Increasing prevalence of asthma diagnosis and symptoms in children is confined to mild symptoms

G Ng Man Kwong, A Proctor, C Billings, R Duggan, C Das, M K B Whyte, C V E Powell, R Primhak

Abstract

**Background**—The prevalence of childhood asthma is increasing but few studies have investigated trends in asthma severity. We investigated trends in asthma diagnosis and symptom morbidity between an eight year time period in a paired prevalence study.

**Methods**—All children in one single school year aged 8–9 years in the city of Sheffield were given a parent respondent questionnaire in 1991 and 1999 based on questions from the International Survey of Asthma and Allergy in Children (ISAAC). Data were obtained regarding the prevalence of asthma and wheeze and current (12 month) prevalences of wheeze attacks, speech limiting wheeze, nocturnal cough and wheeze, and exertional symptoms.

**Results**—The response rates in 1991 and 1999 were 4580/5321 (85.5%) and 5011/6021 (83.2%), respectively. There were significant increases between the two surveys in the prevalence of asthma ever (19.9% v 29.7%, mean difference 11.9%, 95% confidence interval (CI) 10.16 to 13.57, p<0.001), current asthma (10.3% v 13.0%, mean difference 2.7%, 95% CI 1.44 to 4.03, p<0.001), wheeze ever (30.3% v 35.8%, mean difference 5.7%, 95% CI 3.76 to 7.56, p<0.001), wheeze in the previous 12 months (17.0% v 19.4%, mean difference 2.5, 95% CI 0.95 to 4.07, p<0.01), and reporting of medication use (16.9% v 20%, mean difference 3.0%, 95% CI 1.46 to 4.62, p<0.001).

There were also significant increases in reported hayfever and eczema diagnoses.

**Conclusions**—Diagnostic labelling of asthma and lifetime prevalence of wheeze has increased. The current 12 month point prevalence of wheezes has increased but this is confined to occasional symptoms. The increased medication rate may be responsible for the static prevalence of severe asthma symptoms. The significant proportion of children receiving medication but reporting no asthma symptoms identified from our 1999 survey suggests that some children are being inappropriately treated or overtreated.

(Thorax 2001;56:312–314)

Keywords: asthma prevalence; children; diagnostic labelling; asthma treatment

Childhood asthma is common, especially in the UK. Several studies have reported increases in the prevalence of asthma and associated asthma morbidity symptoms using serial questionnaire surveys, but there has been controversy as to whether or not the prevalence of asthma is still increasing. The International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire has been validated and has been used to investigate the prevalence of asthma throughout the world. We used a parent respondent questionnaire based on the ISAAC questions to investigate changes in asthma morbidity and treatment between 1991 and 1999 in two large cohorts of Sheffield children aged 8–9 years.

**Methods**

The methods for the 1991 survey have been described previously and were replicated in the 1999 study. Briefly, all primary schools in Sheffield with year 4 pupils (aged 8–9 years) were approached for the 1999 survey. Individually labelled questionnaires were distributed to schools with instructions for children to take them home for their parents to complete. Non-responders were sent a second identical questionnaire. The χ² test was used to compare the differences between the surveys. The study was approved by the South Sheffield Research Ethics Committee and the Sheffield Education Authority.

**Results**

The results of the 1991 Sheffield schools survey have been reported previously. A total of 5011 of 6021 questionnaires (83.2%) were returned from the 1999 survey. Of all responses where sex was specified, 2459 of 4912 (50.1%) were male. 156 of 5011 respondents (3.1%) indicated that they did not wish to take part in the survey. 4340 questionnaires were returned with all 15 questions completed (354 and 66 returned questionnaires had 14 of the 15 and 13 of the 15 questions completed respectively; a further 253 had fewer than 13 questions completed). Wherever possible answers from part completed questionnaires were included in the data analysis.

Symptoms reported in the preceding 12 months in the two surveys are compared in table 1. Although there were significant increases in the prevalence of wheeze and in
Asthma diagnosis and symptoms in children

**Table 1  Prevalence of asthma and asthma morbidity symptoms in 1991 and 1999**

<table>
<thead>
<tr>
<th>Survey year</th>
<th>1991</th>
<th>1999</th>
<th>% change (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheeze in previous 12 months</td>
<td>771/4563 (17.0%)</td>
<td>932/4803 (19.4%)</td>
<td>+2.51 (0.95 to 4.07)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Wheeze ever</td>
<td>1376/4564 (30.3%)</td>
<td>1720/4810 (35.8%)</td>
<td>+5.66 (3.76 to 7.56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current asthma*</td>
<td>466/4539 (10.3%)</td>
<td>624/4800 (13.0%)</td>
<td>+2.73 (1.44 to 4.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Asthma ever</td>
<td>811/4543 (17.9%)</td>
<td>1428/4808 (29.7%)</td>
<td>+11.86 (10.16 to 13.57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Wheeze attacks &lt;3/month</td>
<td>438/4560 (9.6%)</td>
<td>551/4766 (11.6%)</td>
<td>+1.96 (0.71 to 3.20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Wheeze attacks &gt;3/month</td>
<td>324/4560 (7.1%)</td>
<td>353/4766 (7.4%)</td>
<td>+0.35 (0.12 to 0.57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nocturnal wheeze at least once a week</td>
<td>220/4548 (4.8%)</td>
<td>251/4757 (5.3%)</td>
<td>+0.44 (+0.45 to 1.33)</td>
<td>NSD</td>
</tr>
<tr>
<td>Nocturnal cough at least once a week</td>
<td>363/4435 (8.1%)</td>
<td>392/4784 (8.2%)</td>
<td>+0.05 (+0.06 to 1.17)</td>
<td>NSD</td>
</tr>
<tr>
<td>Frequent exertional wheeze or cough</td>
<td>174/4493 (3.9%)</td>
<td>121/4901 (4.4%)</td>
<td>+0.55 (+0.25 to 1.36)</td>
<td>NSD</td>
</tr>
<tr>
<td>Speech limiting wheeze in last year</td>
<td>136/4558 (3.0%)</td>
<td>125/4749 (2.6%)</td>
<td>+0.4 (+0.14 to 0.30)</td>
<td>NSD</td>
</tr>
<tr>
<td>Eczema ever</td>
<td>820/4523 (18.1%)</td>
<td>1497/4809 (31.1%)</td>
<td>+13.0 (11.27 to 14.72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hay fever ever</td>
<td>554/4508 (12.3%)</td>
<td>787/4802 (16.4%)</td>
<td>+4.1 (2.68 to 5.2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are shown as number/denominator (%). 
CI = confidence interval; NSD = no significant difference.

*Defined by a positive answer to the question “Does your child have asthma at present?”

The prevalence of asthma in children has increased over time. This increase is likely due to a combination of factors, including environmental changes and improved diagnostic methods. The prevalence of asthma among children has doubled in the past two decades, with a significant increase in the diagnosis of asthma among children aged 5–11 years.

Other studies have found that asthma prevalence rates have increased more in urban areas than in rural areas. This suggests that environmental factors, such as pollution and area deprivation, may be playing a role in the increasing prevalence of asthma.

The increase in asthma prevalence rates has also been linked to changes in diagnostic labelling. In the past, asthma was often diagnosed based on symptoms alone, without the use of objective measures such as peak flow measurements. This may have led to an over-diagnosis of asthma.

Another factor that may be contributing to the increasing prevalence of asthma is the increased use of inhaled corticosteroids. This is supported by the increase in reported medication usage in asthmatic children. In a population prevalence study in children aged 7.5–8.5 years from a single London borough, the prevalence of frequent wheeze attacks was unchanged between 1978 and 1991 while markers of severe asthma fell over the same period. The authors concluded that this finding was due to an “improvement in treatment received by wheezy children”.

However, our findings suggest that at least some of the increase in asthma prevalence is due to non-responders. Despite this, the differences in diagnostic criteria and the increased use of inhaled corticosteroids are likely contributing to the rising prevalence of asthma.
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 Clari Billings, Simon Billings, and Sarah Primhak for their help with data input.

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

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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 3.7% to 8.0%)) 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 osteoelastic activity is reduced and that osteoclastic activity is increased.1 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 (Calci chew 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, Hologic, 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/cm²) 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/cm²) 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/m² (NS); and 49.0 (18.1) v 52.7 (22.6)% predicted (NS), respectively. One patient in the control group was pancreatic insufficient. 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/cm²) 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, 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. 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.56

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 calciotriol 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.

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