean age 10.4 years, range 7–13 years) who received neridronate (4 intravenous, 1 intramuscular) were included. All patients had failed previous medical treatments (NSAIDs in 4, local steroids in 2, gabapentin, vitamin D and calcium supplementation in 1) and non-medical therapies (physiotherapy in 4, magnetotherapy in 2, laser in 1). Four out of five patients reported a significant improvement in pain (average VAS pre-treatment 9.6, post-treatment 2.6), recovery of physical function, and a reduced need for pain medications. Before treatment, all patients underwent MRI which revealed bone oedema that disappeared in the three of them after treatment. Neridronate was well-tolerated as only one patient experienced mild flu-like symptoms.

Conclusion

Our data suggest that in children as in adults with CRPS I, neridronate may represent an effective and safe treatment option, particularly in those who do not respond to other pain treatments

Key words

neridronate, complex regional pain syndrome, child, pain

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Introduction

Complex regional pain syndrome (CRPS) is characterised by localised pain, discoloration, oedema, temperature changes, and decreased function, usually affecting extremities following trauma or nerve injury (1). CRPS is divided into two types: CRPS-I and II, characterised by absence or presence of nerve injury, respectively (2). CRPS can affect adults and children, especially teenagers and females (1). The diagnosis might be challenging, as no laboratory or radiologic data are specific (3, 4). Biphosphonates have shown effectiveness in CRPS in adults but data in children are very scarce (5, 6).

The present study aims to describe five children with refractory CRPS-I, diagnosed according to Budapest criteria (4), successfully treated with neridronate.

Case descriptions

Case 1

A 10-year-old boy presented persistent pain in right foot without history of trauma so non-steroidal anti-inflammatory drugs (NSAIDs) were started without benefit. After intra-articular corticosteroid injection and physical rehabilitation, he presented persistent pain and walking limitation, MRI showed marked, extensive oedema of the cuboid, scaphoid and medial cuneiform bones. On examination, allodynia, temperature asymmetry and atrophic hair were observed so a diagnosis of CRPS-I was made, and the patient underwent three courses of iv neridronate (2 mg/kg with a 2–3 month interval). At nine months, the pain completely disappeared and MRI showed resolution of the oedema.

Case 2

A 12-year-old female reported left ankle pain for 6 months, without history of trauma or infection. Oedema and pain on passive mobilisation of the ankle were noted with local hyperesthesia, but without skin discoloration or local temperature changes. MRI showed bone oedema of talus, calcaneus, scaphoid, tarsus and first cuneiform bones (Fig. 1A-C). Lab tests were normal except for mild hypovitaminosis D. Occasional intake of NSAIDs and laser-therapy were without benefit. Diagnosis of CRPS-I was made, and three courses of neridronate infusion (2 mg/kg with 1–2-month interval) were administered. At 6 months, the pain stably resolved (VAS score 1) and the MRI showed disappearance of the oedema (Fig. 1B-D).

Case 3

An 11-year-old male presented persistent pain for 6 months on the right calcaneus. He reported a trauma with an x-ray showing 4th metatarsal infraction, so a soft cast was applied. Heel pain persisted and MRI of the foot showed oedema of the calcaneus in intraspongiosa infraction of the anterior apophysis. The boy underwent physiotherapy with transient improvement. The patient had been previously treated by an orthopaedic surgeon with NSAIDs and three intra-articular corticosteroid injections without improvement. On physical examination, he presented dark shaded skin on the right foot, limping gait, pain at dorsiflexion and allodynia at the plantar site, so a diagnosis of CRPS-I was posed. The patient underwent three courses of intravenous neridronate (2 mg/kg, 2-month interval) with clinical, radiological and laboratory improvement.

Case 4

A 10.9-year-old-girl experienced, 2 months after a mild trauma, persistent pain in the right foot (VAS 9) associated with oedema and purplish colour skin over right leg and foot with allodynia and decreased ankle range of motion. She was not weight bearing and used a wheelchair. X-rays were negative and a soft cast was placed without improvement. MRI showed oedema of the astragalus and calcaneus bones, so she underwent magnetotherapy and physiotherapy but to no effect. A Tc99 bone scan showed diffuse hypoperfusion on the right foot and ankle, confirming the clinical diagnosis of CRPS-I. The patient underwent four infusions of neridronate (2 mg/kg each at 3–4 days apart) with rapid and significant reduction of pain, allodynia and vasomotor changes, so the patient regained weight bearing. After the first infusion only she presented mild a flu-like syndrome lasting 24 hours.

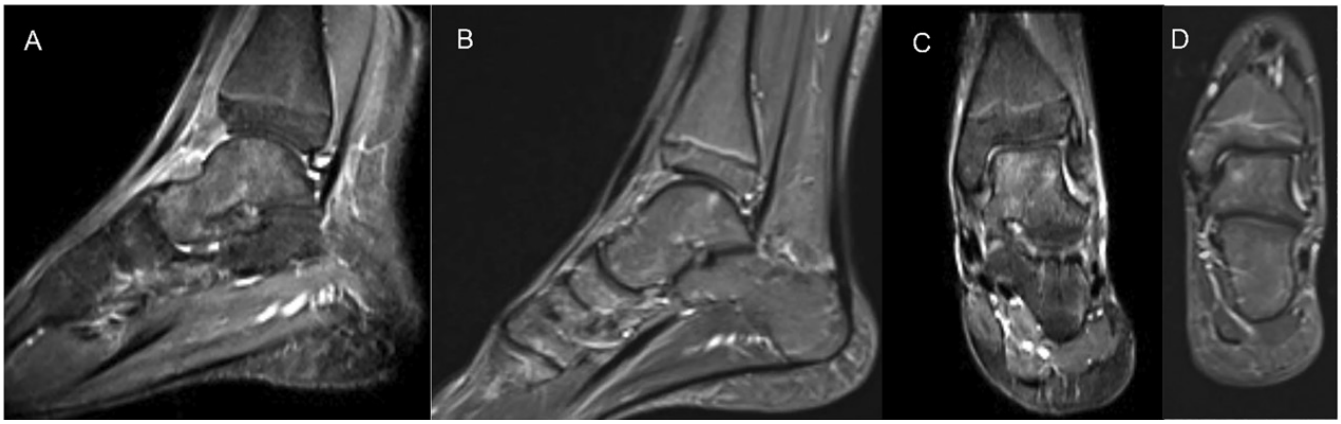

Fig. 1. MRI of Case 2 before and 6 months after treatment with neridronate
Sagittal Axial Short Inversion Time Inversion Recovery (STIR) sequences (1**A**-**B**): slight areas of increased signal intensity due to intraspongiosa bone oedema involving all the astragalus bone (1**A**). Marked reduction of the clinical picture with minimum residual oedema at the talar dome 6 months after treatment (1**B**). Coronal Axial STIR sequences: similar characteristics compared to the sagittal sequences are described in the coronal sequences (1**C**-**D**).

Case 5

An 11-year-old girl presented persistent pain in her left ankle. Three months prior, she had experienced a minor trauma. Fractures were ruled out through x-rays, and a soft cast was applied. After cast removal, she complained of severe and persistent pain, with the inability to walk. On MRI, a widespread calcaneal bone oedema, a patchy involvement of the talus and the anterior tarsus were documented. Hyperalgesia and allodynia were appreciable in the distal part of left foot up to the leg, with mild oedema and skin thinning. Her history revealed difficulties in school socialisation in the previous 2 years, therefore she underwent a close psychotherapy and physiotherapy programme along with magnetotherapy, NSAIDs, gabapentin and triazolam, but without significant improvement.

Five months after the trauma, intramuscular neridronate (25 mg for four consecutive days, then weekly for one month) was administered and well tolerated with slight reduction of symptoms and functional limitation. The girl spontaneously recovered eleven months after disease onset, following several other ineffective treatments, including nerve block. The clinical characteristics of the patients are summarised in Table I.

Discussion

The use of bisphosphonates in children is based on established experience, particularly in patients with osteogenesis imperfecta. (6-8) Studies on their mechanism of action demonstrated their ability to increase bone growth and periosteal bone formation, especially in growing children, while reducing bone remodelling (6, 7). Additionally, some inflammatory or neoplastic bone conditions, such as chronic non-bacterial osteomyelitis (CNO), benign bone tumours may also be modified by biphosphonates, although the mechanism remains unclear (6-8).

Neridronate is a second-generation bisphosphonate, initially used to treat Paget disease, that is effective in reducing pain and bone turnover markers. In light of its efficacy on pain relief, there is growing evidence supporting its role in the treatment of CRPS I. In adults, the first randomised controlled trial (RCT) investigating efficacy and safety of neridronate for the management of musculoskeletal pain was published in 2013 (9). This led to its approval for the treatment of CRPS I by the Italian Medicines Agency (AIFA) also for individuals under 18 years of age. (6) In that study neridronate was administered intravenously and was significantly more effective than placebo in reducing pain (73.2% of patients reported >50% VAS score reduction) at the 40-day follow-up and after 1 year. These results were accompanied by efficacy in other features of CRPS, such as resolution of oedema, pain at passive motion, allodynia, hyperalgesia, reduction of bone oedema and normalisation of bone scan uptake (9) More recently, comparable results were achieved in adults using intramuscular neridronate. (10)

To our knowledge, the present study is the first providing evidence of neridronate use in children with CRPS I, although use of other bisphosphonates has been reported with less convincing results. In a study by Walfish *et al*., discrete improvement (global impressions of change, reduction of pain intensity and need for pain medications) was reported in 9/16 patients treated with zoledronic acid and pamidronate, with a median follow-up time of 16 months (11). In our case series the real effectiveness of neridronate was difficult to ascertain only in case 5 because of a stubborn refusal to various attempts at weight-bearing that unlocked only after intense and prolonged psychological support and administration of mood stabilising medications.

Mild side effects, particularly flu-like symptoms, after the first administration of bisphosphonates are common (12, 13). Bisphosphonate-induced hypocalcemia and/or hypophosphataemia are also possible but are usually not severe. Adequate calcium intake and vitamin D supplementation, in case of deficiency, should be maintained post-infusion (12, 13).

In our case series, only one patient experienced low-grade fever and myalgias 24 hours after the first neridronate infusion, no other side effects were observed. This contrasts with previous findings of adverse effects, mostly flu-like symptoms, in 81% of patients

Table I. Clinical characteristics, radiological features and treatment of patients.

	Case 1	Case 2	Case 3	Case 4	Case 5
Sex (M/F)	M	F	M	F	F
Age (years)	10	13	11	11	7
BMI (kg/cm^2)	24,7	18,3	17.6	14,7	-
Acute traumatic event	No	No	Yes	Yes	Yes
Symptoms	Pain, inability to walk	Pain	Pain	Pain, decreased range of motion	Pain, moderate trophic changes
Duration of pain (months)	4	6	6	3	4
Localisation	Right foot	Left ankle	Right foot	Right foot	Left foot and leg
Radiological investigations	x-ray of the hip MRI of the foot	MRI of the foot and ankle	x-ray of the foot x-ray of the foot	MRI of the foot	MRI of the foot MRI of the foot
Time interval from pain onset and MRI (months)	4	6	6	2	3
MRI results	Local bone oedema	Local bone oedema	Mild osteopenia and	Local bone oedema	Bone oedema
Family history	Osteoporosis, psoriasis, type 2 diabetes, tyroiditis	Migraine, Behçet, psoriasis	-	-	-
Comorbidities	-	Migraine	-	-	Cystic fibrosis
Previous therapies	NSAIDs, local steroids	NSAIDs	NSAIDs, local steroids	NSAIDs	Gabapentin, Vit D, Calcium
Non-medical therapies	Physiotherapy	Laser-therapy	Physiotherapy	Physiotherapy, magnetotherapy	Physiotherapy, magnetotherapy
Biphosphonate	Neridronate	Neridronate	Neridronate	Neridronate	Neridronate
Number of infusions	3	3	3	4	8
Dose (mg/kg)	2	2	2	2	2
Route of administration	Intravenous	Intravenous	Intravenous	Intravenous	Intramuscular
Intervals	Once every 12 weeks	Once every 6 weeks	Once every 8 weeks for 4 times,	Once a day every 3-4 days then once a week for one month	Once a day for 4 days,
Results	Resolution of pain	Resolution of pain	Resolution of pain	Resolution of pain and ympathetic symptoms	No resolution of pain with biphosphonates
Side effects	No	No	No	fever and myalgia	No
Post-treatment MRI	Yes	Yes	Yes	No	No
Results	No bone oedema	No bone oedema	No bone oedema	-	-
Patient VAS before treatment	9	10	10	9	10
Patient VAS after treatment complete	1	1	3	1	7

treated with zoledronic acid and pamidronate (10). Rare but severe side effects, as symptomatic iritis, atypical femoral fractures, osteonecrosis of the jaw and oesophagitis, are reported in sporadic cases (14).

To monitor the efficacy of bisphosphonates and evaluate bone remodelling, bone turnover markers have been studied particularly in adult osteoporosis and P1NP and CTX are the recommended biochemical markers of bone formation and resorption, respectively (12).

The use of radiology for the diagnosis of CRPS is controversial and not universally accepted in the literature (15). The differential diagnosis of bone marrow oedema in children is very broad but, when associated with typical signs and symptoms such as sensory and vasomotor/sudomotor alterations, patient discomfort, and impaired quality of life, is consistent with CRPS. In our study, MRI proved useful in excluding inflammatory or neoplastic conditions and showing significant improvement of oedema after neridronate in three patients that repeated MRI after treatment.

In conclusion, we described a case series of children with CRPS I not responding to prior medical and non-medical treatments wherein the use of neridronate resulted in a significant improvement and, in most cases, resolution of the condition. Although with the limitation of the small number of patients our results suggest that neridronate may reduce pain intensity and sympathetic manifestations like vasomotor/sudomotor symptoms, therefore improving the overall patients' function. The efficacy seems to be independent of the time interval regimen, while in our study we cannot confirm that the route of administration does not affect it, as suggested by the adult literature, because the only patient treated with intramuscular injections did not present a significant improvement. Indeed, we reported that neridronate was well tolerated as our patients presented no serious adverse events, the need for pain medications rapidly reduced after treatment in most of them and persisted several months later.

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