

INTRAVENOUS PAMIDRONATE TREATMENT IN MUCOLIPIDOSIS II/III

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Children with ML have many issues with chronic pain that may result in loss of mobility, sleep disturbances, loss of concentration, chest infections, and a general feeling of being unwell. Quality of life can be severely compromised by the age of 8-10 years, as families report a noticeable decline in mobility, an increase in pain and stiffness, as well as difficulty in their ability to complete day to day tasks. Bone density testing with DEXA Scans and blood and urine tests in these children commonly demonstrates a significant loss in bone density known as *osteopenia*, or in its more severe form, *osteoporosis*.

In a select group of children and young adults in New Zealand, and Australia, Pamidronate treatment has provided a dramatic improvement in mobility, well-being and general physical ability. Some of these children are reporting that they have no pain at all, and others are reporting that they have significantly less pain. Families who took part in the initial study were reporting that there was a reduction in chest infections. This may be due to the ability to cough without pain.

Rationale

Bisphosphonates are a class of drugs now being widely used in the treatment of osteoporosis, and in the treatment of bone related pain in other lysosomal storage diseases, such as Gaucher disease. Traditionally, Bisphosphonates are used to decrease bone resorption by inhibiting normal bone metabolism, thus allowing an increase of normal bone mass and balance to occur. Anecdotally, many individuals have reported a dramatic decrease in pain as well.

The Bisphosphonate being used in patients with mucopolipidosis is called *disodium Pamidronate*. (Pamisol/Aredia). In mucopolipidosis the Bisphosphonate, *Pamidronate*, appears to have a beneficial clinical effect which results in decreased bone pain, increased mobility and reversal of some ML bone pain related symptoms.

Indications

The treatment of patients with *Pamidronate* is experimental, and at present, it is hoped that its use will be investigated as part of an international multi-center collaborative study. Before patients begin therapy, the benefits should be weighed against the known and potential side-effects (see Adverse Reactions below).

Because this is an experimental therapy, strict guidelines for the use of Pamidronate have been established. This therapy could be considered in individuals with mucopolipidosis type III in whom there

is clinical and radiographic evidence of progressive bone loss, documented osteopenia, or at any stage of the disorder where activity related pain has become a significant detriment to quality of life and may be attributed to bone disease. In individuals with mucopolipidosis type II, treatment may begin after resolution of the secondary neonatal hyperparathyroidism (usually after 3 months of age), if there is progressive osteodystrophy and in whom suitable intravenous access can be established.

Baseline tests

There are many baseline tests to be done prior to commencing the first infusion of *Pamidronate*. These tests include blood work, imaging and urine tests, and are important for establishing the need for Bisphosphonate therapy and for tracking the effectiveness in each individual. These tests are outlined in the guidelines for treatment, which are available from ISMRD. www.ismrd.org

Auxology (hearing tests)
Dexa Scan
Full Skeletal Survey
Bone Age (Left wrist and hand)
Lateral Spine (AP if Scoliosis)
Renal Ultrasound
Serum Calcium
Serum Phosphate, Alkaline Phosphatase
Vitamin D metabolites
Serum Osteocalcin
Urinary Deoxypyridinoline cross-linking
Other tests as outlined in the guidelines for Pamidronate treatment in ML.

Dose

Dosing regimens have been established, and should be discussed with your treating physician.

Adverse Reactions

Some children will have “flu like” symptoms (i.e. fever, nausea, vomiting, headache and body aches and pains) which usually occur following the first infusion, within the first 12 – 24 hours, and generally subside within 48 hours. With subsequent infusions these symptoms do not usually occur but if they do, it is to a lesser degree. Some children have reported general aches and pains lasting up to 7 days. Two children reported having sore feet.

Other reported side effects are disturbances in blood electrolytes such as calcium, phosphate, potassium and magnesium, decreased white blood cell counts and anemia, and difficulties controlling fluid balance and blood pressure. Most of these side effects can be easily monitored and treated.

Additionally, after market studies have demonstrated the development of *osteonecrosis* of the jaw bone, which is loss of bone vascularity in the jaw leading to loose teeth, sharp edges of exposed bone or bone spurs, or breaking loose of small bone spicules or dead bone. This has been primarily described in older patients with cancer, using a treatment/protocol that is more aggressive in therapy and dose than the protocols followed with mucopolipidosis patients. The protocol for ML II/III is of a lower dose infused over a longer period of time. It is noted that the patients who have been on

treatment for 5 years are not showing the above problems, but should be kept in consideration while taking *pamidronate*.

Ibuprofen and *acetaminophen* (Tylenol) can be given to help with this initial pain. It is recommended that the children be admitted to hospital for the first two infusions to monitor these “flu like” symptoms.

As always, it is recommended that families seek further information and advice from their doctors.

Endpoints

At this time there are no end points for treatment. It is acknowledged that an international multi- center collaborative trial is needed, which in turn will produce definite guidelines that can be made available for treating physicians.

The questions being posed now are what do we do when the children/young adults reach normal bone density range and are almost pain free or are pain free?

There are children in Australia and New Zealand moving on to trial other types of bisphosphonates either by the oral route, or by continuing with IV treatment given at longer intervals. The ultimate goal of this treatment is to keep the children and young adults pain free so that they continue to have quality of life.

References

The following references and papers are available to download from ISMRD www.ismrd.org

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http://www.mucopolysaccharidosis.org/library/BISPHOSPHONATE_THERAPY_IN_MUCOLIPIDOSIS_342.doc

http://www.mucopolysaccharidosis.org/library/Pamidronate_infusion_guidelines_for_Mucopolysaccharidosis

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