apparent increase may be due to changes in the perception of minor wheezing symptoms.

A final point to be noted in our results is the high use of asthma medication in children who lack either a recent history of wheeze or a diagnosis of asthma. This suggests that asthma is being overtreated or overdiagnosed in a significant number of children and reinforces the need to review and step down asthma treatment in children when symptom control is adequate.

In conclusion, our results suggest an increase in the prevalence of both diagnosed asthma and current wheeze between 1991 and 1999 in 8–9 year old Sheffield children. This appears to be due to the combination of an increase in minor wheeze symptoms and a rise in diagnostic labelling. We found no significant change in asthma severity. Although this may be due in part to an increase in prescription of anti-inflammatory medication, the large number of children without current wheeze who are receiving asthma medication suggests that there may be significant overtreatment of children with such drugs.

We would like to thank the schools and parents who contributed to the study and Clare Billings, Simon Billings, and Sarah Primhak for their help with data input.

Funding: GNMK, RD, and CG received salary support from GlaxoWellcome (for an unrelated clinical study) and AP from the Special Trustees of the former United Sheffield Hospitals.
Conflict of interests: none.

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Thorax 2001;**56**:314–316

Effect of intravenous pamidronate on bone mineral density in adults with cystic fibrosis

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Received 5 June 2000
Returned to authors
3 October 2000
Revised version received
8 November
Accepted for publication
18 December 2000

Abstract

***Background*—Low bone mineral density (BMD) is prevalent in adults with cystic fibrosis. The aim of this study was to assess the effect of intravenous pamidronate on BMD in these subjects.**

***Methods*—Patients were invited to participate if they had a BMD Z score of –2 or less in the lumbar spine, proximal femur, or distal forearm. Patients were randomised to receive either 30 mg intravenous pamidronate every 3 months + 1 g calcium daily (pamidronate group) or 1 g calcium daily (control group). All pancreatic insufficient patients were prescribed oral vitamin D supplements.**

***Results*—After 6 months of treatment the pamidronate group (n=13) showed a significant increase in absolute BMD compared with the control group (n=15) in the lumbar spine (mean difference 5.8% (CI 2.7% to 8.9%)) and total hip (mean difference 3.0% (CI 0.3% to 5.6%)). However, the pamidronate group showed a reduction in BMD compared with the control group in the distal forearm (mean difference –1.7% (CI –3.7% to 0.3%)). The use of pamidronate was associated with a high incidence of bone pain in non-corticosteroid treated individuals.**

***Conclusion*—Intravenous pamidronate increases axial BMD in adults with cystic fibrosis, but the high incidence of bone pain associated with this treatment might limit its use.**

(*Thorax* 2001;**56**:314–316)

Keywords: cystic fibrosis; bone mineral density; osteoporosis; pamidronate; bisphosphonates

Low bone mineral density (BMD) is prevalent in adults with cystic fibrosis.[1 2] Biochemical and histomorphometric studies suggest that osteoblastic activity is reduced and that osteoclastic activity is increased.[3 4] As bisphosphonates are potent inhibitors of osteoclastic bone resorption, they are a logical therapeutic choice to treat adult cystic fibrosis patients with low BMD. The aim of this study was to assess the effect of intravenous pamidronate on BMD in adults with cystic fibrosis.

Methods

STUDY POPULATION

In 1998, after 1 year of follow up in a longitudinal BMD study, patients with cystic fibrosis aged 18 years of over who had a BMD Z score of –2 or less in the lumbar spine, proximal femur, or distal forearm were offered the option of participating in this treatment trial. Thirty one of the 44 eligible patients (70%) agreed to participate.

All patients were attending the Manchester Adult Cystic Fibrosis Unit and the diagnosis of cystic fibrosis was confirmed by gene analysis. The study was approved by the South Manchester research ethics committee and each patient provided written informed consent.

STUDY DESIGN

Patients were randomised to receive for a 1 year period either 30 mg intravenous pamidronate (Aredia Dry Powder, Novartis, Camberley, Surrey, UK) every 3 months + 1 g calcium daily (Calcichew Forte, Shire Pharmaceuticals, Andover, Hants, UK) or 1 g calcium daily. All pancreatic insufficient patients were prescribed vitamin D supplements (900 IU daily) long term.

BMD was measured in the lumbar spine and proximal femur (total hip) by dual energy *x* ray absorptiometry (QDR 4500 Acclaim densitometer, Hologic, Waltham, Massachusetts, USA) and in the distal forearm by single energy *x* ray absorptiometry (Osteometer DTX-100 densitometer, Osteometer Meditech, Rødovre, Denmark) at the beginning and end of the study. The short term departmental precision for each bone densitometry technique was derived from repeated measurements in 10 subjects. Expressed as a coefficient of variation (CV), the short term precision was 1.1% in the lumbar spine, 1.3% in the total hip, and 1.0% in the distal forearm. The long term precision was derived from scanning an appropriate phantom, giving a CV of 0.63% for the Osteometer DTX-100 forearm scanner and 0.22% for the Hologic QDR 4500 scanner. The baseline BMD results were expressed as Z scores and the reference data were provided by the densitometer manufacturers. The percentage change in BMD over the treatment period was calculated from the absolute BMD values (g/cm^2) recorded at the beginning and end of the study.

STATISTICAL ANALYSIS

Data were analysed using SPSS version 7.0 (SPSS Inc, Chicago, Illinois, USA). The continuous variables were normally distributed and summarised using the mean (SD) values. Differences between groups were identified using the unpaired Student's *t* test.

Table 1 Percentage change in bone mineral density (g/cm^2) after 6 months of treatment

	Pamidronate group (n=13)	*Control group (n=15)*	*Mean (95% CI) difference in changes between groups*	*p value*
Lumbar spine	4.1%	–1.7%	5.8% (2.7% to 8.9%)	0.001
Total hip	1.7%	–1.3%	3.0% (0.3% to 5.6%)	0.029
Distal forearm	–1.1%	0.6%	–1.7% (–3.7% to 0.3%)	0.095

Results

PATIENT CHARACTERISTICS

Thirty one patients were recruited to the trial, none of whom had received bone sparing agents in the past. Fifteen patients were randomised to the pamidronate + calcium group (pamidronate group) and 16 patients were randomised to the calcium only group (control group). Three patients did not complete the study; one patient in each group died of respiratory failure and one patient in the pamidronate group received a double lung transplant.

On recruitment to the study the mean (SD) age, body mass index, and forced expiratory volume in one second in the pamidronate group compared with the control group were: 25.1 (6.3) *v* 26.9 (5.4) years (NS); 20.3 (2.4) *v* 21.8 (2.9) kg/m^2 (NS); and 49.0 (18.1) *v* 52.7 (22.6)% predicted (NS), respectively. One patient in the control group was pancreatic sufficient. All other patients were prescribed long term oral vitamin D supplements (900 IU daily). On recruitment to the study the mean (SD) 25-hydroxyvitamin D level in the pamidronate group was 22.4 (18.5) ng/ml compared with 19.5 (10.5) ng/ml in the control group (NS). Of the patients who completed the trial, four in the pamidronate group and nine in the control group required one or more courses of oral corticosteroid therapy during the treatment period.

BONE MINERAL DENSITY

The baseline BMD Z scores in the pamidronate and control groups were –2.2 (1.1) *v* –2.3 (0.9) in the lumbar spine (NS), –2.0 (0.9) *v* –1.6 (0.7) in the total hip (NS), and –1.7 (0.9) *v* –1.4 (0.8) in the distal forearm (NS). The percentage change in absolute BMD (g/cm^2) at each skeletal site during the treatment period is shown in table 1.

ADHERENCE

Of the patients who completed the trial, all those in the pamidronate group received two pamidronate infusions during the 6 month treatment period and the mean (SD) adherence with calcium supplementation, calculated by a residual tablet count, was 75 (27)% in the pamidronate group and 76 (26)% in the control group (NS).

ADVERSE EVENTS

As previously reported,[5] 11 of the 15 patients randomised to receive intravenous pamidronate developed moderate to severe bone pain after the first dose. None of the patients who developed bone pain were taking oral corticosteroid therapy at the time of pamidronate infusion.[6] However, three of the four patients (p=0.009) who were pain free had been taking 10–15 mg prednisolone long term (two for unstable lung disease and one for allergic bronchopulmonary aspergillosis). The pattern of bone pain was less consistent following the second pamidronate infusion; most patients experienced pain, but it was of a lesser severity. None of the patients in the control group developed bone pain. The duration of the trial

was shortened from 1 year to 6 months because of the adverse events.

Discussion

In adult patients with cystic fibrosis related low BMD intravenous pamidronate + oral calcium resulted in a significant increase in lumbar spine and total hip BMD compared with oral calcium alone. A significant side effect was bone pain in non-corticosteroid treated individuals.[5 6]

This is the first study to evaluate the efficacy of bisphosphonate treatment in non-transplanted cystic fibrosis patients with low BMD. An intravenous bisphosphonate was chosen to circumvent the upper gastrointestinal side effects and poor absorption associated with oral bisphosphonates. After 6 months of treatment BMD in the lumbar spine increased by 4.1% in patients receiving pamidronate + calcium compared with a reduction of 1.7% in patients receiving calcium alone. This 5.8% difference between treatment groups compares favourably with the use of alendronate in postmenopausal women in whom there was an 8.8% difference in lumbar spine BMD between treatment and placebo groups after 3 years of follow up.[7] In the present study BMD also increased significantly in the total hip, but there was a reduction in forearm BMD. Similar divergent changes in regional BMD have been reported with the short term use of intravenous pamidronate in Paget's disease.[8] A subsequent study in this patient group showed that calcium and calcitriol prevented peripheral bone loss after intravenous pamidronate.[9] This emphasises the importance of optimising vitamin D levels before starting bisphosphonate treatment.

This study has a number of limitations. Firstly, the data must be interpreted in the context of the small number of patients enrolled and the shortened period of follow up. Secondly, the BMD results might have been influenced by the greater use of corticosteroids in the control group than in the treatment group. Thirdly, sex might have influenced the results as there were a disproportionate number of female patients randomised to the pamidronate group compared with the control group. Despite the above reservations, a recent study using intravenous pamidronate in post-transplant patients with cystic fibrosis reported similar treatment responses.[10] Together these studies emphasise that low BMD is a continuum in cystic fibrosis patients before and after transplantation and that it is amenable to treatment.

In conclusion, intravenous pamidronate caused a rapid increase in axial BMD in adult patients with cystic fibrosis, but the high incidence of bone pain associated with this intervention might limit its use. This study suggests that bisphosphonates may have a role in the management of cystic fibrosis related low BMD. Further studies are required to evaluate their long term safety and efficacy in preventing fragility fractures.

This study was supported by a grant from the Cystic Fibrosis Research Trust, UK. The authors are indebted to D Ledgeton, M Hodgkinson, C Alsop, and R Larder for performing the bone densitometry measurements.

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