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Postoperative Cox inhibitors and late prosthetic loosening—suspicion increases!

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Editorial

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Several drugs can influence bone formation. Animal experiments have shown effects of common drugs such as low molecular weight heparins, beta-blockers and Cox inhibitors (NSAIDs) on bone repair. It is striking that so few studies have been done to evaluate the clinical consequences of these known effects. Clinical studies on drug effects often have to be large, and the cost and bureaucratic obstacles prevent almost all orthopedic surgeons from undertaking such an enterprise in an academic setting. However, in this issue (pages 735–740), Per-Erik Persson and collaborators show in a long-term follow-up of a randomized study that a Cox inhibitor given for a short time postoperatively, to prevent ectopic bone formation, is likely to increase the incidence of revision for late prosthetic loosening. Although sensational, this finding is not unexpected, considering the known inhibitory effects on bone formation. The exact mechanisms are unknown, but it appears that prostaglandins, produced mostly via the Cox-2 enzyme, are vital for initiation of bone formation. Later phases of repair are also affected, but to a lesser extent.

Persson's findings were first published in a thesis in 2004, and now reach a wider readership. They need to be confirmed by other studies. A prospective randomized RSA study is under way in my institution, and from the Danish arthroplasty registry, an increased risk of loosening of uncemented hip prostheses has been presented in abstract form. We need much more data to make a judgement about the role of Cox inhibitors in orthopedics. At the moment, clinical guidelines have to be based on guesswork. However, data from clinical studies on prophylaxis of ectopic bone formation—together with animal data—suggest that the inflammatory phase of a few weeks is crucial. In other words, if Cox inhibitors are to be avoided, it should be during the painful postoperative period (and after that there is usually no need for them).

Sometimes an increased risk of complications is worth taking. When deciding, one should be aware that cement-less prostheses are more dependent on immediate bone formation to avoid microinstability than cemented prostheses, and are therefore probably more sensitive to Cox inhibition. The same with fractures: some have greater risk of delayed union than others. Although it appears prudent to avoid Cox inhibitors during the inflammatory phase after arthroplastic surgery, and perhaps tendon repair, they may well be harmless in undisplaced metaphyseal fractures.

The debate about Cox inhibitors in orthopedics highlights the relationship between scientific reasoning, clinical tradition and a faulty definition of evidence in medicine. The issue of Cox inhibitors was recently raised when Cox-2 knockout mice were found to have poor fracture repair (Simon et al. 2002, Zhang et al. 2002). Scientific reasoning would then advocate increased caution with Cox inhibitors in arthroplastic surgery, because the biology of early implant fixation is obviously being tampered with. However, many clinicians argued that they never saw any problems with it and referred to a simplified aspect of evidence-based medicine, claiming that as long as there have been no sufficiently large, double-blind randomized studies, there is no evidence worth considering, and therefore no reason for caution. This way of thinking is dangerous. Just because randomized clinical studies are easier to interpret, logic reasoning based on common biological knowledge and experimental results must not be disrespected! The currently increasing emphasis on levels of evidence leads to a risk of throwing away the baby with the bathwater.

The paper of Persson et al. also emphasizes the biological nature of implant fixation: cellular events immediately after the operation can be influenced by drugs, leading to changes in implant fixation.

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This has been shown previously for bisphosphonates, although with improved rather than impaired fixation (Hilding et al. 2000). Moreover, Persson's data corroborates the concept that postoperative cellular events can have consequences many years later. This is worth considering by those who claim that prosthetic loosening is caused exclusively by wear debris. There is no reason to believe that postoperative Cox inhibitors increase wear.

Other drugs may also impair implant fixation. Dramatic inhibition of fracture repair has been demonstrated with low molecular weight heparins in animal experiments (Street et al. 2000). This is not unexpected, because these drugs work by inhibiting thrombin, which plays an important role in initiating tissue repair. For some reason, this has attracted little attention. There are few orthopedic institutions who can afford to follow-up on this kind of finding with clinical studies. However, the Nordic arthroplasty registries can do it. I think they should all consider registering drugs with known effects on bone repair that are given after the operations. Good bone carpentry is crucial, but we must not forget biology!

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