Questions and Answers about Bisphosphonates

In recent years the investigational use of bisphosphonates to treat children and adults with osteogenesis imperfecta has received increasing attention from the medical research community, parents of children with OI and adults who have OI. While approved by the US FDA to treat various conditions including Paget's Disease of the Bone, osteoporosis and other osteoporotic conditions in adults, these drugs are still being studied for treatment of OI in both children and adults. Animal studies and clinical trials are on-going in the US, Canada, Australia, France and England. The OI Foundation is cautiously optimistic that bisphosphonate therapy represents a significant possibility as a non-curative treatment for osteogenesis imperfecta and is encouraging further research to study both short and long-term effects.

What is a bisphosphonate?
Bisphosphonates are analogous to compounds that naturally occur in the human body, but are metabolized in a different manner. There are a number of versions of these compounds, each having slightly different characteristics including mode of administration and potency. Until recently, interest was focused exclusively on pamidronate (Aredia®), given by intravenous infusion and alendronate (Fosamax®), available in tablet form. New and more potent bisphosphonates (risedronate and zoledronate) are now also being studied in relation to OI. Zoledronate is in clinical trials at this time.

There are two main cell groups in the bone. The osteoblasts, which make bone, and the osteoclasts that break down the bone (bone resorption). Both types of cells are very active, even in the adult, and work together to keep the bone intact and responding to stress. Current knowledge suggests that bisphosphonates slow down the process of bone resorption by shortening the life of the osteoclasts and prolonging the life of the osteoblasts, thus tilting the balance towards the production of bone. The prolonged osteoblast still produces mutant collagen. Thus, the patient is still making "OI bone," but resorbing less of it.

Early treatment studies have reported an increase in bone density, an increase in cortical bone width, a decrease in cortical bone porosity, and a reduction in bone pain. It is still controversial as to whether this also results in a decrease in the number of fractures. Some animal studies of bisphosphonate treatment have shown that the femurs were less elastic, which would not be desirable in people with OI. It is also not clear at this time whether the bisphosphonates will have the same effect on the bone of the spine, which is mainly trabecular, and the bone of long bone, which is mainly cortical.

Bisphosphonates are not metabolized in the body. Fifty percent of the medication goes directly to the bone, and 50 percent is excreted in the urine. Current studies are just beginning to measure how long bisphosphonates remain in the body, which will affect how often treatment is administered. Typically, treatment is repeated every 3-4 months for intravenous bisphosphonates, and weekly for oral bisphosphonates.

Pamidronate is given by slow intravenous infusion over 3-4 hours. Treatment takes 1-3 days. In South America and Europe, pamidronate is also available for oral administration. Zoledronate is given by a rapid intravenous injection of approximately 5-15 minutes. Alendronate (Fosamax®) and risedronate (Actonel) are given by mouth. Current directions include a weekly dose, with specific guidelines regarding taking it first thing in the morning on an empty stomach, at least 30 minutes before eating or laying down. The weekly dose appears to provide similar benefits to the daily regimen, but with less gastrointestinal discomfort.

One short-term side effect reported by the Shriners Hospital for Children, in Montreal, Quebec, Canada, after treating more than 200 children with pamidronate is a flu-like syndrome, including high fever, during the first day after the first treatment. Some babies react with decreased blood cells, but return to normal values in 48-72 hours. A more recently reported intermediate-term side effect, reported by groups in both Canada and Australia, is slow bone healing of osteotomy cuts. The Australian researchers have discontinued use of bisphosphonates for several months before surgeries in which osteotomies will be required.

This fact sheet was prepared with assistance from Joan Marin, MD, PhD, Chair of the OI Foundation's Medical Advisory Council; Jay Shapiro, MD, Member of the Medical Advisory Council; and Horacio Plotkin, MD.
Persons taking alendronate or risedronate can have gastric discomfort or even severe burning of the esophagus (the tube connecting the mouth with the stomach) if the drug is not taken properly or if the individual has a history of gastric disturbance (such as ulcer or gastric reflux). Additional problems that have been seen in adults and described in medical literature include muscle pain, eye irritation and headaches.

There is some evidence that bisphosphonates may cause birth defects if taken at the time of conception or during pregnancy. There is no evidence that they affect fertility in people who have been taking them.

At this time, there is no evidence that bisphosphonates cause dental problems. They do not improve dentinogenesis imperfecta (DI) when the treatment is started after three years of age. Whether bisphosphonate treatment for infants will lead to a reduction in the seriousness of DI is under investigation. There is some concern that bisphosphonates might decrease the effectiveness of orthodontic treatments, but this is only beginning to be studied.

**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 literature suggests that this therapy can be useful for the management 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?**

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 than 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.

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This fact sheet was prepared with assistance from Joan Marini, MD, PhD, Chair of the OI Foundation's Medical Advisory Council, Jay Shapiro, MD, Member of the Medical Advisory Council, and Horacio Plotkin, MD.

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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 program. In general, research programs will have more experience with the use of the drug and the knowledge gained can benefit other persons with OI.