

Correspondence

Cox inhibitors and bone healing

Sir—We read with great interest Aspenberg's editorial on cox inhibitors and bone healing (Aspenberg 2002). However, we regard Aspenberg's choice of references and conclusions as having an unfavorable effect on an important treatment area that really deserves an evidence-based approach.

The study on the results of cox inhibitors on human bone healing that Aspenberg condemned most is written by Giannoudis et al. (2000) on fracture nonunion. They used a logistic regression model with retrospective data and a case-control design, and found an odds ratio of 10.74 for NSAIDs as predictors for nonunion of intramedullary nailing for fractures of the diaphysis of the femur 1–2 years after surgery. Of 377 patients, 32 developed nonunion; from the remaining 345 patients, a control group of 67 patients with union were chosen as regards their characteristics—i.e., the use of NSAID, type of nail, reaming procedure, and smoking habits. At least three points about the results are questionable: 1) the nonunion group had considerably more confounders (in particular, smoking) than the union group, which had twice as many smokers in the nonunion group (44% vs 25%). A correct comparison should be nonsmokers vs nonsmokers with or without NSAIDs, but no such data were given in this study. 2) They also gave no data on the amount and duration of NSAID therapy in the two groups, which must be considered mandatory: Can one, in fact, be certain that patients complied with the medication prescribed, and did they take over-the-counter analgesics as well? We do not know. 3) A study on the effect of pain treatment, which is not randomized fails in its basic scientific premise: Those taking NSAIDs might be doing so for a very good reason—i.e., unacceptable pain after incomplete fracture healing. If this is the case, the medication for pain may be given because of nonunion rather than the cause. In conclusion, the study by Giannoudis et al. (2000) is unsatisfactory for more basic scientific reasons.

Aspenberg (2002) ignores the best study on fracture healing in humans (Davis and Ackroyd 1988). They did a prospective study on Colles' fractures randomized to treatment with flurbiprofen for 2 weeks or no treatment, with a 1-year follow-up. Although this study is a poor quality randomized clinical trial with uncertain blinding or confounder control, it remains the best evidence so far. The authors found no differences as regards nonunion or fracture displacement in the two groups.

On the basis of the available literature, Aspenberg (2002) should have taken a less biased approach to his subject. We agree that the known effect of prostaglandins on bone metabolism favor evaluation of the clinical effects of cox inhibitors on fracture healing and aseptic loosening of arthroplasties. However, such conclusions must be based on scientific high-quality studies and not on incomplete retrospective studies, animal experiments of poor quality and case reports. Aspenberg (2002) is clearly arguing for a harmful effect of NSAIDs without looking at the evidence: "... not all studies trying to show this inhibitory effect have been successful", "(no adverse effect on fracture repair) ... may be true only because one has not looked for it", and "it can be feared that the use of postoperative cox inhibition will increase in the near future"; "Avoid cox inhibitors ...!". These are the words of somebody with a political agenda, not a science-oriented clinician.

Moreover, Aspenberg (2002) fails to extend his discussion to spinal fusion studies or porous ingrowth after joint arthroplasty. Had these topics been included, the clinical study by Glassman et al. (1998) would be the main concern of his hypothesis. This retrospective study has the same findings as Giannoudis et al. (2000) in that the nonunion rate at two years is 2.5 times more prevalent in smokers than nonsmokers; the NSAID group had four times as many smokers as the nonNSAID group, which definitely suggests a strong confounder bias. The nonunion rates of nonsmok-

ers differed only slightly (9/86 NSAIDs vs 1/61 controls) with nonunion rates less than 10% in both groups, which is well within normal limits given the smallness of the population. This also applies to two retrospective studies (Reuben 2001, Reuben et al. 2002).

Finally, poor ability for ingrowth and risk of aseptic loosening with NSAIDs following hip replacement are even less well documented. The best study is by Wurnig et al. (1999). They did a prospective study of the 6-year survival rate of cementless hip replacement in 80 patients who had received indomethacin for 6 weeks postoperatively and compared them with a historic control group given no NSAID. There were no revisions in either group, and no differences in subsidence (1/60 NSAIDs vs 3/64 controls).

Our conclusion is that hardly any relevant clinical studies have been done and in themselves do not show a significant inhibition of bone healing induced by cox inhibitors (NSAIDs or cox-2 inhibitors) in the clinical circumstances discussed above. We agree that more studies are needed, but we already know the general extent of beneficial or harmful effects of NSAIDs. We urge clinicians to give the patients the benefit of the doubt. Cox inhibitors are needed for pain and mobilization purposes, and seem to carry a low risk of nonunion and aseptic loosening in clinical work.

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Sir—Cox inhibitors reduce bone formation in man. This is clear from many studies concerning ectopic bone formation around the hip, including several by Dr. Kjaersgaard-Andersen himself (Kjaersgaard-Andersen and Schmidt 1991). He and Dr. Jensen are right in their statement that there are no good clinical studies proving that cox inhibitors impair fracture repair or spinal fusion. But there are studies raising the suspicion! That is why we should avoid cox inhibitors in cases requiring

unimpaired bone healing. This conclusion has also been reached in another recent editorial (Einhorn 2002).

Cox inhibitors apparently do not cause loosening or nonunion in all cases, but a moderate increase in risks has not been sought—and how high a risk is acceptable? I admit that metaphyseal fractures are likely to heal in the end anyway. However, since we know that cox 2 function is crucial for bone formation (Zhang et al. 2002), the burden of proof lies upon the proponents of cox inhibitors, who need to show in which cases they might be harmless.

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