NO EFFECTS OF BISPHOSPHONATES ON THE HUMAN FETUS

To the Editor:

Alendronate is a bisphosphonate used for prevention and treatment of postmenopausal osteoporosis. Not much is known about its possible teratogenic effects in humans. Few studies describe prenatal exposure in rats. One study described abnormal fetal bones after exposure to 0.1 mg/kg/day subcutaneously in rats (Patlas et al., 1999) and Minsker et al. (1993) experienced the same abnormalities in rats after giving at least 10 mg/kg/day orally during pregnancy. We report the case of a child who was born after exposure to alendronate 0.12 mg/kg/day orally.

A 49-year-old woman, G3P2, had not menstruated for 2 years and used alendronate 0.12 mg/kg/day orally for presumed postmenopausal osteoporosis. Her weight was 86 kg. She was unaware of the pregnancy until labor began. A girl was born with an estimated gestational age of 36 weeks. Birth weight was 2390 gm (50th centile) (Gerver and de Bruin, 2001). Physical examination showed no abnormalities.

Laboratory investigation showed phosphate 1.97 mmol/l (normal 1.45–2.90 mmol/l), alkaline phosphatase 100 U/l (normal <325 U/l) and ionized calcium 1.27 mmol/l (1.10–1.35 mmol/l). Dual X-rays of skull and wrists showed a normal bone structure and bone density without abnormal calcifications.

After 1 year her weight was 8 kg (10th centile) (Gerver and de Bruin, 2001) and her length 73 cm (50th centile) (Gerver and de Bruin, 2001). Physical examination was normal, as was her psychomotor development.

Alendronate is a synthetic non-hydrolysable analogue of pyrophosphate, an endogenous regulator of mineralization. It is an inhibitor of bone absorption and interferes with normal mineralization of cartilage and bone (Wronska et al., 1993; Geddes et al., 1994; Patlas et al., 1999).

Alendronate is assumed to inhibit bone resorption by interference with the membrane of the osteoclast (Minsker et al., 1993; Patlas et al., 1999). It changes the structure of bone minerals by forming complexes with hydroxyapatite. These complexes are very stable and their half-life is related to bone turnover time (Hannuniemi et al., 1991). In rats, a half-life of more than 433 days has been described (Minsker et al., 1993). Alendronate is cleared from the blood by forming complexes with hydroxyapatite and mineralized bone. These complexes are very stable and their half-life is related to bone turnover time (Hannuniemi et al., 1991). In rats, a half-life of more than 433 days has been described (Minsker et al., 1993). Alendronate is cleared from the blood by forming complexes with hydroxyapatite and mineralized bone.

Studies in rats show that labeled alendronate passes the placenta and accumulates in fetal bone. In the fetus, bone turnover is very rapid. Any agent interfering with bone formation, resorption or mineralization could cause damage in skeletal growth and development (Patlas et al., 1999).

Few studies describe transplacental effects of alendronate in rat fetuses. Patlas et al. (1999) used doses of alendronate of 0.1 mg/kg/day, given as subcutaneous injections. These are comparable to doses used in humans. Minsker et al. (1993) used doses of 10 mg/kg/day alendronate or even higher, which were administered orally.

Both studies reported a reduced birth weight, but could not explain the growth retardation. This patient who was exposed in utero, had a normal birth weight.

A significantly reduced diaphyseal length was found in rat fetuses exposed to alendronate (Patlas et al., 1999). This was not observed in this patient.

Large effects of alendronate on bone structure and bone density have been described in rats. The amount of diaphyseal bone trabeculae in rat fetuses was increased, causing a higher bone density. Bone volume in the diaphyseal cavity was increased, but bone marrow volume was diminished. Calcium concentration in tibiae and femora was higher in rats receiving alendronate (Minsker et al., 1993; Patlas et al., 1999). In this patient, X-rays were normal. Alendronate had no apparent effect on bone growth, bone density, structure, and calcification in this patient.

Abnormalities of bone development were not seen in this patient. Possibly, alendronate does not pass the placenta in humans.

Alendronate was administered orally in this pregnancy, whereas it was given subcutaneously in the study of Patlas et al. (1999). Peak levels may be lower after oral than after parenteral administration (Liberman et al., 1995; Patlas et al., 1999). This could be the reason that we did not find any abnormality in this patient.

Minsker et al. (1993) used oral doses of at least 10 mg/kg/day, which were much higher than doses used in this patient. The discrepancy in congenital abnormalities in rats and in this patient could be explained by the dose-response relationship. The biological effect of alendronate in the human fetus could differ from that in rat fetuses.

Late effects on bone growth and development of other organs have not been reported. We did not find congenital abnormalities or psychomotor development disorders in this patient at the age of 1 year.

In conclusion, prenatal exposure to alendronate at this dose in this pregnancy did not appear to be harmful.

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