Low doses of pamidronate for the treatment of osteopenia in non-ambulatory children

Commentary

In recent years, bisphosphonates, primarily intravenous (iv) pamidronate, have become very widely used in children with severe osteogenesis imperfecta (OI). This has occurred without the well-controlled clinical trials usually required before a medication becomes 'standard care'. Without placebo-controlled trials it is difficult to define precisely the risks and the benefits, but in children with very severe OI and numerous fractures the risk/benefit ratio is so clearly favorable that widespread use of pamidronate in this situation appears appropriate.

Children with physical disabilities such as cerebral palsy (CP), muscular dystrophy, and myelodysplasia, that significantly impair ambulation, typically have profound osteopenia. Collectively this group comprises by far the largest number of children with significant osteopenia. Prospective longitudinal studies in such children with CP find that the annual fracture rate is approximately 5%,[1,2] which is more than twice the fracture rate found in normal children. Furthermore, the fractures in children with physical disabilities typically occur with minimal or even unrecognized injuries. These are very compelling reasons to consider treatment.

It is inappropriate to assume that the risks and benefits of bisphosphonate treatment are the same in children with physical disabilities as in children with severe OI. Physicians should require more data before utilizing bisphosphonates as 'standard care' for osteopenia in children without OI. So what data is required? Certainly a randomized, placebo-controlled clinical trial using fracture reduction as the primary outcome measure, and safety monitoring that includes iliac-crest bone biopsies and frequent blood tests would be ideal. A 3-year study involving over 300 participants would be required to prove clinical benefit, assuming an untreated fracture rate of 5% a year which is reduced 60% by treatment.

So at present we are limited to less than ideal studies. One compromise is to use any of multiple measures loosely referred to as 'bone density' as proxy measures for fractures. Using bone density as the primary outcome it is possible to prove in a prospective, randomized, double-blinded, placebo-controlled clinical trial that iv pamidronate has a huge treatment effect in children with quadriplegic CP.[3] Only 12 participants followed for 18 months were necessary to prove this. But the clinical relevance of this and hundreds of other studies of pediatric osteopenia is dependent on the assumption that the particular measure of bone density is a reliable proxy measure for fracture risk.

It is well established that bone density measures do help to predict subsequent fracture risk in the elderly, hence the basis for the widespread assumption that this must also be true in children with osteopenia. Actually, the only published study to prospectively evaluate fracture risk in any pediatric osteopenic condition found that DXA measures of lumbar spine bone density did not relate to fracture risk in children with quadriplegic CP.[1] The reasons for this counter-intuitive finding are likely multiple, but at least, in part, that in these children most of all fractures occur in the long bones of the limbs, and only with exceptional rarity in the spine. One must never overlook that fractures are what truly matter, and recognize that the particular measure may have little or no clinical relevance.

In this issue Plotkin et al.[4] report a clinical case series in which osteopenic non-ambulatory children were treated with iv pamidronate. There are significant limitations. The primary outcome variables are measures of bone density. The participants are not randomized, there is no blinding, and there is no control group. These too are obviously important limitations, but experienced investigators recognize the very significant costs and complexities of conducting studies that address these limitations. Another issue is that for most participants the indications for treatment did not include prior fracture. One should seriously question whether existing data justifies this treatment to prevent fractures in a child who has not, and may never, sustain a fracture. Conversely, should a physician wait until a child with profound disabilities and at high risk for fracture goes through the pain and consequences of a fracture before initiating treatment, if that physician feels that safe and effective treatment is available?

Despite the limitations, Plotkin and colleagues[4] are to be commended. The series is reasonably large and the study was conducted by physician investigators at the forefront of the field, under IRB approval, and with informed consent. This is clinically, scientifically, and ethically quite different than the rapidly growing number of well intentioned physicians who are 'trying' bisphosphonates on a few children. In the absence of the funding necessary for 'ideal' clinical trials, physicians should require more published experience with bisphosphonates before they become 'standard care' for pediatric osteopenia.

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Richard Henderson

References

1. Henderson RC. (1997) Bone density and other possible predictors of fracture risk in children and adolescents with spastic quadriplegia. *Dev Med Child Neurol* **39:** 224–227.
2. Stevenson RD, Conaway M, Barrington JW, Cuthill SL, Worley G, Henderson RC. Fracture rate in children with cerebral palsy. *Pediatri Rehab.* (Forthcoming)
3. Henderson RC, Lark RK, Kecskemethy H, Miller F, Harcke HT, Bachrach S. (2002) Bisphosphonates to treat osteopenia in children with quadriplegic cerebral palsy: a randomized, placebo-controlled clinical trial. *J Pediatr* **141:** 644–651.
4. Plotkin H, Coughlin S, Kreikemeier R, Heldt K, Bruzoni M, Lerner G. (2006) Low doses of pamidronate to treat osteopenia in children with severe cerebral palsy. *Dev Med Child Neurol* **48:** 709–712.