



Cliff Diver - Acapulco, Mexico

PIC QUESTION OF THE WEEK: 1/31/11

Q: What are the risks of osteoporosis due to use of heparin and its analogs?

A: Osteoporosis is a systemic skeletal disease in which bone mass is decreased, placing the patient at risk for increased fractures. A bone mineral density (BMD) value at least 2.5 standard deviations below the average BMD is diagnostic of osteoporosis. For several decades, it has been recognized that long term administration (\geq 5-8 months of therapy) of heparin has been associated with the development of osteoporosis. This effect has been demonstrated in both animal studies and *in vitro* examination of human osteoblasts. The true incidence of heparin-induced osteoporosis is difficult to quantify, but believed to be between 2-5%. Data compiled from several studies suggests that up to one-third of patients requiring long-term heparin will suffer a significant decrease in BMD. Cessation of heparin therapy may not be sufficient to reverse bone loss, with reduced BMD still present at least three years later. There are two proposed mechanisms for heparin's negative effects on bone tissue. Cytokines such as interleukin (IL)-1, IL-6, IL-11, and tumor necrosis factor (TNF)- α , stimulate the differentiation of mesenchymal cells into mature osteoblasts. Heparin appears to inhibit this process. Osteoblasts also require insulin-like growth factors (IGF) and express surface proteins to bind them. Heparin also adheres to these proteins, thus antagonizing the influence of IGF on osteoblastic maturation. These mechanisms result in both decreased osteoblast production (decreased bone formation) and increased osteoclast production (increased bone destruction). Low molecular weight heparins (LMWHs) are heparin derivatives with several advantages over unfractionated heparin including fixed dosage, absence of a requirement for routine laboratory monitoring, and lower incidence of thrombosis and thrombocytopenia. They also inhibit bone formation, but are associated with a lower risk for developing osteoporosis than heparin. LMWHs also decrease the number of osteoblasts; however, unlike heparin, they do not increase the quantity of osteoclasts. Fondaparinux, the most recent drug in this class, is considered the "lowest" molecular weight heparin at 1728 daltons. Preliminary *in vitro* studies with fondaparinux do not suggest a deleterious effect on bone, possibly due to its lack of immunomodulatory properties. In addition, fondaparinux does not inhibit osteoblastic activity as do heparin and LMWHs. It appears that the risk of osteoporosis with parenteral anticoagulants is related to their molecular weight, thus highest risk is associated with heparin and the lowest with fondaparinux.

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