



Review

Biphosphonates for the therapy of complex regional pain syndrome I – Systematic review

Florian Brunner^{a,*}, Annina Schmid^b, Rudolf Kissling^a, Ulrike Held^c, Lucas M. Bachmann^c

^aDepartment of Physical Medicine and Rheumatology, Balgrist University Hospital, Forchstrasse 340, 8008 Zurich, Switzerland

^bDepartment of Physical Therapy and Rheumatology, Balgrist University Hospital, Forchstrasse 340, 8008 Zurich, Switzerland

^cHorten Centre for Patient Oriented Research, University of Zurich, Bolleystrasse 40, Postfach Nord, CH-8091 Zurich, Switzerland

ARTICLE INFO

Article history:

Received 10 August 2007

Received in revised form 15 January 2008

Accepted 2 March 2008

Available online 28 April 2008

Keywords:

Reflex sympathetic dystrophy

Biphosphonates

Drug therapy

ABSTRACT

Objectives: Several studies found that biphosphonates counteract locally increased bone resorption and associated pain in patients with complex regional pain syndrome I (CRPS I). We performed a systematic review of all randomised controlled trials to assess the benefit of biphosphonates in the treatment of CRPS I patients with bone loss.

Data sources: We searched Medline, Embase (April 2007) and the Cochrane Library and screened bibliographies of included studies.

Review methods: We selected randomised trials comparing biphosphonates with placebo, with the goal of improving pain, function and quality of life in patients with CRPS I. Two reviewers independently assessed trial eligibility and quality, and extracted data. Where data were incomplete or unclear, conflicts were resolved with discussion and/or trial authors were contacted for further details. We calculated the study size weighted pooled mean reduction of pain intensity (measured with a visual analogue scale (VAS)).

Results: Four trials of moderate quality fulfilled our inclusion criteria. In respect to function and quality of life there was a trend in favour of biphosphonates but differences in outcome assessment impeded pooling of results. Two trials provided sufficient data to pool pain outcomes. Biphosphonates reduced pain intensity by 22.4 and 21.6 mm on a VAS after 4 and 12 weeks of follow-up. Data on adverse effects were scarce.

Conclusions: The very limited data reviewed showed that bisphosphonates have the potential to reduce pain associated with bone loss in patients with CRPS I. However, at present there is not sufficient evidence to recommend their use in practice.

© 2008 European Federation of Chapters of the International Association for the Study of Pain. Published by Elsevier Ltd. All rights reserved.

1. Introduction

Complex regional pain syndrome I (CRPS I) is a common, disabling and poorly understood disorder (Kock et al., 2003). The syndrome is characterized by pain and various combinations of autonomic, sensory, motor, and trophic changes (Veldman et al., 1993; Merskey and Bogduk, 1994; Bruehl et al., 1999). The precise causes of CRPS I are unknown; it often develops after a trauma, such as an injury or surgery (Maihofner and Birklein, 2007).

Due to the complexity of this disorder, involving the peripheral as well as the central neural system, there is no evidence of an effective treatment (Maihofner and Birklein, 2007). No definite treatment algorithm has been established, although numerous therapeutic approaches have been described in the past with varying success (Forouzanfar et al., 2002). According to the currently

available guidelines, treatment is usually based on a multimodal concept including medical treatment, physical therapy, occupational therapy and psychotherapy (Stanton-Hicks et al., 1998, 2002; Perez et al., 2007; Harden, 2006).

Among other physical agents, the use of biphosphonates in the treatment of CRPS I was recommended when calcitonin is inefficient or when calcitonin injections are not well tolerated (Chauvin-eau et al., 2005). Biphosphonates are potent antiosteoclastic agents which are often used for the treatment of several bone related pathologies such as Paget's disease, metastatic cancer, myeloma and acute vertebral fractures.

CRPS I may be associated with a localized bone resorption in the affected limb which results from osteoclastic hyperactivity (Adami et al., 1997). Therefore, several authors hypothesized that the use of biphosphonates might be beneficial in the treatment of CRPS I because these agents counteract bone resorption and show some analgetic effect. (Reviewed in Schott (1997)) We set out to perform a systematic review of all randomized controlled trials testing the

* Corresponding author.

E-mail address: florian.brunner@balgrist.ch (F. Brunner).

benefit of biphosphonates in CRPS I treatment and to summarize the value of this promising drug.

2. Methods

This systematic review was performed applying rigorous published methods (Center for Reviews and Dissemination, Report 4, 2001).

2.1. Identification of studies

We searched Medline (PubMed Version) and Embase (Ovid® interface) from inception to April 2007 using the search terms complex regional pain syndrome, CRPS, algoneurodystrophy, algodystrophy, shoulder–hand syndrome, reflex sympathetic dystrophy, RSD, and Sudeck. Searches in the Cochrane Central Register of Controlled Trials (2007, Issue 2) and screening bibliographies of all included studies complemented our searches. We imposed no language restrictions. We looked for randomised trials comparing biphosphonates with placebo, with the goal of improving pain, function and quality of life in patients with CRPS I.

2.2. Study selection

One reviewer (FB) designed the search strategy and performed the searches. Two reviewers (FB and AS) independently screened the titles, keywords and abstracts of all retrieved records against the inclusion criteria. They looked for randomised studies including patients with the diagnosis of CRPS 1 and comparing biphosphonates against placebo. Then, the reviewers assessed the full text of potentially eligible papers to ascertain that the studies met the inclusion criteria. Disagreements on inclusion were resolved by discussion or through arbitration by a third reviewer (LMB).

2.3. Data extraction

Two reviewers (FB, AS) independently extracted the salient features from each trial using a data extraction form that was pre-tested using one included trial. From each study we secured setting (e.g. year, country of origin), number of participants, and site of CRPS, type of intervention, dosage and application mode and duration of intervention. We also registered types of outcome measures, timing of outcome assessments and the corresponding results. Finally, we registered all published adverse effects.

2.4. Assessment of study quality

Two reviewers (FB, AS) independently evaluated the methodological quality of each included trial. Based on existing recommendations (ter Riet and Kessels, 1997) we developed a quality assessment form. The form was piloted on the first paper to check for any misunderstandings when addressing the items and revised where necessary. Disagreements were resolved by consensus. A third reviewer (LMB) arbitrated persisting disagreements.

2.5. Statistical analysis

In this study, we assessed the agreement according to published recommendations between two reviewers using kappa statistics (Kirkwood and Sterne, 2006). The kappa statistics is based on comparing the observed proportion of agreement between two readings (A_{obs}) made by the two testers, with the proportion of agreements that would be expected simply by chance (A_{exp})

$$\text{Kappa} = (A_{\text{obs}} - A_{\text{exp}}) / (1 - A_{\text{exp}})$$

Landis and Koch propose the following interpretation of the kappa statistic: kappa > 0.75 represents excellent agreement, values of kappa between 0.4 and 0.75 represent fair to good agreement, and kappa values less than 0.4 show moderate or poor agreement (Landis and Koch, 1977). Where available, we calculated differences in outcome parameters from baseline per group and analysed differences between groups. We decided to pool the results of studies if they reported on the same outcome measure and timing. These data were only available for pain assessment using a visual analogue scale at four and twelve weeks of follow-up. Mean VAS differences were pooled using variance weights.

3. Results

Our searches retrieved 1767 records from which 16 appeared to be potentially relevant. Full text assessment resulted in exclusion of 12 additional studies. In total four trials were included in this review (Adami et al., 1997; Varenna et al., 2000; Manicourt et al., 2004; Robinson et al., 2004). (For study selection details please see Fig. 1.)

3.1. Description of studies

In total 118 patients (intervention group $n = 59$, control group $n = 59$) with CRPS 1 were treated. All four RCT's were small, including less than 30 patients in one study arm. Mean age was 51.7 years; mean disease duration was 12.5 months (range 3.5–21.6 months). The site of CRPS 1 was more in the lower extremity ($n = 89$) than in the upper extremity ($n = 30$). Trauma ($n = 38$) and fracture ($n = 28$) were the most frequent initiating events causing CRPS 1. The participants were treated either with oral ($n = 1$) (Manicourt et al., 2004) or intravenous administration ($n = 3$) (Adami et al., 1997; Varenna et al., 2000; Robinson et al., 2004) of a biphosphonate compound. Alendronate was used in two studies, pamidronate (Robinson et al., 2004) and clondronate (Varenna et al., 2000) were administered once. Side effects were evaluated in all four studies and were rare.

The characteristics of the included trials are summarized in Table 1.

3.2. Methodological quality of included studies

The agreement between the two reviewers was excellent. (Agreement on 78 of the 88 item scores (89%); kappa = 0.80). No arbitration was necessary.

All four included studies were considered to be of moderate quality (Table 2).

3.3. Evidence of improvement of quality of life and function

Two studies showed a significant improvement of joint mobility (Adami et al., 1997; Manicourt et al., 2004). Due to different measures of range of motion, statistical pooling was not possible (goniometer (Manicourt et al., 2004) vs. arbitrary score (Adami et al., 1997)). One study showed a significant improvement of physical function in the treatment group by assessing SF-36 after 1 and 3 months (Robinson et al., 2004). None of the studies considered measuring the aspect of quality of life.

3.4. Evidence of effectiveness

Due to the variability in respect to interventions, enrolment criteria, control treatments, duration of follow-up visits and outcome measures, only two out of four studies were considered clinically comparable regarding pain intensity (VAS) after 4 and 12 weeks

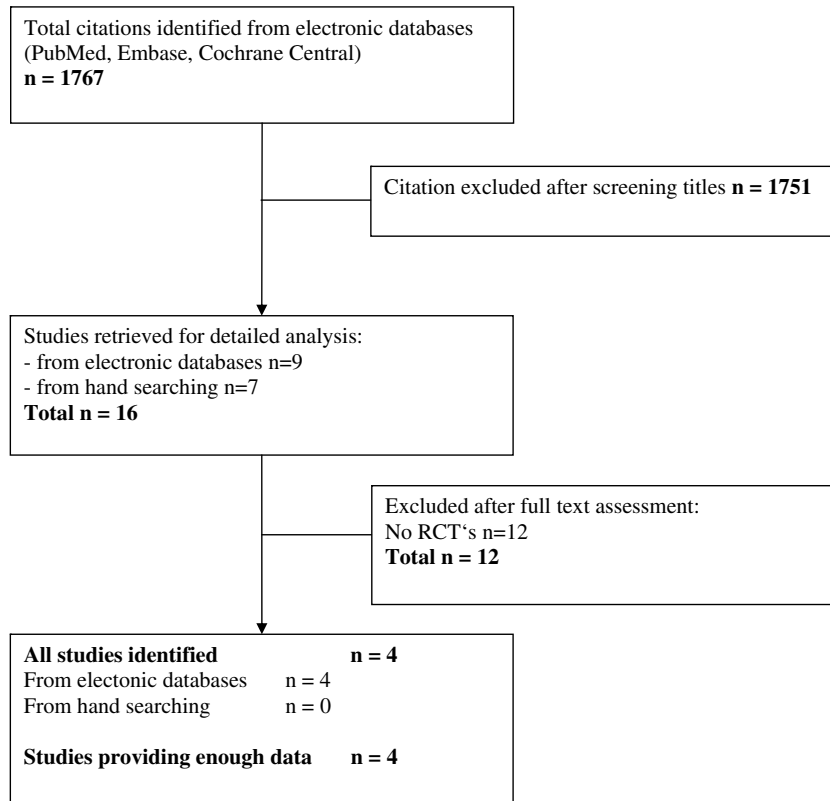


Fig. 1. Study flow from identification to final inclusion of studies.

(Manicourt et al., 2004; Robinson et al., 2004). Statistical pooling showed a weighted average of -22.4 after 4 weeks and -21.6 after 12 weeks on a scale of 100.

4. Discussion

4.1. Main findings

This review has two findings. Evidence from trials investigating the effects of bisphosphonates in CRPS I are still scarce. Pooled analysis of two small trials suggests that these agents have a favourable effect on pain management. In respect to other clinically relevant outcomes four studies show trends towards favourable effects but differences in trial design impede exhaustive quantitative assessments at this stage.

4.2. Results in light of existing evidence

In a narrative review published in 2005 in French, Chauvineau and colleagues (Chauvineau et al., 2005) made a first attempt to summarize the effects of bisphosphonates in CRPS I treatment. In that review, which did not include a formal meta-analysis, the authors felt that current evidence was insufficient to set proper indication for treatment or to estimate treatment effects (Chauvineau et al., 2005). The review did not apply up to date systematic review methodology, did not search all relevant electronic databases and was incomplete in respect to quality assessment. Since electronic searches were limited to 2003 they missed two studies (Manicourt et al., 2004; Robinson et al., 2004) out of which one study contributed data to our meta-analysis (Manicourt et al., 2004). On the other hand, Chauvineau and colleagues included two studies that we excluded from our analysis. The paper by Liens

et al. (1995) studied patients with questionable cases of CRPS I and the paper by Cohen and Uebelhart (1998) used an active control (calcitonin).

4.3. Strength and limitations

The strength of this study includes the application of robust systematic review methodology. We made strenuous efforts to minimize the risk of selection bias. Relevant reports were searched systematically and without language restriction. Also, we attempted to perform a meta-analysis. But, due to the limited number of available studies, the variability in terms of study population, interventions, duration of follow-up and outcome measures, pooling of results was limited to pain intensity (VAS) after 4 and 12 weeks. Other clinically relevant outcomes such as improvements in range of motion, oedema and quality of life could not be assessed meta-analytically. In addition, all studies were rather small resulting in imprecise estimates.

4.4. Implications for practice

The current guideline published by a consensus report in 1998 does not recommend bisphosphonates in CRPS I treatment. Stanton-Hicks et al. only recommend the use of subcutaneous calcitonin for a mild effect on spontaneous pain, the use of oral or intravenous bisphosphonates was not part of their recommendations (Stanton-Hicks et al., 1998). We think, that it is still too early to recommend broad application of bisphosphonates in CRPS I management. Treatment should be initiated only within research protocols that clearly define exposures, and involve standardised outcome assessments. Moreover, treatment regimens should always be based on a multidisciplinary approach rather than the use of a single medication.

Table 1
Summary of included trials

Author, year	Number of subjects (intervention/control)	Active component, dosage, administration	Duration of exposure	Outcomes	Follow-up duration	Side effects	Results
Adami et al. (1997)	20 (10/10)	Alendronate 7.5 mg intravenous	3 days, after 14 days open labelled for all participants for 3 days	VAS (spontaneous pain and tenderness), arbitrary score for motion (0–4) assessed by physician, circumference (skin labelling), bone mineral content	Twice before treatment, 2 and 4 weeks	3 patients from control group with fever	<ul style="list-style-type: none"> Intervention group: spontaneous pain, tenderness, swelling was statistically significant decreased from baseline, also when compared to first 14 days of control group and from week 2 to 4. Improvement of motion. Control group: no relevant symptomatic changes after first of 14d follow-up, but response to open alendronate therapy given afterwards. Bone mineral content was lower in 12 patient with affected hand.
Varenna et al. (2000)	32 (15/17)	Clondronate 300 mg/d intravenous	10 days	VAS, clinical global assessment (0–3), efficacy verbal score, hydroxyprolin/kreatinin ratio	Before treatment, 40 days, 90 days, 180 days, (phone: 9 and 12 months)	3 patients from control group with asymptomatic hypocalcemia	<ul style="list-style-type: none"> Intervention group with significant differences in all clinical variables. Pooling results of all 32 patients after clondronate: 30 patients significantly improved. Inverse correlation between baseline hydroxyprolin/kreatinin ratio and decrease of VAS were found after 90 days (predictive factor).
Manicourt et al. (2004)	39 (19/20)	Alendronate 40 mg/d orally	8 weeks, 4 weeks nontherapeutic period, 8 weeks open extension	VAS, tenderness (dolorimeter), edema (circumference), joint mobility (goniometer), N-Telopeptide	4, 8, 12, 16, 20, 24 weeks	One drop out from control group due to gastrointestinal side effect	Alendronate group marked and sustained improvement: pain, pressure tolerance, joint mobility, N-Telopeptide
Robinson et al. (2004)	27 (14/13)	Pamidronate 60 mg intravenous	Single infusion	VAS, global assessment of disease severity score, SF-36	1, 3 months	5 patients from treatment group and two patients from control group with influenza typed symptoms, 2 patients from control group with infusion site reaction	<ul style="list-style-type: none"> Improvement in pain score, patient's global assessment of disease severity score and physical function in intervention group at 3 months Improvement in physical function at 1 and 3 months

Table 2
Methodological quality assessment of included studies

	Author, year			
	Adami et al. (1997)	Varena et al. (2000)	Manicourt et al. (2004)	Robinson et al. (2004)
<i>Descriptors</i>				
<i>External validity</i>				
Population	1	1	1	1
Intervention(s)	1	1	1	1
Outcomes	1	1	1	1
Duration of follow-up	1	1	1	1
Assessment of adverse effects	1	1	1	1
<i>Internal validity</i>				
Selection of a prognostically homogenous study population	2	3	1	3
Blinding of persons who assess inclusion criteria	2	4	4	4
Pre-stratification on prognostically relevant variables	4	4	4	3
Random allocation (description of procedure)	2	1	1	2
Registration of loss to follow-up	1	1	1	1
Blinding of patients	1	1	1	1
Blinding of persons(s) who implement interventions	1	1	4	1
Registration of co-interventions that bear on outcome for each group	2	1	3	3
Blinding of persons(s) who assess treatment effects	4	1	4	4
Check to what extent blinding was successful	2	2	4	2
<i>Data description and analysis</i>				
Measures of central tendency and their confidence intervals	1	1	1	1
Statistical methods	1	1	1	1
The way missing values were dealt with	2	3	3	1
An intention to treat analysis	2	2	2	1
The distributions of baseline characteristics	3	1	1	1
The way any unbalance in prognostic variables was adjusted for (if deemed necessary)	2	1	2	1
<i>Compliance</i>				
Compliance (dose, timing)	1	1	1	1

1: appropriately addressed; 2: partially addressed; 3: inappropriately addressed and 4: not addressed.

5. Conclusions

In conclusion, the very limited data reviewed showed that bisphosphonates have the potential to reduce pain in patients with CRPS I. However, at present there is not sufficient evidence to recommend their use in practice. To prove the possible beneficial effect in reducing pain, we recommend high quality randomised studies with clear inclusion and exclusion criteria and with a sufficient sample size. The outcome measures should include overall improvement in function and decreasing pain, quality of health status, return to work and side effect. In addition, optimum dosage, frequency and duration of treatment must be further examined.

References

- Adami S, Fossaluzza V, Gatti D, Fracassi E, Braga V. Bisphosphonate therapy of reflex sympathetic dystrophy syndrome. *Ann Rheum Dis* 1997;56(3):201–4.
- Bruehl S, Harden RN, Galer BS, Saltz S, Bertram M, Backonja M, et al. External validation of IASP diagnostic criteria for complex regional pain syndrome and proposed research diagnostic criteria. *International Association for the Study of Pain. Pain* 1999;81(1–2):147–54.
- Center for Reviews and dissemination, Report 4 – Undertaking systematic reviews of research on effectiveness: CRD's guidance for carrying out or commissioning reviews. 2nd ed. University of York, UK; March 2001.
- Chauvineau V, Codine P, Herisson C, Pellas F, Pelissier J. What is the place of diphosphonates in the treatment of complex regional pain syndrome I? *Ann Readapt Med Phys* 2005;48(3):150–7.
- Cohen P, Uebelhart D. Indications du Pamidronate disodique dans le traitement des algodystrophies post-traumatiques ou post-chirurgicales de l'extremite distale du membre supérieur. In: Simon L, Pelissier J, Hérisson C, editors. *Progres en MPR*. Paris: Masson; 1998. p. 510–4.
- Forouzanfar T, Koke AJ, van Kleef M, Weber WE. Treatment of complex regional pain syndrome type I. *Eur J Pain* 2002;6(2):105–22.
- Harden N, editor. *Complex regional pain syndrome: treatment guidelines*. Milford, CT: RSDSA Press; 2006.

- Kirkwood B, Sterne J. *Essential medical statistic*. Oxford, UK: Blackwell Publishing Limited; 2006.
- Kock FX, Borisch N, Koester B, Grifka J. Complex regional pain syndrome type I (CRPS I). Pathophysiology, diagnostics, and therapy. *Orthopade* 2003;32(5):418–31.
- Landis JR, Koch GG. An application of hierarchical kappa-type statistics in the assessment of majority agreement among multiple observers. *Biometrics* 1977;33(2):363–74.
- Liens D, Lavoignat D, Meunier P, Delmas P. Biphosphonates et Algodystrophie Réflexes. In: Simon L, Péllissier J, Hérisson C, editors. Paris: Masson; 1995. p. 380–2.
- Maihofner C, Birklein F. Complex regional pain syndromes: new aspects on pathophysiology and therapy. *Fortschr Neurol Psychiatr* 2007;75(6):331–42.
- Manicourt DH, Brasseur JP, Boutsen Y, Depreux G, Devogelaer JP. Role of alendronate in therapy for posttraumatic complex regional pain syndrome type I of the lower extremity. *Arthritis Rheum* 2004;50(11):3690–7.
- Merskey H, Bogduk K. *Classification of chronic pain: definitions of chronic pain syndromes and definition of pain terms*. Seattle: IASP Press; 1994.
- Perez RS, Zollinger PE, Dijkstra PU, Thomassen-Hilgersom IL, Zuurmond WW, Rosenbrand CJ, et al. Clinical practice guideline 'Complex regional pain syndrome type I'. *Ned Tijdschr Geneesk* 2007;151(30):1674–9.
- Robinson JN, Sandom J, Chapman PT. Efficacy of pamidronate in complex regional pain syndrome type I. *Pain Med* 2004;5(3):276–80.
- Schott GD. Bisphosphonates for pain relief in reflex sympathetic dystrophy? *Lancet* 1997;350(9085):1117.
- Stanton-Hicks M, Baron R, Boas R, Gordh T, Harden N, Hendler N, et al. Complex regional pain syndromes: guidelines for therapy. *Clin J Pain* 1998;14(2):155–66.
- Stanton-Hicks MD, Burton AW, Bruehl SP, Carr DB, Harden RN, Hassenbusch SJ, et al. An updated interdisciplinary clinical pathway for CRPS: report of an expert panel. *Pain Pract* 2002;2(1):1–16.
- ter Riet G, Kessels A. Validity checklist for clinical trials. *Complement Ther Med* 1997;116–8.
- Varena M, Zucchi F, Ghiringhelli D, Binelli L, Bevilacqua M, Bettica P, et al. Intravenous clodronate in the treatment of reflex sympathetic dystrophy syndrome. A randomized, double blind, placebo controlled study. *J Rheumatol* 2000;27(6):1477–83.
- Veldman PH, Reynen HM, Arntz IE, Goris RJ. Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients. *Lancet* 1993;342(8878):1012–6.