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Bone formation induced in an infant by systemic prostaglandin-E_2 administration

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We report a case of long-term systemic administration of prostaglandin E_2 (PGE_2) to a newborn infant with ductus-dependent congenital heart disease. After 46 days of treatment, radiography showed cortical hyperostosis of the long bones. The child died 62 days after discontinuation of prostaglandin treatment. Histologic examination of tubular bones showed hyperostosis presumably due to prostaglandin-induced rapid formation of primitive bone. The additional finding of extensive resorption of the outer cortical surface and bone formation at the inner surface suggested a reversible phase after discontinuation of treatment.

Although several studies indicate a close relation between prostaglandin and bone resorption (Raisz and Martin 1985), it has also been reported that prostaglandin applied locally can influence bone formation (Jee et al. 1984, Shih and Norridin 1986). In vitro studies have shown a dose-related proliferative stimulation of osteoblastic cells (Feyen et al. 1985); and from in vivo studies (Jee et al. 1984, Shih and Norridin 1986), it is obvious that arachidonic acid metabolism can enhance bone formation and remodeling.

Our case illustrates that prostaglandin given systemically can interfere with the modeling of the human skeleton.

Case history

A 2-day-old girl was admitted to the intensive care unit because of cyanosis after an uncomplicated delivery. She had a dextropositioned heart with large atrial and ventricular septal defects and pulmonary artery atresia. Because an aorticopulmonic shunt operation initially was found too risky, treatment with PGE_2 was initiated on Day 3 to prevent occlusion of the ductus arteriosus. After an initial dosage of 0.09 ag/kg per min, the PGE_2 was reduced to 0.008 ag/kg per min given continuously through a central intravenous catheter. The girl improved with a stable circulation, a disappearance of the cyanosis, and a rise in pO_2

On Day 50, tenderness and a circumferential increase of the lower limbs were observed, and radiography disclosed a 2-mm-thick cortical hyperostosis of the humerus and ulna. In the lower extremities a 1-mm laminal periosteal thickening of the right fibula was found. On Day 75, an aorticopulmonic shunt operation was performed, and the PGE was tapered off to be discontinued on Day 82. On Day 91, radiography of the extremities and skull showed a 5-mm laminal periosteal thickening in the humeri and a 2-mm thickening in the lower limbs (Figure 1).

On Day 144, the girl died of sepsis. The autopsy confirmed congenital heart disease. The surgical shunt was open, and the ductus arteriosus was closed by fibrosis. Asplenic syndrome, hepatomegalia, and acute stasis of various organs were found, but there were no signs of inflammatory disease.

Radiography of the skeleton showed regression of the periosteal hyperostosis of the long bones observed earlier. Histologically, the right ulna had a fibrous thickening of the periosteal mem-

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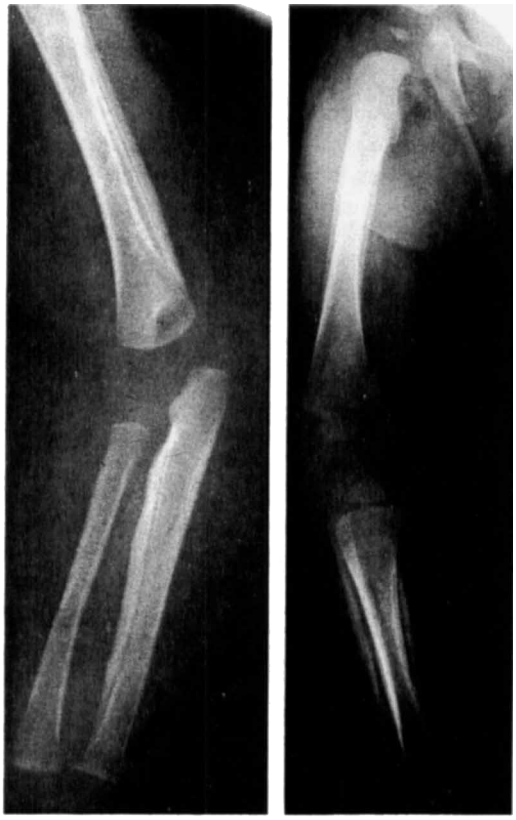

Figure 1

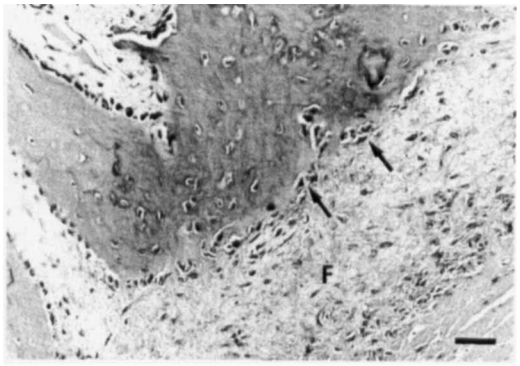

Figure 2

Figure 1. Radiographs on Day 91, 9 days after cessation of prostaglandin treatment, showing the induced periosteal hyperostosis. The laminal periosteal thickness was 5 mm in the humerus and 2 mm in the lower extremity.

Figure 2. Cortical surface of the right ulna removed at autopsy. Periosteal fibrosis (F) is seen together with cortical dominance of osteoclastic resorption (arrows). Bar = 57μ. Hematoxylin and eosin.

brane under which a layer of primitive woven bone was found. The outer surface of the hyperostosis had signs of resorption, whereas the inner surface showed only new bone formation (Figure 2).

Discussion

In humans the role of prostaglandins in bone formation has been demonstrated indirectly by use of indomethacin, a potent inhibitor of the cyclooxygenase pathway, preventing ectopic ossification (Kjærsgård-Andersen and Schmidt 1986). Reports of the direct effect of prostaglandins on human bone are few. Ueda et al. (1980), however, reported 2 cases of cortical hyperostosis following long-term administration of PGE in infants with cyanotic congenital heart disease. A biopsy specimen from the rib of 1 of their patients was microscopically normal. Radiographically, the condition seems reversible and dose-related (Ueda et al. 1980, Hoevels-Guerich et al. 1984, Silove et al. 1985). In our case the histologic findings of the ulna were the most striking, with a fibrous thickening of the periosteal membrane under which hyperostotic woven bone was present. The structure of the bone was not indicative of accelerated, normal appositional growth, but rather of rapid formation of reactive bone. The latter feature was supported by serial radiography. If the hyperostosis had been in progression just before death, the outer surface would have been bone-forming. Instead, this surface was undergoing pronounced bone resorption, whereas the inner surface was almost exclusively osteogenic. This observation indicated that the previously enhanced new bone formation was reversible and that the hyperostotic bone was being remodeled towards normality. Enhanced local production of prostaglandins in bone has been shown to be present at the site of injury (Denkel et al. 1981) or mechanical stress (Davidovitch et al. 1984). In Shih and Norridins (1986)

study of the effect of prostaglandin on regional remodeling during fracture healing in beagles, increased periosteal bone formation in addition to increased endosteal formation was found. In man, presumably the effects of prostaglandins are predominantly local, because prostaglandins are rapidly inactivated in the lungs. However, in infants with congenital cardiac defects and decreased effective pulmonary blood flow, the clearance of intravenously administered prostaglandins may be poor, leading to systemic effects.

Prostaglandin treatment thus seems to initiate enhanced bone formation on the outer surface of the cortex leading to hyperostosis. The bone exhibits an abnormal woven structure similar to that observed after local application of prostaglandin in rats (Jee et al. 1984). After discontinuation of treatment, the changes seem to be reversible.

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