Comment

Bisphosphonate-Induced Osteopetrosis

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This case report is about a 7 3/4 year-old boy with a high level of activity of alkaline phosphatase and bone pain. Bone mineral density as measured by DEXA was normal (Z score= -1), and he had a history of one fracture of his distal radius after significant trauma. Markers of bone formation and resorption were normal, reflecting no acceleration of skeletal turnover.

Pamidronate was started for pain and increased alkaline phosphatase. Initially, a dose of 10 mg (0.37 mg per kilogram of body weight) was infused intravenously on three consecutive days. The rationale for treatment is not clear from the case report.

By eight years of age, he was receiving a 60-mg dose of pamidronate intravenously over a three-hour period approximately every three weeks (2.2 mg/kg in one dose approximately) The dose of pamidronate was later increased to 80 mg and then to 100 mg (2.8 and 3.4 mg per kilogram, respectively), infused over a period of four to five hours, but it was reportedly administered somewhat less regularly.

The x-rays showed signs compatible with osteopetrosis.

There are several points to comment on. First, “the difference between a treatment drug and a poison is the dose”. This is not about a side effect of a treatment. This is about an overdose of a drug. The doses of pamidronate and intervals used were far above the current protocols in use. Different protocol use 1 mg/kg in a single dose every month or 1.5 mg/kg in three consecutive days every four months. This yields an annual dose of about 12 mg/kg. The patient described in the case report received an annual dose of about 114.4 mg/kg/yr when he was receiving 2.2 mg/kg every three weeks. This was probably higher later, although the interval between doses is not clear.

The radiological changes were completely different to what is seen in cases treated with standard doses.

The effect of bisphosphonates on fracture healing is a matter of concern. It appears that long-term use of bisphosphonates can interfere with fracture healing. We are administering a lower dose of pamidronate to our patients and we expect to minimize this adverse effect. In fact, one of our patients was in “standard” doses of pamidronate and had a non-union fracture. This resolved shortly after the dose was reduced.

Bone density is often used as the main end-point of the treatment. I believe that bone density is not as important as clinical improvement and decreased incidence of fractures. After all, people with mild OI have very low bone density, and they do not usually fracture. If we can turn a patient with severe OI into a patient with clinically mild OI, despite low bone density, I think we are doing the right thing.

The main message from this case report is not to use pamidronate without a rationale for treatment, and be very careful about the dosage. After all, nobody would even think of giving 10 times the recommended dose of any other drug.

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