



BISPHOSPHONATE TREATMENT OF OSTEOGENESIS IMPERFECTA

What are Bisphosphonates?

The bisphosphonates are a group of drugs that were first developed in the 1970s and were initially used only in adults with osteoporosis or a condition called Paget's disease. They have a similar chemical structure to a substance called pyrophosphate which is present naturally in the body and is responsible for preventing deposits of calcium being formed in the wrong place eg skin and urine. The chemical structure of bisphosphonates allows them to attach to calcium-containing crystals in bone. As a result of this action they affect the activity of a group of cells within bones known as osteoclasts. There are now many different bisphosphonate drugs that vary in the strength of their effects.

How they work

There are two main types of cell within bones which are responsible for normal bone turnover. Bone turnover is a continuous activity that takes place in the bones of both children and adults and ensures that old bone is replaced by newly formed bone. One type of bone cell, the osteoblasts, are responsible for new bone formation whilst the other type of cell, the osteoclasts, are responsible for removing old bone, a process known as bone resorption. Normally there is a balance between the amount of old bone removed and new bone that is formed to replace this. However in individuals with Osteogenesis Imperfecta there is evidence of an imbalance in this process with more bone being removed than is replaced. Bisphosphonates act by reducing the activity of the osteoclasts and as a consequence reduce the amount of bone that is removed. However new bone continues to be formed by the osteoblasts thus tilting the balance in favour of new bone formation.

Research

Studies undertaken in children with Osteogenesis Imperfecta since the mid 1990s have shown that bisphosphonates may be of benefit in a number of different ways including an increase in bone density, a reduction in bone pain and in some studies a reduction in the number of fractures. These drugs can be given either intravenously (into a vein via a drip) or orally (by mouth). Many of the early studies were undertaken with Pamidronate. These studies were usually performed in children who were moderately or severely affected with OI. More recently, studies have been published using bisphosphonates given by mouth - Risedronate and Alendronate - and some studies have been in more mildly affected children. There is additional work using other intravenous bisphosphonates such as Neridronate and Zoledronic Acid either published or "in the pipeline".

Side Effects

There are some potential side effects which have been identified in their use. The intravenous bisphosphonates often produce a reaction when they are first used which takes the form of flu-like symptoms with a temperature and aches and pains that usually is not severe and settles within two to three days. This reaction does not normally recur with subsequent treatment

courses. Another side effect that has been recognised in children with OI who have been receiving treatment for some time is slower healing of bones after an operation to cut across a bone (an osteotomy) to insert a metal rod within the centre of the bone (an intramedullary rod).

In view of this many centres using these drugs stop the treatment for a few weeks before a planned surgical operation in which an osteotomy is required and only recommence treatment when there is good evidence of bone healing. There is no evidence that the use of these drugs slows down the process of bone healing following a fracture or interferes with a child's growth. Some of the oral bisphosphonates can cause stomach discomfort or irritation of the oesophagus if not taken as recommended by the manufacturers.

Another possible side effect that has been reported in adults receiving bisphosphonates is a condition called Osteonecrosis of the jaw. This is an area of dead bone within the jaw which heals very slowly and is painful. This side effect has been mainly seen in adults with cancer who receive frequent high doses of the intravenous bisphosphonates, Pamidronate or Zoledronate. It has also been reported in adults with poor dental hygiene who are receiving high doses of intravenous bisphosphonates. There are no reports at present of this problem occurring in individuals with Osteogenesis Imperfecta and specifically no reports of this occurring in children. However it is recommended that children and adults with OI have regular dental checks and maintain good oral hygiene and the dentist is aware if treatment with a bisphosphonate is being received before any planned procedure such as teeth extraction (See dental factsheet).

Although these drugs appear to be of benefit in selected children and adults with OI they are not a cure for the underlying collagen defect. It is recommended that they are used in centres who can provide the multidisciplinary care necessary for individuals with OI which includes access to experienced orthopaedic surgeons, physiotherapy and occupational therapy.

Frequently Asked Questions

Could bisphosphonate therapy improve any of the other problems associated with OI?

Osteogenesis imperfecta is caused by a defect in Type I Collagen. Besides fragile bones, this defective collagen causes loose joints, muscle weakness and various degrees of short stature in most persons with OI. To date, there is no evidence that any of the bisphosphonates encourage growth, but neither do they seem to inhibit normal growth in children. Loose joints and tendon problems are not affected by bisphosphonate treatment.

Some of the published literature suggests that early use of bisphosphonate therapy can help delay or even prevent the onset of scoliosis in people who have OI.

How long might a person with OI need to stay on bisphosphonates? Is the improved density permanent?

While some persons taking bisphosphonates through the various research protocols are reported to have reached normal bone density, it is not possible to predict how any particular individual will respond to the drug. When some of these individuals were taken off bisphosphonates, their bone density gradually decreased over several years. However, it is also important to note that increased bone density does not necessarily translate into increased bone strength. Furthermore, bone density is just one aspect that is modified by the drug. There is also relief of pain. Long term studies are needed to determine how to optimize duration and frequency of drug administration and to determine how long changes last after drug administration ends.

What is the role of Physical Therapy, and/or nutritional supplements for a person receiving bisphosphonate therapy?

Studies of osteoporosis and other osteoporotic conditions show that bisphosphonate therapy is most effective when accompanied by calcium/vitamin D supplementation and a professionally designed exercise program. An exercise program is always beneficial for people with OI.

Since research is on-going, what isn't known about bisphosphonate therapy?

Bisphosphonates have now been used for over ten years in some patients with OI, mostly children. The effects described in the literature seem generally positive for children, less so for adults. It still isn't clear why this is the case.

The side effects described in OI patients seem to be relatively minor. There are still concerns that there may be a slower rate of bone healing after surgery, but there does not appear to be an effect of bisphosphonate healing on the rate of fracture healing. In children treated with bisphosphonates, the ends of long bones in the legs and arms are generally a bit wider, but this does not seem to affect whether or not fractures occur there.

Bone density does go up in almost everyone who receives bisphosphonate treatment; the most recently published large scale study using risedronate in children with OI (the study was called "POISE") reported a 50% reduction in fracture risk as well as increased bone density.

The reduction in fracture risk may be simply the effect of having more bone, or it may reflect in part the reduction in the activity of the bone cells (osteoclasts) that eat bone away; the reduction in fracture risk in the risedronate study seemed to begin before there would have been a significant increase in bone density.

It isn't clear whether some people need more (or less) bisphosphonate than others to achieve the same effect; however, the alendronate study undertaken in the USA by the Shriner's network hospitals failed to show the same benefit that was seen in the risedronate study. The main difference between the studies was that more severely affected patients were enrolled into the Shriner's study; most of the children enrolled into the POISE risedronate study were more mildly affected. This implies that if you have more severe disease, either intravenous therapy, or a higher dose of oral therapy may be needed.

There has been only one study that has looked at a wide range of doses of bisphosphonate, and that was another risedronate study of moderately and severely-affected children with OI undertaken in Sheffield, Birmingham and Glasgow. That study showed that higher doses of risedronate were needed to increase bone density, but the study wasn't big enough to look at the effects on fracture frequency.

As to the criteria for starting treatment with bisphosphonates – this has not been looked at in any systematic way; in many instances, the rationale for starting is clear – multiple fractures of the vertebrae, fractures leading to significantly impaired mobility, or resulting in multiple operations to correct deformity, or intractable pain, are all indications which physicians worldwide recognize. The issue of when to start in more mildly affected individuals is still unclear, however, and a matter for discussion with the treating team.

Other approaches can also have positive effects – increasing physical activity has positive effects on building up bone, and ensuring an adequate intake of vitamin D and calcium each day also helps maintain bone health.

Although the reduction in fracture risk of 50% shown in the POISE study is very welcome, it would be even better if a treatment could completely prevent fractures. Bisphosphonates have brought improvements to the lives of many, but more still needs to be done. It is likely that in

the near future, studies will start looking at new treatments. Until those studies are complete, we won't know whether they are better than current approaches – watch this space!

The studies originally sponsored by the drug companies focused on conditions such as osteoporosis that primarily affect older adults. Little attention was paid to long-term side effects. Researchers who are familiar with Osteogenesis Imperfecta are posing a number of questions including the following:

- ◆ Are there any long-term negative side effects?
- ◆ Will changes in bone density lead to significant improvement in bone strength?
- ◆ Does bisphosphonate treatment change the composition of the matrix of OI bone?
- ◆ Do bisphosphonates affect the bone of the spine differently from the long bones in legs and arms?
- ◆ What is the role of physical therapy in the bone density improvement that is being seen?
- ◆ What may be the most effective dosage, and mode of administration for persons with the different types of OI and for persons of different ages?
- ◆ Is bisphosphonate therapy appropriate for children with mild OI?

It seems that children and adults react differently to bisphosphonate therapy. Adults seem to have fewer side effects to intravenous therapy. Children seem to have more rapid changes in bone density.

Since the bisphosphonates are an investigational drug for OI, persons with OI who are interested in receiving a member of this drug family are encouraged to do so as part of a research programme. In general, research programmes will have more experience with the use of the drug and the knowledge gained can benefit other persons with OI.

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Note: Information for this factsheet has been taken from information produced for the BBS by Dr Nick Shaw, Birmingham Children's Hospital and also FAQs from an information sheet produced by the OIF in USA.



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Working with People
who live with
Osteogenesis Imperfecta.