Original Article

Amino-bisphosphonates in heterotopic ossification: first experience in five consecutive cases

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Study design: Retrospective, observational study in five consecutive cases.

Objectives: The management of heterotopic ossification (HO), a frequent complication after spinal cord injury (SCI) and after orthopaedic surgery, is a therapeutic challenge with high recurrence rates of over 50%. Conflicting data were reported for Etidronate. The use of the more potent new generation of amino-bisphosphonates has been put forward in different inflammatory, dysmorphic bone disease. In order to try and halt the underlying dysfunctional bone metabolism we have studied the action of pamidronate in five consecutive high-risk patients with established HO of different etiology undergoing surgical removal.

Setting: University Hospital of Basel, Switzerland, Division of Endocrinology, Diabetology and Clinical Nutrition and the Department of Orthopedic Surgery.

Methods: In all five patients, ranging from 47 to 68 years of age, we used continuous pamidronate infusions perioperatively at a dosage of 120 mg in the first 12 h and subsequent reduction to 75–60–30–15 mg/12 h over a period of 10–14 days.

Results: None of these patients showed clinical, radiographical and laboratory signs of HO recurrence or new forming HO in the follow-up 5–54 month after surgery. Potential side effects of high-dose bisphosphonate therapy such as osteoporosis and osteomalacia were not reported in any case.

Conclusion: We postulate that pamidronate might have pronounced beneficial effects in high-risk patients with established HO undergoing excision surgery. Since the therapeutic window of amino-bisphosphonates has not yet been defined and the minimal necessary doses for preventing new HO are unknown, further studies are encouraged to confirm our findings and to identify the necessary dosage and duration of treatment and to pinpoint, which patients will benefit most from this treatment.

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Keywords: observational study; heterotopic ossification (HO); high-risk patients; established ossification; excision surgery; pamidronate; amino-bisphosphonate

Introduction

Heterotopic ossification (HO) is the formation of pathological, heterotopic bone in muscle or soft tissue. The incidence of HO varies greatly among different patient populations and among different classification systems. In patients after spinal cord injury (SCI) the incidence ranges from 10 to 53%.¹ After total hip replacement the incidence was historically reported to amount to 15–90%.^{2–4} In 59 000 patients after total hip arthroplasty (THA) a total incidence of 43% for HO was found, 9% of them being classified as severe.⁵

Estimating that worldwide more than 800 000 total hip replacements are carried out every year, the overall incidence of severe HO even with preventive preoperative nonsteroidal anti-inflammatory drugs (NSAIDs) treatment would be required in over 30 000 patients/year.

HO can be divided into two groups with distinct pathophysiological mechanisms. The acquired form occurs after orthopaedic interventions or after spinal cord and central nervous system injury, respectively. The hereditary form is a rare disease also known as fibrodysplasia ossificans progressiva (FOP) or myositis ossificans progressiva. The gene responsible for FOP has not been identified. A disturbance in the balance

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between the bone morphogenetic protein 4 (BMGP-4) and its antagonists is thought to be crucial for the formation of pathological bone.^{6–10} The mechanism underlying acquired HO is not well understood. The transformation of pluripotent, mesenchymal cells into osteogenic precursor cells is thought to be one of the prerequisites for HO. This transformation of cells differs from other mechanisms of tissue calcification, namely metastatic calcification or dystrophic calcification of necrotic tissue.^{11–13}

Symptoms of acquired HO may appear 3–12 weeks after spinal cord and central nervous system injury or orthopaedic interventions. Typically, patients present with joint and muscle pain, paresthesias and tissue swelling in the involved region accompanied, by mild fever.^{14–17} HO may cause severe morbidity and limits the success of orthopaedic procedures. A considerably compromised range of motion and loss of hip motility and function (including ankylosis) may occur. In the early stages of HO clinical signs of inflammation are nonspecific.¹⁸ Measurement of biochemical markers, that is, osteocalcin and alkaline phosphatase, and three-phase bone scan have improved early diagnosis of HO and made early treatment interventions possible.^{19–21} Nevertheless, HO remains a therapeutic challenge. Recent studies have documented a beneficial effect of NSAID and radiation in the prevention of HO.^{18,22–26} However, patients with already established HO undergoing surgical removal have a very high-risk of recurrence. In these high-risk cases a recurrence rate of over 50% has been reported even with prophylactic radiation therapy.^{1,27–34} A protective effect of Etidronate, a first-generation bisphosphonate, in established HO, was found in some but not other studies.^{14,35–38}

A rapidly growing body of literature supports amino-bisphosphonates for the treatment of diseases associated with disturbed bone morphogenesis. Therefore, we speculated that amino-bisphosphonates could be administered not only because of their antiosteoclastic effect, but also for their immunomodulatory and anti-inflammatory properties.^{39–43} Only single case reports have been published for the treatment with the more potent new generation of amino-bisphosphonates.⁴⁴ Herein we report our observational experience using the amino-bisphosphonate Pamidronate in five consecutive patients with established HO. Thereafter, a therapeutic algorithm is suggested.

Case records

We retrospectively evaluated seven consecutive patients. One patient died of suicide for personal reasons and one patient moved to a different location and was lost to follow up. Herein we report therefore baseline and follow-up data from five male patients who presented with HO at different locations. Three patients presented with neurogenic HO after SCI. One patient suffered from FOP and another from HO after THA. The diagnosis of HO was based on the presence of typical

clinical, laboratory and radiographic signs and symptoms. All patients underwent excision-surgery for removal of their HO deposit. Pamidronate was administered intravenously peri- and postoperatively, starting at a dose level of 120 mg for the first 12 h, followed by gradually tapering dosages of 75–60–30–15 mg per 12 h for a total duration of 6–14 days.

Each patient was closely monitored in the post-operative course, that is, regular clinical examination combined with biochemical blood and urinary measurements. For the final follow-up evaluation after 4–54 months a standardized protocol was used (summarized in Table 1), focusing primarily on (a) evidence for recurrence or new formation of HO and (b) ruling out possible side effects of the bisphosphonate therapy. It was combined with a questionnaire of the patient's personal opinion and a clinical examination. A 3-point score was used for each symptom, (0) meaning absence and (3) meaning maximal intensity of each symptom. In addition, an endocrine and routine laboratory check and X-rays of the region of former HO were performed. Radiographs were evaluated by different experienced radiologists.

Case 1

The patient, an experienced diver underwent a diving accident due to decompression, also referred to as Caisson's disease. Total tetraplegia resulted with a level on the 4th thoracic spine, and the patient was admitted to a specialized centre for paraplegics. During rehabilitation painful swelling of the left thigh was noted due to extensive para-articular ossification. The flexion of the hip and therefore physiotherapy became impossible. Surgical excision of the ossification focus was performed on Pamidronate protocol. On the 9th postoperative day painful local swelling developed again in the surgical area combined with a moderate increase of body temperature. A recurrence of the local calcifying process was suspected and the dose of pamidronate was increased once more for 75 mg/12 h for three additional days. The subsequent course was uneventful and rehabilitation could be intensified so that a normal flexion of the right thigh was ultimately attained.

Case 2

This patient suffered from severe meningococcal infection with subsequent septic shock and tetraplegia, which gradually improved during recovery. Multiple periarticular ossifications developed following the septic shock. This led to stiffness of both hips and the right upper arm with fixation of the elbow resulting in the patient's unavailability to feed himself. Excision of the major calcium deposits of the hip was performed on bisphosphonate protection. Following the two surgical procedures the patient regained partial walking capacity and an improved use of his right arm. He now is able to feed himself.

Table 1 Follow-up of the five patients (1–5)

	<i>Patient 1</i>	<i>Patient 2</i>	<i>Patient 3</i>	<i>Patient 4</i>	<i>Patient 5</i>
Age	52 years	68 years	56 years	51 years	47 years
Sex	M	M	M	M	M
Underlying disease	Caisson disease	Septic tetraplegia	<i>E. coli</i> sepsis	Osteoarthritis	FOP
Diagnosis	Neurogenic HO	Neurogenic HO	Neurogenic HO	After THA	FOP
Region of HO	Left hip and thigh	Both hips, elbow	Right hip	Right hip	Subscapulary
Duration of therapy	11 days	14 days	7 days	6 days	11 days
Total amount of pamidronate (mg)	850	1200	680	850	850
Follow-up					
Time since treatment	4 months	54 months	10 months	10 months	20 months
Need for 2nd surgery	No	No	No	No	No
Patient's opinion					
General well being	2	2	3	2	3
Pain at operation side	0	0	1	2	0
Recurrence of HO	0	0	0	1	0
HO at new location	0	0	0	0	0
Overall satisfaction with treatment	3	3	2	2	3
Clinical evidence for HO					
Pain after palpation in operation side	0	0	1	1	0
Hardening at operation side	1	0	0	1	0
Reddening/swelling at operation side	0	0	0	0	0
Decreased range of motion	1	0	1	1	0
Radiographic evidence for recurrence	0	0	0	0	0
Evidence for HO at new location	0	0	0	0	0
Treatment side effects					
General bone pain	0	0	0	0	0
Low back pain	0	0	0	0	1
Need for pain medication	1	0	0	1	0
Muscular weakness/myopathy	0	0	0	0	0
Height before evaluation (cm)	170	170	184.3	181.5	182.6
Height at evaluation (cm)	170.1	171.5	184.2	182.1	182.4
Fractures since treatment	0	0	0	0	0
Documented side effects	0	0	0	0	0
Laboratory testing					
Creatinine ($\mu\text{mol/l}$)	80	123	84	109	50
Osteocalcin ($\mu\text{g/l}$)	26.6	15.7	23.3	9.8	18.1
Alkaline phosphatase (U/l)	106	29.1	118	58	104
Alk.phosphatase (bone spec.)(IE/lp)	35	33	39	19.3	34.4
PTH (pmol/l)	4.8	4.1	9.3	3.2	4.1
Calcium (mmol/l)	2.12	2.31	2.31	2.34	2.33
Phosphorus (mmol/l)	0.96	1.3	0.82	0.85	0.83
Urinary testing					
Calcium (mmol/l)	1.6	0.029	1.17	0.7	3.16
Deoxypyridinolin/crea (nmol/mol)	6	40	43	5	13
Pyridinolin/crea (nmol/mol)	36	7	7	29	56

3-point score for each symptom: (0) meaning absence and (3) meaning maximal intensity; Laboratory testing (normal reference values): creatinine (53–115 $\mu\text{mol/l}$), osteocalcin (6.3–30.7 $\mu\text{g/l}$), alkaline phosphatase (≤ 58 U/l), bone-specific alkaline phosphatase (10–45 IE/l), parathyroid hormone (PTH, 1.5–6.9 pmol/l), calcium (2.1–2.65 mmol/l), phosphor (0.85–1.45 mmol/l); urinary testing: deoxypyridinoline/creatinine (5–20 nmol/mmol), pyridinoline/creatinine (25–100 nmol/mmol)

Case 3

Following abdominal surgery the patient developed pneumonia, septicaemia and critical illness polyneuropathy. During his recovery in the intensive care unit a painful HO appeared in the right hip muscles leading to partial fixation

of the right hip joint. A large periarticular ossification focus was removed without any postoperative complications. Bisphosphonate treatment was stopped on the 7th postoperative day. The patient recovered gradually due to intense physiotherapy and regained partial professional activity.

Case 4

Endoprosthesis was installed in the right hip because of destructing coxarthrosis. Subsequently, painful local periarticular ossification developed inhibiting the patient to extend his right thigh and to walk normally. At 8 months after the first operation this ossification deposit was surgically removed elsewhere without any preventive treatment and a few weeks later a new metaphastic bone focus was detected causing considerable pain and inhibiting again normal walking. A second surgical removal of the newly formed ossification focus was planned, this time on Pamidronate. The patient recovered without any further ossification problems. Ultimately slight limping remained with a residual hip pain on the right side.

Case 5

FOP was known since the patient's early childhood. Various phases of the disease led to the amputation of the right forefoot and to partial disability with contractions in the hip, knee back and shoulder region. However, the patient developed normally and reached a normal adult height. Owing to continued intense rehabilitation he gained full professional activities as a commercial employee.

Following puberty calcareous deposits remained unchanged for years. At the age of 47 years the patient noted an important painful swelling below the right scapula, which was detected to be a new calcium deposit in the thoracic muscles. Surgical excision was performed on bisphosphonate protection. The patient was discharged from hospital in good general condition and no new ossification foci were noted during the subsequent years.

Follow-up

Follow-up was performed in all five patients 4–54 months after surgical excision and bisphosphonate therapy. In every patient, a standardized questionnaire was completed and radiographic evaluation (grading according to Brooker *et al*⁴⁵) as well as laboratory studies were carried out. The results of the follow-up evaluation are summarised in Table 1. Total Pamidronate doses applied amounted to 680 and 1200 mg. None of the patients needed a second surgical intervention.

Overall, the personal opinion about the procedure was positive in all five patients. One patient (Pat 3) complained of persisting pain and discomfort, but clinical examination, radiographic findings and laboratory measurements showed no evidence of HO recurrence.

The region of former HO was evaluated clinically in each patient. Typical symptoms of HO such as pain, hardening and reddening, swelling and impaired range of motility were not detected in any case. X-ray control did not reveal any new local calcium deposits and there was no evidence for HO foci in other locations. In no instance clinical symptoms of possible side effects related to the bisphosphonate treatment, such as fever and

haematological changes, gastrointestinal or nephrological toxicity, were reported. Laboratory assessment of serum creatinine, calcium and phosphorus, parathyroid hormone (PTH), osteocalcin and the urinary crosslinks pyroline and deoxypyroline were within the normal range in all patients. Patient 3 showed an elevated level of PTH with 9.3 pmol/l (normal range: 1.5–6.9 pmol/l) and a slightly decreased phosphorus level of 0.83 (normal range: 0.85–1.45 mmol/l). However, this finding had been observed already prior to bisphosphonate therapy.

Discussion

Treatment and prevention of HO in high-risk patients following surgery or after spinal cord/central nervous system injury and/or septic shock remains an unsolved problem. NSAIDs, steroids or radiation therapy are unsatisfactory.^{31,34,38,46–48} We therefore evaluated the preventive effect of high doses of intravenous Pamidronate in patients undergoing excision surgery for severe HO of different origin. Several factors contribute to an increased risk for developing acquired HO such as gender, age, type of fracture and operation technique. However, a patient undergoing surgery for already existing HO is at highest risk for recurrence. Even with prophylactic radiotherapy a recurrence rate of over 50% has been reported.^{27–34}

In none of our five cases we found clinical or radiographic evidence for recurrence or new formation of HO following surgery. In addition, biochemical markers such as osteocalcin and alkaline phosphatase were within the normal range in all our patients. These markers have been shown to closely correlate with the likelihood of HO development and to have a good predictive value.¹⁹ Thus, based on our retrospective data from five consecutive patients, high intravenous dosage of nitrogen containing bisphosphonates apparently prevents recurrence of HO in 'high risk' patients, confirming earlier, anecdotal reports.^{44,48,49}

Pharmacologically, bisphosphonates can be classified into two groups with distinct molecular mechanisms of action. First-generation bisphosphonates such as Etidronate are analogues of inorganic pyrophosphate. Their mode of action involves cytotoxic metabolites in osteoclasts and inhibition of the protein tyrosine phosphatase.^{50,51} In the late 1960s, a study suggested that first-generation bisphosphonates do not only inhibit formation of calcium phosphate crystals *in vitro* but also pathological calcification *in vivo*.⁵² Mechanisms discussed included inhibiting of the precipitation of calcium phosphate from unsaturated solutions, delaying of the aggregation or blocking of the conversion of calcium-phosphate into hydroxyl apatite. Early results from small clinical studies of oral Etidronate in the prophylaxis after SCI were promising.^{53–56} Beneficial results were also confirmed in a population of Japanese patients undergoing total hip arthroplasty.⁵⁷ However, a large placebo controlled trial in 177 patients after total hip arthroplasty showed contradictory results. In this

study, the incidence of HO was higher in the group receiving oral bisphosphonates than in the placebo group.^{14,35} Thereafter, intravenous Etidronate was used in an attempt to achieve a high initial drug concentration at the site of active ossification. In all, 40 patients after SCI and positive 3D bone scans were treated with 300 mg of Etidronate daily for 3 days followed by an oral dose of 20 mg/kg/day for 6 months. After early beneficial results, a high number of HO rebound occurred suggesting a delay rather than true prevention.^{20,36} Taken together, evidence for a clinical benefit of Etidronate alone or in combination with surgery has never clearly been demonstrated.

The newer generation of nitrogen-containing bisphosphonates, such as Pamidronate, acts by inhibition of the mevalonate pathway in osteoclasts.^{50,51} While the main effect of bisphosphonates on bone is antiresorptive by blocking osteoclasts, they also suppress calcification and may even induce osteomalacia in higher doses. The new generation of bisphosphonates is more potent in their antiresorptive action and, thus, these adverse effects in bone mineralization are seen less frequently and only in very high doses.⁵⁸ In addition, amino-bisphosphonates also show immunomodulatory and anti-inflammatory activity by interacting with proinflammatory cytokines, such as interleukin (IL)-1, the tumour necrosis factor and IL-6, and therefore inhibiting the antigen-presenting capacity of macrophages.^{39–42} What this different mode of action implicates for the clinical potential in the treatment of HO is unknown. Thus, the new generation of bisphosphonates may produce less osteomalacia but theoretically may also have a lower potential of inhibiting HO. Therefore very high doses of intravenous amino-bisphosphonates administered over a longer period of time are theoretically needed in the treatment of HO. Our dose schedule was adapted to the normal Pamidronate dose given for the treatment of Paget's disease (eg 60–90 mg Pamidronate/day for three consecutive days) and amounted to a total of 680–1200 mg.^{59,60} However, this approach is empirical and the optimal dose schedule still needs to be established.

Amino-bisphosphonate is a potential agent for the treatment of diseases of osteoclast overactivity such as metastatic bone disease. Currently, its uses include hypercalemic states due to neoplastic bone involvement, active Paget's disease and high turn over osteoporosis. Interestingly, recent studies and case reports support its efficacy in different inflammatory, dysmorphic bone disease such as diabetic neuropathy (Charcot), reflex sympathetic dystrophy (M Sudeck), ankylosing spondylitis, or the SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis and osteitis).^{39–43,61,62} In these inflammatory syndromes of largely unknown cause and pathophysiology, amino-bisphosphonates are administered not only because of their antiosteoclastic effect, but rather for their immunomodulatory and anti-inflammatory properties. If bisphosphonate therapy has been suggested to control bone metabolism activity in these multiple destructive inflammatory bone condi-

tions, it is reasonable to believe that it may have a role in controlling osteoblast and osteoclastic activity in the acute inflammatory phase of HO.

Our study suggests that this strategy was effective and high doses of intravenous Pamidronate appeared to be safe in our five patients with HO of different origin. None of our patients showed signs of early side effects of the treatment such as fever and haematological changes, gastrointestinal or nephrological toxicity or hepatic failure.⁶³ However, caution is warranted in the long-term use of high doses of Pamidronate. Undesirable effects on the healthy bone, such as a possible decrease of bone turnover, resulting in osteomalacia or osteoporosis, have been reported. Thus bone treated with high doses of bisphosphonates may become brittle rather than better.⁶⁴ In addition, bisphosphonates have a prolonged half-life in bone tissue and they could have a cumulative toxic effect. It has been suggested that close monitoring of biochemical markers of bone turnover should help to guide clinicians.^{64–66} However, none of our patients showed clinical symptoms of osteomalacia such as general bone pain or lower back pain, muscular weakness, or osteoporosis with decrease in height and pathological fractures. Laboratory studies, including bone-specific alkaline phosphatase, alkaline phosphatase, osteocalcin and urinary crosslinks showed uniformly normal results, arguing against impaired bone turnover. However, we did not perform bone biopsies for histological confirmation.

Biochemical analysis of one patient showed elevated levels of PTH and a slightly decreased phosphorus level. However, this finding had been observed already prior to bisphosphonate therapy. Since no history and no signs of hyperparathyroidism were reported and since all biochemical parameters were within normal limits coincidence is likely.

Our study is tampered with a small, heterogeneous study size and the limitations of any retrospective study without a placebo control group, which is mandatory in further investigations aimed at confirming our results. However, historical data on the natural outcome of excision surgery in this population of patients without treatment indicate a recurrence rate over 50%.^{27–34} Accordingly, a recurrence of HO in at least two of our five patients would be anticipated. But in contrast, in none of our five high-risk patients such a recurrence occurred. To the contrary, patient 4 showed an early rebound after the first excision surgery without Pamidronate protection. Notably, after the second attempt with intravenous Pamidronate there was no recurrence of HO. Since in all instances we dealt with established HO, triple phase scan was not performed but should be included in the future in the follow-up studies before surgery. Such a scan may help to identify the optimal time point for the use of Pamidronate.

In conclusion, our retrospective study suggests a protective effect of the parenteral administration of amino-bisphosphonates to prevent recurrence of HO. Despite this encouraging effect, the issue whether

bisphosphonates will alter the natural course of HO remains unresolved. In view of the therapeutic dilemma and no true medical alternatives our data may help to restudy the problem of HO in a prospective controlled intervention study in a larger cohort of HO patients. Based on our results we propose the following therapeutic algorithm for high-risk patients undergoing excision surgery: continued Pamidronate infusion immediately before the operation at a dosage of 120 mg in the first 12 h and subsequently reduction to 75–60–30–15 mg/12 h over a period of 10–14 days. Further studies are encouraged to identify the necessary dosage and duration of treatment and to pinpoint which patients will benefit most from this treatment.

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