Editorial

Heterotopic ossification

Heterotopic ossification (HO) is an intriguing and fascinating phenomenon; a highly differentiated tissue forms at a location where bone was not meant to be. No other specialized tissue can do this. This capacity is probably related to the ability of bone to regenerate completely after injury. HO may occur in different conditions, but it is commonest in muscle and soft tissues following surgical trauma, especially total hip arthroplasty.

In this issue of *Acta Orthopaedica Scandinavica,* 3 types of prophylactic treatment for heterotopic ossification after total hip arthroplasty are presented. In a randomized study of 200 patients, Dorn et al. (pp 107–110) found that short-term treatment with indomethacin prevented severe HO—but 4 days of treatment was significantly less effective than 8 days. In a double-blind study, Persson et al. (pp 111–115), on the other hand found that 8 days of prophylaxis with ibuprofen was just as effective as 21 days, and that such treatment prevented clinically significant HO. In addition, van Leeuwen et al. (pp 116–118) found that preoperative radiation with 5 gray in a single dose reduced HO in a group of patients at risk compared to controls. Thus, we seem to have at least 2 effective prophylactic treatments for HO. Nevertheless, some questions need to be addressed: (1) Which patients should be treated prophylactically? (2) Which are the treatment options, their efficacy and their side-effects? (3) Should the treated patients be checked in any particular way?

Heterotopic ossification (based on radiographs) is the commonest complication in total hip arthroplasty (Nollen and van Douveren 1993, Knelles et al. 1997). It occurs in more than half of the patients—but is it a significant clinical problem? Fewer than 5% suffer from any consequence of the bone formation. In general, HO must be widespread to cause symptoms (DeLee et al. 1976, Jowsey et al. 1977, Ritter and Vaughan 1977). The commonest symptoms are decreased range of motion or pain. However, the postoperative clinical course in the most advanced cases can mimic a low-grade infection with swelling, tenderness and slightly elevated temperature. These patients often develop severe grades of HO, with early clinical symptoms and radiographic signs of mineralization in the gluteus medius muscle within 1 month of surgery. Some progression of HO then occurs, with maturation of the bone between 3 and 6 months. After 6 months, HO rarely increases in amount, but some further maturation occurs (DeLee et al. 1976, Sodemann et al. 1988). Morphologic and biochemical analysis of the heterotopic bone has shown an intense turnover and a high content of growth factors, indicating a metabolically active tissue (Puzas et al. 1989b). Interestingly, the HO does not decrease in mass with time, despite the fact that the bone is not affected by weight bearing.

The reported incidence of HO after total hip arthoplasty varies between 3% and 90% (Knelles et al. 1997). This great variation is due to different definitions of HO, differences in the surgical procedures, but also different prevalences of risk factors in the patient populations. Using a radiographic definition, new bone in the periprosthetic soft tissues occurs in about 60% of the patients (Nollen and van Douveren 1993). More rarely, HO occurs after prosthetic replacement or trauma to other joints, such as the knee or shoulder, or following trauma to muscles. Further, different muscles seem to have a different propensity to form bone—the gluteus medius and vastus intermedius being especially prone.

The mechanism that causes HO after joint replacement is not known, but trauma to the soft tissues and bone is one cause. However, a fairly standardized trauma, such as hip arthroplasty, results in a spectrum of responses, ranging from no bone induction to ankylosis of the joint. Osteoinductive growth factors, such as the bone morphogenetic proteins (BMPs), transforming growth factor (TGF) beta and insulin-like growth factor (IGF) I are abundant in bone and are probably released at surgery. Hip arthroplasties and internal fixation of acetabular fractures are the surgical procedures most often complicated by HO. In hip arthroplasties, the reaming often causes spread of bone marrow into the muscles. Thus, surgery creates a direct access for osteogenically-competent progenitor cells to a well vascularized muscle site, while osteoinductive factors and growth factors are released from the traumatized tissues, especially the bone, and may induce these cells become osteogenic. In addition, the efficacy of preoperative irradiation suggests that osteogenic precursor cells in the local tissues are important for new bone formation at the heterotopic site (Pellegrini and Gregoritch 1996). The early in-

flammatory reaction following the surgical trauma of THA also appears to be essential to the induction of HO, since modification of this process by NSAIDS results in inhibition of heterotopic bone formation.

In addition to trauma, a genetic factor or "predisposition" is necessary for HO to occur. In HO after hip arthroplasty, several important relationships to bone metabolism and bone response to trauma in general have been reported, which may be described in terms of risk factors for HO:

1) Patients with a previous history of HO almost invariably develop HO after hip arthroplasty (Sodemann et al. 1988, Nollen and van Douveren 1993).

2) Men are more prone to HO than women and the extent of heterotopic bone is also greater (Ritter and Vaughan 1977, Ahrengardt and Lindgren 1993, Nollen and van Douveren 1993).

3) Ankylosing spondylitis, diffuse idiopathic skeletal hyperostosis and hypertrophic OA are conditions associated with increased bone formation—and increased risk of HO (DeLee et al. 1976, Puzas et al. 1989b).

Thus, heterotopic bone formation after a standardized trauma to the soft tissues, such as total hip arthroplasty, is intimately related to the specific bone biology of the individual. This is further supported by the finding that patients with HO have greater spinal bone densities than matched controls (Puzas et al. 1989a).

In addition to trauma, such as surgery or burns, HO may occur in neoplasms, in neurologic injuries (spinal fractures, myelomingocele) and in systemic ossification disorders. Tumors derived from osteogenic cells can produce bone, and bone can also be produced as a reactive phenomenon adjacent to the tumor. Head trauma, especially with prolonged assisted ventilation or a neurologic injury vastly increases the risk of HO, especially of the hip and knee (Puzas et al. 1989b). The mechanism for this is not known but the muscles may be susceptible to trauma in consequence of the neurologic injury—or the nerve system itself may have a regulatory function on the mesenchymal cells (which have receptors for some of the neuropeptides) (Mital et al. 1987, Bjurholm et al. 1988). Interestingly, fracture healing in patients with a neurologic injury occurs with an exuberant callus much like the heterotopic bone in the same patients. In the rare genetic disorder, myositis ossificans progressiva, HO occurs gradually and trauma is only of minor importance.

3 treatments have been recommended to prevent HO both in patients at risk and as a general prophylaxis after THA: (1) pre- or postoperative radiation of the hip, (2) NSAIDs postoperatively and (3) bisphosphonates postoperatively.

Postoperative irradiation as a single dose or divided into 5 doses gives a good preventive effect in patients at risk of HO (Ayers et al. 1978, Coventry and Scanlon 1981, Fingeroth and Ahmed 1995). The finding of a prophylactic effect of preoperative radiation with a low single-dose in high-risk patients (Pellegrini and Gregoritch 1996 and in this issue of *Acta Orthop Scand* (van Leeuwen et al.)) facilitates this treatment, but cost and a potential risk—although very small–of radiation-induced sarcoma still impose a restriction on its use. Radiation reduces bone ingrowth and strength of fixation of porous implants (Sumner et al. 1990). By efficient shielding of the implants, this effect can be minimized.

NSAIDs have been shown effectively to inhibit clinically significant HO and to prevent recurrence of HO after resection (Ritter and Sieber 1985, Schmidt et al 1988, Sodemann et al. 1990). A number of prospective and randomized studies have confirmed the efficacy of NSAIDS in preventing significant grades of HO in both cemented and uncemented THR and in patients at risk (Gebuhr et al. 1996, Wahlström et al. 1991, Pritchett 1995, Knelles et al. 1997, Wurnig et al. 1997). In this issue of *Acta Orthop Scand,* Dorn et al. present results indicating that the prophylactic treatment should not be shorter than 8 days; in a group treated for 4 days with indomethacin, 6% had HO grade III. Persson et al., on the other hand, found no additional preventive effects of treatment for more than 8 days. Thus, the optimal treatment period seems to be the first 8–10 postoperative days.

The main problem with medication using NSAIDS stems from the experimental findings of an inhibitory effect on bone remodeling after trauma (Sudman and Bang 1979), reduced bone ingrowth in porous implants (Keller et al. 1989), and inhibition of new bone formation in response to bone induction (Törnqvist et al. 1985). These findings have raised the question whether medication might increase the risk of mechanical prosthetic loosening. However, no clinical evidence of increased rates of loosening, such as increased radiolucencies (Kjaersgaard-Andersen et al. 1989), increased rates of revision or increased rates of nonunion of trochanter osteotomies (Schmidt et al. 1988) has been shown to date in cemented or uncemented THA, but the numbers and follow-up time are not sufficient to exclude completely an effect on prosthetic fixation. Therefore, it is important to reduce the duration of treatment as much as possible and to monitor treated patients in prospective studies.

Bisphosphonates have now been largely abandoned as prophylaxis since the mineralization process is inhibited but bone matrix is still formed. On discontinuation of medication, the matrix becomes mineralized

(Thomas and Amstutz 1985, Nollen 1986, Puzas et al. 1989b).

The 2 efficient preventive treatments for HO after hip arthroplasty, NSAIDs and local radiation, are reasonably well documented, but are associated with potential side-effects. Thus, it seems desirable to treat patients at risk for severe HO only. Treatment with NSAIDs from the day of surgery for 8–10 days, or preoperative (or postoperative) radiation in a single dose can be recommended: (1) to patients who have developed HO after previous surgery, (2) men with hypertrophic osteoarthrosis and (3) patients with ankylosing spondylitis or DISH.

Heterotopic ossification is a unique and biologically interesting entity. By studying this condition, we may acquire understanding of the factors that elicit new bone formation and regulate bone metabolism.

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