CRD summary
The authors concluded that bisphosphonates in children with osteogenesis imperfecta were associated with improved bone density, reduced fracture risk and improved growth in some (not all) studies. A lack of reporting of review methods and an unfocused synthesis that did not reflect evidence based on a small number of studies of questionable quality meant these conclusions may not be reliable.

Authors' objectives
To evaluate the effects of bisphosphonate treatment in children with osteogenesis imperfecta.

Searching
PubMed, CINAHL and Cochrane Database of Systematic Reviews were searched from inception to April 2007 for studies published in English. Search terms were reported. Reference lists of reviews and studies were screened and researchers contacted for other studies.

Study selection
Studies that evaluated bisphosphonates in children (aged <18 years at time of treatment) with osteogenesis imperfecta were eligible for inclusion. Definitions of osteogenesis imperfecta were provided online (accessed 16/6/09, see URL for Additional Data). Only studies graded level I to III for study design were included in the assessment of efficacy (see validity assessment below).

The included studies compared: bisphosphonates (olpadronate, neridronate and alendronate) with no bisphosphonates; continuation versus discontinuation of pamidronate; and pamidronate versus alendronate. Studies had osteogenesis imperfecta forms I to IV (mostly I, III and IV, related to defects in the type I pro-collagen gene). Most participants were three to 18 years of age; one study included infants (apparently aged 25 to 46 days). The review assessed body function/body structure, activity and participation and environmental factors.

The authors stated neither how papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
The authors classified studies as having strong, moderate or weak validity based on the following criteria: inclusion and exclusion criteria; description of and adherence to the intervention; description, validity and reliability of outcome measures; blinding of outcome assessment; statistical analysis and power calculation; reporting of losses to follow-up and drop-outs and whether losses were less than 20%; and control of confounders. Studies were graded using the hierarchy of study design described by American Academy for Cerebral Palsy and Developmental Medicine; only studies graded level I (randomised controlled trials, RCTs) to III (cohort studies with concurrent control or case-control studies) were quality assessed.

The authors did not state how many reviewers assessed validity.

Data extraction
Each outcome in each study was coded as body function/body structure, activity and participation or an environmental factor. The statistical significance of the difference between treatment groups or change from baseline was extracted for each outcome.

The authors stated neither how data were extracted for the review nor how many reviewers performed the data extraction.
Methods of synthesis
The studies were grouped by type of outcome and combined in a narrative synthesis.

Results of the review
Eight studies (n=200) were included in the assessment of efficacy: seven RCTs and one cohort study. Sample sizes ranged from 10 to 64. It appeared that 41 studies provided information on safety.

Methodological limitations of the efficacy studies included that none of the studies reported a power calculation, a lack of blinded outcome assessment and a lack of reporting of losses to follow-up or losses greater than 20%.

Biphosphonates versus no biphosphonates (five RCTs):
Body function/body structure (seven outcomes). Studies showed inconsistent changes in markers of bone metabolism measured at different sites and in pain and use of analgesia and no conflicting changes in linear growth. Biphosphonates were associated with a reduction in fracture rate in several studies and the reduction was statistically significant in three studies.

Activity and participation. Biphosphonates were associated with an improvement in self-care and well-being in only one of several studies reporting this outcome.

Environmental factors. Biphosphonates were associated with no change in need for caregiver assistance in one study.

Safety. The authors stated that few serious short-term adverse events were reported. The most common complications were fever and body aches associated with the first infusion. Reported complications were listed in the review.

Authors' conclusions
In children with osteogenesis imperfecta, biphosphonates were associated with an improvement in bone density and a reduction in fracture rate and improved growth in some but not all studies. Further research was required.

CRD commentary
The review question was clearly stated. Inclusion criteria were defined for intervention and participants. Criteria for study design were broad. Criteria were not defined for outcomes. Several relevant sources were searched, but no attempts were made to minimise publication and language biases. Methods used to select studies, assess validity and extract data were not described, so it was unknown whether efforts were made to reduce reviewer errors and bias. Only studies of a higher quality design were included in the review of efficacy. Validity was assessed and results were reported. Little information about individual studies was provided in the paper; the bulk of the study details was available online. In view of the diversity among studies, a narrative synthesis was appropriate. Review findings were generally summarised in the text without referencing the studies that supplied the evidence; this made it difficult to verify reported findings. There were discrepancies between results reported in the synthesis and the actual evidence (for example, in the synthesis the reduction in fracture rate was reported to be significantly reduced in biphosphonate groups in three studies, but the tables showed a significant reduction compared with no biphosphonates in only two studies). In addition, it was unclear whether studies that compared continued versus discontinued biphosphonates or compared different types of biphosphonates were included in the synthesis. A lack of reporting on review methods, evidence based on a small number of small studies of questionable quality, an unfocused synthesis that did not accurately reflect the evidence and restriction to studies published in English meant the authors' conclusions may not be reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further higher-quality research was required to evaluate biphosphonates in infants with osteogenesis imperfecta and in children with milder forms of the disease and severe forms that are not due to collagen mutations. There was a need to determine the optimal treatment regimen and monitor long-term side effects. Studies should provide details of potential confounding factors and be multicentred to allow adequate recruitment. Studies that compared different dosing regimens should be considered.
Funding
Not stated.

Bibliographic details

PubMedID
19087101

DOI
10.1111/j.1469-8749.2008.03222.x

Original Paper URL
http://onlinelibrary.wiley.com/journal/121570567/abstract

Additional Data URL

Indexing Status
Subject indexing assigned by NLM

MeSH
Body Height /drug effects; Bone Density /drug effects; Bone Density Conservation Agents /adverse effects /therapeutic use; Child; Diphosphonates /adverse effects /therapeutic use; Evidence-Based Medicine; Fractures, Spontaneous /prevention & control; Humans; Long-Term Care; Osteogenesis Imperfecta /drug therapy; Randomized Controlled Trials as Topic

AccessionNumber
12009102552

Date bibliographic record published
29/04/2009

Date abstract record published
10/03/2010

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.