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Bisphosphonates for Treatment of Severe Idiopathic Infantile Hypercalcemia

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See article on page 160

Hypercalcemia is associated with severe volume contraction, life threatening complications, and even death in the case of unsuccessful therapy. Definition of hypercalcemia is age-dependent and the cutoff values of calcium are different for infants (> 11.3 mg/dL) and children (> 10.8 mg/dL). The underlying diseases in infants are different form children, adolescents, and adults. Hyperparathyroidism and metastasis are the main causes of hypercalcemia in adolescence, but inherited disorders and vitamin D intoxications are the most prevalent in infancy.[1,2] In general, hypercalcemia in infants can be due to parathyroid related disorders, inactivating mutations in

calcium-sensing receptor gene, persistent PTH-related peptide, inborn error of metabolism, vitamin D related disorders, and other nutritional or miscellaneous inherited disorders.

Hypercalcemia leads to severe dehydration, especially in infants and small children. Aggressive fluid resuscitation is an inevitable part of therapy. Although management of hypercalcemia is similar regardless of age, there is no strong evidence behind each step of therapies including loop diuretics, bisphosphonates, steroid, or calcitonin. All evidence about the efficacy of loop diuretics for treatment of hypercalcemia is based on case series and case reports.[3] Loop diuretics and are not recommended because they increase the severity of dehydration and further reduce glomerular filtration rate.[2,3]

The experience with bisphosphonate in children is limited. It has extensively been used for treatment of osteogenesis imperfecta; however, the strength of evidence regarding its efficacy and long-term complications are low.[4,5] Castillo and colleagues systematically reviewed the application of bisphosphonate in children. They revealed that how scant is the information about the impact of therapy on bone density, the quality of life, the need for orthopedic intervention in patients with osteogenesis imperfecta. Hypocalcemia is one of the drawbacks during therapy, and for this reason, bisphosphonate has been used for treatment of hypercalcemia due to metastasis or vitamin D intoxication resistant to conventional therapy.[2,3] The experience of utilizing pamidronate in infants and children is rare and limited to some case reports. Oral or intravenous bisphosphonate has been experienced as an alternative for management of hypercalcemia secondary to conditions such as metastatic disease, William syndrome, congenital mesoblastic nephroma, and subcutaneous fat necrosis. A few case series showed that alendronate was superior to pamidronate in treating hypercalcemia due to vitamin D toxicity. Skalova and coworkers have reported on in the current issue of the *Iranian Journal of Kidney Disease* an infant with severe hypercalcemia, due to *CYP24A1* loss-of-function mutation that impaired degradation of 1,25-dihydroxyvitamin D3, successfully treated with pamidronate.[6] The long-term follow-up confirmed the persistency of remission.

The question is that how an inherited disease of vitamin D can be controlled by a single dose of bisphosphonate. Biphosphonate inhibits osteoclast activity, inhibits osteocytes apoptosis, and indirectly stimulates osteoblast function by its effect on remodeling cycle.[7] The heterogeneous distribution in bone tissue depends on bone turnover. It has an affinity to bind to hydroxyapatite, be endocystosed by osteoclast, inhibit prenylation, and lead to osteoclast apoptosis. When it is bound to the bone surface, bisphosphonate is in active form and becomes inactived when buried in tissue. By resumption of reabsorption of bone, subsequently the deposited bisphosphonate is liberated from bone tissue, and this contributes to remodeling cycle and helps to strengthen the bone. Nitrogen-containing bisphosphonates, ie, alendronate and risedronate, inhibit osteoclast activity by inhibiting cholesterol biosynthesis. They are much more potent osteoclast inhibitors.[7] Omidvar and colleagues studied on an uncontrolled trial the efficacy of pamidronate and alendronate on bone densitometry post renal transplantation .They found no differences in lumbar bone density after 6 months of therapy; however, pamidronate group showed less mineral density of the femur neck.[8] Biphosphonate is excreted unchanged in urine and should be adjusted in chronic kidney disease stage 3 or more.[5] It is interesting that bisphosphonate has a promising role in recovery from tissue calcification and calcyphylaxis even in patients with chronic kidney disease.

Side effects of bisphosphonates are of major concern. Their implication on treatment and prevention of osteoprosis are not unusual. The Food and Drug Administration recently warned against long-term use of bisphosphonate. The recent advice is discontinuation after 3 to 5 years. However, a recent systematic review reported that menopause women who were nonadherent to therapy had 46% increment of fracture risk, especially vertebral fractures.[9] Recently, there is concern about oversuppression of bone that prone the patients to more bone fracture. The osteonecrosis of the jaw has been reported in patients with an underlying cancer that received aminobisphosphonate for treatment of hypercalcemia or prevention of oteoprosis.[10,11] Depending on bone turnover, the half-life of bisphosphonate in bone is varied between 1 and 10 years.

There is a case report of a pregnant woman with Gaucher disease who underwent regular courses of pamidronate for vertebral fractures.[12] The pregnancy

occurred unexpectedly and she gave birth to a healthy newborn with no electrolyte imbalance or bone abnormality. The child had normal bone densitometry after 1.5 year of follow-up. For confirming its safety in child-bearing age women, large cohort studies are needed to be designed.

Acute kidney injury and collapsing focal segmental glomerulosclerosis are the renal side effects of bisphosphonates that warrants checking serum creatinine level and kidney function before any prescription. Ocular symptoms such as uveitis, conjunctivitis, and ocular pain, in addition to transient systemic adverse effects such as fever, myalgia, bone pain, or constipation are the other side effects that have been reported.[10] Two systematic reviews evaluated the impact of bisphosphonate on increment the risk of atrial fibrillation, stroke, and cardiovascular events. The pooled data were heterogeneous and revealed the risk of serious atrial fibrillation was 1.5 times higher in bisphosphonate groups than controls.[13] However, the studies show no association with stroke, cardiovascular events, or atrial fibrillation (serious or nonserious), especially in the current users.[14]

The effectiveness for reducing bone fracture and improvement of bone density in idiopathic juvenile arthritis has been documented.[15] Furthermore, the usage of bisphosphonate in improving the circulation and reducing pain in avascular necrosis has been demonstrated in uncontrolled studies.[16] Nonetheless, all of these reports about the clinical prescription of bisphosphonate are based on case reports, case series and very limited clinical trial with low power or insufficient cohort studies. In order to find the correct duration of therapy, the long-term morbidity, side effects, the implication on bone density in infants and children, and its safety on child-bearing age females and its long-term effects on fetus, there is a need for designing large multicenter controlled studies.

CONFLICT OF INTERSTEST

None declared.

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