MOTHERISK *UPDATE*

Amy E. French Nikolay Kaplan, MD Michael Lishner, MD Gideon Koren, MD, FRCPC

Taking bisphosphonates during pregnancy

ABSTRACT

QUESTION Several of my female patients take bisphosphonates for low bone mineral density (BMD). Two of them are of reproductive age. Are these drugs safe during pregnancy?

ANSWER Very little is currently known about the effects of bisphosphonates on human pregnancy. There have been only two reports of bisphosphonate use during late pregnancy. Animal studies suggest that biphosphonates cross the placenta and that the effect is an extension of the expected pharmacologic effect of bisphosphonates on both fetus and mother. Risks and benefits should be carefully weighed.

RÉSUMÉ

QUESTION Plusieurs de mes patientes prennent des bisphosphonates en raison d'une faible teneur minérale de l'os. Deux d'entre elles sont en âge de procréer. Ces médicaments sont-ils sûrs durant la grossesse?

RÉPONSE On en connaît très peu sur les effets des bisphosphonates sur la grossesse chez l'humain. Il n'existe que deux rapports seulement sur l'utilisation des bisphosphonates durant la fin de la grossesse. Les études chez les animaux font valoir que les bisphosphonates traversent le placenta et que l'effet représente une extension des effets pharmacologiques prévus des bisphosphonates tant chez le fœtus que chez la mère. Les risques et les avantages devraient être soigneusement pris en considération.

Bisphosphonates are a class of agents that inhibit the bone resorption activity of osteoclasts. Bisphosphonates are known to accumulate in bone for long periods (estimated terminal half-life of alendronate is approximately 10 years). While incorporated into the bone matrix, however, the drug is not pharmacologically active.[1] Bisphosphonates are commonly used to treat osteoporosis, other bone disorders, and reflex sympathetic dystrophy. Recently, they have been shown to be useful in treatment of skeletal metastases in cancer patients, particularly breast cancer patients.

Our current knowledge about the effect of bisphosphonates on pregnancy is based almost entirely on animal studies, which have shown that these drugs cross the placenta. Two studies documented a decrease in fetal weight in mice and rats when bisphosphonates were administered during gestation.[2,3] Several groups have found that gestational exposure to bisphosphonates was associated with decreased fetal bone growth and accumulation of the drugs in fetal bone.[3-5] They hypothesized that decreased bone growth might be responsible for the decreased fetal weight previously observed. Okazaki et al[5] also found that after administration of cimadronate late in pregnancy, rat pups experienced abnormal tooth growth after birth.

Minsker et al[6] found that alendronate administered to pregnant rats in doses of 10 and 15 mg/kg daily produced physical signs of

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Motherisk questions are prepared by the **Motherisk Team** *at the Hospital for Sick Children in Toronto, Ont.* **Ms French** *and* **Drs Kaplan** *and* **Lishner** *were members at the time of writing and* **Dr Koren** *is Director of the Motherisk Program.*
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toxicity at parturition, including tremors, dystocia, and death associated with hypocalcemia. The authors concluded that alendronate prevented bone resorption and thereby denied the dams an important source of calcium at a time when fetal demand for it peaked. The alendronate-induced hypocalcemia adversely affected parturition because uterine muscle contraction is a calcium-dependent process. The neonatal death rate was also increased, but that was due to protracted deliveries rather than to a direct effect of alendronate on the pups. There have been no reports of congenital abnormalities associated with use of bisphosphonates in animal teratology studies.

In two published case reports on administration of bisphosphonates during human pregnancy, the drugs were used to treat malignant hypercalcemia. Dunlop and colleagues[7] described a woman who presented at 27 weeks' gestation with bony metastases from a primary breast malignancy. At 34 weeks' gestation she was treated with 30 mg of aminopropylidene diphosphonate (pamidronate) as a 4-hour infusion. At 36 weeks she gave birth to a healthy child weighing 3.06 kg. The child initially had low plasma calcium levels; however, within 5 days of delivery, levels had reached normal limits.

Illidge et al[8] reported a case of a woman who was diagnosed with a metastatic breast tumour in her 24th week of pregnancy. At 28 weeks' gestation, she was administered 90 mg of pamidronate over 8 hours. She was delivered at 29 weeks' gestation. The baby weighed 1.412 kg and required ventilation for respiratory distress. He had elevated blood calcium levels at birth, but they quickly dropped to below normal levels and remained that way until postnatal day 9, when they returned to normal.

One report described use of monthly pamidronate infusions for a breastfeeding woman with reflex sympathetic dystrophy.[9] The level of pamidronate in the breast milk collected for 48 h after the infusion was undetectable (limit of quantitation, 0.4 μmol/L). The baby was healthy and grew normally.

Given the fact that bisphosphonates cross the placenta in animal models, the effects on animal pregnancies appear to be an extension of the predictable pharmacologic effects of bisphosphonates, both on developing fetuses and on pregnant mothers. Given the lack of human data, it is important that the anticipated benefits of bisphosphonate administration should be very carefully weighed against the potential risks for both mother and fetus before drugs are administered to pregnant patients or women planning pregnancy. If clinicians choose to start treatment before delivery, serum calcium levels should be closely monitored. Further studies into use of bisphosphonates during breastfeeding are warranted, even though the published report is reassuring.

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