DRUG INFORMATION
Jonathan Banks
Bob Buckham
Sharon Gardiner

Canterbury DHB
District Health Board
Te Poari Hauora o Waitaha

CLINICAL PHARMACOLOGY
Murray Barclay
Evan Begg
Chris Hutchinson
Petra Lowe
Jane Vella-Brincat
Mei Zhang

SAFETY OF ETIDRONATE IN PREGNANCY

Question:
What is the safety of etidronate in pregnancy?

Answer:
There are extremely limited data available on the use of bisphosphonates in human pregnancy.

Etidronate
Animal studies: Skeletal malformations have been observed in rats and mice following administration of very high intravenous doses of etidronate during pregnancy[1-4]. Oral etidronate in doses up to five times the maximum human dose have not revealed evidence of foetal harm (or impaired fertility) in rats and rabbits[1]. However, at doses 22 times the maximum human dosage, a decrease in live foetuses was observed in rats. In another study, oral administration was been reported to cause foetal death in rabbits[5].

Human studies: We are not aware of any information describing the use of this agent in human pregnancy[6-10].

Pamidronate
Animal studies: The manufacturers have stated that in animal experiments pamidronate did not affect general reproductive performance or fertility[11]. In rats, adverse effects such as prolonged parturition and reduced survival rates were probably secondary to decreased maternal serum calcium concentrations. Pamidronate has been shown to cross the placental barrier and accumulate in foetal rat bone in a manner similar to that observed in mature animals[11].

Human studies: Information on the safety of pamidronate in human pregnancy is extremely limited[6-10]. The manufacturers have stated that administration during pregnancy should be limited to life threatening hypercalcaemia.

We are aware of two cases describing the use of pamidronate in the third trimester of pregnancy[12,13]. The only ill effect described in one neonate was the presence of hypocalcaemia for the first week post delivery[13].

Alendronate
Animal studies: Patlas *et al.* subcutaneously administered alendronate to pregnant rats during the period of active bone development. Radiolabelled 14C-alendronate was shown to pass through the placenta and accumulate in the foetus[14]. Histological examination revealed increased diaphyseal bone trabeculae with a slight shortening of the diaphysis in treated animals compared to controls[14].

In rat fertility studies, alendronate at doses of 10 or 15mg/kg/day produced physical signs of toxicity at parturition[15]. In other developmental toxicity studies, doses up to 25mg/kg per day in rats and 35mg/kg per day in rabbits produced no adverse effects[16].

Bisphosphonates - general

In animal studies, Minsker et al. noted that toxicity seen at parturition such as tremors, prolonged/difficult labour and death was associated with hypocalcemia in the dams, but normocalcaemia in the foetuses[15]. Cases of neonatal death were associated with protracted delivery rather than any direct effect of the bisphosphonate (alendronate) on the pups[15]. These toxic effects were prevented by intravenous administration of calcium.

It is important to remember that as increased foetal calcium demand may be met by mobilisation of maternal bone (resorption), the use of a bisphosphonate may inhibit maternal supplies of this mineral. In addition to the potential for neonatal hypocalcaemia, maternal hypocalcaemia may affect uterine muscle contraction[15].

Conclusions:

In general, use of these drugs in pregnancy is best avoided because of lack of human clinical experience and the inhibitory effects of this class on metaphyseal remodelling in experimental animals. However, it is recognised that extrapolation from animals to humans is extremely difficult. The use of this class of agents in human pregnancy should probably be limited to serious medical situations such as life threatening hypercalcaemia.

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